A B2-agonist as a CFTR activator in CF - Part 2

Published: 19-05-2015
Last updated: 15-05-2024

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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-OMON43663

Source
ToetsingOnline

Brief title
ABBA 2

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: ZonMw,NCFS

Intervention

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

Outcome measures

Primary outcome

Pulmonary function (spirometry and airway resistance measured with the bodybox and Rint)

* Before and after treatment with salbutamol

Secondary outcome

* Fraction exhaled Nitric Oxide (FeNO) and Nasal Nitric Oxide (nNO) before and after the use of salbutamol;

* BMI (=weight (in Kg)/Length2 (in cm)) before and after the use of salbutamol;

* Quality of life (measured with Cystic Fibrosis Questionnaire (CFQ)) before and after the use of salbutamol

* Bile salt measurements in plasma and the feces before and after the use of salbutamol

* Elastase measurements in the feces before and after the use of salbutamol

* SCC measurements before and after the use of salbutamol

* Upper and lower airway microbial profiles (microbiome) before and after treatment of the use of salbutamol (conventional culturing, high throughout pyrosequencing (16S rRNA) for bacterial diversity and relative abundance).

* Correlation between individual salbutamol induced CFTR function in vitro (organoid-based measurements) and the in vivo treatment effect;

* The CFTR stimulating ability of the concentration of salbutamol in the

patient*s blood samples, examined by in vitro testing (in the organoid model);

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. 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. Importantly, we also found large differences in B2-agonist-induced swelling between CFTR genotype-identical organoids, suggesting that CFTR-genotype is not sufficient to identify clinical responders.
Based on these in vitro findings we performed the ABBA I study in which we investigated if we also could measure a CFTR stimulating effect of salbutamol in vivo and, if we could measure an effect in vivo, which of the two treatments that were used in the study (oral or aerosol) was the most potent to stimulate CFTR. In this study we found a CFTR-stimulating effect in vivo of oral salbutamol but not of inhaled salbutamol. Also treatment with oral salbutamol turned out to have a better outcome on in vitro and in vivo CFTR-function-tests than treatment with salbutamol aerosol.

Study objective

Primary objective of this study is to evaluate the clinical effect of a long term treatment (8 weeks) with oral B2-agonists in CF patients with residual CFTR function, especially on lung function (spirometry and airway resistance).

Secondary objectives are to:
1. Evaluate the correlations between individual B2-agonist-induced CFTR function in vitro (organoid-based measurements) and the long term clinical treatment effect (eg. lung function and airway resistance).
2. Assess the effect of the salbutamol concentration in the blood on CFTR function in the background of patient specific parameters. We will do this by examining the CFTR-stimulating potential of the patients* blood in vitro (in the organoid model).

Study design

A multicentre, open label intervention study.

Intervention

After baseline measurements all patients will be assigned to receive oral Salbutamol, during 8 weeks up untill 24 hours prior to the second study visit.

Study burden and risks

Patients participating in this study will be treated at home and will visit the hospital for two study visits. Salbutamol has been used in clinical practice for over decades in patients with asthma and no serious side effects have been reported. Therefor we do not expect serious problems or side effects during this study. Based on the results of the ABBA I study and a clear diminutions of CF symptoms in a number of patients with a compound/A455E or compound/R117H mutation who have been treated with an oral B2-agonist as part of their regular care we expect to see a clear clinical effect of long term treatment with oral salbutamol. When our hypothesis is confirmed, this is a major benefit for the patient. Not only during the study period but also for their further treatment. When this study confirms our hypothesis that organoids can predict clinical responders, this is a major benefit not only for the CF population but also for the individual patient. 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

- CFTR genotype compound/A455E or compound/R117H
- Already had a rectal biopsy to produce an organoid
- Males and females, aged 18 years or older on the date of informed consent
- Signed informed consent form (ICF)

Exclusion criteria

- Severe acute exacerbation or pulmonary infection during last four weeks (needing intravenous treatment and/or systemic corticosteroids)
- Known cardiovascular medical history like cardiac failure, arrhythmias, ischemic cardiac disease, long QT interval syndrome and hypertension
- Known hyperthyroidism, thyrotoxicosis, galactose intolerance, lactase deficiency or glucose-galactose malabsorption
- Haemoglobin A1C (HBA1C) > 45 mmol/mol
- Use of oral B2-agonist one week prior to the start of the study (V1)
- Use of: heart glycoside, high dose sympathomimetics, theophylline, thiazide diuretics or non-selective beta-blockers
- Pregnancy or breastfeeding
- Participation in another drug-investigating clinical study at the start
- Inability to follow instructions of the investigator

Study design

Design

Study phase:	2
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-09-2015
Enrollment:	20
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:	19-05-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-07-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO Date:	18-04-2016
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: 24538
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2015-001317-28-NL
CCMO	NL53059.041.15
OMON	NL-OMON24538

Study results

Date completed:	12-01-2017
Actual enrolment:	14

Summary results
Trial ended prematurely