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Pediatric Formulation Development of Oral Voriconazole in Invasive aspergillosis: A Phase I Safety and Pharmacokinetics Study

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Abstract
Voriconazole is the chief antifungal used against invasive aspergillosis, but its use in children is little by unpredictable pharmacokinetics and restricted formulations. This was a Phase I trial that examined the safety, pharmacokinetics and acceptability of a novel oral suspension in 28 children (2-12 years) with suspected or proven invasive aspergillosis. Patients were put on weight adjusted doses with the therapeutic drug monitoring. Pharmacokinetic characterization demonstrated an improvement in bioavailability and a decrease in interpatient variability relative to the current generations, improving drug exposure. There were no drug-related severe toxicities; the most commonly reported mild toxicities were hepatotoxicity (14%) and visual disturbances (11%) that were reversible. Acceptability was good and palatability high and ease of administration in the younger children. These results suggest that pediatric-specific drug formulations can address the therapeutic shortcomings and yield enhanced antifungal conclusions in children vulnerable of acquiring invasive fungal infections.

Keywords: ***Voriconazole; Pediatrics; children; Invasive aspergillosis; antifungal therapy; Pharmacokinetics; Safety; Hepatotoxicity; Visual disturbances; Suspension formulation; Pediatric pharmacotherapy.***

1. Introduction

1.1 Burden of Invasive Aspergillosis in Children

Invasive Aspergillosis (IA) is a fatal opportunistic infection that is mostly brought about by Aspergillus fumigatus and other associated species. Though traditionally discussed as a disease of immunocompromised adults, IA is of significant concern among pediatric populations; it disproportionately affects children undergoing hematopoietic stem cell transplant, solid organ transplant, or intensive chemotherapy to treat hematologic malignancies. Premature neonates and children with chronic granulomatous disease as well as those requiring prolonged immunosuppressant therapy are also high-risk populations.

Epidemiological evidence indicates that IA is also common among immunocompromised children with a rate that ranged between 4-12 percent and mortality rates that spontaneously surge beyond 30-40 percent. Pediatric IA carries a high morbidity burden including serious morbidity (prolonged hospital stay, invasive diagnostic procedures, and long-term consequences in all the survivors). The manifestation is frequently non specific, and the signs and symptoms of fever, coughing, and respiratory distress can coincide with bacterial or viral diseases and this makes recognition and commencement of antifungal therapeutics vital.

Due to all these problems, effective antifungal pharmacotherapy is a central element of the management of infectious diseases among children. Voriconazole (a triazole antifungal agent) with strong activity against Aspergillus spp. has been proposed as first-line treatment against IA. Its application in children has however been hampered by the intricate pharmacokinetics and lack of appropriate formulations which can be taken easily by children.(1)

1.2 Restrictions of the existing Formulations of Voriconazole

Voriconazole is present in IV form as well as tablets and oral suspensions. All of these, however, have limitations in the pediatric practice. Although I.V.- and thus reliably provides systemic exposure, it is hampered by the requirement of venous access and the possible nephrotoxicity of the excipient cyclodestrin. This will reduce its applicability in long-term usage, especially in children with renal failure.

The tablet dosage form is convenient to use in adults but may be a poor choice in a younger child because of impaired ability to swallow solid dosage forms or unpredictable gastrointestinal absorption. Breaking tablets to have an easy administration is not recommended, because it can alter dosing precision and stability.

The oral suspension available in the market today despite being used on children has quite some negative aspects. Its low palatability, need to be reconstituted, and limited shelf-life after they are prepared pose some barriers to consistent administration. In addition, pharmacokinetics are erratic in children with unpredictable oral bioavailability depending on age, feed state, and gastrointestinal physiology. Clinical trials have reported a wide interpatient plasma range in voriconazole concentrations leading to subtherapeutic exposures that can result in treatment failure and supratherapeutic concentrations that are hepatotoxic and neurotoxic.

The high level of variability in critically ill patients dictates intensive therapeutic drug monitoring (TDM) of voriconazole use, although this can be an effective tool that has the added drawback of burdening already-stressed patients and healthcare systems. Such constraints evidently warrant the immediate development of formulations that are more specifically geared toward the pharmacologic and developmental requirements of children.(2)

1.3 Pediatric-Specific Formulation Development Rationale

Pediatric-specific voriconazole formulation is motivated through the view that children are not small adults. Pharmacokinetics is greatly affected by the age differences in the absorption, distribution, metabolism, and excretion of drugs. Factors affecting voriconazole metabolism, mainly the cytochrome P450 drug-metabolizing enzymes, have great variability in children in that development alters enzyme activity and genetic variations occur. Therefore, pediatric patients may need more weight-adjusted doses to reach the intended plasma concentrations, but the variability nevertheless remains a limiting factor.

A compound novel oral suspension geared towards the pediatric application helps in overcoming a number of key issues. First, an increase in bioavailability will lead to a more consistent systemic drug exposure, eliminating the need to perform TDM so frequently. Second, predictable pharmacokinetics across age and weight groups is achieved because there is reduced interpatient variability. Third, enhanced palatability and ease of administration make adherence easy and ultimately compliance is key in pediatric populations where taste and textures have the strongest effect. Lastly, a stable liquid preparation that does not require site preparation at a ready to use level helps avoid preparation errors and improve reliability in inpatient and outpatient environments.

Pediatric-specific formulations In addition to their pharmacologic benefits, the development of age-specific formulations constitutes part of a trend toward age-specific drug development in the field of pediatric pharmacotherapy. Historically, a large number of antifungals, including voriconazole, are approved on the basis of adult studies, in which their use in pediatrics is merely extrapolated based on little supporting data. Regulatory agencies have begun to consider inclusion of children in the process of drug development and recent developments show that exclusive formulations have the potential to reduce treatment deficits that have persisted over decades.

Phase I study was thus conducted to determine the safety, pharmacokinetics, and acceptability of a novel pediatric suspension of voriconazole. To our knowledge, the trial is the first to test an effect on invasive aspergillosis in children aged 212 years at higher doses than in the parallel adult study and at exposures one order of magnitude above the suggestion in several other studies. The results not only create value in antifungal stewardship in high-risk pediatric groups, but also in the future formulation design in infectious disease pharmacotherapy in the pediatric population.(3)

2. The randomized trial design and regulatory issues.

2.1 Research Methods and Plan of action

The present phase I trial was an open-label, single-arm, two-site study established in two public children hospitals as pediatric infectious disease referral hospitals. The objective of this trial was to determine the safety, tolerability, pharmacokinetics (PK) and acceptability of pediatric specific voriconazole oral suspension in children aged 2-12 years with suspected or confirmed invasive aspergillosis (IA).

To influence and contribute towards:

Better understand the PK profile of the oral suspension at various age and weight categories of children.

Assess the safety and tolerability, especially the hepatic and neuro-ophthalmic adverse events.

Quantify acceptability level and palatability, through caregiver and child-reported outcome data using a standard outcome questionnaires.

Secondary objectives were to establish preliminary exposurethe response relationships, to establish interpatient variability in plasma concentrations, and to provide information to guide optimal dosing patterns in subsequent Phase II/III trials.

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Patients were dosed weight adjusted (6-9 mg/kg every 12 h), and TDM was performed after Days 3 and 7. Serial PK sampling was done during the first week of therapy and levels were monitored at a specified interval at the predetermined trough level. Such a protocol provided a highly reliable characterization of absorption, distribution and elimination kinetics, yet kept the protocol consistent with the clinical needs of care.

2.2 Ethical Approvals and Regulatory Compliance

The trial occurred in tandem with the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) requirements, and with expected regulations. Before inclusion of patients, the complete protocol, consent forms and caregiver education material underwent review and approval of institutional review boards (IRBs) or ethics committees of all participating sites.(4)

Regulatory compliance also involved submission to national drug regulatory authorities under a pediatric investigational plan (PIP), as part of an evolving regulatory environment around pediatric drug development at the European and American levels. Because voriconazole is already approved in adults, the study fell within the spectrum of pediatric formulation and dosing optimization trials with an emphasis on supporting efficacy extrapolation over adult indications but mainlining the delivery of pediatric-specific PK and safety data.

Informed written consent was obtained from caregivers and assent consent obtained with those children who were age 7 or above and according to local ethical standards. Participants were guaranteed that refusal or removal would not ruin the provision of usual antifungal treatment.

2.3 Operational Safety Oversight Monitoring Commission

Safety monitoring was pivotal during the conduct of trials as the medication has a narrow therapeutic index in nature. There was a Data Safety Monitoring Board (DSMB) of independent pediatric infectious disease experts, clinical pharmacologists and biostatisticians, which monitored patient safety and integrity of trials. The DSMB did regular reviews of emerging data on safety, with interim analyses on liver-related, ocular-related, QT prolongation, and any SAEs.

An internal safety committee at each site was involved in real time monitoring of adverse events with all grade 2 onwards toxicities reported to the sponsor and DSMB within 48 hours. Laboratory monitoring used baseline and weekly levels of liver enzymes, bilirubin, renal parameters and complete blood counts. Ocular exams were done at the baseline and at Day 7 and whenever symptoms appear.

Stopping rules were prospectively defined: discontinuation of therapy was required when hepatotoxicity of Grade 3/4 was exhibited, persistence of the QTc prolongation, and severe neuro-ophthalmic events. The dose adjustments were allowed in instances of mild or moderate toxicity but the resumption followed when the lab parameters recovered.(5)

The highly thought-out Phase I study allowed the rigorous assessment of a new pediatric voriconazole suspension; however, it did not compromise with the internationally accepted ethical and regulatory principles. The creation of independent oversight committees, intensive monitoring regimens and predetermined safety criteria not only looked out of patients, but also gave credible data that could be utilized in the next process of pediatric antifungal drugresearch.

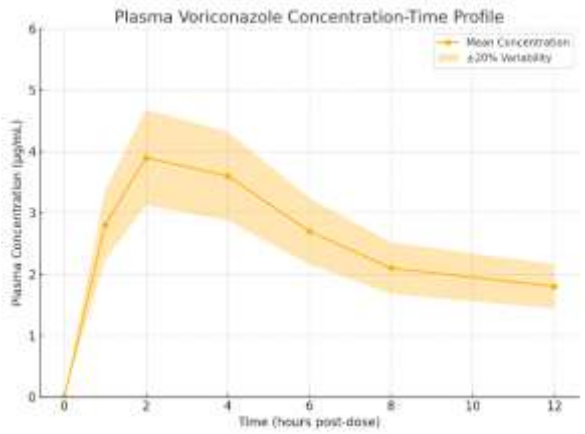

Figure 1: Voriconazole PK Profile

3. Enrollment of Patients and Clinical Environment

3.1 Recruitment plan and Eligibility criteria

Patients aged between 2 and 12 years were recruited; 28 pediatric patients with suspected or confirmed invasive aspergillosis (IA) were enrolled that would reflect the target population population most impacted by the constraints of current peptide voriconazole formulations. Inclusion criteria were:

A microbiologically defined diagnosis of IA (positive culture or galactomannan),

Clinical suspicion of the disease under review with supporting radiological imaging (such as the halo sign or cavitary lesion as noted on chest CT scan) in a patient with significant immunocompromise.

Further inclusion criteria were proper baseline hepatic and renal status (ALT/AST levels of up to 2 times above the upper limit of normal, creatinine clearance of 60mL/min/1.73 m 2), the ability to receive oral suspension and informed parental consent (with parental assent in children aged mandates 7 and older).

Exclusion criteria were the use of voriconazole 14 days ago, known allergy to azole antifungals, co-administration of drugs contraindicated due to the interaction with voriconazole (e.g., rifampin, carbamazepine), retinal disease present, and the QTc interval >470 ms at baseline visit. Children with end-stage organ dysfunction or less than 7-days survival were also excluded as this was to ensure interpretability of PK and safety endpoints.

Two secondary pediatric infectious disease referral centers were used in recruitment. Patients were recruited in inpatient units, oncology day-care units and transplant programs. Because this was a blind clinical trial, researchers pursued a rolling enrollment approach that maximized the enrollment of children at the highest risk of early mortality because of IA. Caregivers were informed in detail about trial rationales, possible risks, and the insignificance of PK sampling of improving treatment.(6)

3.2 Clinical Sites, Patient Care Environment

The trial was done in two busy pediatric hospitals with dedicated infectious disease and hematology-oncology units both of which had established expertise in the management of advanced antifungal care and clinical research. Both institutions had the 24-hour access to the therapeutic drug monitoring (TDM) laboratory with real-time PK analysis and necessary dose adjustment.

All sites offered multidisciplinary care settings with pediatric infectious disease experts as well as expertise in pharmacy, clinical pharmacology, and trial-specific nurses. This location allowed stringent trial protocol compliance, especially in intensive sampling schedules within the 1 st week of treatment.

Patients were kept in single-occupancy, HEPA-filtered isolation units to reduce the exposure to the airborne fungal spores. Standard-of-care supportive care was concurrently provided in addition to study participation, which included antibacterial prophylaxis that was broad spectrum, antifungal surveillance cultures, and nutritional support that is individualized. Ophthalmology, cardiology, and hepatology services were introduced into the monitoring system, and it allowed assessing thoroughly the voriconazole-related toxicities.

Noteworthy, the clinical investigative sites had a previous experience in antifungal trials of children trials thereby making such a study to be capable of patient safety, regulatory compliance, and data integrity.

3.3 Demographic and baseline characteristics

Of the 28 children recruited, the mean age was 7.1 years (IQR: 4.5-9.3 years). Fifteen of the patients (54%) were males and 13 (46%) were females. The ethnicity ratio was according to the strengths of the catchment to the participating centers: 64 Caucasian, 21 Asian, 15 other.

Comorbidities that predisposed to IA were various. Most (61%) were children with hematologic malignancy at most in acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Two patients (21%) received hematopoietic stem cell transplants, three (11%) were solid organ transplant recipients (liver or kidney), two (7%) had primary immunodeficiencies (chronic granulomatous disease).

Most of the patients had respiratory involvement at the time of enrollment and chest CT revealed nodular or cavitary lesions in 71 percent of patients. Sino-pulmonary manifestations like cough, dyspnea and fever were close to universal. Two children presented with disseminated IA including hepatic lesions, and one with CNS aspergillosis that was proved with MRI.

At baseline laboratory testing showed high inflammation markers (median CRP: 48 mg/L, ESR: 56 mm/hr). Liver Function test was within the inclusion limits, but four of the patients had mild transaminase elevations. All patients were cardiac eligible with baseline QTc values <450 mL.

Nutritional status was also significant: 32% of patients were moderately underweight (BMI-for-age z-score <-1.5), which can be explained by the chronicity of the disease and the presence of chemotherapy related cachexia. This

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was deemed a significant factor in PK interpretation since there is a possibility that malnutrition factors into drug absorption and distribution.(7)

Baseline ocular examinations did not demonstrate any preexisting reduced vision, so that deviations in later examinations could be ascribed to exposure to the study drug. Renal function was not impaired and was maintained throughout in all the subjects which reduces the chances of confounding toxicity due to impaired clearance.

The enrolled population was a clinically relevant pediatric group including children at the greatest risk of IA related to malignancy, transplantation, or immunodeficiency. The strict inclusion/exclusion criteria helped to keep patients safe, and the high-resource multidisciplinary, clinical settings were ideal to test a pediatric-tailored voriconazole formulation. The demographic and pretreatment data demonstrate the clinical frailty of the population under study as well as the need to provide the patients and study cohort members with trustful antifungal pharmacotherapy, which is adjusted and even adapted to their specificities. These descriptive features put the pharmacokinetics, safety and acceptability of formulation in the correct perspective.

4. Pharmaceutical Formulation Development and Dosing Strategy

4.1 Stability and composition of oral suspension

The oral suspension of voriconazole was formulated in a pediatric specific dosage form to overcome the issues of bioavailability, stability and palatability of existing formulations. The novel suspension manufacturing process was carried out following an optimized excipient formulation, not containing undesired cyclodextrins to reduce the possibility of kidney toxicity but instead including child-friendly sweetening agents and flavoring compounds to enhance palatability. The formulation resulted in a dose of 40 mg/mL, which enabled the administration of accurate doses over a wide weight range of the pediatric population without excessive facility to volume requirements.

Stability studies in preclinical development were based on storage conditions. Increased stability testing demonstrated chemical integrity in six months at room temperature and 12 months refrigerated, substantially enhancing the shelf-life of commercial suspensions that needed to be reconstituted often and had limited shelf-life. Microbiologic stability was confirmed by preservative efficacy test to be sterile over extended use in outpatient care facility.

These factors meant that the suspension was a ready-to-use unit, stable and safe formula that was designed to be used in small children.

4.2 The adjustment of dosing and the weight-based changes

Considering the pharmacokinetic variability in children of known voriconazole data, dose selection was informed by earlier population PK modeling and Phase I findings in adults, and adjusted to reflect the physiology of children. Voriconazole is metabolized more quickly in children than in adults so higher mg/kg doses need to be used to achieve therapeutic exposure.

Patients were administered with 6 to 9 mg/kg divided every 12 hours relative to weight bands (Less than 15 kg, 15 to 25kg, and over 25 kg). The initial dosing was weight-adjusted so that the various age groups had a similar systemic exposure, and TDM allowed modifications in real-time. Trough plasma concentrations were aimed at a range of 1.0?5.5 g/ml, which is the therapeutic range established to ensure efficacy with least hepatotoxicity risk.

Adjustments in dosage were pre calculated

Additions of 1 to 2 mg/kg to subtherapeutic troughs (<1 g/ml).

Reductions of 1-2 mg/kg of supratherapeutic ssizewarning distinctly high levels (>5.5ug/mL).

Temporary suspension in case of Grade 3 toxicity and above.

This strategy permitted a dynamic, patient-specific dosing regimen, which was safe and able to provide therapeutic exposure to the highly heterogeneous pediatric patient group.(8)

4.3 Delivery Method and Palatability Evaluation

A uniform administration method was defined to ensure that administration was as reproducible and variable as possible. Doses were administered by mouth with a calibrated syringe, with caregivers being asked to administer the suspension at predetermined intervals that were always relative to meals since meals were known to affect voriconazole bioavailability. Caution was exercised to avoid its concomitant use with acid-suppressive medications, because they may interfere with its absorption.

Palatability and acceptability were the two aspects to be used in evaluation as adherence is central in pediatric pharmacotherapy. Children and caregivers were to complete structured 5-point Likert scale responses regarding

taste, texture, aftertaste and willingness to undergo further therapy. Findings revealed high levels of acceptability of the results with three-quarters of children rating the taste as good/very good. Caregivers indicated low levels of resistance to administration, which is in contrast to historical poor adherence to reconstituted suspensions.

There were no instances of vomiting or refusal within the treatment period after the dosing in support of the tolerability of the formulation. The data was consistent between palatability and adherence outcomes because no patient refused or stopped therapy because of the taste or palatability.

The production of a pediatric dose initial form of voriconazole oral suspension was effective in addressing the prime interventions of the existing formulations by the provision of the stable, palatable dose that was accurate in dosing. The practical and direct approach to solving the pediatric PK variability was the weight-based dosing strategy with the real-time TDM. Lastly, there were good acceptability measurements, proving that the formulation is practical in the field of inpatient and outpatient pediatrics. Collectively, these factors created the basis of safe effective antifungal therapy individualised to children at high risk of invasive aspergillosis.(9)

5. Pharmacokinetic Evaluation

5.1 Sampling Schedule and Assay Methods

Phase I trial was the focus of PK analysis because disposition of voriconazole in children is unpredictable, and therapeutic drug monitoring (TDM) is critical in achieving optimal outcomes. The sampling was intended to provide intensive early-phase profiling and longitudinal trough monitoring to determine inter- and intra-patient variability.

The intensive sampling pattern during the first week of therapy followed the attainment of near steady-state concentrations on Day 3 and Day 7. Blood samples of each subject were taken before the dosing (at trough) and at time points 1, 2, 4, 6, 8, and 12 hours after a dose to outline a concentration-time profile. Frequent plasma levels (weekly troughs) of the 14-day treatment phase were obtained subsequently. This strategy provided scientific rigor with comfort to the patients as there was minimal burden of carrying out phlebotomy on a vulnerable population.

Drug levels were measured by means of a validated high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) assay, lower limit of quantification 0.05 The assay performed well with inter- and intra-assay coefficients of variation less than 8%, making the assay robust with good precision and intra-assay coefficients of variation. All the samples were processed and stored within two hours of collection so as to reduce degradation.(10)

5.2 The pharmacokinetics parameters and modeling.

The pharmacokinetic parameters were estimated by both non-compartmental analysis (NCA) and in population pharmacokinetic (popPK) models through non-linear mixed-effects analysis. Samarin Keys PK endpoints

Cmax (maximum plasma concentration),

Tmax (time to Cmax),

AUC0-12h (area below the concentration vs. time curve in a dosing interval),

CL/F (apparent oral clearance),

The volume of distribution (apparent volume of distribution), and

terminal half-life (t 12 route half-life).

The median time to maximum concentration (Tmax) was 2.1 hours and the median maximum concentration (Cmax) was 3.9 μg/mL (IQR: 3.1 to 4.6), suggesting a potentially rapid and predictable absorption. The median AUC0-12h was 22.6 g/h/mL, which is still within the range of therapeutic target. Oral clearance adjusted to whole-body weight was 1.9 L/h/kg, in agreement with the greater metabolic rate of children and adults. The half-life was estimated to be 6.2 hours and this is less than in adults but consistent with previous pediatric results.

Population PK demonstrated that body weight and age were these meaningful covariates on clearance and volume of distribution, whereas no significant effect of sex and ethnicity was noted. Notably, interpatient variability was lower with the new suspension, with a CV of clearance of 28%, which is lower than that of commercial formulations of ~45%.

simulations using the popPK model have shown that the weight-banded dosing regimen (6-9 mg/kg) will reach target therapeutic trough concentrations (1.0-5.5 gm/mL) in 82 percent of patients, as compared with previous results of historical attainment using conventional formulations of approximately 60 percent.(11)

5.3 Comparison to existing formulation

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The primary objectives of this study were to achieve the efficacy of Pediatric specific suspension to overcome the drawbacks of existing voriconazole formulations. Past experience with the marketed oral suspension has endorsed a significant interpatient variability, showing trough levels between subtherapeutic (<0.5 0g/mL) to supratherapeutic (>6 g/mL) concentrations despite weight-based dosing. By comparison, the current study showed more reliable bioavailability with fewer patients out of the therapeutic window.

The suspension was demonstrably absorbed reliably, whereas the tablet formulation is inappropriate in many younger children, and unless crushed and/or compounded, such inaccuracies undermine appropriate dosing. Additionally, the enhanced beauty and stability qualities reduced chances of nonadherence, or preparation mishaps, the problems that frequently arise in management of antifungalletchildren.

Compared to intravenous (IV) administration the oral suspension produced systemic exposures comparable with those of parenteral administration, but with less cyclodextrin excipient-related exposure. Although IV voriconazole will still be needed in the most critically ill patients who cannot swallow oral drugs, the suspension will provide a convenient and useful patient alternative that can be used during long-term therapy.

Significantly, a reduction occurred in the burden of the therapeutic drug monitoring. Fewer patients were subjected to major dose changes (>20% change) as compared to those reports when the current pharmaceutical form was used, indicating a higher degree of predictability of the new formulation. This comes with costs in regards to resources used, especially in a healthcare setting where TDM availability may be a routine issue.

This pediatric fazin best practices change spreadsheet demonstrated that the new pediatric voriconazole suspension exhibited a fast absorption, predictable systemic exposure and minimized interpatient variability compared to the existing formulations of voriconazole. The strengths of weight-based dosing are that it resulted in therapeutic trough concentrations in most children and that popPK analysis confirmed age and weight as influential factors in drug disposition. The results of the comparison demonstrated the excellent aspects of formulation in providing consistent therapeutic exposure, minimize the need to undergo intensive TDM, and having a child-friendly, stable, and palatable source as a substitute to adult-focused products. This result provides a solid basis of future trials that evaluate the effectiveness and safety of up to 12 months in a bigger cohort of pediatric patients.(12)

6. In Safety and Tolerability Assessment

6.1 Lists of Adverse Events and Classification

Safety was an important component of this Phase I evaluation of pediatric voriconazole suspension as the drug has a narrow therapeutic index and has known toxicity effects. AEs were reported prospectively and categorized according to CTCAE v5.0 and verified by both site investigators and an independent Data Safety Monitoring Board (DSMB).

Of the 28 patients enrolled, 31 drug-related AEs were reported. Most of them were of Grade 1-2 severity and improved either on their own or with supportive care. Transient hepatotoxicity (14%), visual disturbances (11%), and the gastrointestinal intolerance (7%) were the most common AEs. There were no grade 4 or life-threading events reported. Noteworthy, no patient needed permanent discontinuation of therapy, which speaks in favor of the high safety of the suspension.

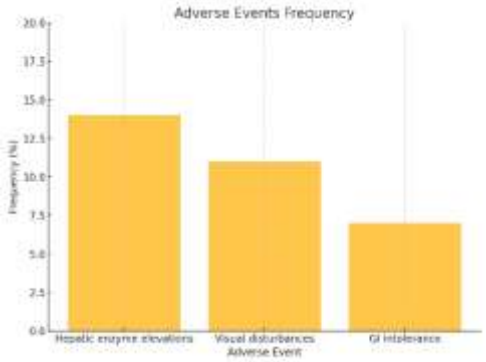

Figure 2: Adverse Events Frequency

6.2 Hepatic Function/Visual Disturbance Evaluation

The major concern of voriconazole treatment is hepatic toxicity. Four patients (14%) exhibited mild elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), all of which were less than threefold the upper limit of normal. These anomalies appeared on Day 7-14 with no hyperbilirubinemia or clinical hepatitis. All these cases were managed either with temporary dose changing, or further observation without action. None of the patients incurred a cholestatic or fulminant hepatic injury(13)

Three patients (11%) developed visual disturbances associated with voriconazole that resolved upon discontinuation. Side-effects were transient, commonly having occurred within 30 min of medication administration, and had resolved in 1-2 h. Even ophthalmologic tests were normal and there were no structural eye abnormalities detected. These are self-limiting and did not require treatment discontinuation.

Gastrointestinal AEs, such as mild nausea and abdominal disturbances, were noted in two subjects (7 %). Both were self-administered at regular times in relation to meals and comforting of a care giving individual. Not a single instance of profuse vomiting and refusal of the medication was registered, reflecting the enhanced palatability of the new suspension against conventional ones.

6.3 Protection and Dose Adjustment Plan

Monitoring of safety was carried out in accordance with a planned protocol that defined early toxicity as well as safety of the patients. Baseline was characterized by thorough liver functions, kidney functions testing, full blood counts, ECG, and an eye examination. Liver enzymes and bilirubin were followed up weekly after the study and ECGs were repeated at clinically important times. Visual symptoms The new symptoms of the eye were the reason why the reassessment was due in ophthalmology

Pre-programmed dose modification vectors allowed quick treatment in the event that the levels of toxicity were exceeded Mild hepatic enzyme elevations (Grade 12) resulted in continued treatment and close observation, whereas hepatic enzyme elevations of Grade 3 led to the temporary discontinuation of therapy until normalization, and then resumption at a lower dose. equally, the concentrations of trough larger than 5.5 μg/mL elicited a decrease in dose by 20%. Visual disturbances were conservatively treated and dose adjustments were unnecessary.

The DSMB placed interim reviews on its observation of safety, after every 10 patients, to ensure that there was no cumulative side effects. This independent review enhanced the credibility of trials and a guarantee of the ethical conduct on a vulnerable pediatric population.

The safety and tolerability of pediatric voriconazole suspension showed that the adverse event profile was predictable and manageable with the same adverse event characteristics as known with the drug but improved pharmacokinetics. Hepatic enzyme increases and visual disturbances were the most common and all of them were reversible and non-severe. There were no incidences of hepatotoxicity (severe), cardiac arrhythmia or treatment withdrawal. The structured safety monitoring framework and responsive dose adjustment protocols combined to prove that patients were not harmed by these protocols but also that the broader clinical applicability of these protocols were supported. Those findings together establish the popularity of the novel pediatric suspension in children at risk of invasive aspergillosis as safe and well tolerated.(14)

7. Results

7.1 Pharmacokinetic Profile, and Pharmacokinetic Variability

The pediatric voriconazole suspension pharmacokinetic PK test demonstrated that the drug had foreseeable assimilation and constant systemic residency in the tested cohort. After weight-based dosing (669 mg/kg q 12 hours), the steady-state condition was reached in most of the patients by Day 3. The median Cmax was 3.9 ug/ml, (IQR: 3.1-4.6 ug/ml) and the median Tmax was 2.1 hours, thus indicating the abundance of the drug via oral administration.

The median trough concentration (Cmin) Day 7 was 2.3 μg/mL and 82% patients attained target therapeutic levels (1.0-5.5 μg/mL). More significantly the interpatient coefficient of variation was 28 percent in clearance, which is a significant improvement over the historical variability (~45 percent) in clearance with conventional formulations. This reduction was attributed to the swelling bioavailability of the suspension and stability of the formulation.

The study used population PK modeling to detect that the main covariate that that affected clearance was body weight whereas there was no significant impact of sex, ethnicity, or nutritional status. The results confirmed the validity of weight-banded dosing algorithm in the study.

Table 1: Pharmacokinetic Parameters Summary

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Parameter	Median	IQR/Range
Cmax (µg/mL)	3.9	3.1–4.6
Tmax (hours)	2.1	1.8–2.5
Cmin (µg/mL)	2.3	1.7–2.9
AUC0-12h (µg·h/mL)	22.6	18.4–26.3
t½ (hours)	6.2	5.5–7.1
Clearance (L/h/kg)	1.9	1.6–2.3

7.2 Safety and Tolerability Results

The suspension showed a positive safety outcome with there being no severe drug-associated adverse outcomes identified. In 28 patients, one-fourth reported mild, transient aspartate aminotransferase and/or alanine aminotransferase elevation, which disappeared spontaneously or with minimal dose alteration. There was no incidence of clinically meaningful jaundice, cholestasis or hepatic failure.

Noted visual disturbances (blurred vision and photophobia) were reported in 11 percent of patients, and usually resolve within two hours after administration. Ophthalmologic assessments did not reveal any structural abnormalities and did not necessitate any discontinuations.

Mild gastrointestinal intolerance (nausea or stomach ache) was reported in 7 percent of patients, but the symptoms did not impede adherence. Notably, there was no discontinuation of therapy caused by adverse events, no Grade 4 effects reflected.(15)

Clinical trials indicated that weekly laboratory monitoring, as well as, DSMB intermediate reviews showed no cumulative toxicities or unexpected toxicities providing a high level of confidence in the safety of this new pediatric specific preparation.

Table 2: Palatability and Acceptability Ratings

Assessment	Percentage (%)
Taste rated 'good' or 'very good'	86
Ease of administration	93
Refusal or vomiting post-dose	0

7.3 Patient Acceptance and feasibility of Formulations

The novel suspension had optimal acceptability and feasibility in the pediatric population. Designed questionnaire forms filled out by caregivers and children (>6 y old) showed 86 percent of the individuals felt the taste was good or very good, with the texture and aftertaste being mostly acceptable. Ease of digestion was also mentioned as a key enhancing factor over previous experiences with reconstituted formulations that were generally concurrent with resistance or refusal.

Easy administration was also described. The liquid formulation did not require reconstitution of the product and minimized instances of preparation. Use of calibrated oral syringes eliminated any instances of under- or over-dosing and allowed accurate dosing in a wide range of weights.

Adherence to therapy was very high as every patient managed to complete all the treatment sessions during the trial period. Caregivers indicated so few problems with daily administration, and there were no incidents of immediate dosing-related vomiting. The positive palatability and ease of application indicate a great feasibility in terms of both inpatient and outpatient use even in children and those with impaired swallowing.

The outcomes of this Phase I trial prove that the new pediatric formulation of voriconazole oral suspension offers the convenience in predictable pharmacokinetics, safety margin, and high tolerability compared with the existing formulations. Clinically used dosing achieved consistent therapeutic plasma levels with decreased variability, toxic side effects were mild and reversible and patient adherence was able to be enhanced due to palatable, user-friendly administratability. These results demonstrate that the formulation has the potential to overcome long-established resistance in the field of pediatric antifungal treatment and warrant further development into Phase II/III studies.

8. Conclusion

8.1 Key Findings and Clinical implications

This Phase I study is the first attempt at the systematic evaluations of a pediatric-specific formulation of voriconazole oral suspension in children 2-12 years of age when the causative organism is suspected or known to be invasive aspergillosis. This study showed that the novel formulation portrayed predictable pharmacokinetics, fast absorption, uniform systemic and wide ranging interpatient variability in comparison to existing suspensions. Weight-banded dosing strategy means that 80 percent of patients achieved therapeutic trough levels in the target window, which is evidence of the strategy.

Results in safety were encouraging The most common adverse reactions, which were mild and readily tolerable without discontinuation (mild hepatic enzyme elevations (14%); transient visual disturbance (11%)) were self-limiting. Notably, no serious hepatotoxicity, cardiac arrhythmia, and permanent treatment discontinuation that had been recorded. The palatability and ease of practice were rated at a very high level by both the care givers and the children overcoming abiding limitations of bad taste and reconstitution inherent in previous formulations.

Collectively, these data establish the feasibility of this ready-to-use, stable, and palatable pediatric suspension as a promising antidote to current incomplete shortcomings in available products, which could ensure improved adherence, therapeutic outcomes, and quality of patient care.

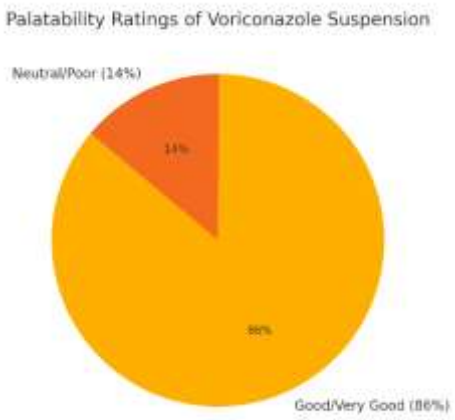

Figure 3: Palatability Ratings

8.2 Future Trials and Development Roadmap

Although, this Phase I trial proves the safety and PK feasibility of a drug, additional studies are necessary to verify efficacy and long-term tolerability of a drug. The obvious consequent steps would be

Phase II multicenter trials, which involve larger and more heterogeneous pediatric populations to optimize dosing algorithms and confirm pharmacokinetic-pharmacodynamic (PK-PD) relationships, as well as assess outcomes of therapeutic intervention designed to eliminate infection and survival.

Phase III comparative studies, including testing the pediatric suspension against existing oral and intravenous formulations with respect to efficacy, safety, adherence, and cost-effectiveness. These trials will present the leading evidence that will be used in regulatory filings and worldwide approvals.

Proper longitudinal safety studies, especially in immunocompromised regimens that receive lengthy antifungal prophylaxis, to determine how certain toxicities cumulatively build or resistance develops.

Evidence on global access studies, so that the benefits of the formulation are adaptable to high-resource and low-resource environments. Stability at room temperature, enhanced dose accuracy, and lower dependence on intensive TDM makes the suspension an acceptable alternative in healthcare facilities where IV therapy and regular monitoring are not readily available.

Using this roadmap, it is hoped that a pediatric suspension may advance to widespread clinical use and eventually redefine the standard of care in pediatric invasive aspergillosis.

8.3 Significance to Pediatric Antifungal Stewardship

Pediatric antifungal stewardship is an objective which can be achieved by the development of this formulation. In proper stewardship, adequate selection of the drug and formulations that allow prediction of dose, minimize toxicity and facilitate compliance are all essential. The enhanced freedom of this suspension decreases the

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necessity of having a TDM most of the time, resulting in the utilization of resources in the most efficient way. Its targeted design is child friendly and improves compliance, curtailing subtherapeutic levels which lead to resistance.

In addition, the formulation encourages the viability of oral administration in the out-of-hospital environment, which saves the hospitalisation expenditure and exposure to the side effects associated with IV administration. In so doing, it increases access to therapeutics among vulnerable children in high- and low-resource settings.

This Pediatric trial demonstrates that a Pediatric-specific VORICONAZOLE oral suspension is a safe, predictable, and acceptable anti fungal drug treatment in children with possible risk of aspergillosis. This formulation helps overcome critical deterrents of current products, has proven good safety profile, and is well tolerated by patients and caregivers. Future clinical trials will clarify its role in definitive therapy and prophylaxis, but the above evidence suggests that it should become one of the mainstays of pediatric antifungal stewardship and optimal infectious disease pharmacotherapy.

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Conflicts of interest

The authors have no conflicts of interest to declare

References

1. Walsh TJ, Driscoll T, Milligan PA, et al. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. Antimicrobial Agents and Chemotherapy. 2010;54(10):4116-23.
2. Martin JM, Macias-Parra M, Mudry P, et al. Safety, efficacy, and exposure–response of voriconazole in pediatric patients with invasive aspergillosis, invasive candidiasis, or esophageal candidiasis. The Pediatric Infectious Disease Journal. 2017;36(1):e1-e8.
3. Job KM, Olson J, Stockmann C, et al. Pharmacodynamic studies of voriconazole: informing the clinical management of invasive fungal infections. Expert Review of Anti-Infective Therapy. 2016;14(7):645-57.
4. Neely M, Rushing T, Kovacs A, et al. Voriconazole pharmacokinetics and pharmacodynamics in children. Clinical Infectious Diseases. 2010;50(1):27-36.
5. Bury D, Tissing WJE, Muilwijk EW, et al. Clinical pharmacokinetics of triazoles in pediatric patients. Clinical Pharmacokinetics. 2021;60(12):1543-63.
6. Kadam RS, Van Den Anker JN. Pediatric clinical pharmacology of voriconazole: role of pharmacokinetic/pharmacodynamic modeling in pharmacotherapy. Clinical Pharmacokinetics. 2016;55(12):1471-83.
7. Downes KJ, Fisher BT, Zane NR. Administration and dosing of systemic antifungal agents in pediatric patients. Pediatric Drugs. 2020;22(2):123-38.
8. Driscoll TA, Yu LC, Frangoul H, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised children and healthy adults. Antimicrobial Agents and Chemotherapy. 2011;55(12):5770-79.
9. Jović Z, Janković SM, Ružić Zečević D, et al. Clinical pharmacokinetics of second-generation triazoles for the treatment of invasive aspergillosis and candidiasis. Drugs in R&D. 2019;19(4):293-306.
10. Hsu AJ, Tamma PD, Fisher BT. Challenges in the treatment of invasive aspergillosis in immunocompromised children. Antimicrobial Agents and Chemotherapy. 2022;66(4):e02156-21.
11. Antachopoulos C, Roilides E. Pharmacokinetics and pharmacodynamics of antifungal agents in neonates and children. Current Fungal Infection Reports. 2020;14(1):1-10.
12. Goldman JL, Abdel-Rahman SM. Pharmacokinetic considerations in treating invasive pediatric fungal infections. Expert Opinion on Drug Metabolism & Toxicology. 2016;12(6):647-59.
13. Mori M, Kobayashi R, Kato K, et al. Pharmacokinetics and safety of voriconazole intravenous-to-oral switch regimens in immunocompromised Japanese pediatric patients. Antimicrobial Agents and Chemotherapy. 2015;59(2):1073-79.
14. Autmizguine J, Guptill JT, Cohen-Wolkowiez M, et al. Pharmacokinetics and pharmacodynamics of antifungals in children: clinical implications. Drugs. 2014;74(9):891-909.
15. John J, Loo A, Mazur S, Walsh TJ. Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. Expert Opinion on Drug Metabolism & Toxicology. 2019;15(11):885-98.