16 September 2021
EMA/590500/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Noxafil

International non-proprietary name: posaconazole

Procedure No. EMEA/H/C/000610/II/0062

Note

Variation 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[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	26 Dec 2020	26 Dec 2020	☐
☐	CHMP Rapporteur Assessment Report	19 Feb 2021	19 Feb 2021	☐
☐	PRAC Rapporteur Assessment Report	26 Feb 2021	19 Feb 2021	☐
☐	PRAC members comments	03 Mar 2021	03 Mar 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	04 Mar 2021	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Mar 2021	11 Mar 2021	☐
☐	CHMP members comments	15 Mar 2021	n/a	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Mar 2021	n/a	☐
☐	Request for supplementary information	25 Mar 2021	25 Mar 2021	☐
	Submission of responses	21 May 2021	21 May 2021	
☐	Start of procedure	24 May 2021	24 May 2021	☐
☐	CHMP Rapporteur Assessment Report	22 Jun 2021	23 Jun 2021	☐
☐	PRAC Rapporteur Assessment Report	25 Jun 2021	23 Jun 2021	☐
☐	PRAC members comments	30 Jun 2021	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	01 Jul 2021	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	08 Jul 2021	08 Jul 2021	☐
☐	CHMP members comments	12 Jul 2021	12 Jul 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 Jul 2021	15 Jul 2021	☐
☐	2nd Request of supplementary information	22 Jul 2021	22 Jul 2021	☐
	Submission of responses	17 Aug 2021	17 Aug 2021	
☐	Start of procedure	18 Aug 2021	18 Aug 2021	☐
☐	CHMP Rapporteur Assessment Report	01 Sep 2021	01 Sep 2021	☐
☐	CHMP members comments	06 Sep 2021	n/a	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	09 Sep 2021	07 Sep 2021	☐
☒	Opinion	16 Sep 2021	16 Sep 2021	☐

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
AST	aspartate aminotransferase
BID	twice a day
CAC	Clinical Adjudication Committee
CHMP	Committee for Medicinal Products for Human Use (of the EMA)
CLSI	Clinical and Laboratory Standards Institute
CNS	central nervous system
EMA	European Medicines Agency
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EU	European Union
FDA	Food and Drug Administration (US)
FLU	fluconazole
GOF	goodness-of-fit
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplant
IA	invasive aspergillosis
IFI	invasive fungal infection(s)
ISA	isavuconazole
ITR	itraconazole
IV	intravenous
MIC90	minimum drug concentration at which organism growth is inhibited by at least 90%
NWT	non-wild-type
OS	oral suspension
PK	pharmacokinetic(s)
POS	posaconazole
QD	once a day
rIFI	refractory invasive fungal infection
SAE	serious adverse event
SOC	system organ class
US	United States
VOR	voriconazole
WT	wild-type

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 26 August 2020 an application for a variation.

The following changes were proposed:

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

Extension of indication to include primary treatment of invasive aspergillosis in adults for Noxafil gastroresistant tablet and concentrate for solution for infusion as result of conclusion of Study P069 (a Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.2 of the RMP has also been submitted.

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

Information on paediatric requirements

N/A.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH has requested scientific advice at the CHMP on January 2007 and February 2016 concerning clinical development of posaconazole in first-line aspergillosis treatment.

2. Scientific discussion

2.1. Introduction

This variation, supported by the results of a single Phase 3 study, MK-5592-069 (hereafter referred to as P069), proposed to extend the use of posaconazole (POS) to include first-line treatment of invasive aspergillosis (IA). The formulations of POS proposed to be used for this indication are the tablets and the solution for infusion.

2.1.1. Problem statement

Disease or condition

Aspergillus species are filamentous fungi, commonly found in the environment that cause a wide spectrum of infections in humans; these infections can be acute and life-threatening, primarily in immunocompromised individuals. Among over 250 species of *Aspergillus*, fewer than 40 are known to cause human infection; of these, *Aspergillus fumigatus* is the most common cause of infections in humans and the most common cause of serious, invasive disease.

Invasive aspergillosis (IA) is a serious, life-threatening disease among patients with prolonged and/or severe impairment of the immune system. Without the initiation of antifungal therapy, the acute mortality rate has been shown to exceed 85%. Despite the use of mold-active antifungal prophylaxis, breakthrough infections caused by *Aspergillus* species remain a serious threat in the immunocompromised population. Breakthrough IA is difficult to diagnose due to low sensitivities of mycological tests for IA. Nonetheless, early diagnosis and prompt initiation of antifungal treatment is the most important predictive factor for a successful outcome in immunocompromised individuals.

A meta-analysis conducted by the MAH of all-cause mortality in patients with IA, after 6 weeks of antifungal treatment, estimated a mortality rate of 23% based on historical data of 3 prospective comparative trials of voriconazole (VOR) given for IA treatment. In 2015, a prospective clinical study of isavuconazole (ISA) vs VOR in patients with IA reported Day 42 (Week 6) all-cause mortality rates of 18.6% and 20.2% in the ISA and VOR treatment arms, respectively. In the same clinical study, a successful clinical response at the end of therapy was noted to be 35.0% (ISA) and 38.9% (VOR).

Management

Current guidelines for the primary treatment of IA recommend early initiation of antifungal therapy while definitive diagnostic evaluation is in progress. Only 2 medications, the triazoles VOR and ISA, have been approved for the primary treatment of IA in the past 20 years (initial approvals in 2002 and 2015, respectively). Recent guidelines (ECIL-6, 2017, ESCMID 2017, IDSA 2016) recommend VOR and/or ISA for the primary treatment of IA, with liposomal amphotericin B being the first alternative and POS, as well as echinocandins, mainly recommended for salvage treatment.

VOR is efficacious but has significant safety concerns that limit its clinical use. These include adverse effects that are more pronounced than observed with other triazoles (i.e., transient visual disturbances, skin rash, erythroderma, photosensitivity, perioral excoriations, visual or auditory hallucinations, and cardiovascular events including tachyarrhythmias). Higher VOR plasma concentrations are associated with higher rates of visual disturbances and hepatic toxicity. Additionally, VOR is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C19, which exhibits genetic polymorphism and can result in marked variability in the PK of VOR.

ISA has also been approved and recommended for the treatment of IA since 2015. Safety information for the use of ISA post approval is limited. Adverse effects that may limit ISA use include shortening of the QT interval, hepatic toxicity, and anemia. Infusion reactions including hypotension, dyspnea, chills, dizziness, and paresthesias have been reported during infusion and may require discontinuation of the infusion. ISA product labeling cautions against coadministration of ISA with CYP3A4/5 inducers such as aprepitant, prednisone, and pioglitazone, as these may result in mild to moderate decreases of ISA plasma levels, thereby reducing its efficacy.

Given the noted limitations of VOR and ISA and the high underlying mortality of IA, a need exists for additional therapies that can overcome the limitations of currently approved IA therapies while providing at least similar levels of efficacy in the primary treatment setting.

2.1.2. About the product

POS is a broad-spectrum antifungal compound in the triazole class and blocks the synthesis of ergosterol, a key component of the fungal membrane, through inhibition of lanosterol 14α–demethylase (CYP51). The antifungal activity of POS against clinically relevant molds includes most strains of *Aspergillus*, as well as other mold fungal pathogens such as the Zygomycetes (e.g., species of *Absidia*, *Mucor*, *Rhizopus*, and *Rhizomucor*).

POS is currently available as oral suspension, tablets and solution for injection formulations, and indicated only in adults. Of note, a paediatric extension for children between 2 to 18 years old, with a new formulation (Noxafil gastro-resistant powder and solvent for oral suspension), is ongoing in parallel of this procedure.

Currently, POS (oral suspension, tablets and solution for injection) is indicated in EU notably for the treatment of invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products. With this application, an indication for the treatment of invasive aspergillosis, whatever the line of treatment, is being proposed for the tablets and solution for injection formulations.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program for the treatment of IA consisted of a single Phase 3, multicenter, randomized, double-blind, active-comparator study of the efficacy and safety of POS versus VOR for the treatment of IA in adults and adolescents (P069). The pivotal P069 study was designed to support the use of POS IV and POS tablet for the primary treatment of IA and to fulfil post-marketing commitments to the CHMP. An open-label Phase 3 study of POS versus VOR in the treatment of deep-seated fungal infection was also conducted at multiple sites in Japan, and used as the basis for licensure in Japan; data from that study are not included in this application with the exception of the population PK analysis.

During the clinical development program of POS for primary treatment of IA, discussions were held with the US and EU health authorities with regard to study design, dose selection, and data endpoints for study P069. The dosing regimens of POS IV and tablet that were approved for prophylaxis and salvage treatment of IFI (salvage treatment approved in the EU) were selected for evaluation. Consistent with regulatory guidance, POS was compared with the approved dosing regimens of VOR IV and oral formulations, which are the standard of care for the treatment of IA. A single study with a double-dummy design was considered acceptable. While study P069 was ongoing, additional regulatory guidance was sought in 2016 in order to switch the original primary study endpoint of global clinical response at Week 6 in the FAS population, based on a non-inferiority margin of 15%, with the key

secondary endpoint of all-cause mortality through Day 42 in the ITT population. Following regulatory discussions with the EMA and the FDA, a non-inferiority study design using a 10% non-inferiority margin for the proposed primary endpoint (all-cause mortality through Day 42 in the ITT population) was considered acceptable by the FDA. In the EU, despite global clinical response being preferred as the primary endpoint, the new proposed primary endpoint was also considered acceptable provided that the original primary endpoint (global clinical response at Week 6 in the FAS population) was also achieved.

2.1.4. General comments on compliance with GCP

The MAH confirmed that study P069 was conducted in accordance with GCP.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

The EPAR table should be updated as this extension application contains new environmental data.

Updated prevalence data:

Indication		**Estimated Size of Population (N) in 2013**
Treatment	Invasive Aspergillosis	64 000 [a]
	Fusariosis	246 [b] [Incidence: 6/1000 for HSCT (41,000 allogenic and autologous)]
	Chromoblastomycosis and mycetoma [c]	Rare [d]
	Coccidioidomycosis [c]	Rare [d]
	Oropharyngeal candidiasise [e]	Estimated 148,000 oral candidiasis and 96,200 oesophageal candidiasis [f]
	Acute Myeloid Leukemia [8]	55,000 [a] (prevalence; 19,000 incidence)
	Myelodyspastic Syndrome [8]	25,000 a (prevalence; 8,000 incidence)
	HSCT (Allogenic) [4]	41,000 allogenic and autologous HSCTs per year (approximately 43% allogeneic)*
Total Population		429,200

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

Summary of main study results

Substance (INN/Invented Name): Noxafil (Posaconazole)					
CAS-number (if available): 171228-49-2					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log D_{ow}	OPPTS 830.7560	pH 7 = 4.15			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	pH 5 = 4.06 pH 7 = 4.15 pH 9 = 4.10			not B
	BCF	29-36 L/kg (fish)			not B
Persistence	DT50	Transformation Products in sediment (20°C): >180 d			vP
Toxicity	NOEC	0.041 mg/l (algae)			not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined (prevalence data) Fpen = 0.0829%	0.33	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Soil: Log Koc = 5.12 to 5.52 Kd = 1875 to 5820 Sludge: Log Koc = 3.6 Kd = 1607			
Ready Biodegradability Test	OECD 301	0% (28d), not readily biodegradable k_{STP} (0 h-1)			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.5-4.5d $DT_{50, sediment}$ = 8.7-11.9d $DT_{50, whole\ system}$ =0.7-13.3d % shifting to sediment = 29.3 (day 28)			$DT_{50\ sediment}$ Transformation products: M1: stable M2: 215.9 d M3: 358.1 d
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	41	µg/L	*Pseudo-kirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	244	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	206	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	10^6	µg/L	Sewage sludge mixed population
Phase IIb					
Calculation	**Value**	**Unit**			**Remarks**
PEC $_{surfacewater}$, refined	0.073	µg/L			Fpen = 0.0829%

					Koc soil (geomean) = 182602.16
PEC sediment	230	µg/kgdwt			Kd soil (geomean) = 3151
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	29-36	L/kg	*Lepomis macrochirus*
Sediment dwelling organism	OECD 218	NOEC	76	mg/kg	*Chironomus riparius*

2.3. Clinical aspects

2.3.1. Introduction

Tabular overview of clinical studies:

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)	Primary Endpoint(s)
Phase 3 Studies				
P069 (completed) [Ref. 5.3.5.1: P069MK5592] 91 sites (Asia/Pacific region, Europe, and North and South America)	Randomized, double-blind study Duration: 12 weeks (84 days; maximum allowed duration up to 98 days) (Treatment of invasive aspergillosis in adults and adolescents at least 13 years of age)	POS (IV or oral)[a]: Day 1b : 300 mg BID Day 2-84: 300 mg QD[c] 288 treated / 184 completed study / 139 completed study treatment VOR IV: Day 1[b]: 6 mg/kg administered BID Day 2-84: 4 mg/kg administered BID VOR oral: Day 1[b]: 300 mg BID Day 2-84: 200 mg BID VOR Total: 287 treated / 177 completed study / 142 completed study treatment	Gender: 344 M / 231 F Median age: 57.0 yrs Range: 14 to 91 yrs <18 yrs: 5 (0.9%) ≥65 yrs: 160 (27.8%)	All-cause mortality through Day 42 in the ITT population

[a] Subjects were to begin IV study drug and then transition to oral study drug. If clinically indicated, subjects could begin study drug with oral therapy instead of IV therapy.

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

[c] 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.

This extension of indication of posaconazole (POS) in the first-line treatment of invasive aspergillosis (IA) is based on a Phase 3 non-inferiority study.

2.3.2. Pharmacokinetics

2.3.2.1. Introduction

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

The currently marketed formulations of POS are an OS (oral suspension), an IV and an oral delayed-release tablet (also as referred to as a gastro-resistant tablet, hereafter referred as tablet).

POS IV solution and tablet are currently approved for use as prophylaxis and salvage treatment (in some regions) of IFI including IA in adults with a dosing regimen of 300 mg QD (BID the first day).

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

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

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

According to these past approvals, a wealth of PK information of POS in adults is available. Hence PK properties are considered as well known in adults. Consequently, this assessment report will focus on specific and relevant PK (and PD aspects) in association with the current submission: extension of the indications of POS IV and tablet for use in the primary treatment of IA.

The POS clinical development program for primary treatment of IA consists of a pivotal Phase 3 study (Study P069) where both formulations were investigated in patients aged ≥ 13 years with IA.

A summary of the PK profile of POS following both formulation in the intended population is presented thereafter. In addition, a population PK analysis (PPK) was performed to characterize POS PK in subjects being treated for IA.

2.3.2.2. Methods

- Analytical methods

  A HPLC/MS/MS assay procedure was used to quantify POS plasma concentration and was validated by PPD® (Middleton, WI and Richmond, VA). The plasma assay isolated POS and its internal standard from plasma using solid phase extraction followed by liquid chromatographic separations. This assay was used to support the clinical study P069. The analytical range from 5 to 5000 ng/mL as presented in Table 1 below.

Table 1: Summary of the validated method for the quantification of POS in plasma

Method Description	PPD Method LCMSC 549 Version 1.00
Analytes	MK-5592 (formerly known as SCH-56592)
Method Validation Report	PPD Validation Report, Project LPW2, MK-5592: Validation of a Liquid Chromatographic-Tandem Mass Spectrometric Method for the Determination of MK-5592 Concentrations in Human Plasma
Reference Standard(s)	Posaconazole (MK-5592), Lot: 12874 [$^{15}N_2$, ^{13}C]-MK-5592, Lots: L-003669433-000M023, L-003669433-004W003
Matrix	Human Plasma
Anticoagulant	Dipotassium EDTA
Method of Detection	UPLC with MS/MS Detection
Sample Aliquot Volume	50.0-µL
Calibration Range	5.00 to 5000 ng/mL
Quality Control (QC) Concentrations	15.0, 150, 400, and 4000 ng/mL
Highest Dilution QC Concentration	25000 ng/mL
Regression, Weighting	Quadratic, $1/conc.^2$
Demonstrated Storage Stability	2268 days at -25°C
Maximum Sample Storage Duration From Collection to Analysis	2247 days at -25°C (within Stability Limits)
Analysis Start Date	14-FEB-2014
Analysis Completion Date	20-FEB-2020

In addition, plasma VOR (voriconazole) were determined using an HPLC/MS/MS assay procedure, validated at Syneos Health Clinic Inc (Quebec). The analytical range for VOR was 5 to 200 ng/mL

- Pharmacokinetic data analysis

No NCA analysis were performed since only trough PK samples (Cmin or Ctrough) per subjects were available.

POS PK data following both IV and tablet formulation from study P069 and all available clinical studies where these formulations were administered (Healthy volunteers or Prophylaxis) were pooled to develop a PPK model using NONMEM, version 7.2 (Globomax, 7250 Parkway Drive, Suite 430, Hanover, MD 21076 USA). The applied estimation method was FOCE with an additive model for RUV on log-transformed data. From this analysis predicted PK metrics (Cavg and Cmin) were derived. Exploratory ER analysis (efficacy and safety) have been also performed.

2.3.2.3. Absorption

- **Absolute bioavailability**

Based on the prescribing information (PI) of the tablet formulation an absolute bioavailability of 54% is reported (PI US 056Q9W, Revised 3/2019).

Based on the final parameter estimates from the PopPK analysis (please refer to section 5.3.2.8), the absolute bioavailability for the tablet formulation has been estimated at 82% (95% CI: 79-85).

- **Food effect**

Based on the prescribing information of the tablet formulation, the food effect as a fed/fasted GMR (90% CI) was 1.51 (1.33-1.72) for AUCinf based on a single-dose comparisons in Phase 1 studies.

Study P069 (Descriptive statistics)

Food effect was also investigated during study P069 on a subset of 179 patients with IA. Comparison of mean trough plasma concentrations across subjects who received POS with a meal of any type compared to fasting subjects showed an overall modestly higher exposure, from 15% at week 1 to approximately 33% to 39% from weeks 2 to through 12 (Table 2). There was no discernible trend in POS exposure with the type of meal consumed (light, medium, heavy) in subjects who took POS with a meal. The trend towards higher POS trough plasma concentrations when POS tablets were administered with a meal versus fasting, regardless of meal type, is evident from both Week 1 data (where subjects received tablet only) and data pooled across Weeks 2 through 12 (where subjects may have been switched from IV solution to tablet). These results demonstrate administration of POS tablet with a meal had a moderate effect (15% to 39%) on POS trough plasma concentrations.

Table 2: Summary statistics for POS trough plasma concentrations by fed or fasted status in subjects receiving POS tablet 200 mg QD

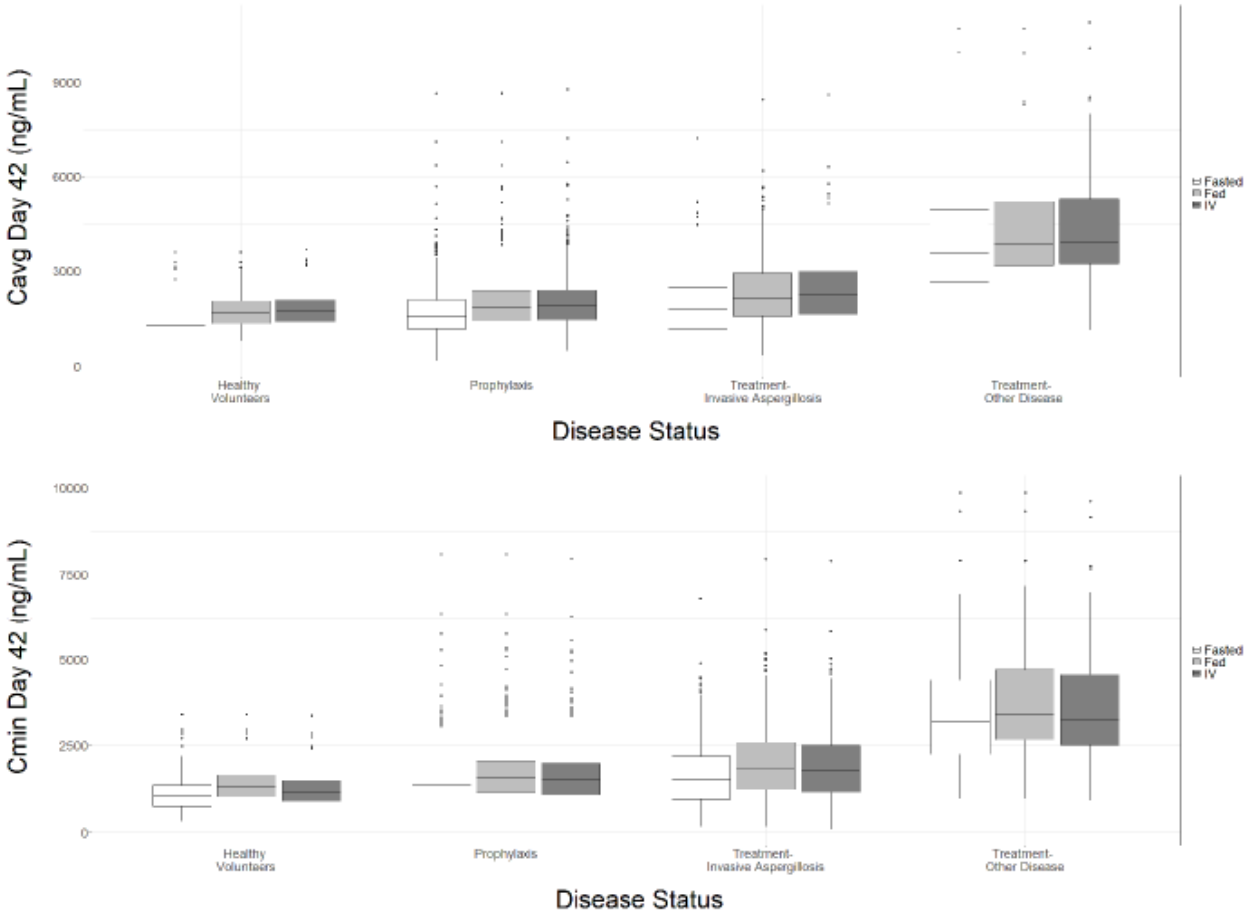
Fed/ Fasted	Week	N	Mean (ng/mL)	SD (ng/mL)	Min (ng/mL)	Median (ng/mL)	Max (ng/mL)	CV (%)	GM (ng/mL)	GM CV (%)
Fed	1	58	1625	902.9	295.0	1450	4210	55.57	1374	67.96
	2	64	1992	1190	422.0	1640	5230	59.76	1668	67.55
	4	67	1994	956.3	347.0	1760	4520	47.96	1740	61.86
	6	65	2005	1333	26.40	1570	6290	66.47	1568	97.27
	12/EOT	49	2169	1255	158.0	1820	4960	57.85	1776	79.77
Fasted	1	24	1411	1185	344.0	997.0	5040	83.99	1075	84.88
	2	33	1494	881.2	285.0	1350	3960	58.99	1232	74.90
	4	43	1480	1078	335.0	1080	4760	72.81	1184	75.17
	6	34	1439	682.5	443.0	1375	3130	47.42	1277	55.25
	12/EOT	35	1691	1083	39.10	1550	4340	64.06	1285	111.96
Unknown	1	11	1600	791.8	464.0	1640	3010	49.48	1385	66.95
	2	9	1739	657.8	784.0	1790	2550	37.83	1612	45.37
	4	12	1915	1470	184.0	1735	4920	76.78	1346	126.81
	6	8	2087	1561	588.0	1725	4830	74.78	1619	90.71
	12/EOT	10	1864	1160	661.0	1410	3810	62.22	1567	68.62

Abbreviations: SD = standard deviation; CV = coefficient of variation; EOT = end of trial GM = geometric mean

All Studies (PPK analysis and simulations)

Based on the final parameter estimates from the PPK analysis (please refer to section 5.3.2.8), food was found to increase by 20% (95% CI: 16-23) POS F1, indicating that POS tablet administered with food (given the estimated F of 82%) is close to being completely bioavailable.

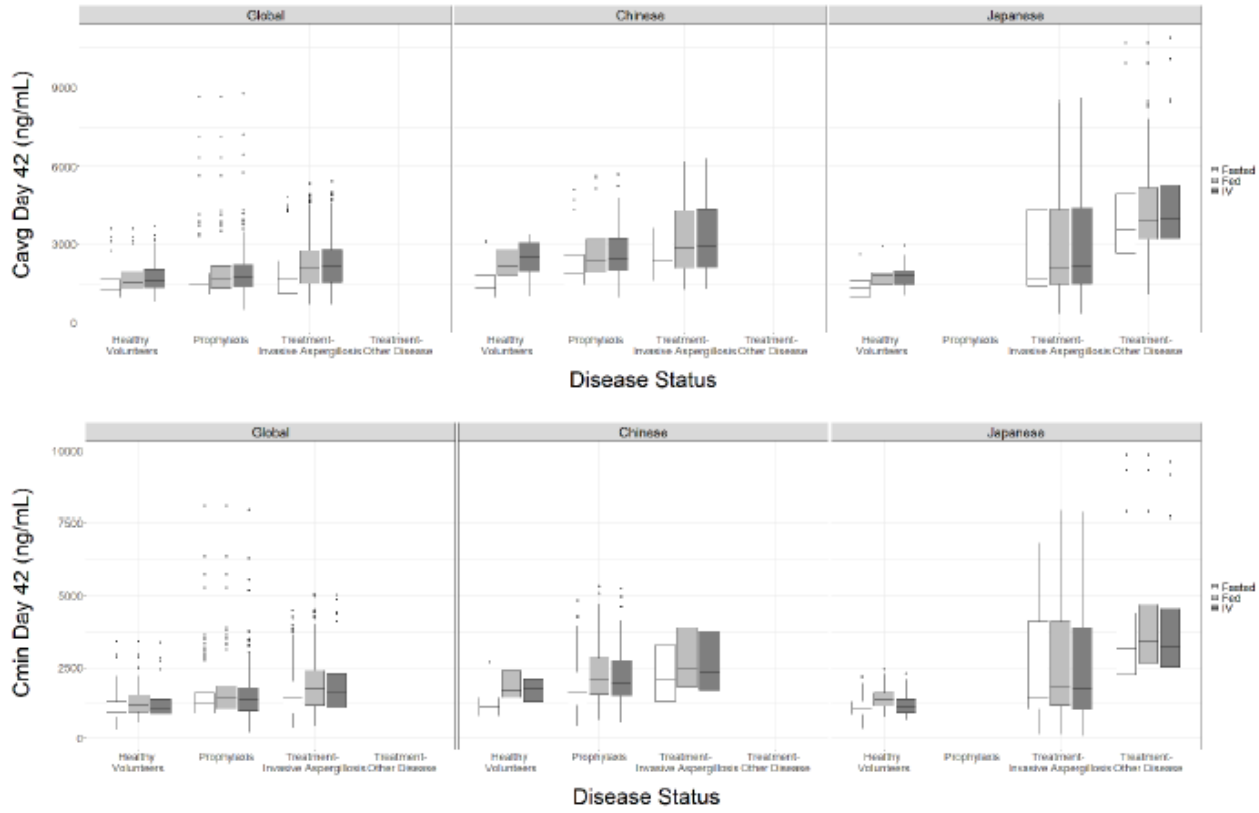
Following simulations, POS exposure parameters (Cmin and Cavg) comparing IV and oral administration in fasted and fed conditions for each disease status are shown in the Figure below. Similar distribution of Cavg in fed state vs IV is observed for all disease status. Also, Cavg in IA patients are slightly increased compared to subject in prophylaxis (effect of the disease status on CL).



Source Rscript 15.2.PK-Results-posthocs-sim-food-vs-nofood-vs-IV; Figure_Posthocs_Boxplot_Disease-Cavg-Fasted-vs-Fed-vs-IV, Figure_Posthocs_Boxplot_Disease-Cmin-Fasted-vs-Fed-vs-IV

Figure 1: Boxplot of predicted Day 42 Cavg and Cmin according to disease status, formulation and fast/fed conditions

Similar results are observed when the regional ethnicity was accounted for. Nevertheless, Chinese subject Cavg were particularly increased compared to global or Japanese subjects as shown in Figure 2.



Source Rscript 15.2.PK-Results-posthocs-sim-food-vs-nofood-vs-IV; Figure_Posthocs_Boxplot_Ethinicity-Disease-Cavg-Fasted-vs-Fed-vs-IV Figure_Posthocs_Boxplot_Ethinicity-Disease-Cmin-Fasted-vs-Fed-vs-IV.png

Figure 2: Boxplot of predicted Day 42 Cavg and Cmin according to ethnicity, disease status, formulation and fast/fed conditions

The CHMP noted that administration of food increased Cmin by 15% at week 1 and by 33 to 39% from week 2 to 12. Overall mean Cmin in fast and fed states ranged from 1411 to 1691 ng/mL and 1625 to 2169 ng/mL, respectively, in IA patients.

Following the PPK analysis, food effect was found to increase by 19.5% POS F1, however given the high eta-shrinkage of F1, the magnitude of the food effect on F1 should be viewed with caution. This is particularly highlighted in the Figure where both simulated Cmin and Cavg following administration of tablet in the fed state approximately equal Cmin and Cavg following IV infusion suggesting (as stated by the MAH), that POS tablet administered with food is close to being completely bioavailable (bearing in mind an estimated F1 of 82%).

Indeed, based on formal clinical studies in HV absolute bioavailability has been estimated at 54% (here 82%) and food effect was associated to a 50% increase of AUCinf.

The CHMP considered that the recommendation that tablets may be taken with or without food as already stated in the SmPC is supported.

2.3.2.4. Distribution

N/A

2.3.2.5. Elimination

N/A

2.3.2.6. Dose proportionality and time dependencies

N/A

2.3.2.7. Intra- and inter-individual variability

N/A

2.3.2.8. Pharmacokinetic in target population

The current Type II variation of extension of the indications of POS in adult patients with IA includes one PPK analysis. This analysis was performed following the results from Study P069.

Study P069

Design

This was a Phase 3, randomized, double blind, double-dummy study to evaluate the efficacy and safety of POS vs voriconazole (VOR) in subject's ≥ 13 years with proven, probable, or possible IA. Study treatments are outlined in Table 3.

Table 3: Treatment arms and study treatments for P069

Treatment Arms	IV Therapy[a]	Oral Therapy
POS	Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD[d]	Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD[d]
VOR	Day 1[b]: 6 mg/kg administered BID Day 2-84[c]: 4 mg/kg administered BID	Day 1[b]: 300 mg BID Day 2-84[c]: 200 mg BID

[a] Subjects were to begin IV study drug and then step down/transition to oral study drug. If clinically indicated, subjects could begin study drug with oral therapy instead of IV therapy.
[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.

Subjects were allowed to begin treatment with the IV formulation then step/down transition to oral therapy or to begin with oral therapy. The duration of treatment was 84 days with a maximal duration of 96 days.

Rationale of the POS dosing regimen

The dosing regimen selected for P069, POS 300 mg QD (BID on Day 1) IV solution or tablet, is the same as the dosing regimen approved for prophylaxis and salvage treatment (in some regions) of IFI.

This past–approval was based on a PK bridging strategy which was designed in consultation with the FDA and EMA supporting extrapolation of the indications supported by OS to tablet and IV. In these

bridging studies, the predefined exposure target (≥ 90% of subjects achieving 500 ng/mL) was met following administration of either tablet or IV solution with acceptable safety and tolerability profiles.

PK sampling

POS and VOR plasma concentration were to be determined in all subjects prior to the first dose of study treatment and pre-dose on week 1, 2, 4, 6, 12/EOT.

For adult subjects in IV therapy, at week 1, an additional POS plasma concentration at the end of the infusion was performed (Cmax)

For adolescents in IV therapy, Cmax were determined in Week 1, 2, 4, 6, 12/EOT.

Results

The overall POS PK population analysis in P069 consisted of 264 subjects (of 288 in the ITT population) who had ≥ 1 reported plasma concentration at any time point during the treatment period. PK data were further used for the PPK analysis. A limited number (N=3) of adolescents received POS in P069 and there is insufficient data to support any conclusion regarding POS plasma concentration in this age group.

Mean POS trough plasma concentrations, pooled across both IV and oral routes of administration, appear to have been approaching SS by the end of week 1. GM trough POS concentration was approximately 1500 ng/mL at all time points through to Week 12 as show in Figure 3 and Table 4.

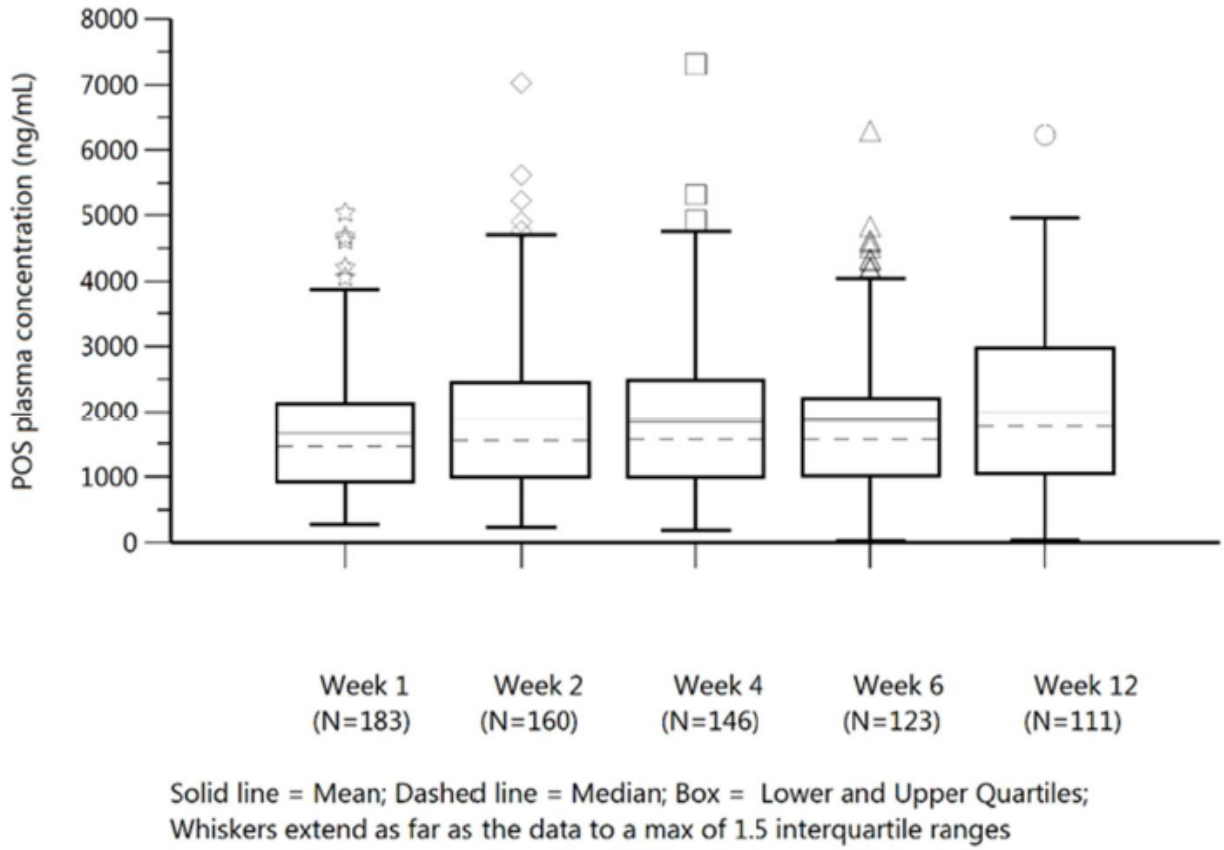


Figure 3: POS Ctrough pooled across subjects receiving either POS IV solution or tablet 300 mg QD

Table 4: Summary statistics for POS Ctrough pooled across subjects receiving IV or tablet

Week	N	Mean (ng/mL)	SD (ng/mL)	Min (ng/mL)	Median (ng/mL)	Max (ng/mL)	CV (%)	GM (ng/mL)	GM CV (%)
1	183	1658	980.6	280.0	1460	5040	59.16	1386	68.76
2	160	1867	1221	228.0	1545	7030	65.39	1521	73.98
4	146	1843	1190	184.0	1570	7310	64.54	1494	77.12
6	123	1859	1195	26.40	1570	6290	64.27	1502	82.66
12/EOT	111	2007	1263	39.10	1770	6230	62.92	1577	93.12
Abbreviations: SD = standard deviation; CV = coefficient of variation; GM = geometric mean									

Population Pharmacokinetic analysis

Model development

The analysis was conducted using all available PK data from clinical trial where POS was administered as IV or tablet formulations. The concentration-time data for POS were modelled using a compartmental approach. Log transform PK data was considered.

Pre-dose POS concentration above the LOQ were excluded. All PK observations which were not associated with a dosing event, were regarded as unevaluable and therefore excluded. BLQ were excluded from the analysis, however in case of the proportion was larger than 5%, the impact of this exclusion approach was investigated by exploring alternative methods to account for these missing data. In addition, a search for outliers as abs CWRES >6 was also performed and effects of these PK outliers were evaluated.

Food, age, body weight, CRCL, sex, disease state (categorized as healthy subjects/prophylaxis of IFI/treatment IA/Other Disease), race and regional ethnicity were assessed as potential covariates for POS pharmacokinetic model parameters. Of these covariates, the impact of race, regional ethnicity and disease state was assessed according different levels for each parameter of interest, in order to prevent identification of these covariates as proxy for any confounded but more mechanistic covariates such as age and CRCL.

The PopPK model was built using nonlinear mixed effects model with the first order conditional estimation method (FOCE) in Nonmem (version 7.4.3, Globomax, 7250 Parkway Drive, Suite 430, Hanover, MD 21076 USA).

Covariates selection was performed using a stepwise/backward procedure. Then the PopPK model was checked using standard goodness-of-fit (GOF) and evaluated using a pcVPC. Finally, a bootstrap analysis was performed.

Then the final PPK model was used to predict the distribution of POS exposure in all subjects included in the analysis on order to derive the POS summary statistics of Cavg and Cmin. Three scenarios have been investigated and Cavg and Cmin were computed accordingly:

- Tablet/fast following 300 mg BID (Day 1), then 300 mg QD up to Day 42, Cavg and Cmin at Day 42
- Tablet/fed following 300 mg BID (Day 1), then 300 mg QD up to Day 42, Cavg and Cmin at Day 42
- IV formulation following 300 mg BID (Day 1), then 300 mg QD up to Day 42, Cavg and Cmin at Day 42

The goals of this analysis was to assess a) the distribution of POS exposures of subjects according their disease status, regional ethnicity, food status, b) the impact of age and BW on the PK exposure

metrics and c) to evaluate the distribution of POS exposures in a Japanese regional treatment of IA patient population.

Results

The analysis dataset included 1092 subjects with a total observations of 11466 evaluable PK samples as presented in Table 5.

A total of 1400 concentrations were not included in the analysis because they were BLQ. Among them 818 reflected a pre-dose sample collected before the first administration and 582 reflected a sample after the first dose of administration (4.8% of the total of observations).

Table 5: Summary of included study data

Study number	Type	Subject N° Active Population	Dose regimen and dose	PK sampling scheme	Number of samples evaluable	Number of excluded samples
P04975 (Global)	Phase 1	Healthy N=16	SD 100 mg	rich	848	4
P05637 (Global)	Phase 1	Healthy N=19	SD 200 mg SD 400 mg MD 200 mg MD 400 mg	rich	675	0
P07764 (Global)	Phase 1	Healthy N=21	SD 400 mg	rich	1253	0
P07783 (Global)	Phase 1	Healthy N=25	SD 300 mg MD 300 mg	rich	526	0
P05615 (Global)	Phase 3	Prophylaxis N=231	MD 200 mg MD 300 mg	rich/ sparse	2140	13
P07691 (Global)	Phase 1	Healthy N=23	SD 100 mg	rich	505	0
PN111/P111 (Chinese)	Phase 1	Healthy N=18	SD 300 mg	rich	665	2
PN117/P117 (Chinese)	Phase 3	Prophylaxis N=65	MD 300 mg	rich/ sparse	498	1
PN067/P067 (Japanese)	Phase 1	Healthy N=28	SD & MD 200 mg MD 300 mg SD & MD 400 mg MD 600 mg	rich	670	0
PN101/P101 (Japanese)	Phase 3	Treatment Other Disease* N=76	MD 300 mg	rich/ sparse	835	2
PN120/P120 (Chinese)	Phase 1	Prophylaxis N=70	MD 300 mg	rich/ sparse	433	0
P05520 (Global)	Phase 1	Prophylaxis N=239	SD 200 mg SD 300 mg MD 200 mg MD 300 mg	rich/ sparse	1395	30
PN069/P069 (Global + Chinese)	Phase 3	Treatment of IA N=290	MD 300 mg	rich/ sparse	1098	23
Total		1121			11541	75
Evaluable		1092			11466	

Table 6 presents a summary of categorical covariates and Table 6, a summary of continuous covariates. A higher proportion of male subjects is included in the analysis (60% versus 40%). Comparable proportions of male and female subjects were observed in the Prophylaxis of IFI and Treatment-IA populations whereas male subjects represented more than 2/3 of the population of Healthy subjects and more than 90% of the population in Treatment-Other Disease patients. White and Asian subjects (62% versus 29%) represented nearly all of the subjects. Chinese and Japanese regional subjects represented 17% and 10% of the population, respectively. Patients treated in prophylaxis of IFI reflected the majority of the analysis population (55%) whereas patient for IA represented 25%.

Table 6: Summary of categorical covariates at baseline for all subjects

Covariate	Category	Nlevel	Ntotal	Percentage
Sex	Male	651	1092	59.6
	Female	441	1092	40.4
Race	White	675	1092	61.8
	Black or African American	55	1092	5
	Asian	316	1092	28.9
	Multiracial	38	1092	3.5
	American Indian	4	1092	0.4
	Native Hawaii	4	1092	0.4
Formulation	Tablet A	8	1092	0.7
	Tablet B	8	1092	0.7
	Tablet C	51	1092	4.7
	Tablet D	544	1092	49.8
	IV	481	1092	44
Food condition	Fasted	953	1092	87.3
	Fed	139	1092	12.7
Disease status	Healthy Subjects	150	1092	13.7
	Prophylaxis of IFI (AML/MDS/ HSTC)	602	1092	55.1
	Invasive-Aspergillosis	273	1092	25
	Other Disease (CPA/Fusariosis/ Zygomycosis)	67	1092	6.1
Chinese ethnicity	Global and Japanese	911	1092	83.4
	Chinese	181	1092	16.6
Japanese ethnicity	Global and Chinese	988	1092	90.5
	Japanese	104	1092	9.5
Global ethnicity	Global	807	1092	73.9
	Chinese and Japanese	285	1092	26.1

Based on the complete dataset, median (range: min-max) age was 51 years (14-90), median BW was 70 kg (31.8-172.4 kg).

Key steps of the base PK structural model building are provided in Table 7. Base structural PK model consisted of a 2 compartment PK model with sequential zero and first-order absorption model and linear elimination parameterized by Ka, CL, Vc, Q, Vd, D1 and F1. BW allometric scaling was considered with estimated exponents. IIV was estimated on all PK parameters except Q.

All model parameters were well estimated, with RSE% values < 13% for the fixed effect parameters and <20% for the random effect parameters. Estimates of the shrinkage for the different parameters suggested that the individual estimates for CL were reasonably robust (shrinkage 14%), whereas the individual estimates of the Vc, Vp, bioavailability (F1) and absorption parameters (KA and D1) were subject to shrinkage and were therefore less reliable (shrinkage values varying from 42% up to 63%). This implies that evaluations of individual post-hoc estimates for these parameters, for example in relation to covariates, should be interpreted with caution.

Table 7: Summary of key models for the structural model

Model	Model Ref	Description	OFV	ΔOFV	Comments
Run01	-	1 compartment sequential zero-first order absorption- No IIV-dependent additive error model	4599.141	-	
Run10	Run01	2 compartment sequential zero-first order absorption- No IIV-dependent additive error model	4055.356	-543.785	Significant
Run11	Run10	Addition lag time on run10	3950.129	-105.227	Significant
Run12	Run11	Allometric scaling added on CL, V_c, V_p and Q1 with estimated exponents	2901.197	-1048.932	Significant
Run12bis	Run12	Allometric scaling added on CL, V_c, V_p and Q1 with fixed exponents	2964.419	+63.22	Not-Significant to fix exponent of allometric scaling
Run13	Run12	Addition IIV on CL V_c Q V_p	-4004.819	-	Significant
Run13bis1	Run13	Addition IIV on D1	-4540.708	-535.889	Most Significant decreases of OFV vs IIV on KA or IIV on F1
Run13bis5	Run13bis1	Addition IIV on F1	-4820.610	-279.902	Most Significant decreases of OFV vs IIV on KA
Run13bis6	Run13bis5	Addition IIV on KA	-4836.416	-15.806	Significant
Run13bis7	Run13bis6	Deletion IIV on Q1	-4834.771	+1.645	Not Significant to keep IIV on Q1
Run14		Correlation KA-D1	-4881.230	-46.46	Significant but correlation prediction very high and problems occurred with the minimization.
Run_Base-Model	Run13bis7	Same model than Run13bis7	-4834.771	0	Base Model

An SCM covariate analysis was performed with the covariates as defined in Table 8 below. Following covariates selection, IOV was investigated on Ka, F1 and D1, however no IOV was retained.

Table 8: Categorical covariates included in SCM

Categorical covariate	Category definition	Number of subcategories
SUB2 for CL, V_c, V_p, D1, F1	Prophylaxis+IA vs HV vs Others	3
HV for CL, V_c, V_p, D1, F1	HV vs Others	2
FOOD for CL, F1	Fed vs Fasted	2
RACE for CL	Asian vs Others	2

Final PK parameter estimates are provided in Table 9. Overall all PK parameters were estimated with a good precision (RSE <20% for fixed and RSE <30% for random effects).

Table 9: Final PK parameter estimates with bootstrap results

Parameter	Estimate	CI95	RSE (%)	Shrinkage	Bootstrap median	Bootstrap CI
Fixed effects						
CL (L/h)	6.8	[6.49-7.12]	2.3		6.79	[6.45;7.09]
V_c (L)	123	[105-141]	7.5		121	[99.8;142]
Q (L/h)	52.7	[46.9-58.5]	5.6		53.1	[44.6;81.2]
V_p (L)	250	[235-265]	3		251	[223;274]
KA (1/h)	0.264	[0.227-0.301]	7.2		0.268	[0.221;0.349]
D1 (h)	1.99	[1.62-2.36]	9.5		2	[1.59;2.34]
F1	0.819	[0.791-0.848]	1.8		0.818	[0.78;0.855]
Lag time (h)	0.419	[0.412-0.425]	0.7		0.417	[0.367;0.778]
WT for CL and Q	0.531	[0.387-0.676]	13.9		0.539	[0.383;0.691]
WT for V_c and V_p	1.41	[1.27-1.56]	5.3		1.41	[1.3;1.54]
Covariate effects						
Food on F1	0.195	[0.159-0.231]	9.4		0.195	[0.141;0.251]
HV ~ V_p	-0.2	[-0.283--0.116]	21.3		-0.195	[-0.265;-0.103]
Other Disease ~ CL	-0.437	[-0.514--0.359]	9.1		-0.436	[-0.502;-0.361]
IA ~ CL	-0.11	[-0.171--0.0495]	28.2		-0.112	[-0.176;-0.0385]
HV ~ V_c	-0.543	[-0.677--0.41]	12.5		-0.547	[-0.737;-0.439]
HV ~ D1	0.63	[0.198-1.06]	35		0.632	[0.392;0.96]
Age ~ CL	-0.234	[-0.327--0.141]	20.3		-0.237	[-0.318;-0.147]
Race-Chinese ~ CL	-0.248	[-0.316--0.18]	14		-0.248	[-0.307;-0.178]
Random effects						
IIV CL (%CV)	45.5	[43-47.8]	2.45	13.9	44.9	[41.5;48.6]
IIV V_c (%CV)	109	[97.2-121]	3.8	40.3	111	[81.1;146]
IIV V_p (%CV)	22.4	[18.6-25.7]	7.8	63.7	21.6	[11.9;31.3]
IIV KA (%CV)	42.7	[26.9-55.2]	14.9	61.8	43	[20;63.1]
IIV D1 (%CV)	71.9	[54.9-87.6]	9.35	54.0	70.7	[60.5;86]
IIV F1 (%CV)	179	[143-221]	5.85	42.7	179	[135;260]
Residual error						
SD[a] (Ph1)	31.3	[30.9-31.6]	0.55	12.2	31.2	[29.2;33.4]
SD[a] (Ph3)	45.5	[43-47.8]	2.45	13.9	44.9	[41.5;48.6]

Food effect was found to have an effect on F1 with an increase of 19.5% in fed conditions suggesting that tablet administration with food results in similar PK levels to IV.

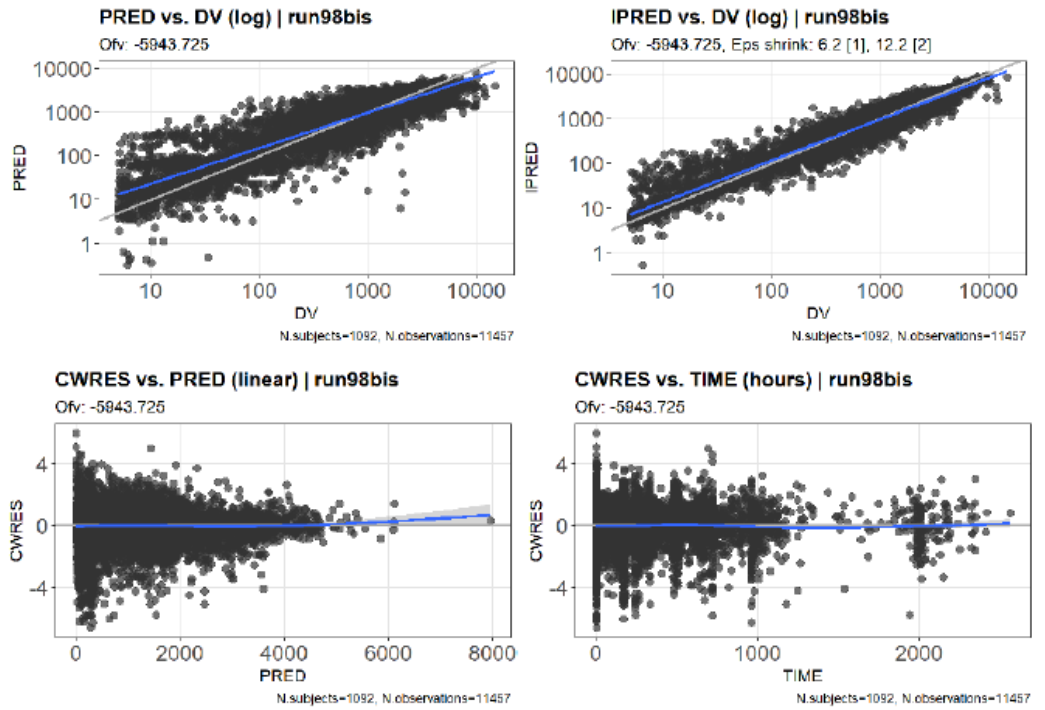
An exponential effect of age on CL was found resulting in an approximately 10% and 5% decrease in CL (corresponding to an 11% and 5% decrease in Cavg) for an 80- year old subject as compared to the median 51-year-old or a 65-year old subject, respectively.

The exponential effect of weight on CL caused a 33% increase for a 120-kg subject (corresponding to a 25% decrease in Cavg) and a 16% decrease for a 50-kg subject (corresponding to a 19% increase in Cavg) compared to the median 70 kg subject.

The disease status effect on CL in the subpopulation treated for IA and Other Disease was predicted with an 11% and 44% reduction (corresponding to 12% and 79% increase in Cavg), respectively. Decreases of 20% and 54% were found in Vc and Vp, respectively, in healthy subjects as compared to the general study population. Healthy subjects also showed a 63% higher D1.

Finally, it was identified that CL in the Chinese regional subjects in the study population was 25% lower (corresponding to a 33% increase in Cavg) compared to the general population.

Standard GOF are provided in Figure 4 and pcVPC in Figure 5. In the IA subpopulation, N=4 concentrations were quantifiable more than 300 h after the last administration driving the trend observed in the plot whereas those concentrations appeared to be more consistent with those obtained before 100 hours. Altogether these plots provide further confirmation that the final model adequately described the observed concentrations and can be used prospectively for predictive purposes.



Note: Dots are individual data; solid blue lines are trend lines. In the two plots of the first row, solid grey lines are lines of identity, while for the plot in the second row this represents a reference (zero) line.

Figure 4: Standard GOF for the integrated IV and tablet model without outliers

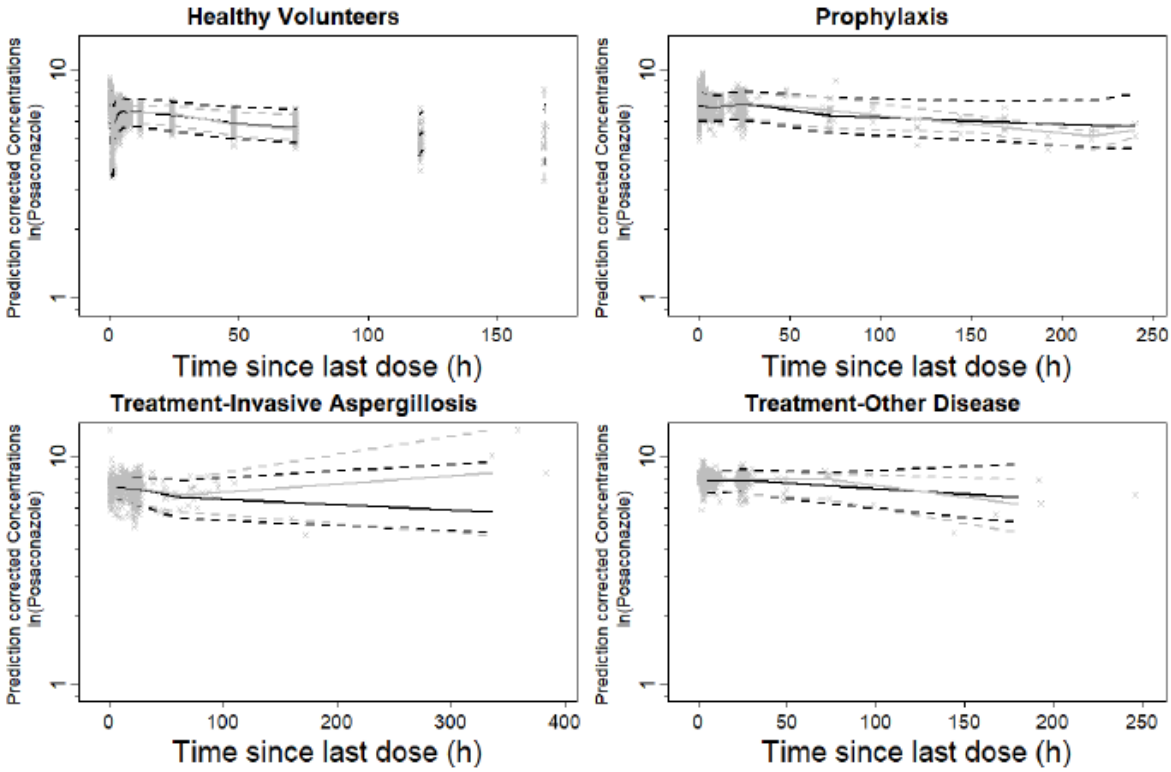


Figure 5: pcVPC of final model describing POS concentration time data in subjects according to disease status

PPK model

The CHMP noted that the PPK model presented by the MAH was based on PK data from N=1092 subjects from which n=11457 PK samples were available. PK data were retrieved from 13 clinical studies where POS was administered as IV or tablet formulation. Whereas PK data from patients with IA represent 290 patients with 1098 PK samples, the proposed analysis is only descriptive and supportive. Nevertheless, for the entire population, results from this analysis (and mainly the simulation exercise) were highlighted in the special populations section in the SmPC.

The PPK model consisted of a 2 cpt PK model parameterized in terms of D1, F1, CL, Q, Vc, Vp and ka. BW allometric scaling with estimated exponents (0.531 for CL and Q, 1.41 for Vc and Vp) were considered. All PK parameters were estimated with a good precision (RSE<30% for both fixed and random effects). CL was estimated at 6.8 L/h and F1 at 0.812. IIV was particularly high for F1 and Vc (< 100%). Eta-shrinkage is acceptable for CL only (<15%), whereas for other PK parameters shrinkage range from 40.3 to 63.7%. Therefore, any output for the covariate screening procedure investigation on these parameters should be interpreted with cautions (Food effect on F1, healthy volunteer status on Vc, Vp and D1). IA or other disease status, age and race were found to have an effect on POS CL.

GOF does not show a particular bias and pcVPC shows good predictive performance (except for the IA population at later time points). Overall, the PPK analysis was considered acceptable by the CHMP.

Simulation

Based on the final population PK model, a series of model predictions was performed for all subjects (N=1092) after IV or oral administration (fasted and fed conditions) of a dose regimen of 300 mg of POS BID at Day 1 and QD up to Day 42 (last day of dosing in P069).

A full PK profile was predicted with the individual POP PK parameters for all subjects in the current analysis in order to calculate the individual exposure parameters Cavg, Cmin. Then, the predictions were compared to explore the impact of food effect by comparing all subjects in fasted and fed conditions, and then per subpopulation of interest, disease status and regional ethnicity levels.

In addition, the effect of weight with three level of stratification (<71 kg and over 71 kg; < 29 kg, 29-<69 kg and over 69 kg; and a band every 10 kg from < 50 and up to ≥ 120 kg). Similarly, the effect of age was also explored with four level of stratification (< 65 y, 65-<75 years and over 75 years; <29 years, 29-<69 years and over 69 years; and a band every 10 years from < 20 years and up to ≥ 80 kg).

Finally, the effect of race (Japanese) was also explored. In order to support the use of POS in Japanese subjects with IA, simulations were performed to create a virtual Japanese IA population. For the purpose of simulations and in order to apply a distribution of age and weight that would optimally reflect a true patient population, the distribution of individual age/weight combinations was obtained from the Global+Chinese regional patients in the current analysis (N=264).

A scaling of age and weight distributions was performed, based on published literature in Japanese IA subjects, to obtain a Japanese IA population. For the scaling, the mean age applied was 55.5 years, comparable to that in Global+Chinese regional IA (53.3 years) and mean weight of 56.5 kg, lower than the mean observed in the Global+Chinese regional IA (68.3 kg).

Therefore, results from three sets of simulation (Table 10) are presented thereafter.

Table 10: Summary of model prediction and simulation with the number of subjects per boxplot

Type of comparison	Methodology	N total
Food Condition; Disease status; Disease status and regional ethnicity	Model Predictions	1092
Age and Weight Impact	Model Predictions	875
Virtual IA Japanese Population	Simulations	264

Results of the different scenarios with age, weight and race will be presented in the Section Special Populations. Results of the different scenarios with fed/fast status are presented in the Section Absorption, food effect.

2.3.2.9. Special Populations

- **Gender**

Results from the PPK analysis indicated that gender was not a significant covariate of any of the available PK parameters.

- **Race**

The PK dataset consisted of 62% of White, 29% of Asian, 17% of Chinese and 10% of Japanese subjects.

Results from the PPK analysis indicated that Chinese status has a significant effect on POS CL. POS clearance in subjects enrolled in clinical studies in China was decreased 25% (corresponding to a 33% increase in Cavg) compared to the global population (ex-China) when all other covariates are held constant. There was no significant effect of race or Japanese regional ethnicity when Chinese regional ethnicity was included in the model.

Figure 2 (section food effect) presents the distribution of the model predicted steady-state POS Cavg in Chinese, Japanese and other races.

Overall the effect of Chinese race is not considered to be clinically meaningful.

Japanese IA population

Based on a simulation exercise, a slight increase of both exposure parameters was observed for Japanese-IA patients in the three scenarios as shown in

Table 11, presumably due to the influence of weight which appears to be slightly lower based upon the virtual population.

Table 11: Summary statistics of model simulated Day 42 Cavg and Cmin between Virtual Japanese IA patients and others following IV or oral administration, in fed/fast state

Parameter	Sim	Population	Min	P10	Q1	Median	Mean	Q3	P90	Max	N
C_{avg} (ng/mL)	Fasted	Japanese IA	272	962	1300	1820	2210	2680	3930	10300	264
		Global+Chinese IA	256	758	1110	1570	1800	2240	3080	7140	264
	Fed	Japanese IA	622	1270	1600	2240	2490	3020	3930	8170	264
		Global+Chinese IA	445	1180	1610	2090	2380	2920	4020	8580	264
	IV	Japanese IA	727	1410	1770	2410	2610	3100	4150	9380	264
		Global+Chinese IA	588	1260	1680	2160	2440	2920	3940	8410	264
C_{min} (ng/mL)	Fasted	Japanese IA	116	710	1040	1500	1910	2350	3550	9660	264
		Global+Chinese IA	133	599	892	1350	1570	1960	2810	6870	264
	Fed	Japanese IA	295	921	1270	1840	2120	2680	3510	7550	264
		Global+Chinese IA	285	934	1300	1820	2060	2620	3580	8150	264
	IV	Japanese IA	413	918	1240	1810	2050	2610	3470	7220	264
		Global+Chinese IA	351	849	1250	1730	1980	2450	3460	7820	264

The CHMP noted that Chinese race was found to have a significant effect on POS CL (increase of Cavg by 33%). However, the effect does not appear to be clinically meaningful.

- **Weight**

Results from the PPK analysis indicated that weight have a significant effect on POS PK parameters, as BW allometric scaling was considered using estimated allometric exponents.

Following a simulation exercise, after administration of tablet under fast conditions, POS exposure parameters taking account for weight level stratification is presented in Figure 6 and summary

statistics in Table 12. The model prediction results show that subjects with a lower body weight have higher exposures. Subjects with a body weight higher than 80kg generally have overlapping distributions of Cmin and Cavg whereas below 80kg, the distributions of Cmin and Cavg are shifted higher with decreasing bodyweight, particularly for subjects with bodyweight <50kg.

Table 12: Summary statistics of predicted Day 42 Cavg and Cmin for all subjects according to Weight bands following administration of tablet in fast state

Parameter	Population	Min	P10	Q1	Median	Mean	Q3	P90	Max	N
C_{avg} (ng/mL)	< 50 kg	714	1230	1770	2140	2380	2700	3880	6350	54
	≥ 50 - < 60 kg	598	1010	1310	1830	2020	2440	3380	5170	156
	≥ 60 - < 70 kg	341	922	1340	1750	1990	2360	3220	8640	206
	≥ 70 - < 80 kg	451	809	1090	1540	1650	1990	2670	5680	197
	≥ 80 - < 90 kg	181	793	1080	1420	1550	1890	2430	3800	145
	≥ 90 - < 100 kg	489	768	988	1370	1440	1850	2220	2990	58
	≥ 100 - < 110 kg	472	1010	1210	1330	1580	2000	2280	4100	33
	≥ 110 - < 120 kg	543	711	1090	1210	1250	1450	1520	2560	14
	≥ 120 kg	958	971	1050	1400	1330	1480	1680	1850	12
C_{min} (ng/mL)	< 50 kg	444	907	1400	1770	2000	2370	3430	5740	54
	≥ 50 - < 60 kg	399	730	990	1490	1710	2130	3010	4890	156
	≥ 60 - < 70 kg	150	675	1070	1480	1710	2030	2830	8100	206
	≥ 70 - < 80 kg	252	587	859	1290	1410	1750	2360	5280	197
	≥ 80 - < 90 kg	127	627	880	1220	1340	1660	2180	3540	145
	≥ 90 - < 100 kg	340	567	776	1200	1250	1610	1980	2780	58
	≥ 100 - < 110 kg	354	843	1050	1170	1390	1770	2020	3360	33
	≥ 110 - < 120 kg	414	541	906	1060	1090	1280	1350	2350	14
	≥ 120 kg	761	856	883	1270	1180	1330	1520	1710	12

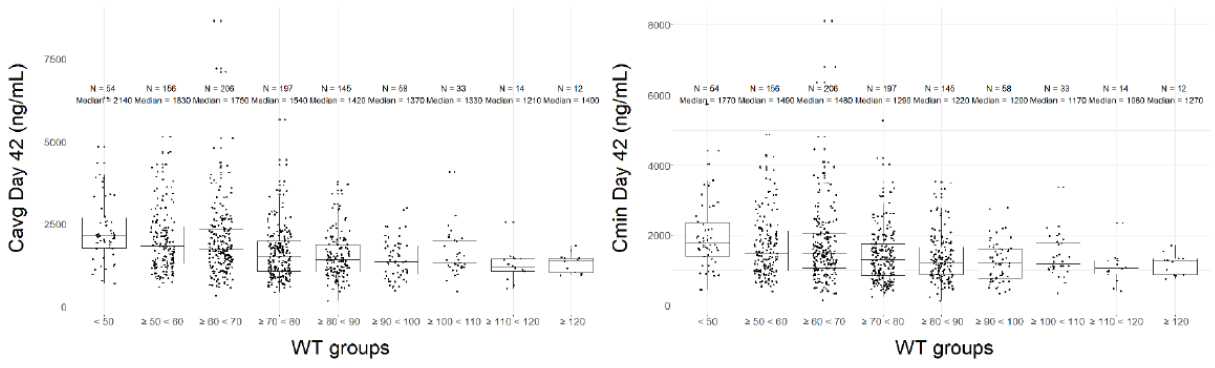


Figure 6: Boxplot of predicted Day 42 Cavg and Cmin for all subjects according to Weight bands following administration of tablet in fast state

In fed state similar trends were observed and are presented in Table 13 below.

Table 13: Summary statistics of predicted Day 42 Cavg and Cmin for all subjects according to Weight bands following administration of tablet in fed state

Parameter	Population	Min	P10	Q1	Median	Mean	Q3	P90	Max	N
C_{avg} (ng/mL)	< 50 kg	1110	1600	2150	2520	2860	3360	4460	6350	54
	≥ 50 - < 60 kg	899	1380	1580	2190	2410	2870	3980	6180	156
	≥ 60 - < 70 kg	341	1200	1620	2130	2330	2680	3560	8640	206
	≥ 70 - < 80 kg	680	1040	1370	1790	1950	2310	3140	5680	197
	≥ 80 - < 90 kg	181	1070	1310	1680	1830	2250	2860	4220	145
	≥ 90 - < 100 kg	661	935	1190	1630	1680	2070	2590	3500	58
	≥ 100 - < 110 kg	565	1220	1420	1590	1830	2210	2450	4600	33
	≥ 110 - < 120 kg	543	759	1290	1450	1490	1680	2130	2810	14
	≥ 120 kg	1100	1160	1240	1540	1540	1770	1880	2220	12
C_{min} (ng/mL)	< 50 kg	630	1180	1740	2090	2400	2830	3960	5740	54
	≥ 50 - < 60 kg	652	991	1230	1800	2030	2510	3570	5840	156
	≥ 60 - < 70 kg	150	884	1310	1770	1990	2330	3200	8100	206
	≥ 70 - < 80 kg	380	741	1090	1540	1680	2010	2850	5280	197
	≥ 80 - < 90 kg	127	819	1080	1430	1580	1960	2620	3990	145
	≥ 90 - < 100 kg	451	734	966	1440	1450	1820	2290	3280	58
	≥ 100 - < 110 kg	423	1110	1220	1400	1600	2070	2230	3770	33
	≥ 110 - < 120 kg	414	582	1060	1280	1300	1460	1940	2580	14
	≥ 120 kg	876	1020	1050	1370	1370	1590	1700	2050	12

For the IV formulation, overall similar results as those obtained for tablet and fed states are observed. Table 14 presents the simulation results for weight bands.

Table 14: Summary statistics of predicted Day 42 Cavg and Cmin for all subjects according to Weight bands following administration of the IV formulation

Parameter	Population	Min	P10	Q1	Median	Mean	Q3	P90	Max	N
C_{avg} (ng/mL)	< 50 kg	1160	1660	2240	2590	2940	3440	4610	6460	54
	≥ 50 - < 60 kg	918	1420	1620	2240	2470	2930	4060	6320	156
	≥ 60 - < 70 kg	353	1230	1660	2180	2380	2730	3630	8780	206
	≥ 70 - < 80 kg	704	1070	1410	1890	2000	2370	3190	5780	197
	≥ 80 - < 90 kg	487	1110	1360	1720	1870	2280	2910	4280	145
	≥ 90 - < 100 kg	678	962	1210	1670	1720	2130	2630	3570	58
	≥ 100 - < 110 kg	577	1250	1460	1620	1860	2260	2490	4660	33
	≥ 110 - < 120 kg	559	776	1310	1490	1520	1700	2250	2840	14
	≥ 120 kg	1120	1180	1260	1560	1570	1800	1910	2260	12
C_{min} (ng/mL)	< 50 kg	513	1100	1630	2020	2260	2690	3970	5550	54
	≥ 50 - < 60 kg	563	895	1120	1690	1930	2390	3440	5800	156
	≥ 60 - < 70 kg	94.8	804	1210	1700	1910	2240	3100	7970	206
	≥ 70 - < 80 kg	322	667	1040	1480	1610	1960	2770	5180	197
	≥ 80 - < 90 kg	194	767	1030	1360	1520	1920	2550	3980	145
	≥ 90 - < 100 kg	409	671	909	1400	1410	1770	2240	3260	58
	≥ 100 - < 110 kg	386	1080	1180	1360	1560	2050	2200	3790	33
	≥ 110 - < 120 kg	385	540	1020	1260	1270	1400	1980	2520	14
	≥ 120 kg	856	993	1020	1340	1340	1570	1660	2030	12

The CHMP noted that subjects with low body weight < 50 kg or high bodyweight ≥ 120 kg have increased POS Cavg by 19% and decreased POS Cavg by 25% respectively, when all PK parameters from the PPK model are held constant.

Median Cavg or Cmin following administration of tablet under fed/fast state or the IV formulation, remain in all the situations above 500 ng/mL.

The Committee considered that for tablet/fed vs IV, Cavg appears similar.

- **Elderly**

Results from the PopPK analysis indicated that age was a significant covariate on CL.

Following a simulation exercise, after administration of tablet under fast conditions taking account for age level stratification, POS exposure parameters is presented in Figure 7 and summary statistics in

Table 15. The model prediction results show that subject with an age ≥ 75 years generally have a slight increase in Cavg and Cmin, this is particularly driven by subjects older than 80 years old.

Table 15: Summary statistics of predicted Day 42 Cavg and Cmin for all subjects according to Age bands following administration of tablet in fast state

Parameter	Population	Min	P10	Q1	Median	Mean	Q3	P90	Max	N
C_{avg} (ng/mL)	< 20 years	667	894	1160	1410	1600	2050	2150	3630	15
	≥ 20 - < 30 years	608	789	1060	1490	1580	1900	2460	3910	91
	≥ 30 - < 40 years	540	784	1090	1570	1740	2070	2540	8640	121
	≥ 40 - < 50 years	598	940	1170	1540	1810	2220	3130	6350	147
	≥ 50 - < 60 years	181	883	1180	1600	1800	2250	2930	7120	209
	≥ 60 - < 70 years	341	927	1270	1680	1850	2200	2820	5170	208
	≥ 70 - < 80 years	655	930	1280	1740	1880	2220	3310	4850	74
	≥ 80 years	1930	2030	2090	2640	2750	3060	3780	4390	10
C_{min} (ng/mL)	< 20 years	583	732	907	1060	1330	1690	1850	3230	15
	≥ 20 - < 30 years	339	565	848	1230	1310	1570	2040	3510	91
	≥ 30 - < 40 years	351	583	879	1300	1470	1770	2280	8100	121
	≥ 40 - < 50 years	399	688	913	1290	1550	1930	2810	5740	147
	≥ 50 - < 60 years	127	648	971	1330	1540	1950	2620	6370	209
	≥ 60 - < 70 years	150	726	1050	1440	1600	1930	2540	4890	208
	≥ 70 - < 80 years	484	702	1060	1470	1630	1930	3020	4430	74
	≥ 80 years	1700	1760	1840	2210	2470	2760	3570	4100	10

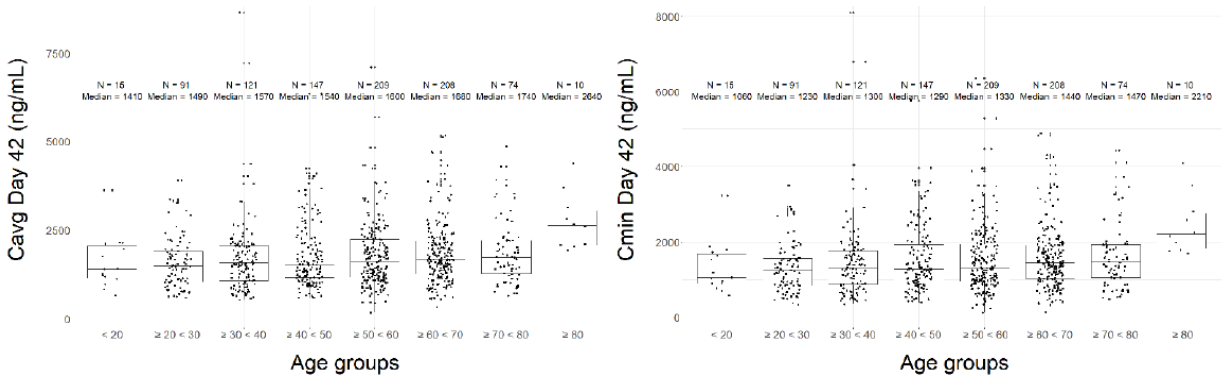


Figure 7: Predicted Day 42 Cavg and Cmin for all subjects according to Age bands following administration of tablet in fast state

In fed state, similar trends were observed and are presented in

Table 16 below.

Table 16: Summary statistics of predicted Day 42 Cavg and Cmin for all subjects according to Age bands following administration of tablet in fed state

Parameter	Population	Min	P10	Q1	Median	Mean	Q3	P90	Max	N
C_{avg} (ng/mL)	< 20 years	1000	1240	1410	1680	1910	2390	2460	4110	15
	≥ 20 - < 30 years	726	970	1330	1800	1900	2270	2690	4670	91
	≥ 30 - < 40 years	656	1000	1400	1870	2040	2320	2920	8640	121
	≥ 40 - < 50 years	746	1150	1410	1830	2130	2590	3620	6350	147
	≥ 50 - < 60 years	181	1140	1410	1930	2120	2570	3350	7120	209
	≥ 60 - < 70 years	341	1180	1570	2030	2190	2540	3190	6180	208
	≥ 70 - < 80 years	878	1190	1610	2100	2230	2630	3800	5680	74
	≥ 80 years	2280	2360	2510	3040	3180	3460	4300	4970	10
C_{min} (ng/mL)	< 20 years	842	996	1150	1270	1590	2000	2080	3660	15
	≥ 20 - < 30 years	405	679	1050	1520	1580	1940	2320	4190	91
	≥ 30 - < 40 years	419	754	1070	1540	1720	1980	2550	8100	121
	≥ 40 - < 50 years	520	877	1100	1550	1810	2270	3320	5740	147
	≥ 50 - < 60 years	127	856	1190	1630	1810	2250	2960	6370	209
	≥ 60 - < 70 years	150	941	1300	1740	1900	2250	2900	5840	208
	≥ 70 - < 80 years	648	839	1340	1760	1930	2240	3450	5180	74
	≥ 80 years	2000	2130	2220	2540	2850	3120	4060	4640	10

For the IV formulation, overall similar results as those obtained for tablet and fed states are observed. Table 17 presents the simulation results for age band.

Table 17: Summary statistics of predicted Day 42 Cavg and Cmin for all subjects according to Age bands following administration of the IV formulation

Parameter	Population	Min	P10	Q1	Median	Mean	Q3	P90	Max	N
C_{avg} (ng/mL)	< 20 years	1020	1270	1500	1720	1960	2430	2500	4170	15
	≥ 20 - < 30 years	742	991	1360	1880	1950	2320	2840	4770	91
	≥ 30 - < 40 years	671	1060	1450	1900	2090	2370	2990	8780	121
	≥ 40 - < 50 years	762	1180	1450	1870	2180	2630	3680	6460	147
	≥ 50 - < 60 years	487	1160	1450	1980	2170	2640	3420	7220	209
	≥ 60 - < 70 years	353	1230	1620	2110	2250	2600	3250	6320	208
	≥ 70 - < 80 years	896	1210	1650	2140	2270	2690	3850	5790	74
	≥ 80 years	2320	2390	2570	3090	3230	3510	4360	5040	10
C_{min} (ng/mL)	< 20 years	804	896	1060	1220	1500	1850	1950	3510	15
	≥ 20 - < 30 years	320	626	1010	1450	1500	1800	2210	4060	91
	≥ 30 - < 40 years	348	682	1040	1460	1630	1900	2390	7970	121
	≥ 40 - < 50 years	440	791	1020	1470	1740	2180	3240	5550	147
	≥ 50 - < 60 years	194	814	1090	1540	1740	2200	2920	6300	209
	≥ 60 - < 70 years	94.8	890	1240	1680	1830	2190	2810	5800	208
	≥ 70 - < 80 years	577	771	1200	1680	1850	2120	3350	5030	74
	≥ 80 years	1930	2030	2130	2390	2760	3020	4040	4560	10

The CHMP considered that age was found to have a significant effect on POS CL. Median Cavg approximately increased by 13.8% from 1880 ng/mL (20-<30 years) to 2140 ng/mL (70-< 80 years).

Elderly subjects (≥ 80 years) have an increased POS Cavg by 11% compared to a typical subject of 50 years, when all PK parameters from the PPK model are held constant.

However, based on the simulation exercise when administered POS tablet under fast /fed conditions or following the IV formulation, it is predicted that more than 50% (tablet fast, median Cavg of 2640 ng/mL) and 75% of the subjects (tablet fed and IV with Q1 of 2510 and 2570 ng/mL) have a Cavg above 2500 ng/mL, a threshold which have been used previously for PK bridging studies (from OS to IV and tablet). In the SmPC, it is recommended to closely monitor the older patients (> 80 years old) for adverse events, which was agreed by the Committee.

- **Children**

Only five adolescents aged 14-17 years were enrolled in study P069 and treated with either formulation (three of whom in the POS arm).

The CHMP noted that just five adolescent patients were included in Study P069. The MAH statement "A limited number (N=3) of adolescents received POS in P069 and there is insufficient data to support any conclusion regarding POS plasma concentration in this age group" was agreed to by the Committee.

With this procedure, the IA indication is claimed for adults only, which is supported by the Committee.

- **Disease status**

The effect of disease status was more formally assessed in the population PK analysis and was identified as having a significant effect on clearance. The effect was estimated to result in an 11% reduction in clearance (corresponding to a 12% increase in Cavg) in the subpopulation treated for IA and a 44% reduction in clearance (corresponding to a 79% increase in Cavg) in the subpopulation being treated for fungal diseases other than IA compared to healthy subjects.

The effect of disease status is illustrated by the distribution of model-predicted steady-state Cavg and Cmin for administration of POS IV solution and tablet (fed and fasted) at the recommended dose of 300 mg QD (BID on Day 1) across all subjects included in the population PK analysis. The results show that the distributions of Cavg in the prophylaxis and IA treatment groups were comparable and largely overlapping, although there was more variability in the IA treatment group. Both groups had higher exposure compared to the healthy group although again the distributions were largely overlapping consistent with the small difference in clearance between these groups identified by the model.

Table 18: Summary statistic of model predicted Cavg and Cmin grouped by disease status

	Regimen	Population	Min	P10	Q1	Median	Mean	Q3	P90	Max	N
Cavg	Oral-Fasted	Prophylaxis	181	874	1170	1550	1710	2070	2690	8640	602
		Treatment-IA	341	879	1180	1780	1980	2470	3540	7230	273
		Healthy Volunteers	423	737	970	1300	1380	1670	2090	3590	150
		Treatment-Other Disease	1080	2100	2670	3550	3980	4960	6580	10700	67
Cavg	Oral-Fed	Prophylaxis	181	1080	1410	1850	2000	2370	3080	8640	602
		Treatment-IA	341	1190	1570	2170	2380	2920	4100	8460	273
		Healthy Volunteers	803	1090	1330	1640	1740	2030	2540	3590	150
		Treatment-Other Disease	1080	2360	3180	3860	4350	5190	6720	10700	67
Cavg	IV	Prophylaxis	487	1100	1450	1890	2050	2410	3150	8780	602
		Treatment-IA	353	1230	1620	2240	2440	2990	4160	8610	273
		Healthy Volunteers	834	1130	1390	1730	1820	2090	2680	3670	150
		Treatment-Other Disease	1120	2430	3240	3930	4430	5300	6820	10900	67
Cmin	Oral-Fasted	Prophylaxis	127	667	940	1330	1460	1760	2400	8100	602
		Treatment-IA	150	663	956	1490	1710	2180	3230	6800	273
		Healthy Volunteers	315	566	752	1020	1110	1340	1740	3410	150
		Treatment-Other Disease	963	1880	2260	3170	3570	4390	5960	9870	67
Cmin	Oral-Fed	Prophylaxis	127	818	1150	1570	1710	2030	2740	8100	602
		Treatment-IA	150	918	1220	1860	2060	2590	3710	7950	273
		Healthy Volunteers	550	841	1020	1290	1400	1640	2140	3410	150
		Treatment-Other Disease	963	2050	2670	3380	3890	4690	6190	9870	67
Cmin	IV	Prophylaxis	194	745	1070	1500	1630	1980	2660	7970	602
		Treatment-IA	94.8	874	1140	1780	1980	2500	3620	7900	273
		Healthy Volunteers	443	743	882	1160	1270	1480	1990	3370	150
		Treatment-Other Disease	901	1920	2520	3210	3740	4550	6130	9630	67

Abbreviations: Cavg = Average plasma concentration over the dosing interval at steady state; Cmin = minimum concentration; IV = Solution for injection/Concentrate for solution for infusion

The CHMP noted that, in general, median Cavg is similar between the IA and the prophylactic treatment groups, and both have Cavg greater than HV.

2.3.3. Pharmacodynamics

Microbiological data

In vitro microbiology activity against isolates from study P069

A total of 127 fungal isolates from study P069 were sent to the reference lab. Among them, 119 were identified as *Aspergillus* spp. (*A. fumigatus* [n=76], *A. flavus* species complex [n=19], *A.* section *Nigri* [n=10], *A.* section *Terrei* [n=7]; and 7 isolates were *Aspergillus* spp not further identified). There were also 5 other mold organisms and 3 *Candida spp*. *In vitro* susceptibility testing was performed by both CLSI microbroth dilution and EUCAST microbroth dilution methodology.

Overall, POS (MIC50/90, 0.5/1 mg/L, range 0.12-8 mg/L) displayed similar activity to VOR (MIC50/90, 0.5/1 mg/L, range 0.12-4 mg/L) against these 119 *Aspergillus* spp. isolates. POS and VOR inhibited 99.2% and 95.8% of *Aspergillus* spp. isolates, respectively:

- *A. fumigatus*: POS (MIC50/90, 0.5/0.5 mg/L, range 0.12-1 mg/L) and VOR (MIC50/90, 0.25/0.5 mg/L, range 0.12-1 mg/L) inhibited all 76 isolates at MIC of 1 mg/L. By EUCAST methodology and susceptibility interpretation criteria, POS 93.4% of the isolates (MIC50/90, 0.12/0.12 mg/L, range 0.03-0.25 mg/L) and VOR inhibited 94.7% of isolates (MIC50/90, 0.5/1 mg/L, range 0.12-2 mg/L).

- *A. flavus*: among 19 isolates recovered from this study, POS (MIC50/90, 0.5/1 mg/L, range 0.25-1 mg/L) and VOR (MIC50/90, 1/1 mg/L, range 0.5-1 mg/L) displayed equivalent activity. Three of 19 isolates (15.8%) were characterized as non-wildtype to POS (MICs, 1 mg/L).

- *A.* section *Nigri*: similar activity for POS (MIC50/90, 1/1 mg/L, range 0.5-1 mg/L) and VOR (MIC50/90, 1/1 mg/L, range 0.5-1 mg/L) was observed against 10 isolates. Seven isolates were recovered in this study. All displayed WT phenotypes against the antifungal agents tested.

- *A.* section *Terrei*: POS (MIC50, 0.5 mg/L) and VOR (MIC50, 0.5 mg/L) inhibited all isolates at MIC of 0.5 mg/L.

- POS (MIC range, 0.5-1 mg/L) showed similar activity to VOR (MIC range, 0.5-2 mg/L) against other *Aspergillus* spp., including *A. lentulus* (n=4), *A. nidulans* species complex (1) and *A. sydowii* (1). POS and VOR displayed high MIC values (VOR MIC, 4 mg/L; POS MIC, >8 mg/L) against 1 *A. ustus* spp. complex isolate.

Five rarely recovered molds were observed in P069 and included the following organisms: *Fusarium incarnatum-equiseti* species complex (n=1), *Mucor circinelloides* (1), *Rhizomucor pusillus* (1), *Rhizopus oryzae* (1), *Lasiodiplodia* spp. (1). POS showed activity against 1 *Fusarium incarnatum-equiseti species* complex (MIC, 2 mg/L), and the 3 *Mucorales* isolates (MIC range, 0.5-2 mg/L). Limited activity was observed by POS against 1 *Lasiodiplodia* spp. isolate.

Efficacy endpoints were not analyzed by the type of fungal species isolated or by the MIC as only 24% of subjects overall (140/575) had fungal culture results reported, and the most commonly reported species (*A. fumigatus*) was identified in only 12.3% (71/575) of subjects. Of those subjects infected with *A. fumigatus,* too few had susceptibility data to evaluate clinical response by MIC value.

The CHMP noted that, overall, the *in vitro* susceptibility of these fungal agents (mainly *A. fumigatus*) to the study drug is similar between POS and VOR groups. However, the clinical consequences of these *in vitro* susceptibilities were not assessed. Considering the proposed indication in first-line IA, similarly than VOR, these microbiological data are reassuring, but the Committee considered that a higher efficacy of POS on VOR-resistant strains is not expected.

In vitro microbiology activity against *Aspergillus* and rare mold isolates from surveillance studies

Two surveillance study of POS *in vitro* activities against filamentous fungi were performed:

- One from 2010 to 2018 with 2,554 isolates of filamentous fungi (2,100 *Aspergillus spp*. and 454 non-Aspergillus molds) with VOR, ITR, caspofungin, anidulafungin, micafungin, and amphotericin B as comparator agents (Pfaller MA, Castanheira M. *Activity of Posaconazole and Comparator Antifungal Agents Tested Against Filamentous Fungi*. JMI Laboratories, Feb 2020).
- One in 2018 with 397 isolates of filamentous fungi (325 *Aspergillus spp*. and 72 non-Aspergillus molds) using the same comparators plus ISA (Carvalhaes C. *Activity of Posaconazole and Comparator Antifungal Agents Tested Against Filamentous Fungi collected in 2018*. JMI Laboratories, Apr 2020).

In the first study, germs were isolated from patients at 75 medical centers in North America (52.2%, Europe (29.6%), the Asia-Pacific (12.5%) region, and Latin America (5.7%).

The most common *Aspergillus* species was *A. fumigatus* (1,483 isolates). For *A. fumigatus*, MIC90 of posaconazole, itraconazole and voriconazole were 0.5 mg/L, 1 mg/L and 0.5 mg/L, respectively.

The MIC90 for POS was ≤ 1 mg/L for *Aspergillus fumigatus*, *Aspergillus* section *Flavi*, *Aspergillus* section *Nidulantes*, *Aspergillus* section *Nigri, Aspergillus* section *Terrei* and *Aspergillus* section *Versicolor*. VOR and ITR had similar *in vitro* activity against these species.

All three azoles were less active in vitro (MIC90: >8 mg/L) vs *Aspergillu*s section *Usti*.

In Europe, the frequency of non-wild type (NWT) strains of *A. fumigatus* increased steadily from 2010 to 2018 for POS (0.2 to 4.5%).

In the second study, the distribution of isolates according to the geographical regions was similar to the isolate distribution in the 2010-2018 surveillance report. The most common *Aspergillus species* was *A. fumigatus* (220 isolates). POS, VOR, ISA, and ITR had similar in vitro activities against the 266 *Aspergillus* isolates (POS, ISA, ITR and VOR MIC90 0.5, 1, 2, and 1 mg/L, respectively).

In conclusion, about these two studies:

POS has comparable activity to VOR, ISA, and ITR against *Aspergillus* spp.

POS was more active *in vitro* than:

• VOR, ISA, or ITR against *Mucorales* group

• VOR or ITR against *Rhizopus oryzae*

• ITR or ISA against *Scedosporium apiospermum/Scedosporium boydii*

The CHMP considered that these surveillance data are consistent with the known *in vitro* activity of azole antifungals and the activity of POS against isolates from study P069.

NWT strains of *A. fumigatus* have increased in Europe during the period 2010-2018 study, steadily and similarly for ITR (0% to 7%), VOR (0% to 4.5%) and POS (1.5% to 4.5%). Of note, there was no consistent trend for an increased frequency of NWT strains in the other geographic areas (North America, Asia-Pacific and Latin America).

2.3.4. PK/PD modelling

Exploratory ER (efficacy and safety) analyses were performed for IA based on PK/PD data retrieve from Study P069. The relationship between key efficacy and safety endpoints and POS exposures in P069 was explored by allocating subjects into quartiles based on trough plasma concentration.

ER-efficacy

For all-case mortality through Day 42 vs quartile of Ctrough, no particular trend is observed as shown in Figure 8. Similarly, no trend was observed in clinical response for Week 6 FAS vs Ctrough as shown in Figure 9.

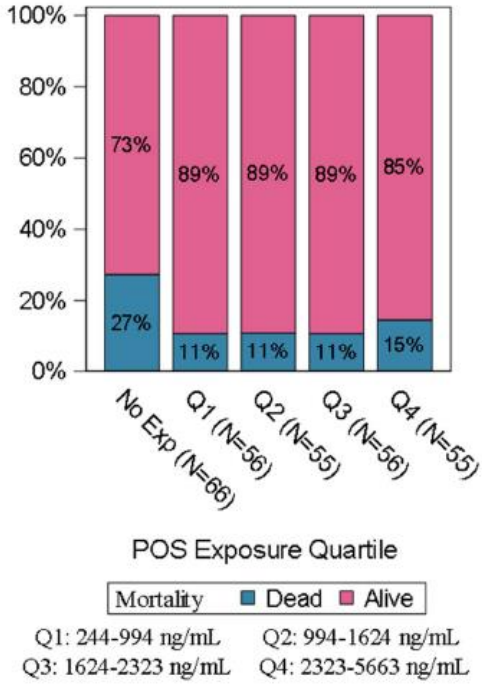


Figure 8: All-cause mortality through Day 42 vs Ctrough quartile following administration of POS IV and tablet

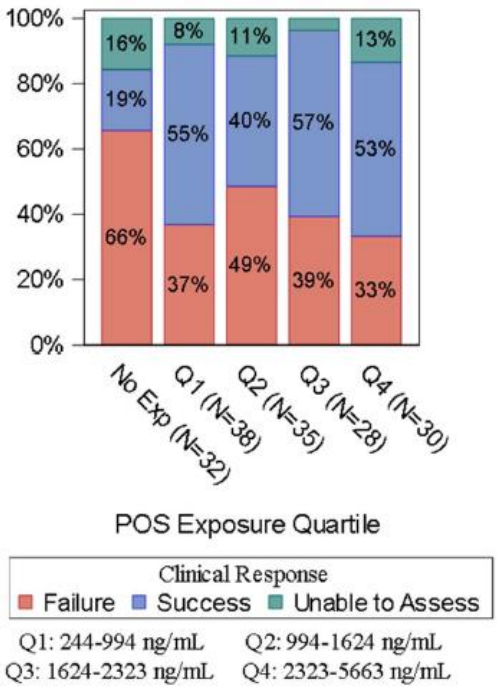


Figure 9: Global clinical response at week 6 vs Ctrough quartile following administration of POS IV and tablet

ER-safety

Exposure-safety relationships of POS by quartile of exposure were evaluated for drug-related AEs and for all AEs. No difference in incidence for all AEs was observed among the quartiles of exposure and no difference in incidence was observed for the majority of the most commonly reported AEs (those reported by ≥10% of subjects) or for SOCs. Among subjects with available trough plasma POS

concentrations, there was a trend toward a higher incidence of drug-related AEs in the highest quartile of POS exposure relative to lower exposure quartiles 1 or 2. Specifically, a higher incidence of drug related ALT increased, nausea, and vomiting were noted with higher POS exposures relative to lower trough plasma concentrations. While there is a trend of a higher incidence of drug related AEs in quartile 4 compared with quartile 1 or 2, it is modest and its non-monotonic increase with exposures is not suggestive of a strong PK relationship. Given the variability between specific AE incidence and exposure quartile noted in the P069 exposure-safety analysis and the absence of any exposure-safety relationship noted in prior studies of POS IV and tablet (with similar exposure), there is not considered to be a relationship between POS exposure and safety.

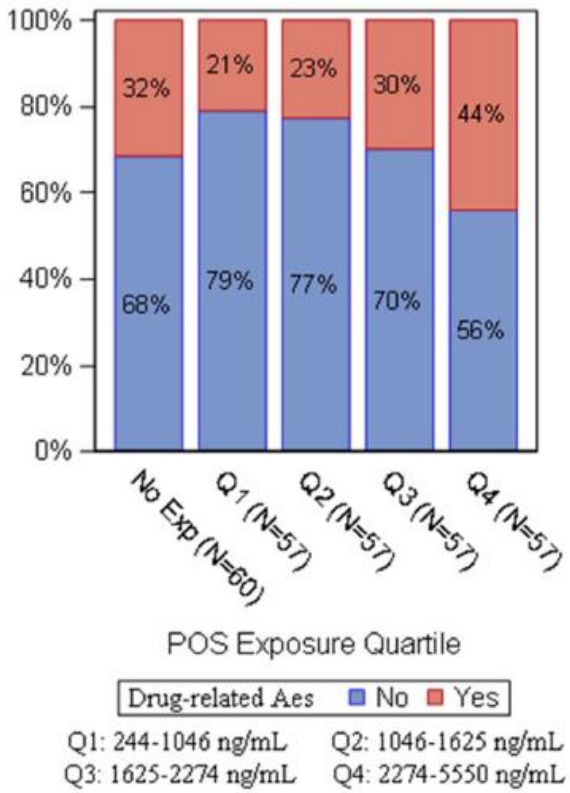


Figure 10: Drug related adverse events vs Ctrough quartile following administration of POS IV and tablet

The CHMP considered that, based on the exploratory ER efficacy analysis in IA patients, no trend between Ctrough and efficacy endpoint is obvious, whereas based on the ER safety as long as Ctrough is increased (above 2274 ng/mL, Q4 quartile), a trend of higher incidence of drug-related AE is proven.

2.3.5. Discussion on clinical pharmacology

In support of an extension of the indication of posaconazole (POS) as a first line treatment of adult and adolescent IA patients aged ≥ 13 years, a dedicated clinical study (P069) was performed where the currently approved IV and tablet formulations were tested following a dosing regimen of 300 mg BID (Day 1) and 300 mg QD thereafter already approved for prophylaxis and salvage treatment for IFI. A PPK model was developed to characterize the PK of POS IV and tablet across populations, this PPK model is considered only descriptive and supportive.

Only 5 adolescent patients were included in Study P069, 3 of which in the POS arm. Therefore, any agreement on the extension of indication for subjects ≥ 13 years appears unreasonable. The MAH statement "A limited number (N=3) of adolescents received POS in P069 and there is insufficient data to support any conclusion regarding POS plasma concentration in this age group" is fully supported. In the SmPC, the IA indication is claimed for adults only, which was supported by the CHMP.

One concern was raised with regards to the need for dose adjustment in the patient aged ≥ 80 years. The MAH explained that, based on the PopPK analysis, age was found to have an effect on POS CL with a predicted decreased by 10% (increased of Cavg by 11%) in elderly subjects compared to a typical subject (when all other covariates are kept constant). However, this result does not reflect what is observed presently, since other covariates may increase the observed Cavg in elderly (like BW, which is expected to be low). They also explained that such inflated Cavg cannot be solely linked to extreme body weight, which was agreed by the Committee. In addition, even if the PK dataset in elderly subject is limited, the MAH pointed out that the safety profile remains similar to that of younger subjects.

Therefore, the MAH proposal to indicate in the SmPC that patients who are ≥80 years of age are more likely to experience higher plasma concentrations of POS and should be closely monitored for adverse events was accepted by the CHMP.

As regards microbiological data, *in vitro* activity of POS on several strains of *Aspergillus* is overall similar to VOR. Higher efficacy of POS on VOR-resistant strains is not expected.

2.3.6. Conclusions on clinical pharmacology

Exposure to posaconazole in adult patients with IA, receiving the commercial formulations, IV solution for infusion or tablet under fed and fast states, at the recommended dosage regimen of 300 mg QD (BID on Day 1), has been shown to be similar to that of patient following a prophylactic treatment of IFI.

2.4. Clinical efficacy

The efficacy was evaluated in a single non-inferiority study P069. This study compared Posaconazole with Voriconazole which is the reference for IA treatment. Isavuconazole is also indicated in first line treatment for IA, supported by a non-inferiority study (study CL-0104). The design of P069 is similar.

- Study P069

Methods

This is a Phase 3, randomized, double-blind study of posaconazole (POS) versus voriconazole (VOR) in subjects ≥13 years of age with proven, probable, or possible invasive aspergillosis (IA). The study used IV form and tablet form of POS. The all-cause mortality rate through Day 42 was the main criteria to assess the non-inferiority with VOR.

Study participants

Subjects with proven or probable IA based 2008 EORTC/MSG definitions (see below). Subjects with possible IA may also be included.

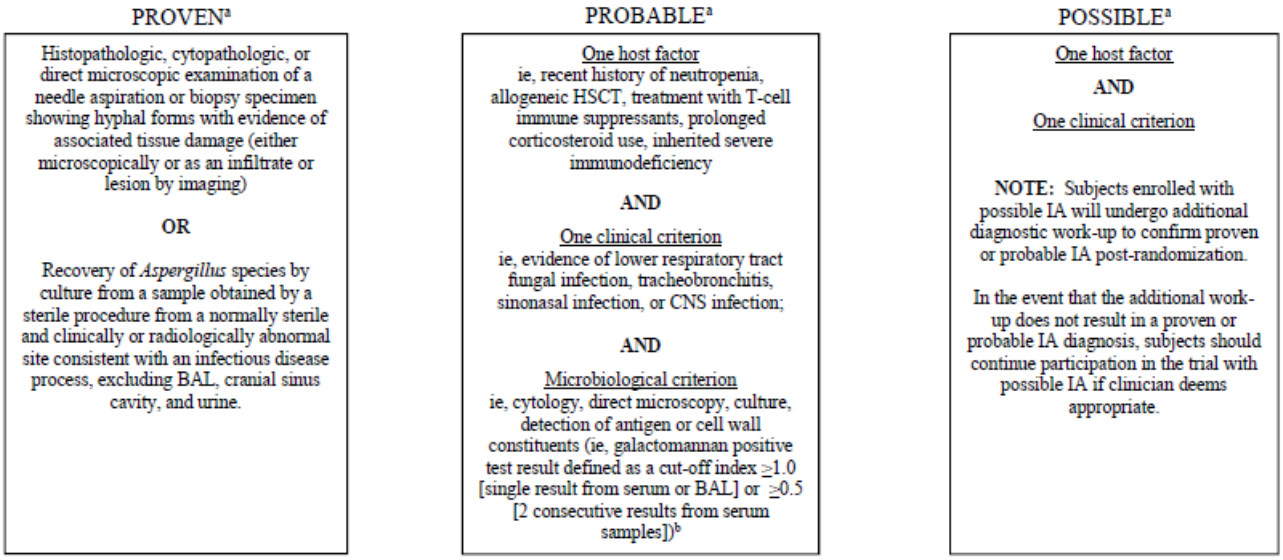
Inclusion criteria:

Patients were male or female from any ethnicity aged 13 years or older, weighing >40 kg to ≤150 kg, with proven, probable or possible IA based on the 2008 revised European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions. Individuals enrolled

with possible IA were to be further evaluated with mycological diagnosis for proven or probable IA within 7 days post-randomization. The IA was to have been acute (duration of clinical syndrome <30 days). Subjects were required to have a central line in place or planned for placement before beginning IV therapy. Pregnant women were not enrolled and women in age of giving birth had to use an adequate birth control.

Figure 9-2

Diagnostic Criteria for Proven, Probable, or Possible IA



[a] Full diagnostic criteria are provided in Appendix 3 of the protocol [16.1.1.6].
[b] Serum galactomannan criteria may not be used to classify patients as a probable infection if a patient is taking piperacillin/tazobactam within 72 hours of serum sampling.

Exclusion criteria:

The main exclusion criteria were:

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

- Sarcoidosis, aspergilloma, or allergic bronchopulmonary aspergillosis (ABPA).

- 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.

- Previous antifungal therapy ≥4 days for this infection episode.

- Current mold-active antifungal prophylaxis.

- Known hypersensitivity or other serious adverse reaction to any azole antifungal therapy.

- 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.

- QTc interval ≥ 500 msec on electrocardiogram performed at screening or baseline.

- Significant liver dysfunction, hepatic cirrhosis, severe hepatic impairment.

- Severe renal insufficiency (estimated creatinine clearance <20 mL/min) or on hemodialysis.

- Known hereditary problem of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

- Acute symptomatic pancreatitis (within 6 months of study entry), chronic pancreatitis.

- Artificial ventilation, subject not expected to survive for at least 1 week post-randomization

The CHMP noted that study subjects were adults and adolescents with possible, probable or proven acute invasive aspergillosis (according to standardized diagnostic criteria). Of note, possible IA will be confirmed with an additional diagnostic. In the event that possible IA was not confirmed, the patients may continue to be treated if clinician deems appropriate.

Importantly, subjects should not have history of chronic, recurrent or refractory IA, neither a current antifungal prophylaxis, consistent with the first line treatment of IA proposed within this application. Subjects may have started an antifungal therapy but no more than 3 days.

Exclusion criteria are in accordance to the known safety profiles and SmPC of posaconazole and voriconazole.

Treatments

Intravenous forms and oral forms were evaluated in this study for POS and VOR. Most subjects began antifungal azole (VOR or POS) therapy via the IV route; however, some began therapy via the solid oral route. Azole therapy was switched from IV route to the solid oral route when the subject is considered clinically stable and able to take oral medication.

Treatment duration was at least 84 days (12 weeks).

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]

The CHMP noted that the dosing regimen of posaconazole and voriconazole are in accordance with their SmPC. Of note, POS was administered as IV or tablet formulations. The oral suspension was not used. As the tablet and oral suspension are not equivalent due to differences between these two

formulations (in frequency of dosing, administration with food and plasma drug concentration achieved), this extension of indications application did not concern the oral suspension formulation.

Objectives

Primary:

To compare **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** (*all randomized subjects who received at least 1 dose of study drug*)

Secondary:

- To evaluate the all-cause mortality for POS vs. VOR through Day 42 in the **FAS population** (*all randomized subjects who were classified as having proven or probable IA (based upon independent adjudication assessment), and received at least 1 dose of study drug*).

- 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.

Outcomes/endpoints

Primary efficacy endpoint:

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

Secondary efficacy endpoints:

- All-cause mortality through Day 42 in the FAS population, and through Day 84 in the FAS and ITT populations

- Global clinical response for POS vs. VOR at Week 6 and 12 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

The CHMP noted that during study P069, the MAH switched the order of the endpoints, whereby the "all-cause mortality" endpoint would become the primary study endpoint, while the "global response rate" endpoint would become the secondary study endpoint, in order to be consistent with the design of isavuconazole study CL-104, which formed the basis of registration for isavuconazole for the treatment of IA in the EU.

The EMA (EMA/CHMP/SAWP/264373/2016) considered that the initially proposed endpoint "global response rate" would be preferred and therefore should be maintained and considered as a key coprimary endpoint. Therefore, the CHMP considered that, in accordance to the EMA scientific advice, both efficacy endpoints ('all-cause mortality through day 42 in the ITT population' and 'global clinical response at 6 week in the FAS population') had to be considered for the non-inferiority assessment of POS vs VOR.

Sample size

Approximately 400 evaluable subjects (approximately 600 randomized and treated) were planned to be enrolled in this study and randomly assigned to receive either POS monotherapy or VOR monotherapy. This sample size (200 evaluable FAS (*All randomized subjects who were classified as having proven or probable IA and who received at least one dose of treatment*) subjects in each azole monotherapy arm) was estimated to have >85% power (with 1-sided alpha=0.025) to show non-inferiority of POS monotherapy compared to VOR monotherapy using a 15% margin assuming a response rate at 6 weeks of 65% for VOR treated subjects. The response rate for this study was assumed to be slightly higher than previously reported for VOR due to both broader inclusion criteria, an anticipated higher percentage of subjects 'probable' IA to be enrolled in this study, and earlier treatment.

Table 19 Power (%) Under Various Assumptions of Response (200/arm, 15% Non-inferiority Margin)

Underlying Global Clinical Response Rate for VOR (%)	Underlying Difference of Global Clinical Response Rates (POS minus VOR)						
	-1.5	-1.0	-0.5	0.0	0.5	1.0	1.5
50	77.1	80.0	82.6	85.1	87.3	89.3	91.0
55	77.2	80.2	82.9	85.4	87.7	89.7	91.4
60	78.2	81.2	84.0	86.5	88.7	90.7	92.4
65	80.1	83.1	85.8	88.2	90.3	92.2	93.8
70	82.8	85.7	88.3	90.5	92.5	94.1	95.5
75	86.4	89.1	91.4	93.4	95.0	96.3	97.3
80	90.8	93.0	94.9	96.3	97.5	98.3	98.9

Note: The power is calculated based on 400 subjects (200/arm and assumes a non-inferiority margin (delta) of 15%

The CHMP noted that the sample size calculation was performed using the initial primary endpoint (global clinical response rate at 6 week). However, this primary endpoint was afterwards switched to the primary endpoint "all-cause mortality through day 42", but the sample size was not re-calculated, assuming that the upper bound of the 95% CI on the difference (POS-VOR) in the all-cause mortality rates will be compared to 10%, and the pre-specified non-inferiority margin observed response rate for POS could only be at most approximately 3 percentage points worse (more) than VOR and still meet the upper bound of 10% with the current sample size.

Both endpoints were to be treated as co-primary endpoints, but the sample size calculation was performed using the initial primary endpoint and was not recalculated when the primary endpoint was switched. In addition, the size of the study population (n=334) was lower than those initially required for a power >85% (n=400). Therefore, the MAH was asked to discuss the implications for the statistical analysis and the robustness of the results.

The MAH explained the reasons for switching the primary endpoint during study P069 (with Amendment 4) as driven by the change in the regulatory standards with a primary endpoint of all-cause mortality at D42 for the treatment of IA.

The MAH also explained why the sample size initially calculated had not been recalculated when the endpoint was switched. The amended study (with the all-cause mortality primary endpoint) for the same sample size (300 ITT population in each arm) has a 80% power to show non-inferiority with a 10% margin and a 6-week mortality rate for voriconazole of 23%.

The study results show that non-inferiority as pre-defined in the protocol was met in both cases.

The CHMP considered the response to indicate that after the endpoint switch the study retained a sufficient power and sample size to determine and meet pre-defined criteria for non-inferiority.

Randomisation

This study has randomization with 1:1 ratio.

Subjects were to be stratified prior to treatment assignment by risk status for mortality/poor outcome.

High Risk: Any one of the following are present at Baseline or in the patient's medical history:

• Allogeneic hematopoietic stem cell transplant (HSCT).

• Relapsed leukaemia, undergoing salvage chemotherapy.

• Liver transplant recipients.

Not High Risk: Any other eligible subject (none of the high risk criteria are present at Baseline or in the subject's medical history)

Blinding (masking)

This is a double blinded study. To maintain the blind in the POS group (whether IV or oral), a placebo is used for the second daily dose.

Statistical methods

Two populations were considered:

- ITT: all randomized subjects who received at least 1 dose of study drug

- FAS: all randomized subjects who were classified as having proven or probable IA (based upon independent adjudication assessment), and received at least 1 dose of study drug.

For the difference between treatment groups in the all-cause mortality rate (for the ITT and FAS populations), the associated stratified 95% confidence interval (CI) on the difference was calculated. If the upper limit of the CI was <10% (the pre-specified non-inferiority margin), then non-inferiority of POS was declared. Survival rates were assessed using Kaplan-Meier methodology.

For the difference between treatment groups in the proportion of subjects in the FAS population who achieved a global clinical response, the associated stratified 95% CI on the difference was calculated. Responses that were missing or could not be determined were considered as failures. The 6-week and 12-week global clinical response assessments will be performed by the clinical adjudication committee (CAC, composed of independent blinded clinicians) based on the following information: clinical data, radiographic findings of infection, serologic testing and fungal culture and histology. This CAC also defined the diagnosis of IA (proven, probable or possible).

The CHMP noted that the 10% non-inferiority margin is the same used in the isavuconazole vs VOR non-inferiority study CL-0104, and was endorsed by the FDA and EMA.

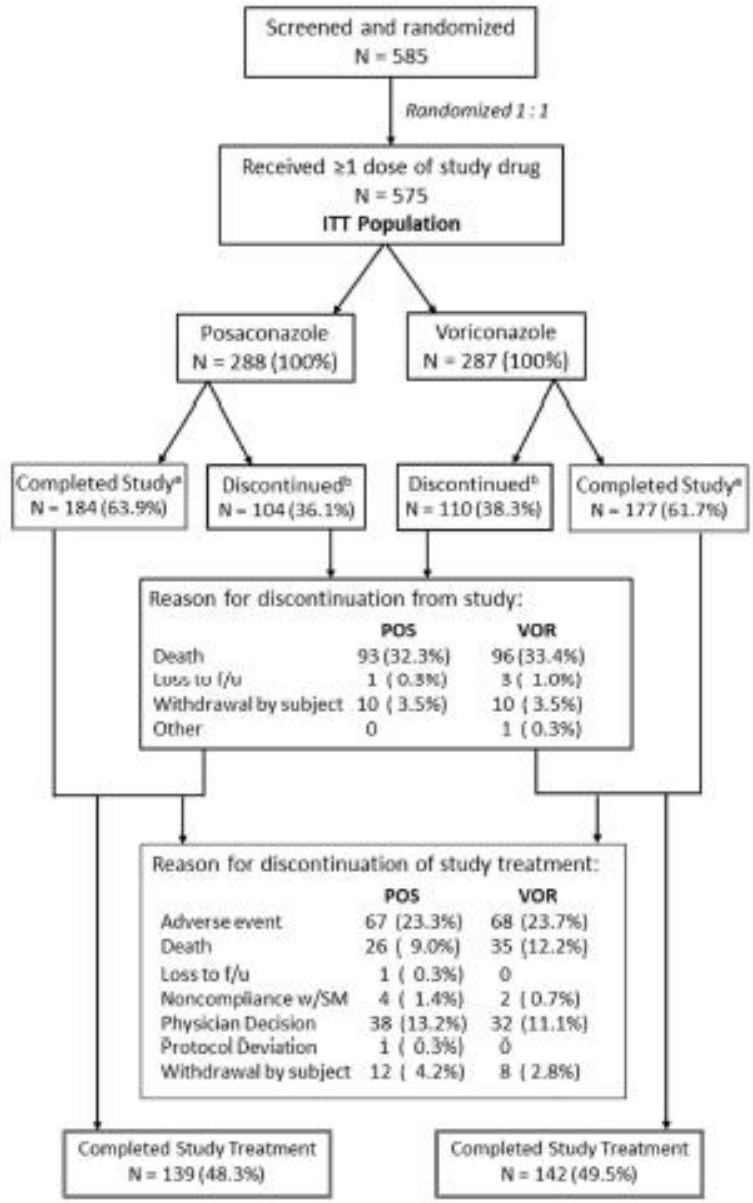
Results

Participant flow

A total of 653 individuals were screened, with 585 subjects randomized across 91 study sites in 26 countries in the Asia/Pacific region, Europe, and North and South America. A total of 575 subjects received 1 or more doses of POS (n=288) or VOR (n=287).

All subjects who were randomized and received at least 1 dose of study drug were to be followed for the entire duration of the study (through Day 114) for survival regardless of the duration of study therapy.

Figure 10-1
Disposition of Subjects: ITT Population



a: Subjects who discontinued study medication could remain in the study as long as consent was not withdrawn.
b: Refers to discontinuation from the study.

The proportions of subjects who completed the study (62.8% overall) and who completed study treatment (48.9% overall) were comparable in the POS and VOR treatment groups.

The most common reason for discontinuation from the study in each treatment group was death, and the most common reason for discontinuation of study treatment was AE.

The CHMP noted that the participant flow is similar between POS and VOR groups. In both groups, only half of participants have completed study treatment, mainly due to deaths and adverse events, reflecting the difficulties to treat IA.

Recruitment

The first patient first visit was 25 October 2013. The last patient last visit was 10 September 2019.

All included subjects were treated for 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.

Conduct of the study

There were 5 amendments of the protocol:

Amendment and Date	Primary Changes
Amendment 1 12-DEC-2012	Clarified the dosing of study treatments (POS or VOR): • Day 1 referred to the first day of subject taking either IV or oral formulation. Subjects were required to take only 1 formulation at a time. • Loading dose of POS oral on Day 1 was 300 mg BID (not 300 mg QD).
Amendment 1 04-APR-2013 Applicable only to Brazil	Removed Future Biomedical Research/Pharmacogenetic sample collection and any associated protocol language.
Amendment 2 26-JUN-2013	Excluded subjects <18 years of age in response to a preliminary, preclinical finding of brain ventricular enlargement in 5 of 8 pre-weaning juvenile dogs administered POS IV for 6 weeks, but not in pre-weaning juvenile dogs administered placebo or saline.
Amendment 2 24-JUL-2013 Applicable only to Brazil	Implemented the same changes as global Amendment 2, plus the following Brazil-specific change: Removed the optional pharmacogenetic sample blood volume from protocol Appendix 9. (The removal was originally intended for Brazil-specific Amendment 1.)
Amendment 3 08-JAN-2015	Based on updated preclinical data, the amendment allowed the enrollment of adolescents outside of the EU (ie, in those regions with an approved indication for use of oral POS in the adolescent age population (≥13 years of age).
Amendment 4 01-AUG-2016	The primary study endpoint of global clinical response at Week 6 (FAS population) was changed to a key secondary study endpoint. The key secondary study endpoint of all-cause mortality at Week 6 (ITT population) was changed to the primary study endpoint.
Amendment 5 07-FEB-2019	Clarified aspects of the protocol and statistical analyses, including key elements of the analyses for the study including: • Approximate sample size and power calculation with the addition of the following statement: This sample (approximately 300 randomized subjects in each azole arm) will have ~82.7% power (with 1-sided alpha=0.025) to show non-inferiority of POS compared to VOR using a 10% margin assuming an all-cause mortality through Day 42 of 23% for both treatment groups. • Time windows allowed for assessment of all-cause mortality and global clinical response with the following statement: Mortality will be evaluated through Day 42 and through Day 84 with no time window applied either before or after the target day. Global clinical response at Week 6 and Week 12 will be evaluated to include the completion of the response components within the visit windows, ±2 weeks for Week 6 and ±4 weeks for Week 12. • Elimination of the following secondary objectives for which data analyses were no longer planned. - To evaluate the time to global clinical response for POS vs. VOR in the FAS population. - To evaluate the global clinical response at Weeks 6 and 12 in subjects with a diagnosis of possible, probable, or proven IA receiving POS vs. VOR in the ITT population.

Important protocol deviations were reported for 62 subjects in this study. See details on the table below. No subject's data were excluded from analyses due to an important protocol deviation.

	Posaconazole		Voriconazole		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	288		287		575	
With one or more important protocol deviations	33	(11.5)	29	(10.1)	62	(10.8)
With no important protocol deviations	255	(88.5)	258	(89.9)	513	(89.2)
Inclusion/ Exclusion Criteria	**3**	**(1.0)**	**1**	**(0.3)**	**4**	**(0.7)**
Has torsades de pointes diagnosis or QTc prolongation (either based on Friderica or Bazett's correction) at screening >500 msec.	3	(1.0)	1	(0.3)	4	(0.7)
Informed Consent	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.2)**
Participants with no documented FBR consent, but FBR samples were drawn.	1	(0.3)	0	(0.0)	1	(0.2)
Prohibited Medications	**10**	**(3.5)**	**7**	**(2.4)**	**17**	**(3.0)**
Sirolimus	1	(0.3)	0	(0.0)	1	(0.2)
Vinca alkaloids (vincristine, vinblastine, or other licensed or investigational members of this class).	9	(3.1)	7	(2.4)	16	(2.8)
Safety Reporting	**18**	**(6.3)**	**14**	**(4.9)**	**32**	**(5.6)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	18	(6.3)	14	(4.9)	32	(5.6)
Study Intervention	**6**	**(2.1)**	**7**	**(2.4)**	**13**	**(2.3)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	1	(0.3)	1	(0.3)	2	(0.3)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	1	(0.3)	2	(0.7)	3	(0.5)
Subjects who received incorrect study treatment.	4	(1.4)	4	(1.4)	8	(1.4)
Trial Procedures	**0**	**(0.0)**	**3**	**(1.0)**	**3**	**(0.5)**
Subject therapy is unblinded and their inclusion in data analysis is not appropriate.	0	(0.0)	3	(1.0)	3	(0.5)

Every subject is counted a single time for each applicable row and column.
A subject may have more than one type of important deviation and will be counted in each applicable row.

Source: [P069MK5592: adam-adsl] [P069MK5592: sdtm-dv]

The CHMP noted that the main relevant protocol amendments were the exclusion of subjects <18 years of age in EU and the change of the primary endpoint. Major protocol deviations are balanced between POS and VOR group (11.5% vs 10.5%). All subjects were part of the analyzed database.

Numbers analysed

The population was classified in two categories for analysis of the different endpoints: ITT (all randomized subjects who received at least 1 dose of study drug) and FAS (all randomized subjects who were classified as having proven or probable IA and received at least 1 dose of study drug population) populations.

Population Reason for exclusion	Posaconazole n (%)	Voriconazole n (%)	Total n (%)
Randomized	293	292	585
Intention to Treat	288 (98.3)	287 (98.3)	575 (98.3)
Not in Intention to Treat - Randomized but not treated	5 (1.7)	5 (1.7)	10 (1.7)
All Subjects as Treated	288 (98.3)	287 (98.3)	575 (98.3)
Not in All Subjects as Treated - Randomized but not treated	5 (1.7)	5 (1.7)	10 (1.7)
Full Analysis Set	163 (55.6)	171 (58.6)	334 (57.1)
Not in Full Analysis Set	130 (44.4)	121 (41.4)	251 (42.9)
Randomized but not in Intention to Treat	5 (1.7)	5 (1.7)	10 (1.7)
Not classified as having proven or probable IA by adjudicator	125 (42.7)	116 (39.7)	241 (41.2)

Comparable proportions of subjects (between 55% and 60%) in the POS and VOR treatment groups were included in the FAS population.

The CHMP noted that the FAS population was 334 subjects. This is below the pre-defined target of 400 FAS subjects (sample size to have power >85%), due to the higher proportion of subjects (41%) for whom their infection was not considered as a proven or probable IA by the CAC.

The MAH explained that the sample size had a 80% power to show non-inferiority with a 10% margin and a 6-week mortality rate for voriconazole of 23%. The study results show that non-inferiority as pre-defined in the protocol has been met in both cases. The response indicates that after the endpoint switch the study retained a sufficient power and sample size to determine and meet pre-defined criteria for non-inferiority.

Baseline data

	Posaconazole		Voriconazole		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	288		287		575	
Gender						
Male	172	(59.7)	172	(59.9)	344	(59.8)
Female	116	(40.3)	115	(40.1)	231	(40.2)
Age (Years)						
<18	3	(1.0)	2	(0.7)	5	(0.9)
18 to 64	200	(69.4)	210	(73.2)	410	(71.3)
≥65	85	(29.5)	75	(26.1)	160	(27.8)
Mean	53.5		53.0		53.3	
SD	16.7		15.9		16.3	
Median	56.5		57.0		57.0	
Range	14 to 85		15 to 91		14 to 91	
Race						
American Indian Or Alaska Native	4	(1.4)	6	(2.1)	10	(1.7)
Asian	62	(21.5)	60	(20.9)	122	(21.2)
Black Or African American	3	(1.0)	4	(1.4)	7	(1.2)
Multiple	25	(8.7)	25	(8.7)	50	(8.7)
American Indian Or Alaska Native, Black Or African American	11	(3.8)	8	(2.8)	19	(3.3)
American Indian Or Alaska Native, Native Hawaiian Or Other Pacific Islander	1	(0.3)	3	(1.0)	4	(0.7)
American Indian Or Alaska Native, White	10	(3.5)	11	(3.8)	21	(3.7)
Black Or African American, White	1	(0.3)	2	(0.7)	3	(0.5)
White, Asian	2	(0.7)	1	(0.3)	3	(0.5)
White	194	(67.4)	192	(66.9)	386	(67.1)
Ethnicity						
Hispanic Or Latino	48	(16.7)	57	(19.9)	105	(18.3)
Not Hispanic Or Latino	220	(76.4)	219	(76.3)	439	(76.3)
Not Reported	16	(5.6)	9	(3.1)	25	(4.3)
Unknown	4	(1.4)	2	(0.7)	6	(1.0)
Weight (kg)						
<40	2	(0.7)	0	(0.0)	2	(0.3)
40 - <50	31	(10.8)	22	(7.7)	53	(9.2)
50 - <60	58	(20.1)	62	(21.6)	120	(20.9)
60 - <75	105	(36.5)	119	(41.5)	224	(39.0)
75 - <120	90	(31.3)	80	(27.9)	170	(29.6)
≥120	2	(0.7)	4	(1.4)	6	(1.0)
Subjects with data	288		287		575	
Mean	68.6		68.1		68.4	
SD	16.1		15.4		15.7	
Median	68.0		65.6		66.4	
Range	39.6 to 125.0		40.2 to 132.0		39.6 to 132.0	
Risk Status as classified by Investigator						
High Risk	113	(39.2)	113	(39.4)	226	(39.3)
No High Risk	175	(60.8)	174	(60.6)	349	(60.7)
Aspergillus Classification[†]						
Proven	26	(9.0)	15	(5.2)	41	(7.1)
Probable	137	(47.6)	156	(54.4)	293	(51.0)
Possible	81	(28.1)	79	(27.5)	160	(27.8)
Cannot be determined	44	(15.3)	37	(12.9)	81	(14.1)
Neutropenic Status (10^9/L)						
< 0.5	132	(45.8)	137	(47.7)	269	(46.8)
≥ 0.5	142	(49.3)	138	(48.1)	280	(48.7)
Unknown	14	(4.9)	12	(4.2)	26	(4.5)

[†] Aspergillus classification is per adjudicator's assessment.

The baseline disease characteristics were indicative of a critically ill study population, with 39.3% of subjects in the ITT population considered to be high risk for IA. In the ITT population, the POS and VOR treatment groups were comparably balanced for most baseline characteristics, including investigators' classification of risk status and laboratory determined presence of neutropenia

A majority of subjects were male (59.8%) and white (67.1%). Two subjects had a baseline weight <40 kg, while 6 had a baseline weight ≥120 kg. The median age was 57 years, with 27.8% of subjects overall aged ≥65 years; 5 subjects were adolescents, of whom 3 were treated with POS and 2 with VOR.

IA was classified by independent adjudicators blinded to study treatment assignment as proven or probable in 58.1% of subjects overall. More POS-treated subjects were classified as having proven IA (9.0%) compared with VOR-treated subjects (5.2%), while fewer POS treated subjects were classified as having probable IA compared with VOR-treated subjects (47.6% and 54.4%, respectively). Subjects with proven or probable IA constituted the FAS population (n=334).

Approximately 14% of subjects in the ITT population did not have an IA classification assigned; the primary reasons for this were insufficient information available to the adjudicators and/or co-morbidities that confounded the classification diagnosis.

The proportions of subjects with specific medical history conditions and with conditions in each SOC were generally comparable in the POS and VOR treatment groups.

Almost all subjects (99.0%) reported use of prior medications, including antimycotics for systemic use (82.3% overall). Prior antimycotics included the study treatments POS (5.6% overall) and VOR (44.0% overall), with reported use balanced across the treatment groups.

Nearly all subjects in each treatment group (ITT population) were compliant (ie, received >80% of assigned study therapy) with their treatment regimen (mean compliance >98% of assigned days of study treatment). Compliance was similarly high in the FAS population.

Mean duration of exposure to study treatment in the ITT population was comparable in the POS and VOR treatment groups (67 days for POS and 64 days for VOR). Approximately 40% of subjects in each treatment group received study treatment for the planned duration of 84 days.

Baseline data of identified germs consists in a total of 140 subjects who had a positive mold fungal culture identified by either the local or central laboratory. A majority (n=116) of these had a culture positive for Aspergillus only (≥1 species) with the remainder having a positive culture for non-Aspergillus mold species only (n=17) or for Aspergillus plus non-Aspergillus mold species (n=7). For those with Aspergillus only, the most commonly identified species were *A. fumigatus* (in 71 subjects), *A. flavus* (22 subjects), *A. niger* (14 subjects), and *A. terreus* (8 subjects). The proportions of subjects infected with organisms from each of these categories were comparable between the treatment groups.

Summary of Subjects with Culture by Fungal Type
Intention to Treat Population

Fungal Species	Posaconazole n (%)	Voriconazole n (%)	Total n (%)
Number of subjects in population	288	287	575
Number of subjects with reported fungal culture result	62 (21.5)	78 (27.2)	140 (24.3)
Subjects with Aspergillus Mold only	**52 (18.1)**	**64 (22.3)**	**116 (20.2)**
Aspergillus	9	13	22
Aspergillus Flavus	9	13	22
Aspergillus Fumigatus	36	35	71
Aspergillus Lentulus	1	2	3
Aspergillus Nidulans	0	1	1
Aspergillus Niger	5	9	14
Aspergillus Sydowii	0	1	1
Aspergillus Tamarii	1	0	1
Aspergillus Terreus	1	7	8
Aspergillus Tubingensis	3	2	5
Aspergillus Ustus	1	0	1
Aspergillus Versicolor	0	1	1
Subjects with Non-Aspergillus Mold only	**7 (2.4)**	**10 (3.5)**	**17 (3.0)**
Cladosporium	1	0	1
Cryptococcus	0	1	1
Fungi	1	1	2
Fusarium	1	1	2
Fusarium Incarnatum-Equiseti	1	0	1
Fusarium Solani	0	1	1
Geotrichum	1	0	1
Mold	0	1	1
Penicillium	2	2	4
Pneumocystis Jirovecii	1	0	1
Rhizomucor Pusillus	0	1	1
Rhizopus	0	1	1
Rhizopus Oryzae	0	1	1
Subjects with Aspergillus + Non-Aspergillus Mold	**3 (1.0)**	**4 (1.4)**	**7 (1.2)**
Absidia+Aspergillus Fumigatus	0	1	1
Aspergillus Flavus+Paecilomyces+Penicillium	0	1	1
Aspergillus Fumigatus+Mucor+Mucor Circinelloides	1	0	1
Aspergillus Fumigatus+Rhizomucor+Rhizomucor Pusillus	1	0	1
Aspergillus Niger+Aspergillus Terreus+Penicillium	0	1	1
Aspergillus Niger+Fungi+Unspeciated Epicoccum	0	1	1
Aspergillus Niger+Fungi+Unspeciated Lasiodiplodia	1	0	1

Subjects may have more than one kind of pathogen identified.
Percentages are based on the number of subjects in the population.

The CHMP considered that, overall, all baseline characteristics were well balanced between both groups. The subjects included in this study were White or Asian adults (only 1% of Black/African American subjects and <1% adolescents) with blood and lymphatic system disorders (82%), with a good representativeness of gender, risk status and neutropenic status. As the study protocol allowed a brief period of systemic antifungal therapy given for the current episode of IA (up to 96 hours) prior to initiation of study antifungal treatment, a large proportion of subjects (82%) had previously been treated with antimycotics treatments, mainly with fluconazole (45%) or voriconazole (44%).

Therefore, efficacy results according to the previous use or not of antifungal treatment should be provided (LOQ).

This study has initially intended to enroll adolescent subjects, but finally included 99% of adults. Therefore, this study could not support alone an adolescent extension of the indication in the treatment of IA. PK bridging between adolescents and adults in IA treatment is required.

Compliance and duration of treatment was also similar between both groups.

Only 58% of the baseline IA diagnosis was probable or proven, and a non-negligible proportion of IA diagnosis (14%) cannot be determined at baseline by the CAC, suggesting that an undetermined number of subjects did not actually have IA. *Aspergillus* is the fungal agent most represented, without imbalance between both groups. However, only 24% of subjects overall had fungal culture results reported. A subgroup efficacy analysis by fungal species was not considered relevant by the MAH, which is endorsed by the CHMP.

Outcomes and estimation

Primary efficacy endpoint

Based on all-cause mortality through Day 42 in the ITT population, POS was demonstrated to be non-inferior to VOR: 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. No subject in the ITT population had a Day 42 mortality assessment that was missing or 'unable to determine', thus all subjects were included in the primary endpoint analysis. The difference in mortality between the POS and VOR treatment groups did not meet the criterion for superiority, as the upper limit of the 95% CI was not <0.

Analysis of All-Cause Mortality Through Day 42
Intention to Treat Population

All Cause Mortality Assessment	Unadjusted Data Summary by Treatment Group		Treatment Difference (Posaconazole - Voriconazole)†		
	Posaconazole n/N (%)	Voriconazole n/N (%)	Estimated Difference (%)	95% CI	p-Value
Dead Alive	44/288 (15.3) 244/288 (84.7)	59/287 (20.6) 228/287 (79.4)	-5.3	(-11.6, 1.0)	<.0001

† Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme. The p-Value is based on the one-sided non-inferiority test. Non-inferiority of posaconazole vs. voriconazole is established if the upper limit of the 95% confidence interval is less than 10%. If non-inferiority is established, it can be further concluded that posaconazole is superior to voriconazole if the upper limit of the 95% confidence interval is less than zero.

Missing or 'unable to determine' responses are considered as failures (dead).

Secondary efficacy endpoints

All-cause mortality through Day 42, FAS Population

These results support the primary endpoint result. In the FAS population, the incidence of all-cause mortality through Day 42 was 19.0% for the POS group and 18.7% for the VOR group with an estimated difference of 0.3% [95% CI: -8.2%, 8.8%].

Analysis of All-Cause Mortality Through Day 42
Full Analysis Set Population

All Cause Mortality Assessment	Unadjusted Data Summary by Treatment Group		Treatment Difference (Posaconazole - Voriconazole)†	
	Posaconazole n/N (%)	Voriconazole n/N (%)	Estimated Difference (%)	95% CI
Dead	31/163 (19.0)	32/171 (18.7)	0.3	(-8.2, 8.8)
Alive	132/163 (81.0)	139/171 (81.3)		

† Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.
Missing or 'unable to determine' responses are considered as failures (dead).

All-cause mortality through Day 84, ITT and FAS Populations

In the ITT population, 3 subjects, all in the VOR treatment group, had unknown or missing mortality status at Day 84 and were therefore counted as dead at that time point as was specified in the protocol.

Analysis of All-Cause Mortality Through Day 84
Intention to Treat Population

All Cause Mortality Assessment	Unadjusted Data Summary by Treatment Group		Treatment Difference (Posaconazole - Voriconazole)†	
	Posaconazole n/N (%)	Voriconazole n/N (%)	Estimated Difference (%)	95% CI
Dead	81/288 (28.1)	88/287 (30.7)	-2.5	(-9.9, 4.9)
Alive	207/288 (71.9)	199/287 (69.3)		

† Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.
Missing or 'unable to determine' responses are considered as failures (dead).

Analysis of All-Cause Mortality Through Day 84
Full Analysis Set Population

All Cause Mortality Assessment	Unadjusted Data Summary by Treatment Group		Treatment Difference (Posaconazole - Voriconazole)†	
	Posaconazole n/N (%)	Voriconazole n/N (%)	Estimated Difference (%)	95% CI
Dead	56/163 (34.4)	53/171 (31.0)	3.1	(-6.9, 13.1)
Alive	107/163 (65.6)	118/171 (69.0)		

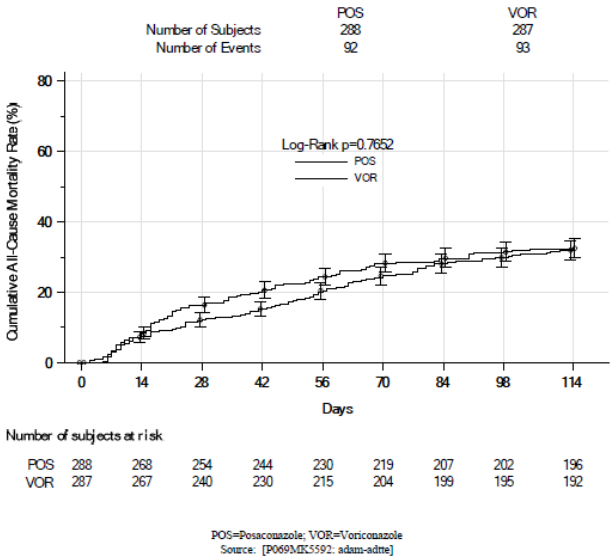
† Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.
Missing or 'unable to determine' responses are considered as failures (dead).

The CHMP considered that the three subjects with unknown status counted as dead in the ITT population do not change the results. The rates of all-cause mortality at day 84 between VOR and POS are comparable and consistent with the non-inferiority of POS vs VOR observed with the primary endpoint.

Time to death (all causes) in the FAS population

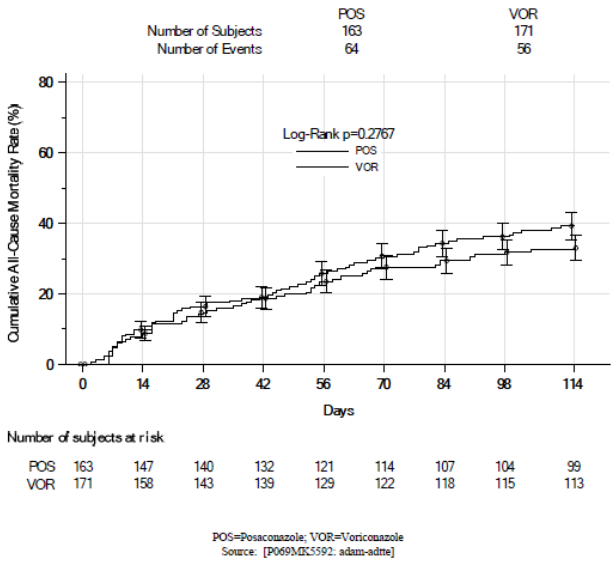
The cumulative all-cause mortality rates throughout the study period (i.e., through Day 114) in the ITT and FAS populations were comparable in the POS and VOR treatment groups.

Kaplan-Meier Plot for Cumulative All-Cause Mortality Rate Through Day 114
Intention to Treat Population



POS=Posaconazole; VOR=Voriconazole
Source: [P069MK5592: adam-adrte]

Kaplan-Meier Plot for Cumulative All-Cause Mortality Rate Through Day 114
Full Analysis Set Population



POS=Posaconazole; VOR=Voriconazole
Source: [P069MK5592: adam-adrte]

Mortality due to IA through Day 42 and Day 84 in the FAS population

The treatment-group comparison for attribution of death by the independent Clinical Adjudication Committee (CAC) to IA, to invasive fungal disease other than IA, or to another cause was limited by the high proportions of deaths adjudicated to an 'indeterminate' cause in the FAS population. This was particularly noteworthy for VOR-treated subjects, among whom 50% to 56% of deaths had an indeterminate attribution, compared with 36% to 41% of POS-treated subjects, depending on the time point.

Among deaths for which the CAC was able to assign an attribution, at Week 6 (Day 42), 16 of 20 (80.0 %) deaths in the POS group were attributed to IA compared with 10 of 14 (71.4%) deaths in the VOR group. At Week 12 (Day 84), 22 of 33 (66.7%) deaths in the POS group were attributed to IA compared with 14 of 22 (63.6%) in the VOR group.

Analysis of Adjudicator's Primary Attribution of Death
Full Analysis Set Population

	Posaconazole	Voriconazole	Difference in % Posaconazole vs Voriconazole
	n (%)†	n (%)†	Estimate (95% CI)††
Number of subjects in population	**163**	**171**	
Number of subjects who died through Day 42	**31**	**32**	
Death Attributed to Invasive Aspergillosis	16 (51.6)	10 (31.3)	20.4(-4.1, 42.7)
Death Attributed to Invasive Fungal Disease Other Than Invasive Aspergillosis	1 (3.2)	0 (0.0)	3.2(-7.8, 16.3)
Death Not Attributable to Invasive Aspergillosis or Other Invasive Fungal Disease	3 (9.7)	4 (12.5)	-2.8(-20.2, 14.6)
Indeterminate Attribution of Death‡	11 (35.5)	18 (56.3)	-20.8(-43.1, 4.0)
Number of subjects who died through Day 84	**56**	**50**	
Death Attributed to Invasive Aspergillosis	22 (39.3)	14 (28.0)	11.3(-6.9, 28.6)
Death Attributed to Invasive Fungal Disease Other Than Invasive Aspergillosis	1 (1.8)	0 (0.0)	1.8(-5.5, 9.5)
Death Not Attributable to Invasive Aspergillosis or Other Invasive Fungal Disease	10 (17.9)	8 (16.0)	1.9(-13.2, 16.4)
Indeterminate Attribution of Death‡	23 (41.1)	28 (56.0)	-14.9(-33.0, 4.2)
Number of subjects who died through Day 114	**64**	**56**	
Death Attributed to Invasive Aspergillosis	23 (35.9)	17 (30.4)	5.6(-11.4, 22.1)
Death Attributed to Invasive Fungal Disease Other Than Invasive Aspergillosis	1 (1.6)	0 (0.0)	1.6(-5.0, 8.4)
Death Not Attributable to Invasive Aspergillosis or Other Invasive Fungal Disease	14 (21.9)	11 (19.6)	2.2(-12.8, 16.8)
Indeterminate Attribution of Death‡	26 (40.6)	28 (50.0)	-9.4(-26.7, 8.5)

† Percentages are based on the number of subjects who died through Day 42/84/114 in the respective section.
†† Based on Miettinen and Nurminen's method.
‡ Death occurred but unable to determine attribution of invasive aspergillosis or other invasive fungal disease and death.
Mortality assessments are presented using Data as Observed.

Source: [P069MK5592: adam-adbase]

The CHMP noted that, when considering the mortality due to IA (according to the CAC), the results are not at the advantage of POS. At each time points (Day 42, Day 84 and Day 114), the mortality attributed to IA is more frequent in POS group compared to VOR group. However, a higher number of indeterminate attribution of death is present in VOR group, which could bias the estimation of the mortality due to IA. Indeed, it is expected that a significant proportion of these undetermined deaths were actually due to IA (probably combined with other pathologies or infections).

Without considering the indeterminate attributions of death, there is still a 10% difference of mortality between POS and VOR groups at day 42 (80% [16/20] vs 71% [10/14]), but the number of subject is too low to draw any conclusion. This difference was not retrieved at Day 84 (67% [22/33] vs 64% [14/22]) and Day 114 (61% [23/38] vs 61% [17/28]).

In conclusion, these results of deaths attributed to IA may be biased due to the imbalance of the number of indeterminate attribution of death by the CAC. Furthermore, these results are not consistent with the other efficacy endpoints, and they cannot alone challenge the non-inferiority of POS vs VOR. To be reassured, the CHMP requested that the MAH reassessed the mortality data of all subjects for whom no cause of death was attributed, and specify among them whether IA was suspected and the number of subjects with probable or proven IA in each groups.

The MAH explained that independent adjudication of each subject was performed by a central adjudication committee (CAC). A listing of the subjects in the FAS population who died through Day 114 and had indeterminate attribution of death as classified by central adjudication is shown below. There were 26 posaconazole treated subjects and 28 voriconazole treated subjects who were classified as having an indeterminate cause of death during the study period (through Day 114). This listing displays the primary cause of death as provided by the study investigators who oversaw the study at a given site. Of the 26 posaconazole treated subjects with indeterminate cause of death by the CAC, no subject was identified as having death related to invasive aspergillosis or an invasive fungal infection. In comparison, of the 28 voriconazole treated subjects with indeterminate cause of death by the CAC, 3 subjects were identified as having death related to aspergillus infection, systemic mycoses, or fungal pneumonia.

The CHMP considered that the MAH satisfactorily clarified that none of the 26 POS treated subjects and three of the 28 VOR subjects with an indeterminate cause of death, were identified as having death caused by IA of other invasive fungal disease. With this reassessment, the proportion of deaths attributable to IA and IFD becomes more balanced: 24/64 for POS and 20/56 for VOR, though overall the number of deaths remains unfavourable to the POS group.

Global Clinical Response at Weeks 6 and 12, FAS Population

Global response was assessed by the CAC as success (partial or complete) or failure (stable response, disease progression, or death). Approximately 10% of subjects in each treatment group, at both Week 6 and Week 12, were given an adjudicated response outcome of "unable to determine" and were counted as 'failures' for the purpose of treatment comparison.

Analysis of Global Clinical Response at Week 6
Full Analysis Set Population

Outcome	Unadjusted Data Summary by Treatment Group		Treatment Difference (Posaconazole - Voriconazole)†	
	Posaconazole n/N (%)	Voriconazole n/N (%)	Estimated Difference (%)	95% CI
Success	73/163 (44.8)	78/171 (45.6)	-0.6	(-11.2, 10.1)
Failure	90/163 (55.2)	93/171 (54.4)		

† Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.
Missing or 'unable to determine' responses are considered as failures.

Analysis of Global Clinical Response at Week 12
Full Analysis Set Population

Outcome	Unadjusted Data Summary by Treatment Group		Treatment Difference (Posaconazole - Voriconazole)†	
	Posaconazole n/N (%)	Voriconazole n/N (%)	Estimated Difference (%)	95% CI
Success	69/163 (42.3)	79/171 (46.2)	-3.4	(-13.9, 7.1)
Failure	94/163 (57.7)	92/171 (53.8)		

† Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.
Missing or 'unable to determine' responses are considered as failures.

Summary of Adjudicated Global Clinical Response
Full Analysis Set Population

Adjudicated Global Clinical Response	Posaconazole n/N (%)	Voriconazole n/N (%)	Total n/N (%)
At Week 6			
Success, Complete Response	11/163 (6.7)	9/171 (5.3)	20/334 (6.0)
Success, Partial Response	62/163 (38.0)	69/171 (40.4)	131/334 (39.2)
Failure, Stable Response	12/163 (7.4)	22/171 (12.9)	34/334 (10.2)
Failure, Progression of Fungal Disease	27/163 (16.6)	21/171 (12.3)	48/334 (14.4)
Failure, Death During the Period of Evaluation	34/163 (20.9)	33/171 (19.3)	67/334 (20.1)
Unable to Assess	17/163 (10.4)	17/171 (9.9)	34/334 (10.2)
At Week 12			
Success, Complete Response	20/163 (12.3)	19/171 (11.1)	39/334 (11.7)
Success, Partial Response	49/163 (30.1)	60/171 (35.1)	109/334 (32.6)
Failure, Stable Response	9/163 (5.5)	7/171 (4.1)	16/334 (4.8)
Failure, Progression of Fungal Disease	13/163 (8.0)	19/171 (11.1)	32/334 (9.6)
Failure, Death During the Period of Evaluation	56/163 (34.4)	51/171 (29.8)	107/334 (32.0)
Unable to Assess	16/163 (9.8)	15/171 (8.8)	31/334 (9.3)
Complete Response: Survival with Resolution of Fungal Disease Evidence Partial Response: Survival and Improvement of Fungal Disease Evidence Stable Response: Survival and Minor or No Improvement of Fungal Disease Evidence Progression of Fungal Disease: Survival and Worsening of Fungal Disease Evidence			

The CHMP pointed out that, according to the CHMP scientific advice on the change of primary endpoint, this endpoint "global clinical response at week 6" should be maintained and considered as a co-primary endpoint.

The results are comparable for all types of response (successes and failures) between POS and VOR at week 6 and week 12, and support the non-inferiority conclusion of the primary endpoint. Of note, this FAS population contains only 334 subjects, which is inferior to the targeted 400 subjects to ensure a power >85% for statistical analysis.

The MAH however explained that the sample size had a 80% power to show non-inferiority with a 10% margin. The study results show that non-inferiority as pre-defined in the protocol was met in both cases. The explanation indicates that after the endpoint switch the study retained a sufficient power and sample size to determine and meet pre-defined criteria for non-inferiority.

Ancillary analyses

Subgroup analyses

Overall, mortality was higher for older subjects and for subjects with extra-pulmonary site(s) of infection or with neutropenia at baseline or with proven IA. When evaluating mortality by treatment group, observed mortality rates were either comparable across treatment groups or lower (with a 95% CI that did not contain 0) in the POS group than in the VOR group. All-cause mortality rates were lower for POS compared with VOR for subjects in the following demographic and baseline disease subgroups: age (18 to 57 [median age]), sex (male), race (white), and baseline adjudication of possible IA. On the contrary, all-cause mortality rates were higher for POS compared with VOR for Asian subjects.

Analysis of All-Cause Mortality Through Day 42 by Subgroup
Intention to Treat Population

Subgroup Criterion	Unadjusted Data Summary by Treatment Group		Treatment Difference (Posaconazole - Voriconazole)†	
	Posaconazole n/N (%)	Voriconazole n/N (%)	Estimated Difference (%)	95% CI
Age (Years)				
<18	1/3 (33.3)	0/2 (0.0)	33.3	(-51.9, 82.0)
18 to 57	14/151 (9.3)	27/151 (17.9)	-8.6	(-16.6, -0.9)
>57	29/134 (21.6)	32/134 (23.9)	-2.2	(-12.3, 7.9)
Sex				
Male	21/172 (12.2)	38/172 (22.1)	-9.9	(-17.9, -1.9)
Female	23/116 (19.8)	21/115 (18.3)	1.6	(-8.7, 11.8)
Region				
US	3/21 (14.3)	0/12 (0.0)	14.3	(-11.9, 35.0)
Ex-US	41/267 (15.4)	59/275 (21.5)	-6.1	(-12.6, 0.4)
Ethnicity				
Hispanic or Latino	7/48 (14.6)	14/57 (24.6)	-10.0	(-25.0, 5.8)
Not Hispanic or Latino	37/220 (16.8)	43/219 (19.6)	-2.8	(-10.1, 4.5)
Unknown	0/20 (0.0)	2/11 (18.2)	-18.2	(-48.2, 0.3)
Race				
American Indian or Alaska Native	0/4 (0.0)	4/6 (66.7)	-66.7	(-90.9, -1.5)
Asian	10/62 (16.1)	4/60 (6.7)	9.5	(-2.1, 21.6)
Black	0/3 (0.0)	0/4 (0.0)	NA	
Multi-Racial	5/25 (20.0)	4/25 (16.0)	4.0	(-18.5, 26.4)
White	29/194 (14.9)	47/192 (24.5)	-9.5	(-17.5, -1.6)
Risk Status				
High Risk	20/113 (17.7)	23/113 (20.4)	-2.7	(-13.0, 7.7)
No High Risk	24/175 (13.7)	36/174 (20.7)	-7.0	(-15.0, 1.0)
Type of IA per Adjudicator's Assessment				
Proven	7/26 (26.9)	4/15 (26.7)	0.3	(-29.6, 26.5)
Probable	24/137 (17.5)	28/156 (17.9)	-0.4	(-9.2, 8.5)
Possible	7/81 (8.6)	18/79 (22.8)	-14.1	(-25.7, -3.0)
Cannot be determined	6/44 (13.6)	9/37 (24.3)	-10.7	(-28.7, 6.5)
Site of IA				
Lung	31/230 (13.5)	39/230 (17.0)	-3.5	(-10.1, 3.1)
Multiple Sites	12/48 (25.0)	17/45 (37.8)	-12.8	(-31.1, 6.2)
Sinus	1/3 (33.3)	2/7 (28.6)	4.8	(-47.5, 62.1)
Other	0/2 (0.0)	1/2 (50.0)	-50.0	(-92.4, 46.8)
Missing	0/5 (0.0)	0/3 (0.0)	NA	
Underlying Disease				
Recent history of prolonged neutropenia temporally related to the onset of fungal disease	30/179 (16.8)	47/189 (24.9)	-8.1	(-16.4, 0.2)
Receipt of an allogeneic HSCT	14/65 (21.5)	9/59 (15.3)	6.3	(-7.8, 20.1)
Treatment with other recognized T-cell immune suppressants	20/126 (15.9)	22/109 (20.2)	-4.3	(-14.5, 5.5)
Prolonged use of corticosteroid	23/93 (24.7)	18/89 (20.2)	4.5	(-7.8, 16.7)
Inherited severe immunodeficiency	0/2 (0.0)	1/1 (100.0)	-100.0	(-100.0, 31.5)
None of the above	3/17 (17.6)	1/18 (5.6)	12.1	(-11.6, 37.0)
Neutropenic Status at Baseline (10^9/L)				
< 0.5	23/132 (17.4)	34/137 (24.8)	-7.4	(-17.1, 2.4)
≥ 0.5	20/142 (14.1)	21/138 (15.2)	-1.1	(-9.6, 7.3)
Unknown	1/14 (7.1)	4/12 (33.3)	-26.2	(-56.2, 5.4)

† Based on Miettinen and Nurminen's method.

Missing or 'unable to determine' responses are considered as failures (dead). Site of IA and Underlying Disease are per Adjudicator's Assessment.

In the FAS population, all-cause mortality rates through Day 42 were generally comparable between treatment groups.

The CHMP considered that, overall, subgroup efficacy analyses for the ITT population were supportive of the primary efficacy endpoint analysis, with non-inferiority of POS to VOR by subgroup variables.

However, the mortality in the Asian population was higher in the POS group (16%, 10/62) than the VOR group (6.7%, 4/60). This higher mortality rate is also observed within the FAS population (POS: 21% (9/43); VOR: 6.5% (3/46)). Based on PPK analysis, no subexposure is expected within the Asian population, with furthermore a lower POS clearance and thus an increase of POS Cavg by 33% in Chinese patients. This increase was not considered clinically meaningful. Considering the low number of subjects in this subgroup, and the lack of efficacy concerns particularly observed in the Asian population with the current use of POS, these subgroups results are not considered relevant. Subgroup analysis including prior medication with antimycotics during the 3 days before starting the study treatment was requested.

The provided Subgroup analysis of study subjects that received prior antimycotic therapy showed that a large proportion (80%) of subjects in both groups (227/288 in the POS group and 229/287 in the VOR group) received prior antimycotics, which was allowed by the protocol. Overall, the use of antimycotics by class is balanced between the two treatment groups. The influence of prior treatment on the primary outcomes are rather inconclusive. However, as the proportion of pre-treated patients is very high, it drives the overall response results:

All-cause mortality:

All cause-mortality at D42 in ITT	Pre-treated with antimycotics (% death)	Not pre-treated with antimycotics	Overall results
POS	16.7%	9.8%	15.3%
VOR	21.8%	15.5%	20.6%

Global clinical response:

Global clinical response at D42 in FAS	Pre-treated with antimycotics (success)	Not pre-treated with antimycotics	Overall results
POS	44.6%	45.5%	44.8%
VOR	48.5%	36.6%	45.6%

As the proportion of pre-treated subjects as well as the primary outcomes are comparable between the two groups (POS and VOR), the CHMP considered that it could be assumed that there is no impact on the non-inferiority results.

The CHMP additionally noted that in the POS SmPC, the recommended treatment duration for IA is 6-12 weeks. It was also noted that approximately 40% of subjects have been treated with POS or VOR for less than 6 weeks, including 30-35% for less than 4 weeks.

The MAH was asked to provide efficacy outcomes according to treatment duration (<6 weeks, 6 weeks to <12 weeks, ≥12 weeks) and to justify the recommended treatment duration for IA.

The MAH provided justification for the treatment duration: the study was designed for a 12 week treatment duration, and it was noted that failure rate in the sub-group treated for less than 42 days was more than 40% compared to the overall rate of 15% for the all-cause mortality and respectively more than 90% compared to the overall failure rate of 55% for the global clinical response. More importantly, the results are comparable between the POS and VOR treatments, regardless of the treatment duration and are consistent with the overall non-inferiority results.

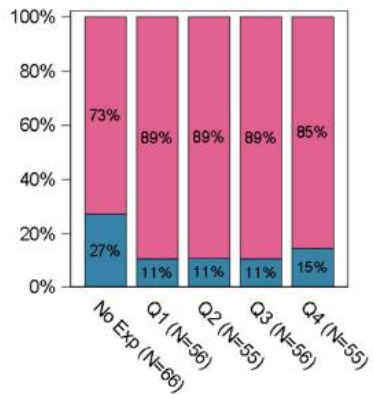
Therefore, the data suggests a duration of treatment of more than 6 weeks. It seems that the overall success rate does not improve beyond 12 weeks of treatment. Therefore, the CHMP considered the proposed statement in the SmPC: '*Recommended total duration of therapy is 6-12 weeks*' to be supported.

Exposure-Efficacy Relationship (see also PK/PD section)

For subjects with evaluable exposure data, there was no discernible trend across quartiles of POS trough plasma concentrations for the key efficacy endpoint of all-cause mortality through Day 42 in the ITT population. Same results are noted for the global clinical response at Week 6. These data suggest that POS exposures achieved in P069 with the IV and tablet formulations were on the plateau of the exposure-efficacy curve, where efficacy is relatively insensitive to changes in exposure.

However, it can be noted that subjects without evaluable POS exposure data had higher mortality rates than subjects with such data. The lower efficacy in these subjects may be a consequence of the fact that subjects who died or remained seriously ill were less likely to have evaluable exposure data, potentially introducing bias into the exposure-efficacy analysis.

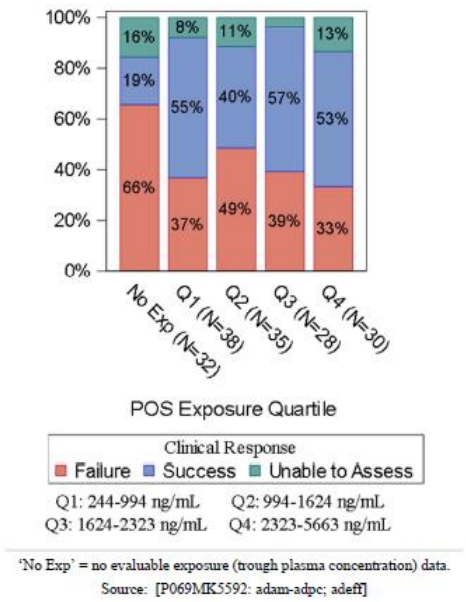
All-Cause Mortality Through Day 42 by Quartiles of Within-Subject Mean Posaconazole Trough Plasma Concentration (ITT population)



Q1: 244-994 ng/mL Q2: 994-1624 ng/mL
Q3: 1624-2323 ng/mL Q4: 2323-5663 ng/mL

'No Exp' = no evaluable exposure (trough plasma concentration) data.
Source: [P069MK5592: adam-adpc; adeff]

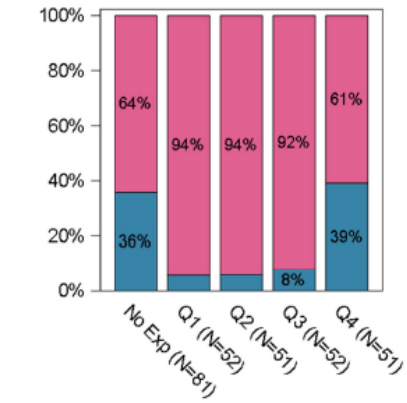
Global Clinical Response at Week 6 by Quartile of Within-Subject Mean Posaconazole Trough Plasma Concentration (FAS Population)



'No Exp' = no evaluable exposure (trough plasma concentration) data.
Source: [P069MK5592: adam-adpc; adeff]

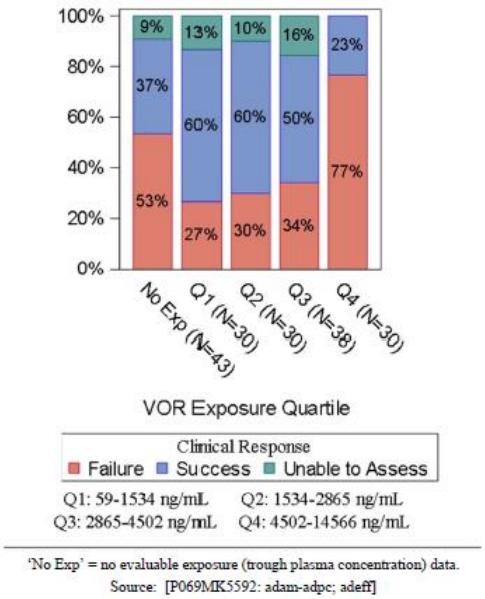
For VOR, subjects in the highest quartile of VOR trough plasma concentration and those without evaluable VOR exposure data had higher all-cause mortality through Day 42 than subjects in the lower 3 quartiles of VOR trough concentration in the ITT population. Same results for the global clinical response at Week 6.

All-Cause Mortality Through Day 42 by Quartiles of Within-Subject Mean Voriconazole Trough Plasma Concentration (ITT population)



'No Exp' = no evaluable exposure (trough plasma concentration) data.
Source: [P069MK5592: adam-adpc; adeff]

Global Clinical Response at Week 6 by Quartile of Within-Subject Mean Voriconazole Trough Plasma Concentration (FAS Population)



'No Exp' = no evaluable exposure (trough plasma concentration) data.
Source: [P069MK5592: adam-adpc; adeff]

The CHMP considered that these data suggest a larger therapeutic margin with POS than with VOR, with higher rates of mortality and lower clinical response with the higher exposures of VOR, conversely to POS where higher exposures seem to not impact these endpoints.

The lower efficacy of POS or VOR treatment in the population without available exposition data may be subject to interpretations. As stated by the MAH, these data may reflect that subjects with higher advanced disease (and a poor prognosis) were less likely to have evaluable exposure data, potentially introducing bias into the exposure-efficacy analysis. These data may also suggest that a therapeutic drug monitoring of POS or VOR is associated to a better outcome.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19: Summary of Efficacy for trial P069

Title: A Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults and Adolescents			
Study identifier	**P069**		
Design	Multicenter, parallel assignment (randomized 1:1), double blind, active comparator		
	Duration of main phase:	12 weeks	
Hypothesis	Demonstrate that POS is non-inferior to VOR in first line therapy of IA **Primary hypothesis:** The all-cause mortality rate through Day 42 in the POS treatment group is non-inferior to that in the VOR treatment group. **Secondary hypothesis** (as EMA request): The global clinical response for POS at Week 6 in the FAS population is non inferior to that in the VOR treatment group.		
Treatments groups	Posaconazole (IV or tablets)		300 mg BID (IV or tablets) at Day 1, then 300 mg QD (IV or tablets) + placebo QD (to ensure double-blind) for 12 weeks. **293 subjects randomised, 288 subjects treated**
	Voriconazole (IV or capsules)		IV: 6 mg/kg BID at Day 1, then 4 mg/kg BID for 12 weeks. OR capsules: 300 mg BID at Day 1, then 200 mg BID for 12 weeks. **292 subjects randomised, 287 subjects treated**
Endpoints and definitions	Primary efficacy endpoint	All-cause mortality	To compare all-cause mortality for POS with that of 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)
	Co-primary efficacy endpoint (as request by EMA)	Global clinical response	To evaluate the global clinical response for POS vs. VOR at Week 6 in the FAS population
Database lock	10 sept 2019 (last patient last visit)		
Results and Analysis			
Analysis description	**Primary Analysis** All-cause mortality at day 42: Statistical methodology: The primary endpoint was assessed using a non-inferiority margin of 10%; if the upper limit of the 95% CI, adjusted for stratification factors for the difference in success rates, was less than 10%, non-inferiority was to be declared. If non-inferiority was declared, superiority of POS over VOR was to be assessed and declared if the upper limit of the 95% CI was <0%.		

Analysis population and time point description	**Intent to treat (ITT)** population: All randomized subjects who received at least 1 dose of study drug		
Descriptive statistics and estimate variability	Treatment group	Posaconazole (POS)	Voriconazole (VOR)
	Number of subjects	**288**	**287**
	Mortality rate at day 42	44/288 (15.3%)	59/287 (20.6%)
	Estimated difference 95% confidence interval P value	-5.3% [-11.6 ; 1.0%] <0.0001	
Conclusion	POS is non-inferior to VOR in the treatment of IA with regard to all-cause mortality through Day 42.		
Analysis description	**Co-primary Analysis** Global clinical response at week 6: Methodology: A subject was considered to have a successful global clinical response if the subject was FAS-evaluable and judged by the Clinical Adjudication Committee (CAC) to be alive and to have had a complete or partial response at the time point of interest. The CAC also adjudicated IFI-attributable mortality through Day 42		
Analysis population and time point description	**Full analysis set (FAS):** All randomized subjects who were classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 EORTC/MSG definitions), and received at least 1 dose of study drug.		
Descriptive statistics and estimate variability	Treatment group	Posaconazole (POS)	Voriconazole (VOR)
	Number of subject	**163**	**171**
	Proportion of complete or partial response (=success)	73/163 (44.8%)	78/171 (45.6%)
	Estimated difference 95% confidence interval	-0.6% [11.2% ; 10.1%]	
Conclusion	While there was no formal statistical evaluation of global clinical response in the FAS population, it was noted that the proportions of observed global clinical responses were similar in the POS and VOR treatment groups at Week 6.		
Notes	Approximately 10% in each group were unable to assess and not counted as success or failure.		

Additional clinical data

The MAH has performed a systematic literature review to understand the efficacy/effectiveness of POS as monotherapy or combination therapy in the treatment of IFIs other than IA, consisting of the following: chromoblastomycoses (caused by *Fonsecea*, *Phialophora*, *Cladosporium*, *Exophilia*, or Chromoblastomycosis not specified), fungal mycetoma (caused by *Eumycetoma*, mycotic mycetoma, and fungal mycetoma not specified), hyalohyphomycosis/phaeohyphomycosis (caused by *Fusarium*,

Scedosporium, *Pseudoallescheria*, *Talaromyces*, and *Penicillium* spp.), and mucormycosis (caused by *Rhizopus*, *Mucor*, *Cunnighamella*, *Apophysomyces*, *Lictheimia* (*Absidia*), *Saksenaea*, *Rhizomucor*, Mucormycetes not specified, and Zygomycosis not specified).

Over the past 14 years, 351 articles have been published describing the efficacy of POS in the treatment of these rare IFIs (chromoblastomycosis, fungal mycetoma, hyalohyphomycosis/phaeohyphomycosis and mucormycosis). The literature-based evidence consists of observational evidence (mostly case reports). The majority of evidence was found in mucormycosis followed by hyalohyphomycosis/ phaeohyphomycosis, and chromoblastomycosis. Positive clinical outcomes with POS therapy were observed in 66.7% (564/845) of mucormycosis cases, 53.3% (49/92) of hyalohyphomycosis/ phaeohyphomycosis cases, and 73.9% (17/23) of chromoblastomycosis cases. Very sparse evidence was found for fungal mycetoma (2 positive cases).

2.4.1. Discussion on clinical efficacy

Posaconazole (IV and tablet forms) is currently indicated in the treatment and prophylaxis of the following IFI in adults: Invasive aspergillosis (in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products); fusariosis (in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B); chromoblastomycosis and mycetoma (in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole); coccidioidomycosis (in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products).

In current practice, voriconazole is used as first line therapy in IA. Isavuconazole showed non inferiority to voriconazole in CL-104 study and has also the indication in IA since 2015.

Regarding difficulties to treat IA and the known adverse events and DDI of voriconazole and isavuconazole, there is a need a need for additional therapies with at least similar levels of efficacy.

Design and conduct of clinical studies

This extension of indication is based on the non-inferiority study P069 performed in patients with possible, probable or proven IA. Subjects with baseline possible IA have additional diagnostic to confirm the IA. In the event that possible IA was not confirmed, the patients may continue to be treated if clinician deems appropriate. Subjects should not have history of chronic, recurrent or refractory IA, consistency with the claimed first line treatment of IA, but an antifungal therapy started since 3 days maximum is tolerated. All patients were randomized 1:1 to receive POS or VOR with IV or oral formulation, according to the clinical status of the patient. POS oral suspension was not used, this extension of indication did not concern this formulation due to the differences between tablets and oral suspension in frequency of dosing, administration with food and plasma drug concentration achieved.

Two populations were studied:

- ITT population: all randomized subjects who received at least 1 dose of study drug
- FAS population: all randomized subjects who were classified as having proven or probable IA (based upon independent adjudication assessment by the CAC), and received at least 1 dose of study drug.

To assess the non-inferiority of POS vs VOR, the primary endpoint was changed during study and was defined as the all-cause mortality through day 42 in the ITT population, similarly than the non-inferiority study CL-104 (ISA vs VOR). However, in accordance to the EMA scientific advice, the initial

primary endpoint - global clinical response at week 6 in the FAS population - must be also considered as a co-primary endpoint for the non-inferiority assessment of POS vs VOR. The 10% non-inferiority margin is endorsed.

Efficacy data and additional analyses

Overall, 575 subjects were part of the ITT population and randomized in a 1:1 ratio (POS = 288, VOR = 287). 26 countries in the Asia/Pacific region, Europe and North and South America were represented. Baseline data are similar between POS and VOR groups. A majority of subjects were male (59.8%) and white (67.1%), with a median age at 57 years. Only 5 subjects were adolescents <18 years old, although this study has initially intended to enrol both adolescent and adult subjects. Therefore, this study could not support alone an adolescent extension of the indication in the treatment of IA. Only 1% of subjects were black/African American, but the known PK data of POS suggest the lack of significant effect of race on POS exposure for the tablets and IV formulations.

Only 58% of the baseline IA diagnosis was probable or proven, but a non-negligible proportion of IA diagnosis (14%) cannot be determined at baseline by the CAC. *Aspergillus* (and especially *A. fumigatus*) is the fungal agent most represented, without imbalance between both groups. However, only 24% of subjects had fungal culture results reported.

The non-inferiority of POS vs VOR in the first-line treatment of IA was demonstrated. In the ITT population, the mortality rate at Day 42 was 15.3% in the POS group and 20.6% in the VOR group, after stratification for risk of mortality/poor outcome (difference: -5.3% [95% CI: -11.6, 1.0%]). In the FAS population, the global clinical response at 6 week (considered as a co-primary endpoint) also demonstrate a non-inferiority of POS vs VOR. Proportion of success were 44.8% for POS and 45.6% for VOR, with comparable proportion in complete and partial success (difference: -0.6% [95% CI: -11.01, 10.1]).

Other secondary endpoints support the non-inferiority of POS vs VOR, excepted the secondary endpoint "mortality due to IA (according to the CAC)", with higher rates at each time points in the POS group than in the VOR group (Day 42: 51.6% vs 31.3% ; Day 84: 39.3% vs 28.0% ; Day 114: 35.9% vs 30.4%). However, approximately half of the deaths have an indeterminate relationship with IA or other IFI, with a higher proportion in the VOR group, which could bias the estimation of the mortality due to IA. Indeed, it is expected that a significant proportion of these undetermined deaths were actually due to IA (probably combined with other pathologies or infections). Upon request by the CHMP, the MAH reassessed the mortality data of all subjects for whom no cause of death was attributed, and specified among them whether IA was suspected and the number of subjects with probable or proven IA in each groups. The MAH satisfactorily clarified that none of the 26 POS treated subjects and three of the 28 VOR subjects with an indeterminate cause of death, were identified as having death caused by IA of other invasive fungal disease. With this reassessment, the proportion of deaths attributable to IA and IFD becomes more balanced: 24/64 for POS and 20/56 for VOR, though overall the number of deaths remains unfavourable to the POS group.

Subgroup analysis are supportive to the non-inferiority results. Considering that prior medication with antimycotics was authorized for 3 days maximum before to start study treatment, which potentially may influence the outcome, a subgroup analysis by prior medication with antimycotics should be added.

Assessment of paediatric data on clinical efficacy

An indication of POS for the first-line treatment of IA in paediatric patients is not claimed at this stage. The efficacy in IA was not demonstrated for paediatric patients in P069 study, with only 5 adolescents enrolled.

2.4.2. Conclusions on the clinical efficacy

In conclusion, POS is non-inferior to VOR for the first-line treatment of adults with probable, possible or proven IA, based on the all-cause mortality rate and global clinical response at 6 weeks.

2.5. Clinical safety

Introduction

Safety analyses in P069 were based on the APaT population, consisting of all randomized subjects who received ≥1 dose of study treatment. The ITT population, consisting of all randomized subjects who received ≥1 dose of study drug, was used for the primary efficacy analysis (all-cause mortality through Day 42). The APaT and ITT populations were identical.

The overall adverse event (AE) profile in P069 was reflective of the known AE profile of POS IV and tablet, as described in product labeling, and was consistent with a critically ill study population. Furthermore, the types and incidences of AEs, drug-related AEs, and serious adverse events (SAEs) in the POS treatment group in P069 were similar to those reported in previous clinical studies of POS IV and tablet despite P069 having a longer duration of treatment (average therapy duration of >60 days for the treatment of IA) compared with previous studies of POS IV and tablet (average therapy durations of <30 days in a prophylaxis setting).

The proportion of subjects with a drug-related AE was lower in the POS treatment group (29.9%) than in the VOR treatment group (40.1%). Treatment was discontinued due to a drug-related AE in 6.3% of POS-treated subjects compared with 9.8% of VOR-treated subjects. No POS-treated subject died due to a drug-related SAE compared with 3 VOR-treated subjects. The incidences of AEs, SAEs, deaths, and discontinuations due to AEs were similar for subjects in the POS and VOR treatment groups.

Patient exposure

In study P069, 288 subjects were randomized and treated with POS IV or tablet at a dose of 300 mg QD (300 mg BID on Day 1) compared with 287 subjects randomized and treated with VOR 4 mg/kg IV BID (6 mg/kg IV BID on Day 1) or 200 mg oral BID (300 mg oral BID on Day 1). The median duration of exposure in the ITT population was 67 days in the POS group and 64 days in the VOR group. Approximately 40% of subjects in each treatment group received study treatment for the planned duration of 84 days (maximum allowed duration of 98 days).

Approximately 55% to 60% of subjects started treatment with the IV formulation of either POS or VOR.

Adverse events

Overall, the AE profile was reflective of a critically ill study population. Nearly all subjects in both treatment groups experienced 1 or more AEs during the treatment period or within 30 days following the last dose. The proportion of subjects with drug-related AEs was lower in the POS treatment group

than in the VOR treatment group; the incidences of AEs, SAEs, deaths, and discontinuations due to AEs were similar for subjects in the POS and VOR treatment groups.

The overall proportions of subjects with AEs in a given SOC were comparable between the 2 treatment groups; AEs categorized within the SOCs of Infections and Infestations and Gastrointestinal disorders were the most frequently reported.

In this critically ill population, the most frequently reported AEs were hypokalaemia, pyrexia, nausea, vomiting, diarrhoea, ALT increased, and febrile neutropenia in the POS group; and pyrexia, diarrhoea, nausea, and hypokalaemia in the VOR group. The frequencies and types of AEs were generally comparable across both treatment groups, although the AE of hypokalaemia was reported more frequently for POS-treated subjects (28.5%) than for VOR-treated subjects (17.1%).

The proportion of subjects with AEs that were considered by the investigator(s) to be related to study drug (i.e. drug-related) was lower in the POS group compared with the VOR group (-10.2%; 95% CI: -17.9, -2.4). The only drug-related AEs reported for >5% of subjects (in either treatment group) were ALT increased, AST increased, and blood alkaline phosphatase increased.

When analyzed by drug-related AEs occurring in ≥4 subjects in either treatment group (ie, Tier-2 events, as prespecified in the protocol, a lower proportion of POS-treated subjects than VOR-treated subjects reported drug-related AEs applicable to the SOCs of Eye disorders (-8.0%; 95% CI: -12.2, -4.5) and Psychiatric disorders. These differences were driven by between-group differences in the AEs of dyschromatopsia, vision blurred, visual impairment, and hallucination, each of which was reported at a lower incidence for POS-treated subjects compared with VOR-treated. A higher proportion of subjects with drug-related AEs in the Metabolism and Nutrition disorders SOC was noted for the POS treatment group compared with the VOR group (estimate: 3.8%; 95% CI: 0.5, 7.5), with the AE of hypokalaemia being the basis for this treatment difference.

Table 20 Analysis of Subjects with Drug-Related Adverse Events (Incidence ≥ 4 Subjects in One or More Treatment Groups) - All Subjects as Treated

	Posaconazole		Voriconazole		Difference in % vs Voriconazole
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	288		287		
with one or more adverse events	86	(29.9)	115	(40.1)	-10.2 (-17.9, -2.4)
with no adverse events	202	(70.1)	172	(59.9)	10.2 (2.4, 17.9)
Blood and lymphatic system disorders	**2**	**(0.7)**	**6**	**(2.1)**	**-1.4 (-3.9, 0.7)**
Eye disorders	**5**	**(1.7)**	**28**	**(9.8)**	**-8.0 (-12.2, -4.5)**
Dyschromatopsia	0	(0.0)	6	(2.1)	-2.1 (-4.5, -0.8)
Photopsia	2	(0.7)	6	(2.1)	-1.4 (-3.9, 0.7)
Vision blurred	3	(1.0)	10	(3.5)	-2.4 (-5.4, -0.0)
Visual impairment	0	(0.0)	6	(2.1)	-2.1 (-4.5, -0.8)
Gastrointestinal disorders	**23**	**(8.0)**	**25**	**(8.7)**	**-0.7 (-5.4, 3.9)**
Abdominal pain	2	(0.7)	4	(1.4)	-0.7 (-2.9, 1.3)
Diarrhoea	4	(1.4)	2	(0.7)	0.7 (-1.3, 2.9)
Nausea	12	(4.2)	11	(3.8)	0.3 (-3.1, 3.8)
Vomiting	9	(3.1)	5	(1.7)	1.4 (-1.3, 4.3)
General disorders and administration site	**7**	**(2.4)**	**8**	**(2.8)**	**-0.4 (-3.3, 2.5)**

conditions					
Hepatobiliary disorders	**9**	**(3.1)**	**10**	**(3.5)**	**-0.4 (-3.6, 2.8)**
Hepatic function abnormal	5	(1.7)	4	(1.4)	0.3 (-2.0, 2.8)
Investigations	**43**	**(14.9)**	**35**	**(12.2)**	**2.7 (-2.9, 8.4)**
Alanine aminotransferase increased	22	(7.6)	18	(6.3)	1.4 (-2.9, 5.7)
Aspartate aminotransferase increased	18	(6.3)	16	(5.6)	0.7 (-3.3, 4.7)
Blood alkaline phosphatase increased	7	(2.4)	16	(5.6)	-3.1 (-6.7, 0.1)
Blood bilirubin increased	8	(2.8)	5	(1.7)	1.0 (-1.6, 3.9)
Blood lactate dehydrogenase increased	4	(1.4)	3	(1.0)	0.3 (-1.8, 2.6)
Gamma-glutamyltransferase increased	5	(1.7)	11	(3.8)	-2.1 (-5.2, 0.7)
Total bile acids increased	0	(0.0)	4	(1.4)	-1.4 (-3.5, -0.1)
Metabolism and nutrition disorders	**18**	**(6.3)**	**7**	**(2.4)**	**3.8 (0.5, 7.5)**
Decreased appetite	4	(1.4)	1	(0.3)	1.0 (-0.7, 3.2)
Metabolism and nutrition disorders	**18**	**(6.3)**	**7**	**(2.4)**	**3.8 (0.5, 7.5)**
Hypokalaemia	11	(3.8)	1	(0.3)	3.5 (1.4, 6.4)
Nervous system disorders	**9**	**(3.1)**	**14**	**(4.9)**	**-1.8 (-5.3, 1.6)**
Psychiatric disorders	**6**	**(2.1)**	**22**	**(7.7)**	**-5.6 (-9.5, -2.2)**
Hallucination	4	(1.4)	12	(4.2)	-2.8 (-5.9, -0.1)
Hallucination, visual	1	(0.3)	5	(1.7)	-1.4 (-3.7, 0.4)
Renal and urinary disorders	**4**	**(1.4)**	**3**	**(1.0)**	**0.3 (-1.8, 2.6)**
Respiratory, thoracic and mediastinal disorders	**5**	**(1.7)**	**3**	**(1.0)**	**0.7 (-1.5, 3.1)**
Skin and subcutaneous tissue disorders	**5**	**(1.7)**	**12**	**(4.2)**	**-2.4 (-5.6, 0.4)**

[†] Based on Miettinen & Nurminen method.

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

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

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Adverse events are reported from the first dose of study treatment through 30 days after the last dose.

The CHMP considered that, in this study, the safety profile for POS was well established. Adverse events incidence was high in all groups, which was expected in this critically ill population.

In this critically ill population, the most frequently reported AEs were hypokalaemia, pyrexia, nausea, vomiting, diarrhoea, ALT increased, and febrile neutropenia in the POS group

Serious adverse event/deaths/other significant events

Death

A total of 173 (30.1%) subjects died during the full study period, through Day 114. In the POS group, no subject had a drug-related AE that resulted in death. In the VOR group, 3 subjects had drug-related AEs (pancreatitis, cerebral disorder, encephalopathy) that resulted in death.

Other Serious Adverse Events

The proportions of subjects with SAEs were generally comparable across both groups, as were the proportions of subjects with drug-related SAEs, discontinuations due to SAEs, and discontinuations due to drug-related SAEs.

The frequencies and types of SAEs were generally comparable in both treatment groups, with the exception of SAEs of hypokalaemia and haemoptysis, which were reported more frequently in the POS group (n=4 each SAE) than in the VOR group (n=0 each SAE).

The overall proportion of subjects with drug-related SAEs was ≤7.0% in each group. The most commonly reported drug-related SAEs were ALT increased (n=3) in the POS treatment group and encephalopathy (n=3) in the VOR treatment group.

Adverse Events of Special Interest – Analysis of Adverse Events by Organ System or Syndrome

Hepatic Safety Events

Tier-1 hepatic safety events comprised AST or ALT laboratory values ≥ 3xULN together with both an elevated total bilirubin value ≥ 2xULN and an alkaline phosphatase value < 2xULN.

Comparable rates of Tier-1 hepatic safety events were noted for subjects in POS (3.8%) and VOR (3.5%) treatment groups.

Central Nervous System and Visual Safety Events

Approximately one-third of subjects in each treatment group experienced an AE in the CNS and visual safety cat. A lower proportion of subjects in the POS group (6.6%) reported AEs in the SOC of Eye disorders compared with the VOR group (12.5%).

Treatment differences were not observed in the incidence of Tier-1 AEs associated with the SOCs of Nervous System disorders (POS: 20.8%; VOR: 18.5%) or Psychiatric disorders (POS: 12.2%; VOR: 16.4%). Within the Psychiatric disorders SOC, the most commonly reported Tier-1 AEs were confusional state (3.5% in the POS group, 5.6% in the VOR group) and hallucination (2.1% and 5.2%, respectively); the between-group treatment difference (-3.1%; 95% CI: -6.6, -0.1) in the incidence of hallucination favored POS.

Treatment-related Central Nervous System and Visual Safety Events

The overall proportion of subjects with drug-related AEs reported in the CNS and visual safety category was lower in the POS group (5.6%) compared with the VOR group (16.4%).

The incidence of drug-related Tier-1 AEs classified within the SOC of Eye disorders was lower in POS-treated subjects (1.7%) than in VOR-treated subjects (9.4%) (-7.7%; 95% CI: -11.8, -4.2). Specifically, drug-related AEs of dyschromatopsia, vision blurred, and vision impairment occurred less frequently in the POS group than in the VOR group.

There were no notable between-group differences in drug-related Tier-1 AEs associated with the SOC of Nervous System disorders.

A difference in the incidence of drug-related Tier-1 AEs for the SOC of Psychiatric disorders was observed, with a lower proportion of POS-treated subjects (2.1%) experiencing AEs classified for the Psychiatric disorder SOC compared with VOR-treated subjects (6.6%) (-4.5%; 95% CI: -8.3, -1.3). In particular, it was noted that the incidence of drug-related hallucination was lower in POS-treated subjects (1.4%) than in VOR-treated subjects (4.2%).

The most frequently reported (incidence ≥1%) drug-related CNS and visual safety AEs were as follows:

- POS treatment group: hallucination (1.4%) and vision blurred (1.0%)
- VOR treatment group: hallucination (4.2%), vision blurred (3.5%), dyschromatopsia (2.1%), photopsia (2.1%), visual impairment (2.1%), visual hallucination (1.7%), dizziness (1.0%), and encephalopathy (1.0%).

Serious Central Nervous System and Visual Safety Events

The overall proportion of subjects with SAEs in the Nervous System or Eye Disorder SOC was low in the POS (3.8%) and VOR (5.6%) treatment groups. There were no meaningful treatment differences in the incidences of SAEs categorized within the SOCs of Eye disorders, Nervous System disorders, or Psychiatric disorders, and there were no meaningful differences in SAEs within these SOCs leading to treatment discontinuations.

Dermatologic Events

The incidences of subjects who had a Tier-1 AE in the dermatologic reactions category (i.e., prespecified PTs in the SOCs of Immune System disorders and Skin and Subcutaneous Tissue disorders were comparable in the POS (16.3%) and VOR (19.2%) treatment groups. The most frequently reported AE in the dermatologic reactions category was rash (approximately 7% in each treatment group).

There were no drug-related AEs within the SOC of Immune System disorders. The incidence of drug-related AEs categorized as Skin and Subcutaneous Tissue disorders was low in both treatment groups.

Events Related to Adrenal Steroidogenesis or Hypotension

Comparable incidences of AEs in the Adrenal Steroidogenesis category (i.e., prespecified PTs in the SOCs of Endocrine disorders and Vascular disorders) were reported for subjects in the POS (8.0%) and VOR (7.0%) treatment groups. Hypotension was reported by approximately 7% of subjects in each group.

Two subjects, both in the POS group, had drug-related AEs in either the Endocrine disorder SOC or Vascular disorder SOC. One subject had drug-related adrenal insufficiency, and 1 subject had drug-related hypotension.

Most Frequently Reported Adverse Events by Posaconazole Plasma Concentration Quartile

Exposure-safety relationships of POS by quartile of exposure were evaluated for all AEs as well as treatment-related AEs. Exposure Cmin quartiles were: 244 to 1046 ng/mL (Q1); 1046 to 1625 ng/mL (Q2); 1625 to 2274 ng/mL (Q3); and 2274 to 5550 ng/mL (Q4). The range of POS trough concentrations was consistent with the known exposure profile of POS IV and POS tablet.

In the evaluation of exposure-safety relationships of POS by quartile of exposure, there were no meaningful differences in the AE incidence overall or for any given SOC across quartile exposure ranges. Additionally there were analyses (bimodal) for specific AEs of interest that did not suggest a trend of exposure with the occurrence of these AEs.

Of those AEs reported by ≥10% of subjects, the incidence of any given AE or of all AEs within a given SOC category was not notably different across the exposure quartiles, or did not follow any overall pattern with respect to increasing exposure, with few exceptions, including ALT increased. The AEs of pyrexia, AST increased, hypomagnesemia, fatigue, and asthenia were reported more frequently for subjects in Q4 relative to those in Q1. The reverse was true for subjects in Q1 who generally had a higher prevalence of diarrhea, dyspnea, bacteremia, and neutropenia than did subjects in Q4. Given this critically-ill population, and the variability of AE incidence across the quartile ranges of exposure, these findings are not considered clinically meaningful.

Adverse Events Related to Study Treatment by Posaconazole Plasma Concentration Quartile

Among subjects with available trough plasma POS concentrations, there was a trend toward a higher incidence of drug-related AEs in the highest quartile of POS exposure relative to lower-exposure quartiles 1. Specifically, a higher incidence of drug-related ALT increased, nausea, and vomiting were noted with higher POS exposures relative to lower trough plasma concentrations. While there is a trend of a higher incidence of drug-related AEs in quartile 4 compared with quartile 1 or 2, it is a modest one, and its non-monotonic increase with exposures is not suggestive of a strong PK relationship.

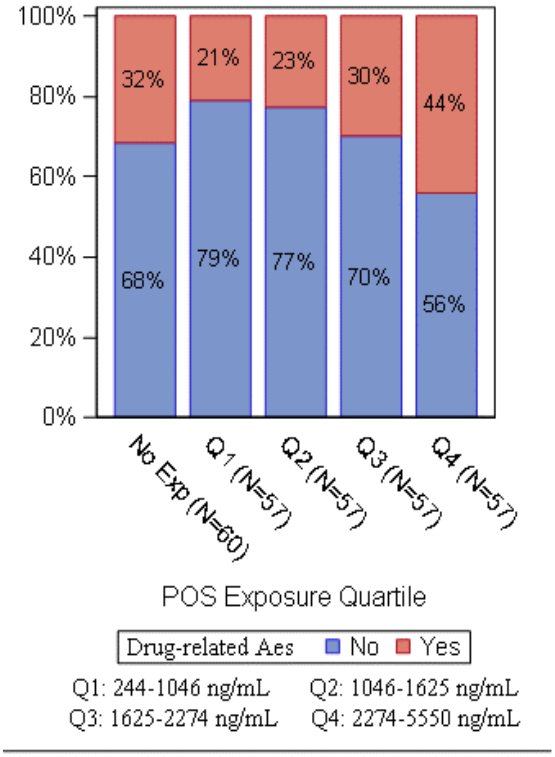


Figure 11 Proportion of Subjects with Treatment-Related AEs by Quartile of Within-Subjects Mean Posaconazole Trough Concentration

This observation is in contrast to that reported for earlier studies of POS IV (Study P05520; MK-5592-059) and POS tablet (Study P05615; MK-5592-065) in which the same dosing regimen was used (300 mg/day after BID dosing on Day 1 with QD dosing thereafter) given as antifungal prophylaxis to patients at high risk for an IFI. Exposure-safety quartile relationships for these 2 earlier studies were evaluated across a similar range of exposures.

For the earlier POS tablet study described above, a quartile analysis (n= 205) found no discernible correlation between POS plasma exposures and safety in terms of AEs or drug-related AEs, including no correlation between higher POS exposure and an increase in hepatic or cardiac AEs. Specifically, the

incidence of drug-related AEs was lower for the fourth highest quartile of exposure when compared with the first lowest quartile of exposure (38% versus 57%).

Exposure-safety findings for the POS IV study P05520 were similar. Overall, the safety profiles in P05520 and P05616 for those subjects who achieved high POS exposures following administration of POS IV and POS tablet, respectively, are consistent with the safety profiles for those subjects who achieve normal/low POS exposures. In these 2 studies, no new safety signals were identified in subjects with high POS exposures, and specific AEs expected to be seen with POS were not more commonly seen in the high-exposure group.

The CHMP noted that, in the POS group, no subject had a drug-related AE that resulted in death

The frequencies and types of SAEs were generally comparable in both treatment groups, with the exception of SAEs of hypokalaemia and haemoptysis, which were reported more frequently in the POS group. Therefore, the Committee asked the MAH to explain this difference and also discuss if these events were the drug-related.

The MAH reviewed the reports of serious adverse events of hypokalaemia and hemoptysis (4 each) in P069. In line with the investigators' assessment, the MAH considered none of this SAEs drug-related. This was endorsed by the CHMP.

The CHMP considered that treatment differences were not observed in the incidence of Tier-1 AEs associated with the SOCs of Nervous System disorders or Psychiatric disorders (POS: 12.2%; VOR: 16.4%). Within the Psychiatric disorders SOC, the most commonly reported Tier-1 AEs were confusional state and hallucination.

The most frequently reported AE in the dermatologic reactions category was rash (approximately 7% in each treatment group).

There were no drug-related AEs within the SOC of Immune System disorders. The incidence of drug-related AEs categorized as Skin and Subcutaneous Tissue disorders was low in both treatment groups.

Comparable incidences of AEs in the Adrenal Steroidogenesis category (i.e. prespecified PTs in the SOCs of Endocrine disorders and Vascular disorders) were reported for subjects in the POS and VOR treatment groups. Hypotension was reported by approximately 7% of subjects in each group.

Two subjects, both in the POS group, had drug-related AEs in either the Endocrine disorder SOC or Vascular disorder SOC. One subject had drug-related adrenal insufficiency, and 1 subject had drug-related hypotension.

The CHMP considered that, in this study, the safety profile of POS was well established.

Among subjects with available trough plasma POS concentrations, there was a trend toward a higher incidence of drug-related AEs in the highest quartile of POS exposure relative to lower-exposure quartiles 1. Specifically, a higher incidence of drug-related ALT increased, nausea, and vomiting were noted with higher POS exposures relative to lower trough plasma concentrations. While there is a trend of a higher incidence of drug-related AEs in quartile 4 compared with quartile 1 or 2. This observation is in contrast to that reported for earlier studies of POS IV (Study P05520; MK-5592-059) and POS tablet (Study P05615; MK-5592-065). According to the MAH, this difference may be attributed, at least in part, to differences in bioavailability between formulations (tablet bioavailability 54% under fasting conditions). It may also reflect that subjects who remained on IV

were more seriously ill and unable to transition to an oral formulation since a similar trend (higher IV concentration) was observed for VOR, which has high oral bioavailability (96%). With regard to an evaluation of the effect of food on POS tablet absorption, the modest (15% to 39%, depending on time point) increase in POS exposure when POS tablets were administered with a meal versus fasting is not considered to be clinically meaningful. A detailed comparison of POS exposure across studies based on a population PK analysis was reported separately.

Laboratory findings

There were comparable rates of hepatic function elevations for the 2 treatment groups. In particular, with regards to the incidence of prespecified Tier-1 hepatic safety event (AT ≥3× ULN and BILI ≥2× ULN and ALP <2× ULN), there was no evidence of an increase in Tier-1 hepatic events for POS compared with VOR (3.9% vs 3.5%, respectively).

Electrocardiogram findings

ECG data were collected in accordance with the protocol, which included stipulation that subjects on IV therapy have their Week 1 ECG performed at the completion of the 90-minute infusion to coincide with the time of anticipated Cmax and plasma sample collection. No clinically meaningful ECG findings were noted at the time of Cmax in subjects on IV therapy; therefore, an exposure-ECG-response analysis was not conducted.

For ECG findings meeting predetermined criteria, POS-treated subjects, relative to VOR-treated subjects, had a lower incidence of QTc >500 msec, QTc increases from baseline >60 msec, and any change in prespecified QTc parameters.

Discontinuation due to adverse events

AEs leading to treatment discontinuation were reported for 33.9% of subjects.

Drug-related AEs leading to treatment discontinuation were reported for 8.0% of subjects. Fewer POS-treated subjects (6.3%) discontinued treatment for a drug-related AE compared with VOR-treated subjects (9.8%). In both groups, drug-related AEs leading to treatment discontinuation were most commonly classified within the SOCs of Investigations, Nervous System disorders, and Psychiatric disorders. The most commonly reported drug-related AE leading to treatment discontinuation in both groups was hallucination (n=3 in each group).

SAEs leading to treatment discontinuation were reported for 27.5% of subjects. The most frequently reported SAEs leading to treatment discontinuation were septic shock (2.8%) and respiratory failure (2.4%) in the POS group, and septic shock (2.8%) and acute myeloid leukaemia (2.8%) in the VOR group.

The CHMP noted that fewer POS-treated subjects (6.3%) discontinued treatment for a drug-related AE compared with VOR-treated subjects (9.8%). The most commonly reported drug-related AE leading to treatment discontinuation in both groups was hallucination (n=3 in each group).

Post marketing experience

POS has been registered and approved in more than 70 countries since its first approval on 25-Oct-2005. Currently there are 3 marketed formulations of POS: oral suspension, delayed-release tablet, and concentrate for solution for IV infusion. There are no records of any registration being revoked or withdrawn for safety reasons. The benefit-risk information on POS received by the MAH's

AE reporting and review system has been summarized in the PSUR and is currently conducted on a 3-year cycle in the EU.

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

As of 25-Oct-2019, there were 6240 AE reports containing 13,091 events (7725 nonserious, 5366 serious) from spontaneous and noninterventional post-marketing study reports in the Company's global safety database. There were no new safety signals identified in the most recent PSUR for POS.

A cumulative analysis of post-marketing AEs, as of 25-Oct-2019, did not identify new safety issues for POS. The safety profile revealed by the current analysis is consistent with those presented in PSURs submitted to date and those in the product label. The overall benefit-risk balance for POS continues to be positive for use in the approved indications. The MAH will continue to monitor the safety of POS through established routine pharmacovigilance processes.

A cumulative analysis of post-marketing AEs, as of 25-Oct-2019, did not identify new safety issues for POS. The overall benefit-risk balance for POS continues to be positive for use in the approved indications. The MAH will continue to monitor the safety of POS through established routine pharmacovigilance processes.

2.5.1. Discussion on clinical safety

The safety findings of this study were consistent with those reported for prior clinical studies of POS in prophylaxis and secondary invasive fungal infection treatment. POS was well tolerated and, while almost all subjects had one or more reported AEs, most frequently these were AEs representing the underlying disease conditions of immunosuppression and hematologic malignancy requiring treatment. The high frequency of co-morbid conditions impedes the ability to identify drug-associated toxicity when considering the overall AE profile. Therefore, an evaluation of drug-related AEs is useful in identifying and comparing drug-associated toxicities between the study treatment.

Overall, drug-related AEs were less frequently reported with POS treatment than with VOR treatment (29.9% vs 40.1% respectively). With regard to specific categories of drug-related AEs, visual and psychiatric disorders were more common with VOR treatment, while hypokalaemia was more common with POS treatment. Comparable rates of gastrointestinal disorders and hepatic disorders were reported across the treatment groups. In addition to the higher rates of drug-related visual and psychiatric AEs among VOR-treated subjects, there was also a higher rate of discontinuation of VOR-treated than POS-treated subjects due to drug-related AEs overall. The lack of tolerance to VOR has been previously reported to limit the ability to complete a necessary course of antifungal therapy, which is of concern when treating a life-threatening infection such as IA. The safety findings for P069 are similar to those reported in the prior comparative study of ISA vs. VOR where VOR-treated subjects had higher rates of drug-related visual and psychiatric AEs, with a rate similar to those reported in this study.

Overall, POS exposure in this study, as measured by trough plasma concentration, was within the range observed in prior clinical trials of POS IV and tablet. In a prior study of POS IV 300 mg QD (BID on Day 1), POS IV administration resulted in a mean trough concentration of 1320 ng/mL at steady state. In a similar study, POS tablet 300 mg QD (BID on Day 1) resulted in a mean trough concentration of 1720 ng/mL at steady state. In the current study, POS plasma trough concentrations were higher throughout the course of study treatment in subjects who received POS exclusively via IV

administration. This difference may be attributed, at least in part, to differences in bioavailability between formulations (tablet bioavailability 54% under fasting conditions. It may also reflect that subjects who remained on IV were more seriously ill and unable to transition to an oral formulation since a similar trend (higher IV concentration) was observed for VOR, which has high oral bioavailability (96%). With regard to an evaluation of the effect of food on POS tablet absorption, the modest (15% to 39%, depending on time point) increase in POS exposure when POS tablets were administered with a meal versus fasting is not considered to be clinically meaningful. A detailed comparison of POS exposure across studies based on a population PK analysis will be reported separately.

Exposure-safety relationships of POS by quartile of exposure were evaluated for all AEs as well as for drug-related AEs. While there was no relationship between exposure and the incidence of reported AEs overall (regardless of investigator-reported relationship), an association was seen between higher exposure (top quartile of exposure) and the incidence of drug-related AEs. This association has not been noted in prior studies of POS IV or tablet in which similar or higher exposures have been achieved. Similarly, with POS oral suspension, no exposure-safety adverse relationship has been noted, although exposures with the oral suspension are generally lower than those achieved with the IV or tablet formulations. A potential contributing factor to the observed association in the current study is that a larger proportion of subjects who were more seriously ill were likely to have been receiving the IV formulation rather than the tablet formulation, and thus would likely have had higher exposures. Furthermore, the severity of their illness would have led to a higher incidence of AEs. No association between POS exposure and Tier 1 AEs, and no relevant effect on QTc at the time of Cmax, was seen. Overall, the safety profile of POS IV and tablet in P069 was similar to that reported in POS product labelling of POS IV, tablet, and oral suspension.

2.5.2. Conclusions on clinical safety

POS is generally well tolerated, with fewer drug-related AEs in POS-treated than in VOR-treated subjects. The overall AE profile of POS-treated subjects in P069 is consistent with the safety profile established in current product labelling of POS IV and tablet and periodic safety reporting for POS IV and tablet.

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.

3. Risk management plan

The MAH submitted an RMP version (16.2, data lock point 01 February 2020, dated 10 September 2020) with this application to support the use of posaconazole for the treatment of invasive aspergillosis in adults, and the update to the safety concerns (important identified risks, important potential risks and missing information) for posaconazole following the completion of the Post Authorisation Efficacy Study in adults (PN069). The summary of significant changes in this RMP are:

RMP Part/Module	Major change(s)
PART I Product Overview	Added 'treatment of invasive aspergillosis' as new indication
PART II Safety Specification	
Module SII Non-clinical part of the safety specification	Updated the clinical implication of safety pharmacology findings in Table SII.1
Module SIII Clinical trial exposure	Updated overall exposure and demographic information
Module SIV Populations not studied in clinical trials	Updated to include exposure from PN069
Module SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP	Removed 6 Important Identified Risks, 7 Important Potential Risks, 1 Missing Information
Module SVII.3.2 Presentation of the Missing Information	Removed Use in patients with hepatic impairment Summary
Module SVIII Summary of safety concerns	Updated safety concerns table
PART III Pharmacovigilance Plan (including Post Authorisation Safety Studies)	
Module III.1 Routine Pharmacovigilance Activities	Removed PN069 as another form of routine pharmacovigilance activities
PART IV Plans for Post Authorisation Efficacy Studies	Updated to reflect completion of PN069
PART V Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)	
Module V.1 Routine Risk Minimization Measures	Updated according to revised safety concerns
Module V.3 Summary of Risk Minimization Measures	Updated according to revised safety concerns
PART VI Summary of the Risk Management Plan by Product	Updated indications and safety concerns

The (main) proposed RMP changes were the following:

PART II SAFETY SPECIFICATION

Module SVII Identified and potential risks

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

The MAH proposes to remove the **important identified risks** 'Elevated liver enzymes', 'Hepatotoxicity', 'Hepatic failure', 'Hepatitis', 'Thrombotic thrombocytopenia purpura', 'Hemolytic uremic syndrome', 'Torsade de Pointes/QTc prolongation', 'Drug interaction', 'Adrenal Insufficiency' and 'Hypokalaemia' as identified risks that are not considered important for inclusion in the RMP, in accordance with GVP Module V (Rev 2), and therefore to remove from the list of safety concerns. The

rationales (summarized) for the proposed changes to the list of safety concerns are briefly presented below.

The MAH proposes to reclassify the **important potential risks** 'Heart failure', 'Myocardial infarction', 'Convulsion', 'Pulmonary haemorrhage', 'Hypertension', 'Venous thrombosis', 'Photopsia', 'Visual brightness' and 'Visual disturbances' as potential risks that are not considered important for inclusion in the RMP, therefore to remove from the list of safety concerns. The rationales (summarized) for the proposed changes to the list of safety concerns are briefly presented below.

The MAH proposes to remove the **Missing Information** 'Use in patients with hepatic impairment' based on the completion of Study PN069. The rationales (summarized) for the proposed changes to the list of safety concerns are briefly presented below.

Important Identified Risks removed from the List of Safety Concerns

Elevated liver enzymes; Hepatotoxicity, Hepatic failure, Hepatitis

Elevated liver enzymes, hepatotoxicity, hepatic failure and hepatitis have been removed from the list of Important Identified Risks. No new safety concerns related to elevated liver enzymes, hepatotoxicity, hepatic failure and hepatitis have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative postmarketing data through 01-Feb-2020. No additional PV activities are ongoing or planned as the risk has been well-characterised and the risk is mitigated by routine risk minimization measures provided in the Product Information including the recommendation for liver function monitoring in the Special warnings and precautions of the SmPC and as an adverse reaction seen in clinical trials and/or post-marketing use under Undesirable effects in the SmPC.

Since routine PV activities and routine risk minimization measures are considered to be sufficient to support a favourable benefit-risk profile, no new clinical studies will be performed to further characterise this identified risk. Therefore, elevated liver enzymes, hepatotoxicity, hepatic failure and hepatitis have been removed from the list of Important Identified Risks. The MAH will continue to monitor elevated liver enzymes, hepatotoxicity, hepatic failure and hepatitis through routine PV.

Thrombotic Thrombocytopenic Purpura and Haemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura and haemolytic uremic syndrome have been removed from the list of Important Identified Risks. No new safety concerns related to thrombotic thrombocytopenic purpura and haemolytic uremic syndrome have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative postmarketing data through 01-Feb-2020. No additional PV activities are ongoing or planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, which lists thrombotic thrombocytopenic purpura and haemolytic uremic syndrome as rare adverse reactions reported in clinical trials and/or post-marketing use in the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as these routine measures are considered to be sufficient. No further clinical trials or non-interventional studies will be performed to further characterise this identified risk. Therefore, thrombotic thrombocytopenic purpura and haemolytic uremic syndrome have been removed from the list of Important Identified Risks. The MAH will continue to monitor thrombotic thrombocytopenic purpura and haemolytic uremic syndrome through routine PV.

Torsade de Pointes and QTc prolongation

Torsade de Pointes and QTc prolongation have been removed from the list of Important Identified Risks. No new safety concerns related to torsade de pointes and QTc prolongation have been identified

in the recently completed IA treatment study (PN069), and a review of the cumulative postmarketing data through 01-Feb-2020. No additional PV activities are ongoing or planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, including medications that should not be co-administered with posaconazole due to increased risk of QTc prolongation or torsades de pointes in the Contraindications section of the SmPC, the recommendation to use with caution in patients with pro-arrhythmic conditions in the Special warnings and precautions for use section of the SmPC, and torsade de pointes and QTc prolongation as uncommon adverse reactions seen in clinical trials and/or post-marketing use under Undesirable effects in the SmPC.

No additional risk minimization activities are planned as these routine measures are considered to be sufficient. No further clinical trials or non-interventional studies will be performed to further characterise this identified risk. Therefore, torsade de pointes and QTc prolongation have been removed from the list of Important Identified Risks. The MAH will continue to monitor torsade de pointes and QTc prolongation through routine PV.

Drug Interaction

Drug interaction has been removed from the list of Important Identified Risks. No new safety concerns related to drug interaction have been identified in the recently completed IA treatment study (PN069) and the review of cumulative postmarketing data through 01-Feb-2020. No additional PV activities are ongoing or planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk of drug interactions pertaining to CYP3A inhibition in particular is mitigated by routine risk minimization activities that are provided in the Product Information including information regarding medications that are contraindicated for coadministration with posaconazole in the Contraindications section of the SmPC and information regarding use with other medications metabolized by CYP3A4 under Special warnings and precautions for use in the SmPC.

No additional risk minimization activities are planned as these routine measures are considered to be sufficient. No further clinical trials or non-interventional studies will be performed to further characterise this identified risk. Therefore, drug interaction has been removed from the list of Important Identified Risks. The MAH will continue to monitor drug interaction through routine PV.

Adrenal Insufficiency

Adrenal insufficiency has been removed from the list of Important Identified Risks. No new safety concerns related to adrenal insufficiency have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative post-marketing data through 01-Feb-2020. No additional PV activities are planned as the risk has been well-characterised and routine PV activities support a favorable risk-benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, which lists adrenal insufficiency as an adverse reaction reported in clinical trials and/or post-marketing use under the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as these routine measures are considered to be sufficient. No further clinical trials or non-interventional studies will be performed to further characterize this identified risk. Therefore, adrenal insufficiency has been removed from the list of Important Identified Risks. The MAH will continue to monitor adrenal insufficiency through routine PV.

Hypokalaemia

Hypokalaemia has been removed from the list of Important Identified Risks. No new safety concerns related to hypokalaemia have been identified in the recently completed IA treatment study (PN069), and a review of cumulative post-marketing data through 01-Feb-2020. No additional PV activities are planned as the risk has been well-characterised and routine PV activities support a favourable risk-

benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, which lists hypokalaemia as a common adverse reaction reported in clinical trials and/or post-marketing use under the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as these routine measures are considered to be sufficient. No further clinical trials or non-interventional studies will be performed to further characterise this identified risk. Therefore, hypokalaemia has been removed from the list of Important Identified Risks. The MAH will continue to monitor hypokalaemia through routine PV.

Important Potential Risks removed from the List of Safety Concerns

Heart failure

Heart failure has been removed from the list of Important Potential Risks. No new safety concerns related to heart failure have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative postmarketing data through 01-Feb-2020. No additional PV activities are planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, which lists heart failure as a rare adverse reaction reported in clinical trials and/or post-marketing use under the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as routine measures are considered to be sufficient. No further clinical trials or non-interventional studies will be performed to further characterise this potential risk. Therefore, heart failure has been removed from the list of Important Potential Risks. The MAH will continue to monitor heart failure through routine PV.

Myocardial Infarction

Myocardial Infarction has been removed from the list of Important Potential Risks. No new safety concerns related to myocardial infarction have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative post-marketing data through 01-Feb-2020. No additional PV activities are planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, which lists myocardial infarction as a rare adverse reaction reported in clinical trials and/or post-marketing use under the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as routine measures are considered to be sufficient. No clinical trials or non-interventional studies will be performed to further characterize this potential risk. Therefore, myocardial infarction has been removed from the list of Important Potential Risks. The MAH will continue to monitor myocardial infarction through routine PV.

Convulsion

Convulsion has been removed from the list of Important Potential Risks. No new safety concerns related to convulsion have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative post-marketing data through 01-Feb-2020. No additional PV activities are ongoing or planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, which lists convulsion as an uncommon adverse reaction reported in clinical trials and/or post-marketing use under the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as routine measures are considered to be sufficient. No clinical trials or non-interventional studies will be performed to further characterise this potential risk. Therefore, convulsion has been removed from the list of Important Potential Risks. The MAH will continue to monitor convulsion through routine PV.

Pulmonary Haemorrhage

Pulmonary Haemorrhage has been removed from the list of Important Potential Risks. A review of safety data from the recently completed IA treatment study (PN069) and the cumulative post-marketing data through 01-Feb-2020 did not support the initial supposition of potential association between pulmonary haemorrhage and use of posaconazole. The underlying medical conditions such as pulmonary fungal infection and coagulopathy appear to be the more probable causes of pulmonary haemorrhage in patients with haematological malignancy treated with posaconazole. The MAH will continue to monitor reports of pulmonary haemorrhage through routine PV.

Hypertension

Hypertension has been removed from the list of Important Potential Risks. No new safety concerns related to hypertension have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative post-marketing data through 01-Feb-2020. No additional PV activities are ongoing or planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, which lists hypertension as a common adverse reaction reported in clinical trials and/or post-marketing use under the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as routine measures are considered to be sufficient. No clinical trials or non-interventional studies will be performed to further characterise this potential risk. Therefore, hypertension has been removed from the list of Important Potential Risks. The MAH will continue to monitor hypertension through routine PV.

Venous Thrombosis

Venous Thrombosis has been removed from the list of Important Potential Risks. No new safety concerns related to venous thrombosis have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative post-marketing data through 01-Feb-2020. No additional PV activities are ongoing or planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk is mitigated by routine risk minimization activities provided in the Product Information, which lists venous thrombosis as a rare adverse reaction reported in clinical trials and/or post-marketing use under the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as routine measures are considered to be sufficient. No clinical trials or non-interventional studies will be performed to further characterise this potential risk. Therefore, venous thrombosis has been removed from the list of Important Potential Risks. The MAH will continue to monitor venous thrombosis through routine PV.

Photopsia, Visual Brightness and Visual Disturbances

Photopsia, Visual Brightness, and Visual Disturbances has been removed from the list of Important Potential Risks. No new safety concerns related to photopsia, visual brightness, and visual disturbances have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative post-marketing data through 01-Feb-2020. No additional PV activities are ongoing or planned as the risk has been well-characterised and routine PV activities support a favourable risk-benefit profile. The risk is mitigated by routine risk minimization activities that are provided in the Product Information, which lists eye disorders under adverse reactions reported in clinical trials and/or post-marketing use under the Undesirable effects section of the SmPC. No additional risk minimization activities are planned as routine measures are considered to be sufficient. No further clinical trials or non-interventional studies will be performed to further characterise this potential risk. Therefore, photopsia, visual brightness, and visual disturbances has been removed from the list of Important Potential Risks. The MAH will continue to monitor Photopsia, Visual Brightness, and Visual Disturbances through routine PV.

The MAH's proposal to remove the important *identified* risks 'Elevated liver enzymes', 'Hepatotoxicity', 'Hepatic failure', 'Hepatitis', 'Thrombotic thrombocytopenia purpura', 'Haemolytic uremic syndrome', 'Torsade de Pointes/QTc prolongation', 'Drug interaction', 'Adrenal Insufficiency' and 'Hypokalaemia' from the summary of safety concerns as well as the rationales for the proposed changes was endorsed. Routine risk minimisation measures are in place to sufficiently address the risks of ''Elevated liver enzymes', 'Hepatotoxicity', 'Hepatic failure', 'Hepatitis', 'Thrombotic thrombocytopenia purpura', 'Haemolytic uremic syndrome', 'Torsade de Pointes/QTc prolongation', 'Drug interaction', 'Adrenal Insufficiency' and 'Hypokalaemia' is included as an adverse drug reaction in SmPC section 4.3, 4.4, 4.5 and 4.8. In addition, routine pharmacovigilance is sufficient to further characterise these risks. Moreover, according to the revised GVP Module V, risks that do not need further evaluation as part of pharmacovigilance plan or additional risk minimisation activities are recommended to be removed from the list of safety concerns.

The MAH's proposal to remove the important *potential* risks 'Heart failure', 'Myocardial infarction', 'Convulsion', 'Pulmonary haemorrhage', 'Hypertension', 'Venous thrombosis', 'Photopsia', 'Visual brightness' and 'Visual disturbances' from the summary of safety concerns was also endorsed. Routine pharmacovigilance is sufficient to characterise these risks. No new safety concerns have been identified in the recently completed IA treatment study (PN069), and a review of the cumulative post-marketing data through 01-Feb-2020. Moreover, according to the revised GVP Module V, risks that do not need further evaluation as part of pharmacovigilance plan or additional risk minimisation activities are recommended to be removed from the list of safety concerns.

Missing information removed from the List of Safety Concerns

Use in patients with hepatic impairment

Use in patients with hepatic impairment has been removed from the list of Missing Information. No new safety concerns related to use in patients with hepatic impairment have been identified in the recently completed IA treatment study (PN069), as well as a review of post-marketing data through 01-Feb-2020. The safety concern is mitigated by routine risk minimization activities that are provided in the Product Information including the recommendation to exercise caution when posaconazole is used in patients with hepatic impairment in the Posology and method of administration, Special warnings and precautions for use and Pharmacokinetic properties sections of the SmPC.

No additional PV and risk minimization activities are ongoing or planned as routine measures are considered to be sufficient. No new clinical studies will be performed in patients with hepatic impairment to further address this missing information. Therefore, use in patients with hepatic impairment has been removed from the list of Missing Information. The MAH will continue to monitor use in patients with hepatic impairment through routine PV.

The MAH's proposal to remove 'Use in patients with hepatic impairment' classified as missing information was endorsed. No new safety concerns related to use in patients with hepatic impairment have been identified in the recently completed IA treatment study (PN069), as well as a review of post-marketing data through 01-Feb-2020. No additional PV and risk minimization activities are ongoing or planned as routine measures are considered to be sufficient. No new clinical studies will be performed in patients with hepatic impairment to further address this missing information. Moreover, according to the revised GVP Module V, risks that do not need further evaluation as part of pharmacovigilance plan or additional risk minimisation activities are recommended to be removed from the list of safety concerns.

Module SVIII Summary of the Safety Concerns

Table SVIII.1 Summary of the Safety Concerns (MAH proposal, removed in red font and strike through)

Summary of Safety Concerns	
Important identified risks	~~Hepatic : Elevated liver enzymes; Hepatotoxicity; Hepatic failure; Hepatitis~~ ~~Blood : Thrombotic thrombocytopenia purpura; Hemolytic uremic syndrome~~ ~~Cardiac : Torsade de Pointes/QTc prolongation~~ ~~General : Drug interaction~~ ~~Endocrine : Adrenal Insufficiency~~ ~~Metabolism :Hypokalaemia~~ None*
Important potential risks	~~Cardiac : Heart failure; Myocardial infarction~~ ~~CNS : Convulsion~~ ~~Respiratory : Pulmonary haemorrhage~~ ~~Vascular : Hypertension; Venous thrombosis~~ ~~Visual : Photopsia; Visual brightness; Visual disturbances~~ None*
Missing information	~~Use in patients with hepatic impairment~~ Experience in children

* 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.

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

The MAH removed the PN069 study from the Other Forms of Routine Pharmacovigilance Activities for Safety Concerns. This is endorsed.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

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

The MAH states that routine risk minimisation activities are sufficient to manage the safety concerns of Noxafil. No additional risk minimisation measures are proposed.

The PRAC considered that the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

3.1. Overall conclusion on the RMP

The changes to the RMP are acceptable.

4. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1 and 5.2, 6.2 and 6.6 of the SmPC were updated. The Package Leaflet (PL) is updated accordingly.

Some editorial PI adjustments were carried out to the suspension SmPC:

The statement "*Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care in the high-risk patients for which posaconazole is indicated as prophylaxis"* was moved in the oral formulation SmPCs so to appear at the beginning of Section 4.2, as it does in the IV SmPC. The following grammatical amendment to the sentence was also carried out:

*Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care **of** ~~in the~~ high-risk patients for which posaconazole is indicated as prophylaxis.*

As a result of QRD comments, 'dextrose' (not a standard term in the EU pharmacopoeia) was changed into 'glucose' to comply with the compilation of QRD decisions on use of terms, impacting Sections 6.2 and 6.6 of the SmPC and the relevant section of the PL for the IV formulation.

Additionally, the opportunity was taken to update to the clinical breakpoint of *Candida dubliniensis* in the Noxafil PI according to the published EUCAST clinical breakpoints.

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

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

IA is a serious, life-threatening disease among patients with prolonged and/or severe impairment of the immune system. Without the initiation of antifungal therapy, the acute mortality rate has been shown to exceed 85%. *Aspergillus fumigatus* is the most common cause of IA.

5.1.2. Available therapies and unmet medical need

Current guidelines for the primary treatment of IA recommend early initiation of antifungal therapy while definitive diagnostic evaluation is in progress. Guidelines recommend VOR and/or ISA for the primary treatment of IA, with liposomal amphotericin B being the first alternative and POS, as well as echinocandins, mainly recommended for salvage treatment. Given the side effects and DDI of VOR and ISA, and the high underlying mortality of IA, a need exists for additional therapies that can overcome the limitations of currently approved IA therapies.

5.1.3. Main clinical studies

POS is currently indicated for refractory IA or for patients with intolerance to 1st line therapy of IA. The extension of indication of POS for the first-line treatment of IA is based on the non-inferiority study P069. This study was performed in subjects with possible, probable or proven IA, and compare POS vs the first-line treatment VOR.

5.2. Favourable effects

POS is non-inferior to VOR for the first-line treatment of adults with IA, based on the rate of all-cause mortality in the ITT population and the global clinical response in the FAS population (i.e. subjects with probable or proven IA) after 6 weeks of treatment. Likewise, non-inferiority was also observed at Week 12. Subgroups analysis support this non-inferiority.

In vitro data from study P069 and surveillance studies show that POS has comparable activity to VOR, ISA, and ITR against *Aspergillus* spp.

5.3. Uncertainties and limitations about favourable effects

There is no relevant efficacy data in paediatric subjects, with only 5 adolescents included in this study.

Only 58% of the baseline IA diagnosis was probable or proven, and a non-negligible proportion of IA diagnosis (14%) cannot be determined at baseline by the CAC. This suggest that an undetermined number of subjects in this study did not actually have IA.

When considering the mortality due to IA (according to the CAC), the results are not at the advantage of POS. At each time points (Day 42, Day 84 and Day 114), the mortality attributed to IA is more frequent in POS group (51.6%, 39.3% and 35.9%, respectively) compared to VOR group (31.3%, 28% and 30.4%, respectively). However, a higher number of indeterminate attributions of death is present in VOR group (56.3% vs 35.5% at Day 42), which could bias the estimation of the mortality due to IA.

The mortality in Asian population is higher in POS group (16%, 10/62) than VOR group (6.7%, 4/60). This higher mortality rate is also observed within the FAS population (POS: 21% (9/43); VOR: 6.5% (3/46)).

Surveillance studies show that NWT strains of *A. fumigatus* have increased in Europe since 10 years, reaching 4.5% of strains resistant to VOR and POS in 2018.

5.4. Unfavourable effects

Overall, drug-related AEs were less frequently reported with POS treatment than with VOR treatment (29.9% vs 40.1% respectively). With regard to specific categories of drug-related AEs, visual and psychiatric disorders were more common with VOR treatment, while hypokalaemia was more common with POS treatment.

Comparable rates of gastrointestinal disorders and hepatic disorders were reported across the treatment groups. In addition to the higher rates of drug-related visual and psychiatric AEs among VOR-treated subjects, there was also a higher rate of discontinuation of VOR-treated than POS-treated subjects due to drug-related AEs overall.

5.5. Uncertainties and limitations about unfavourable effects

Exposure-safety relationships of POS by quartile of exposure were evaluated for all AEs as well as for drug-related AEs. While there was no relationship between exposure and the incidence of reported AEs overall (regardless of investigator-reported relationship), an association was seen between higher exposure (top quartile of exposure) and the incidence of drug-related AEs. This association has not been noted in prior studies of POS IV or tablet in which similar or higher exposures have been achieved. Similarly, with POS oral suspension, no exposure-safety adverse relationship has been noted, although exposures with the oral suspension are generally lower than those achieved with the IV or tablet formulations. A potential contributing factor to the observed association in the current study is that a larger proportion of subjects who were more seriously ill were likely to have been receiving the IV formulation rather than the tablet formulation, and thus would likely have had higher exposures.

5.6. Effects Table

Table 21: Effects Table for Noxafil in the first-line treatment of IA

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Clinical improvement and decrease of mortality in subjects with IA	All-cause mortality	% of all-cause mortality at Day 42 (ITT population)	POS IV or tablets	VOR IV or tablets	POS: 15.3% VOR: 20.6% Difference: -5.3% 95%CI: -11.6, 1.0	Study P069
	Global clinical response according to independent CAC	% of treatment success at Week 6 (FAS population = probable or proven IA)			POS: 44.8% VOR: 45.6% Difference: -0.6% 95%CI: -11.2, 10.1	
Decrease of mortality due to IA?	Death attributed to IA by the CAC	% of deaths attributed to IA at Day 42 (FAS population)	POS IV or tablets	VOR IV or tablets	POS: 51.6% VOR: 31.3% Difference: 20.4% 95%CI: -4.1, 42.7 Probable bias due to the high number of indeterminate attribution of death (POS: 35.5%, VOR: 56.3%)	Study P069
Unfavourable Effects						
Hepatic Safety Events	ASAT increased ALAT increased	%	POS IV or tablets	VOR IV or tablets	POS (3.8%) VOR (3.5%)	Study P069
Central Nervous System Event - Visual Safety Events	Hallucination Vision blurred	%	POS IV or tablets	VOR IV or tablets	POS (1.4%) VOR (4.2%) POS (1.0%) VOR (3.5%)	Study P069

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

IA is a severe disease with high level of mortality (over 85% without antifungal therapy). Study P069 has demonstrated that POS is non-inferior to the reference VOR for the first-line treatment of IA in adults, with similar mortality rate (15-20%) and treatment success (45%) at 6 weeks after the beginning of treatment.

The overall adverse event (AE) profile in P069 was reflective of the known AE profile of POS IV and tablet, as described in product labeling, and was consistent with a critically ill study population. Furthermore, the types and incidences of AEs, drug-related AEs, and serious adverse events (SAEs) in the POS treatment group in P069 were similar to those reported in previous clinical studies of POS IV and tablet despite P069 having a longer duration of treatment (average therapy duration of >60 days for the treatment of IA) compared with previous studies of POS IV and tablet (average therapy durations of <30 days in a prophylaxis setting).

5.7.2. Balance of benefits and risks

POS and VOR are both azole antifungals effective on the majority of strains of *Aspergillus*. No relevant efficacy difference between these treatments has been demonstrated. Safety and DDI considerations should be taken into account for the choice of first-line treatment of Invasive Aspergillosis.

Considering the limited available therapeutic options and the high mortality rate of such infection, the benefit-risk balance for this extension of indication of POS in the first-line treatment of Invasive Aspergillosis in adults is considered positive.

5.8. Conclusions

The overall B/R of Noxafil is positive.

6. Recommendations

Outcome

Based on the review of the submitted data, this application regarding the following change:

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

Extension of indication to include primary treatment of invasive aspergillosis in adults for Noxafil gastroresistant tablet and concentrate for solution for infusion as result of conclusion of Study P069 (a Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 6.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.2 of the RMP was approved with this procedure.

is recommended for approval.

Amendments to the marketing authorisation

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