EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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/P46/030

Note

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

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1. Introduction

On 9 Mar 2020, the MAH submitted a completed paediatric study for NOXAFIL, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study was re-submitted on 12 May 2020.

A short critical expert overview has also been provided.

This submission intends to address the request to submit all paediatric data for the 5 adolescent participants enrolled in study P069, integrated in one document with corresponding tables, and to submit a full clinical overview with an assessment of all available paediatric data for study P069.

The current submission contains all applicable listing tables for the 5 adolescent participants in the body of module 2.5.

The MAH understands this extensive content is not normally provided in the Clinical overview for an Article 46 submission but considers this to be the best way to consolidate the response into one document.

1.1. Information on the development program

In accordance with Article 46 of Commission Regulation (EC) n°1901/2006, the MAH is submitting here with a study report summarizing the results from a single study for posaconazole (NOXAFIL), Protocol 069.

The study P069 was a Phase 3, randomized, double-blind, global study designed to compare the all-cause mortality of posaconazole (POS) compared to voriconazole (VOR) in the first-line treatment of invasive aspergillosis (IA).

This study included adults and adolescents ≥ 13 years of age with proven, probable, or possible invasive aspergillosis (IA).

With agreement from the Paediatric Committee, obtained with the EU PIP modification procedure EMEA-000468-PIP02-12-M03 (EMA Decision of 11-APR-2017), P069 was removed from the EU PIP due to the very low enrolment of paediatric subjects into the study. However, given that P069 is a MAH-sponsored trial involving POS, and that there were adolescent subjects enrolled and treated, the MAH herewith presents study results pursuant to the regulatory requirements of Article 46 under Regulation (EC) No. 1901/2006.

Due to the small number of paediatric subjects (n=5), the paediatric experience in P069 is limited; therefore, individual-level subject efficacy and safety data are listed and displayed according to their treatment assignments.

The overall efficacy conclusion from the study, including these 5 subjects, is that POS is noninferior to VOR in the treatment of IA with regard to all-cause mortality through Day 42.

The overall safety conclusion from P069, including these 5 subjects, is that POS is generally well tolerated and safe, with fewer drug-related AEs in POS-treated than in VOR-treated subjects.

The MAH proposes no amendments to the Product Information of Noxafil are required for the paediatric population based on the results of this study.

1.2. Information on the pharmaceutical formulation used in the study

The following study medications will be used in the trial:

- Posaconazole 100 mg IV, 18mg/mL, 5.6mL fill

- Posaconazole 200 mg IV, 18mg/mL, 11.2mL fill

- Voriconazole 200 mg IV

- Posaconazole 100 mg tablets

- Posaconazole Placebo tablets

- Voriconazole 100 mg capsules

- Voriconazole Placebo capsules

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for the following study:

A Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults and Adolescents

Protocol No. MK-5592-069

1.3.2. Clinical study

A Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults and Adolescents

Protocol No. MK-5592-069

Methods

The hypothesis associated with the primary study objective was: The all-cause mortality rate through Day 42 in the POS treatment group is non-inferior to that in the VOR treatment group.

The Intention to Treat (ITT) population was defined as all randomized subjects who received at least 1 dose of study treatment; the Full Analysis Set (FAS) population was defined as all subjects in the ITT who were classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 EORTC/MSG definitions).

Inclusion in the FAS also required at least 1 post-randomization observation for the analysis endpoint subsequent to at least 1 dose of study treatment (and baseline data for those analyses requiring baseline data).

The All Patients as Treated (APaT) population was defined as all randomized subjects who received at least 1 dose of study treatment. Day 1 was defined as the day that the first dose of study treatment was administered.

Objective(s)

Day 1 was defined as the day that the first dose of study treatment was administered.

Primary Objective, Hypothesis, and Endpoint

To compare the all-cause mortality for POS compared to VOR in the first line treatment of IA through Day 42 in all randomized subjects who received at least one dose of study treatment (in the ITT population).

Hypothesis: The all-cause mortality rate through Day 42 in the POS treatment group is noninferior to that in the VOR treatment group.

Primary endpoint: All-cause mortality through Day 42 in the ITT population.

Secondary Objectives

• To evaluate the all-cause mortality for POS vs. VOR through Day 42 in the FAS population.

• To evaluate the all-cause mortality for POS vs. VOR through Day 84 in both the FAS and ITT populations.

• To evaluate mortality due to IA through Day 42 and Day 84 for POS vs. VOR in the FAS population.

• To evaluate the time to death (all causes) for POS vs. VOR in the FAS population.

• To evaluate the global clinical response for POS vs. VOR at Week 6 in the FAS population.

• To evaluate the global clinical response for POS vs. VOR at Week 12 in the FAS population.

• To evaluate the safety and tolerability of POS and VOR by analyzing Tier 1 Safety events and all AEs in the All-Patients-as-Treated (APaT) population.

• To evaluate the safety of POS compared to VOR therapy in the APaT population

• To evaluate, in the subset of subjects who have pharmacokinetic data and food intake records, the pharmacokinetic profile of POS and VOR, including an evaluation of the effect of food intake on the POS tablet steady-state pharmacokinetic profile, and to evaluate the exposure-response (efficacy and safety endpoints) relationships of POS and VOR in a subset of subjects with available data.

Secondary Endpoints

Secondary Efficacy Endpoints	Safety Endpoints
All-cause mortality through Day 42 in the FAS population	Proportion of subjects with Tier 1 AEs and all AEs in the APaT population
Global clinical response for POS vs. VOR at Week 12 in the FAS population	Proportion of subjects with AEs; vital signs, ECG parameters, and laboratory measurements, including change from baseline in the APaT population
All-cause mortality through Day 84 in the FAS and ITT populations	
Global clinical response for POS vs. VOR at Week 6 in the FAS population	
Time to death (all causes) in the FAS population	
Mortality due to IA through Day 42 and Day 84 in the FAS population	
Plasma concentration of POS or VOR	

Exploratory Objectives

1. To explore the effects of CYP2C19 polymorphisms and predicted metabolic enzyme activity on POS and VOR plasma concentration.

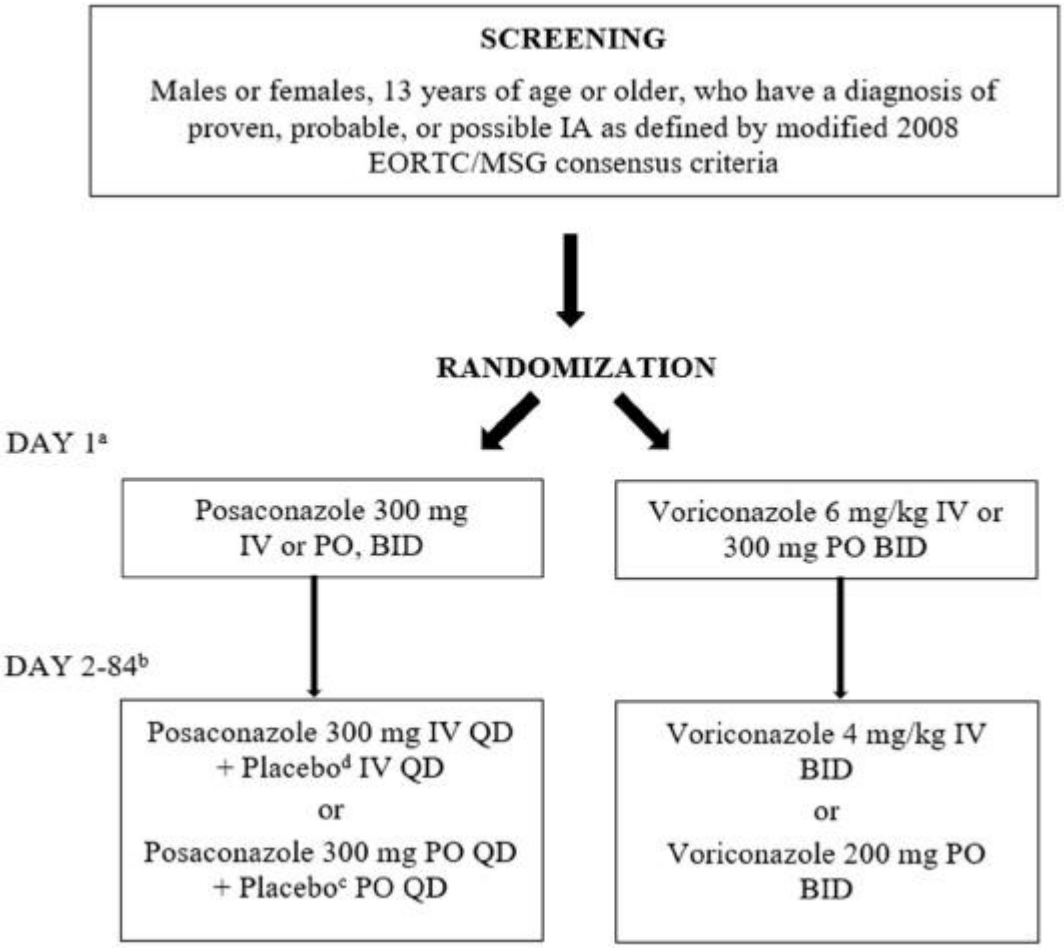
2. To explore pharmacogenetic endpoints and their association with key efficacy and safety parameters.

3. To explore the effect of treatment on serological biomarkers (e.g., serum galactomannan EIA, beta-D-glucan).

Study design

Diagnostic Criteria for Proven, Probable, or Possible IA

PROVEN[a]	PROBABLE[a]	POSSIBLE[a]
Histopathologic, cytopathologic, or direct microscopic examination of a needle aspiration or biopsy specimen showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging) OR Recovery of *Aspergillus* species by culture from a sample obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL, cranial sinus cavity, and urine.	One host factor ie, recent history of neutropenia, allogeneic HSCT, treatment with T-cell immune suppressants, prolonged corticosteroid use, inherited severe immunodeficiency AND One clinical criterion ie, evidence of lower respiratory tract fungal infection, tracheobronchitis, sinonasal infection, or CNS infection; AND Microbiological criterion ie, cytology, direct microscopy, culture, detection of antigen or cell wall constituents (ie, galactomannan positive test result defined as a cut-off index ≥1.0 [single result from serum or BAL] or ≥0.5 [2 consecutive results from serum samples])[b]	One host factor AND One clinical criterion NOTE: Subjects enrolled with possible IA will undergo additional diagnostic work-up to confirm proven or probable IA post-randomization. In the event that the additional work-up does not result in a proven or probable IA diagnosis, subjects should continue participation in the trial with possible IA if clinician deems appropriate.



Study population /Sample size

This was a Phase 3, randomized, double-blind study of POS versus VOR in subjects with proven, probable, or possible IA as defined by modified 2008 EORTC/MSG consensus criteria.

Approximately 600 subjects were planned to be randomized and treated, beginning on Day 1.

Subjects were stratified according to risk status for mortality and poor outcome (high-risk or not high-risk) and randomized within each stratum in a 1:1 ratio to POS or VOR for a total treatment duration of 12 weeks (84 days), with a maximum allowable duration up to 98 days.

A follow-up visit was required 30 days after completion of treatment.

The study utilized both the IV and tablet formulations of POS and VOR. The tablet formulation of VOR was over-encapsulated to maintain the study blind; dummy tablets of POS were prepared to maintain the blinding.

Subjects could begin study therapy with oral therapy if clinically indicated, although it was anticipated that most subjects would begin study treatment with IV therapy. Treatment was switched from the IV to the oral route when a subject was considered clinically stable and able to take oral medication. If indicated, subjects could resume IV therapy if unable to continue on oral medication.

Baseline diagnostic data, IFI-attributable mortality data, and other efficacy data from all subjects, including classification of the baseline fungal infection as proven, probable, or possible IA, were reviewed by an independent, blinded CAC.

Adjudicators serving on the CAC classified each subject as having proven, probable, or possible IA, or as "unable to determine" if co-morbidities or insufficient data precluded classification.

The CAC also assessed the subject's global clinical response to treatment at Week 6 and Week 12 using the 2008 EORTC/MSG guidelines; windows for analysis were ±2 weeks and ±4 weeks at those time points, respectively.

The criteria that define global clinical response (with success categorized as complete or partial response and failure categorized as stable response, progression of fungal disease, or death) are based on clinical signs and symptoms, imaging, serologic testing, and fungal culture and histology.

The CAC could also define global clinical response as "unable to determine" if comorbidities or insufficient data precluded evaluation of the response at the pre-specified time points.

Main inclusion criteria

1. Each subject must be willing and able to provide written informed consent for the trial.

2. Each subject must be ≥13 years of age weighing >40 kg [88 lb] and ≤150 kg [330 lb] at the time of randomization. Each subject between 13 and 14 years of age must weigh ≥50 kg [110 lb].

3. Each subject must meet the criteria for proven, probable, or possible IA per 2008 EORTC/MSG disease definitions at the time of randomization.

4. Each subject with possible IA at time of randomization must be willing or be in process of an ongoing diagnostic work up which is anticipated to result in a mycological diagnosis of proven or probable IA post-randomization.

5. Each subject must have a central line (eg, central venous catheter, peripherally-inserted central catheter, etc.) in place or planned to be in place prior to beginning IV study therapy. Subjects without central catheter access must be clinically stable and able to receive oral study therapy

6. Each subject must have acute IA defined as duration of clinical syndrome of <30 days.

7. Each subject must be willing to adhere to dosing, study visit schedule, and mandatory procedures as outlined in the protocol.

8. The subject must have the ability to transition to oral study therapy during the course of the study.

9. Female subjects of child-bearing potential must be using a medically accepted method of birth control before beginning study treatment and agree to continue its use for 30 days after stopping the medication, or have been surgically sterilized (eg, hysterectomy or tubal ligation).

10. To participate in the pharmacogenetic analysis, the subject must be willing to give written informed consent for the pharmacogenetic testing and able to adhere to dose and visit schedules.

11. Subject is not taking prohibited antifungal prophylaxis or treatment as defined by the protocol.

Main exclusion criteria

1. The subject has chronic (>1-month duration) IA, relapsed/recurrent IA, or refractory IA which has not responded to prior antifungal therapy.

2. The subject has pulmonary sarcoidosis, aspergilloma, or allergic bronchopulmonary aspergillosis.

3. The subject has a known mixed invasive mold fungal infection including Zygomycetes, and/or a known invasive Aspergillus fungal infection in which either study drug may not be considered active.

4. The subject has received any systemic (oral, intravenous, or inhaled) antifungal therapy for this infection episode for 4 or more consecutive days (≥96 hours) immediately prior to randomization.

5. The subject has developed the current episode of IA infection (possible, probable, or proven infection) during the receipt of more than 13 days of an azole or polyene antifungal agent given for prophylaxis that is considered to be a mold-active, antifungal agent (including itraconazole, posaconazole, voriconazole, isavuconazole, inhaled or systemic amphotericin or lipid-associated amphotericin). Any duration of echinocandin antifungal use is allowed (prior to randomization).

6. The subject has received POS or VOR as empirical treatment for this infection for 4 days (96 hours) or more within the 15 days immediately prior to randomization.

7. The subject has received any treatment specifically listed in the protocol which is more recent than the indicated washout period prior to randomization.

8. A subject must not have any condition that, in the opinion of the investigator, may interfere with optimal participation in the study.

9. The subject has known hypersensitivity or other serious adverse reaction to any azole antifungal therapy, or to any other ingredient of the study medication used.

10. The female subject is pregnant, intends to become pregnant, or is nursing at the time of randomization.

11. The subject has any known history of torsade de pointes, unstable cardiac arrhythmia or proarrhythmic conditions, or a history of recent myocardial infarction within 90 days of study entry.

12. The subject has QTc (either Fridericia or Bazett's correction) interval ≥500 msec on electrocardiogram performed at screening or baseline.

13. The subject has significant liver dysfunction (defined as total bilirubin >1.5 times upper limit of normal AND AST or ALT >3 times upper limit of normal with normal ALP on screening labs) at the time of randomization.

14. The subject has hepatic cirrhosis or a Child-Pugh score of C (severe hepatic impairment) at the time of randomization.

15. The subject has severe renal insufficiency (estimated creatinine clearance <20 mL/min) or is on hemodialysis at the time of randomization or is likely to require dialysis during the study.

16. The subject has a known hereditary problem of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

17. The subject has acute symptomatic pancreatitis within 6 months of study entry or has a diagnosis of chronic pancreatitis at the time of randomization.

18. The subject has an active skin lesion consistent with squamous cell carcinoma at the time of randomization, or a current or prior history of malignant melanoma within 5 years of study entry.

19. The subject is on artificial ventilation or receiving acute CPAP/BPAP at the time of randomization.

20. A subject has known or suspected Gilbert's disease at the time of randomization.

21. The subject requires treatment with other medications that cannot be stopped and for which there is a known contraindication to co-administration of one or more of the study drugs.

22. The subject is not expected to survive for at least 1 week post-randomization.

23. The subject must not have prior enrollment in this study. The subject must not have prior enrollment in other POS studies within 90 days of study entry.

Stratification

The presence of any of the following high-risk criteria at baseline or in a subject's medical history determined whether the subject was assigned a stratification status of high-risk or not high-risk.

High risk criteria were the following:

• Allogeneic HSCT

• Relapsed leukemia, undergoing salvage chemotherapy

• Liver transplant

Treatments

At Baseline/Day 1 subjects will be stratified into two strata; high risk or not high.

Within each stratum, subjects will be randomly assigned to one of two possible treatment arms: POS or VOR for a total duration of therapy of 12 weeks.

Subjects will be randomized to POS or VOR in a 1:1 ratio.

Overview of Active Study Treatment Dosing by Treatment Groups

Treatment Arms	IV Therapy[a]	Oral Therapy
Treatment Group 1- Posaconazole (POS)	POS IV: Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD[d]	POS oral: Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD[d]
Treatment Group 2 – Voriconazole (VOR)	VOR IV: Day 1[b]: 6 mg/kg per body weight administered BID Day 2-84[c]: 4 mg/kg per body weight administered BID	VOR oral: Day 1[b]: 300 mg BID Day 2-84[c]: 200 mg BID

[a] Subjects were to begin VOR or POS study treatment via the IV route, then transition to the oral route, unless the oral route was clinically indicated (ie, subject was clinically stable and able to take oral medication). Study treatment was to be switched from the IV route to the oral route when clinically indicated.

[b] Day 1 refers to the first day of subject taking either IV or oral therapy. Subjects were to take only one formulation at a time, either IV or oral.

[c] The planned duration of study therapy was 12 weeks (84 days) with a maximum allowable duration of up to 98 days.

[d] To maintain the blind, POS (whether IV or oral) was to be administered as the first daily dose and placebo as the second daily dose.

IV=intravenous; POS=posaconazole; VOR=voriconazole

Source: Table 3 of the protocol [16.1.1.6]

Arm 1 POS:

POS IV loading dose, 300 mg IV BID on Day 1; followed by 300 mg POS IV QD beginning on Day 2; followed by POS tablet 300 mg QD to begin following transition from POS IV.

Transition to oral therapy may occur when the subject is considered clinically stable and able to take oral medication.

Most subjects will initiate IV therapy, and then transition to oral; however, some subject may initiate via the oral route if clinical indicated. Subjects taking oral therapy on Day 1 will receive POS tablet 300 mg BID as a loading dose; followed by POS tablet 300 mg QD.

Subjects randomized to Arm 1 POS will receive a placebo infusion of 5% dextrose in water once a day to make the total number of infusions per day (2) similar for both treatment arms. Subjects will also receive double-dummy capsules with appearance consistent with VOR capsules when transition to oral therapy.

Arm 2 VOR:

VOR IV loading dose, 6 mg/kg IV BID on Day 1; followed by 4 mg/kg VOR IV BID maintenance dose, beginning on Day 2; followed by oral VOR capsule 200 mg BID to begin following transition from VOR IV. Transition to oral therapy may occur when the subject is considered clinically stable and able to take oral medication.

Most subjects will initiate IV therapy, and then transition to oral; however, some subject may initiate via the oral route if clinical indicated. Subjects taking oral therapy on Day 1 will receive VOR capsule 300 mg BID as a loading dose; followed by VOR capsule 200 mg BID.

Subjects randomized to Arm 2 VOR will also receive double-dummy tablets with appearance consistent with POS tablets when transition to oral therapy.

Results

Recruitment/ Number analysed for all the study population (adults and paediatric patients)

Number of subjects randomized/treated/ongoing/discontinued:

•In the POS treatment group, 293 subjects were randomized, 288 were treated and therefore comprised the ITT population, 184 (63.9%, ITT) completed the study overall and 139 (48.3%) completed study treatment.

•In the VOR treatment group, 292 subjects were randomized, 287 were treated and therefore comprised the ITT population, 177 (61.7%, ITT) completed the study overall and 142 (49.5%) completed study treatment.

Overall Median Age (range): 57.0 years (14 to 91 years).

A total of 5 subjects (3 in the POS group and 2 in the VOR group) were aged 14 through 16 years.

Gender: 344 (59.8%) male, 231 (40.2%) female

Ethnicity: 439 (76.3%) not Hispanic or Latino, 105 (18.3%) Hispanic or Latino, 25 (4.3%) not reported, 6 (1.0%) unknown

Race: 10 (1.7%) American Indian or Alaska Native, 122 (21.2%) Asian, 7 (1.2%) black or

African American, 50 (8.7%) multiple races, 386 (67.1%) white

Baseline data for paediatric patients (n=5)

Listing of Subject Adjudicator's Characterization of Baseline Diagnosis
Intention to Treat Population, Baseline Age <18 years

Subject ID/Gender/Age (yrs)	IA Assessment	IA-Ser	IA-C/MH	Location Category of Infection	Location Site of Infection	Risk Factors
Posaconazole						
PPD	Probable Invasive Aspergillosis	Y	N,N	Lower Respiratory Tract Disease Plus Other Organ	Multiple	Recent History Of Prolonged Neutropenia Temporally Related To The Onset Of Fungal Disease, Receipt Of An Allogeneic Hsct, Treatment With Other Recognized T-Cell Immune Suppressants, Prolonged Use Of Corticosteroid
	Possible Invasive Aspergillosis	Y	N,N	Lower Respiratory Tract Disease Only	Lung	Treatment With Other Recognized T-Cell Immune Suppressants
	Probable Invasive Aspergillosis	Y	N,N	Lower Respiratory Tract Disease Only	Lung	Recent History Of Prolonged Neutropenia Temporally Related To The Onset Of Fungal Disease, Prolonged Use Of Corticosteroid
Voriconazole						
PPD	Possible Invasive Aspergillosis	Y	N,N	Lower Respiratory Tract Disease Only	Lung	Recent History Of Prolonged Neutropenia Temporally Related To The Onset Of Fungal Disease, Treatment With Other Recognized T-Cell Immune Suppressants, Prolonged Use Of Corticosteroid
	Cannot Be Determined	N	N,N	Non-Lower Respiratory Tract Disease Only	Sinus	Recent History Of Prolonged Neutropenia Temporally Related To The Onset Of Fungal Disease

IA: Invasive Aspergillosis, IA-Ser: IA Classification by Serology, IA-C/MH: IA Classification by Culture/Microscopy/Histopathology

Source: [P069/MK5592: adsm-adsl] [P069/MK5592: sdtm-fa; suppfa]

Efficacy results for all the study population (adults and pediatric patients)

The overall efficacy conclusions in the intention to treat population (including paediatric and adolescent subjects) from P069 is that POS is noninferior to VOR in the treatment of IA with regard to all-cause mortality through Day 42.

Primary Efficacy Endpoint

• POS was demonstrated to be non-inferior to VOR based on all-cause mortality through Day 42 in the ITT population (15.3% of subjects in the POS group, 20.6% in the VOR group), after stratification for risk of mortality/poor outcome, with an estimated difference of -5.3% [95% CI: -11.6, 1.0%]. Non-inferiority of POS was demonstrated by the upper bound of the 95% CI on the estimated treatment difference being <10%, with a p-value of <0.0001.

Secondary Efficacy Endpoints

• All-cause mortality rates were comparable through Day 42 in the POS and VOR treatment groups in the FAS population (19.0% and 18.7%, respectively, with an estimated difference of 0.3% [95% CI: -8.2, 8.8%]).

• All-cause mortality through Day 84 was observed at comparable rates in the POS and VOR treatment groups in the ITT population (28.1% [POS] and 30.7% [VOR]; estimated difference of -2.5% [95% CI: -9.9, 4.9%]) and in the FAS population (34.4% [POS] and 31.0% [VOR]; estimated difference of 3.1% [-6.9, 13.1%]).

• The time to death due to all causes (ie, all-cause mortality rate through Day 114) was comparable in the POS and VOR treatment groups in both the ITT and FAS populations. In the ITT population, 71.9% and 69.3% of subjects were alive at Day 84, as were 65.6% and 69.0% in the FAS population.

• No conclusion could be made for treatment-group comparison for attribution of death, by the independent CAC, to IA, to invasive fungal disease other than IA, or to another cause due to the high proportions of deaths adjudicated to an 'indeterminate' cause: of all deaths at various time points, 50% to 56% among VOR-treated subjects and 32% to 39% among POS-treated subjects had an indeterminate attribution of death.

• Global clinical response outcomes of 'success', based on adjudicators' assessments, were seen at comparable rates in the treatment groups in the FAS population at Week 6 (45.4%[POS], 45.0% [VOR]; estimated difference 0.7% [95% CI: -10.0, 11.3%]) and at Week 12 (42.9% [POS], 45.6% [VOR]; estimated difference -2.2% [95% CI: -12.7,8.4%]). Among these subjects, adjudicators assessed a complete response in comparable proportions of subjects in the two treatment groups: 6.7% (POS) and 5.3% (VOR) at Week 6 and in 12.3% (POS) and 11.1% (VOR) at Week 12.

• Subgroup efficacy analyses of all-cause mortality for the ITT population were supportive of the primary efficacy endpoint analysis (all-cause mortality at Day 42). Observed mortality rates through Day 42 were comparable for most subgroups and lower (with a 95% CI that did not contain 0) for POS compared with VOR for several subgroups. In the FAS population, subgroup efficacy analyses indicated comparable all-cause Day 42 mortality rates across treatment groups.

Efficacy results for pediatric patients (n=5)

The individual-level subject efficacy data for the paediatric subjects are listed and displayed below.

Of the 5 paediatric subjects, 1 was 14 years old, 3 were 15 years old, and 1 was 16 years old. All subjects weighed 40 kg or greater.

Two subjects were classified as high risk at baseline (1 POS, 1VOR).

For subjects treated with POS and classified with probable IA, 1 had a clinical response classified as failure due to death at Day 16, and 1 was classified with a clinical response of success.

The POS subject with possible IA was alive through Day 114 and had a clinical response classified as unable to assess.

For the 2 subjects treated with VOR (1 classified as possible aspergillosis and 1 with aspergillosis classification of unable to determine), both had a clinical response of unable to assess, and both were alive through Day 114.

Subject Characteristics Listing
And Efficacy Responses
Intention to Treat Population
Baseline Age <18 years

Subject ID	Gender	Age (Years)	Race	Ethnicity	Weight (kg)	Risk Status	Aspergillus Classification	Neutropenic Status(10^9/L)	Date of Death [Relative Day of Death,Death due to Invasive Aspergillosis]	Status at Day 42	Status at Day 84	Status at Day 114	Adjudicated Global Clinical Response at Week 6	Adjudicated Global Clinical Response at Week 12
Posaconazole														
PPD						High Risk	Probable	<0.5	PPD [16]	Dead	Dead	Dead	Failure	Failure
						No High Risk	Possible	≥0.5		Alive	Alive	Alive	Unable To Assess	Unable To Assess
						No High Risk	Probable	<0.5		Alive	Alive	Alive	Success	Success
Voriconazole														
PPD						High Risk	Possible	<0.5		Alive	Alive	Alive	Unable To Assess	Unable To Assess
						No High Risk	Cannot be determined	≥0.5		Alive	Alive	Alive	Unable To Assess	Unable To Assess
Aspergillus classification is per adjudicator's assessment.														

Source: [P069MK5592: adam-adsl; adeff]

There were no paediatric subjects with a positive mold fungal culture result.

All paediatric subjects were considered compliant with study medication.

Listing of Subject Compliance to Study Medication
All Randomized Subjects
Baseline Age <18 years

Trial Number, Site Number	Treatment Group	Unique Subject ID	Subject ID	Compliance (%)
5592-069 PPD	Posaconazole	PPD		100.0
	Voriconazole			100.0
5592-069	Voriconazole			100.0
5592-069	Posaconazole			100.0
5592-069	Posaconazole			94.0

Source: [P069MK5592: adam-adsl] [P069MK5592: sdtm-ex; suppex]

Assessment comments

Study P069 enrolled 5 paediatric subjects (adolescent patients aged between 14 and 16 years old) among 585 patients screened and randomized.

The efficacy data for paediatric patients in this study are consequently very limited.

Efficacy data in all study population (adults and paediatric patients) :

IIT population: n=288 patients in the POS treatment group and n=287 patients in the VOR group.

Regarding primary efficacy endpoint:

POS was demonstrated to be non-inferior to VOR based on all-cause mortality through Day 42 in the ITT population [15.3% of subjects in the POS group (n= 44/288), 20.6% in the VOR group (n=59/287)], after stratification for risk of mortality/poor outcome, with an estimated difference of -5.3% [95% CI: -11.6, 1.0%].

Regarding the secondary efficacy endpoint: global clinical response outcome of success:

Global clinical response outcomes of 'success', based on adjudicators' assessments, were seen at comparable rates in the treatment groups in the FAS population:
- at Week 6 (45.4% n= 74/163 [POS], 45.0% n=78/171[VOR]; estimated difference 0.7% [95% CI: -10.0, 11.3%])
- at Week 12 (42.9% n= 91/163 [POS], 45.6% n=93/171 [VOR]; estimated difference -2.2% [95% CI: -12.7,8.4%]).

Among these subjects, adjudicators assessed a complete response in comparable proportions of subjects in the two treatment groups: 6.7% (POS) and 5.3% (VOR) at Week 6 and in 12.3% (POS) and 11.1% (VOR) at Week 12.

Efficacy data in pediatric population:

Among these paediatric subjects 3 were enrolled in the POS treatment group and 2 in the VOR group.

In the POS group:
- 2 patients had probable IA; 1 had a clinical response classified as failure due to death at Day 16, and 1 was classified with an adjucated global clinical response of success at week 6 and week 12
- one patient had possible IA: was alive through Day 114 and had a clinical response classified as unable to assess.

In the VOR group:
- 1 patient had possible IA and 1 patient IA assessment could not be determined:
Both had a clinical response of unable to assess, and both were alive through Day 114.

Among all 5 paediatric patients, no statistical subgroup analysis is made due to very small size with description of available efficacy data resulting as 1 death, 1 clinical successful response and 3 clinical response unable to assess

The data are too limited for any efficacy conclusion for the pediatric population participating to of this study: no information can be included in the SmPc regarding efficacy data for the paediatric population based on the results of this study.

Safety results

The overall safety conclusions in the intention to treat population (including paediatric and adolescent subjects) from P069 is that POS is generally well tolerated and safe, with fewer drug-related AEs in POS-treated than VOR-treated subjects. The individual-level subject medical history and safety data for the paediatric subjects are described below. The 2 subjects in the VOR treatment group did not experience any adverse events.

Listing of Reported Medical History ITT

An underlying diagnosis of leukaemia (acute lymphocytic leukaemia, acute myelomonocytic leukaemia, and acute T-cell leukaemia) was given for each of the 3 POS subjects. One POS subject had also received an allogeneic bone marrow transplant and developed graft vs host disease. Both VOR subjects had an underlying diagnosis of acute lymphocytic leukaemia.

Listing of Study Medication Status

Only 1 paediatric subject completed the 84-day course of therapy, while the other 4 subjects discontinued study therapy early, receiving less than 3 weeks of study drug. Of the 3 POS treated subjects, 1 discontinued study medication at Day 15 due to physician decision, (with subsequent subject death the following day due to an event considered unrelated to study therapy), 1 discontinued study medication at Day 20 due to withdrawal by subject, and 1 completed the 84-day course of therapy. Of the 2 VOR-treated subjects, 1 discontinued study medication at Day 4 due to withdrawal by subject and 1 discontinued study medication at Day 14 due to physician decision.

Adverse Event Summary for Paediatric Subjects Aged <18 Years

Each of the 3 POS subjects experienced one or more adverse events, while no adverse events were reported for either VOR subject.

Adverse Event Summary
All Subjects as Treated
Baseline Age <18 years

	Posaconazole		Voriconazole		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	3		2		5	
with one or more adverse events	3	(100.0)	0	(0.0)	3	(60.0)
with no adverse event	0	(0.0)	2	(100.0)	2	(40.0)
with drug-related† adverse events	1	(33.3)	0	(0.0)	1	(20.0)
with serious adverse events	2	(66.7)	0	(0.0)	2	(40.0)
with serious drug-related adverse events	1	(33.3)	0	(0.0)	1	(20.0)
who died	1	(33.3)	0	(0.0)	1	(20.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
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 are reported from the first dose of study treatment through 30 days after the last dose.

Source: [P069MK5592: adam-adsl; adae]

Listing of Subjects with Adverse Events

All 3 POS-treated subjects reported multiple adverse events. One subject experienced multiple adverse events considered to be related to study therapy (rash, hyperbilirubinemia, and AST increased).

Listing of Subjects with Tier 1 Adverse Events

There were 2 POS-treated subjects with a Tier 1 adverse event. One subject had a mild rash considered related to study therapy that resolved without discontinuation of study treatment, and 1 subject experienced severe posterior reversible encephalopathy syndrome that occurred during study treatment (Day 48) and resolved 6 days later. This event was not considered related to POS study therapy and study treatment was continued.

Listing of Subjects with Drug-Related Adverse Events

One POS-treated subject reported 3 adverse events that were considered related to study drug: rash, hyperbilirubinemia, and AST increased.

Listing of Subjects with Serious Adverse Events

There were 2 subjects (both treated with POS) who experienced serious adverse events. One subject had a serious adverse event of hyperbilirubinemia which was considered related to study therapy. This subject also experienced serious adverse events of emphysematous cholecystitis, neutropenia, and respiratory disorder, and a fatal SAE of shock, all of which were considered unrelated to study therapy. One subject had several hospitalizations for febrile neutropenia throughout the treatment and follow-up period that were considered unrelated to study therapy. Neither VOR subject was reported to have had a serious adverse event.

Listing of Subjects with Adverse Events Resulting in Death

One POS-treated subject had an AE of shock, with onset on Day 15, and died during the study. The AE was considered unrelated to study therapy.

Listing of Subjects with Adverse Events Resulting in Discontinuation

No subject had an adverse event resulting in study drug discontinuation. Four of the 5 paediatric subjects discontinued study therapy early, however, none of the early discontinuations was due to an adverse event.

Listing of Subjects with Liver Function Laboratory Findings That Met Predetermined Criteria; All Subjects as Treated; Treatment Phase; Baseline Age<18 years

One POS-treated subject had liver function parameters that met these criteria: the subject had rising bilirubin during study treatment and study drug was discontinued on Day 15 (the day prior to death). The hepatic criteria were met when the transaminase values continued to increase shortly prior to the subject's death. One VOR-treated subject had elevated AST and ALT (Grade 2) on Day 15 (the day following the discontinuation of study medication).

Listing of ECG Results

There were no paediatric subjects in either treatment group with a finding of abnormal QTc values and/or changes from baseline.

Assessment comments

The safety data for paediatric patients in this study are limited. Indeed, this overview is being submitted to support the fulfilment of the legal obligation related to Article 46 of the Paediatric Regulation, as study P069 enrolled 5 paediatric subjects. Among these paediatric subjects 3 were

enrolled in the POS treatment group.

One POS-treated subject reported 3 adverse events that were considered related to study drug: rash, hyperbilirubinemia, and AST increased. No new adverse events were seen then already known and described in the SmPC. Appropriate warnings for liver function disturbances are already described in the SmPC

One POS-treated subject had an AE of shock, with onset on Day 15, and died during the study. The AE was considered unrelated to study therapy by the investigator.

According to the limited paediatric data no conclusion could be drafted and no updates were proposed by the MAH to the POS labelling for the paediatric population based on the results of this study.

1.3.3. Discussion on clinical aspects

Clinical results

Study P069 enrolled 5 paediatric subjects (adolescent patients aged between 14 and 16 years old) among 585 patients screened and randomized.

The efficacy data for paediatric patients in this study are consequently very limited.

The data are too limited for any efficacy conclusion for the pediatric population participating to of this study: no information can be included in the SmPc regarding efficacy data for the paediatric population based on the results of this study.

Safety results

Among these paediatric subjects 3 were enrolled in the POS treatment group. No new adverse events were seen then already known and described in the SmPC. Nevertheless, due to the limited paediatric data no conclusion could be drafted, and no updates were proposed by the MAH to the POS labelling for the paediatric population based on the results of this study.

2. CHMP overall conclusion and recommendation

As proposed by the MAH, no changes to the Product Information (PI) for Noxafil based on study MK-5592-069 results are required at this point on time.

These paediatric efficacy and safety data should be included in the submission file with all available pediatric data in the context of the planned request for extension of the indication to the paediatric population.

☒ Fulfilled:

No regulatory action required.