Prospective validation and clinical evaluation of a new posaconazole dosing regimen for children and adolescents with cystic fibrosis and Aspergillus infection

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- In silico definition of the most optimal posaconazole dose for children and adolescents with CF aged 8 to 17 years.- Assess the prevalence of Aspergillus infection in children and adolescents with CF aged 8 -17 years.- An intensive sampling...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Respiratory disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54920

Source
ToetsingOnline

Brief title
A new posaconazole dosing regimen for children with cystic fibrosis

Condition

- Respiratory disorders congenital
- Fungal infectious disorders
- Bronchial disorders (excl neoplasms)

Synonym
Aspergillus infection, cystic fibrosis

Research involving

Human

Sponsors and support

Primary sponsor: IRCCS Ospendale Pediatrico Bambino Gesu
Source(s) of monetary or material Support: Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA

Intervention

Keyword: Aspergillus infection, Cystic fibrosis, Phase 2/3, Posaconazole

Outcome measures

Primary outcome

In view of the dual objectives for this trial, which is reflected in the

design, there are two primary endpoints.

Primary endpoints:

-For validation of the dosing algorithm: The number of children and adolescents

with CF and Aspergillus infection aged 8 to 17 years reaching the pre-defined

area under the concentration time curve (AUC) of posaconazole at the first

assessment (between day 5 and 10) based on the adult reference concentrations

for treatment of susceptible pathogens.

-For clinical efficacy: The number of children with negative sputum sample for

Aspergillus infection at 3 months.

Secondary outcome

-The number of children and adolescents with CF and Aspergillus infection aged

8 to 17 years reaching the pre-defined area under the concentration time curve

(AUC) of posaconazole at the second and third assessment (day 21-35 and EOT)

based on the adult reference concentrations for treatment of susceptible

pathogens.

- To assess the safety and tolerability of posaconazole.

- To assess any relation between posaconazole exposure and toxicity.

- Forced expiratory volume (FEV1) at 3, 6 and 12 months post randomisation to evaluate if posaconazole is beneficial for CF-related Aspergillus infection.

- Aspergillus in the airways (positive sputum culture) 6 and 12 months post randomisation to evaluate if posaconazole is able to clear CF-related Aspergillus infection.

- Levels of Aspergillus specific IgG and IgE 3, 6 and 12 months post randomisation to evaluate if posaconazole is able to normalize those levels.

- Airway inflammation as measured by proteome profiling of sputum at baseline and 3 months post randomisation to evaluate if posaconazole is able to dampen inflammation in CF-related Aspergillus infection.

- Clinical disease severity (as measured by pulmonary exacerbation rate, days on antibiotics and corticosteroids, hospital admissions, change in FEV1, change in BMI) 3, 6 and 15 months post randomisation to evaluate if posaconazole has a beneficial clinical effect.

- Patient reported outcomes 3, 6 and 12 months post randomisation to evaluate if posaconazole has a beneficial effect on people*s life.

Study description

Background summary

Cystic fibrosis (CF) is the most common inherited life-limiting disease in North European people affecting 90,000 people worldwide with about 45,000

registered in the Patient Registry of the European Cystic Fibrosis Society (ECFS). Progressive lung damage caused by recurrent infection and persistent inflammation is the major determinant of survival with a median age of death at 29 years. Approximately 60% of CF patients are infected with A. fumigatus [1], a ubiquitous environmental fungus, and its presence is associated with accelerated lung function decline. Half of the patients infected with Aspergillus are < 18 years of age. Evidence to guide clinical management of CF-related Aspergillus disease is lacking [2-4]. A recent survey showed considerable variability in clinical practice among CF consultants [5]. Two-thirds would treat Aspergillus colonization in patients with CF and two-thirds would use an azole antifungal in addition to steroids in the first line treatment of CF-related allergic bronchopulmonary aspergillosis (ABPA). The results of this survey underscore the limited evidence available to guide management of Aspergillus infection in CF.
Posaconazole, being one of the 4 licensed triazole antifungals with good efficacy against Aspergillus species has been chosen as the study drug as it has a better tolerability compared to itraconazole, less toxicity and drug-drug interactions compared to voriconazole, and can be administered once daily. Posaconazole is licensed in Europe for the prevention of invasive aspergillus in adult neutropenic patient populations and as salvage therapy for invasive aspergillosis. A number of studies have reported on the safety and tolerability of the use of posaconazole in children and adolescents with either haematological malignancies, or chronic granulomatous disease, or those undergoing haematopoietic stem cell transplantation [6-15]. Currently, no dosing algorithm is available to guide posaconazole dosing in children and adolescents with CF.
In clinical practice (based on feedback from individual centres), posaconazole is often preferred above itraconazole if antifungal treatment is initiated in children with CF. Nevertheless, the dosages prescribed are randomly chosen as posaconazole is not licensed for use in patients < 18 yrs of age and it remains unclear what the optimal dose for this age group will be.

Study objective

- In silico definition of the most optimal posaconazole dose for children and adolescents with CF aged 8 to 17 years.
- Assess the prevalence of Aspergillus infection in children and adolescents with CF aged 8 -17 years.
- An intensive sampling pharmacokinetic study of posaconazole in a limited number of children and adolescents with CF and Aspergillus infection aged 8 to 17 years to validate the model predicted dose and optimize the proposed dosing algorithm.
- Prospective clinical evaluation of the defined posaconazole dosing regimen in children and adolescents with CF and Aspergillus infection aged 8 to 17 year.
- Assess the tolerability and safety of posaconazole in children and adolescents with CF and Aspergillus infection aged 8 to 17 years.
- Assess the clinical efficacy of posaconazole in terms of (1) clearance of

Aspergillus from the airways; (2) dampening airway inflammation, and (3) clinical outcomes (as measured by pulmonary exacerbation rate, days on antibiotics and corticosteroids, hospital admissions, change in FEV1, change in BMI, CT-chest abnormalities)

Study design

Open-label, randomized, multi-center study.
An open-label randomized clinical study design has been chosen as the primary aim of the study is the validation of a paediatric posaconazole dosing regimen and is not a primary efficacy trial. We also have taken into consideration the already existing onerous treatment burden of children and adolescents with CF. The study is powered to validate a new posaconazole dosing regimen. In addition, we will collect clinical and laboratory data to evaluate if posaconazole has a beneficial effect in terms of clearance of the Aspergillus infection, dampening inflammation and clinical outcomes. These data will be used to inform a future efficacy trial.
Currently, posaconazole is not licensed for paediatric patients. It remains unclear what the optimal dose for this age group will be. The first stage of the research proposal is to define in silico the optimal dose for patients with CF aged 8 - 17 years. For this purpose the new solid oral formulation will be used as this pharmaceutical formulation has the best oral bio-availability and allows for treatment in an outpatient setting. In addition recommendations will be made for the oral suspension. The likelihood of its use during the present study is low as the company (MSD) is preparing a new oral solution with optimized bioavailability. Nevertheless, some patients may not be able to swallow the posaconazole tablets and will require the oral solution.
We will derive a posaconazole dosing algorithm, for both the oral solution as well as the delayed release tablet, by use of in silico modelling which is a preferred new tool to prevent extensive *old-fashioned* PK studies with a high number of samples per patient being taken. The modelling and Simulation Working Party (MSWP) of the EMA is dedicated to drive towards a greater integration of modelling and simulation in the development and regulatory assessment of medicines. The EMA considers this methodology a powerful tool to provide the opportunity to improve the efficiency of medicine development. It is specifically considered to be of value in the paediatric population. [https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/modelling-simulation-working-party]. We will use state-of-the-art modelling techniques to define the dose of posaconazole, which will be further improved by full PK data in a small cohort (n=24) of patients. Consequently, the defined optimal dose will be used in the study population for validation.
The care of children and adolescents with CF is well structured and this study will take advantage of that. The screening phase of the study is characterized by a low-intensity study and will make use of samples and clinical data being collected during regular clinic visits. For the intervention study, the majority of the study visits are designed to be combined with regular clinical

visits, so additional study visits are limited in number.

Intervention

In the screening phase:
Sputum samples are obtained as part of the standard of care practices with blood samples taken at least once a year during annual review. The sputum and blood sample needed for the screening will be obtained jointly with the sampling doing for clinical reasons.

In the intervention phase:
Group 1:
Patients in group 1 will be treated with posaconazole for 12 weeks. Patients will be divided in 3 weight based groups (< 30 kg; 30-40 kg; > 40 kg) to validate the model predicted dose. Twenty-four patients will undergo intensive PK sampling between day 5-10 of treatment with oral posaconazole. The patients will be admitted to the hospital for one day and they will have an IV, for taking the bloodsamples.
All the patients receiving posaconazole will come in for additional visits between day 5 and 10 and between day 21 and 35; and at end-of-treatment for therapeutic drug monitoring (TDM) and safety bloods (e.g. haematology and biochemistry bloods) (WP IIIb; limited TDM sampling strategy to further improve the model and reduce residual variability). Additional TDM measurements will be performed if exposure is insufficient at the 2 time points defined. At end-of-treatment patients will undergo the following assessments: Lung function (FEV1), blood sample for Aspergillus-IgE and -IgG, safety monitoring bloods, fungal culture on sputum, sputum inflammatory markers, BMI, pulmonary exacerbations, days on i.v. antibiotics & oral corticosteroids, quality of life, patient reported outcomes, quality of life (QoL; CFQ-R age specific). (CT-chest optional).

Group 2:
Patients in group 2 (no antifungal treatment) will come in at 12 weeks (+/- 2 weeks to allow for combining study visit with routine outpatient clinic appointment) and undergo the following assessments: Lung function (FEV1), blood sample for Aspergillus-IgE and -IgG, fungal culture on sputum, sputum inflammatory markers, BMI, pulmonary exacerbations, days on i.v. antibiotics & oral corticosteroids, quality of life (QoL: CFQ-R age specific), patient reported outcomes. (CT-chest optional).

Study burden and risks

The burden of this study is low to moderate.
The vast majority of the study visits are designed to coincide with the regular clinical assessments. As lung function tests and sputum cultures are taken as part of the standard of care, those will not add to the burden of taking part

to the screening part of our study. Blood samples are taken at least annually in children with CF, and we will aim to combine the blood samples needed for the screening part of the study (Aspergillus serology) as much as possible (screening of children and adolescents during clinical annual review visit). For those patients randomized to receive posaconazole, an additional 3 study visits are needed to assess posaconazole plasma concentrations and safety. Twenty-four patients will undergo an 8-hrs PK curve which will include the insertion of an i.v.-line and admission to the day-care unit of the hospital.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

135 children and adolescents will be included. We strive to include 45 children

each in the following weight bands: 20-30 kg; 30-40 kg; >40 kg body weight
Inclusion criteria for the screening phase of the study (n<=1500):
Subjects must meet the following criteria to be eligible for participation in the screening phase:
1. Diagnosed with CF (genetic diagnosis and/or abnormal sweat test and clinical phenotype of lung disease).
2. Age * 8 yrs and < 18 yrs.
3. Able to produce sputum sample (spontaneous or induced sputum).
4. Informed Consent given.

Inclusion criteria for the posaconazole trial
1. Diagnosed with CF (genetic diagnosis and clinical phenotype of lung disease).
2. Age * 8 yrs and < 18 yrs.
3. Body weight *20 kg
4. Signs of Aspergillus infection as defined for this study.
5. Clinically stable condition without a significant change in lung function (FEV1 +/- 10%) or significant worsening of respiratory symptoms in the month preceding signing of the ICF
6. Able to perform lung function test (FEV1%).
7. Able to produce a sputum sample (spontaneous or induced sputum)
8. Informed Consent given.
9. If female and of childbearing age must be using highly effective contraception (and must agree to continue for 7 days after the last dose of investigational medicinal product

Exclusion criteria

Exclusion criteria for the screening phase of the study (n=1500):
1. Non-CF lung disorder
2. Age < 8 yrs of age or * 18 yrs of age
3. Body weight <20 kg
4. Not able to provide sputum sample
5. Informed Consent not given

Exclusion criteria for the posaconazole trial (n=135)
1. Non-CF lung disorder
2. Age < 8 yrs or * 18 yrs
3. Body weight < 20 kg
4. Not able to perform lung function test (FEV1%)
5. Unable to produce a sputum sample (spontaneous or induced sputum)
6. Clinically unstable condition with significant change in lung function or significant worsening of respiratory symptoms
7. Unable to tolerate oral medication
8. Known hypersensitivity to itraconazole or posaconazole, or it*s excipients.
9. On active transplant list or transplant recipient

10. Azole resistant Aspergillus sp. cultured
11. Patients receiving terfenadine, ergot alkaloids, astemizole, cisapride, pimozide, halofantrine, quinidine, or HMG-CoA reductase inhibitors metabolised through CYP3A4 (eg. simvastatin, lovastatin, and atorvastatin)
12. Patients receiving omalizumab
13. Received systemic mould-active antifungals in the last month
14. Shortened or elongated QT interval
15. Cardiac failure
16. ALT * 200 U/L
17. AST * 225 U/L
18. Alkaline phosphatase * 460 U/L
19. Bilirubin * 50 umol/L
20. eGFR < 20 ml/min/1.73 m2 (calculated with the Schwartz formula
21. Patients with known glucose-galactose malabsorption problems
22. Pregnancy2 or breastfeeding
23. Females of childbearing age who do not intend to use contraception measures.
24. Informed Consent not given

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Noxafil

Generic name:	Posaconazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-04-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-01-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004511-31-NL
CCMO	NL72882.091.21
Other	Nog onbekend

Study results

Results posted:	26-07-2022

Summary results
Trial never started

First publication
21-07-2022