# The influence of pancreatic function on the pharmacokinetics of ivacaftor in patients with cystic fibrosis

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Our primary objective of the study is:- To evaluate if pancreas sufficiency leads to a higher absorption and exposure of ivacaftor in CF patients than pancreas insufficiency. This will be done by comparing pharmacokinetic parameters (AUC, Cmax, Tmax…

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Chromosomal abnormalities, gene alterations and gene variants |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON51011

**Source**
ToetsingOnline

**Brief title**
IPAI

### Condition

- Chromosomal abnormalities, gene alterations and gene variants

**Synonym**
Cystic Fibrosis, mucoviscidosis

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** HagaZiekenhuis
**Source(s) of monetary or material Support:** Er zijn diverse subsidies aangevraagd.

## Intervention

**Keyword:** Cystic Fibrosis, Ivacaftor, Pancreatic function, Pharmacokinetics

## Outcome measures

### Primary outcome

- Pharmacokinetic paramaters (AUC, Tmax, Cmax and T*) of ivacaftor for pancreas sufficient patients and pancreas insufficient patients.

### Secondary outcome

- Pharmacokinetic parameters for absorption and exposure of ivacaftor (AUC, Tmax, Cmax and T*) for pancreas insufficient patients with and without pancreas enzymes. The RAUC of ivacaftor (AUC with pancreas enzymes divided by AUC without pancreas enzymes) for pancreas insufficient patients.
- Number of adverse and serious adverse events

Other study parameters:

- Age
- Gender
- Height
- Weight
- Body mass index (BMI)
- Fat free mass index (FFMI)
- Use of co-medication

# Study description

## Background summary

Cystic Fibrosis (CF) is the most common life-shortening hereditary disease among the Caucasian population. The disease is caused by mutations in the gene that encodes for the CF transmembrane conductance regulator (CFTR). A disruption in the production or functioning in the CFTR causes a malfunction in several organ systems. 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 limited quality of life and a shortened life expectancy.

Recently, drugs to directly target the mutation-specific defects of the CFTR protein have been authorised to the market. These are potentiators (ivacaftor) that enhance CFTR channel gating and correctors (lumacaftor, tezacaftor and elexacaftor) that correct CFTR misprocessing. In 2018, symkevi, which consists of a combination of tezacaftor and ivacaftor, has been reimbursed for CF patients who are homozygous for the Phe508del mutation. Recently, symkevi has also been registered for CF patients heterozygous for the Phe508del mutation and a CFTR residual function mutation. Standard daily dosage prescription for symkevi is one dose of tezacaftor/ivacaftor (100 mg/ 150 mg) in the morning and one dose of ivacaftor (150 mg) in the evening. The dosing advice is the same for pancreatic insufficient and pancreatic sufficient patients. The major part of CF patients is pancreatic insufficient and despite treatment with pancreatic enzymes, still suffer from fat malabsorption. Administered as an oral dose, tezacaftor/ivacaftor and ivacaftor are absorbed directly from the gut. It is advised to administer ivacaftor together with fat containing food, because this increases the exposure to ivacaftor.

Recently, we investigated the pharmacokinetics of ivacaftor in people with cystic fibrosis and healthy volunteers (article currently under review). Our data showed a higher exposure to ivacaftor in healthy people than in CF patients. All CF patients were pancreas insufficient. Therefore, we hypothesize that a decreased and slower absorption of ivacaftor due to pancreatic insufficiency in the CF patients has contributed to the observed difference in exposure. In this study, the influence of pancreatic function on the absorption and exposure of ivacaftor in patients with CF will be investigated by comparing pharmacokinetic parameters of pancreas insufficient CF patients with pancreas sufficient CF patients. Also, the effect of pancreatic enzyme suppletion on ivacaftor exposure and absorption in pancreatic insufficient patients will be examined. We expect that pancreas sufficiency will lead to a higher absorption and exposure of ivacaftor in CF patients than pancreas insufficiency. This study aims to gain insight if current dosing advice need to be reconsidered.

## Study objective

Our primary objective of the study is:
- To evaluate if pancreas sufficiency leads to a higher absorption and exposure of ivacaftor in CF patients than pancreas insufficiency. This will be done by comparing pharmacokinetic parameters (AUC, Cmax, Tmax and T*) of pancreatic sufficient patients with pancreatic insufficient patients.

Our secondary objectives are:
- To evaluate if the administration of pancreatic enzymes leads to a higher absorption and exposure of ivacaftor in pancreatic insufficient CF patients than no administration of pancreatic enzymes.
- To evaluate the number of adverse events and serious adverse events.

**Study design**

This study will be a single-centre study.

**Study burden and risks**

Pancreatic sufficient patients will visit the hospital 2 times and pancreatic insufficient patients 3 times. All patients will be screened during the first visit, which takes approximately 2 hours. Blood will be collected at 7 fixed time points (7x15 ml blood) via a peripheral venous catheter, during the second and third (if applicable) visit, lasting 8-9 hours each.

We do not consider this study a high-risk study. The drugs that the patients will take during the study (ivacaftor/tezacaftor and amylase/lipase/protease (creon 10.000)) are all approved by the FDA and EMA and are already in use by the patients on a daily basis. In addition, the dose that we use does not exceed the registered dose. Pancreatic insufficient patients normally use their pancreatic enzymes before every meal, skipping their enzymes once may result in short-term mild abdominal symptoms.

# 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

- Signed informed consent form (ICF )
- 18 years or older on the date of signed informed consent
- Diagnosis of cystic fibrosis confirmed by genotype analysis
- Current use of tezacaftor/ivacaftor in combination with ivacaftor
- If pancreas insufficient, current use of amylase/lipase/protease, creon 10.000

## Exclusion criteria

- Use of drugs that have a known influence on the CYP3A enzyme (inducers or inhibitors)
- Pulmonary exacerbation with hospital admission in the month before study participation (defined as need for intravenous antibiotics)
- Pregnancy or breast feeding

# Study design

## Design

**Study type:** Observational invasive

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 31-05-2021 |
| Enrollment: | 20 |
| Type: | Actual |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 12-05-2021 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>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 |
| --- | --- |
| CCMO | NL77001.058.21 |