# Elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis using tacrolimus, a drug - drug interaction study

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Primary Objectives: To investigate the pharmacokinetic interaction of elexacaftor/tezacaftor/ivacaftor and tacrolimus in adult CF patients using tacrolimus after renal or liver transplantation by:- quantitating the effect of elexacaftor/tezacaftor/...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Respiratory disorders congenital |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON52229

**Source**
ToetsingOnline

**Brief title**
Kaftac

### Condition

- Respiratory disorders congenital
- Congenital respiratory tract disorders

**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, Drug-drug interaction study, Kaftrio, Tacrolimus

## Outcome measures

**Primary outcome**

- Pharmacokinetic parameters: T1/2, Tmax, Cmax, Cmin , AUC all measured without and with co-administration of elexacaftor/tezacaftor/ivacaftor in order to measure RAUC of tacrolimus (RAUC=AUCtacro with elexacaftor/tezacaftor/ivacaftor/AUCtacro) in week 1, 2, 3 and 4 after starting elexacaftor/tezacaftor/ivacaftor.

- Change in pk parameters after co-administration of elexacaftor/tezacaftor/ivacaftor per individual : T1/2 (T1/2 tacro with elexacaftor/tezacaftor/ivacaftor * T1/2 tacro), Tmax (Tmax tacro with elexacaftor/tezacaftor/ivacaftor * Tmax tacro), Cmax (Cmax tacro with elexacaftor/tezacaftor/ivacaftor * Cmax tacro) , Cmin (Cmin tacro with elexacaftor/tezacaftor/ivacaftor * Cmin tacro) measured in week 1, 2, 3 and 4 after starting elexacaftor/tezacaftor/ivacaftor

- Number and level of dose adjustments made in order to stay within target tacrolimus values.

**Secondary outcome**

- Absolute change in lung function (FVC and FEV1), absolute change in quality of life (CFQ), , absolute change in nutritional status (weight, BMI) in week 1, 2, 3 and 4 after starting elexacaftor/tezacaftor/ivacaftor. Absolute change in sweatchloride from baseline through end of the study.

- Through concentrations of elexacaftor, tezacaftor and ivacaftor measured in week 1, 2, 3 and 4 after starting elexacaftor/tezacaftor/ivacaftor.

- Safety and tolerability based on the number and type of (S)AEs, laboratory values and vital signs.

## Study description

**Background summary**

Cystic fibrosis is a chronic, hereditary, multi-organ disease caused by absence or dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Over the past decade, CFTR protein modulators have been developed, which improve CFTR function either through potentiation of the abnormal protein channel at the cell surface (ivacaftor) or through correction of protein transport to the cell surface (lumacaftor, tezacaftor, elexacaftor); these treatments have now been approved by the European Medicines Agency and US Food and Drug Administration for use in people with cystic fibrosis and certain genotypes. Recent trials show an impressive clinical effect of combination therapy with elexacaftor plus tezacaftor plus ivacaftor. Heijerman et al. showed in patients homozygous for the Phe508 del mutation an increase in ppFEV1 of 10 percentage points ([95% CI 7·4 to 12·6], p<0.0001) after 4 weeks of treatment with elexacaftor/tezacaftor/ivacaftor compared to tezacaftor/ivacaftor. Also, elexacaftor/tezacaftor/ivacaftor was shown to be efficacious in patients with cystic fibrosis with Phe508del-minimal function genotypes, in whom previous CFTR modulator regimens were ineffective. For this genotype, Middleton et al, showed a 13.8 points higher ppFEV1 at 4 weeks and 13.4 points through week 24 compared to placebo. These results are promising and show the potential of life changing improvements for these patients. Although many patients will benefit from treatment with these highly effective

modulators, its use is not recommended for CF patients after solid organ transplantation because of expected drug-drug interaction.

During their lives, patients with cystic fibrosis suffer from problems in several organ systems. In some CF patients, a kidney or liver transplantation is indicated due to severe organ failure. After transplantation these patients are treated with anti-rejection therapy, mostly tacrolimus, a calcineurin inhibitor and a substrate of CYP3A4. Co-administration of elexacaftor/tezacaftor/ivacaftor with tacrolimus is thought to increase the exposure of tacrolimus and thereby may increase the risk for toxicity (e.g. nephro- and neurotoxicity and hyperglycaemia) and over-immunosuppression, especially because tacrolimus is considered a narrow therapeutic index drug. As a CYP3A4 inhibitor, tacrolimus itself may increase levels of elexacaftor/tezacaftor/ivacaftor. Currently only one case report has been published reporting two cases of lumacaftor/ivacaftor in two liver transplantation patients under tacrolimus(6). Unlike other CFTR modulators, lumacaftor is a CYP3A4 inducer, leading to decreased tacrolimus levels, observed in this case report. The drug-drug interaction of elexacaftor/tezacaftor/ivacaftor with tacrolimus has not been investigated before. Regarding the robust clinically benefit of elexacaftor/tezacaftor/ivacaftor in both patients with a phe508del mutation/minimal function mutation and patients homozygous for the phe508del mutation, the need to investigate the pharmcokinetic interaction of elexacaftor/tezacaftor/ivacaftor with other drugs becomes more important. In this study we aim to investigate the drug-drug interaction when co-administrating elexacaftor/tezacaftor/ivacaftor and tacrolimus in liver or kidney transplanted adult CF patients.

**Study objective**

Primary Objectives:
To investigate the pharmacokinetic interaction of elexacaftor/tezacaftor/ivacaftor and tacrolimus in adult CF patients using tacrolimus after renal or liver transplantation by:
- quantitating the effect of elexacaftor/tezacaftor/ivacaftor on the bioavailability of tacrolimus in CF patients with a history of liver or kidney transplantation and current on tacrolimus treatment.
- quantitating the dose adjustment of tacrolimus during co-administration of elexacaftor/tezacaftor/ivacaftor.

Secondary Objectives:
- To investigate the clinical effect of elexacaftor/tezacaftor/ivacaftor in CF patients using tacrolimus after renal or liver transplantation.
- To quantitate the exposure to elexacaftor/tezacafor/ivacaftor in week 1, 2, 3 and 4 after starting elexacaftor/tezacaftor/ivacaftor.
- To quantitate the number of side effects (adverse events and serious adverse

events) when when co-administrating the elexacftor/tezacaftor/ivacaftor with tacrolimus.

## Study design

Single centre, open label drug-drug interaction study

## Intervention

Elexacaftor/tezacaftor/ivacaftor combination with ivacaftor (Elexacaftor/tezacaftor/ivacaftor).
All subjects will be treated from day 1 of the study with the standard dose elexacaftor/tezacaftor/ivacaftor 100mg/50mg/75mg 2 tablets in the morning and ivacaftor 150 mg 1 tablet in the evening.

Study drug will be administered orally together with a standardized fat-containing snack and 3 creon tablets.

## Study burden and risks

Study load:
Screening: 1 hour: check in and exclusion criteria, medical history and informed consent procedure

The other 6 visits will take half a day:
Completing the questionnaire (day -14,1,18 and 28), Measuring vital signs, physical examination, lung function (day -14,1,18 and 28), sweat test (only day -14 and day 28), Safety blood test (including liver functions) and blood test for PK measurements at t = 0 (just before taking tacrolimus), t = 1 hour and t = 3 hours after taking tacrolimus.

For the safety blood collection,3 tubes of 5ml are required
For the PK sampling, 1 tube of 10ml is required per time point.

During the complete study, the patient will take a small blood sample 3 times a week via a finger prick (dry blood spot method) and will send this to the laboratory by mail. This will take about 15 minutes at a time.

With the above mentioned study procedures there are no risks associated.

Because drug interactions are expected, the health of the participants and their tacrolimus exposure will be closely monitored to ensure that tacrolimus blood levels are within target ranges. If this is not the case, immediate consultation will take place with the attending transplant doctor and, if necessary, a dosage adjustment of tacrolimus will follow.

It is expected that in combination with elexacaftor / tezacaftor / ivacaftor there is a risk of increased tacrolimus levels in the blood. In addition, tacrolimus may inhibit the degradation of elexacaftor / tezacaftor / ivacaftor, possibly resulting in increased elexacaftor / tezacaftor / ivacaftor exposure. Given the narrow therapeutic window of tacrolimus, it is important to monitor its exposure closely. We expect to minimize the risks of side effects.

# Contacts

**Public**
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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)

## Inclusion criteria

- Males and females aged 18 years or older on the date of informed consent
- Diagnosis of cystic fibrosis with a genotype registered for the use of elexacaftor/tezacaftor/ivacaftor confirmed by genotype analysis
- Kidney or liver transplantation; at least 1 year ago
- Current use of tacrolimus

- Signed informed consent form (ICF)

### Exclusion criteria

- Use of drugs that are metabolized by the CYP3A enzyme or have a known influence on the CYP3A enzyme (inducers or inhibitors)
- Having a contra indication for the use of elexacaftor/tezacaftor/ivacaftor
- Organ rejection within the last 3 months
- Pulmonary exacerbation within one month before the study period (defined as need for intravenous antibiotics)
- Pregnancy or lactation
-Pregnancy wish

## Study design

### Design

**Study type:** Interventional

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

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 25-02-2022 |
| Enrollment: | 5 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Kaftrio |
| Generic name: | elexacaftor/tezacaftor/ivacaftor |
| Registration: | Yes - NL intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 04-01-2021 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 01-05-2021 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 17-03-2022 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 11-04-2022 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<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 |
|---|---|
| EudraCT | EUCTR2020-005224-12-NL |
| CCMO | NL75837.058.20 |

# Study results

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|---|---|
| Date completed: | 03-06-2022 |
| Actual enrolment: | 5 |