A B2-agonist as a CFTR activator in CF

Published: 11-02-2014
Last updated: 19-03-2025

Primary objective of this pilot study is to evaluate the in vivo effect of a B2-agonists in CF patients with residual CFTR function, using dosages which are clinically used in patients with asthma. Secondary objective is to evaluate the difference...

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

Summary

ID

NL-OMON40957

Source
ToetsingOnline

Brief title
ABBA-study

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Cystic Fibrosis, Mucoviscidosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,NCFS

Intervention

Keyword: CFTR activation, CFTR residual function, personalized medicine, Salbutamol

Outcome measures

Primary outcome

Main study parameters will be the nasal potential difference (NPD) and sweat chloride concentration (SCC) before and after treatment with Salbutamol.

Secondary outcome

Secondary endpoints will include:

* Difference between change in NPD and SCC when treated with B2-agonist per inhalation and oral B2-agonist

* Correlation between individual B2-agonist-induced CFTR function (organoid-based measurements) and in vivo treatment effect (NPD,SCC).

* The CFTR stimulating effect of patients* blood samples in vitro, on autologous organoid cultures.

Study description

Background summary

The cystic fibrosis trans membrane regulator (CFTR) protein is essential for ion and fluid homeostasis of epithelial surfaces, and mutated in cystic fibrosis (CF). CF disease severity is highly variable between subjects and associated with CFTR mutations that confer CFTR residual function. We hypothesized that CF subjects with significant CFTR residual function benefit from therapeutic interventions that activate signal transduction pathways that increase CFTR function. Using various primary cell models from CF patients (organoids), we found beta-2 adrenergic receptor agonists (B2-agonists) as potent activators of CFTR in patients with residual CTFR function. Restoration of the CF phenotype in vitro by a B2-agonist is variable between patients.

Study objective

Primary objective of this pilot study is to evaluate the in vivo effect of a B2-agonists in CF patients with residual CFTR function, using dosages which are

clinically used in patients with asthma. Secondary objective is to evaluate the difference between B2-agonist treatment per inhalation and oral B2-agonist treatment. Another secondary objective is to evaluate the correlations between individual B2-agonist-induced CFTR function in vitro (organoid-based measurements) and the in vivo treatment effect (nasal potential difference (NPD) and sweat chloride concentration (SCC)). Last secondary objective is to assess whether the dosage of Salbutamol used in the clinical study is sufficient to stimulate CFTR function, by testing the CFTR stimulating effect of patients* blood samples in vitro.

Study design

A pilot open label cross-over dose finding study

Intervention

All patients will be randomly assigned to receive four times daily 200 mcg Salbutamol per inhalation (treatment 1) or four times daily 4 mg Salbutamol per os (treatment 2), during four days. After a wash-out period of at least seven days of no Salbutamol use, patients who had treatment 1 will receive treatment 2 during four days and patients who had treatment 2 will receive treatment 1 during four days.

Study burden and risks

Patients participating in this study already had a rectal biopsy to produce an organoid as part of their regular care or another study. They will be treated at home and will visit the hospital for four study visits. During each visit several tests will be performed, including NPD, SCC, spirometry and taking blood samples. Besides that, patients are asked to use Salbutamol during two periods of four days (4 days of oral treatment and 4 days of treatment per inhalation). Salbutamol has been used in clinical practice for over ten years in patients with asthma and no serious side effects have been reported. We therefore do not expect serious problems or side effects during this study. When the hypothesis is confirmed and Salbutamol turns out to not only activate the residual CFTR function in vitro but also in vivo, this can be a major benefit for the patient. When this study confirms our hypothesis that organoids can predict clinical respons to medication, this is a major benefit not only for the individual patient but also for the CF population. With the use of organoids we will then be able to generate optimal treatment strategies for individuals based on (combinations of) current and future drugs with only limited patient discomfort.

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);
* Males and females, aged 18 years or older on the date of informed consent;
* CFTR genotype compound/A455E or compound/R117H.

Exclusion criteria

* Severe acute exacerbation or pulmonary infection (needing intravenous treatment and/or systemic corticosteroids);
* Uncontrolled CF related Diabetes;
* Participation in another drug-investigating clinical study at the start or within 1 month prior to the start;

* Treatment with B2 agonist at the start of the study or a week prior to the start of the study;
* Inability to follow instructions of the investigator;
* Increased risk on side-effects of Salbutamol
* Use of medication that are known to potentially interact with Salbutamol
* (Potential) pregnancy or breastfeeding.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-06-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Salbutamol
Generic name:	Salbutamol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	11-02-2014
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-04-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 21450
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2014-000057-37-NL
CCMO	NL47622.041.14
Other	Nog niet ontvangen
OMON	NL-OMON21450

Study results

Date completed:	19-02-2015

Actual enrolment:	10