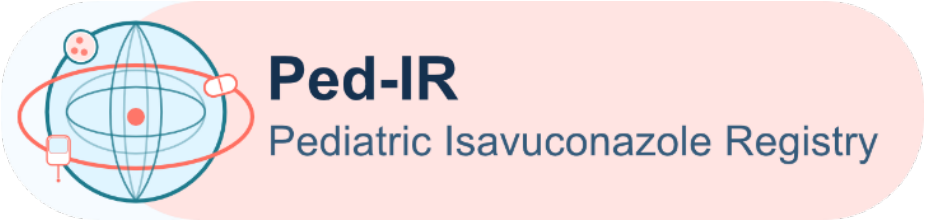
FUNGISCOPE SUBSTUDY

Isavuconazole for Treatment of Proven, Probable or Possible Invasive Mold Disease in Pediatric Patients

A Retrospective Multinational Study



Acronym	Pediatric Isavuconazole Registry (Ped-IR)
Responsible Organization	FungiScope® – A Global Registry for Invasive Fungal Infections
Principal Investigators	Zoi-Dorothea Pana, Andreas H. Groll, Thomas Lehrnbecher, Sarina Butzer, Luise Martin, Daniel Ebrahimi-Fakhari, Oliver A. Cornely, Danila Seidel
Partners	Participating institutions and the FungiScope® Pediatric Network
Industrial Sponsoring	Pfizer Inc.
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BACKGROUND & RATIONALE

Invasive fungal infections (IFIs) are significant causes of morbidity and mortality among immunocompromised pediatric patients, including those with hematologic malignancies or undergoing hematopoietic cell therapies (HCT), and there is a continuous need for safe and effective treatments (Pana et al. 2017).

Isavuconazole, administered as the water-soluble prodrug isavuconazonium sulfate, is an i.v. and oral antifungal triazole approved since 2015 in adults for first-line treatment of invasive aspergillosis and treatment of mucormycosis (FDA, 2015, Maertens et al. 2016). The compound has a broad spectrum of antifungal activity, linear pharmacokinetics, a long half-life and high oral bioavailability. Its interaction and safety profile are similar to those of other triazoles with advantages regarding hepatotoxicity, visual adverse effects and neurotoxicity in comparison with voriconazole (Downes et al. 2020).

Using a population pharmacokinetic model developed in adults, allometric scaling and Monte Carlo simulations, a dosage of 10 mg/kg isavuconazonium sulfate (equivalent to 5.4 mg of isavuconazole) with a maximum of 372 or 200 mg, respectively, administered i.v. every 8 hours for the first 2 days (loading doses) and once daily thereafter (maintenance dose), was predicted to likely result in adequate steady/state exposures in pediatric patients 2–17 years of age. This dosage regimen was then studied in an age-stratified phase 1 clinical trial in 46 immunocompromised pediatric patients after either i.v. or oral dosing. Using population pharmacokinetics and stepwise covariate modeling, no covariates with significant effects on pharmacokinetic parameters could be identified. Assessment of target attainment (AUC time curve at steady state range, 60–233 µg·h/mL) revealed predicted plasma drug exposures within the target range between >80% and >76% of simulated pediatric patients after i.v. or oral administration of isavuconazole, respectively. Isavuconazole was well tolerated with adverse events leading to study drug discontinuation in five patients (Arrieta, Neely et al. 2021, Groll, Roilides et al. 2022).

In a subsequent phase 2, open-label, non-comparative study, patients aged 1 to <18 years with at least possible invasive mold disease received 10 mg/kg isavuconazonium sulfate daily (maximum 372 mg; equivalent to 5.4 mg/kg or 200 mg isavuconazole) for up to 84 (invasive aspergillosis) or 180 days (invasive mucormycosis). Of 31 patients enrolled, 61.3% were 1–<12 years old; 58.1% had underlying hematologic malignancies. Day 42 all-cause case fatality was 6.5%; 93.5% experienced treatment emergent adverse events (TEAEs), and two patients discontinued treatment due to drug-related TEAEs. Dosing at 10 mg/kg (maximum dose: 372 mg) met the pre-defined exposure threshold of above the 25th percentile for the area under the concentration-time curve (≥60 mg·h/L). Isavuconazole was well tolerated in children, with exposure consistent with adult studies. Successful

response was documented in 54.8% of patients (Segers, Deville et al. 2024).

Based on the combined analysis of these two studies, isavuconazole was approved by the U.S. Food and Drug Administration (FDA) for pediatric patients aged 1 year and older for the treatment of invasive aspergillosis and invasive mucormycosis in December 2023 and by the European Medicines Agency (EMA) in October 2024 for treatment of invasive aspergillosis and treatment of invasive mucormycosis (in cases in whom treatment with amphotericin B is not appropriate).

However, despite the existence of two well-designed pediatric registration trials, data on the use of isavuconazole in the pediatric population remains limited. A small number of reports (Borg et al. PBC 2018; Ashkenazi-Hoffnung et al., PIDJ 2020; Decembrino et al., AAC 2020; Rose et al. JPHO 2020; Zimmermann et al. Pharmaceuticals 2022; Kunvariee et al. JPHO 2024) have been published in whom isavuconazole was administered for treatment of proven or probable invasive mold disease at dosages extrapolated from the adult dosage recommendations. While these reports attest to the safety of the compound in the pediatric setting, interpretation of other outcomes is restricted to casuistic observations.

Given the current situation and the need for improved management of pediatric patients with invasive mold disease, the Pediatric Isavuconazole Registry (Ped-IR) aims to systematically collect real-world data on the use of isavuconazole in pediatric patients. This initiative seeks to expand our existing gaps in knowledge by providing important insights into the safety, efficacy, and appropriate dosing of isavuconazole in this vulnerable population.

OBJECTIVES

Primary objective

To evaluate the safety and effectiveness of isavuconazole in treatment of **possible, probable and proven** invasive **mold** infections in pediatric patients

Secondary objectives

- To assess dosing patterns and treatment duration in clinical practice
- To assess adverse events, drug interactions, and tolerability
- To evaluate clinical and microbiological outcomes

STUDY DESIGN

Type: Retrospective, multinational, observational cohort study (FungiScope registry)

Setting: Pediatric Hematology/ Oncology; Pediatric Hematopoietic Cell Transplantation (HCT); Pediatric Infectious Diseases

STUDY POPULATION

Inclusion criteria

- Pediatric patients (< 18 years of age at the time of isavuconazole administration)
- Receiving isavuconazole for treatment of proven/probable/possible invasive mold infection, i.e., aspergillosis, mucormycosis and others [see Appendix]
- Start of isavuconazole treatment from January 2024 to December 2025

STATISTICAL CONSIDERATIONS

Sample size determination

No formal sample size is planned for this study because of its primarily descriptive nature. The expected enrollment is between 50 to 100 patients.

Statistical analyses

All data collected will be summarized using appropriate descriptive statistics: absolute and relative frequencies for discrete variables; mean, standard deviation, median and interquartile range for continuous ones. If relevant mortality is observed, uni- and multivariate analyses for associated risk factors may be considered.

DATA COLLECTION [see Appendix 2]

Demographics and Baseline Data

Age, sex, underlying disease, transplant or cellular therapy status, recently resolved or ongoing neutropenia, receiving other recognized T-cell immune suppressive regimens and prolonged use of corticosteroids, previous antifungal therapies including prophylaxis

Isavuconazole Use

Dose, duration with careful attention on the difference between isavuconazonium sulfate and isavuconazole, respectively, given as monotherapy or combination therapy; concomitant antifungal therapy (combination treatment); TDM performed (yes or no; observed

concentrations; consequences for dosing, if any), oral vs. intravenous; de-escalation

Indication (treatment of possible, probable or proven infection)

Safety and Tolerability

Adverse events, drug-related toxicities, laboratory abnormalities, discontinuations due to AEs; ALT, AST, Bili, AlkPhos, BUN, Krea at start of isavuconazole treatment, at the end of isavuconazole treatment, and the most pathological value during treatment

Effectiveness Outcomes

Clinical response (resolution or improvement of infection), microbiological response, radiological response and survival at defined time points (all-cause case fatality rate through day 42; all-cause case fatality rate through day 84 and at end of treatment) – these time points were also endpoints for response assessment. [see also Appendix 1]

ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the protocol and will be carried out in accordance with ethical principles based on the latest version of the Declaration of Helsinki (agreed by the 64th General Assembly of the World Medical Association, in Fortaleza, Brazil, in October 2013), the Good Clinical Practice and applicable regulations. Data will be managed and stored in an anonymized fashion in the database. Access to the database will be given to authorized personnel only. The protocol of this study will be reviewed and approved by the local/national Ethical Committee of the University Hospital of Cologne, Germany and national and local ethic committees as required by national or institutional requirements.

Recruitment procedures

Patients will be identified by investigators at centers or through local/regional networks. Children who received isavuconazole for proven, probable or possible mold infections January 01, 2024 through December 31, 2025 will be subject to investigation. All data will be recorded in the database in an anonymous fashion. No biological samples will be collected for this study.

COLLABORATING INSTITUTIONS

The study is performed by FungiScope – International Registry for Invasive Fungal Infections. Groups or societies with an interest in pediatric fungal infections may be contacted to inform their members about the option to participate and contribute eligible cases.

TIMELINE

Activity	Timeline
Case enrollment	Jan 1, 2026 – Jun 30, 2026
Data analysis	Jul – Sep, 2026
Manuscript preparation, submission	Oct – Dec, 2026

All partners participating in this study will be acknowledged in publications arising from this collaboration.

Authorship will be granted to institutions contributing eligible clinical cases in accordance with predefined contribution thresholds and generally accepted authorship criteria (e.g., ICMJE).

Exceptions may apply in cases of substantial non-case-based contributions, such as study conception, protocol development, data management, statistical analysis, or manuscript drafting. Such exceptions will be reviewed and decided by the core study team on a case-by-case basis.

EXPECTED IMPACT

- Improved understanding of the use of isavuconazole in pediatric patients in daily practice.
- Contribution of data to future pediatric antifungal treatment guidelines.
- Potential to provide data for expanded regulatory and clinical practice adaptations.

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APPENDIX 1 – DEFINITIONS

IFIs Definitions according to MSG/EORTC revised criteria (Donnelly JP, et al. Clin Infect Dis. 2020)

Criteria of proven invasive fungal infection

Fungus	Microscopic Analysis: Sterile Material	Culture: Sterile Material	Blood Serology	Tissue Nucleic Acid Diagnosis	Notes
Molds	Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL fluid, a paranasal or mastoid sinus cavity specimen, and urine	Blood culture that yields a mold (e.g., Fusarium species) in the context of a compatible infectious disease process	Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue	If culture is available, append the identification at the genus or species level from the culture results.

Definitions of Probable Invasive Pulmonary Mold Diseases (Donnelly JP, et al. Clin Infect Dis. 2020)

Host factors

- Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of invasive fungal disease
- Hematologic malignancy
- Receipt of an allogeneic stem cell transplant
- Receipt of a solid organ transplant
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
- Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days
- Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib
- Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)
- Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids

Clinical features

Pulmonary aspergillosis

The presence of 1 of the following 4 patterns on CT:

- Dense, well-circumscribed lesions(s) with or without a halo sign
- Air crescent sign
- Cavity
- Wedge-shaped and segmental or lobar consolidation

Other pulmonary mold diseases

As for pulmonary aspergillosis but also including a reverse halo sign

Tracheobronchitis

- Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis

Sino-nasal diseases

- Acute localized pain (including pain radiating to the eye)
- Nasal ulcer with black eschar
- Extension from the paranasal sinus across bony barriers, including into the orbit

Central nervous system infection

1 of the following 2 signs:

- Focal lesions on imaging
- Meningeal enhancement on magnetic resonance imaging or CT

Mycological evidence

Any mold, for example, *Aspergillus*, *Fusarium*, *Scedosporium* species or Mucorales recovered by culture from sputum, BAL, bronchial brush, or aspirate

Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold

Tracheobronchitis

- *Aspergillus* recovered by culture of BAL or bronchial brush

- Microscopic detection of fungal elements in BAL or bronchial brush indicating a mold

Sino-nasal diseases

- Mold recovered by culture of sinus aspirate samples
- Microscopic detection of fungal elements in sinus aspirate samples indicating a mold

Aspergillosis only

Galactomannan antigen

- Antigen detected in plasma, serum, BAL, or CSF

Any 1 of the following:

- Single serum or plasma: ≥1.0
- BAL fluid: ≥1.0
- Single serum or plasma: ≥0.7 and BAL fluid ≥0.8
- CSF: ≥1.0
- *Aspergillus* PCR

Any 1 of the following:

- Plasma, serum, or whole blood 2 or more consecutive PCR tests positive
- BAL fluid 2 or more duplicate PCR tests positive
- At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid
- *Aspergillus* species recovered by culture from sputum, BAL, bronchial brush, or aspirate

Definition of successful outcome (Segers et al. AAC 2024).

Clinical Response

- Resolution of all attributable clinical symptoms and physical findings
- Partial resolution of attributable clinical symptoms and physical findings

Mycological Response

- Eradication
- Presumed eradication

Radiological Response

- Improvement from screening
- No signs on radiological images at screen (only for proven invasive fungal infections based on other investigations)

Definition of Treatment and Follow-Up Assessment (Segers et al. AAC 2024)

Discontinuations will be recorded with categorization by reason, including:

- adverse events,
- lack of efficacy,
- withdrawal by participant or guardian,
- other investigator-determined causes.

APPENDIX 2 – Case Report Form

[see PedIR_CRF.pdf]