Pharmacokinetic interactions between ivacaftor and cytochrome P450 3A4 inhibitors in cystic fibrosis patients and healthy controls

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON46971

Source
ToetsingOnline

Brief title
IACI

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Cystic fibrosis, mucoviscoidosis

Research involving
Human

Sponsors and support

Primary sponsor: HagaZiekenhuis

Source(s) of monetary or material Support: Ministerie van OC&W,met geld uit diverse subsidies zijn de spiegelbepalingen ontwikkeld.

Intervention

Keyword: cystic fibrosis, Cytochrome P450 3A4, ivacaftor

Outcome measures

Primary outcome

The principal outcome variable is the ratio (RAUC) of total area under the

plasma concentration curve (AUC) for oral ivacaftor during co-administration of

inhibitor (AUCI : ritonavir, clarithromycin and azithromycin) divided by the

AUC in the control condition with no inhibitor (AUC0) :

RAUC = (AUCI)/(AUC0)

Secondary outcome

Number of adverse and serious adverse events

The maximum observed plasma concentration (Cmax), the time to achieve Cmax

(Tmax), the mean terminal half-life of ivacaftor.

Other study parameters

* Age

* Gender

* Height

* Weight

* Pregnancy test (if applicable)

Study description

Background summary

Most therapies for cystic fibrosis (CF) are mainly symptomatic. However, multiple compounds have been identified recently that target mutation-specific defects of the CFTR (Cystic fibrosis transmembrane conductance regulator) protein, including potentiators that enhance the CFTR channel gating and correctors that correct CFTR misprocessing. The potentiatior *ivacaftor* has been FDA- and EMA approved for CF patients carrying a CFTR class III mutation based on an impressive clinical improvement. Ongoing trials examine the safety and efficacy of ivacaftor and combination of corrector/potentiator drugs in several other CFTR mutations. Ivacaftor is mainly metabolized by cytochrome P450 3A4. As patients with CF are often treated with drugs that inhibit the activity of cytochrome P450 3A4 there is need for information on the interaction between ivacaftor and these drugs in relation to serum drug levels. With this study we will investigate the efficacy and safety of co-administration of CYP3A4 inhibitors and ivacaftor in healthy controls and CF patients.

Study objective

The primary objective of this study is to evaluate the effect of multiple doses of azithromycin, clarithromycin and ritonavir on the pharmacokinetics, safety and tolerability of a single oral 150 mg dose of ivacaftor in healthy controls and in cystic fibrosis patients.
Secondary Objectives are to:

-Calculate an optimal dosing scheme for ivacaftor therapy in cystic fibrosis patients when it is co-administered with a weak, strong and very strong CYP3A inhibitor.
-Compare the results of healthy controls and cystic fibrosis patients.

Study design

a single center open label intervention study.

Intervention

In phase 2, all subjects will receive a single dose of oral ivacaftor. In phase 3, all subjects will receive 7 doses of oral ritonavir an 1 dose of oral ivacaftor. In phase 4, all subjects will receive 5 doses of oral clarithromycin and 1 dose of oral ivacaftor. In phase 5, all subjects will receive 3 doses of oral azithromycin and 1 dose of oral ivacaftor.

Study burden and risks

Patients participating in this study will be treated at home. Patients will visit the hospital for 4 study visits. At time points 24, 48, 72 hours a member of our research team will visit the patient at home in order to collect blood by a venapunction (10 times in total). During the 4 hospital visits a peripheral venous catheter will be placed in order to collect 7 blood samples. Ivacaftor and the CYP3A4 inhibitors are all registered drugs and the dose we prescribe does not exceed the registered dose. Therefore we do not expect serious problems or side effects during this study.
CYP3A4 inhibitors are often prescribed to our cystic fibrosis patients in daily practice. Most studies on ivacaftor excluded patients using this medication. In order to prescribe this very important drug to CF patients using a CYP3A4 inhibitor this study is needed to give a founded dosage advice regarding safety issues and efficacy

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria for Healthy controls
-Males and females, aged 18 years or older on the date of informed consent
-No medical history and no medication
-Signed informed consent form (ICF)
- Able to understand and comply with protocol requirements, restrictions, and instructions, and likely to complete the study as planned, as judged by the investigator.;Inclusion criteria for Cystic Fibrosis patients
-Males and females, aged 18 years or older on the date of informed consent
-Cystic fibrosis (confirmed by genotype analysis, Class 1 and 2)
-Exocrine pancreatic insufficiency
-Signed informed consent form (ICF)
- Able to understand and comply with protocol requirements, restrictions, and instructions, and likely to complete the study as planned, as judged by the investigator

Exclusion criteria

For both healthy controls as CF-patients the following exclusion criteria apply:
- Use of ivacaftor
- History of clinically significant cirrhosis with or without portal hypertension.
- Severe renal impairment (creatinine clearance * 30 ml/min);
- Use of drugs that are metabolized by the CYP3A enzyme or have a known influence on the CYP3A enzyme (inducers or inhibitors): see appendix.
- Known allergy/intolerance to clarithromycin, ritonavir or azithromycin
- Pregnancy or lactation
- Pregnancy wish
- Pulmonary exacerbation with hospital admission within one month before the study period (defined as need for intravenous antibiotics) ;For the Healthy controls an extra Exclusion Criterium applies:
- Blood relationship in the first or second degree with a CF-patient

Study design

Design

Study type:	Interventional
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-11-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kalydeco
Generic name:	ivacaftor
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Klacid
Generic name:	clarithromycin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	norvir
Generic name:	ritonavir
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	zithromax
Generic name:	azithromycin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-01-2018

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-05-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2016-001440-18-NL
CCMO	NL58561.098.17