Kinetics of ivacaftor at Switch Orkambi Symkevi study

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In this study, we want to investigate the effect of the change in co-medication from lumacaftor to tezacaftor on the kinetics and exposure levels of ivacaftor described by the through concentrationsPrimary Objective: - the through concentration of...

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

Summary

ID

NL-OMON47982

Source
ToetsingOnline

Brief title
SOS

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: eigen middelen

Intervention

Keyword: CF, ivacaftor, lumacaftor, tezacaftor, through concentrations

Outcome measures

Primary outcome

- The primary study endpoint is the ivacaftor through concentration.

Secondary outcome

- tezacaftor and lumacaftor through concentrations

- hydroxymethyl-ivacaftor and ivacaftor-carboxylate concentrations

- ivacaftor, tezacaftor and lumacaftor concentration at T-max

Study description

Background summary

CF is the most prevalent lethal genetic disease in the Caucasian population(1). It is caused by a disruption in the CFTR gene, which leads to the production of a dysfunctional or absent CFTR protein. The majority of the CFTR protein is expressed on the surface of apical epithelial cells, where it regulates chloride ion transport in and out of the cell (2). A disruptions in the production or functioning of these ion-channels causes a malfunction in several organ systems (3). Most predominantly are the pulmonary symptoms like bronchiectasis, small airways obstruction, and progressive respiratory impairment. Other affected organs include the liver, pancreas, sweat glands and vas deferens, leading to a severely limited quality of life and a life expectancy of approximately 40 years(2-4).

For years the treatment of CF has been mostly symptomatic, but recently the first drug to directly target the mutation-specific defects of the CFTR protein has been authorised to the European market. This product, Ivacaftor, is a CFTR potentiator. It works by increasing the probability of CFTR mediated ion channel opening at the cell surface and thereby enhancing ion transport(5). The effectiveness of ivacaftor in CF-therapy has been established in combination therapy with another class of drugs, the CFTR correctors (6, 7). The CFTR correctors work by improving the cellular processing of CFTR protein, leading to an increase in CFTR expression at the cell surface. The two currently registered CFTR correctors are tezacaftor and lumacaftor(8).

Currently patients in the Netherlands with CF who are homozygous for the Phe508del mutation are eligible for treatment with lumacaftor/ivacaftor (9),a combination of ivacaftor and lumacaftor given twice a day. This combination has shown to be effective in increasing the pulmonary function (increasing FEV1 and reduced number of exacerbations) and nutritional state (bodyweight)(6). But in 2018 Vertex launched the follow up of lumacaftor/ivacaftor, with a similar effectiveness profile and an increased safety profile, called Symkevi(8). This product consists of a combination of twice daily ivacaftor and once tezacaftor. The expectation is that when tezacaftor/ivacaftor will be available in the Netherlands a major part of the will lumacaftor/ivacaftor users will switch to tezacaftor/ivacaftor .

Pharmacokinetics
The half-life of ivacaftor when given with lumacaftor is approximately 9 hours and with tezacaftor approximately 9.3 hours. The half-life is 155 hours for tezacaftor and 25 hours for lumacaftor(10, 11).

Ivacaftor is mainly metabolised by CYP3A4 and CYP3A5 into the metabolites hydroxymethyl-ivacaftor and ivacaftor-carboxylate. The pharmacological activity of these metabolites is respectively 1/5th and 1/50th of ivacaftor(10, 11). Because of the metabolism by CYP3A4, the pharmacokinetics of ivacaftor are known to change when co-administered with a CYP3A4 inducer or inhibitor. One of the most notable differences between tezacaftor and lumacaftor is the pharmacokinetic influence on ivacaftor metabolism. Lumacaftor is a strong CYP3A4 inducer thereby causing an increase in the metabolic rate of Ivacaftor when co-administered. This leads to lower ivacaftor concentrations (10,12). Tezacaftor has no inducing effect on CYP3A4 and therefore does not influence the metabolism of ivacaftor (11, 13).

To bypass the influence of CYP3A4 induction a different Ivacaftor dose is advised based on the co-administered corrector. When used with lumacaftor the recommended daily dose of ivacaftor is 500 mg daily (2 x 250 mg) and when combined with tezacaftor 300 mg (2 x 150 mg)(10, 11). What the effect is of lumacaftor or tezacaftor on the ivacaftor concentration has not thoroughly been investigated up until now.

Apart from the effect of the correctors on the ivacaftor concentration, also little is known about the variability between patients and the impact of patient characteristics on the ivacaftor concentrations. This stretches the need for a population-based study into the pharmacokinetics and pharmacodynamics of ivacaftor.

The serum concentration gives insight in several pharmacokinetic parameters, dependent on the time of concentration measurement. Most commonly used is the through concentration, a measurement of the concentration right before the next administration. The through concentration tells if the drug exposure is sufficient during the entire time span up until the next administration of the

gift. Nonetheless, the through concentration does not give concluding information on the pharmacokinetics of a pharmaceutical substance. Therefore, more measurements are needed at different time intervals. In this study the main aim will be directed towards the through concentration, but a smaller group of patients will also be asked for a second peak level blood sample. A second sample makes it possible to investigate other factors like the half-life and volume of distribution.

The introduction of tezacaftor/ivacaftor provides an opportunity to gain insight in the pharmacokinetics of ivacaftor in a real world patient population and with different co-medication. Knowledge from this study will give insight into the relation between patient characteristics, co-medication, treatment response and exposure to CF modulators and could therefore be a start to a more personalized treatment of CF. The main aim of this study is to investigate the effect of switching from lumacaftor/ivacaftor to tezacaftor/ivacaftor in a regular clinical setting on the kinetics and exposure of ivacaftor. The protocol aims to outline the level of exposure in both regimens. A pharmacokinetic difference leading to a different level of exposure might be the case, if a statistically significant difference in through-concentration is found, taking into account the measured plasma concentration and variation within.

The data we will gather comprises of:
- Sex
- Age
- Name
- Address
- Through concentrations of tezacaftor, lumacaftor en ivacaftor
- T-max concentrations of tezacaftor, lumacaftor en ivacaftor (only in optional part)
- Concentrations of hydroxymethyl-ivacaftor andivacaftor-carboxylate
- Lung function
- If available: chloride sweat test
- Height and weight
- BMI (Body Mass Index)
- Kidney function: urea, eGFR, Creatin
- Liver function: ASAT, ALAT, GGT, Alkaline phosfatase, total bilirubin
- Comedication
- Adverse Events that are related to the blood sampling

Study objective

In this study, we want to investigate the effect of the change in co-medication from lumacaftor to tezacaftor on the kinetics and exposure levels of ivacaftor described by the through concentrations

Primary Objective: - the through concentration of ivacaftor

Secondary Objective(s):
- to investigate the effect of the change in co-medication from lumacaftor to tezacaftor on hydroxymethyl-ivacaftor and ivacaftor-carboxylate concentrations.
- to investigate the serum concentrations and kinetics of tezacaftor in CF-patients treated with tezacaftor combined with ivacaftor.
- to investigate the serum concentrations and kinetics of lumacaftor in CF-patients treated with lumacaftor combined with ivacaftor.
- to explore the relation between patient characteristics, co-medication and serum concentrations of ivacaftor/ lumacaftor/ tezacaftor.

Study design

This study is an observational, open-label , multi center, study. Approximately 100 CF-patients will be included. The study will be conducted at the Haga Teaching Hospital and the UMC Utrecht. Analysis will be performed at the Apotheek Haagse Ziekenhuizen.

The study will be performed during regular outpatient visits. With the introduction of tezacaftor/ivacaftor, most of the current lumacaftor/ivacaftor users will switch to the new therapy. This presents the opportunity for a study in a real world setting. Subjects included in the study will have used lumacaftor/ivacaftor for at least one month. After this period, a blood sample will be taken during a regular visit at the outpatient clinic of the Haga Teaching Hospital or the UMC Utrecht. This sample will be taken prior to the lumacaftor/ivacaftor morning dose. Ivacaftor, ivacaftor metabolites and lumacaftor concentrations will be measured in serum. After switching from lumacaftor/ivacaftor to tezacaftor/ivacaftor a second blood sample will be obtained, again during a regular outpatient clinic visit at least six weeks after starting treatment with tezacaftor/ivacaftor. In the second blood sample, ivacaftor, ivacaftor metabolites and tezacaftor concentrations will be measured.

For serum measurement, through levels of the CFTR-modulators will be measured. Therefore, blood has to be drawn in a window of four hours before the next lumacaftor/ivacaftor or tezacaftor/ivacaftor administration. Information about the previous administration, time of blood sampling and whether the last administration was combined with fat containing food, will all be documented on the lab form. To make sure through concentrations can be collected, patients will be asked to withhold their lumacaftor/ivacaftor or tezacaftor/ivacaftor until after the blood sampling. Subjects will also be asked to take the medication in a similar way at both visits, e.g. together with fat containing food. In tezacaftor/ivacaftor therapy the standard dose consists of 125 mg tezacaftor and 150 mg ivacaftor once daily in the morning (equal to 1 tablet Symkevi) and 150 mg ivacaftor once daily in the evening (equal to 1 tablet Kalydeco). In lumacaftor/ivacaftor therapy the standard dose consists of 400 mg lumacaftor and 250 mg ivacaftor twice daily (equals 4 tablets Orkambi per day). It is important to mind the fact that tezacaftor/ivacaftor and

lumacaftor/ivacaftor should both be taken together with fat-containing food.

The SOS study also includes an optional part. Participants will be asked if they want to participate in this optional part of the study as well. In the optional study, another blood sample will be taken from the subjects at T-max; between 3 and 5 hours after the lumacaftor/ivacaftor or tezacaftor/ivacaftor administration. These blood samples will be taken at the same day the pre-dose samples are drawn. We aim to include 20 patients in this part of the study.

Other data and patient characteristics described at the study parameters section will be extracted from the hospital information system HIX and verified with the subject. Apart from the blood sampling and a possible delay in administration of the medication, no deviations from standard care are needed during this study.

Study burden and risks

MAIN Study:
The burden for participating subjects main study consists of:
- 2 blood draws of 4 ml each, 8 ml in total
- 40 minuten of their time

Risks due to participation are:
- undergoing a venipincture can cause some discomfort and may lead to a bruise near/on the puncture site

OPTIONAL Study: (additional consent required)

The burden for participating subjects optional study consists of:
- 4 blood draws of 4 ml each, 16 ml in total
- 8 hours and 40 minuten of their time

Risks due to participation are:
- undergoing a venipincture can cause some discomfort and may lead to a bruise near/on the puncture site

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

* The subject is homozygous for the F508del mutation in the CFTR gene.
* The subject is aged 18 years or older.
* The subject used lumacaftor/ivacaftor continuous for at least a month before enrolling in the study.
* The subject used lumacaftor/ivacaftor in a dose of twice-daily 2 tablets of 200/125 mg lum/iva.
* The subject will switch from lumacaftor/ivacaftor therapy to tezacaftor/ivacaftor.
* The subject will initiate Symkevi therapy with a dosage of once-daily 1 tablet of 100/150 mg
tez/iva and once-daily 1 tablet of 150 mg iva
* The subject has signed and dated a written informed consent.

Exclusion criteria

* The subject is deemed unfit to participate in this study by the treating physician.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-08-2019
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kalydeco
Generic name:	ivacaftor
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Orkambi
Generic name:	lumacaftor/ivacaftor
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Symkevi
Generic name:	tezacaftor/ivacaftor
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	06-05-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	01-07-2019
Application type:	First submission
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	EUCTR2019-001314-41-NL
CCMO	NL69501.098.19