NDA Multidisciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	sNDAs 207500/S-015; 207501/S-013
Priority or Standard	Priority
Submit Date(s)	June 9, 2023
Received Date(s)	June 9, 2023
PDUFA Goal Date	December 9, 2023
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	See electronic signature date
Established/Proper Name	Isavuconazonium sulfate
Trade Name	Cresemba
Pharmacologic Class	Azole antifungal
Applicant	Astellas Pharma US, Inc.
Dosage form	Capsules (NDA 207500), Intravenous (NDA 207501)
Applicant Proposed Dosing Regimen	Cresemba for Injection, 372 mg/vial: • (b) (4) • For (b) (4) kg, loading dose of 372 mg IV every 8 h for 6 doses followed by maintenance dose of 372 mg IV daily Cresemba capsules, 74.5 mg: • For (b) (4) kg, loading dose of two capsules (149 mg) orally every 8 h for 6 doses followed by maintenance dose of two capsules (149 mg) daily • For (b) (4) kg, loading dose of three capsules (223.5 mg) orally every 8 h for 6 doses followed by maintenance dose of three capsules (223.5 mg) daily • For (b) (4) kg, loading dose of four capsules (298 mg) orally every 8 h for 6 doses followed by maintenance dose of four capsules (298 mg) daily • For (b) (4) kg, loading dose of five capsules (372 mg) orally every 8 h for 6 doses followed by maintenance dose of five capsules (372 mg) daily
Applicant Proposed Indication(s)/Population(s)	Treatment of Invasive Aspergillosis and Invasive Mucormycosis in pediatric patients (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Cresemba for Injection: • Treatment of invasive aspergillosis and invasive mucormycosis in pediatric patients 1 year of age and older

	Cresemba capsules: • Treatment of invasive aspergillosis and invasive mucormycosis in pediatric patients 6 years of age and older who weigh 16 kg and greater
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	721798004 |Invasive aspergillosis (disorder)| 76627001 |Mucormycosis (disorder)|
Recommended Dosing Regimen	Cresemba for Injection, 372 mg/vial: • For 1 year to <3 years of age and body weight <18 kg, loading dose of 15 mg/kg IV every 8 h for 6 doses followed by maintenance dose of 15 mg/kg IV daily • For 3 years to <18 years of age: — For <37 kg, loading dose of 10 mg/kg IV every 8 h for 6 doses followed by maintenance dose of 10 mg/kg IV daily — For ≥37 kg, loading dose of 372 mg IV every 8 h for 6 doses followed by maintenance dose of 372 mg IV daily Cresemba capsules, 74.5 mg: • For 6 years to <18 years of age: — For 16 to <18 kg, loading dose of two capsules (149 mg) orally every 8 h for 6 doses followed by maintenance dose of two capsules (149 mg) daily — For 18 to <25 kg, loading dose of three capsules (223.5 mg) orally every 8 h for 6 doses followed by maintenance dose of three capsules (223.5 mg) daily — For 25 to <32 kg, loading dose of four capsules (298 mg) orally every 8 h for 6 doses followed by maintenance dose of four capsules (298 mg) daily — For ≥32 kg, loading dose of five capsules (372 mg) orally every 8 h for 6 doses followed by maintenance dose of five capsules (372 mg) daily • Cresemba capsules are not intended for use in pediatric patients <6 years of age

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multidisciplinary Review and Evaluation

Regulatory Project Manager	Alison Rodgers
Chief, Regulatory Project Management Staff	Gregory DiBernardo
Nonclinical Reviewer	Owen McMaster, PhD
Nonclinical Supervisor	Terry Miller, PhD
Clinical Microbiology Reviewer	Shukal Bala, PhD
Clinical Microbiology Team Leader	Avery Goodwin, PhD
Office of Clinical Pharmacology Reviewer(s)	Anthony Nicasio, PharmD
Office of Clinical Pharmacology Reviewer (s)	Tajhia Whigham, PharmD
Office of Clinical Pharmacology Reviewer (s)	Miyoung Yoon, PhD
Office of Clinical Pharmacology Team Leader	Dakshina Chilukuri, PhD
Office of Clinical Pharmacology Team Leader	Justin Earp, PhD
Office of Clinical Pharmacology Team Leader	Yuching Yang, PhD
Clinical Reviewer	Shrimant Mishra, MD
Clinical Team Leader	Heidi Smith, MD, PhD
Statistical Reviewer	Cheryl Dixon, PhD
Statistical Team Leader	Daniel Rubin, PhD
Cross-Disciplinary Team Leader	Heidi Smith, MD, PhD
Associate Director for Labeling	Abimbola Adebowale, PhD
Deputy Division Director	Dmitri Iarikov, MD, PhD
Division Director	Peter Kim, MD, MS

Additional Reviewers of Application

OPQ	Jason Deck, PhD, David Lewis, PhD, Anh-Thy Ly, PharmD, Ramesh Gopalaswamy, PhD
Microbiology	Shukal Bala, PhD, Avery Goodwin, PhD
OPDP	Syed Qumerunnisa, PharmD, Sam Skariah, PharmD, RAC
DPMH	Carla Epps, MD, Shamir Tuchman, MD, Evangela Covert, BS
OSE	Amy Chung, MS
OSE/DMEPA	Deborah Myers, RPh, MBA, Valerie Vaughan, PharmD,
DMPP	Lonice Carter, MS, RN, CNL, Marcia Williams, PhD

Abbreviations: DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Owen McMaster, PhD	OID/DPTID	Sections: 5	**Select one:** __X_ Authored ___ Approved
	Signature: Owen G. Mcmaster -S Digitally signed by Owen G. Mcmaster -S Date: 2023.12.06 11:56:36 -05'00'			
Nonclinical Supervisor	Terry Miller, PhD	OID/DPTID	Sections: 5	**Select one:** ___ Authored _X__ Approved
	Signature: Terry J. Miller -S Digitally signed by Terry J. Miller -S Date: 2023.12.06 12:38:46 -05'00'			
Clinical Microbiology Reviewer	Shukal Bala, PhD	OID/DAI	Sections: 4.3	**Select one:** _X__ Authored ___ Approved
	Signature: Shukal Bala -S Digitally signed by Shukal Bala -S Date: 2023.12.06 14:27:10 -05'00'			
Clinical Microbiology Team Leader	Avery Goodwin, PhD	OID/DAI	Sections: 4.3	**Select one:** ___ Authored _X__ Approved
	Signature: Avery C. Goodwin -S Digitally signed by Avery C. Goodwin -S Date: 2023.12.06 16:36:52 -05'00'			

Product Quality Team Leader	Ramesh Gopalaswamy, PhD	OPQ/OLDP/DPMAI/PMBII	Sections: 4.2	**Select one:** ___ Authored _X__ Approved
	Signature: Ramesh Gopalaswamy -S Digitally signed by Ramesh Gopalaswamy -S Date: 2023.12.06 15:51:39 -05'00'			
Clinical Pharmacology Reviewer	Anthony Nicasio, PharmD	OTS/OCP/DIDP	Sections: 6, 11, 15.4.1, 15.4.2	**Select one:** __x_ Authored ___ Approved
	Signature: Anthony M. Nicasio -S Digitally signed by Anthony M. Nicasio -S Date: 2023.12.06 15:03:50 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Dakshina Chilukuri, PhD	OTS/OCP/DIDP	Section: 6, 11, 15.4.1, 15.4.2, 15.4.3	**Select one:** ___ Authored × Approved
	Signature: Dakshina M. Chilukuri -S	Digitally signed by Dakshina M. Chilukuri -S Date: 2023.12.06 15:15:00 -05'00'		
Pharmacometrics Reviewer	Tajhia Whigham, PharmD	OTS/OCP/DIDP	Section: 15.4.3, 15.4.4	**Select one:** _X_ Authored ___ Approved
	Signature: Tajhia L. Whigham -S	Digitally signed by Tajhia L. Whigham -S Date: 2023.12.07 08:26:32 -05'00'		
Pharmacometrics Team Leader	Justin Earp, PhD	OTS/OCP/DIDP	Section: 15.4.3, 15.4.4	**Select one:** ___ Authored _x__ Approved
	Signature: Justin C. Earp -S	Digitally signed by Justin C. Earp -S Date: 2023.12.07 08:30:11 -05'00'		
PBPK Reviewer	Miyoung Yoon, PhD	OTS/OCP/DPM	Section: 15.4.5, 15.4.6	**Select one:** _x__ Authored ___ Approved
	Signature: Miyoung Yoon -S	Digitally signed by Miyoung Yoon -S Date: 2023.12.07 08:36:55 -05'00'		

PBPK Team Leader	Yuching Yang, PhD	OID/OCP/DPM	Sections: 15.4.5, 15.4.6	**Select one:** ___ Authored _x__ Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2023.12.07 10:42:20 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Shrimant Mishra, MD	OID/DAI	Sections: 1, 2, 8.2	**Select one:** _ _X_ Authored ___ Approved
	Signature: Shrimant Mishra -S Digitally signed by Shrimant Mishra -S Date: 2023.12.06 12:55:29 -05'00'			
Cross Disciplinary Clinical Team Leader	Heidi Smith, MD, PhD	OID/DAI	Sections: 1, 9-13 (authored), 1-15 (approved)	**Select one:** _x_ Authored _x__ Approved
	Signature: Heidi L. Smith -S Digitally signed by Heidi L. Smith -S Date: 2023.12.06 12:48:30 -05'00'			
Division Director (Clinical)	Peter Kim, MD, MS	OID/DAI	Sections: 1-15	**Select one:** ___ Authored X___Approved
	Signature: Peter W. Kim -S Digitally signed by Peter W. Kim -S Date: 2023.12.08 06:37:36 -05'00'			
Deputy Division Director (Clinical)	Dmitri Iarikov, MD, PhD	OID/DAI	Sections: 1-15	**Select one:** ___ Authored _X___ Approved
	Signature: Dmitri E. Iarikov -S Digitally signed by Dmitri E. Iarikov -S Date: 2023.12.07 11:05:13 -05'00'			

Statistical Reviewer	Cheryl Dixon, PhD	OB/DBIV	Sections: 8.1, 8.3	**Select one:** _X__ Authored ___ Approved
	Signature: Cheryl A. Dixon -S Digitally signed by Cheryl A. Dixon -S Date: 2023.12.06 15:41:49 -05'00'			
Secondary Statistical Reviewer	Daniel Rubin, PhD	OB/DBIV	Sections: 8.1, 8.3	**Select one:** ___ Authored __X_ Approved
	Signature: Daniel Rubin -S Digitally signed by Daniel Rubin -S Date: 2023.12.06 15:46:20 -05'00'			
Regulatory Project Manager	Alison Rodgers	DRO-ID/DAI	Sections: 3	**Select one:** __X_ Authored ___ Approved
	Signature: Alison K. Rodgers -S Digitally signed by Alison K. Rodgers -S Date: 2023.12.07 07:47:57 -05'00'			
Chief, Regulatory Project Management Staff	Gregory DiBernardo	DRO-ID/DAI Chief	Sections: 3	**Select one:** ___ Authored ___ Approved
	Signature: Gregory Dibernardo -S Digitally signed by Gregory Dibernardo -S Date: 2023.12.07 08:17:29 -05'00'			
Associate Director for Labeling	Abimbola Adebowale, MS, PhD	OID/DAI	Sections: 11	**Select one:** _X Authored __X_ Approved
	Signature: Abimbola O. Adebowale -S Digitally signed by Abimbola O. Adebowale -S Date: 2023.12.06 16:01:59 -05'00'			

Glossary

AC	adjudication committee
ACM	all-cause mortality
ALT	alanine transaminase
APP	All Pediatric Population
AST	aspartate transaminase
AUCR	area under the concentration-time curve ratios
AUC_{ss}	steady-state area under the curve
BA	bioavailability
CL	clearance
DDI	drug-drug interaction
DMPP	Division of Medical Policy Programs
DSMB	Data Safety Monitoring Board
EBE	Empirical Bayes Estimates
ECG	electrocardiogram
EORTC/MSG	European Organization for Research and Treatment of Cancer/Mycoses Study Group
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
GM	galactomannan
IA	invasive aspergillosis
ICH	International Conference on Harmonisation
IFD	invasive fungal disease
IM	invasive mucormycosis
IR	information request
ISS	integrated summary of safety
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
NCA	noncompartmental analysis
NDA	new drug application
NG	nasogastric
OSIS	Office of Study Integrity and Surveillance
PBPK	physiologically based pharmacokinetics
PI	prescribing information
PK	pharmacokinetics
popPK	population PK

PWR	Pediatric Written Request
QC	quality control
QD	once daily
RSE	relative standard error
SAE	serious adverse event
SAF	safety analysis set
TEAE	treatment emergent adverse event
TQT	thorough QT
ULN	upper limit of normal
USPI	United States Prescribing Information

1 Executive Summary

1.1. Product Introduction

Cresemba (isavuconazonium sulfate) is a prodrug of the azole antifungal isavuconazole approved for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) in adults. Cresemba for injection is available as a lyophilized powder for intravenous use (NDA 207501) and Cresemba oral capsules are available in two strengths (74.5 mg of isavuconazonium sulfate and 186 mg of isavuconazonium sulfate; NDA 207500). Cresemba for injection is also approved for administration via nasogastric tube.

The safety and efficacy of Cresemba for the treatment of IA and IM was established in adults based on data from a single adequate and well-controlled non-inferiority trial of IA treatment and a single-arm study of IM treatment compared with untreated historical controls. Since Cresemba's approved indications have Orphan Drug Designation, there was no requirement for Pediatric Research Equity Act postmarket requirements when the NDAs were approved in 2015. In 2017, the Applicant submitted a Proposed Pediatric Study Request for studies to evaluate the pharmacokinetics (PK), safety, and efficacy of Cresemba in pediatric patients 1 year to <18 years of age. FDA issued a Pediatric Written Request (PWR) to evaluate isavuconazonium for the treatment of IA and IM that included two studies: a phase 1 open-label PK and safety study of intravenous (IV) Cresemba in pediatric patients who may benefit from anti-mold prophylaxis (Study 1) and a phase 2 non-comparative PK, safety, and efficacy study of IV and/or oral Cresemba for treatment of IA or IM in pediatric patients (Study 2). The PWR was amended in 2022 to extend the time frame for submission of the final pediatric study reports.

The current efficacy supplements (NDA 207501/S-013 for Cresemba for injection and NDA 207500/S-015 for Cresemba capsules) were submitted in response to the PWR and propose to add pediatric patients 1 year to <18 years of age to the approved indications for the treatment of IA and IM. Of note, the Applicant requested pediatric exclusivity determination. The submission contains data from Study 1 (maximum treatment duration of 28 days for prophylaxis) and Study 2 (maximum treatment duration of 84 days for IA and 180 days for IM). The studies do not contain data from oral administration of Cresemba capsules in patients less than 6 years of age or nasogastric administration of Cresemba for injection in any pediatric patients.

The completed studies met the requirements for granting pediatric exclusivity and on December 1, 2023, the Applicant was informed that pediatric exclusivity had been granted for studies conducted on isavuconazonium sulfate under Section 505A of the Federal, Food, Drug, and Cosmetic Act (21 U.S.C 355a effective November 29, 2023).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness to support approval of Cresemba for the treatment of IA and IM in pediatric patients aged 1 to <18 years was extrapolated from adult trials of IA and IM. Extrapolation is appropriate given the similarities between adult and pediatric patients in the pathophysiology of IA and IM and the mechanism of action of the study drug, as well as, confirmed pharmacokinetic exposure targets in adults that could be replicated in children (see Section 6.2).

The Applicant's proposed Cresemba dosages in pediatric patients were revised based on the data available to ensure efficacious exposures would be achieved at the recommended doses. These revisions included: (1) an increase in the recommended dosage of Cresemba for injection to 15 mg/kg in pediatric patients less than 3 years of age (b) (4) and (2) limitations on the use of Cresemba capsules for oral administration and Cresemba for injection for nasogastric tube administration to pediatric patients at least 6 years of age (due to lack of PK data on oral administration of Cresemba in pediatric patients <6 years of age).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant has demonstrated an overall positive benefit-risk profile to support extending the current isavuconazole treatment indications (treatment of invasive aspergillosis and invasive mucormycosis) from adults to children aged one year and older. Evidence of efficacy was demonstrated primarily through pharmacokinetic extrapolation from the adult phase 3 trials. Both intravenous (one year of age and older) and oral (six years of age and older) formulations were used in the pediatric trials. For the intravenous formulation, efficacy could be extrapolated from adults to pediatric patients 1 to <18 years of age, though a dose increase to 15 mg/kg is recommended for patients 1 to <3 years of age [redacted] (b) (4) Oral administration of isavuconazole was not studied in pediatric patients <6 years of age so the final labeling will not include dosage recommendations for Cresemba capsules or nasogastric tube administration of Cresemba for injection in pediatric patients <6 years of age due to the lack of pharmacokinetic data following these forms of oral administration. The clinical efficacy endpoints assessed in the pediatric trials were descriptive in nature; mortality in the pediatric population was nominally lower than what was observed in the adult invasive aspergillosis (IA) and invasive mucormycosis (IM) trials.

Safety was assessed in two single-arm trials that enrolled 77 pediatric patients with possible, probable, or proven invasive fungal infections (including invasive aspergillosis and invasive mucormycosis) or with comorbid conditions wherein antifungal prophylaxis was presumed to be beneficial. Safety findings were similar to those observed in adults. Notably, gastrointestinal adverse reactions were common (including diarrhea, abdominal pain, nausea, and vomiting), and the adverse reactions currently listed in the United States Prescribing Information (USPI) under the Warnings and Precautions section, such as infusion reactions and elevated transaminases, were also noted in the pediatric population. Three deaths occurred in the pediatric studies, but none were considered by investigators or the FDA clinical reviewer as related to study drug. The types of serious adverse reactions and adverse reactions leading to discontinuation were similar to those listed in the current USPI, and no significant findings were noted in laboratory evaluations.

Extrapolation is appropriate given the similarities between adult and pediatric patients in the pathophysiology of IA and IM and the mechanism of action of the study drug, as well as, confirmed pharmacokinetic exposure targets in adults that could be replicated in children. No new safety concerns were identified in the two pediatric trials. Therefore, the treatment indications for IA and IM should be extended to pediatric patients aged 1 year and older for IV administration of Cresemba for injection and to pediatric patients aged 6 years and older for oral administration of Cresemba capsules and nasogastric administration of Cresemba for injection.

The availability of isavuconazole for the treatment of IA and IM in pediatric patients would expand the treatment armamentarium as current treatment options for pediatric patients with IA and IM are limited by adverse reactions, drug-drug interactions, and limitations in terms of oral access.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• IA and IM are serious infectious diseases with considerable morbidity and mortality. • In children as with adults, these infections generally affect individuals with serious underlying conditions including malignancy, receipt of hematopoietic stem cell (or solid organ) transplantation, serious immunodeficiencies, etc. These individuals are typically on multiple medications associated with numerous adverse reactions.	IA and IM are serious infections in pediatric and adult patients for which advances in medical management would be of significant clinical benefit.
Current Treatment Options	• Currently, liposomal amphotericin B (and amphotericin B lipid complex), voriconazole, and, to a lesser extent, posaconazole and echinocandins represent potential treatment options for IA and IM. • However, current treatments are limited by adverse reactions (nephrotoxicity, infusion reactions, electrolyte disorders, hepatic effects, central nervous system effects, etc.) and also by age restrictions; some	The availability of a treatment option with oral and IV formulations, a tolerable adverse reaction profile, and with similar efficacy to current treatment options would enhance the current armamentarium for the treatment of pediatric patients with IA and IM.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	options are only approved for treatment in adolescents and adults. • Moreover, oral formulations are not available for treatment options such as amphotericin B, thus leading to significant access issues.	
Benefit	• Evidence of effectiveness was demonstrated primarily through extrapolation of efficacy via exposure matching from trials of isavuconazole for treatment of IA and IM in adults to pediatric patients. • Extrapolation is appropriate given the similarities between the pathophysiology of IA and IM adult and pediatric patients and the similar mechanism of action of isavuconazole on fungal targets. • Confirmed pharmacokinetic exposure targets in adults could be replicated in pediatric patients with IV administration of isavuconazole in patients at least 1 year of age (with an adjustment in dosage to 15 mg/kg in patients less than 3 years of age) and with oral administration of isavuconazole in patients at least 6 years of age. • Mortality in pediatric patients administered isavuconazole for treatment of suspected IA and IM was nominally lower than what was observed in the adult IA and IM trials. This finding is descriptive in nature and cannot be compared reliably to the findings in the adult trials.	Efficacy of isavuconazole for treatment of IA and IM has been established in adults and can be extrapolated to pediatric patients 1 year of age and older. Based on the available exposure information, dosing recommendations can be made for intravenous administration in pediatric patients at least one year of age and for oral administration in pediatric patients at least six years of age.
Risk and Risk Management	• Safety findings observed in the pediatric population (e.g., gastrointestinal adverse reactions, elevated transaminases, infusion reactions, and injection-site reactions) were similar to those seen in	While labeling should be updated to describe the safety findings from the pediatric trials, no significant change in safety monitoring is

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	adults.	recommended. The risks associated with isavuconazole can be adequately addressed through product labeling and routine postmarketing pharmacovigilance.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		

☐	**Patient experience data that were not submitted in the application, but were considered in this review:**		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
X	**Patient experience data was not submitted as part of this application.**		

2 Therapeutic Context

2.1. Analysis of Conditions

Invasive aspergillosis can present in a variety of ways including primary pulmonary disease and disseminated forms. Invasive mucormycosis can also present in many forms including rhinocerebral, pulmonary, and disseminated disease (Centers for Disease Control and Prevention 2020).

The risk factors for invasive aspergillosis are similar between adults and children and include prolonged neutropenia (such as with hematologic malignancy), allogeneic hematopoietic stem cell and solid organ transplantation, use of systemic corticosteroids, and inherited immune deficiencies such as chronic granulomatous disease (Patterson et al. 2016). Mortality rates can approach 50% (Centers for Disease Control and Prevention National Center for Health Statistics 2022). In the year 2000, the annual incidence rate of invasive aspergillosis in immunosuppressed children was 0.4%. Mortality rates in children range from 45%-85% depending on the underlying population (Apsemidou et al. 2018).

Invasive mucormycosis in adult and pediatric populations can result from many of the same risk factors as for invasive aspergillosis including diabetes, solid organ transplantation, prolonged neutropenia and hematologic malignancy (Francis et al. 2018). Mortality rates in both adults and children are high and range from 50-90% with treatment; survival without antifungal therapy is rare. Treatment in the pediatric population is similar to adults and involves surgical management (debulking) as well as antifungal treatment (Francis et al. 2018).

2.2. Analysis of Current Treatment Options

Current first-line recommendations for treatment of invasive aspergillosis in pediatric patients are similar to those for adults (Patterson et al. 2016) and include voriconazole (2 years of age and older for IV and oral formulations) and liposomal amphotericin B (1 month of age and older; IV formulation only). Second-line recommendations include caspofungin, amphotericin B lipid complex, posaconazole (13 years of age and older; oral and intravenous formulations) and combination therapy (such as voriconazole with caspofungin). For invasive mucormycosis, only amphotericin B formulations (liposomal, lipid-based, etc.) are approved for treatment in pediatric populations 1 month of age and older.

Voriconazole is associated with adverse reactions including CNS effects and has numerous drug-drug interactions. Liposomal amphotericin B is associated with nephrotoxicity and infusion reactions and may be poorly tolerated.

3 Regulatory Background

3.1. US Regulatory Actions and Marketing History

The original NDAs 207500 for Cresemba (isavuconazonium sulfate) capsules and 207501 for Cresemba (isavuconazonium sulfate) for injection were approved on March 16, 2015, for the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

Orphan Drug Designation was granted for the treatment of invasive aspergillosis on May 6, 2013, and for the treatment of zygomycosis on October 25, 2013.

These efficacy supplements (207500/S-015 and 207501/S-013) were submitted on June 9, 2023, and provide for the addition of pediatric patients 1 year of age and older to the approved indications.

These supplemental applications were granted priority review. The Applicant submitted a pediatric exclusivity request with the supplements.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 1. Summary of Presubmission/Submission Regulatory Activity

Date	Meeting/Correspondence/Outcomes
January 9, 2015	Late-cycle meeting: As pediatric studies are not required under the PREA based on Orphan designation, FDA suggested that the Applicant submit a PPSR for studying the treatment of invasive aspergillosis and invasive mucormycosis in pediatric patients. If the FDA agreed with the PPSR, they might issue a PWR. The Applicant agreed to consider the proposal and informed FDA that they had juvenile toxicology work ongoing.
September 16, 2016	Type C Meeting: The Applicant submitted a proposed pediatric PK study synopsis for FDA's review. FDA asked the Applicant to provide a proposal for an additional study to assess the pharmacokinetics, safety and efficacy of pediatric patients receiving isavuconazole for the treatment of invasive aspergillosis and invasive mucormycosis to evaluate the safety and efficacy of isavuconazonium in pediatric patients with these infections at the final proposed dose regimens. FDA also recommended that the Applicant develop an age-appropriate oral formulation to allow for conversion from IV to oral dosing in pediatric patients. The Applicant explained that pediatric formulation development had been complicated due to technical difficulties with producing smaller capsules (b) (4) FDA agreed that the Applicant's juvenile toxicology data were adequate to initiate a proposed study in pediatric patients.
February 23, 2017	The Applicant submitted a PPSR including the phase 1 PK study protocol as per FDA's request and an open label PK, safety, and efficacy study:

Date	Meeting/Correspondence/Outcomes
	Study 1 - 9766-CL-0046 A Phase 1, open-label study to evaluate the PK and safety of IV Cresemba in children and adolescents ages 1 to less than 18 years of age who may, in the judgment of the investigator, benefit from systemic anti-mold prophylaxis. Study 2 - 9766-CL-0107 A Phase 2, interventional, non-comparative, open-label, multi- center study to evaluate the pharmacokinetics, safety, and efficacy of IV and/or oral Cresemba in children and adolescents ages 1 to less than 18 years of age.
October 24, 2017	FDA issued a PWR requesting the Applicant submit information from two clinical studies: Study 1: A Phase 1, open-label study to evaluate the PK and safety of IV Cresemba in children and adolescents ages 1 to less than 18 years of age who may, in the judgment of the investigator, benefit from systemic anti-mold prophylaxis. Study 2: A Phase 2, interventional, non-comparative, open-label, multi-center study to evaluate the pharmacokinetics, safety, and efficacy of IV and/or oral Cresemba in children and adolescents ages 1 to less than 18 years of age.
August 31, 2020	The Applicant submitted sNDAs 207500/S-008 and 207501/S-007 to add information regarding nasogastric tube administration of Cresemba for injection to the Cresemba prescribing information. The supplements were approved on April 22, 2021.
July 28, 2022	The Applicant submitted sNDAs 207500/S-013 and 207501/S-011 to propose a new capsule strength, 74.5 mg, as an alternative route of oral administration for adults. The supplements were approved on November 22, 2022.
July 29, 2022	The Applicant submitted a request for an extension of the date for submission of final pediatric study reports from December 15, 2022, as stated in the October 24, 2017, PWR, until December 15, 2023, due to enrollment delays in study 9766-CL-0107.
October 6, 2022	FDA issued a Revised Written Request with the timeframe for submitting final reports of the pediatric studies extended to December 15, 2023.
June 9, 2023	Pediatric efficacy supplements, NDAs 207500/S-015 and 207501/S-013, were submitted to FDA. These submissions included data and final reports for two clinical studies (Studies 9766-CL-0046 and 9766-CL-0107). The Applicant submitted a request for pediatric exclusivity with the supplements.

Abbreviations: NDA, new drug application; IV, intravenous; PK, pharmacokinetic; PPSR, Proposed Pediatric Study Request; PREA, Pediatric Research Equity Act; PWR, Pediatric Written Request

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations and Office of Study Integrity and Surveillance

The review team determined that clinical site inspections were not necessary for this supplement. The number of patients enrolled at each site was small in the pediatric studies submitted. Efficacy was extrapolated from the data obtained in the adult phase 3 studies (Study 9766-CL-0104 for treatment of IA and Study 9766-CL-0103 for treatment of invasive fungal diseases including mucormycosis). Inspections performed at the time of the original NDA review did not identify any concerns regarding the reliability of the data.

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical Remote Regulatory Assessment for Studies 9766-CL-0046 and 9766-CL-0107 conducted at (b) (4) . No objectionable conditions were observed and there were no identified concerns regarding the reliability of data for these studies.

4.2. Product Quality

Cresemba is currently commercially available for adults in the following formulations: a lyophilized powder for intravenous use (single dose vial containing 372 mg of isavuconazonium sulfate, equivalent to 200 mg isavuconazole; under NDA 207501) and as capsules for oral use in two different strengths (74.5 mg of isavuconazonium sulfate, equivalent to 40 mg isavuconazole and 186 mg of isavuconazonium sulfate, equivalent to 100 mg isavuconazole; under NDA 207500). The Cresemba labeling also contains preparation instructions for nasogastric tube administration of the injection formulation (approved in NDA 207500/S-008 and NDA207501/S-007). No new chemistry, manufacturing, and controls information was included in the current submission.

4.3. Clinical Microbiology

The nonclinical and clinical microbiology studies were reviewed previously (for details see clinical microbiology reviews dated December 9, 2014, and January 12, 2021). In this pediatric efficacy supplement, the Applicant has provided reports of two completed clinical studies in pediatric patients (Study Nos. 9766-CL-0046 and 9766-CL-0107) to fulfill the requirements of the PWR. In the Phase 1 study (No. 9766-CL-0046), patients enrolled included those at high risk for invasive fungal disease and who, in the opinion of the treating physician, could benefit from isavuconazonium sulfate in a prophylactic setting; no formal prospectively defined efficacy assessments were planned.

In the phase 2 study (No. 9766-CL-0107), 31 pediatric subjects with invasive fungal diseases (IFDs) were enrolled; 12 subjects were diagnosed with proven or probable IA and 1 subject with proven or probable IM; the remaining 18 subjects were diagnosed as either possible IFDs (n=16) or other fungal diseases (n=2). For more details regarding the study design, see Section 8 of this review. Of the 12 subjects with proven or probable IA, *Aspergillus* species were identified in 3 subjects in broncho-alveolar lavage fluid, sputum or lung; *A. fumigatus* in two subjects (ID # 9766-CL-0107-(b) (6) and 9766-CL-0107-(b) (6)) and *A. flavus* in addition to *A. fumigatus* in one subject (ID # 9766-CL-0107-(b) (6)). *Rhizopus* species was identified in 1 subject (ID # 9766-CL-0107-(b) (6)) with proven or probable IM. The all-cause mortality was low (8% at Day 42 and 16.7% at Day 84) (see Table 11 and Table 13 in Section 8). Overall, the efficacy in pediatric subjects appears to be consistent with the data in adult patients reviewed previously (see Table 15 of this review).

The Applicant has proposed to extend the current indications for isavuconazonium sulfate to include patients 1 year of age and older, based on the results of the two pediatric studies, and on extrapolation of the adult efficacy and safety data to the pediatric population. No changes in Section 12.4 (Microbiology) and Section 14 (Clinical Studies) of the labeling are proposed. From a Clinical Microbiology perspective, this is acceptable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

The original NDA for Cresemba details the toxicology profile of this drug. There were no differences in the toxicology profile of Cresemba whether adult or juvenile animals were evaluated. In a 13-week repeated dose oral toxicity study of isavuconazonium sulfate in juvenile rats followed by a 4-week recovery period, isavuconazonium sulfate was administered orally by gavage to Sprague-Dawley SPF rats [Crl:CD(SD), 27 animals/sex/group, 4 days of age at the start of treatment] once daily for 13 weeks at dose levels of 0 [Control: water for injection (pH 4.0)], 10, 30 and 90 mg/kg/day. Exposure levels in the 90 mg/kg/day dose group were in a similar range for 9 days old pups and adults. At 10 mg/kg/day, there were no treatment-related toxicologically relevant changes in either sex. At 30 mg/kg/day, reversible increases in liver weight and centrilobular hepatocellular hypertrophy were noted in both males and females. At 90 mg/kg/day, increased liver and thyroid gland weights and centrilobular hepatocellular hypertrophy and thyroid follicular cell hypertrophy were noted in both males and females. There are no nonclinical data that would preclude the approval of this formulation for pediatric patients.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology information submitted in the NDA supplement supports the approval of isavuconazonium sulfate for the treatment of invasive aspergillosis and invasive mucormycosis as an intravenous formulation in pediatric patients who are 1 year and older and as an oral formulation in pediatric patients who are 6 years and older. Of note, pediatric patients <6 years will be without an oral route of administration for isavuconazonium sulfate. This is due to formulation development challenges and swallowing concerns for pediatric patients <6 years with the currently approved capsule sizes of 74.5 mg and 186 mg. See Table 2 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 2. Summary of OCP Recommendations and Comments on Key Review Issues

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness and safety	Effectiveness The effectiveness of the Applicant's proposed isavuconazonium sulfate dosages for the proposed indications in pediatric patients is based on the extrapolation of effectiveness from the approved isavuconazonium sulfate dosage for the treatment of IA and IM in adult patients. Specifically, the extrapolation is based on comparing isavuconazole AUC_{ss} exposures from pediatric patients (1 to <18 years) administered isavuconazonium sulfate IV or pediatric patients (6 to <18 years) administered isavuconazonium sulfate oral capsule (from Study 9766-CL-0046 and Study 9766-CL-0107) to adult patients administered the approved isavuconazonium sulfate IV or oral dosing regimen (from SECURE phase 3 trial, 9766-CL-0104) (See Section 8.1). Pediatric AUC exposures (assessed by population PK estimates) across age groups (3 to <6 years, 6 to <12 years, and 12 to <18 years) were generally comparable to the exposures observed in the adult population. For pediatric patients 1 to <3 years, exposure estimates were lower than in adults with the 10 mg/kg dose, but exposures were comparable to adults when the dose was increased to 15 mg/kg (based on virtual 1 to <3 years population from Monte Carlo Simulations and the individual patient Empirical Bayes Estimates for 15 mg/kg). Safety The evidence for safety was derived from Study 9766-CL-0046 and Study 9766-CL-0107. See Section 8.2 for the evaluation of safety findings. Further supportive safety evidence is derived based on the comparison of isavuconazole AUC exposures from the two studies in pediatric patients 1 to <18 years and 6 to <18 years with the IV and oral formulation, respectively, exhibiting exposures that were below a supratherapeutic isavuconazonium sulfate oral dose of 1116 mg in healthy adult subjects (from phase 1 TQT study, 9766-CL-0017).

General Dosing Instructions

The recommended dosing regimens of isavuconazonium sulfate IV and oral capsule is in the table below:

Table 3. Recommended Dosing Regimens of Isavuconazonium Sulfate IV and Oral Capsule

Dosage Form	Age	Body Weight (kg)	Loading Dose	Maintenance Dose*
isavuconazonium sulfate for injection, 372 mg‡ per vial	1 to <3 years	<18 kg	15 mg/kg IV every 8 hours for 6 doses (48 hours)	15 mg/kg IV once daily
	3 to <18 years	<37 kg	10 mg/kg IV every 8 hours for 6 doses (48 hours)	10 mg/kg IV once daily
		≥37 kg	372 mg IV every 8 hours for 6 doses (48 hours)	372 mg IV once daily
isavuconazonium sulfate capsules, 74.5 mg # per capsule	6 to <18 years	16 to <18 kg	Two capsules (149 mg) orally every 8 hours for 6 doses (48 hours)	Two capsules (149 mg) orally daily
		18 to <25 kg	Three capsules (223.5 mg) orally every 8 hours for 6 doses (48 hours)	Three capsules (223.5 mg) orally daily
		25 kg to <32 kg	Four capsules (298 mg) orally every 8 hours for 6 doses (48 hours)	Four capsules (298 mg) orally daily
		≥32 kg	Five capsules (372 mg) orally every 8 hours for 6 doses (48 hours)**	Five capsules (372 mg) orally daily**

‡ 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole
# 74.5 mg of isavuconazonium sulfate is equivalent to 40 mg of isavuconazole
* Start maintenance doses 12 to 24 hours after the last loading dose
** Five 74.5 mg isavuconazonium sulfate capsules are equivalent to two 186 mg isavuconazonium sulfate capsules
Abbreviations: IV, intravenous

Two modifications were made to the dosing regimens originally proposed by the Applicant.

(b) (4)

Review Issues	Recommendations and Comments
	[redacted] (b) (4) The oral dose adjustment based on body weight for 2 capsules was changed from [redacted] (b) (4) to 16 to <18 kg. The change occurred because [redacted] (b) (4)
Dosing in patient subgroups (intrinsic and extrinsic)	For pediatric patients, no dose individualization is recommended based on intrinsic or extrinsic factors.
Labeling	The Applicant's proposed labeling was reviewed, and the review team's proposed revisions to the content and format of Clinical Pharmacology section 12.3 (See Labeling Recommendations in Section 11 of this review).

Source: Reviewer table
Abbreviations: AUC, area under the concentration-time curve; CDC, Center of Disease Control and Prevention; IV, intravenous; NHANES, National Health and Nutrition Examination Survey; OCP, Office of Clinical Pharmacology; PO, oral administration

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness for the proposed indication of treating IA and IM in pediatric patients 1 to <18 years with IV isavuconazonium sulfate and pediatric patients 6 to <18 years with oral isavuconazonium sulfate. Specifically, the effectiveness of the Applicant's proposed isavuconazonium sulfate dosage is extrapolated from effectiveness of isavuconazonium sulfate for treating IA and IM in adult patients.

The clinical pharmacology program consists of: 1) safety, tolerability, and PK data from a phase 1 noncomparative, open-label study (9766-CL-0046) in pediatric patients 1 to <18 years who are at high risk for an invasive fungal disease, 2) safety, tolerability, efficacy, and PK data from a phase 2 noncomparative, open-label study (9766-CL-0107) in pediatric patients 1 to <18 years receiving antifungal treatment for IA and IM, and 3) isavuconazole population PK analyses. The isavuconazole exposure comparison-based extrapolation (summarized in the next section) is supported based on the assumptions that: 1) isavuconazole has the same mechanism of action in adult and pediatric patients in which the drug's activity against IA and IM is similar in adult and pediatric patients, and 2) the pathophysiology and the clinical manifestations of the course of infectious disease for IA and IM are similar in adults and pediatrics.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant proposed isavuconazonium sulfate dosing regimens (see Table 4) are acceptable for pediatric IA and IM patients 3 to <18 years for IV and 6 to <18 years for oral administration. Specifically, it is acceptable based on the findings related to an exposure comparison (summarized below) between pediatric and adult patients at the approved adult dose (for additional details, refer to Section 15.4). However, as summarized below, the proposed isavuconazonium sulfate IV dosing regimens for patients 1 to <3 years was not acceptable, as (b) (4), the 15 mg/kg dosage for IV administration is recommended for patients 1 to <3 years age.

Table 4. Proposed Dosage and Administration for Isavuconazonium Sulfate in Pediatrics

Dosage Form	Body Weight (kg)	Loading Dose	Maintenance Dose*
isavuconazonium sulfate for injection, 372 mg‡ per vial	<37 kg	10 mg/kg IV every 8 hours for 6 doses (48 hours)	10 mg/kg IV once daily
	≥37 kg	372 mg IV every 8 hours for 6 doses (48 hours)	372 mg IV once daily
isavuconazonium sulfate capsules, 74.5 mg # per capsule	(b) (4)	Two capsules (149 mg) orally every 8 hours for 6 doses (48 hours)	Two capsules (149 mg) orally daily
	18 to <25 kg	Three capsules (223.5 mg) orally every 8 hours for 6 doses (48 hours)	Three capsules (223.5 mg) orally daily
	25 kg to <32 kg	Four capsules (298 mg) orally every 8 hours for 6 doses (48 hours)	Four capsules (298 mg) orally daily
	≥32 kg	Five capsules (372 mg) orally every 8 hours for 6 doses (48 hours)**	Five capsules (372 mg) orally daily**

‡ 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole
# 74.5 mg of isavuconazonium sulfate is equivalent to 40 mg of isavuconazole
* Start maintenance doses 12 to 24 hours after the last loading dose
** Five 74.5 mg isavuconazonium sulfate capsules are equivalent to two 186 mg isavuconazonium sulfate capsules
Abbreviations: IV, intravenous

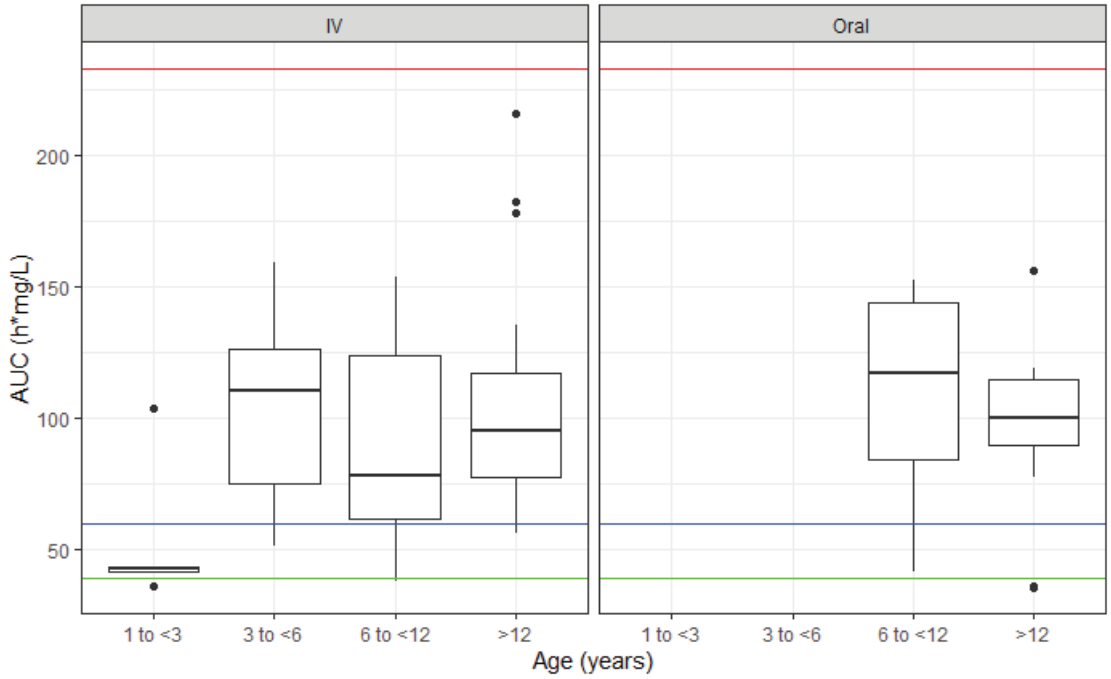
The Applicant's analysis relied on population PK (popPK) modeling analysis developed from pediatric patient PK data collected from the phase 1 and 2 studies and 24 adult subjects with normal and mild renal impairment PK data collected from phase 1 study (9766-CL-0018) to support the proposed pediatric dosing regimens. Specifically, the Applicant relied on comparing the steady-state area under the curve (AUC_{ss}) values (derived for individual patients that were based on the estimated clearance values obtained from the popPK model) from each age group for IV (1 to <6 years, 6 to <12 years, and 12 to <18 years) and oral (6 to <12 years and 12 to <18 years) administration to an established target range of 60 and 233 mg*h/L.

The comparability target range was established based on: 1) the 25th percentile AUC_{ss} range from adult IA patients who received the approved IV and oral dose in the phase 3 study (9766-CL-0104, SECURE) and 2) the minimum AUC_{24h} value from a phase 1 thorough QT/QTc (TQT) study in adults (Study 9766-CL-0017), where a isavuconazonium sulfate dose of 1116 mg was administered and increased adverse effects were observed compared to the approved adult dose or placebo (for additional details, refer to Section 15.4.2). The target plasma drug exposures of AUC_{ss} 60 to 233 mg*h/L were defined after analysis of the adult isavuconazole plasma drug exposures, and the efficacy and safety associated with these plasma drug AUC values in the SECURE and VITAL (adult IM patients in phase 3 study 9766-CL-0103) studies and safety associated with the isavuconazonium sulfate 1116 mg dose in the adult phase 1 TQT study.

Intravenous Formulation

The median estimated AUC_{ss} for the different age groups were contained within the AUC target range. However, when stratifying the 1 to <6 year age group (1 to <3 years and 3 to <6 years), four of five pediatric patients 1 to <3 years were below the target of 60 mg*h/L, near the 5th percentile AUC_{ss} of the adult patients in the phase 3 study (SECURE) at 39 mg*h/L (Figure 1).

Figure 1. Boxplot of Calculated AUC_{ss} Values Corresponding to First Maintenance Dose (Dose 7) Based on Empirical Bayes Estimates Versus Age Group, for Study 9766-CL-0046 and Study 9766-CL-0107 Pediatric Patients



Source: Reviewer's Analysis
Green line represents 39 h*mg/L, the 5th percentile of AUC_{ss} in adults from the SECURE study, 9766-CL-0104. Blue line represents 60 h*mg/L, the 25th percentile of AUCss in adults from the SECURE study, 9766-CL-0104. Red line represents the minimum (233 h*mg/L) AUC_{ss} value for 1116 mg dose from Thorough QT study in adults, 9766-CL-0017.
Abbreviations: AUC, area under the concentration-time curve; IV, intravenous

In addition, the median AUC_{ss} of this age group (1 to <3 years) was approximately 2-fold lower compared to other age groups (3 to <6 years, 6 to <12 years, and 12 to <18 years) at the proposed doses. Similarly, lower exposures were also seen with the observed median trough concentrations in the 1 to <3 years age group when compared to other pediatric age groups (over 1.5-fold difference on days 7, 14, and 21). Although the basis for the lower exposures was not identified, the Applicant postulated two reasons: 1) natural variability of a small sample size, or 2) lower plasma protein binding resulting in larger fraction of unbound isavuconazole concentrations, increased volume distribution and increased clearance (Rowland and Tozer 2010; Lu and Rosenbaum 2014). Isavuconazole is highly lipophilic, has a >99% protein binding (predominately from albumin at ~99%, followed by high density lipoprotein and low-density lipoprotein at ~90 - 95%), and it has a low extraction rate (CL of 2.5 L/h).[1] Due to these factors, it is possible that patients 1 to <3 years with isavuconazole AUC <60 mg*h/L exhibited less

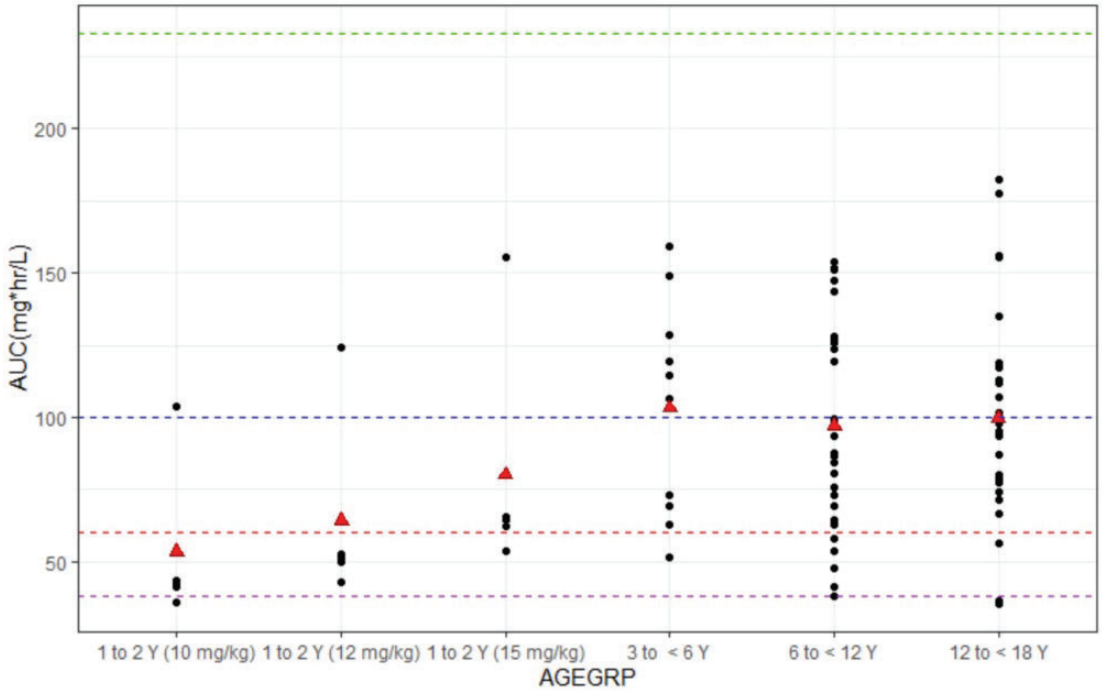
[1] NDA207500/207501. Clinical Pharmacology Review; DARRTS date: 12/9/2014

plasma protein binding which could have led to increased volume distribution and increased clearance.

Of note, the overall efficacy outcomes from the pediatric phase 2 study (9766-CL-0107) were considered favorable and generally consistent with the adult phase 3 study (9766-CL-0104) (Table 15), but the pediatric study was underpowered and not designed for inferential testing of effectiveness. Therefore, it is not clear if the lower exposures of isavuconazole in the 1 to <3-year-old age group compared to other age groups would be as effective as in adults with IA and IM. In addition, since pediatric patients with IA are typically severely immunocompromised (Wattier and Ramirez-Avila 2016) and given the limited available treatment options in the 1 to <3-year-old age group, ensuring a dose with exposures similar to adults was considered important. To address the lower AUC_{ss} and ensure the appropriate dose for this 1 to <3 years pediatric patient population, isavuconazole exposures at higher doses of 12 and 15 mg/kg were estimated with two approaches: 1) Monte Carlo Simulations (MCS) of 794 virtual patients using the pediatric population PK model for the 1 to <3 year old group; and 2) derived AUC values for the higher doses from the individual patient (n=5 patient 1 to <3 years) Empirical Bayes Estimates (EBE) that were obtained from the popPK model.

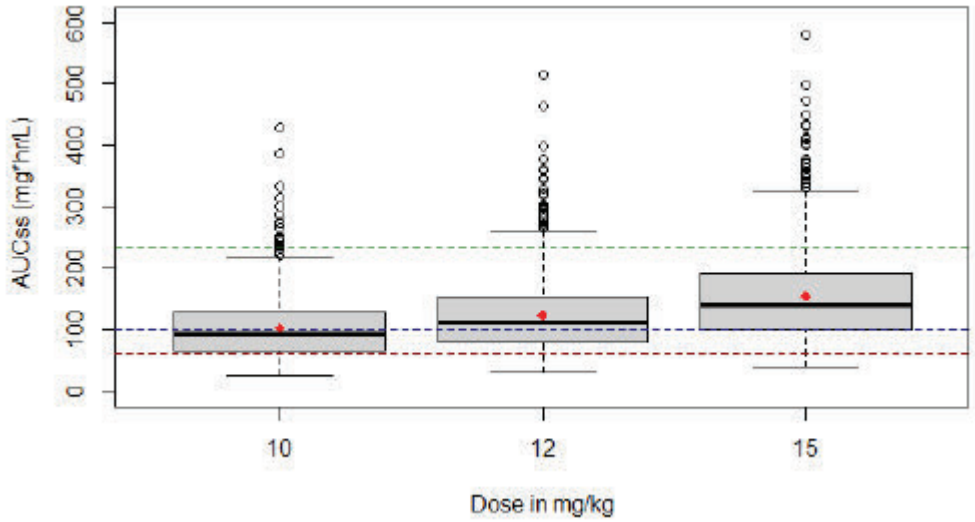
As shown in Figure 2, Figure 3, and Table 5, the EBE derived or MCS estimated median AUC_{ss} values for a dose of 15 mg/kg in the 1 to <3 year pediatric patient population were contained within the AUC target range of 60 – 233 mg*h/L and slightly higher (1.3 to 1.6-fold) than the median AUC_{ss} values for other pediatric age groups with 10 mg/kg dose. The 12 mg/kg dose was removed from consideration for the 1 to <3 years age group as the EBE derived median AUC_{ss} values remained below the AUC target value of 60 mg*h/L (Table 5). In addition, the mean EBE derived AUC_{ss} value of 50 mg*h/L in the 1 to <3 year (excluding one 2-year-old patient with AUC_{ss} value of 124.2 mg*h/L) was also below the AUC target of 60 mg*h/L. The review team also evaluated the C_{max} values following administration of 15 mg/kg in relation to the minimum C_{max} of the supratherapeutic isavuconazonium sulfate dose of 1116 mg administered to healthy adults (TQT phase 1 study). However, since the popPK model was not established to evaluate C_{max} (only evaluate AUC_{ss}) and given that isavuconazole is dose-proportional for C_{max} and AUC, the noncompartmental derived C_{max} and estimated AUC for 15 mg/kg were extrapolated from a 2 year old pediatric patient with the highest observed C_{max} among three pediatric patients 1 to <3 years with PK samples within same 24 hour PK profile, and a 2 year old pediatric patient with the highest estimated AUC_{ss} (Table 6). The findings show that isavuconazole exposures at doses of 15 mg/kg in pediatric patients 1 to <3 years are less than the minimum C_{max} and AUC_{24} observed with the supratherapeutic dose from the TQT phase 1 study (Table 6).

Figure 2. Scatter Plot of Derived AUC_{ss} Values Based on Empirical Bayes Estimates for Different Doses (10 mg/kg, 12 mg/kg, and 15 mg/kg) for Patients 1 to <3 Years and 10 mg/kg or 372 mg for Patients 3 Years or Older



Source: Applicant's analysis and figure submitted on 11/8/2023 (Information Request to the Applicant).
Dose of isavuconazonium sulfate for 3 to <6 Y, 6 to <12 Y, and 12 to <18 Y was either 10 mg/kg or 372 mg.
Black circles represent the individual derived AUC_{ss} values. Red triangle represents the mean derived AUC_{ss} for that age and dose group.
Dashed blue line is the mean AUC_{ss} (100 mg*h/L) from the SECURE study. Dashed green line is the minimum (233 mg*h/L) AUC24 value that led to increased toxicity in a high dose adult study (1116 mg). Dashed red line is the lowest targeted value (25th percentile, with AUC_{ss} of 60 mg*h/L) based on exposures from the SECURE study. Dashed purple line is the 5th percentile AUC_{ss} value of 39 mg*h/L based on exposures from the SECURE study.
Abbreviations: AGEGRP, age group; AUC, area under the concentration-time curve; Y, years

Figure 3. Box Plot Comparison of AUC_{ss} Values at Various Dose Levels From Simulated (MCS) Pediatric Patients 1 to <3 Years in Context of Target Exposure Range (60 to 233 mg*h/L)



Source: Applicant's analysis and figure submitted on 10/31/2023 (Information Request to the Applicant).
Dashed blue line is the mean AUC_{ss} (100 mg*h/L) from the adult AUC_{ss} from the SECURE study. Dashed green line is the minimum (233 mg*h/L) AUC24 value that led to increased toxicity in a high dose adult study (1116 mg). Dashed red line is the lowest targeted value (25^{th} percentile, with AUC_{ss} of 60 mg*h/L) based on exposures from the SECURE study.
Abbreviations: AUC_{ss}, steady-state area under the curve; MCS, Monte Carlo Simulated

Table 5. Comparison of Isavuconazole AUC_{ss} Values of Simulated (MCS) and EBE in Pediatric Patients 1 to <3 Years on Isavuconazonium Sulfate 12 and 15 mg/kg and Pediatric Patients on Isavuconazonium Sulfate 10 mg/kg (Age Groups: 3 to <6 Years, 6 to <12 Years, and 12 to <18 Years)

AUC_{ss} (mg*h/L)	1 to <3 Years 12 mg/kg N=5 (EBE)	1 to <3 Years 12 mg/kg N=794 (MCS)	1 to <3 Years 15 mg/kg N=5 (EBE)	1 to <3 Years 15 mg/kg N=794 (MCS)	3 to <6 Years 10 mg/kg N=10	6 to <12 Years 10 mg/kg N=29	12 to <18 Years 10 mg/kg N=29
Mean (SD)	66.9 (28.2)	128.1 (73.6)	80.2 (28.2)	160.1 (92.0)	103.2 (37.5)	97.3 (37.8)	104.2 (41.8)
Median	53.6	112.7	64.3	140.9	110.3	87.7	97.7
25^{th} - 75^{th} percentile	46.3 - 88.3	76.8 -161.1	57.9 – 110.4	95.9 - 201.4	67.5 - 133.7	63.9 - 127.1	77.7 - 118.0

Source: Applicant's dataset (AUC-12mg-kg-simulated-values and AUC-15mg-kg-simulated-values) and Table 4 in Response-to-info-request document submitted on 11/8/2023 (Information Request), and study report A9766-PK-0010 Amendment 1 from 8/21/2023 (Information Request). Subject number (b) (6) (15-year-old) AUC_{ss} value was incorrectly listed in study report as 355.3 mg*h/L instead of 35.5 mg*h/L.
Abbreviations: AUC_{ss}, steady-state area under the curve; EBE, Empirical Bayes Estimates; MCS, Monte Carlo Simulated; N, patients; SD, standard deviation

Table 6. A Comparison of Isavuconazole C_{max} and AUC Values (Extrapolated From 15 mg/kg) From Two Individual Pediatric Patients (1 to <3 Year) and the Minimum Isavuconazole C_{max} and AUC_{24} Values From Healthy Adult Subjects at Supratherapeutic Dose (Phase 1 TQT Study)

Parameter	2-Year-Old Patient at 15 mg/kg Dose† Subject # (b) (6) (Extrapolated)	2-Year-Old Patient at 15 mg/kg Dose‡ Subject (b) (6) (Extrapolated)	Minimum Exposures With Supratherapeutic Dose of 1116 mg*
C_{max}, mg/L	11.9	N/A	13.4
AUC, mg*h/L	65.6	155.3	233

Source: ADAM dataset ADPC (Study 9766-CL-0107) from 6/9/2023 supplement NDA submission, Study report A9766-PK-0010 Amendment 1 from 8/21/2023 information request, and ADAM dataset ADPP (Study 9766-CL-0017) from 7/8/2014 original NDA submission.
† Pediatric patient (subject number (b) (6)) is a 2 year old (10.9 kg) on 10 mg/kg IV with 5 plasma PK samples within a 24 hour dosing interval (pre-dose and post start of infusion at 1, 4-8, 8-12, and 16-24 hours) on Days 3, 7, 28 of IV therapy; highest noncompartmental analysis derived C_{max} (i.e., Day 3) was 7.9 mg/L and estimated AUC_{ss} derived from popPK model on 10 mg/kg dose was 43.7 mg*h/L. Both values were extrapolated by 1.5-fold for 15 mg/kg dose.
‡ Pediatric patient (subject number (b) (6) is a 2-year-old (12 kg) on 10 mg/kg IV dose with an estimated AUC_{ss} derived from popPK model was 103.5 mg*h/L; AUC_{ss} was extrapolated by 1.5-fold for 15 mg/kg dose. Note, only pre-dose plasma PK samples were collected from this patient on Days 7, 14, 21, 28, and 42.
* Minimum noncompartmental analysis derived C_{max} and AUC at 24 hours from 32 healthy adult subjects on supratherapeutic isavuconazonium sulfate oral dose of 1116 mg (Phase 1 Thorough QT Study, 9766-CL-0017).
Abbreviations: AUC, area under the curve; C_{max}, maximum observed plasma concentration; N/A, not available

Oral Formulation

The 186 mg oral capsule was previously shown to have comparable bioavailability (BA) to the IV formulation in adult healthy subjects with an absolute BA of ~98%.[1] The 74.5 mg oral capsule and 186 mg oral capsule were also shown to be bioequivalent.[2] Based on this information and the similarity in exposures between IV and oral capsule in the pediatric phase 1 study (for additional details, refer to Section 15.4 and Table 20), interchangeability of administration between IV and oral capsule was allowed in the phase 2 study in pediatric patients 6 to <18 years. Due to concerns with swallowing isavuconazonium sulfate capsules including the 74.5 mg capsule, patients <6 years old were restricted from receiving the oral route of administration in the phase 1 and 2 studies. Subsequently, no PK information was available for patients <6 years old administered the oral capsules.

The Applicant stated that they experienced several challenges when developing an age-appropriate oral formulation for pediatrics <6 years. Subsequently, they proposed an alternative oral route, the reconstitution of isavuconazonium sulfate powder for IV solution and administration to pediatrics 1 to <6 years with a nasogastric (NG) tube. However, no pediatric patient 1 to <18 years with an NG tube received the NG tube administration of the IV formulation in either pediatric clinical study (9766-CL-0046, 9766-CL-0107). Given that this alternative oral route of administration (NG tube administration of IV reconstituted solution) achieved bioequivalence to oral capsules in adults[3] and the exposures of the oral capsules in patients 6 to <18 years are within the target AUC range of 60 to 233 mg*h/L of adult exposures (Figure 1), it is reasonable to consider this alternative route for only patients 6 years and older.

NG tube administration of the IV formulation and oral capsules are not recommended for use in patients who are <6 years old because the oral route of administration was not assessed in this pediatric patient age cohort.

Exposure-Response Analyses

Exposure-response analyses were not performed for efficacy or safety in pediatric patients. From the adult data, there was no clinically meaningful ER relationship for efficacy or safety identified during the review of the original NDA submission[1].

[2] NDA207500/207501. Clinical Pharmacology Review; DARRTS date: 11/4/2022

[3] NDA207500/207501. Clinical Pharmacology Review; DARRTS date: 01/12/2021

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The effect of intrinsic and extrinsic patient factors on isavuconazole PK was evaluated in adults previously during the review of the original NDA submission.[1] No new information on individualized dosing regimen or management strategy for subpopulation on intrinsic or extrinsic patient factors is submitted. The population PK analysis of the pooled pediatric and adult PK data did not identify additional intrinsic or extrinsic patient factors.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The effect of food and drug-drug interactions for isavuconazole were evaluated in adults previously during the review of the original NDA submission.[1] For this submission, the Applicant used physiologically based pharmacokinetic (PBPK) analysis to predict the drug-drug interaction (DDI) effects of isavuconazole on the PK of vincristine in pediatric patients. The PBPK analysis suggested that the effects of isavuconazole on the systemic exposure of vincristine are expected to be weak, resulting in less than a 2-fold increase in vincristine AUC, in pediatric patients. The predicted DDI effects are mainly due to P-glycoprotein inhibition by isavuconazole. Refer to the PBPK review in the Section 15.4.5 for further details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7. Tabular Listing of Pediatric Studies: Completed

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK/S	9766-CL-0046	Pharmacokinetics and safety of IZs (PO vs IV)	Phase 1, open-label, non-comparative study of IZs	Loading dose of IZs (IV or oral) every 8 hours (±2 hours) on days 1 and 2 followed by once-daily maintenance dosing	Part 1: 29 Part 2: 20	Male or female patients 1 to <18 years of age (IV), 6 to <18 years (oral)	Up to 28 days
PK/E/S	9766-CL-0107	Efficacy and safety of IZs (PO vs IV)	Phase 2, open-label, non-comparative study of IZs	Loading dose of IZs (IV or oral) every 8 hours (±2 hours) on days 1 and 2 followed by once-daily maintenance dosing	31	Male and female patients aged 1 to <18 years old with proven, probable, or possible invasive fungal infections	Up to 180 days

Source: Applicant's eCTD module 5.2, (submission #134)- Tabular Listing of Clinical Studies
Abbreviations: PK, pharmacokinetics; S, safety; E, efficacy; PO, oral administration; IV, intravenous; IZ, Isavuconazole

7.2. Review Strategy

Study 9766-CL-0107 was an open-label, non-comparative, multicenter study designed to assess the safety and tolerability, efficacy, and PK of Cresemba for treatment of IA and IM in pediatric patients. The efficacy results of the study were summarized descriptively overall and by categorization of IFD in Section 8.1. For evaluation of safety, the safety data from Study 9766-CL-0107 was integrated with data from Study 9766-CL-0046, a phase 1 open-label study to evaluate the PK and safety of IV Cresemba in pediatric patients who may benefit from systemic anti-mold prophylaxis. Please refer to the discussion in Section 8.2.1 for the safety review strategy.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 9766-CL-0107

Trial Design

Study 9766-CL-0107 was an open-label, non-comparative, multicenter study designed to assess the safety and tolerability, efficacy, and PK of isavuconazonium sulfate for the treatment of IA or IM in pediatric subjects 1 year to <18 years of age. The study was a multinational study conducted at 10 centers from 3 countries: the United States, Spain, and Belgium.

Eligible subjects included males or females aged 1 year to <18 years with possible, probable, or proven IA or IM per the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 criteria. Subjects with “possible” IFD were eligible for enrollment; however, diagnostic tests to confirm the IFD as “probable” or “proven” according to the EORTC/MSG 2008 criteria were to be completed within 10 calendar days after the first dose of study drug. In addition to the criteria set for mycological criteria by the EORTC/MSG 2008, and only for subjects with an underlying hematologic malignancy or recipients of hematopoietic stem cell transplant who also have clinical and radiologic features consistent with invasive fungal infection, a single galactomannan (GM) value for serum or bronchoalveolar lavage fluid of ≥1.0 or two serum GM values of ≥0.5 were acceptable mycological evidence for enrollment or upgrading the diagnosis to probable IA.

Subjects were not eligible if they had an IFD other than possible, probable, or proven IA or IM; had chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis; received mold active systemic antifungal therapy, effective against the primary invasive mold infection, for more than 4 days during the 7 days preceding the first dose; or were unlikely to survive 30 days in the investigator’s opinion.

All subjects received isavuconazonium sulfate via intravenous or oral administration at the investigator's discretion. The oral formulation could only be given to subjects 6 to <18 years of age and with a body weight of at least 12 kg. The route of administration for patients eligible for both IV and oral isavuconazonium sulfate could change at the investigator's discretion as needed for treatment purposes because the resulting exposure from the 2 routes of administration is considered equivalent on a mg:mg basis. Subjects received a loading regimen which consisted of a 10 mg/kg dose every 8 hours (±2 hours) on days 1 and 2 (for a total of 6 doses), followed by once daily maintenance 10 mg/kg dosing for up to 84 days (IA) or 180 days (IM) of dosing. Dose selection was based on data from Study 9766-CL-0046.

Study treatment was administered until the subject had a successful outcome as judged by the investigator or for a maximum duration of 84 days (IA) or 180 days (IM), whichever occurred first. Subjects were followed for up to 60 days post-last dose for safety. Study visits occurred at Days 14, 28, and 56 as well as 2 follow-up visits at 30 and 60 days post last dose.

A Data Safety Monitoring Board (DSMB) was responsible for ongoing monitoring of the safety of subjects during the conduct of the trial. The DSMB consisted of 3 physicians with experience in the management of subjects with infectious diseases and in the conduct and monitoring of clinical studies. They were not employees of the Applicant and were not otherwise involved with the study conduct. Over the course of the study, the only recommendation from the DSMB was to continue the study without change.

The DSMB members also acted as the adjudication committee (AC). The AC adjudicated, independently from the Applicant and the Investigator, the diagnosis of each subject and evaluated clinical, mycological, radiological, and overall response at each study timepoint (days 42, 84 and end of treatment [EOT]). Additionally, for deaths during study, the AC assessed the attribution of IFD to death.

Study Endpoints

The primary objective of the study was to assess the safety and tolerability of isavuconazonium sulfate in pediatric subjects. The efficacy objective was to assess the efficacy of isavuconazonium sulfate for the treatment of IA or IM in pediatric subjects.

Efficacy was assessed primarily by all-cause mortality (ACM) through Day 42. Key secondary endpoints were ACM through day 84 and EOT. Additional secondary efficacy endpoints were overall, clinical, radiological, and mycological response through days 42 and 84 and EOT.

Safety was evaluated through assessment of adverse events, vital signs, electrocardiogram (ECGs), and laboratory parameters.

Statistical Analysis Plan

The statistical analysis plan was finalized as Version 1 dated October 17, 2019.

Analysis Populations

The safety analysis set (SAF) consists of all enrolled subjects who received at least one dose of study medication. The SAF is used for all safety analyses.

The full analysis set (FAS) consists of all enrolled subjects who received at least one dose of study medication. This is the primary analysis set for efficacy analyses. For this study, the FAS and the SAF are the same.

The modified FAS (mFAS) is a subset of FAS subjects who have either a probable or proven IA or IM diagnosis at baseline or up to 10 days after the first dose. This population was used by the Applicant as a secondary analysis set for select efficacy analyses.

Analysis Methods

No hypothesis testing was conducted. The efficacy results of the study are summarized descriptively overall and by categorization of IFD. The crude ACM rate is calculated by dividing the number of deaths by the number of FAS subjects, and a 2-sided exact 95% CI for the rate is calculated.

Sample Size Calculation

The sample size chosen for the study was not based on statistical considerations. A sample size of 30 evaluable subjects was planned. Every effort was made to have at least 5 evaluable subjects per age cohort to <12 years of age and 12 to <18 years of age.

Protocol Amendments

The original protocol, Version 1, was dated August 24, 2018. There were 4 amendments to the protocol with the first 2 amendments made prior to enrolling any subjects. A total of 6 subjects were enrolled under Version 2 of the protocol. The remaining subjects were enrolled under Version 4. Substantial changes that impacted aspects of study design included the following:

- Protocol Version 2 (February 12, 2019) added 24-hour PK samples to be obtained between days 21 and 42 while subjects were still receiving study drug and clarified the GM criteria allowed for upgrading to a probable IA diagnosis.
- Protocol Version 3 (May 8, 2019) added the use of the oral route of administration using the 74.5 mg isavuconazonium sulfate capsules for subjects aged 12 to 18 years.
- Protocol Version 4 (September 5, 2019) changed the lower limit of age for using the oral formulation to 6 years with a body weight of at least 12 kg; added a table to provide guidance to investigations defining the elements of a successful outcome to aid in decision making for determining the end of treatment; and expanded the maximum

time window for subjects in the mFAS to have a probable or proven IA or IM diagnosis from 1 week after the first dose to 10 days after the first dose.

The modifications to the protocol did not have an impact on the integrity of the trial or the interpretation of the results.

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant states that: "This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the following: consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines; applicable ICH Good Clinical Practice Guidelines; and applicable laws and regulations."

Financial Disclosure

The Applicant has noted no investigators with financial arrangements, payments, or interests requiring disclosure under 21 CFR 54.4(a)(3) for study 9766-CL-0107 (information for one sub-investigator was not available); this is referenced on Form FDA 3454.

Patient Disposition

A total of 31 subjects with at least possible IFD requiring systemic mold-active antifungal therapy were enrolled in the study. All enrolled subjects received at least one dose of study medication. Therefore, the SAF and the FAS consisted of 31 subjects. Thirteen of the subjects had either a probable or proven IA or IM diagnosis by the investigator at baseline or up to 10 days after first dose and were included in the mFAS.

Table 8. Analysis Sets

Analysis Set	Total N (%)
Enrolled	31 (100)
Safety	31 (100)
FAS	31 (100)
mFAS	13 (41.9)

Source: Table 3 of Clinical Study Report
Abbreviations: FAS, full analysis set; mFAS, modified full analysis set

Overall, 61% of enrolled subjects completed treatment and 39% discontinued treatment. The reasons for discontinuing treatment included an adverse event, lack of efficacy, and other. Of the 4 subjects who discontinued treatment due to lack of efficacy, 1 died 4 days after treatment discontinuation due to progressive IFD. Four of the 5 subjects who discontinued for a reason of "other" were due to not having the fungus intended for the study or not having a definitive

diagnosis of IA or IM, however, all met the possible IFD criteria at study entry. The last other reason was due to worsening of underlying condition.

The majority (90%) of subjects completed the study through the 60-day follow-up visit. Three subjects prematurely discontinued the study due to death. All of the deaths were considered unrelated to study treatment by the investigator. However, one subject discontinued treatment due to lack of efficacy on day 10 and died as a result of progressive IFD on day 15.

Table 9. Subject Disposition (FAS)

Parameter Category	Total (N=31)
Completed Treatment	19 (61.3)
Discontinued Treatment	12 (38.7)
Adverse event	3 (9.7)
Lack of Efficacy	4 (12.9)
Other	5 (16.1)
Completed Study	28 (90.3)
Discontinued Study	3 (9.7)
Death	3 (9.7)

Source: Adapted from Table 4 of Clinical Study Report
Abbreviations: FAS, full analysis set

Protocol Violations/Deviations

Two subjects were recorded as having a major protocol deviation. Both cases involved receiving the wrong treatment or incorrect dose. One subject received only 1 of the 5 capsules intended on 4 occasions (actual dose 74.5 mg rather than the intended 372 mg). This subject remained on study drug for 47 days and was judged by the investigator to have a successful outcome. The second subject was a 5-year-old who was given permission by the Applicant upon investigator request to receive oral study drug (participant exceeded the minimum weight for oral formulation).

Demographic and Other Baseline Characteristics

Table 10 summarizes demographic and baseline characteristics of subjects in the FAS population. The majority of the subjects were female (80.6%), white (61.3%), and 1 to <12 years of age (61.3%). Approximately 52% of the subjects were from the United States. The mean baseline weight was 37.7 kg. The primary underlying condition was malignancy in 61.3% of subjects.

Overall, 12 subjects had a diagnosis of proven or probable IA. There was one subject with a proven diagnosis of IM. Two subjects were found by day 10 to have IFDs other than IA or IM (1 with fusariosis and 1 with coccidioidomycosis). The remaining 16 subjects were thought to have possible IFD by the Investigator. It should be noted that 2 of these subjects were assessed by the AC as not having IFD rather than possible IFD. For one subject, the investigator indicated that a galactomannan value of >3.5 guided their treatment decision despite the subject not

having host factors or characteristic radiology to meet the clinical features. The other subject had a positive PCR for *Aspergillus fumigatus*, as well as high galactomannan values, despite not having a hematologic malignancy and not having clinical features that met the EORTC/MSG 2008 criteria.

Table 10. Demographic and Baseline Characteristics (FAS)

Parameter	Total (N=31) n (%)
Sex	
Male	6 (19.4)
Female	25 (80.6)
Age (years)	
Mean (SD)	9.7 (5.0)
Median	10.0
Min, max	1, 17
Age Group (years)	
1 to <12	19 (61.3)
12 to <18	12 (38.7)
Race	
White	19 (61.3)
Black or African American	1 (3.2)
Asian	5 (16.1)
Other	4 (12.9)
Not Specified	2 (6.5)
Ethnicity	
Hispanic or Latino	10 (32.5)
Not Hispanic or Latino	19 (61.3)
Not Specified	2 (6.5)
Country	
United States	16 (51.6)
Belgium	11 (35.5)
Spain	4 (12.9)
Weight (kg)	
Mean (SD)	37.7 (19.2)
Median	42.6
Min, max	9.0, 84.3
Underlying Condition	
Malignancy	19 (61.3)
Non-Malignancy	12 (38.7)
Diagnosis of IFD	
Proven or Probable IA	12 (38.7)
Proven or Probable IM	1 (3.2)
Possible IFD	16 (51.6)
Other IFD	2 (6.5)

Source: Adapted from Tables 6, 7, and 12.1.2.3 of Clinical Study Report
Abbreviations: FAS, full analysis set; IA, invasive aspergillosis; IFD, invasive fungal disease; IM, invasive mucormycosis; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects in the Safety population used at least 1 concomitant medication. Overall, 20 (64.5%) subjects were reported as having received concomitant antifungal therapy during the study. The 3 most used antifungal medications were voriconazole (35.5%, 11/31), liposomal amphotericin B (29.0%, 9/31) and micafungin (19.4%, 6/31). Ten subjects started or ended the systemic antifungal therapy on the same day as study drug was initiated or discontinued. Systemic antifungal therapy was administered at the same time as study drug in only 2 subjects. One subject received empiric caspofungin that continued until day 2 of the study. The other subject received micafungin concomitantly with study drug from days 69 to 71. Five subjects received commercially supplied isavuconazonium sulfate outside of the study during the follow-up period as treatment or maintenance.

Efficacy Results – Primary Endpoint

Table 11 summarizes ACM through Day 42 for the FAS population overall and by categorization of IFD. Overall, 2 subjects (6.5%) died by Day 42. This included 1 subject with proven or probable IA and 1 subject with possible IFD. For the subject with proven or probable IA, the cause of death was considered attributable to the IA infection.

Table 11. All-Cause Mortality Through Day 42 (FAS)

	Categorization of IFD				
Outcome	Proven or Probable IA (n=12)	Proven or Probable IM (n=1)	Possible IFD (n=16)	Other IFD (n=2)	Overall (n=31)
ACM	1 (8.3)	0	1 (6.3)	0	2 (6.5)
Exact 95% CI	(0.2, 38.5)	(0, 97.5)	(0.2, 30.2)	(0, 84.2)	(0.8, 21.4)

Source: Adapted from Table 20 of Clinical Study Report
Abbreviations: ACM, all-cause mortality; FAS, full analysis set; IA, invasive aspergillosis; IFD, invasive fungal disease; IM, invasive mucormycosis

ACM through Day 42 by various subgroups is summarized in Table 12 for the FAS population. Interpretation of these results must be made with caution given the extremely limited sample sizes especially when broken down by categorization of IFD.

Table 12. All-Cause Mortality Through Day 42 for Various Subgroups (FAS)

	Categorization of IFD				
Subgroup Category	Proven or Probable IA (n=12)	Proven or Probable IM (n=1)	Possible IFD (n=16)	Other IFD (n=2)	Overall (n=31)
Sex					
Male	0/2	0/1	0/3	-	0/6
Female	1/10 (10.0)	-	1/13 (7.7)	0/2	2/25 (8.0)
Race					
White	1/4 (25.0)	0/1	1/13 (7.7)	0/1	2/19 (10.5)
All others	0/8	-	0/3	0/1	0/12

Subgroup Category	Categorization of IFD: Proven or Probable IA (n=12)	Proven or Probable IM (n=1)	Possible IFD (n=16)	Other IFD (n=2)	Overall (n=31)
Age group					
1 to <12 years	0/7	-	0/11	0/1	0/19
12 to <18 years	1/5 (20.0)	0/1	1/5 (20.0)	0/1	2/12 (16.7)

Source: Adapted from Updated Table 12.3.1.2 of Clinical Study Report
Abbreviations: ACM, all-cause mortality; FAS, full analysis set; IA, invasive aspergillosis; IFD, invasive fungal disease; IM, invasive mucormycosis

Efficacy Results – Secondary and Other Relevant Endpoints

One additional subject died between days 42 and 84. Therefore, the all-cause mortality rate through Day 84 in the FAS was 9.7%. This subject had proven or probable IA and the attribution of IFD to the death was considered indeterminate by the AC. All deaths occurred after treatment with study drug had been discontinued.

Table 13. All-Cause Mortality Through Day 84 (FAS)

Outcome	Categorization of IFD: Proven or Probable IA (n=12)	Proven or Probable IM (n=1)	Possible IFD (n=16)	Other IFD (n=2)	Overall (n=31)
ACM	2 (16.7)	0	1 (6.3)	0	3 (9.7)
Exact 95% CI	(2.1, 48.4)	(0, 97.5)	(0.2, 30.2)	(0, 84.2)	(2.0, 25.8)

Source: Adapted from Table 21 of Clinical Study Report
Abbreviations: ACM, all-cause mortality; FAS, full analysis set; IA, invasive aspergillosis; IFD, invasive fungal disease; IM, invasive mucormycosis

Overall response as assessed by the AC at EOT and Days 42 and 84 for the FAS is summarized in Table 14. Per the protocol, information with respect to clinical signs and symptoms, mycological evidence, and radiological findings only needed to be recorded in the electronic case report form while the patient was receiving treatment with study drug. Therefore, the AC did not provide an assessment at a specific timepoint if study treatment had been completed prior to that timepoint.

At EOT, the AC-assessed overall response rate for the FAS was 54.8%. Of the 12 subjects with proven or probable IA, 8 (66.7%) subjects had a successful overall response at EOT as assessed by the AC. The single patient with proven IM was assessed by the AC as a failure at EOT due to progression.

Table 14. Overall Response as Assessed by the Adjudication Committee (FAS)

	Categorization of IFD				
Timepoint Response	Proven or Probable IA (n=12)	Proven or Probable IM (n=1)	Possible IFD (n=16)	Other IFD (n=2)	Overall (n=31)
EOT					
Success	8 (66.7%)	0	9 (56.3%)	0	17 (54.8%)
Complete	3 (25.0%)	0	3 (18.8%)	0	6 (19.4%)
Partial	5 (41.7%)	0	6 (37.5%)	0	11 (35.5%)
Failure	2 (16.7%)	1 (100.0%)	1 (6.3%)	0	4 (12.9%)
Stable	0	0	0	0	0
Progression	2 (16.7%)	1 (100.0%)	1 (6.3%)	0	4 (12.9%)
Not evaluable	2 (16.7%)	0	6 (37.5%)	2 (100.0%)	10 (32.3%)
Day 42					
Success	4 (33.3%)	0	5 (31.3%)	0	9 (29.0%)
Complete	0	0	1 (6.3%)	0	1 (3.2%)
Partial	4 (33.3%)	0	4 (25.0%)	0	8 (25.8%)
Failure	0	0	2 (12.5%)	0	2 (6.5%)
Stable	0	0	1 (6.3%)	0	1 (3.2%)
Progression	0	0	1 (6.3%)	0	1 (3.2%)
Not evaluable	1 (8.3%)	0	6 (37.5%)	0	7 (22.6%)
No assessment by AC	7	1	3	2	13
Day 84					
Success	5 (41.7%)	0	3 (18.8%)	0	8 (25.0%)
Complete	1 (8.3%)	0	1 (6.3%)	0	2 (6.5%)
Partial	4 (33.3%)	0	2 (12.5%)	0	6 (19.4%)
Failure	0	0	0	0	0
Stable	0	0	0	0	0
Progression	0	0	0	0	0
Not evaluable	0	0	3 (18.8%)	0	3 (9.7%)
No assessment by AC	7	1	10	2	20 (64.5%)

Source: Table 22 of Clinical Study Report
If a participant did not reach day 42 or 84 of therapy, the AC did not perform these assessments. Overall response was based on a composite of clinical, mycological, and radiological responses. Overall response was considered 'Not evaluable' when one of the composite responses was 'Not Assessed'.
Abbreviations: AC, adjudication committee; EOT, end of treatment; FAS, full analysis set; IA, invasive aspergillosis; IM, invasive mucormycosis; IFD, invasive fungal disease

8.1.3. Assessment of Efficacy Across Trials

There is only one trial submitted in support of the efficacy of isavuconazonium sulfate in the pediatric population aged 1 year to <18 years for the treatment of IA/IM.

8.1.4. Integrated Assessment of Effectiveness

A single non-comparative study 9766-CL-0107 was conducted to provide information regarding the efficacy of isavuconazonium sulfate in pediatric subjects aged 1 year to <18 years for the treatment of IA/IM. This trial was considered acceptable since the causative pathogens, course of disease, and approach to treatment are similar in adult and pediatric patients. Therefore, achievement of comparable exposures to adult patients is expected to result in similar efficacy

in pediatric patients allowing for extrapolation of efficacy in the pediatric population from the adult data.

Overall, the results observed in Study 9766-CL-0107 for isavuconazonium sulfate were favorable and generally consistent with those observed in the adult isavuconazonium sulfate pivotal study, Study 9766-CL-0104. The rates of ACM through Day 42 and overall response at EOT for isavuconazonium sulfate in Studies 9766-CL-0107 and 9766-CL-0104 are presented in Table 15.

Table 15. Efficacy Outcomes for Isavuconazonium Sulfate in Pediatrics and Adults

Endpoint	Pediatric Study 9766-CL-0107	Adult Study 9766-CL-0104
ACM though Day 42	6.5% (2/31)	18.6% (48/258)*
Overall response at EOT	54.8% (17/31)	35.0% (43/123)**

Source: Adapted from Table 11 and Table 14 of this review and Tables 8 and 9 of current Cresemba package insert
*Based on all randomized subjects who received at least one dose of study drug
**Based on subgroup of subjects with proven or probable invasive aspergillosis
Abbreviations: ACM, all-cause mortality; EOT, end of treatment

8.2. Review of Safety

8.2.1. Safety Review Approach

This safety review covers the integrated safety information derived from 2 studies in pediatric patients, Study 9766-CL-0046 (Study 0046) and Study 9766-CL-0107 (Study 0107). Study 0107 has been described in Section 8.1 of this review. Study 0046 was a two-part phase 1 study conducted in pediatric patients aged 1<18 years old at high risk for IFD in order to identify a dosing regimen for both intravenous (part 1 of study) and oral formulations (part 2) of isavuconazole that achieved adult target exposures. Based on these results, a dosing regimen was chosen that was then evaluated in Study 0107 (a phase 2, open-label, noncomparative, multicenter study to assess the safety and pharmacokinetics of isavuconazole in pediatric participants for the treatment of IA or IM). Together, these studies had a combined sample size of 77 patients who received at least one dose of IV/oral isavuconazole (the All Pediatric Population). These two studies were combined into an integrated safety review given similarities in the types of patients being treated (similar underlying conditions such as acute lymphocytic and myelogenous leukemia), similarity of dosing, and similar approaches to the collection of safety information. However, it should be noted that there was a significant difference in the duration of dosing, particularly as regards to the dosing of oral drug between the two studies, with subjects in Study 0107 having roughly 3 to 4 times the duration of oral dosing (median 64 days) as those subjects in part 2 of Study 0046 (median dosing 11-20 days). If important safety information was not available as an integrated analysis, priority was given to findings in Study 0107 given that such subjects were being treated for suspected or confirmed IA or IM.

8.2.2. Review of the Safety Database

Overall Exposure

As noted above, the All Pediatric Population (APP)/Safety Population consisted of 77 subjects who received at least one dose of IV/oral study drug. Study 0046 had a safety population of 46 subjects and Study 0107 had a safety population of 31 patients. The dosage regimen for subjects in both studies was as follows: 10 mg/kg (equivalent to 5.4 mg/kg of the active moiety, isavuconazole) every 8 hours on days 1 and 2 (total of 6 doses), followed by 10 mg/kg once daily. The milligram dose was capped at a maximum of 372 mg (equivalent to 200 mg of the active moiety, isavuconazole) per administration. The median duration of dosing was 15 days though as noted earlier this differed considerably by route of administration (longer durations for oral dosing) and by study (longer oral durations in study 0107; median oral dosing in study 0107 was 64 days versus 24 days in the All Pediatric Population). By comparison, the median dosing in the adult studies was 57 days (see Table 16 below).

Table 16. Summary of Study Drug Exposure in the All Pediatric and All Adult Studies (Safety Analysis Set)

Characteristic	All Pediatric (N=77)	All Adult (N=403)
Total duration (days)	77	403
Mean (SD)	31.68 (36.75)	76.05 (91.16)
Median	15.00	57.0
Min - Max	1 - 181	1 - 882
Duration of IV dosing only (days)	53	357
Mean (SD)	20.64 (23.56)	9.86 (10.86)
Median	13.00	6.0
Min - Max	1 - 99	0.5 - 84
Duration of oral Dosing only (days)	35	320
Mean (SD)	38.40 (37.62)	84.77 (93.11)
Median	24.00	70.50
Min - Max	5 - 169	0.5 - 882
Total duration category (days), n (%)		
1 to 7	18 (23.4)	53 (13.2)
8 to 14	16 (20.8)	35 (8.7)
15 to 21	10 (13.0)	29 (7.2)
22 to 42	14 (18.2)	51 (12.7)
43 to 56	4 (5.2)	33 (8.2)
57 to 84	9 (11.7)	97 (24.1)
>84	6 (7.8)	105 (26.1)
Cumulative total duration category (days), n (%)		
≥7	68 (88.3)	361 (89.6)
≥14	46 (59.7)	318 (78.9)
≥21	34 (44.2)	288 (71.5)
≥42	19 (24.7)	241 (59.8)
≥56	15 (19.5)	206 (51.1)
≥84	12 (15.6)	144 (35.7)
Participants without oral dosing, n (%)		
n (%)	42 (54.5)	83 (20.6)

Characteristic	All Pediatric (N=77)	All Adult (N=403)
Participants without IV dosing, n (%)		
n (%)	24 (31.2)	46 (11.4)

Source: Adapted from Applicant's Summary of Clinical Safety, Table 2 and Applicant's Study Report Body for Study 0107
Abbreviations: IV, intravenous; SD, standard deviation

The median age was 10.0 years in the APP and subjects were approximately evenly divided between the 6 to <12 year and the 12 to <18 year age categories (30 subjects [39.0%] versus 32 subjects [41.6%], respectively). Fifteen subjects (19.5%) were in the 1 to <6 years age category. A total of 42 subjects (54.5%) were female and 52 subjects (67.5%) were White. The other races represented in the APP included Asian (8 subjects [10.4%]) and Black or African American (6 subjects [7.8%]). The median BMI was roughly 18 kg/m^2.

Adequacy of the Safety Database

The safety database of 77 pediatric subjects is acceptable given that the study drug is from a known class of drugs with a well-known safety profile (azole antifungal class) and given that at least 30 individuals with the proposed indications were treated at the proposed dose. Data from the adult studies also help to inform the pediatric safety findings. Given that this is an orphan indication, finding study participants is challenging, and thus the current safety database is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission includes a statement from the Applicant that all clinical studies were conducted according to Good Clinical Practice as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. No clinical inspections were performed by the Office of Scientific Investigations given that no serious deficiencies were noted in the conduct of the adult trials and given the small size of the pediatric program.

Categorization of Adverse Events

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Specifically, MedDRA version 23.0 was used for integrated safety analyses.

Routine Clinical Tests

Clinical laboratory evaluations (including hematology, biochemistry, and liver function testing) vital signs analyses, and electrocardiogram (ECG) analyses were recorded for both studies. It should be noted that the only laboratory testing included for the integrated safety analyses was liver function testing. In this review, only Study 0107 will be used to evaluate hematology and biochemistry laboratory results given the similar treatment population/dosing duration to adults.

8.2.4. Safety Results

Deaths

There were 3 deaths (3.9%) in the All Pediatric population, all in Study 0107. Narratives are provided below followed by a medical assessment by the Clinical Reviewer.

Subject 3200210027

This was a 16-year-old White female diagnosed with acute myeloid leukemia who had recently been treated with cytarabine, methotrexate, clofarabine, cyclophosphamide, and etoposide. The participant also had an ongoing history of *Escherichia coli* sepsis, hypotension, septic shock, and multi-organ failure.

On Day 1, the participant started IV isavuconazonium sulfate for possible IFD and developed hypotension, subdural hemorrhage, severe pericardial effusion, septic shock and was hospitalized. It is unclear from the available data the exact time course of the hypotension in relation to the isavuconazonium sulfate infusion and subdural hemorrhage. Treatment for the events included oxygen, norepinephrine, morphine, vasopressin, platelets, midazolam, epinephrine, and magnesium sulfate. Isavuconazonium sulfate dose was reduced due to worsening septic shock on Day 5, and ultimately withdrawn (last dose Day 6) due to the ongoing hypotension. Also, on Day 6, the patient had cardiocirculatory arrest for which cardiopulmonary resuscitation was provided with vasopressive/inotropic medications and the participant was intubated. The participant also started on dialysis.

On Day 10, the participant developed severe venoocclusive liver disease. On Day 12, the participant had icterus and on Day 16 the participant developed anuria. On Day 25, the participant developed severe septic shock (assessed by the Investigator as not related to isavuconazonium sulfate), and needed intubation, vasopressor drugs, and a switch to continuous veno-venous hemofiltration. On the same day, a computed tomography scan showed a slight increase of hemorrhage and abdominal ascites, and a blood culture was positive for *Pseudomonas aeruginosa*. Treatment for septic shock included vancomycin, norepinephrine, midazolam hydrochloride, meropenem, ketamine hydrochloride, hydrocortisone sodium succinate, epinephrine, and dobutamine hydrochloride. On Day 26,

laboratory tests showed alanine transaminase (ALT) 1413 U/L (45.58 × upper limit of normal [ULN]), aspartate transaminase (AST) 10674 U/L (344.32 × ULN), and bilirubin 8.42 mg/dL (7.14 × ULN). The participant died the same day due to septic shock. An autopsy was not performed, and the death certificate was not provided.

Medical Officer Assessment: Given the recurrent/worsening sepsis, subdural hemorrhage, multiorgan failure including renal failure requiring dialysis and hepatic shock/failure, pericardial effusion, and ascites, it is difficult to clearly attribute the patient's death to use of isavuconazonium sulfate, particularly as the death occurred 20 days after withdrawal of study drug. The drug may have contributed to clinical signs such as hypotension and hepatotoxicity which could have worsened the patient's overall condition, but no clear relationship between the study drug and occurrence of death can be delineated.

Subject (b) (6)

This was a 15-year-old White female with atypical type 2 Griscelli syndrome and relevant medical history of gram-negative rod bacteremia, septic shock and sepsis, cytomegalovirus viremia, adenovirus disease, acute abdominal GVHD, and intermittent elevated liver function tests (the last ongoing for 2 years before study enrollment).

Isavuconazole was started on Day 1 for probable invasive pulmonary aspergillosis. Study drug was withdrawn due to worsening of clinical condition related to comorbidities (unclear if aspergillosis had improved at this time; patient switched to micafungin) on Day 38.

On Day 56, the participant developed rapid progression of hemophagocytic lymphohistocytosis with new seizures. On Day 57, the participant's family requested that resuscitation not be performed in the event of cardiac collapse. On Day 59, laboratory tests showed ALT 337 U/L (11.23 × ULN), AST 400 U/L (7.02 × ULN), and total bilirubin 145.38 µmol/L (8.50 × ULN). On Day 61, the family chose to focus on comfort care and the participant died the same day.

The autopsy report indicated that post-mortem findings were consistent with the participant's clinical history of multiorgan infection. Microscopic sections from the brain showed evidence of angioinvasive fungal infection, the spleen showed numerous histiocytes with evidence of hemophagocytosis, the liver findings were consistent with sepsis, and the heart showed scattered, small numbers of individually necrotic myocytes.

Medical Officer Assessment: No clear relationship between study drug and occurrence of death can be delineated. The death occurred 23 days after the withdrawal of study drug and in the setting of significant comorbid conditions including multiple infections (including possible worsening fungal infection)/worsening sepsis, hemophagocytic lymphohistocytosis progression, and liver failure.

Subject (b) (6)

This was a 16-year-old White Hispanic or Latino female with primary pulmonary hypertension who had previously received a lung transplant on an unspecified date and was receiving immunosuppressive medications. Ongoing medical history included acute humoral rejection of the lung transplant since Day -172. The participant was hospitalized on an unspecified date prior to study entry. On Day 1, treatment with isavuconazole was started for probable invasive aspergillosis (subsequently proven on biopsy).

On Day 10, the participant developed severe bilateral pneumonia and respiratory failure. Treatment included meropenem, dexmedetomidine, propofol, norepinephrine bitartrate, morphine, furosemide, cistracurium, ketamine, and non-mechanical ventilation. On Day 11, the participant had respiratory distress and a fungal culture was positive for *Aspergillus fumigatus* and *Aspergillus flavus* complex. On the same day, isavuconazonium sulfate was withdrawn due to lack of efficacy.

On Day 12, the participant had diffuse alveolar hemorrhage and cardiac failure, with treatment including levosimendan, epinephrine, and dobutamine. On Day 13, the participant was diagnosed with *P. aeruginosa* and *Streptococcus pneumonia* respiratory infection. On Day 15, the participant died due to cardiorespiratory arrest. An autopsy was not done, and the death certificate was not provided.

Medical Officer Assessment: There is no clear relationship between study drug and occurrence of death. Death occurred 5 days after withdrawal of study drug and in the setting of pulmonary bacterial and fungal infection and significant cardiorespiratory compromise.

Serious Adverse Events

There were 38 (49.4%) subjects in the APP who had a serious adverse event (SAE). Table 17 below lists the SAEs by preferred term that occurred in more than one subject in the APP.

Table 17. Serious TEAEs Occurring in More Than One Pediatric Patient in the APP

MedDRA v23.0 Preferred Term	All Pediatric (N=77)	All Adult (N=403)
Overall	38 (49.4%)	223 (55.3%)
Septic shock	3 (3.9%)	20 (5.0%)
Febrile neutropenia	4 (5.2%)	16 (4.0%)
Pneumonia	2 (2.6%)	14 (3.5%)
Pyrexia	5 (6.5%)	10 (2.5%)
Abdominal pain	2 (2.6%)	6 (1.5%)
Neutropenia	2 (2.6%)	4 (1.0%)
Diarrhea	3 (3.9%)	4 (1.0%)
Vomiting	2 (2.6%)	4 (1.0%)
Cytomegalovirus infection	2 (2.6%)	3 (0.7%)
Bacteremia	2 (2.6%)	3 (0.7%)
Graft versus host disease	2 (2.6%)	2 (0.5%)
Stomatitis	2 (2.6%)	0
Mucosal inflammation	2 (2.6%)	0

Source: adapted from Applicant's Table 6 in Summary of Clinical Safety and ISS table 3.2.3
Abbreviations: APP, all pediatric population; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

As can be seen in Table 17, the vast majority of SAEs were likely related to the underlying condition (including concomitant therapy). Observed SAEs that may have been related to study drug (abdominal pain, diarrhea, vomiting) were also seen in the adult trials and are currently listed in the United States Prescribing Information (USPI).

Three subjects in the APP experienced the following SAEs that were assessed as related to study drug treatment by the investigator: tachycardia, nausea, vomiting, pyrexia, injection site reaction, infusion site pain, infusion site pruritus, infusion-related reaction, and electrocardiogram prolonged QT. Similar to above, these SAEs are likely related to the underlying disease or are already described in the USPI. Brief narratives provided by the Applicant regarding these 3 subjects follow below:

- The treatment emergent adverse event (TEAE) of electrocardiogram QT prolonged in Study 9766-CL-0046 occurred in a 16-year-old female (Subject ID # (b) (6)) on day 7 of study treatment. The adverse event was a single episode and moderate in severity. This SAE resulted in discontinuation of study drug on day 8. The episode was considered resolved on day 15.

  Medical Officer assessment: Isavuconazole has been associated with shortening the QT interval in clinical studies, thus making the above association unusual and likely unrelated.

- The TEAEs of vomiting, pyrexia, nausea, and tachycardia in Study 9766-CL-0046 all occurred in a single subject, a 10-year-old female (Subject ID#: (b) (6) with underlying acute lymphocytic leukemia and a medical history of nausea and vomiting. Tachycardia, increased nausea, increased vomiting and low-grade pyrexia were reported

on day 18 of treatment. All events were of severe intensity, except for pyrexia, which was mild. Study drug was withdrawn on day 20 of treatment for the TEAEs of nausea, vomiting, and pyrexia.

Medical Officer assessment: Nausea and vomiting are already described in the USPI and in this case could be related to underlying disease. Tachycardia could be related to nausea and vomiting, and pyrexia could be related to underlying disease.

- The 4 TEAEs in Study 9766-CL-0107 occurred in a single individual, a 13-year-old male (Subject ID# (b) (6) on days 1 and 2 of treatment. These events were infusion site pain, infusion site pruritus, injection site reaction and infusion related reaction, all moderate in intensity. One of these, injection site reaction on day 2, led to withdrawal of study treatment on the same day.

  Medical Officer assessment: Infusion related reactions and injection site reactions are already described in the USPI.

Dropouts and/or Discontinuations Due to Adverse Effects

There were 9 (11.7%) subjects in the APP who had a TEAE leading to permanent discontinuation of study drug. The TEAEs were: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, electrocardiogram QT prolonged, hemoptysis, abdominal pain upper, nausea, vomiting, pyrexia, injection site reaction, mucosal inflammation, and hypotension. All were considered related to study drug except for hemoptysis and mucosal inflammation. All of the TEAEs are already described in the current USPI or are likely related to underlying disease.

Significant Adverse Events

Please see discussion of SAEs, TEAEs, and discontinuations. Elevated liver transaminases will be discussed in the "Laboratory Findings" section.

Treatment Emergent Adverse Events and Adverse Reactions

Almost all of the subjects in the APP had a TEAE, similar to the study population in the adult phase 3 trials. Table 18 lists TEAEs that occurred with a frequency of ≥10% in the APP population. The TEAEs are most likely related to underlying disease (such as anemia, thrombocytopenia, mucosal inflammation, etc.) or are already listed in the current USPI (nausea, vomiting, diarrhea, etc.). It should be noted that though hypertension occurred at a frequency of 10.4%, hypotension also occurred at a rate of 9.1%, making any relationship between hypertension and study drug unclear.

Table 18. TEAEs That Occurred in ≥10% of the APP

MedDRA v23.0 Preferred Term	All Pediatric (N=77) n (%)	All Adult (N=403) n (%)
Overall	72 (93.5)	386 (95.8)
Anemia	11 (14.3)	16 (4.0)
Tachycardia	10 (13.0)	20 (5.0)
Abdominal pain	14 (18.2)	38 (9.4)
Diarrhea	20 (26.0)	88 (21.8)
Nausea	10 (13.0)	105 (26.1)
Vomiting	16 (20.8)	100 (24.8)
Mucosal inflammation	13 (16.9)	28 (6.9)
Pyrexia	30 (39.0)	81 (20.1)
Pain in extremity	10 (13.0)	18 (4.5)
Headache	9 (11.7)	67 (16.6)
Epistaxis	10 (13.0)	28 (6.9)
Febrile neutropenia	8 (10.4)	39 (9.7)
Thrombocytopenia	9 (11.7)	13 (3.2)
Pruritus	9 (11.7)	30 (7.4)
Hypertension	8 (10.4)	33 (8.2)

Source: Adapted from ISS Table 3.2.1
Abbreviations: APP, all pediatric population; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

TEAEs assessed by investigators as related to study drug that occurred in more than one subject were diarrhea, nausea, vomiting, infusion site pain, procedural nausea, procedural vomiting, infusion-related reaction, alanine aminotransferase increased, aspartate aminotransferase increased, and headache. All of these TEAEs are currently listed in the USPI.

Laboratory Findings

Hematology

Hematology laboratory results were not evaluated in the Applicant's integrated summary of safety (ISS). In Study 0107, median changes from baseline to the end of treatment were evaluated (as per the Study 0107 Report Body Table 12.6.2.1.1) for hematology parameters including hemoglobin, platelets, leukocytes, and neutrophils. No clinically significant changes were noted.

Chemistry

Chemistry laboratory results were not evaluated in the Applicant's ISS. In Study 0107, median changes from baseline to the end of treatment were evaluated (as per the Study 0107 Report Body Table 12.6.2.1.2) for chemistry parameters including sodium, potassium, chloride, creatinine, magnesium, calcium, creatine kinase, and glucose levels. No clinically significant changes were noted.

Hepatic Panel/Liver Function Tests

There were three subjects in the APP who met Hy's law by laboratory criteria (all from Study 0107); however, all three had other clinical explanations for the elevations including a history of elevated liver enzymes and concomitant septic shock/circulatory collapse.

There were 5 subjects with transaminase elevations of at least 5 x ULN:

- 5 subjects with peak ALT or AST elevations at least 5 x ULN
- 2 subjects with peak ALT or AST elevations at least 10 x ULN and 2 subjects with peak ALT or AST elevations at least 20 x ULN (please note that the same two individuals had elevations of at least 10 and 20 X ULN; Subject #'s (b) (6) and (b) (6)

Four of the five subjects were from Study 0107. Please note that the current USPI contains a Warning for 'Hepatic Adverse Drug Reactions' including elevations in liver-related laboratory tests associated with isavuconazole treatment, thus the current findings are not unexpected.

Vital Signs

There was no vital signs analysis performed in the Applicant's ISS, so changes in relevant vital signs values were reviewed for the individual studies (0046 and 0107). No clinically significant median changes from baseline were noted.

Electrocardiograms

There was no integrated safety analysis of ECG findings in the Applicant's ISS, thus results from Study 0107 were the focus of this review. Three subjects were noted to have a change from normal ECG at baseline to clinically significant changes (as judged by the investigator) on ECG at any point post-treatment. In one subject (Subject ID # (b) (6) the changes noted were related to mild prolonged QT and the subject discontinued the study drug on Day 7 due to this (this patient was described in the Serious Adverse Event section of this review). In a second subject, the Day 3 ECG showed left atrial rhythm and possible left and right ventricular hypertrophy deemed clinically significant by the investigator. Similar findings were noted at later visits, however, and were deemed to be not clinically significant as assessed by the investigator. A third subject was found to have right atrial enlargement at Day 14 and left axis deviation and T wave inversion in the inferior leads at Day 28; both ECG findings were deemed to be clinically significant by the investigator. However, by the EOT visit (Day 84), the ECG showed normal sinus rhythm and nonspecific T wave abnormality, not clinically significant as assessed by the investigator. Overall, there was no clear relationship between study drug and abnormal ECG findings observed in these 3 subjects.

QT

TQT studies were submitted with the initial NDA. Currently, the USPI lists a dose-related shortening of the QT interval with isavuconazole rather than prolonged QT. No AEs related to QT shortening were noted in the APP. While tachycardia was noted in several subjects, this was presumed by both the investigators and this reviewer to be related to underlying disease/comorbidities including concomitant infection. Three subjects had an adverse event related to prolonged QT changes on ECG, one of which was assessed by the investigator to be related to study drug (see earlier discussion under SAEs).

Immunogenicity

Not applicable as isavuconazole is a small molecule not expected to evoke an immune response.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant defined adverse events of special interests based on risks identified during the original NDA submission (and postmarket). They included anaphylactic reactions, infusion related reactions, severe cutaneous adverse reactions, elevated liver transaminases and hepatitis, and arrhythmia due to QT shortening. In the pediatric studies, infusion reactions, potential allergic reactions, and elevated liver transaminases were all observed. As noted in the previous sections, such findings aligned with current labeling and alterations in the safety monitoring of such reactions are not needed in pediatric subjects taking isavuconazole.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Various subgroup analyses were performed by the Applicant, however given the small and unbalanced sample sizes among subgroups, it is difficult to draw any conclusions regarding the occurrence of TEAEs/types of TEAEs by subgroup. For example, when pediatric subgroups were split into the three age cohorts studied (1 to <6 years old, 6 to <12 years old, and 12 to <18 years old), the sample sizes were 15, 30, and 32 subjects, respectively. Similarly, Whites comprised more than 50% of the study population, making subgroup analyses difficult to interpret. With gender, where the distribution was somewhat more equitable (males =35 subjects, females =42 subjects), there was a trend toward more SAEs and TEAEs leading to discontinuation in females, but the significance of this finding is unclear.

8.2.8. Specific Safety Studies/Clinical Trials

Both studies (0046 and 0107) were primarily safety and PK studies.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable/evaluable in these uncontrolled studies of non-chronic use of study drug. Results of animal carcinogenicity studies are described in the current USPI.

Human Reproduction and Pregnancy

No new data were submitted. The current USPI contains a warning for embryo-fetal toxicity based on findings from animal reproduction studies.

Pediatrics and Assessment of Effects on Growth

Patients in the ISS were not followed long-term to determine effects of the drug on growth or other developmental parameters. Weight was measured at baseline and at EOT in Study 0107; no clear relationship could be delineated between study drug and weight gain/loss (this would be difficult to interpret regardless given the significant concomitant comorbidities and treatments received by the subjects).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This was not evaluated in these studies. The Applicant notes that isavuconazole does not have abuse potential. There is no specific antidote for isavuconazole; in cases of overdose, supportive treatment is recommended.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No new safety concerns were identified in these two postmarket pediatric studies (Study 0046 and Study 0107) and safety findings generally align with the safety findings in adults. Similarly, the Applicant notes that it has identified no differences in adverse drug reactions between adults and the pediatric population from routine pharmacovigilance activities.

In this submission, the Applicant describes a retrospective, non-interventional, noncomparative, descriptive cohort study in pediatric patients taking isavuconazole for a variety of fungal infections, including invasive aspergillosis, invasive mucormycosis, candidiasis, and unspecified mycoses. Seventy-six patients were included and approximately 30% of the subjects experienced an adverse event; all-cause mortality at Day 84 was 10.5%. The most common adverse events were related to electrolyte disturbances including hypomagnesemia,

hypophosphatemia, hypoglycemia, and hypokalemia. These adverse events differ from what was seen in the pediatric study data included in the current submission. The reason for this is unclear.

Expectations on Safety in the Postmarket Setting

Safety findings in the pediatric population align with the safety findings in adults and can be addressed through labeling and routine pharmacovigilance.

8.2.11. Integrated Assessment of Safety

Overall, safety analyses must be viewed in the context of the relatively small sample size (77 subjects from 2 uncontrolled pediatric studies), and for Study 0046, a slightly different pediatric patient population that included subjects receiving antifungal prophylaxis for a shorter duration of therapy relative to the treatment indication. Given that, the safety profile appears similar between adults and children, with a high incidence of gastrointestinal adverse events and notable adverse events (elevated transaminases, infusion reactions, etc.) already described in current labeling. Therefore, risk/benefit profile for isavuconazole remains favorable for the proposed pediatric population.

8.3. Statistical Issues

Comparative efficacy data for the pediatric population is not available as the single trial conducted was an uncontrolled study. Furthermore, the sample size of the study was small, so any interpretation of the efficacy data must be performed with caution. However, evidence of efficacy in the pediatric population is primarily based on extrapolation from the adult population for these indications.

8.4. Conclusions and Recommendations

The risk-benefit profile of isavuconazole for the treatment of invasive aspergillosis and invasive mucormycosis is similar between adults and children. Drug exposures demonstrating efficacy in adult trials of isavuconazole for IA and IM treatment can be achieved in pediatric patients using the intravenous and oral formulations, with the dosing instructions and age restrictions outlined for the pediatric population as proposed in Section 6 Clinical Pharmacology. There are no new safety findings in children relative to the adult population and no significant changes are needed with regards to pharmacovigilance and labeling (beyond a description of the findings in the pediatric trials). Isavuconazole should be approved for the treatment of invasive aspergillosis and invasive mucormycosis in children ages one year and older.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this supplemental NDA submission.

10 Pediatrics

Cresemba capsules (NDA 207500) and Cresemba for injection (NDA 207501) were approved in 2015 for the treatment of IA and IM in adults. Subsequent sNDAs were approved to add a smaller Cresemba capsule strength (74.5 mg isavuconazonium sulfate, NDA207500/S-013 and NDA 207501/S-011) and a nasogastric tube route of administration for reconstituted Cresemba for injection (NDA 207500/S-008 and NDA 207501/S-007) in adults, supported by data from bioequivalence studies.

Since both approved indications have Orphan Drug Designation, there was no requirement for PREA postmarket requirements at the time of initial approval. The current supplements were submitted in response to a Pediatric Written Request (described in Section 3 of this review) and contain safety and efficacy data supporting the extension of the approved indications to pediatric patients aged 1-18 years. The safety and efficacy of Cresemba in pediatric patients less than 1 year of age have not been established.

The studies in these pediatric efficacy supplements did not include PK data from oral administration of Cresemba in pediatric patients less than 6 years of age. Due to swallowing concerns, study participants less than 6 years old were not administered Cresemba capsule formulations. Nasogastric tube administration of Cresemba for injection was not included as a route of administration in the pediatric studies for any age group. Since there are no PK data following oral administration of Cresemba in pediatric patients less than 6 years of age that can be used to demonstrate comparable exposures to the adult patients receiving Cresemba for treatment of IA and IM in previous efficacy trials, the safety and efficacy of the oral routes of administration (Cresemba capsules and nasogastric administration of Cresemba for injection) have not been established in patients less than 6 years old.

The Applicant has reported difficulty with developing oral formulations of Cresemba suitable for use in pediatric patients <6 years of age. Development of an oral solution was (b) (4)

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

This prescribing information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (the PI that will be approved or close to being approved). The finalized PI was compared with the currently approved PI and the Applicant's draft PI (see Table 19). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with the labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 19. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Currently Approved PI and Applicant's Draft PI
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	The indications for treatment of IA and IM were extended to include pediatric patients 1 year of age and older for Cresemba for injection and adults and pediatric patients 6 years of age and older who weigh 16 kg and greater for Cresemba capsules. The Applicant's proposal (b) (4) was not accepted (b) (4)
2 DOSAGE AND ADMINISTRATION	The Applicant's proposal for pediatric dosage and administration for both intravenous (IV) and oral capsule (PO) was revised by the review team and included in a new subsection 2.3 (Recommended Dosage and Administration in Pediatric Patients). For Cresemba for injection, the following key modifications were made by the review team: • The loading dose and maintenance dose (b) (4) 15 mg/kg in pediatric patients 1 to less than 3 years of age with a body weight limit of 18 kg. As per CDC NHANES growth charts, ~18 kg is the highest expected body weight for a patient 1 to less than 3 years of age. Refer to Section 6.2 of the Integrated Assessment Review for additional information. • The table (Recommended Dosage and Administration for Cresemba in Pediatric Patients) includes columns for age and body weight.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Currently Approved PI and Applicant's Draft PI
	For Cresemba capsules, the following key modifications were made by the review team: • An age range of 6 to less than 18 years of age was included in the table (Recommended Dosage and Administration for Cresemba in Pediatric Patients), due to swallowing concerns in patients less than 6 years of age. • The proposed dose adjustment of 2 capsules for a body weight of (b) (4) 16 to less than 18 kg. As per CDC NHANES growth charts, ~16 kg is the lowest expected body weight for a patient 6 years of age and older. Refer to Section 6.2 of the Integrated Assessment for additional information. For nasogastric tube administration of Cresemba for injection, the following key modifications were made by the review team: • The Applicant revised Section 2.6 (formerly (b) (4)) to include nasogastric tube administration of Cresemba for injection formulation for pediatric patients. The review team modified the age range to only include pediatric patients 6 to less 18 years of age and weighing at least 16 kg, as the oral route of administration was not assessed for PK and safety in pediatric patients less than 6 years of age. Refer to Section 6.2 of the Integrated Assessment for additional information. • Since there is no method for preparation and administration of Cresemba capsules via a nasogastric tube, the statement "Do not administer Cresemba capsules through a nasogastric tube" was added as per the labeling recommendations in the Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations guidance (June 2021)
4 CONTRAINDICATIONS	No change from currently approved PI.
5 WARNINGS AND PRECAUTIONS	No change from currently approved PI.
6 ADVERSE REACTIONS	Subsection 6.1 Clinical Trials Experience was revised. The Applicant added a subsection describing the clinical trials experience in pediatric patients with a summary of the safety findings in the 77 patients who received at least one dose of IV or oral Cresemba in the two uncontrolled studies. The review team revised the summary to include a description of the age distribution of the pediatric patients and the median treatment duration. The descriptions of (b) (4) were removed (b) (4). A conclusion was added to state adverse reactions (including serious adverse reactions and adverse reactions leading to permanent discontinuation of study drug) were similar to those

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Currently Approved PI and Applicant's Draft PI
	observed in adults. Refer to Section 8.2 of the Integrated Assessment for additional information.
7 DRUG INTERACTIONS	The Applicant added vincristine to the table (The Effect of Cresemba on the Pharmacokinetics of Other Drugs) and recommended to use vincristine with caution when concomitantly administered with Cresemba in pediatric patients. The review team revised the table and recommended to avoid concomitant use of vincristine and Cresemba in both pediatric and adult patients. Refer to Section 6.2 of the Integrated Assessment for additional information.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Subsection 8.4 Pediatric Use was revised. The Applicant added a statement that the safety and efficacy of Cresemba for the treatment of invasive aspergillosis and invasive mucormycosis have been established in pediatric patients 1 year of age and older and that use of Cresemba in this age group is supported by evidence in adult patients and additional PK and safety data in pediatric patients one year and older. The Applicant also added a statement that dosing recommendations are weight based. The review team made the following revisions based on the Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling guidance (March 2019) and the revised dosing recommendations after review of the submitted PK data: • Editing the section to discuss the IA and IM treatment indications separately and providing additional information on the adult trials used in the extrapolation of efficacy. • Revising the pediatric use statements to clarify the formulations approved for use by age group to state: — Safety and efficacy of Cresemba for injection for the treatment of IA/IM have been established in pediatric patients 1 year of age and older — Safety and efficacy of Cresemba capsules for the treatment of IA/IM have been established in pediatric patients 6 year of age and older weighing 16 kg and greater. • Adding a statement that the adverse reactions in this pediatric population were similar to those observed in the adult population.
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	The review team recommended an update in terminology to change [redacted (b) (4)]" to "adverse reactions" in this section.

12 CLINICAL PHARMACOLOGY	Subsection 12.3 was revised. The Applicant included the following items in Subsection 12.3: • Added Table 8, which summarizes the derived steady-state isavuconazole AUC values in pediatric patients by age group (b) (4) [redacted] • Two sentences were added to the section: — Summarized that pharmacokinetics were evaluated in 73 pediatric subjects from 2 studies which included 28 patients with IA or possible IM. — (b) (4) [redacted]. • (b) (4) [redacted] The review team made the following major changes to Subsection 12.3: • Four changes were made to Table 8 as follows (Refer to Section 6.2 of the Integrated Assessment for additional information): — The age group (b) (4) [redacted] 1 to <3 years of age and 3 to <6 years of age, (b) (4) [redacted] — For the group 1 to <3 years of age, the AUC values were based on the individual patient Empirical Bayes Estimates for 15 mg/kg. — Table was revised to include dosage for each age group. — A footnote was included below the table indicating the routes of administration that correspond with the derived AUC values by age group. • To align with the Guidance for Industry: Clinical Pharmacology Section of Labeling (December 2016), the review team removed the sentence (b) (4) [redacted]. • The review team made the following changes summarizing the interaction between Cresemba and vincristine. — Based on the physiologically based pharmacokinetic analysis, the attributable DDI effects (vincristine exposure predicted to

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Currently Approved PI and Applicant's Draft PI
	increase less than 2-fold) were mainly due to P-glycoprotein inhibition by isavuconazole. — The DDI effects of concomitant vincristine and Cresemba were expected to occur in both pediatric and adult patients.
13 NONCLINICAL TOXICOLOGY	There was no change in the content of this section from the approved PI, but the review team recommended organization of Section 13.1 into subsections (Carcinogenesis, Mutagenesis, Impairment of Fertility) to improve readability.
14 CLINICAL STUDIES	Minor editorial changes from currently approved PI.
17 PATIENT COUNSELING INFORMATION	There was no change in the content of this section from the approved PI, but the review team recommended organization into subsections (Important Administration Instructions, Drug Interactions, Pregnancy, Allergic Reactions) to improve readability.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	The following clarifications were added to the Dosage and Administration sections describing instructions for reconstitution of Cresemba for injection for intravenous or nasogastric tube administration: • [redacted] (b) (4) will be 74.4 mg/mL of isavuconazonium sulfate. • Discard any unused portion of the reconstituted solution. The following clarifications was added to the Dosage and Administration and the How Supplied/storage and Handling sections: • Reconstituted solution should be used immediately, or stored between 5°C to 25°C (41°F to 77°F) [Temperature range provided by the Applicant] Refer to the Integrated Quality Assessment in DARRTS for additional information.

Source: Reviewers' table
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviations: ACM, all-cause mortality; AUC, area under the curve; CDC NHANES, Centers for Disease Control and Prevention; National Health and Nutrition Examination Survey; DDI, drug-drug interaction; FAS, full analysis set; IA, invasive aspergillosis; IFD, invasive fungal disease; IM, invasive mucormycosis; IV, intravenous; PI, prescribing information

Other Prescription Drug Labeling

The Patient Labeling Team from the Division of Medical Policy Programs (DMPP) reviewed the Cresemba Patient Package Insert and recommended changes to reduce redundancy, to make patient information more consistent and concise, and to include the information necessary for patients to safely take their medication (see DMPP review in DARRTS dated 11/15/2023 for additional details).

Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Information

12 Risk Evaluation and Mitigation Strategies

No risk evaluation and mitigation strategies are recommended. At this time, there are no data to indicate the risks associated with Cresemba use in the pediatric population are different than in the adult population. Any risks can be communicated in the labeling for Cresemba, as is the case for the adult population.

13 Postmarketing Requirements and Commitment

No postmarketing requirements or postmarketing commitments will be issued upon approval of these efficacy supplements. Postmarketing commitments to develop additional oral pediatric formulations were considered but the Applicant notified FDA that the Cresemba prodrug physiochemical properties preclude the development of an age-appropriate formulation other than the 74.5 mg capsule.

14 Division Director (Clinical) Comments

I agree with the review team's assessment and recommendations.

15 Appendices

15.1. References

Literature

Apsemidou, A, N Petridis, TA Vyzantiadis, and A Tragiannidis, 2018, Invasive Aspergillosis in Children: Update on Current Guidelines, Mediterr J Hematol Infect Dis, 10(1):e2018048.

Barnett, S, F Hellmann, E Parke, G Makin, DA Tweddle, C Osborne, G Hempel, and GJ Veal, 2022, Vincristine dosing, drug exposure and therapeutic drug monitoring in neonate and infant cancer patients, Eur J Cancer, 164:127-136.

Fedeli, L, M Colozza, E Boschetti, I Sabalich, C Aristei, R Guerciolini, A Del Favero, R Rossetti, M Tonato, P Rambotti, and et al., 1989, Pharmacokinetics of vincristine in cancer patients treated with nifedipine, Cancer, 64(9):1805-1811.

Francis, JR, P Villanueva, P Bryant, and CC Blyth, 2018, Mucormycosis in Children: Review and Recommendations for Management, J Pediatric Infect Dis Soc, 7(2):159-164.

Lee, CM, NR Zane, G Veal, and DR Thakker, 2019, Physiologically Based Pharmacokinetic Models for Adults and Children Reveal a Role of Intracellular Tubulin Binding in Vincristine Disposition, CPT Pharmacometrics Syst Pharmacol, 8(10):759-768.

Lu, H and S Rosenbaum, 2014, Developmental pharmacokinetics in pediatric populations, J Pediatr Pharmacol Ther, 19(4):262-276.

Patterson, TF, GR Thompson, 3rd, DW Denning, JA Fishman, S Hadley, R Herbrecht, DP Kontoyiannis, KA Marr, VA Morrison, MH Nguyen, BH Segal, WJ Steinbach, DA Stevens, TJ Walsh, JR Wingard, JA Young, and JE Bennett, 2016, Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America, Clin Infect Dis, 63(4):e1-e60.

Pilla Reddy, V, AJ Fretland, D Zhou, S Sharma, B Chen, K Vishwanathan, DF McGinnity, Y Xu, and JA Ware, 2021, Mechanistic physiology-based pharmacokinetic modeling to elucidate vincristine-induced peripheral neuropathy following treatment with novel kinase inhibitors, Cancer Chemother Pharmacol, 88(3):451-464.

Prasad, B, A Gaedigk, M Vrana, R Gaedigk, JS Leeder, L Salphati, X Chu, G Xiao, C Hop, R Evers, L Gan, and JD Unadkat, 2016, Ontogeny of Hepatic Drug Transporters as Quantified by LC-MS/MS Proteomics, Clin Pharmacol Ther, 100(4):362-370.

Rowland, M and TN Tozer, 2010, Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications; 4th edition, LWW.

Stage, TB, S Hu, A Sparreboom, and DL Kroetz, 2021, Role for Drug Transporters in Chemotherapy-Induced Peripheral Neuropathy, Clin Transl Sci, 14(2):460-467.

Triarico, S, A Romano, G Attina, MA Capozza, P Maurizi, S Mastrangelo, and A Ruggiero, 2021, Vincristine-Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment, Int J Mol Sci, 22(8)

Upreti, VV and JL Wahlstrom, 2016, Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling, J Clin Pharmacol, 56(3):266-283.

van de Velde, ME, JC Panetta, AJ Wilhelm, MH van den Berg, IM van der Sluis, C van den Bos, FCH Abbink, MM van den Heuvel-Eibrink, H Segers, C Chantrain, J van der Werff Ten Bosch, L Willems, WE Evans, and GL Kaspers, 2020, Population Pharmacokinetics of Vincristine Related to Infusion Duration and Peripheral Neuropathy in Pediatric Oncology Patients, Cancers (Basel), 12(7)

van Groen, BD, E van de Steeg, MG Mooij, MMH van Lipzig, BAE de Koning, RM Verdijk, HM Wortelboer, R Gaedigk, C Bi, JS Leeder, RHN van Schaik, J van Rosmalen, D Tibboel, WH Vaes, and SN de Wildt, 2018, Proteomics of human liver membrane transporters: a focus on fetuses and newborn infants, Eur J Pharm Sci, 124:217-227.

Wattier, RL and L Ramirez-Avila, 2016, Pediatric Invasive Aspergillosis, J Fungi (Basel), 2(2)

Guidance for Industry

Guidance for Industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016)

ICH Guidance for Industry *ICH guideline M10 on bioanalytical method validation and study sample analysis* (July 2022)

Draft Guidance for Industry *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations* (June 2021)

Guidance for Industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019)

Guidance for Industry *Bioanalytical Method Validation Guidance for Industry* (May 2018)

Other

Astellas, 2015, Cresemba prescribing information, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207500s011,207501s009lbl.pdf.

Centers for Disease Control and Prevention, 2020, Fungal Diseases, accessed, https://www.cdc.gov/fungal/diseases/mucormycosis/health-professionals.html.

Centers for Disease Control and Prevention National Center for Health Statistics, 2022, Growth Charts, accessed, https://www.cdc.gov/growthcharts/index.htm.

Hospira, 1996, Vincristine sulfate injection prescirbing information, accessed, https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=49596de6-ab18-49d1-9e5b-30968fc21c36&type=display.

15.2. Financial Disclosure

The Applicant has noted no investigators with financial arrangements, payments, or interests requiring disclosure under 21 CFR 54.4(a)(3) for study 9766-CL-0107 (information for one sub-investigator was not available); this is referenced on Form FDA 3454.

Covered Clinical Study (Name and/or Number): Study 9766-CL-0107

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 29		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Not applicable.

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.4.1. Clinical Pharmacology Studies

Study 9766-CL-0046

This was a phase 1 non-comparative, open-label study to characterize the PK, safety, and tolerability of isavuconazonium sulfate in pediatric patients (1 to <18 years for IV or 6 to <18 years for oral) who are at high risk for invasive fungal disease (e.g., hematological malignancy). The study was conducted in two sequential parts: part 1 consisted of 3 IV dosing cohorts (1 to <6 years, 6 to <12 years, and 12 to <18 years); and part 2 consisted of two oral dosing cohorts (6 to <12 years and 12 to <18 years). Subjects received a loading dose (a dose every 8 hours ±2 hours on days 1 and 2, followed by once daily maintenance dosing for up to 26 additional days or a maximum of 28 days of dosing).

The doses for parts 1 and 2 were derived from modeling and simulation to meet the proposed AUC range shown to be safe and effective (as described in Section 6.2 and 15.4.3). The pediatric IV doses were 10 mg/kg for ≤40 kg and 372 mg for >40 kg, and pediatric oral doses were based on body weight (i.e., 16 to 17 kg – two capsules, 18 to 24 kg – three capsules, 25 to 31 kg – four capsules, ≥32 kg – five capsules). The capsule strength was 74.5 mg.

A preliminary population PK model was developed from the PK data of eight subjects (irrespective of age) for both part 1 and part 2, and it was used to estimate the PK parameters for determining if any dosing modifications were warranted for the remaining subjects in both parts 1 and 2.

For PK assessment in Part 1, five blood samples (15 minutes prior to start of infusion, and 1 hour, 4 to 8 hours, 8 to 12 hours, and 16 to 24 hours after start of infusion) for a 24-hour PK profile were collected on days 3 (+1 day), 7 (±1 day), and at day 28 or EOT visit (or within 2 days prior to the last dose). If the patient was able to provide PK samples beyond day 7, trough sampling was performed weekly, ~24 hours after prior day's infusion through day 28 or EOT.

For the PK assessment in part 2, plasma samples for a 24-hour PK profile were collected on day 7 (±1 day) at pre-dose, 1, 2, 3, 4, 6, 8, and 24 hours after drug administration. In addition,

plasma PK samples were collected before the first dose on days 2, 3, 5, 14 (±2 days), 21 (±2 days, and 28 (±2 days).

In part 1, a total of 27 of 29 patients (1 to <18 years) enrolled were administered at least 1 dose of study drug and included in the safety profile, 26 patients provided at least 1 valid PK sample, and 24 subjects completed the study. In part 2, a total of 19 of 20 patients (6 to <18 years) enrolled were administered at least one dose of study drug, 19 patients provided at least one valid PK sample, and 14 patients completed the study. Demographic and PK parameter estimates based on noncompartmental analysis are shown in Table 20.

Table 20. Demographic and Pharmacokinetic Profile of Pediatric Patients 1 to <18 Years Administered Isavuconazonium Sulfate IV or Oral

Parameter	Cohort 1 (IV) 1 to <6 Years (n=9)	Cohort 2 (IV) 6 to <12 Years (n=8)	Cohort 3 (IV) 12 to <18 Years (n=9)	Cohort 4 (Oral) 6 to <12 Years (n=9)	Cohort 5 (Oral) 12 to <18 Years (n=10)
Sex (% female)	33.3	25.0	22.2	44.4	60.0
Weight (kg)	15.7 (2.6)	33.8 (16.1)	67.6 (19.7)	32.0 (12.0)	55.4 (19.1)
Day 3					
Ctrough (mg/L)	4.2 (34%)	4.3 (49%)	2.5 (45%)	4.7 (52%)	3.7 (52%)
C_{max} (mg/L)	7.8 (11%)*	7.8 (21%)†	5.5 (42%)*	n/a	n/a
AUC_{tau} (h* mg/L)	112 (22%)*	102 (35%)†	70 (30%)*	n/a	n/a
Day 7					
Ctrough (mg/L)	3.3 (52%)	3.0 (57%)	2.7 (42%)#	4.0 (46%)	3.1 (52%)†
C_{max} (mg/L)	7.3 (17%)	6.8 (31%)	5.0 (24%)* #	6.0 (37%)	5.0 (43%)*¥
AUC_{tau} (h* mg/L)	97 (49%)*	87 (38%)	77 (27%)†#	111 (45%)†	83 (40%)‡¥

Source: Adapted from Table 12.4.1 and 12.4.2 (Study report 9766-CL-0046) and ADAM datasets ADPC and ADPP
Demographic data are presented as mean (standard deviation), except sex (% female);
PK profile data are presented as mean (CV%)
*: 1 patient was excluded from the data analysis, because no administration time or dose available, PK implausibility, or PK sampling error
†: 2 patients were excluded from the data analysis, because of a PK sampling error, PK implausibility, and/or no dose/time available
‡: 4 patients were excluded from the data analysis, because elimination phase was not defined (PK implausibility), no dose/time available.
#: only included 8 patients, as 1 patient discontinued study drug on Day 3
¥: only includes 9 patients, as 1 patient discontinued study drug on Day 6
Abbreviations: $AUC_{tau,}$ area under the curve from 0h to tau; C_{max}, maximum concentration; Ctrough, trough concentration; IV, intravenous; N, number of patients in category; n/a, not available; PK, pharmacokinetic

Study 9766-CL-0107

This pediatric study was a phase 2, open-label, non-comparative, multicenter study to assess the safety and tolerability, efficacy and PK of isavuconazonium sulfate in pediatric patients for the treatment of IA or IM. Dose selections were derived from modeling and simulation and data from the phase 1 pediatric study. Patients received a loading dose (a dose every 8 hours ±2 hours on days 1 and 2, followed by a once daily maintenance dose starting 12 - 24 hours after the last loading dose for both IV and oral formulations for a maximum duration of 84 days (IA) and 180 days (IM). The pediatric IV doses were 10 mg/kg for ≤37 kg and 372 mg for >37 kg for

patients 1 year to <18 years, and the pediatric oral doses were based on body weight (i.e., 12 to 17 kg – 2 capsules, 18 to 24 kg – 3 capsules, 25 to 31 kg – 4 capsules, and ≥32 kg – 5 capsules) for patients 6 years to <18 years. The capsule strength was 74.5 mg. Since the phase 1 exposures between IV and oral were similar and given the high bioavailability, interchangeable administered between IV and oral capsule was allowed in the study.

A total of 31 patients (1 to <18 years) enrolled were administered at least one dose of study drug and included in the safety profile. Throughout the treatment duration, 15 patients received IV only, five patients received oral only, and 11 received both IV and oral. A pre-dose PK sample (~17-to-26 hours post-dose) was collected from 28 patients (Table 21). In addition, four to six plasma samples were collected within a 24 hour dosing interval between Day 14 and 42 from a subpopulation of patients (12 patients -seven patients were administered IV route and five patients were administered oral route) for a 24 hour PK assessment (Table 22 and Table 23).

Table 21. Mean (%CV) Trough Plasma Concentrations of Patients Administered Isavuconazonium Sulfate

Parameter	1 to 2 Years IV	3 to 5 Years IV	6 to <12 Years IV	12 to <18 Years IV	6 to <12 Years Oral	12 to <18 Years Oral
CtroughDay 7,mg/L	3.0 (76%) N=4	3.0 (22%) N=2	3.2 (38%) N=6	3.7 (38%) N=7†	5.0 (37%) N=5	4.2 (25%) N=3
CtroughDay 14,mg/L	1.7 (135%) N=4	3.6 (10%) N=2	2.9 (55%) N=3	4.3 (61%) N=4	4.2 (59%) N=7*†	4.9 (36%) N=4‡
CtroughDay 21,mg/L	1.5 (85%) N=4	2.4 (2%) N=1†	2.2 (57%) N=2	3.9 (70%) N=2	3.6 (50%) N=6‡	4.7 (26%) N=3‡

Source: Adapted from Table 12.4.1.1 (Study report 9766-CL-0107) and ADAM dataset ADPC
Data are presented as mean (%CV)
†: 1 patient had 2 pre-dose samples on same day ±2 days, and they were both included in the analysis.
*: 2 patients received IV on Day 7 and were included in $Ctrough_{Day7}$ analysis.
‡: 1 patient received IV on Day 7 and was included in $Ctrough_{Day7}$ analysis
Abbreviations: $Ctrough_{Day7}$, trough (pre-dose) concentration on Day 7±2 days; $Ctrough_{Day14}$, trough (pre-dose) concentration on Day 14±2 days; $Ctrough_{Day21}$, trough (pre-dose) concentration on Day 21±2 days; N, number of patients in category; IV, intravenous

Table 22. Subpopulation 24-Hour Pharmacokinetic Profile of Isavuconazole IV

Age	Patients N	Route	1 h	4-10 h	16-24 h	Predose
1 to <3 years	2	IV	4.4 (45%) mg/L	2.0 (14%) mg/L	1.2 (24%) mg/L	1.4 (5%) mg/L
6 to <12 years	2	IV	12.0 (38%) mg/L	6.3 (48%) mg/L	4.2 (48%) mg/L	3.9 (50%) mg/L
12 to <18 years	3	IV	11.6 (50%) mg/L	5.3 (67%) mg/L	4.1 (53%) mg/L	4.2 (69%) mg/L

Source: Adapted from Table 12.4.2.1 (Study report 9766-CL-0107) and ADAM dataset ADPC
Data are presented as mean (%CV)
Abbreviations: h, hour; IV, intravenous; N, number of patients

Table 23. Subpopulation 24-Hour Pharmacokinetic Profile of Isavuconazole Oral

Age	Patients N	Route	1 h	3 h	4 h	6-8 h	24 h	Predose
6 to <12 years	4	Oral	4.1 (36%) mg/L	5.7 (23%) mg/L	5.8 (33%) mg/L	5.1 (38%) mg/L	3.6 (46%) mg/L*	3.9 (39%) mg/L
12 to <18 years	1	Oral	3.3 mg/L	5.0 mg/L	6.3 mg/L	5.9 mg/L	3.4 mg/L	3.6 mg/L

Source: Adapted from Table 12.4.2.1 (Study report 9766-CL-0107) and ADAM dataset ADPC
Data are presented as mean (%CV)
*: 3 patients had a sample collected
Abbreviations: h, hour; IV, intravenous; N, number of patients

15.4.2. Summary of Bioanalytical Method Validation and Performance

The bioanalytical method validation addendum was made to support additional evaluations (specificity, lipemia, matrix factor, additional stability, and equivalency between di-potassium EDTA and tri-potassium EDTA). The updated assay met the FDA 2018 guidance, entitled, Guidance for Industry - Bioanalytical Method Validation (May 2018). However, the matrix effect evaluation had several deviations from the 2022 ICH guidance, entitled, Guidance for Industry-Method Validation and Study Sample Analysis (July 2022): 1) they only evaluated the eight matrix source lots one time for the low and high quality controls (QCs) as opposed to three replicates for low and high QCs; and 2) each individual matrix lot evaluated should be within ±15% of the nominal concentration, but one of the eight samples in the low QC was over 15% and three of eight samples in high QC were over 15%. For both pediatric studies, the method performance was satisfactory.

An inspection by the OSIS was requested at the filing meeting for the Clinical Research Organizations ((b) (4) that performed the bioanalytical method validations and performances. OSIS conducted an analytical remote regulatory assessment of both studies, and they observed no objectionable conditions and no identifiable concerns regarding the reliability of the data.

15.4.3. Comparison of Isavuconazole Pharmacokinetics Across Pediatrics and Adult Patients

For comparing isavuconazole PK between pediatrics and adults, the Applicant relied on a prespecified target drug exposure range of isavuconazole AUCss of 60 h*mg/L to 233 h*mg/L. The target drug exposure range was defined after analysis of the adult isavuconazole plasma drug exposures, as well as the efficacy and safety associated with these plasma drug exposures from 372 mg isavuconazonium sulfate IV infusion or as oral capsules in the SECURE study and safety associated with a supratherapeutic isavuconazonium sulfate oral dose (1116 mg isavuconazonium sulfate) in an adult phase 1 TQT study (9766-CL-0017). The target range lower boundary of 60 h*mg/L corresponds to 25th percentile value of the adult plasma drug exposure range in the SECURE study. The mean, median and range of the AUC_{ss} from the SECURE study and adult phase 1 TQT study (9766-CL-0017) is presented in Table 24.

Table 24. Exposures From the Invasive Aspergillosis Study (SECURE) for 372 mg Dose of Isavuconazonium Sulfate and 9766-CL-0017 Study

	SECURE Study	9766-CL-0017 Study (1116 mg Dose)
Parameter	AUC_{ss} (mg*hr/L)	AUC_{0-24} (mg*hr/L)
Mean (SD)	101 (56)	353 (72)
Minimum to maximum	10-343	233 - 545
Median	90	345

AUC_{0-24}: area under the isavuconazole concentration-time curve at 24 hours; SD: standard deviation.
Source: A9766-PK-0010 Amendment 1 Table 4

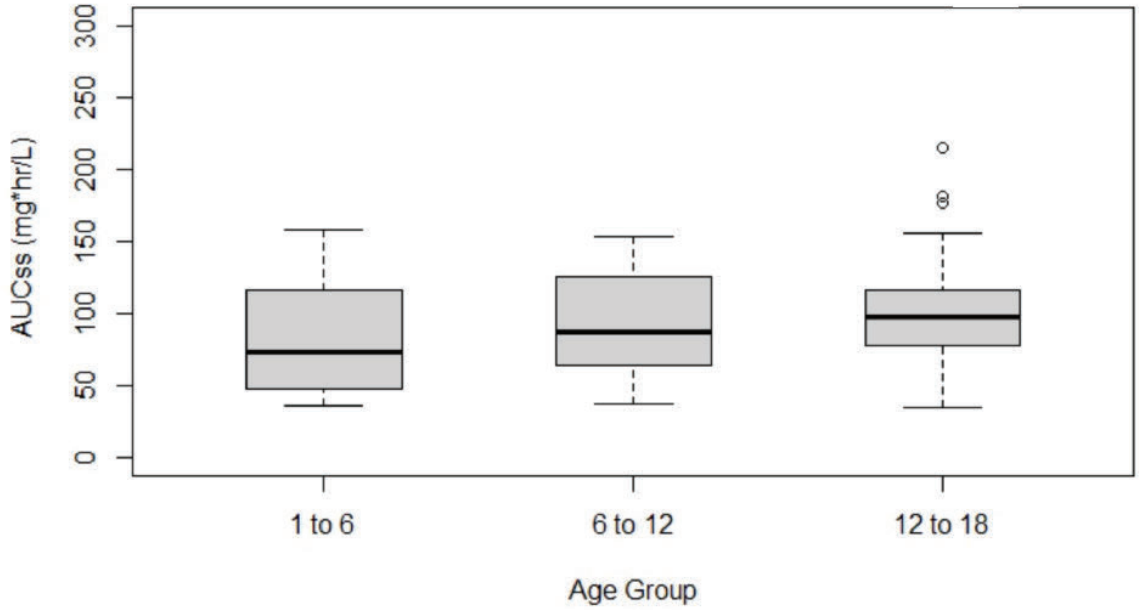
This exposure matching approach was based on a comparison of model-predicted isavuconazole AUCss in pediatric patients from the phase 1 (9766-CL0018) and phase 2 (9766-CL-0046) trials compared to the prespecified target drug exposure boundary. Using these estimates, the mean, median and range, of AUC_{ss} for the following age groups were determined and compared to prespecified target range: 1 to <6 years, 6 to <12 years, 12 to <18 years of age, and full population. The Applicant postulated similar exposure in the pediatric population to the adult population since the mean and median pediatric exposures for the entire pediatric population studied, as well as within each of the three age groups, was within the target drug exposure prespecified boundaries, and that the range for the entire pediatric population was contained within the bounds of the minimum observed in the SECURE study and minimum observed in the adult phase 1 TQT study(9766-CL-0017). The mean, median and range of the pooled phase 1 (9766-CL0018) and phase 2 (9766-CL-0046) trials by age group is presented in Table 25 and a plot of the distribution of the AUCss is shown in Figure 4.

Table 25. Isavuconazole AUC (mg*hr/L) Values at Steady-State by Age Group

	AUC Values		
Age Group	1 to < 6 years (n = 15)	6 to < 12 years (n=29)	12 to < 18 years (n= 29)
Mean	86.6	97.2	104
Median	73.0	87.4	97.7
Min-Max	35.8 - 159	37.7 - 154	35.5 - 215

Source: A9766-PK-0010 Amendment 1 Table 8
Abbreviations: AUC, area under the curve

Figure 4. Box Plot of Calculated AUC Values at Steady-State by Age Group



Box-and-whisker plots of drug exposure AUCss in pediatric age groups
Source: A9766-PK-0010 Amendment 1 Table 4 Figure 4
Abbreviations: AUC_{ss}, steady-state area under the curve

Reviewer Comments: *To evaluate and compare isavuconazole exposures between pediatric and adult patients, the Clinical Pharmacology Review Team relied exclusively on independently derived isavuconazole exposures (AUCss) from an independent analysis using the Applicant population PK model. Additionally, trough concentration (Ctrough) observation records filtered from the population PK dataset, defined as concentration observations sampled 20 to 26 hours post-dose, were used as supportive data.*

The pediatric PK data used for noncompartmental analysis (NCA) estimates originated from the Applicant's population PK dataset which contains phase 1 (9766-CL0018) and phase 2 (9766-CL-0046) pediatric trials. For these analyses, we compared exposures in pediatric patients based on the Applicant's stated age groups, as well as by each year of age separately, and the Applicant's stated body weight bands proposed in the draft labeling to the prespecified target drug exposure boundaries. As detailed in Section 6.2.2, the isavuconazole AUC_{ss} and Ctrough for pediatrics of all age cohorts and body weight bands were generally comparable to the adult patient population with the exception of pediatric patients 1 to <3 years of age.

15.4.4. Pharmacometrics Review

15.4.4.1. Population PK Analysis

Review Summary

The Cresemba (isavuconazonium sulfate) capsules, for oral use and Cresemba (isavuconazonium sulfate) for injection, for IV use, pediatric efficacy supplements seek to extend the indications for treatment of IA and IM to a pediatric population, ages 1 to 17 years of age, by extrapolation of efficacy from reference adult data. Isavuconazole is the active moiety of water-soluble prodrug isavuconazonium sulfate. Isavuconazonium has been observed to rapidly metabolize to isavuconazole by plasma esterases in in vitro experiments (half-life <2 minutes).

For both IV and oral dosing, a loading dose is required, one dose every 8 hours for a total of 6 doses, followed by a maintenance dose once daily, with the first maintenance dose administered 12 to 24 hours post last loading dose. The same weight-based dose amount is used for loading and maintenance doses, as discussed in Section 6.1, only differing in the frequency.

Previously a popPK model was developed in the adult population (refer to the Clinical Pharmacology Primary Review dated 12/09/2014 in DARRTS), however the adult model was not used as a starting point for the pediatric model in the current submission.

A pediatric popPK model, described in popPK study report A9766-PK-0010 Amendment 1 dated August 2023, was developed to estimate the pediatric PK parameters using data from the pediatric population with rich sampling schemes in the Phase 1 study, sparse data from the Phase 2 study, and additional data from an adult study. The Applicant added the adult data to the pediatric data set to stabilize the model. Pediatric model development was accomplished in a stepwise fashion as data from pediatric studies detailed in Table 27 became available for modeling. PopPK study reports A9766-PK-0006, A9766-PK-0007, A9766-PK-0008, A9766-PK-0010, and A9766-PK-0010 Amendment 1 describe the stepwise model development process, and the final model selected corresponding to each iterative version of the data set.

Individual clearance (CL) estimated by the final model was used to determine individual exposure as AUC_{ss} for purposes of exposure matching, as shown in popPK study report A9766-PK-0010 Amendment 1. Section 9.4.

For comparing isavuconazole PK between pediatrics and adults, the Applicant relied on prespecified comparability bounds, discussed in Section 15.4.3.

The Applicant reported the mean and median of the AUC_{ss} by age group, was within the prespecified boundaries, as presented in Table 8 and Figure 4 of popPK study report A9766-PK-0010 Amendment 1.

Specifically, the developed model was used to support the current submission as outlined in Table 26.

Table 26. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model		Reviewer's Comments
Support Applicant's proposed labeling statements about Pediatric Patients in Section 2.2, and 12.3 Derive exposure metrics for exposure matching	AUC_{ss}	The Applicant's final model is generally acceptable for generating exposure metrics for exposure-matching (Table 29). However, the shrinkage for CL/F was 26% and therefore the post hoc individual estimates of CL/F and AUC_{ss} derived from CL/F should be used with caution.

Source: Reviewer derived
Abbreviations: AUC_{ss}, steady-state area under the curve; CL/F, apparent oral clearance, ; PK, pharmacokinetics

Introduction

The primary objectives of Applicant's analysis were to:

- Characterize the structural PK model and quantify the population variability in the PK parameters of isavuconazole in pediatric patients.
- Examine effects of intrinsic and/or extrinsic factors on isavuconazole exposure by covariate model development.
- Generate individual clearance estimates for patients in Phase 1 and 2 studies that can be used to determine AUC_{ss} estimates for pediatric patients for the purpose of pediatric extrapolation by means of exposure matching to adult exposure range.

Model Development

Data

The analyses were based on PK data from 3 studies. The study design, study population, and timing of blood samples varied among the 3 clinical studies. Brief descriptions of the studies included are presented in Table 27.

Pediatric PK data were pooled with select historical adult PK data and popPK models were developed by Applicant to describe the PK of isavuconazole pediatric data from one Phase 1 pediatric study, 9766-CL-0046, and one Phase 2 study, 9766-CL-0107. Note that all the adult PK data included in PopPK analysis are from a clinical study that evaluated the effect of renal impairment on the PK of isavuconazole, however only data from subjects with mild renal impairment defined as creatinine clearance of 50 mL/min/1.73 m^2 to 80 mL/min/1.73 m^2 or

healthy volunteers defined as creatinine clearance of >80 mL/min/1.73 m^2 were included in the popPK dataset.

The final NONMEM data file for analysis contained 1142 PK observations from 97 participants, of which 714 PK observations were from 73 pediatric patients. Table 28 provides summary statistics of the baseline demographic covariates in the analysis dataset.

APPEARS THIS WAY ON ORIGINAL

Table 27. Summary of Studies With PK Sampling Included in Population PK Analysis

Protocol # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type	Dose(s) [mg]
9766-CL0018: Phase 1 Open-Label, 2-Part, Parallel Group Study to Investigate the Effect of Renal Impairment on the Pharmacokinetics of Isavuconazole	Single dose IV solution of isavuconazonium sulfate administered to evaluate effects of renal impairment on PK, safety & tolerability	24 male and female adult participants of varying renal function 16 healthy subjects, with CLcr >80 mL/min/1.73 m^2 8 participants with mild renal impairment, with CLcr of 50 – 80 mL/min/1.73 m^2	IV: 372 mg, infused over 1 hour
9766-CL-0046: Phase 1, open label, multicenter, non-comparative pharmacokinetic and safety study of intravenous isavuconazonium sulfate in pediatric patients	Isavuconazonium sulfate administered for up to 28 days to evaluate PK, safety & tolerability in pediatric participants. Participants received a loading dose of isavuconazonium sulfate, followed by once daily maintenance dosing for up to 26 additional days (for a maximum of 28 days of dosing).	45 male and female pediatric participants who may, in the judgment of the investigator, benefit from systemic antifungal prophylaxis with isavuconazonium sulfate. Part 1 of the study was IV administration in pediatric participants 1 to <18 years of age; Part 2 was oral administration of isavuconazonium sulfate in pediatric participants 6 to <18 years of age	IV: 10 mg/kg infused over 1 hour, with maximum dose of 372 mg Oral: **Body Weight (kg)** / **Dose (mg)** 12-17 / 149 18-24 / 223.5 25-31 / 298 ≥32 / 372.5 Loading Dose Frequency: every 8 hours for 6 doses (48 hours)

Protocol # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type	Dose(s) [mg]
9766-CL-0107: Phase 2, Open-Label, Non- Comparative, Multicenter Study to Evaluate the Safety and Tolerability, Efficacy and Pharmacokinetics of isavuconazonium Sulfate for the treatment of IA or IM in Pediatric Subjects	Isavuconazonium sulfate administered for up to 180 days to evaluate PK, safety & tolerability in pediatric patients. Participants received a loading dose of isavuconazonium sulfate, followed by once daily maintenance dosing for up to a maximum duration of 84 days (IA) or 180 days (IM), whichever occurred first.	28 male and female pediatric patients (1 to <18 years of age) who had been diagnosed with proven, probable or possible IA or IM were enrolled in this study. The route of administration can be interchangeable from IV to oral or oral to IV for patients age >6 years and weight >12 kg.	Maintenance Dose Frequency: once daily starting 12 to 24 hours after the last loading dose Oral doses administered without respect to food (fed or fasted state).

Source: Reviewer derived from A9766-PK-0010 Amendment 1 dated August 2023, Section 3.1 and Table 1
Abbreviations: CLcr: creatinine clearance; IA, invasive aspergillosis; IFD, invasive fungal disease; IM, invasive mucormycosis; IV, intravenous; PK, pharmacokinetics; popPK, population pharmacokinetics

Table 28. Summary of Baseline Demographic Covariates for Analysis

Covariate Statistic	9766-CL-0046 (n=45)	9766-CL-0107 (n=28)	9766-CL-0018 (n=24)	Total
Baseline body weight (kg)				
N	45	28	24	97
Mean (SD)	41.39 (23.73)	38.15 (20.06)	79.64 (17.29)	49.92 (27.16)
Median (min,max)	40.1 (10.9-104)	43.1 (9, 84.3)	79.2 (53.8, 118)	47.5 (9, 118.3)
Baseline body height (cm)				
N	45	28	24	97
Mean (SD)	138.6 (26.5)	134.1 (30.6)	169.9 (12.3)	145.1 (28.8)
Median (min,max)	145.6 (77, 181)	141 (72.5, 178)	172 (148, 187)	153 (72.5, 187)
Age (yr)				
N	45	28	24	97
Mean (SD)	10.2 (4.49)	9.5 (5.2)	53.1 (10.9)	20.6 (19.9)
Median (min,max)	10 (1, 17)	9.5 (1, 17)	54.5 (19, 65)	13 (1, 65)
Alanine transaminase (U/L)				
N	45	28	24	97
Mean (SD)	47.4 (42.1)	37.5 (34.9)	23.4 (19.4)	38.6 (36.5)
Median (min,max)	33 (6, 188)	26 (6, 153)	19.5 (7, 105)	25 (6, 188)
Aspartate transaminase (U/L)				
N	45	28	24	97
Mean (SD)	37.3 (25.4)	34.7 (22.5)	21.7 (9.6)	32.7 (22.4)
Median (min,max)	31 (4, 105)	30.5 (9, 104)	20 (10, 62)	25 (4, 105)
Alkaline phosphatase (U/L)				
N	45	27	24	96
Mean (SD)	132.8 (45.8)	134.3 (65.9)	70.9 (20.2)	117.7 (54.7)
Median (min,max)	126 (52, 250)	129 (44, 282)	67.5 (42, 125)	113 (42, 282)
Total Bilirubin (mg/dL)				
N	45	28	24	97
Mean (SD)	0.47 (0.26)	0.52 (0.30)	0.58 (0.20)	0.51 (0.26)
Median (min,max)	0.4 (0.1, 1.2)	0.45 (0.1, 1.1)	0.6 (0.2, 1.1)	0.5 (0.1, 1.2)
Baseline Serum Creatinine (mg/dL)				
N	45	28	24	97
Mean (SD)	0.404 (0.158)	0.603 (0.998)	0.885 (0.232)	0.580 (0.585)
Median (min,max)	0.4 (0.15, 0.8)	0.295 (0.08, 5.47)	0.84 (0.65, 1.70)	0.4 (0.08,5.47)
Albumin (g/dL)				
N	45	27	24	96
Mean (SD)	3.46 (0.51)	3.31 (0.50)	4.30 (0.27)	3.62 (0.602)
Median (min,max)	3.4 (2.2, 4.4)	3.2 (2.2, 4.2)	4.35 (3.7, 4.7)	3.6 (2.2, 4.7)
Sex				
Male	28 (62)	5 (18)	15 (62)	48 (49.5)
Female	17 (38)	23 (82)	9 (38)	49 (50.5)
Missing	-	-	-	
Race				
White	32 (71)	18 (69)	22 (92)	72 (75.8)
Black	5 (11)	1 (4)	2(8)	8 (8.4)
Asian	3 (7)	5 (19)	-	8 (8.4)
Other	5 (11)	2 (8)	-	7 (7.4)
Missing	-	2	-	2

Covariate Statistic	9766-CL-0046 (n=45)	9766-CL-0107 (n=28)	9766-CL-0018 (n=24)	Total
Ethnicity				
Hispanic Latino	18 (41)	7 (27)	9 (38)	34 (36.2)
Non-Hispanic, Non-Latino	26 (59)	19 (73)	15 (62)	60 (63.8)
Missing	1	2	-	3

Source: Reviewer derived from dataset isapedppkcombined46107updated.csv
Abbreviations: N, number of subjects; SD, standard deviation

Base Model

The current submission evaluated several approaches for model fitting. The final base model was a three-compartment PK model with combined zero and first-order absorption and first-order linear elimination. The effect of weight was included as a fixed allometric exponent on clearance, CL/F, and inter-compartmental clearance, Q3/F and Q3/F, and on volume of distribution of central compartment, V2/F, and volumes of distribution of peripheral compartments, V3/F and V4/F.

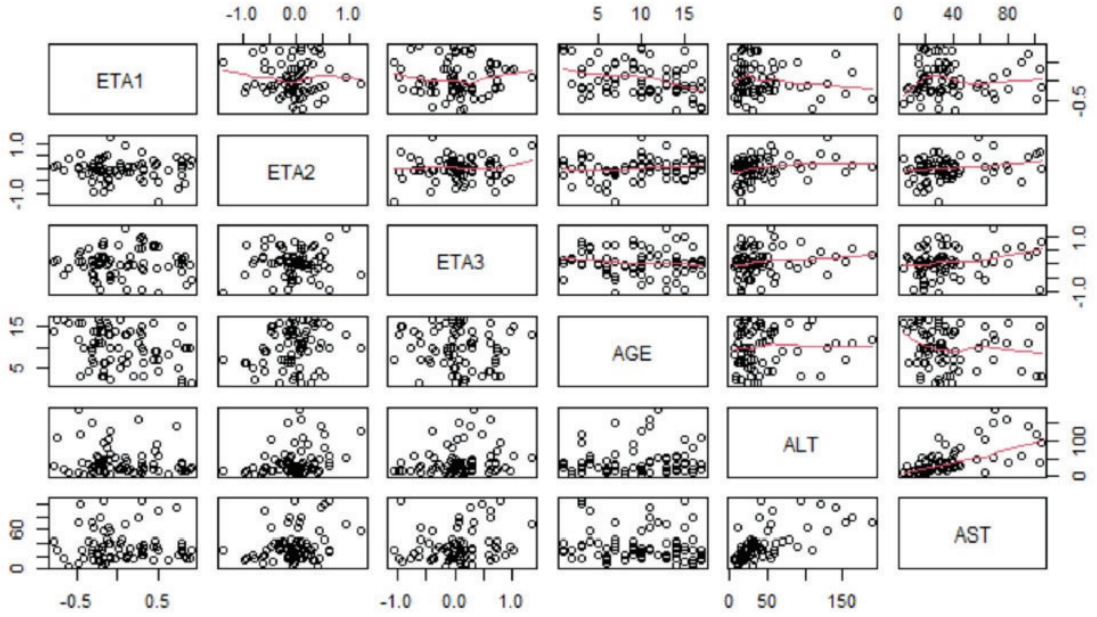
Inter-individual variability was modelled assuming a log-normal distribution for patient level random effects. The Ln-Ln transformation of both the model and the data was used to stabilize the residual variance. Residual variability was tested as additive on the Ln-Ln transformed model. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value, accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Covariate Analysis

Covariate of interest, including gender, race, ethnicity, age, ALT and AST were added to the base model using stepwise covariate modeling by forward inclusion (p-value of 0.01 for entry) and backward elimination (p-value of 0.001 for retention) steps. Continuous covariates were standardized to median values. Clinical judgment, physiologic relevance, and mechanistic plausibility were used to determine which covariates should be tested with the various PK parameters. Covariate plots against inter-individual variability are shown in Figure 5 and Figure 6.

The pediatric popPK model did not identify any significant covariates on the pediatric PK of isavuconazole.

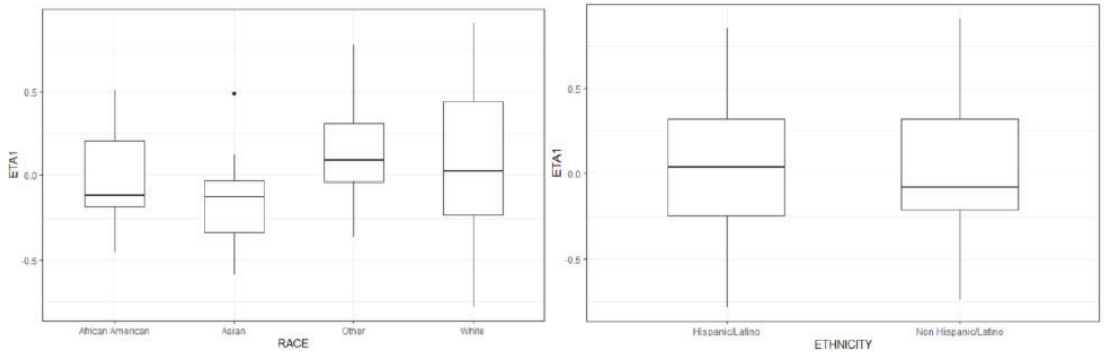
Figure 5. Correlation of Parameter of Interest and Demographics



ETA1 is variability associated with clearance, ETA2 is variability associated with volume of distribution of peripheral compartment (V_4), ETA3 is variability associated with inter-compartmental clearance (Q4) , AGE is age in years, ALT is alanine aminotransferase, AST is aspartate aminotransferase

Source: A9766-PK-0010 Amendment 1 dated August 2023, Figure 2

Figure 6. Box Plot Showing Correlation Between Clearance and Race and Ethnicity



ETA1 is variability associated with Clearance

The box is the interquartile range (IQR) representing the 25th and 75th Percentile. The whiskers represent the last point within 1.5 times the IQR of the 25th and 75th Percentile. Circles represent all points beyond this threshold.

Source: A9766-PK-0010 Amendment 1 dated August 2023, Figure 3

Final Model

The parameter estimates for the final covariate model are listed in Table 29. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 7.

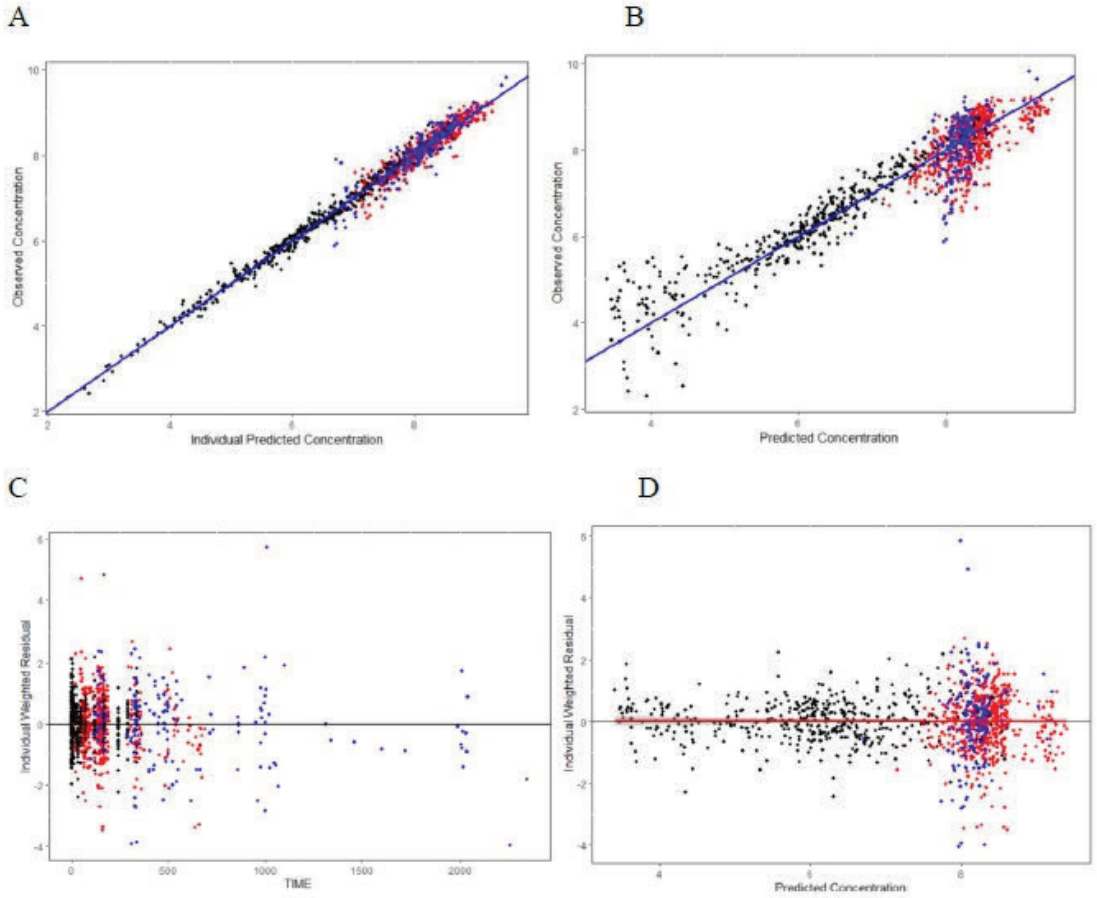
Table 29. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

Parameter	Units	Value	SE	% RSE	Bootstrap Mean	Bootstrap 95 % CI
CL	L/hr	2.53	0.15	6	2.53	2.34- 2.72
V_2	L	18.80	2.90	15	17.23	9.69 – 27.84
Q_3	L/hr	32.20	7.27	23	37.68	18.16 – 64.33
V_3	L	25.70	3.06	12	27.10	17.45 – 33.93
Q_4	L/hr	21.60	2.30	11	21.51	17.92 – 25.28
V_4	L	237.0	15.40	6	235.9	214.8 – 258.6
KA	hr	0.19	0.03	17	0.20	0.14 – 0.25
F1		0.84	0.04	6	0.84	0.75 – 0.93
Variability (%)						
CL		45.49	0.02	14	44.72	40.12 – 48.98
V_4		49.89	0.07	31	50.00	33.16 – 61.64
Q_4		62.44	0.18	46	60.00	31.62 – 82.46
Residual Error σ^2		44.94	0.1	7	44.94	42.42 – 46.90

All values are rounded to nearest decimal. Population parameter estimates, standard errors of the estimates (SE), percent relative standard errors (%RSE), Bootstrap mean and Bootstrap 95% confidence intervals.
CL= clearance, V_2= volume of distribution of central compartment, Q_3 and Q_4= inter-compartmental clearance values, V_3 and V_4= volume of distribution of peripheral compartments, KA = absorption rate constant, F1= bioavailability

Source: A9766-PK-0010 Amendment 1 dated August 2023, Table 7
Abbreviations: RSE, relative standard errors

Figure 7. Goodness-of-Fit Plots for Final Covariate Model



Goodness-of-fit plots for the best covariate model. (A) Log of individual predicted concentrations versus log of observed concentrations. (B) Log of predicted concentrations versus log of observed concentrations. (C) Plot of individual weighted residual versus time. (D) Plot of individual weighted residual versus log of predicted concentrations.

Black circles represent adult data, red circles represent pediatric data from 9766-CL-0046 study and blue circles represent pediatric data from 9766-CL-0107 study

Source: A9766-PK-0010 Amendment 1 dated August 2023, Figure 1

Reviewer Comments: *In general, the Applicant's pooled popPK analysis is reasonable in capturing the central tendency of isavuconazole disposition after intravenous and oral dosing.*

Exposure Metrics

Applicant concluded that AUC_{ss} calculated from estimated CL for pediatric study participants, reported in Section 9.4 of popPK study report A9766-PK-0010 Amendment 1, was comparable to target drug exposure range, as discussed in Section 15.4.3.

Reviewer Comments: *The Applicant's popPK analysis is considered acceptable for the purpose of prediction of steady state exposure (AUC_{ss}) for purposes of exposure matching between adult*

patients and pediatric patients aged 1 to 17 years of age. The Applicant's popPK analysis has an unacceptable predictive ability for the purpose of prediction of the maximum concentration (C_{max}) for purposes of exposure matching between adult patients and pediatric patients aged 1 to 17 years of age, as individual weighted residual values at the observed C_{max} were as high as 5. The Applicant's popPK model did not provide evidence of a trend between individual weighted residual values and either concentration or time.

15.4.4.2. Reviewer's Independent Analysis (Issue-Based Analysis)

Introduction

The Applicant's popPK analyses were verified by the reviewer, with no significant discordance identified. Estimated parameter values, standard error, and percent relative standard errors in reviewer's analysis were similar to those shown in Table 29.

The Applicant's final popPK model adequately described the observed isavuconazole plasma concentrations in pediatric patients ages 1 to <18 years of age administered an IV infusion of isavuconazonium sulfate and pediatric patients ages 6 to <18 years of age administered isavuconazonium sulfate oral capsules. Estimated CL for the final model had acceptable precision with relative standard error (RSE) of 6%, and inter-individual variability of 45%, but the shrinkage was high, at 26%. The other parameter estimates were reasonably precise, with RSE ranging from 6% to 23%. The inter-individual variability on V4, and Q4, was high, at 50%, and 62%, respectively. The shrinkage for inter-individual variability on V4, and Q4, was high, at 45%, and 26%, respectively. The goodness-of-fit plots showed a general agreement between the observed and the individual predicted concentrations, but residuals approached 5, without any obvious bias over time or predicted concentrations. Considering the high shrinkage observed in the final model, the popPK model remains a conservative methodology for estimation of clearance and calculation of exposure (AUC_{ss}), for purposes of comparison to the prespecified exposure target range, with the additional support from NCA data.

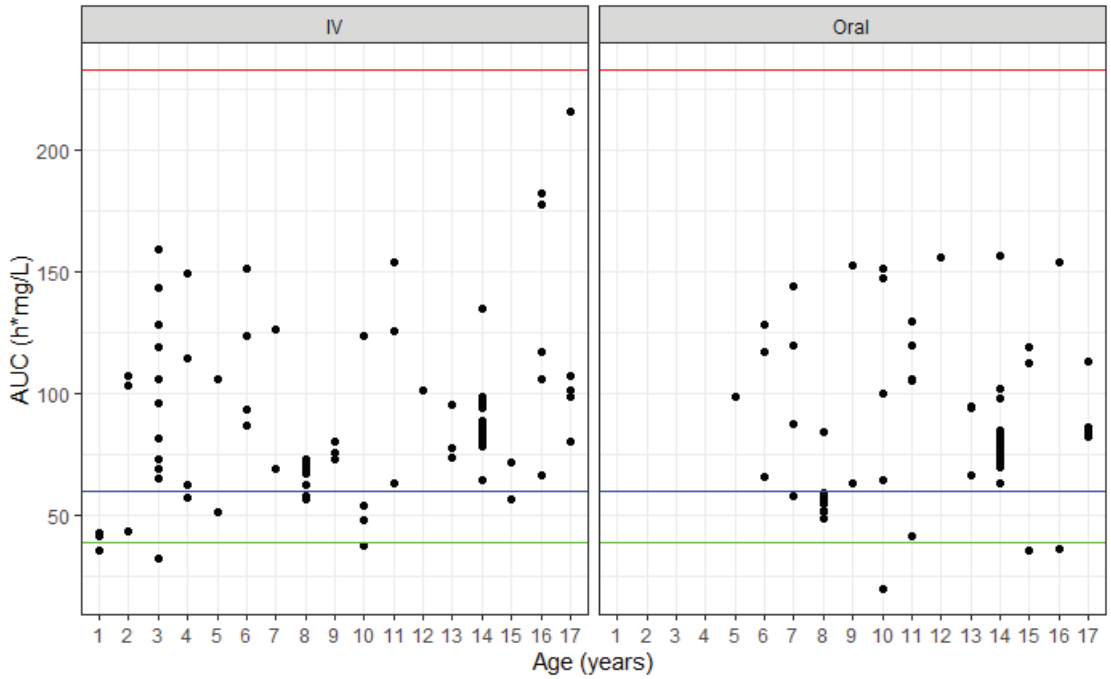
The Applicant calculated AUC_{ss} from the estimated CL from the popPK analysis, dose, and the bioavailability, with bioavailability of 1 for IV route. We noted that the AUC_{ss} calculation reported appeared to correlate with the first maintenance dose for each subject and did not reflect subsequent changes in either dose or route for the subject. The Applicant's calculated AUC_{ss} from Section 9.4 of popPK study report A9766-PK-0010 Amendment 1 were verified by the reviewer, with two significant differences identified.

- The reviewer noted that the Applicant reported exposure above the upper boundary of the target ranges for subject (b) (6) of AUCss equal to 355.25 h*mg/L. Our analysis confirmed the dose, bioavailability, and clearance reported for subject (b) (6) but did not confirm this value for the AUC_{ss}. We calculated AUC_{ss} equal to 35.62 h*mg/L for subject (b) (6)

- The reviewer noted that the Applicant reported the dose for subject [redacted] (b) (6) as 10 mg/kg for purposes of AUC_{ss} calculation. Our examination of the popPK dataset determined the dose was 8.5 mg/kg for subject [redacted] (b) (6) Using the dose of 8.5 mg/kg, we calculated AUCss similar to that reported by the Applicant for a dose of 10 mg/kg for subject [redacted] (b) (6)

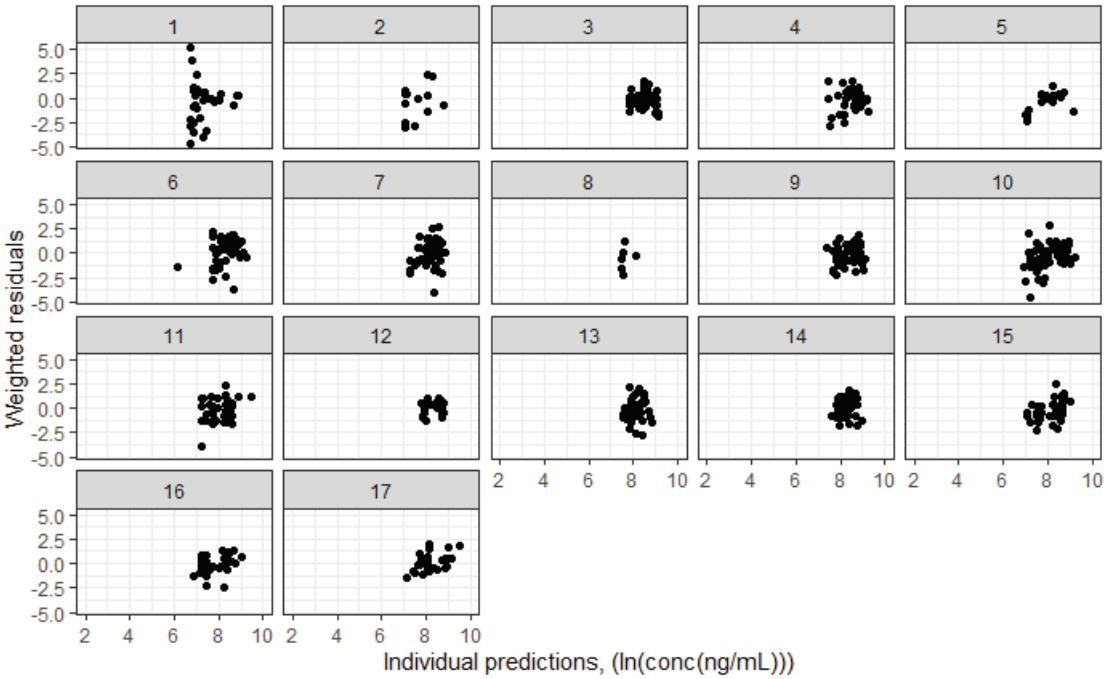
The Division noted that the exposures the Applicant reported for age less than 3 trended lower than those of for ages 3 to 17 inclusive, which was independently verified by reviewer analysis, as shown by the plot of exposure as AUC_{ss} versus age shown in Figure 8. The reviewer also noted that the highest variance in predictions occurred at the lowest age in the dataset, as shown in Figure 9. Further investigation into potential causes of the variance at ages less than 3 years of age did not demonstrate any trends between inter-individual variance estimates (ETA1, ETA2, and ETA3) and the covariates of interest. The correlation between age and weight was the only notable correlation between the covariates of interest.

Figure 8. Scatterplot of Calculated AUC_{ss} Values Based on Empirical Bayes Estimates Versus Age, by Route, for Study 9766-CL-0046 and Study 9766-CL-0107 Pediatric Patients, From Reviewer Analysis



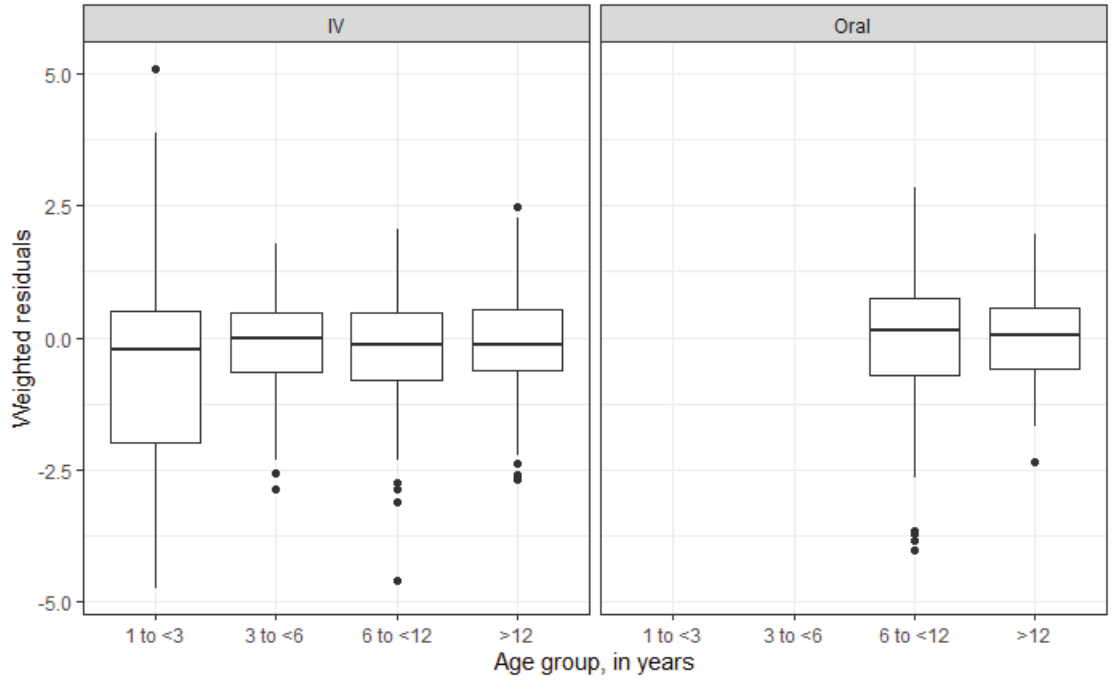
Source: Reviewer's Analysis
Green line represents 39 h*mg/mL, the 5th percentile of AUC_{ss} in adults from the SECURE study, 9766-CL-0104. Blue line represents 60 h*mg/mL, the 25th percentile of AUC_{ss} in adults from the SECURE study, 9766-CL-0104. Red line represents 233 h*mg/mL, the minimum AUC_{ss} for 1116 mg dose from TQT study in adults, 9766-CL-0017.
Note: multiple AUC_{ss} values per subject plotted for subjects who experienced a change in body weight, a change in dosing, or a change in route over the course of the study. If a change in body weight is recorded, the CL estimate changes, which changes the calculated AUC_{ss}. A change in dosing amount or dosing route changes the calculated AUC_{ss}.
Abbreviations: AUC_{ss}, steady-state area under the curve

Figure 9. Goodness-of-Fit Plot From Reviewer Analysis, Scatterplot of Weighted Residuals versus Individual Predicted Values by Age



Source: Reviewer's Analysis

Figure 10. Boxplot of Weighted Residuals by Age Group



Source: Reviewer's Analysis
Abbreviations: IV, intravenous

The Applicant's analyses were reasonable in predicting AUC_{ss} when compared to Day 7 $AUC_{tau.}$ from NCA (report MGC1800624 from study ISN 9766-CL-0046), but not comparable to Day 3 $AUC_{tau.}$ from NCA. The loading doses are administered over the first 48 hours (Day 1 and 2), and the first maintenance dose is administered 12 to 24 hours following the last loading dose, then once every 24 hours thereafter. It is possible that the $AUC_{tau.}$ from Day 3 is not sufficiently representative of steady-state due to the variability in administration of the first maintenance dose, whereas by Day 7 the maintenance dosing frequency is less variable.

As shown in Figure 10, weighted residuals approaching 5 were observed in the age group 1 to less than 3 years of age receiving 10 mg/kg IV isavuconazonium sulfate, which reflects the poor predictive ability of the Applicant's popPK model to predict concentrations within this age group. Although there is uncertainty in the Applicant's popPK model to predict concentrations within the age group 1 to less than 3 years of age, this uncertainty did not significantly impact the AUC_{ss} values based on empirical Bayes estimates, when compared to the Day 7 AUC_{tau} for the one subject within the age group 1 to less than 3 years of age which had a Day 7 AUC_{tau} reported, as shown in Table 30.

The Applicant responded to the lower exposure average estimated AUC_{ss} from both studies (9766-CL-0046 and 9766-CL-0107) for patients less than 3 years of age (n=5) in an information request received by FDA on 01Nov2023. The Applicant proposed one possible reason for the lower exposures, i.e., lower protein binding in the five pediatric patients age less than 3 years of age. The Reviewer confirmed that each of the five patients less than 3 years of age had clinical hypoalbuminemia recorded during the study, as shown in Table 30. As shown in Table 28, the mean and median baseline albumin values for both pediatric studies trended lower, and the values for 1 and 2 year olds were within the spread observed for 3 to 17 year olds.

Table 30. Select Demographics and Applicant Reported Exposure as AUC_{ss} Values Based on Empirical Bayes Estimates, and AUC_{tau} for Study 9766-CL-0046 and Study 9766-CL-0107 Pediatric Patients in popPK Dataset Less Than 3 Years of Age

Study	ID	Baseline Age (years)	Baseline Weight (kg)	Albumin Range (g/dL)	AUC_{ss} (h*mg/L)	NCA Day7 AUC_{tau} (h*mg/L)
9766-CL-0046	(b) (6)	1	10.9	2.8 to 3.5	42.65	43
9766-CL-0107		1	9	2.3 to 3.7	35.82	-
9766-CL-0107		2	12.5	3.2 to 4.2	43.67	-
9766-CL-0107		2	12	3.0 to 4.3	103.5	-
9766-CL-0107		1	9.7	3.1 to 4.6	41.43	-

Source: Reviewer's Analysis
Abbreviations: AUC_{ss}, steady-state area under the curve; $AUC_{tau,}$ area under the curve from 0h to tau; NCA, noncompartmental analysis; popPK, pharmacokinetics

The Applicant's analysis is sufficient for predicting AUC_{ss} for pediatric patients ages 1 to 17 years of age at weight greater than 9 kg.

Objectives

Analysis objectives are:

- Sensitivity analysis: As part of the review, several outliers in the dataset were observed in revised dataset isapedppkcombined46107updated.csv. Confirm these outliers do not skew clearance estimated for this subject by conducting a sensitivity analysis where the rows of the dataset corresponding to the outlier are commented out, and the NONMEM estimation of parameters is repeated using the final model control stream. Specific outliers examined are as follows:
  - Row 3527, Subject (b) (6) reports a weight of 78.9 kg, but all other entries for this subject report 48.9 kg [Sensitivity analysis 1].
  - Row 3389, Subject (b) (6) reports a trough value which exceeds C_{max} of Cresemba USPI and is not comparable to other trough values for this patient [Sensitivity analysis 2].
  - Rows 3789, 3791, 3792, and 3793, Subject (b) (6) reports a trough value which is approximately the C_{max} of Cresemba USPI and other observations of that same day are in trend with a high bias [Sensitivity analysis 3].
- To simulate CL and determine steady-state exposure (AUC_{ss}) of isavuconazole for the pediatric study subjects using actual dose amounts, timing, and duration reported in the studies [Simulation analysis 2]
- To simulate CL and determine steady-state exposure (AUC_{ss}) of isavuconazole for the following groups under labelled IV dosing of 10 mg/kg and under alternate dosing regimen of IV 12 mg/kg:
  - ages 1 to 3 years of age [Simulation analysis 1 and 3]
  - body weight less than 10 kg [Simulation analysis 4]
- To simulate CL and determine steady-state exposure (AUC_{ss}) of isavuconazole for hypothetical 16 kg 6-year-old patient under alternate dosing regimen of 223.5 mg (3 capsules) oral dose. [Sensitivity analysis 5]

Methods

Sensitivity Analysis

To conduct sensitivity analysis for the outliers identified in revised dataset isapedppkcombined46107updated.csv, three NONMEM datasets were created from revised dataset isapedppkcombined46107updated.csv, each of which only different from the parent dataset by commenting out the rows corresponding to the outlier identified.

Simulations were performed with the three sensitivity datasets, and AUC_{ss} was determined from individual clearance predictions. The base model of the Applicant (three-compartment PK model with combined zero and first-order absorption and first-order linear elimination combined with an additive residual error model on the Ln-Ln transformed model) were utilized for the simulations. Graphical and statistical analysis of the simulation output was used to evaluate the exposure in the virtual populations.

Simulations

To conduct simulation in the patient population using actual dosing values, a NONMEM dataset was created from revised dataset isapedppkcombined46107updated.csv, with the DV and LNDV values replaced with NULL values.

To conduct simulation in the target populations, two virtual populations were created by random resampling with replacement from the National Health and Nutrition Examination Survey 2017-prepandemic 2020 demographic and body measures datasets, after filtering to the desired range. The first virtual population (n=300) was an equal distribution of age 1-, 2-, and 3-year-old subjects (n=100 each), sampled after filtering of age ≥1 and ≤3 years. The second virtual population (n=300) was sampled after filtering for age ≥1 year and weight ≤10 kg. For each virtual population, unique subject ID, age, weight, gender, and a race and ethnicity factor were retained. A third dataset for simulation of oral dosing was created with 300 subjects, all with hypothetical weight of 16 kg, age of 6 years, and no sex or racial characteristics.

Table 31. Summary of Baseline Demographic Covariates for Virtual Populations

Covariate Statistic	Virtual Population 1	Virtual Population 2
Body Weight (kg)		
N	300	300
Mean (SD)	13.7 (3.0)	9.40 (0.53)
Median (min,max)	13.4 (8.2, 35)	9.5 (7.9, 10)
Age (yr)		
N	300	300
Mean (SD)	2 (0.8)	1.1 (0.34)
Median (min,max)	2 (1, 3)	1 (1, 2)
Sex N (%)		
Male	173 (57.7)	131 (43.7)
Female	127 (42.3)	169 (56.3)
Race and Ethnicity N (%)		
Mexican American	30 (10.0)	46 (15.3)
Other Hispanic	38 (12.7)	16 (5.3)
Non-Hispanic White	110 (36.7)	101 (33.7)
Non-Hispanic Black	72 (24.0)	104 (34.7)
Non-Hispanic Asian	14 (4.7)	16 (5.3)
Other & Multi-Racial	36 (12.0)	17 (5.7)

Source: Reviewer's Analysis
Abbreviations: N, number of subjects; SD, standard deviation

Virtual population sampling and NONMEM simulation dataset preparation was conducted using R. NONMEM version VII was used for simulation. The diagnostic and other plots were generated with R.

Simulations were performed with the actual patient population, and the three virtual populations, and AUC_{ss} was determined from individual clearance predictions. The base model of the Applicant (three-compartment PK model with combined zero and first-order absorption and first-order linear elimination combined with an additive residual error model on the Ln-Ln transformed model) were utilized for the simulations. Graphical and statistical analysis of the simulation output was used to evaluate the exposure in the virtual populations.

Results

Sensitivity Analysis

Overall, similar parameter values were estimated for the popPK sensitivity analysis 1, 2, and 3. Slight changes in %RSE for parameters were observed for sensitivity analysis 1, and 2, however large increases in %RSE, up to double the original value, were observed in sensitivity analysis 3. The individual clearance estimated for the subjects with data commented out of the sensitivity analysis is shown in Table 32.

In sensitivity analysis 1, the change in weight recorded for subject (b) (6) was significant with regards to the calculated AUC_{ss}. As the Applicant only reported the AUC_{ss} for the first maintenance dose, which corresponded to a reported weight of 48.9 kg for subject (b) (6) there is no impact to this finding. In sensitivity analysis 2 and 3, the exclusion of the high concentration values resulted in 1.1-fold and 1.0-fold change in calculated AUC_{ss}. subject (b) (6) and subject (b) (6) respectively, which is not a significant change, therefore there is no impact to these findings.

Table 32. Summary of Clearance and Exposure Following Sensitivity Analysis

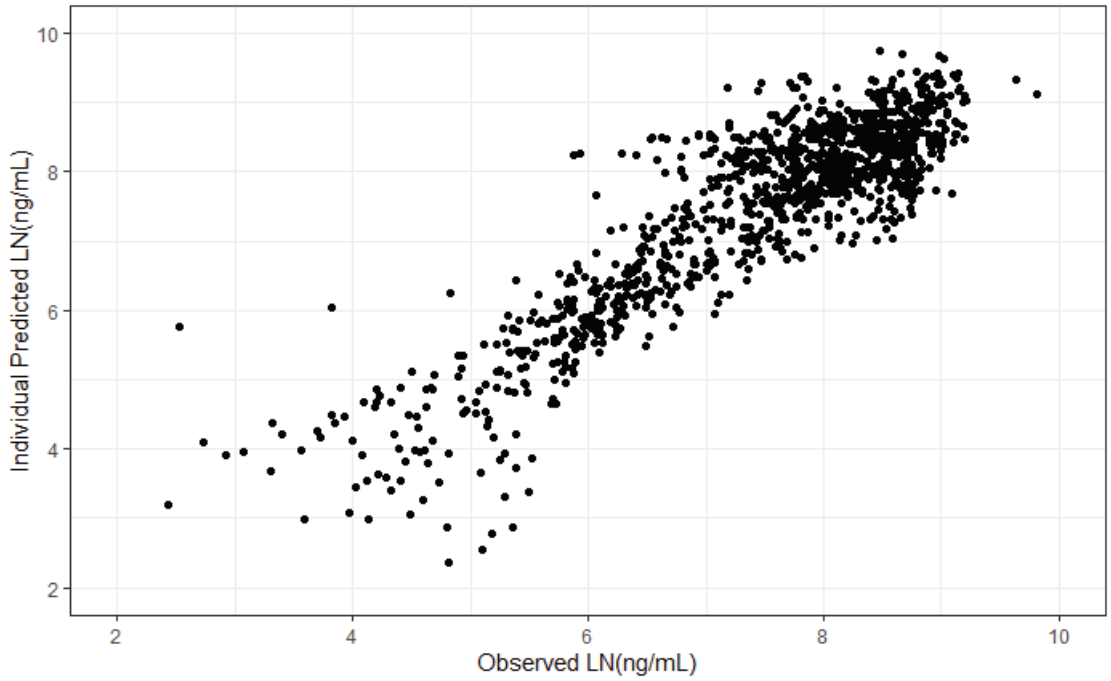
Sensitivity analysis	Rows Commented Out	Subject ID	Individual Estimated CL (L/h)	Individual Calculated AUC_{ss} (h*mg/L) From Sensitivity Analysis	Comments
1	3527	(b) (6)	1.777	94.91	1.4-fold change in AUC_{ss}
2	3389	(b) (6)	0.78822	128.21	1.1-fold change in AUC_{ss}
3	3789, 3791, 3792, and 3793	(b) (6)	0.96057	208.2097	1.0-fold change in AUC_{ss}

Source: Reviewer's Analysis
Abbreviations: AUC_{ss}, steady-state area under the curve; CL, clearance

Simulations

For the simulation of the actual patient population using actual dosing values, the agreement between simulated and observed concentrations was generally acceptable, as shown in Figure 11.

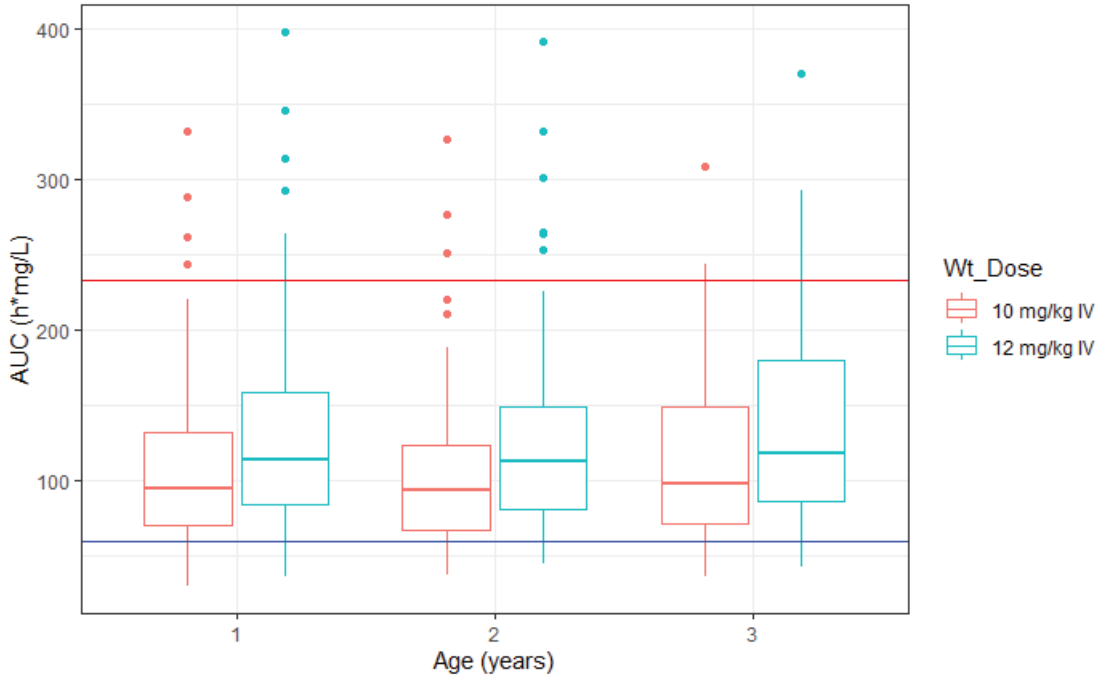
Figure 11. Scatterplot of Simulated Versus Observed Concentrations for Study 9766-CL-0046 and Study 9766-CL-0107 Pediatric Patients



Source: Reviewer's Analysis

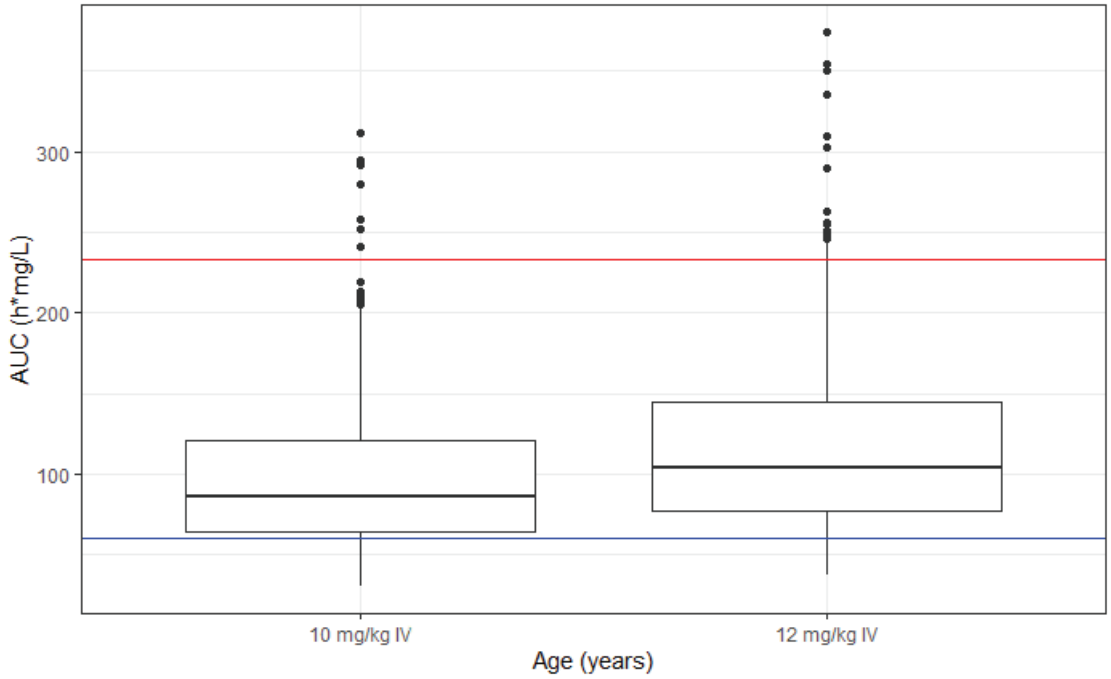
A comparison of the two dosing regimens evaluated in a resampled population with ages 1 to 3 years of age using virtual population 1 is shown in Figure 12, and in a resampled population with ages greater than 1 year and weight less than 10 kg using virtual population 2 is shown in Figure 13. The variability in the Applicant's final model leads to variability in the predictions from the simulation, limiting the utility of the simulation. As shown in Figure 12 and Figure 13, the predicted AUC_{ss} covers several orders of magnitude, including a range below and above the target exposure range. No conclusions can be drawn regarding dosing regimens in the selected age and weight ranges examined by virtual population 1 and 2 due to the inherent variability of the model.

Figure 12. Boxplot of Derived AUC_{ss} Values Based on Empirical Bayes Estimates for Different Doses (10 mg/kg, and 12 mg/kg) for Versus Age, by IV Weight-Based Dose, Using Virtual Population 1 (Age Less Than 3 Years)



Source: Reviewer's Analysis
Blue line represents 60 h*mg/mL, the 25th percentile of AUC_{ss} in adults from the SECURE study, 9766-CL-0104. Red line represents 233 h*mg/mL, the minimum AUC_{ss} for 1116 mg dose from TQT study in adults, 9766-CL-0017.
Abbreviations: AUC_{ss}, steady-state area under the curve; IV, intravenous

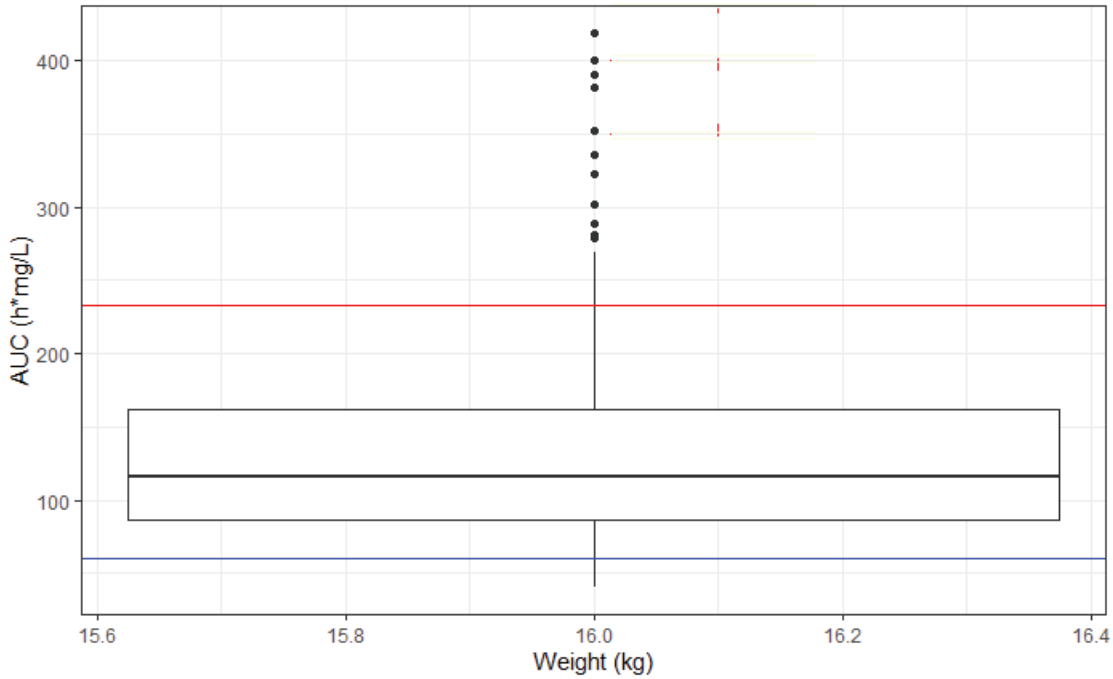
Figure 13. Boxplot of Derived AUC_{ss} Values Based on Empirical Bayes Estimates for Different Doses (10 mg/kg, and 12 mg/kg) Versus IV Weight-Based Dose (10 mg/kg or 12 mg/kg), for Simulation Using Virtual Population 2 (Weight Less Than 10 kg)



Source: Reviewer's Analysis
Blue line represents 60 h*mg/mL, the 25th percentile of AUC_{ss} in adults from the SECURE study, 9766-CL-0104. Red line represents 233 h*mg/mL, the minimum AUC_{ss} for 1116 mg dose from TQT study in adults, 9766-CL-0017.
Abbreviations: AUC_{ss}, steady-state area under the curve; IV, intravenous

A plot of exposure for a hypothetical population age 6 years of age and 16 kg receiving 223.5 mg (3 capsules) oral dosing is shown in Figure 14. As mentioned earlier, the variability in the Applicant's final model limits the utility of the simulation. As shown in Figure 14, the predicted AUC_{ss} covers several orders of magnitude, including a range below and above the target exposure range. No conclusions can be drawn regarding the alternate dosing regimen of 223.5 mg (3 capsules) oral dose at 16 kg for 6 years of age due to the inherent variability of the model.

Figure 14. Boxplot of AUC_{ss} Versus Weight, for Simulation Using Virtual Population 3 (Weight Equal to 16 kg) With Oral Dosing of 3 Capsules (223.5 mg)



Source: Reviewer's Analysis
Blue line represents 60 h*mg/mL, the 25th percentile of AUC_{ss} in adults from the SECURE study, 9766-CL-0104. Red line represents 233 h*mg/mL, the minimum AUC_{ss} for 1116 mg dose from TQT study in adults, 9766-CL-0017.
Abbreviations: AUC_{ss}, steady-state area under the curve; IV, intravenous

15.4.5. Physiologically Based Pharmacokinetic Analysis Review

Table 33. Physiologically Based Pharmacokinetic Modeling Review

Study Information	Details
Application Number	NDA 207500/s-015 and 207501/s-013
Drug Name (Generic)	Isavuconazonium sulfate
Proposed Indication	Treatment of invasive aspergillosis and invasive mucormycosis in pediatric patient (b) (4)
PBPK Consult request	Anthony Nicasio, Pharm.D., CDER/OTS/OCP/DIDP
Primary PBPK Reviewer	Miyoung Yoon, Ph.D., CDER/OTS/OCP/DPM
Secondary PBPK Reviewer	Yuching Yang, Ph.D., CDER/OTS/OCP/DPM
Applicant	Astellas Pharma US Inc.

Abbreviations: PBPK, physiologically based pharmacokinetic

15.4.5.1. Executive Summary

The objective of this review was to evaluate the adequacy of the Applicant's PBPK modeling and simulation analyses for the purpose of evaluating potential DDI between isavuconazole and vincristine in pediatric subjects. Specifically, the PBPK objective was to predict the potential change in vincristine exposure in pediatric cancer patients due to isavuconazonium sulfate

coadministration to propose DDI recommendations in the labeling. In response to FDA's information request (IR), the Applicant conducted the PBPK analysis in adults as well (dated November 1, 2023).

To determine the adequacy of the Applicant PBPK analysis to support the proposed purpose, the Division of Pharmacometrics reviewed the Applicant's submitted information including the PBPK report (9766-pk-0009), the responses to the FDA's IRs (received September 6, October 12, and November 1, 2023), the PBPK report addendum (9766-pk-0009-addendum-1), as well as the submitted modeling and simulation files, and conducted independent PBPK analysis for risk assessment. The Division of Pharmacometrics concluded that the Applicant's PBPK analysis is reasonable to evaluate the effects of isavuconazole on the PK of vincristine in pediatric and adult patients, (b) (4) .

Based on the PBPK analysis, the effects of isavuconazole on the systemic exposure of vincristine were predicted to be weak, resulting in less than a 2-fold increase in vincristine exposure in pediatric and adult patients. The predicted DDI effects are mainly due to P-gp inhibition by isavuconazole, and contribution of CYP3A4/5 inhibition by isavuconazole was predicted to be minimal. Vincristine is a P-gp substrate and the current labeling states that: 1) the concomitant use of P-gp inhibitor or inducers should be avoided as concomitant use of P-gp modulators may affect PK or pharmacodynamics of vincristine (Hospira 1996).

We conclude that concomitant use of vincristine and Cresemba should be avoided to be consistent with recommendations regarding concomitant use of P-gp modulators in the Vincristine labeling. We determined that it is acceptable to include PBPK analysis results in Section 12.3 of the Cresemba labeling to report the simulated DDI trial between Cresemba and vincristine.

15.4.5.2. Background

Cresemba (isavuconazonium sulfate) is currently approved for adults (18 years and older) for treatment of IA and IM. This submission proposes Cresemba for pediatric patients (b) (4) . Isavuconazonium sulfate is a water-soluble prodrug of isavuconazole. The prodrug is rapidly hydrolyzed to isavuconazole (the active drug) in plasma by esterases and by chemical hydrolysis in the gut lumen after oral administration. The prodrug is generally not detected in plasma or urine.

After oral administration of isavuconazonium, isavuconazole C_{max} is reached around 2-3 hrs, the absolute bioavailability of isavuconazole is about 98%, which indicates complete absorption. Isavuconazonium IV and oral formulations are shown to be bioequivalent (BE) in adults. Isavuconazole exhibits dose proportional PK (100 mg to 600 mg per day). The mean half-life of isavuconazole is approximately 130 hrs. Isavuconazole clearance (CLtot) is approximately

2.4 L/h. Steady state was achieved within 14 days of once daily (QD) oral or IV administration. Isavuconazole AUC was increased approximately 4- to 5-fold following maintenance oral doses of 50 and 100 mg QD.

Following a single oral dose [cyano-14C]-labelled isavuconazonium, the mean radioactivity recovered in feces and urine were 46.1% and 45.5%, respectively, and isavuconazole was the predominant radioactivity in plasma and feces (Study 9766-CL-0016). Renal excretion of isavuconazole as unchanged was less than 1% of the administered dose.

Isavuconazonium hydrolysis producing isavuconazole occurs mainly by butyrylcholinesterase in plasma (Study 9766-ME-1008). In vitro, isavuconazole is mainly metabolized by CYP3A4 and CYP3A5 (Study 9766-ME-1009). In vitro, isavuconazole is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2D6, and an inducer of CYP3A4 (up to 3.43-fold increase in activity and 6.43-fold increase in mRNA expression), CYP2B6, CYP2C8, and CYP2C9. Isavuconazole CYP3A4 Ki was determined as 0.622 uM to 1.93 uM[4] (Study 9766-ME-1005).

Isavuconazole shows high permeability in vitro, whereas the prodrug isavuconazonium showed low permeability (Study 9766-ME-1026). Isavuconazole is not a substrate of P-gp and BCRP but is an inhibitor of P-gp and BCRP (Study 9766-ME-1006).

Based on the clinical DDI studies, coadministration of strong CYP3A4 inhibitors and strong CYP3A4 inducers are contraindicated with Cresemba in the approved labeling (Astellas 2015). Concomitant administration of ketoconazole with isavuconazonium increased isavuconazole AUC by 422%, whereas rifampin decreased isavuconazole AUC by 97%. Isavuconazonium is a moderate inhibitor of CYP3A4 and increased AUCs of midazolam, sirolimus, and tacrolimus (CYP3A substrates) by about 2-fold, whereas increased digoxin (P-gp substrate) AUC by about 25% (following oral isavuconazole 200 mg QD). The approved labeling recommends caution when immunosuppressants such as tacrolimus, sirolimus, and cyclosporine and drugs with narrow therapeutic window that are P-gp substrates such as digoxin are coadministered with isavuconazonium sulfate (Astellas 2015).

The Applicant developed vincristine PBPK model based on the two published PBPK models (Lee et al. 2019; Pilla Reddy et al. 2021). Vincristine is metabolized by CYP3A enzymes, preferentially by the polymorphic CYP3A5, and is a substrate of P-gp (see the corresponding labeling (Hospira 1996). Vincristine exposure (AUC) was increased by 3.4-fold when administered with nifedipine (CYP3A4 and P-gp inhibitor) in adults (Fedeli et al. 1989). Concurrent administration of vincristine sulfate with itraconazole or fluconazole (known inhibitors of the CYP3A metabolic pathway) has been reported to cause an earlier onset and/or an increased severity of neuromuscular side effects (Hospira 1996). The current labeling states that the concomitant use

[4] Ki of 1.93 uM and 0.622 uM with testosterone and midazolam, respectively, as CYP3A4 substrate.

of strong CYP3A inhibitors and CYP3A inducers with vincristine sulfate should be avoided and patients be frequently monitored for adverse reactions with the concomitant use of moderate CYP3A inhibitors. The labeling also states that the concomitant use of P-gp inhibitor or inducers should be avoided as vincristine sulfate is a substrate for P-gp (Hospira 1996).

The purpose of PBPK modeling in this submission was to predict the effect of isavuconazonium on vincristine exposure in pediatric and adult patients in support of including drug interaction information and warnings in the drug labeling regarding concomitant use of isavuconazonium and vincristine in pediatric and patients.

The FDA assessment was focused on discerning the contribution of CYP3A versus P-gp inhibition in the isavuconazole's effects on vincristine exposure in pediatric and adult patients considering that vincristine as a substrate of P-gp as well as CYP3A4 and CYP3A5 and the approved vincristine label recommends avoiding concomitant use of P-gp inhibitor and inducer.

15.4.5.3. Methods

The Applicant's PBPK analysis from the PBPK report and the addendum-1[5] (Report 9766-pk-0009 report-addendum-1) is described below.

Software

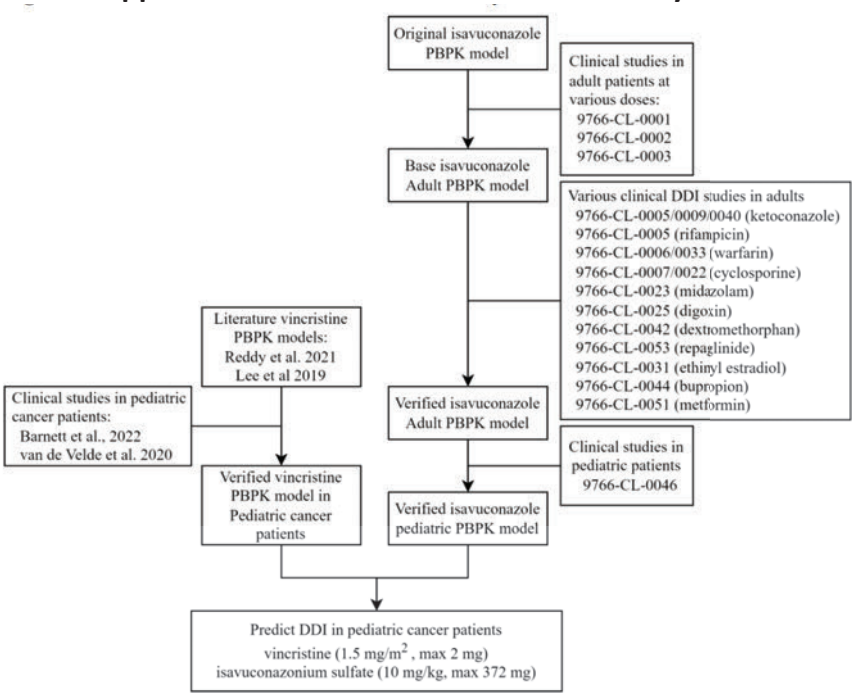
Simcyp population-based simulator (Version 22) was used.

Modeling Strategy

The Applicant's modeling strategy is outlined in Figure 15.

[5] To respond to the FDA's IR, the Applicant updated the PBPK model, which was used to conduct additional simulations as well as to repeat the previously conducted simulations submitted in the PBPK report 9766-PK-0009. This review discussed the updated PBPK analysis results that were submitted in the IR response and the PBPK report addendum on September 6, 2023.

Figure 15. Applicant's Overall Workflow of PBPK Analysis of Isavuconazole and Vincristine



Source: Figure 2 in the Applicant's PBPK report addendum (9766-pk-0009-addendum-1).
Abbreviations: PBPK, physiologically based pharmacokinetic

Model Structure and Parameters

The final model input parameters in the isavuconazole IV route pediatric PBPK model and the vincristine pediatric PBPK model are summarized in Table 34.

Table 34. Input Parameters in the Isavuconazole and Vincristine Pediatric PBPK Models

A. ISAVUCONAZOLE

Parameter		Value	Assumption(s) and references
Physicochemical properties and blood binding			
Compound type		Small molecule	Investigator's Brochure ed 19
Molecular weight		437.47	Investigator's Brochure ed 19
Log P		4.1	Investigator's Brochure ed 19
Charge		Neutral	Investigator's Brochure ed 19
B/P ratio		0.6	9766-CL-0016, 9766-CL-0050
f_u		0.00737	9766-ME-1011
Plasma binding protein		HSA	Investigator's Brochure ed 19
Distribution			
Distribution model		Full PBPK	
Prediction method of V_{ss}		Method 2 (Rodgers)	
V_{ss} (L/kg)		4.48	Predicted by Simcyp
K_p scalar		1	Default
Elimination			
CL_R (L/h)		0.0125	Investigator's Brochure ed 19
CYP3A4 CL_{int} (µL/min/pmol)		0.570	Simcyp calculated by retrograde analysis: CL_{IV} 3.5 L/h with 95% CYP3A4
CYP3A5 CL_{int} (µL/min/pmol)		0.0349	Simcyp calculated by retrograde analysis: CL_{IV} 3.5 L/h with 5% CYP3A5
CL_{int} (Bile) (µL/min/10^6)		22.7	Simcyp calculated by retrograde analysis: CL_{IV} 3.5 L/h with 46.1% $f_{CL,Bile}$
Interaction			
CYP3A4	K_i (µmol/L)	0.180	Optimized based on 9766-CL-0007
	Ind_{max}	9.47	Calculated based on 9766-ME-1004
	$Indc_{50}$ (µmol/L)	5.60	Calculated based on 9766-ME-1004
CYP3A5	K_i (µmol/L)	0.180	Assumed same as CYP3A4
	Ind_{max}	9.47	Calculated based on 9766-ME-1004
	$Indc_{50}$ (µmol/L)	5.60	Calculated based on 9766-ME-1004
P-gp	K_i (µmol/L)	0.0100	Optimized based on 9766-CL-0025

B. VINCRISTINE

Parameter	Value	Assumption(s) and references
Physicochemical properties and blood binding		
Compound type	Small molecule	
Molecular weight	824.96	Lee CM, et al., 2019
Log P	2.82	Lee CM, et al., 20191
Charge	Monoprotic acid	Reddy VP et al., 2021
pKa 1	5.15	Reddy VP et al., 2021
B/P ratio	1.2	Reddy VP et al., 2021
f_u	0.51	Lee CM, et al., 2019
Plasma binding protein	AGP	Lee CM, et al., 2019
Distribution		
Distribution model	Full PBPK	
Prediction method of V_{ss}	Method 2	
V_{ss} (L/kg)	20.2	Simcyp predicted
K_p scalar	90	Optimized to match observed [Reddy VP et al., 2021]
Elimination		
CYP3A4		
V_{max} (pmol/min/pmol isoform)	0.9	Lee CM, et al., 2019 and DIDB
K_m (µmol/L)	19.7	Lee CM, et al., 2019 and DIDB
CYP3A5		
V_{max} (pmol/min/pmol isoform)	14.3	Lee CM, et al., 2019 and DIDB
K_m (µM)	8.1	Lee CM, et al., 2019 and DIDB
fu_{mic}	0.75	Calculated from Dennison JB et al., 2006
CL_R (L/h)	6.8	Optimized to 8% urine recovery [Bedikian AY et al., 2006]
Transporter		
P-gp		
Jmax (pmol/min/million cells)	77	Reddy VP et al., 2021 and DIDB
Km (µmol/L)	17.1	Reddy VP et al., 2021 and DIDB
RAF/REF	1.5	Simcyp default for MDCK cells
CL_{PD} - liver (mL/min/million hepatocytes)	0.37	Reddy VP et al., 2021
fu_{BW} - liver	0.036	Reddy VP et al., 2021
fu_{BW} - liver	1.0	Reddy VP et al., 2021

Source: Extracted from the Tables 2 & 3 in the Applicant PBPK report addendum 1 (9766-pk-0009-addendum-1).
Abbreviations: PBPK, physiologically based pharmacokinetic

Reviewer Comments: *CYP3A5 Vmax and Km are incorrect (values switched) in the parameter table, but model simulations were performed using correct parameter values.*

Model Development

Isavuconazole Model

Adult and pediatric PBPK models were developed for isavuconazole, the active metabolite of the prodrug, isavuconazonium sulfate.

Model describes oral dose as IV as the two formulations were considered interchangeable. Infusion time was adjusted to mimic oral T_{max} in oral dose simulations.

Reviewer Comments: *This is reasonable. Isavuconazonium sulfate is rapidly hydrolyzed and not detected after oral administration or detected at low level only during IV infusion in adults. The absolute BA of oral capsules (as determined by isavuconazole AUC) was about 98% and oral and IV PK were BE. The prodrug was not found to interact with any CYPs or transporters in the gut and has low permeability. Thus, it is likely that isavuconazole is absorbed to the systemic circulation after the prodrug is hydrolyzed in the gut lumen. If absorption after oral administration is lower in pediatric patients, the model would overpredict isavuconazole (perpetrator) concentrations in pediatric patients, but this would not change the predicted magnitude of DDI effects within a 2-fold.*

The model allocated 46.1% of the observed total clearance of isavuconazole (CL_IV) to biliary excretion pathway assuming the % dose detected in feces in the mass balance study (9766-CL-0006) as isavuconazole excreted as an unchanged form. Simcyp retrograde model was used to estimate isavuconazole CYP3A4 and CYP3A5 Clint using fmCYP3A4 and fmCYP3A5 as 95% and 5%, respectively, along with the fCL_Bile of 46.1%.

Reviewer Comments: *The Applicant updated the model to accurately describe quantitative contributions of metabolic and biliary excretions to the total isavuconazole clearance in response to the FDA's IR (dated August 18, 2023). Originally, the Applicant assumed over 99% of isavuconazole elimination is attributable to metabolism, which raised a concern for predicting isavuconazole PK across ages using ontogeny in metabolic enzymes. The Applicant conducted sensitivity analysis (Table 20 in the PBPK report addendum-1), which showed minimal impacts of varying fCL,Bile in the isavuconazole model on the predicted vincristine AUC ratio. By varying fCL,Bile from 46.1% (default) to 0% or 60% resulted in up to 3% differences in the predicted vincristine AUC ratio with and without isavuconazole.*

Isavuconazole's inhibitory potential (Ki) for CYP3A and P-gp were optimized using clinical DDI data. Isavuconazole CYP3A4 Ki was optimized using the cyclosporin DDI data (9766-CL-0007 and 9766-CL-0022), which was used as CYP3A5 Ki as well. Isavuconazole P-gp Ki was optimized using the digoxin DDI data (9766-CL-0025), which was used for both gut and liver P-gp.

Reviewer Comments: *Two formulations of cyclosporin were used in the clinical DDI studies, Neoral capsule (9766-CL-0022) and Sandimmune Optoral capsule (9766-CL-0022). The Applicant used the default cyclosporin model (SV-Cyclosporine_Neoral model, V20) for both simulations, with which the observed area under the concentration-time curve ratios (AUCR) (1.10 and 1.29 in Sandimmune and Neoral studies, respectively) were reasonably captured (the simulated AUCR of 1.10 and 1.25).*

The Applicant was requested to provide midazolam DDI simulation in support of the optimized CYP3A4/5 Ki and their rationale for assuming CYP3A5 Ki the same as CYP3A4 Ki (FDA's IR, dated August 18, 2023). See the Assessment Section for further discussion regarding CYP3A4/5 Ki in the model (Section 15.4.5.5).

The adult model was translated to pediatrics with all model parameters remained the same. CYP3A4/5 Clint values were estimated using Simcyp's retrograde model using CL_IV of 3.5 L/hr, which reproduced the observed clearance in pediatric patients. Final input parameter values in the isavuconazole PBPK model is provided above (Table 34).

Vincristine Model

The Applicant developed the vincristine pediatric model based on the published model by Lee et al. (2019). Model parameters from another published model by Pilla Reddy et al. (2021) were also used. Final input parameters for pediatric vincristine model are listed above (Table 34).

Vincristine elimination was described via CYP3A4, CYP3A5 and P-gp transporter pathways. Two CYP3A5 phenotypes (extensive and poor metabolizer) were incorporated in the analysis by using a default frequency of 0.83 for poor metabolizer in all virtual populations.

Reviewer Comments: *The Applicant updated CYP3A4 and CYP3A5 input parameters (now using values from Lee et al. (2019) in response to the FDA's IR requesting to clarify the sources of the parameters. The reviewer noticed that the Applicant changed P-gp parameters as well (which was not requested in the IR) citing Reddy et al. as the source, which cited DIDB for Jmax (77 pmol/min/million cells). DIDB reported the unit as pmol/min/mg. Of note, the previous version of the model used Lee et al. (2019) in vitro data for Jmax and Km as 416 pmol/min/million cells and 17.1 uM. Additional sensitivity analysis was performed given the noted uncertainty in P-gp parameters, although with these P-gp parameters (Jamx 77 and Km 17.1uM) the model was able to capture the fecal excreted fraction in the mass balance study, and the observed adult and pediatric PK of vincristine.*

The Applicant clarified quantitative assignment of vincristine elimination in response to FDA's IR. The simulated pathway mass balance, which showed 80% recovery of the administered dose with 43% excreted in feces (not reabsorbed), 13% excreted in urine, and 24% metabolized by the liver, was consistent with the literature/vincristine labeling (Hospira 1996).

The default CYP3A4 ontogeny in Simcyp pediatric populations was used, whereas no pediatric ontogeny was used for P-gp abundance. CYP3A4-CYP3A5 correlation was used for CYP3A5 abundance with a frequency of 0.83 for CYP3A5 non-expressors. No other changes were made to the default parameters provided by Simcyp for the pediatric cancer population.

Reviewer Comments: *The reviewer tested alternative CYP3A4 ontogeny (profile 2 in Simcyp V22 based on Upreti and Wahlstrom (2016) and P-gp abundance as risk assessment. See the Assessment Section for further details (Section 15.4.5.5).*

Model Verification

Adult isavuconazole model performance was evaluated by comparing the simulated versus observed isavuconazole PK parameters following single and multiple administrations of isavuconazonium at various doses and methods of administration (IV and oral).

As described above, isavuconazole CYP3A4 and CYP3A5 Clint values were optimized using the ketoconazole and rifampin DDI data (9766-CL-0040 and 9766-CL-0005) and CYP3A4/5 Ki and P-gp Ki values were optimized using the cyclosporin (9766-CL-0007 and 9766-CL-0022) and digoxin DDI data (9766-CL-0025). The healthy volunteer population provided by Simcyp (Sim-Healthy Volunteers) was used without modification.

Reviewer Comments: *It is not ideal to estimate CYP3A4/5 Ki values using DDI data with cyclosporin. Please see the Assessment section for further discussion (Section 15.4.5.5).*

Pediatric isavuconazole model was evaluated by comparing the simulated versus observed isavuconazole PK parameters. Weight-based dosing was used for ages 1 to <12 years-old and the maximum capped dose was used for ages 13 to <18 years old. The pediatric population with hematologic cancers (Sim-Paed-Cancer-Haem) provided by Simcyp was used without modification.

Pediatric vincristine model performance was evaluated by comparing the simulated versus observed vincristine PK parameters reported in Barnett et al. (2022) and van de Velde et al. (2020).

Model Applications

The Applicant's verified isavuconazole pediatric model and vincristine pediatric model were used to simulate vincristine PK changes by isavuconazole coadministration in pediatric cancer patients.

Pediatric cancer patients were simulated using Simcyp Paed-Cancer-Haem population with modification to incorporate 83% frequency of CYP3A5 non-expression (*3/*3) genotype.

DDI simulations were performed for pediatric patients of ages 1 to 17 years old. The dosing scheme was as follows: *200 mg (372 mg isavuconazonium sulfate) or 5.38 mg/kg (10 mg/kg isavuconazonium sulfate) isavuconazole 1 hr IV infusion Q8H for 2 days (6 doses = loading dose) followed by 1 hr infusion daily from day 3 to 7 or 17 (maintenance dose). IV bolus administration of 2 mg (1.79 mg salt correction) or 1.5 mg/m3 (1.34 mg/m2 salt correction) of vincristine on day 5 or day 15.*

Sensitivity analysis was performed for isavuconazole CYP3A4 Ki, CYP3A5 Ki (same as 3A4 Ki) and Pgp Ki (liver = gut) on vincristine $C_{max}R$ and AUCR after coadministration. For this analysis, the following dosing scenario was used: *BSA-base dosing of isavuconazole (5.38 mg/kg) for patients ages 1 to <12 years old, maximum dose of vincristine (1.79 mg) and of isavuconazole (200 mg) for patients ages 12 to <18 years old; 12-hour post loading dose of isavuconazole, and vincristine administered on day 5 of isavuconazole dosing.*

15.4.5.4. Results

Can the PBPK model reasonably describe the PK profiles of Isavuconazole following administration of isavuconazonium sulfate in adult and pediatric subjects?

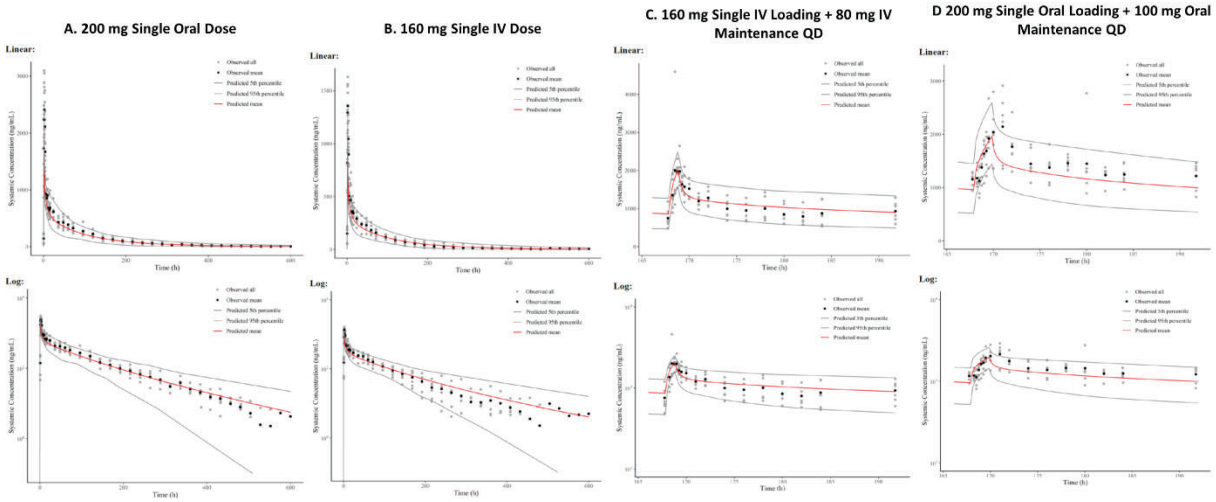
Yes, the isavuconazole PBPK model reasonably described isavuconazole PK following the single and multiple dose administration of isavuconazonium over a range of doses in healthy adult subjects in oral and IV formulations (Table 35 and Figure 16).

Table 35. Predicted Versus Observed Isavuconazole PK Parameters in Adult Healthy Volunteers

	Observed AUC	Simulated AUC	**Sim/Obs_AUC**	Observed Cmax	Simulated Cmax	Sim/Obs_Cmax
SD in HV Adult						
100 mg Oral	36200	34700	**0.96**	1440	1080	0.75
200 mg Oral	77300	65700	**0.85**	2550	2090	0.82
400 mg Oral	208000	140000	**0.67**	5560	4270	0.77
40 mg IV	10700	11300	**1.06**	440	632	1.44
80 mg IV	25500	26400	**1.04**	1020	1270	1.25
160 mg IV	71100	60400	**0.85**	2450	2510	1.02
MD in HV Adult DAY 1						
80 mg L + 40 mg M IV	7190	7110	**0.99**	1270	1270	1.00
160 mg L + 80 mg M IV	12700	14800	**1.17**	2280	2570	1.13
100 mg L + 50 mg M Oral	8610	8900	**1.03**	8610	8900	1.03
200 mg L + 100 mg M Oral	17800	17600	**0.99**	1830	2120	1.16
MD in HV Adult DAY 8						
80 mg L + 40 mg M IV	11800	10900	**0.92**	972	984	1.01
160 mg L + 80 mg M IV	23800	25200	**1.06**	2380	2120	0.89
100 mg L + 50 mg M Oral	17600	14900	**0.85**	1190	1030	0.87
200 mg L + 100 mg M Oral	33500	28300	**0.84**	2280	1970	0.86
MD in HV Adult DAY 14						
80 mg L + 40 mg M IV	69500	54400	**0.78**	1150	1040	0.90
160 mg L + 80 mg M IV	240000	151000	**0.63**	2440	2280	0.93
100 mg L + 50 mg M Oral	21600	16600	**0.77**	1390	1110	0.80
200 mg L + 100 mg M Oral	41100	31300	**0.76**	2590	2110	0.81
MD in HV Adult DAY 21						
100 mg L + 50 mg M Oral	119000	85600	**0.72**	1350	1140	0.84
200 mg L + 100 mg M Oral	228000	153000	**0.67**	2530	2160	0.85

Source: Reviewer summarized the information extracted from the Tables 6-10 in the Applicant's PBPK report addendum-1.
Abbreviations: HV, healthy volunteers; IV, intravenous infusion; L, loading dose; M, maintenance dose; MD, multiple dose; obs, observed; SD, single dose; sim, simulated

Figure 16. Predicted Versus Observed Isavuconazole PK Profiles Following Single or Multiple Dose Administration in Healthy Adult Volunteers



Source: Reviewer extracted and combined the plots from the Applicant's PBPK report addendum-1, Figures 4, 8, and 20. Symbols and lines in each plot represent all observed data (gray dots), observed mean (black dots), predicted 5th and 95th percentiles (gray lines), and predicted mean (red line).
Abbreviations: PK, pharmacokinetics

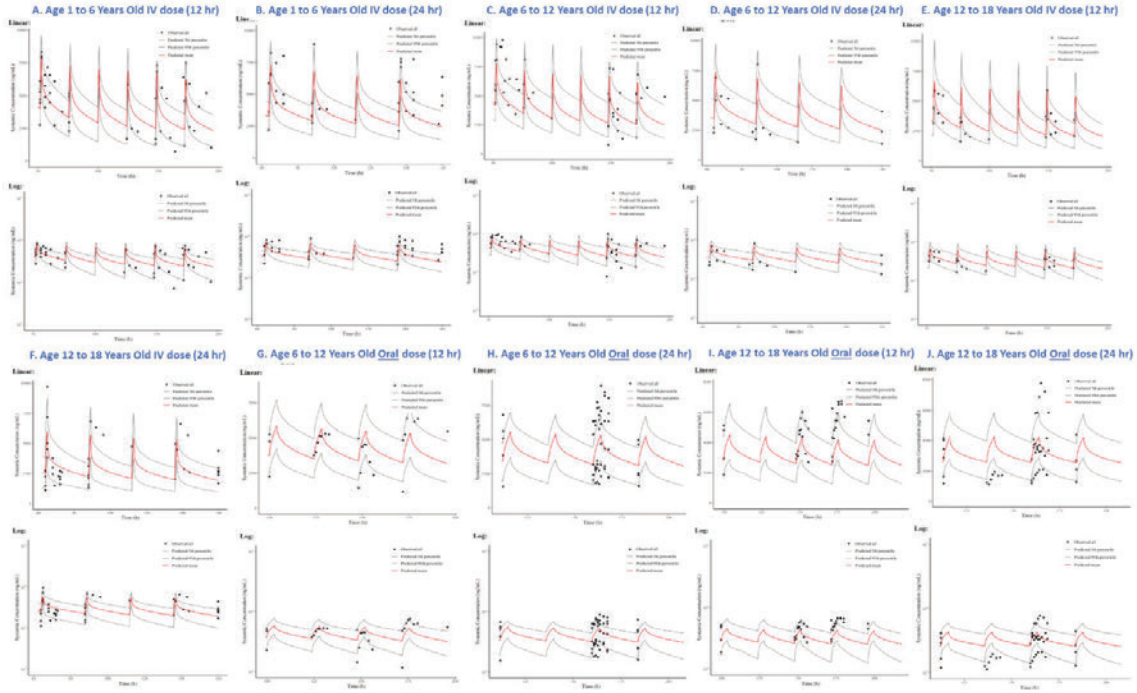
The pediatric isavuconazole model reasonably well captured the observed PK of isavuconazole in pediatric patients 1 to 18 years old following multiple doses of isavuconazonium via IV and oral administration (Table 36 and Figure 17).

Table 36. Predicted Versus Observed Isavuconazole PK Parameters Following Multiple Dose Administration in Pediatric Cancer Patients

	Observed AUC	Simulated AUC	**Sim/Obs_AUC**	Observed Cmax	Simulated Cmax	Sim/Obs_Cmax
MD in Pediatric Cancer DAY 3						
Age 1-6 IV	110000	96500	**0.88**	7770	7800	1.00
Age 6-12 IV	96400	101000	**1.05**	7630	7860	1.03
Age-12-18 IV	65500	73900	**1.13**	5130	6280	1.22
MD in Pediatric Cancer DAY 7						
Age 1-6 IV	86500	80285	**0.93**	7220	7004	0.97
Age 6-12 IV	82200	76100	**0.93**	6490	6580	1.01
Age-12-18 IV	74500	60300	**0.81**	4890	5600	1.15
MD in Pediatric Cancer DAY 7						
Age 1-6 Oral	na	na	na	na	na	na
Age 6-12 Oral	100000	90500	**0.91**	5630	5310	0.94
Age-12-18 Oral	77200	71000	**0.92**	4520	4160	0.92

Source: Reviewer summarized the information extracted from the Tables 13 and 14 in the Applicant's PBPK report addendum-1.
Abbreviations: IV, intravenous infusion; MD, multiple dose; obs, observed; sim, simulated

Figure 17. Predicted Versus Observed Isavuconazole PK Profiles Following Multiple Dose Administration in Pediatric Patients



Source: Reviewer extracted and combined the plots from the Applicant's PBPK report addendum-1, Figures 23-32. Symbols and lines in each plot represent all observed data (black dots), predicted 5th and 95th percentiles (gray lines), and predicted mean (red line). Duration between the last loading dose and the initiation of the maintenance dose (12 hr or 24 hr) is indicated in parenthesis in each plot title.
Abbreviations: PK, pharmacokinetics

Reviewer Comments: *In response to the FDA's IR, the Applicant provided model performance assessment for individual subjects in the 1 to <6 years old group by 1-year increment. Although limited number of subjects, model performance was reasonable (AUC ratios of simulated versus*

observed ranged from 0.57 to 1.34 for Day 3 and 0.41 to 1.5 for Day 7 post-dosing simulations) and did not show age-related trends.

Can the PBPK model reasonably capture the vincristine PK in pediatric subjects?

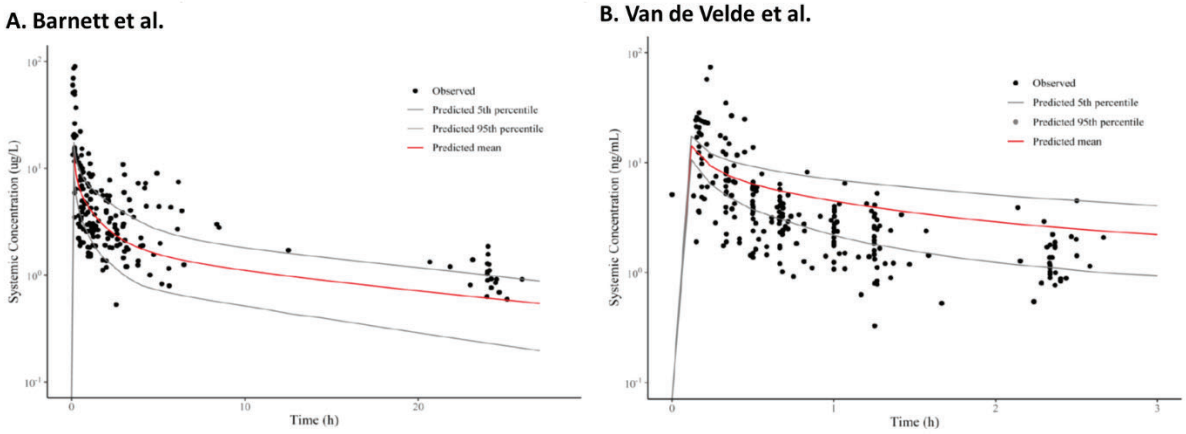
The performance of the submitted vincristine PBPK model to describe the vincristine PK parameters in pediatric patients in the published studies are showed in Table 37 and Figure 18.

Table 37. Predicted Versus Observed Vincristine PK in Pediatric Clinical Studies

	Observed		**Simulated**		**Sim/OBS**	Sim/OBS
	AUC	Cmax	**AUC**	Cmax	**AUC**	Cmax
Barnett et al. (2022), N=30, Mean	72.9	83.7	**54.20**	67.5	**0.74**	0.81
van de Velde et al. (2020), N=20, Median	38.6	72.4	**52.60**	63	**1.36**	0.87

Source: Reviewer summarized the information extracted from the Table 17 in the ***Applicant's PBPK report addendum-1.***
Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; PK, pharmacokinetics

Figure 18. Observed Versus Predicted Plasma Concentration-Time Profile of Vincristine in Pediatric Participants



Source: The reviewer extracted and combined plots from Figures 40 and 41 in the Applicant's PBPK report addendum-1.

Reviewer Comments: *For the above comparison in Table 37, the age range of >1 and <21 years data from Barnett study, which included 18 and 5 pediatric patients aged 2-12 years and 13-24 years, respectively, and the data from van de Velde study with the mean and SD of the patient ages of 10.06 and 5.6, respectively, were used. The Applicant estimated age and weight distributions to match these in order to simulate these two studies. Reviewer considered the performance of the pediatric vincristine PBPK model is acceptable but noted the clinical data in pediatric patients is limited.*

Is the PBPK model adequate for the purpose of predicting the effect of isavuconazonium administration on vincristine exposure in pediatric patients?

Yes, the PBPK analysis can be used to assess the effect of isavuconazole following isavuconazonium administration on the exposure of vincristine in pediatric patients across ages from 1 to 17 years old (Table 38). The PBPK analysis predicted the magnitude of vincristine exposure change due to isavuconazole to be less than a 2-fold including CYP3A5 poor metabolizers. Refer to the Assessment Section below for the breakdown of the results into age groups of age 1-11 and age 12-17 and additional sensitivity analysis discerned the relative role of P-gp versus CYP3A inhibition in the predicted isavuconazole DDI effects on vincristine.

Table 38. Vincristine C_{max} and AUC Ratios in the Presence of Isavuconazole

	Simulated	
	AUC_{inf} Ratio	C_{max} Ratio
12 hr post loading dose, vincristine given on day 5†		
CYP3A5 *1/*1 (EM)	1.26 (1.22, 1.30)	1.00 (1.00, 1.00)
CYP3A5 *3/*3 (PM)	1.93 (1.88, 1.97)	1.00 (1.00, 1.00)
Combined	1.78 (1.73, 1.83)	1.00 (1.00, 1.00)
24 hr post loading dose, vincristine given on day 5‡		
CYP3A5 *1/*1 (EM)	1.25 (1.21, 1.29)	1.00 (1.00, 1.00)
CYP3A5 *3/*3 (PM)	1.92 (1.87, 1.96)	1.00 (1.00, 1.00)
Combined	1.77 (1.72, 1.82)	1.00 (1.00, 1.00)
12 hr post loading dose, vincristine given on day 15§		
CYP3A5 *1/*1 (EM)	1.24 (1.20, 1.28)	1.00 (1.00, 1.00)
CYP3A5 *3/*3 (PM)	1.87 (1.83, 1.91)	1.00 (1.00, 1.00)
Combined	1.73 (1.68, 1.78)	1.00 (1.00, 1.00)
24 hr post loading dose, vincristine given on day 15¶		
CYP3A5 *1/*1 (EM)	1.24 (1.20, 1.28)	1.00 (1.00, 1.00)
CYP3A5 *3/*3 (PM)	1.88 (1.84, 1.92)	1.00 (1.00, 1.00)
Combined	1.74 (1.69, 1.79)	1.00 (1.00, 1.00)

Data presented as geometric mean (90% confidence interval)
EM: extensive metabolizer, PM: poor metabolizer
†Cited from files [A9766-vincristine_task01_ddi01.xlsx] and [A9766-vincristine_task01_ddi01_2.xlsx]
‡Cited from files [A9766-vincristine_task01_ddi02.xlsx] and [A9766-vincristine_task01_ddi02_2.xlsx]
§Cited from files [A9766-vincristine_task01_ddi03.xlsx] and [A9766-vincristine_task01_ddi03_2.xlsx]
¶Cited from files [A9766-vincristine_task01_ddi04.xlsx] and [A9766-vincristine_task01_ddi04_2.xlsx]

Source: Table 19 of the Applicant's PBPK report addendum-1. Simulations were performed using weight-based dosing for pediatric patients in accordance with both the vincristine and isavuconazole model (i.e., 10 mg/kg of isavuconazonium sulfate which corresponds to 5.38 mg/kg of isavuconazole, max 372 mg of isavuconazonium sulfate corresponding to 200 mg for isavuconazole and 1.5 mg/m2, max dose 2 mg for vincristine.
Abbreviations: AUC, area under the curve; Cmax, maximum concentration; PK, pharmacokinetics

15.4.5.5. Assessment

To be confident in the PBPK-predicted DDI effects of isavuconazole on the PK of vincristine in pediatric subjects, this review assessed whether the Applicant's PBPK analysis was adequate for

accurate prediction/description of: 1) plasma concentrations of isavuconazole in pediatric subjects, 2) CYP3A and P-gp inhibition (Ki) parameters of isavuconazole, and 3) relative contribution of CYP3A versus P-gp in the total clearance of vincristine in pediatric subjects. FDA's assessment was summarized in Table 39 and Table 40 and discussed with details below.

This review also focused on discerning the relative contribution of P-gp versus CYP3A inhibition in the predicted isavuconazole DDI effects as the current vincristine label recommends to avoid coadministration of P-gp inhibitor and inducer, while moderate CYP3A inhibitors can be coadministered with caution/frequent patient monitoring. Note the suggested risk factors that include transporters/role of drug transporters for vincristine-induced neurotoxicity (Stage et al. 2021; Triarico et al. 2021). (b) (4) . FDA's independent sensitivity analysis showed that the DDI effects are due to P-gp inhibition by isavuconazole (Table 39), which the Applicant confirmed in their IR response (Table 41).

The FDA reviewer conducted sensitivity analysis to evaluate uncertainties in the optimized CYP3A and P-gp Ki values given that the observed isavuconazole DDI effects in the clinical DDI studies were weak (Table 39). Of note, in these clinical studies isavuconazonium was orally administered.

While isavuconazole increased cyclosporin AUC by 10% and midazolam AUC by 103%, the Applicant only used cyclosporin data to optimize CYP3A Ki. This was justified that the isavuconazole model describes IV route only, so the expected contribution of gut CYP3A4/5 to midazolam DDI could not be captured (underpredicted AUCR 1.19 versus observed 2.03) (Table 39). Of note, the final input value for CYP3A4 Ki was 0.18 uM, which was about 3.5 to 10-fold lower than the in vitro measured values of 1.93 uM and 0.622 uM with testosterone and midazolam as substrate, respectively. Sensitivity analysis showed that the model was able to better capture the observed midazolam AUC increase (predicted AUC increase is about 80% which is comparable to the observed increase of 103%) by further lowering the CYP3A4/5 Ki about 3.5-folde lower to 0.05 uM. In this sensitivity analysis, it was assumed that the observed midazolam DDI is entirely due to hepatic CYP3A inhibition for a risk mitigation purpose. For risk assessment in the prediction of DDI effects on vincristine, a 10x lower CYP3A4/5 Ki (=0.018uM) was tested to further address this uncertainty (Table 40).

Isavuconazole inhibition of P-gp is expected to affect vincristine exposure via hepatic P-gp as vincristine is an IV drug, while the observed digoxin DDI effects are based on both gut and hepatic P-gp. To understand the uncertainty in the hepatic P-gp Ki optimized using the digoxin DDI data, the reviewer conducted sensitivity analysis, which suggested that digoxin AUC was marginally sensitive to P-gp Ki. The magnitude of AUC increase was 27%, 31%, and 36% when P-gp Ki was lowered by 3x, 5x and 10x fold, respectively. Of note, the final input parameter for P-gp Ki (0.01uM) is much lower than the in vitro measured IC_{50} of 25.7 uM, which was measured at [S] lower than 1/25 of Km and thus was considered close to Ki (Fedeli et al. 1989). Another

note is the IV isavuconazole PBPK model only simulated hepatic P-gp inhibition, which may explain that digoxin AUC was not as sensitive to the change in P-gp Ki as expected. The reviewer conducted further simulations as risk mitigation for the P-gp Ki used in the Applicant's PBPK DDI analysis in pediatric patients (Table 40).

Table 39. Simulation of Isavuconazole Effects on the PK of CYP3A and P-gp Substrates

Substrate	Type	Dosing regimen		Substrate PK Parameter Ratio		Trial
		Substrate	Isavuconazole	AUCR	CmaxR	
Cyclosporin (Sandimmune)	CYP3A4/5 substrate	400 mg on D1 + 100 mg QD D2-D20	300 mg on D15	**1.10**	**1.05**	**Sim**
				1.10	1.09	Obs
				1.00	0.96	Sim/Obs
Cyclosporin (Neoral)	CYP3A4/5 substrate	200 mg TID on D1-D2 + 200 mg QD D3-D8	300 mg on D5	**1.24**	**1.11**	**Sim**
				1.29	1.06	Obs
				0.97	1.04	Sim/Obs
Midazolam	CYP3A4/5 substrate	200 mg TID on D1-D2 + 200 mg QD D3-D8	3 mg on D10	**1.19**	**1.09**	**Sim**
				2.03	**1.72**	Obs
				0.59	0.63	Sim/Obs
Digoxin	P-gp substrate	200 mg TID on D1-D2 + 200 mg QD D3-D8	0.5 mg on D5	**1.16**	**1.13**	**Sim**
				1.25	**1.33**	Obs
				0.92	0.85	Sim/Obs

Source: Reviewer's summary using the information from Table 11 in the Applicant's PBPK report addendum-1.
Abbreviations: PK, pharmacokinetics; QD, once daily; TID, three times a day

As noted earlier, vincristine is an IV drug, thus the concerned P-gp-mediated DDI with isavuconazole is at the systemic (hepatic) level. Nifedipine (CYP3A4 and P-gp inhibitor) increased vincristine AUC by 3.4-fold in adults (Fedeli et al. 1989), but the relative contribution between CYP3A4 and P-gp on this is not known. The Applicant's model reasonably recapitulated the reported vincristine mass balance data in adults (Hospira 1996). This provides support to the assigned metabolic, biliary, and renal elimination pathways in the vincristine model. As the vincristine model describes metabolic clearance and biliary excretion entirely by CYP3A4/5 and P-gp, respectively, the predicted CYP3A4 and P-gp mediated DDI effects are expected to conservative, meaning the PBPK analysis covers the worst-case scenarios. The fractional contribution of CYP3A versus P-gp in vincristine clearance in pediatric patients can be different from the adults as CYP3A4/5 and P-gp ontogeny profiles differ. Of note, the Applicant used the Simcyp default CYP3A4 ontogeny, while assumed no ontogeny for P-gp. The reviewer tested Upreti CYP3A4 ontogeny which increases CYP3A4 contribution relative to P-gp in vincristine clearance than that in the Applicant's PBPK analysis, especially in younger ages. The predicted isavuconazole effects on vincristine AUC were reduced with Upreti ontogeny in age 1-11 group, while remained almost the same for age 12-17 group (Table 40). Of note, the default CYP3A4 ontogeny reasonably captured isavuconazole and vincristine PK in pediatric patients. Another note is because both vincristine and isavuconazole are metabolized by CYP3A4, this

Upreti ontogeny scenario affected the PK of substrate and inhibitor as well as the magnitude of the DDI effects.

The FDA reviewer tested additional scenarios to further evaluate the impact of P-gp Ki uncertainty and to evaluate CYP3A related uncertainties. Tested scenarios used a 10-fold lower P-gp Ki, P-gp liver abundance reduced to 60% of the default (based on the literature information suggesting that P-gp protein expression is lower in infants and children than in adults (Prasad et al. 2016; van Groen et al. 2018), and a 5-fold higher P-gp Jmax (this is the in vitro measured value reported in Lee et al. (2019). the reviewer's analysis using this Jmax, vincristine biliary excretion and its total clearance were overpredicted by about 50% -60%). In addition, a scenario with 100% of poor metabolizer CYP3A5 phenotype frequency in the population (poor metabolizer will be more sensitive to DDI effect via metabolism inhibition) along with a 10-fold lower CYP3A4/5 Ki. The reviewer's sensitivity analysis results are consistent with the Applicant's (Table 38). Some scenarios predicted isavuconazole DDI effects on vincristine over 100% in the younger age group (age 1-11) such as with 10x lower CYP3A Ki, 10x lower P-gp Ki and 5 x higher Jmax, which were intended for risk mitigation.

Table 40. Changes in Vincristine Exposure in the Presence of Isavuconazole

Age	Time*	Vincristine on D5	Isavuconazole D1-D7	Applicant's Analysis	Reviwer Sensitivity Analysis							
				AUCR	AUCR	AUCR	AUCR	AUCR	AUCR			
				Default CYP3A4 ontogeny	Upreti CYP3A4 ontogeny	CYP3A5 all PM + CYP3A4/5 Ki = 0.018 uM	P-gp expression (reduced to 60% in the liver)	P-gp Jmax = 416**	P-gp Ki=0.001***	**No CYP3A inhibiton**	**No P-gp inhibition**	**No P-gp inhibition + CYP3A Ki = 0.018 uM**
Age 1-11	12 hr	1.34 mg/m2	5.38 mg/kg	1.93	1.74	2.61	1.93	2.36	2.35	**1.72**	**1.04**	**1.19**
Age 12-17	12 hr	1.79 mg	200 mg	1.64	1.66		1.64	1.89	1.96	**1.5**	**1.04**	
Age 1-11	24 hr	1.34 mg/m2	5.38 mg/kg	1.91	1.73							
Age 12-17	24 hr	1.79 mg	200 mg	1.63	1.65							
* Time after last loading dose												
** 5 fold higher than the applicant's model												
*** 10 fold lower than the applicant's model												

Source: Applicant's PBPK report addendum-1 and simulation output files (A9766-vincristine_task01_ddi01.wksz, A9766-vincristine_task01_ddi01_2.wksz, A9766-vincristine_task01_ddi02.wksz, and A9766-vincristine_task01_ddi02_2.wksz). Reviewer SA means the FDA reviewer's sensitivity analysis with the described modifications. AUCR means the ratio of geometric mean AUCs with and without inhibitor (isavuconazole). This table provides an age-group breakdown of the Applicant's Table 19 in the PBPK report addendum-1 reported the results for age 1-17 years.

The reviewer's sensitivity analysis suggested that the predicted DDI effects of isavuconazole are due to P-gp inhibition, with minimal contribution of CYP3A inhibition (Table 40). Of note, this conclusion remains the same when a 10-fold lower CYP3A4/5 Ki was used (see No P-gp inhibition + CYP3A4 Ki =0.018 uM column in Table 40). In their response to the Agency's IR, the Applicant confirmed that the predicted increase in vincristine exposure is due to P-gp inhibition (Table 41).

Table 41. C_{max} and AUC Ratios of Vincristine in the Presence of Isavuconazole

	Simulated	
	AUC_{inf} Ratio	**C_{max} Ratio**
P-gp Inhibition (no CYP3A inhibition or induction)†		
Geometric mean	1.66	1.00
90% Confidence Interval	(1.61, 1.71)	(1.00, 1.00)
CYP3A inhibition/induction (no P-gp inhibition)‡		
Geometric mean	1.04	1.00
90% Confidence Interval	(1.03, 1.04)	(1.00, 1.00)

Source: Table 1 from the Applicant's IR response (received October 12, 2023).
Abbreviations: AUC, area under the curve; C_{max}, maximum concentration

The Applicant responded to the FDA's IR (dated November 1, 2023) that requested DDI potential evaluation in adults. The predicted DDI potential in adults was weak, showing less than 2-fold increase in vincristine AUC due to isavuconazole (Table 42). The reviewer conducted sensitivity analysis using the Applicant submitted model (for 12 hr post loading dose, vincristine given on day 5, combined scenario). The PBPK-predicted DDI is due to isavuconazole inhibition of P-gp in adults as well. Without P-gp inhibition, the predicted AUC ratio is 1.04 compared to that with P-gp inhibition (the AUC ratio of 1.84).

Table 42. C_{max} and AUC Ratios of Vincristine in the Presence of Isavuconazole in Adults

	Simulated	
	AUC_{inf} Ratio	C_{max} Ratio
12 hr post loading dose, vincristine given on day 5†		
CYP3A5 *1/*1 (EM)	1.24 (1.18, 1.29)	1.01 (1.01, 1.01)
CYP3A5 *3/*3 (PM)	1.96 (1.89, 2.03)	1.01 (1.00, 1.01)
Combined	1.84 (1.77, 1.92)	1.01 (1.00, 1.01)
24 hr post loading dose, vincristine given on day 5‡		
CYP3A5 *1/*1 (EM)	1.23 (1.18, 1.29)	1.01 (1.01, 1.01)
CYP3A5 *3/*3 (PM)	1.94 (1.87, 2.01)	1.01 (1.00, 1.01)
Combined	1.82 (1.75, 1.90)	1.01 (1.00, 1.01)
12 hr post loading dose, vincristine given on day 15§		
CYP3A5 *1/*1 (EM)	1.26 (1.19, 1.33)	1.01 (1.01, 1.01)
CYP3A5 *3/*3 (PM)	1.98 (1.91, 2.06)	1.01 (1.00, 1.01)
Combined	1.86 (1.79, 1.94)	1.01 (1.00, 1.01)
24 hr post loading dose, vincristine given on day 15¶		
CYP3A5 *1/*1 (EM)	1.26 (1.19, 1.32)	1.01 (1.01, 1.01)
CYP3A5 *3/*3 (PM)	1.99 (1.91, 2.06)	1.01 (1.00, 1.01)
Combined	1.86 (1.79, 1.94)	1.01 (1.00, 1.01)

Data presented as geometric mean (90% confidence interval)
EM: extensive metabolizer, PM: poor metabolizer
Source: Table 2 from the Applicant's IR response (received November 1, 2023).
Abbreviations: AUC, area under the curve; C_{max}, maximum concentration

Overall, the Applicant's PBPK analysis was considered reasonable to simulate DDI effects of isavuconazole on vincristine in pediatric and adult patients. The PBPK-predicted DDI effects are weak resulting in less than a 2-fold increase in vincristine exposure and the effects are due to P-gp inhibition.

15.4.5.6. Conclusion

Overall, the PBPK analysis suggested that DDI effects of Cresemba on the exposure of vincristine in pediatric and adult patients are expected to be weak. However, the PBPK analysis revealed the predicted DDI effects are mainly mediated by P-gp inhibition. Thus, (b) (4) the current label of vincristine recommends avoiding concomitant use of P-gp inhibitors and inducers.

15.4.6. PBPK Impact on the Labeling

Section 7

Table 43. The Effect of Cresemba on the Pharmacokinetics of Other Drugs

Vincristine	Avoid Concomitant Use	Avoid concomitant use with Cresemba in pediatric and adult patients. Cresemba is predicted to increase vincristine exposure in pediatric and adult patients *[see Clinical Pharmacology (*12.3*)]*, which may increase the risk of adverse reactions.

Source: Table 5 in the Section 7 of the label.

Section 12.3

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Vincristine: Vincristine (P-gp substrate) exposure is predicted to increase by less than 2-fold in pediatric and adult patients following concomitant administration with Cresemba.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHRIMANT MISHRA
12/08/2023 07:55:00 AM

PETER W KIM
12/08/2023 07:57:15 AM