A Phase 3 randomised, double-blind, controlled trial of inhaled 7% hypertonic saline versus 0.9% isotonic saline for 48 weeks in patients with Cystic Fibrosis at 3-6 years of age in parallel with the North American SHIP clinical trial

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1: Compare the differences in the PRAGMA-CF score: the volume proportion of the lung with structural airways disease (%Dis), measured from chest CT images at 48 weeks between treatment arms 2: Compare the differences in PRAGMA-CF subscores: the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON46189

Source
ToetsingOnline

Brief title
Ship-CT study

Condition

- Congenital and hereditary disorders NEC

Synonym
CF

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Cystic Fibrosis Foundation Therapeutics CFFT

Intervention

Keyword: CF, CT, hypertonic saline, pre-schoolers

Outcome measures

Primary outcome

The difference in PRAGMA-CF %Dis between HS and IS study arm at end of study

(48 weeks), measured from standardized chest CT.

Secondary outcome

Longitudinal change in airway disease (%Dis), bronchiectasis (%Bx) trapped air

(%TA), and airway dimensions, as well as the proportion of patients with

bronchiectasis progression established by %BX and AA-system, airway wall

thickness established by the AA-system, from baseline to end of study as

established by PRAGMA-CF and the AA-system, on chest CTs*

Longitudinal change in LCI from baseline to 48 weeks measured by N2 MBW

Protocol defined pulmonary exacerbation rate

Health-related quality of life as measured by the modified parent-reported

CFQ-R for preschoolers (excluding European sites)

Study description

Background summary

There is growing interest in early initiation of therapies to prevent or delay the progression of lung disease in cystic fibrosis (CF). Absence of functional CF transmembrane regulator (CFTR) in the airway epithelium results in depletion of water from the airway surface and impaired mucociliary clearance, leading to a favourable environment for chronic infection and inflammation. Thus, restoration of salt and water balance in the airways of patients with CF is the goal of many therapeutic strategies. Ivacaftor, a CFTR potentiator, has demonstrated substantial efficacy, but targets specific gating mutations that only affect ~4% of patients with CF worldwide. Other mutation-specific CFTR modulators are being developed, but it may be years before these therapeutics are available to the youngest patients with CF. In the meantime, inhaled 7% hypertonic saline (HS) is an attractive agent to ameliorate airway surface liquid tonicity and improve mucociliary clearance.

Cystic Fibrosis Foundation Therapeutics (CFFT) and the National Institute of Health recently sponsored a randomised, controlled trial of HS (active agent) vs. 0.9% isotonic saline (IS, control agent) in patients with CF <6 years of age (the Infant Study of Inhaled Saline (ISIS) trial). There was no significant difference in the primary endpoint, pulmonary exacerbation rate, over the 48-week treatment period. However, there was evidence of possible treatment effects in two smaller sub-studies that assessed physiologic measures. In a subgroup of 45 participants <17 months of age at baseline, the change in the forced expiratory volume in 0.5 seconds (FEV0.5) measured by infant pulmonary function testing was significantly greater in those randomised to HS than IS. The second study assessed ventilation inhomogeneity measured by multiple breath washout (MBW). MBW has been shown to be highly feasible in young children, and its main endpoint, the lung clearance index (LCI), has been shown to be sensitive to detecting early lung disease and identifying response to treatment in CF. In a subgroup of 25 Toronto participants in the ISIS trial, the change in LCI over the 48-week treatment period was significantly greater in those randomised to HS than IS. In a previous study, the Toronto group had also demonstrated a significant treatment effect of HS on LCI in school-age children with CF who had normal spirometry. Given its feasibility, sensitivity and non-invasive nature as well as the recent ISIS findings, LCI is a promising endpoint to assess treatment response in young children with CF, however, it is unclear whether LCI is sensitive enough to reflect relevant structural changes of CF lung disease.

Several observational studies have shown that CF patients* *6 years of age have clinically silent airway damage. A plausible explanation for the lack of an observed treatment effect in the ISIS study is that the pulmonary exacerbation endpoint was not sensitive enough to detect early, regional lung disease in these outwardly healthy children. Given the positive trends observed for FEV0.5 and LCI in the two ISIS sub-studies, physiologic measures rather than clinical endpoints may be more suitable to detect treatment effects in young children. LCI measurements in preschool children have a higher success rate and greater sensitivity than spirometry, and commercial equipment that can be used in a

multi-centre trial is now available.

The primary hypothesis of the SHIP study (SHIP001) which runs in North America, is that compared to IS, HS will improve the LCI, a measure of ventilation heterogeneity, during the 48 week treatment period among preschool children with CF. The SHIP-CT study will use a near identical study design as the SHIP study, with similar eligibility criteria and treatment arms, to determine whether HS reduces structural lung disease as measured by chest computed tomography (CT), in addition to stabilizing or improving functional outcomes as measured by LCI. Thus, we aim to conduct a randomised, double-blind, controlled trial of inhaled HS vs. IS for 48 weeks in patients with CF 3-6 years of age in parallel with the North American SHIP clinical trial.

In SHIP-CT, we will evaluate treatment effects of HS relative to IS on measures of structural lung disease obtained from chest computed tomography (CT) using a novel scoring system sensitive to early lung changes, the Perth-Rotterdam Annotated Grid Morphometric Analysis method for CF (PRAGMA-CF), that quantifies the volume percentage of diseased airways (%Dis), bronchiectasis (%Bx), and trapped air (%TA). As a secondary evaluation of structural airway damage, we will use an image analysis system to measure airway dimensions relative to adjacent arteries (AA-system). Longitudinal changes in CT measures will also be compared to changes in lung function measured by LCI and to clinical outcomes.

Our primary hypothesis is that HS will reduce structural lung disease as assessed by the PRAGMA-CF computed tomography score relative to IS during the 48 week treatment period.

Study objective

1: Compare the differences in the PRAGMA-CF score: the volume proportion of the lung with structural airways disease (%Dis), measured from chest CT images at 48 weeks between treatment arms
2: Compare the differences in PRAGMA-CF subscores: the volume proportions of the lung with bronchiectasis (%Bx) and trapped air (%TA), as well as airway dimensions measured from chest CT images at 48 weeks between treatment arms
3: Compare the change in LCI, measured by N2 MBW, from baseline to 48 weeks between treatment arms.
4: Elucidate the longitudinal relationships between measures of structural lung disease evaluated by chest CT (PRAGMA-CF (%Dis, %Bx, %TA) and airway dimensions), LCI measured by multiple breath washout and clinical outcomes (pulmonary exacerbations, health-related quality of life) over the 48-week treatment period.

Study design

Multicentre, randomised, double-blind, controlled, parallel group trial

Intervention

Participants will be randomised 1:1 to receive 4 ml 7% HS (treatment arm) vs. 4 ml 0.9% IS (control arm) administered twice daily via jet nebulizer for 48 weeks.

Study burden and risks

CT protocols used will be according to the As Low As Reasonably Achievable (ALARA) principle of radiation minimization in medical imaging. Thus, the lowest radiation dose will be used to obtain CTs of diagnostic quality for SHIP-CT outcomes. Based on the recent SCIFI project, we have acquired phantom scan data for a 5 year old patient that allows us to define for each participating centre the optimal balance between radiation dose and image quality. The median dose used by the SCIFI centres is in the order of 1 mGy for the TLC CT and 0.5 mGy for the FRC CT. The total dose for the FRC and TLC CT scans both at enrollment and end of study, depending on the type of scanner and software at the participating centre will be 2 mSv. The risks related to this protocol are considered low [43, 44].

Some participating centres use biennial (Rotterdam, Leuven, Barcelona) or annual (Perth, Melbourne) chest CT as part of routine annual clinical examination. Thus, for Rotterdam, Leuven, and Barcelona one extra CT will be added to the routine clinical protocol of biennial CTs. For Perth and Melbourne no extra CTs will be needed. For the other centres that do not use chest CT routinely, baseline and end of study CTs will be in addition to standard care. In order to minimize radiation exposure, patients should have had their last clinical chest CT at least 8 months prior to enrollment in the study, so that one of the scans will replace a routine CT scan. To allow centres to optimally time the first study CT in relation to the last routine CT, a specified number of patients will be allocated to each centre and 18 months is allowed for enrolment.

Each centre will have a recommended CT protocol from the ErasmusMC coordinating centre to optimally balance image quality against radiation dose. After the scan is made, key features of the protocol will be entered in the CRF by the sites. Images will be transferred to the LungAnalysis centre (as per the Study Manual) for the assessment of the protocol followed and to assess image quality. LungAnalysis will give feedback to the centres within 2 weeks following arrival of each CT.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Diagnosis of CF as evidenced by one or more clinical feature consistent with the CF phenotype or positive CF newborn screen AND one or more of the following criteria: a) A documented sweat chloride * 60 mEq/L by quantitative pilocarpineiontophoresis (QPIT) b) A documented genotype with two disease-causing mutations in the CFTR gene ;Informed consent by parent or legal guardian;Age * 36 months and *72 months at Screening visit ;Ability to comply with medication use, study visits and study procedures as judged by the site investigator;***Ability to execute a technician controlled or spirometer controlled chest CT scan***????

Exclusion criteria

Chest CT within 8 months prior to the Screening visit;Acute intercurrent respiratory infection, defined as an increase in cough, wheezing, or respiratory rate with onset within 3 weeks preceding Screening or Enrolment visit;Acute wheezing at Screening or Enrollment visit ;Oxygen saturation < 95% (<90% at centres above 4000 feet elevation) at Screening or Enrollment visit ;Other major organ dysfunction, excluding pancreatic dysfunction;Physical

findings that would compromise the safety of the participant or the quality of the study data as determined by site investigator;Investigational drug use within 30 days prior to Screening or Enrolment visit;Treatment with inhaled hypertonic saline at any concentration within 30 days prior to Screening or Enrolment visit;Start of any additional inhaled saline solution at any concentration, or other hydrating agent such as mannitol or mucolytic drug such as dornase alpha within 30 days prior or following the Screening or Enrollment visit;Chronic lung disease not related to CF ;Inability to tolerate first dose of study treatment at the Enrolment visit

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2016
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sodium chloride solution for inhalation
Generic name:	Sodium Chloride solution for inhalation 7%
Product type:	Medicine
Brand name:	Sodiumchloride 0.9% solution for inhalation
Generic name:	Sodiumchloride 0.9% solution for inhalation

Ethics review

Approved WMO Date:	21-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-08-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-004143-39-NL
CCMO	NL55240.078.15

Study results

Date completed: 08-05-2020

Actual enrolment: 14

Summary results
Trial is onging in other countries