Clinical trial results:
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

Summary

EudraCT number	2015-004143-39
Trial protocol	NL BE DK FR ES IT
Global end of trial date	22 December 2020

Results information

Result version number	v1 (current)
This version publication date	22 September 2022
First version publication date	22 September 2022
Summary attachment (see zip file)	SHIP-CT publication (SHIP-CT publication.pdf)

Trial information

Trial identification

Sponsor protocol code	SHIP002

Additional study identifiers

ISRCTN number	ISRCTN13083896
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Toetsingonline: NL55240.078.15

Notes:

Sponsors

Sponsor organisation name	ErasmusMC
Sponsor organisation address	Wytemaweg, Rotterdam, Netherlands, 3015CN
Public contact	Program manager, Erasmus MC, 0031 010703668, j.vandeputtelaar@erasmusmc.nl
Scientific contact	Program manager, Erasmus MC, 0031 010703668, j.vandeputtelaar@erasmusmc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the difference in PRAGMA-CF total percent disease (%Dis) between HS and IS study arm at end of study (48 weeks), measured from standardized chest CT.

Protection of trial subjects:

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 enrolment and end of study, depending on the type of scanner and software at the participating centre will be approximately 3 mGy. The risks related to this protocol are considered low [43, 44].
Some participating centres use biennial (Rotterdam, Leuven, Barcelona) or annual 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. 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 enrolment in the study, so that one of the scans will replace a routine CT scan.
Each centre will have a recommended CT protocol from the Erasmus MC 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.

Background therapy:

Bronchodilator’s and delivery device: In order to minimize cough and bronchospasm associated with saline inhalation, participants will be pre-treated prior to each dose with a short-acting B2 bronchodilator, 2 puffs or as per local guidelines via metered dose inhaler via a valved holding chamber. In participants that do not tolerate the metered dose inhaler with spacer, a short-acting B2 bronchodilator may be delivered by nebulizer (distinct from the nebulizer used to administer study treatment).

Evidence for comparator:

1.3. Results of the ISIS trial
ISIS was a multicentre, randomised, double-blind, placebo-controlled trial conducted from 2009 to 2011 evaluating the efficacy and safety of 7% hypertonic saline versus isotonic saline (IS, control agent) inhaled twice daily for 48 weeks among children 4 to 60 months of age [7]. A total of 321 participants were enrolled at 30 sites in the United States and Canada. Enrolment was rapid, highlighting the enthusiasm for early intervention studies among providers and patients. There were no significant differences in the primary endpoint, pulmonary exacerbation rate, or any secondary clinical endpoints (height, weight, respiratory rate, oxygen saturation, cough, respiratory symptoms scores) between those randomised to HS vs IS.

Seventy-three infants at 15 sites enrolled in a sub-study in which infant lung function tests were performed at the beginning and end of the treatment period. Among the 45 infants who had acceptable raised volume measurements at both visits, there was a significant difference between groups in the 48-week change in forced expiratory volume in 0.5 seconds: the mean change in FEV0.5 was 38 mL greater in the HS group compared to the IS group. In a second sub-study performed only in Toronto, MBW was performed at the beginning and end of the study in 27 participants; 25 (98%) had acceptable

measurements at both time points. The change in LCI z-score over the treatment period was significantly greater in those randomised to HS vs. IS. Results of this study are detailed below.

We hypothesize that the ISIS study failed to detect a treatment effect because the primary endpoint of pulmonary exacerbations was not sensitive to early, regional lung disease. The results of our two sub-studies, while preliminary and only hypothesis generating, suggest that HS may have an important effect on physiologic outcomes in these relatively asymptomatic young children. As stated in the editorial accompanying the ISIS publication [8

Actual start date of recruitment	01 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	116
EEA total number of subjects	68

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	116
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruitment period:
6 oct 2016 until 6 january 2020

Pre-assignment

Screening details:

134 children screened for eligibility
2 ineligible or did not meet inclusion criteria: 1 acute respiratory infection; 1 already on hypertonic saline.
132 eligible for inclusion
4 did not complete enrolment visit: 1 withdrew consent; 1 reason for no enrolment visit unknown; 2 could not comply with CT training at screening and enrolment visit

Period 1

Period 1 title	baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

• Access to the randomisation code will be strictly controlled.
• Packaging and labeling of test and control treatments will be identical.
• Only the following persons will have access to the blinded data: authorized CC personnel and the medical monitor.
• The following perswill have access to the unblinded data: the PI of the CC, biostatistician and project manager of the CC, and members of the DSMB as appropriate.

Arms

Are arms mutually exclusive?	Yes
Arm title	treatment group

Arm description:

patients who received hypertonic saline

Arm type	Active comparator
Investigational medicinal product name	Hypertonic Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Hypertonic/isotonic saline: Participants will be instructed to place 4 ml of study saline in the nebulizer and nebulize until sputtering or for 15 minutes, whichever occurs first. Any remaining, unused solution in the opened study drug vial will be discarded. Study drug will be inhaled twice daily, with pre-treatment prior to each dose with a short-acting beta2-agonist (B2) bronchodilator. Participants will be instructed to continue with study treatments until the final study visit.

Arm title	placebo group

Arm description:

patients who received isotonic saline

Arm type	Placebo

Investigational medicinal product name	Isotonic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Hypertonic/isotonic saline: Participants will be instructed to place 4 ml of study saline in the nebulizer and nebulize until sputtering or for 15 minutes, whichever occurs first. Any remaining, unused solution in the opened study drug vial will be discarded. Study drug will be inhaled twice daily, with pre-treatment prior to each dose with a short-acting beta2-agonist (B2) bronchodilator. Participants will be instructed to continue with study treatments until the final study visit.

Number of subjects in period 1	treatment group	placebo group
Started	56	60
Completed	49	55
Not completed	7	5
perceived treatment as too great	2	-
perceived treatment burden as too great	-	3
intolerant of study drug	2	-
Lost to follow-up	3	2

Baseline characteristics

End points

End points reporting groups

Reporting group title	treatment group
Reporting group description: patients who received hypertonic saline	
Reporting group title	placebo group
Reporting group description: patients who received isotonic saline	
Subject analysis set title	Complete group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects included in the study were analyzed according to the intention-to-treat method	

Primary: difference between groups int he percentage of total lung volume occupied by abnormal airways (PRAGMA-CF % disesase) measured by chest CT at 48 weeks.

End point title	difference between groups int he percentage of total lung volume occupied by abnormal airways (PRAGMA-CF % disesase) measured by chest CT at 48 weeks.
End point description:	
End point type	Primary
End point timeframe: Measured during the last study visit for each patient	

End point values	treatment group	placebo group	Complete group	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	55	116	
Units: Percentage				
number (not applicable)	49	55	116	

Statistical analyses

Statistical analysis title	difference PRAGMA-CF

Statistical analysis description:

The primary outcome, the difference between the treatment groups in PRAGMA-CF %Disease at 48 weeks, was investigated using a multiple linear regression model. We used %Disease at 48 weeks as the outcome and included treatment group, mean baseline %Disease value, and mean baseline age as the covariates in the model. The differences in %Bronchiectasis, %Trapped air, and LCI2·5 between the treatment groups at 48 weeks were assessed using the same approach.
To assess change in LCI2·5 from

Comparison groups	placebo group v treatment group

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.67
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.08

Adverse events

Adverse events information	
Timeframe for reporting adverse events: collected during the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1.0

Reporting groups	
Reporting group title	placebo group
Reporting group description: subject who received placebo during the study.	
Reporting group title	treatment group
Reporting group description: all study participants who received hypertonic saline during the study	

Serious adverse events	placebo group	treatment group	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 60 (18.33%)	13 / 56 (23.21%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
nasal congestion			
subjects affected / exposed	2 / 60 (3.33%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
otitis / otitis media			
subjects affected / exposed	2 / 60 (3.33%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 60 (3.33%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

pulmonary exacerbation			
subjects affected / exposed	5 / 60 (8.33%)	5 / 56 (8.93%)	
occurrences causally related to treatment / all	5 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
cough			
subjects affected / exposed	3 / 60 (5.00%)	3 / 56 (5.36%)	
occurrences causally related to treatment / all	6 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
infection - pseudomonas			
subjects affected / exposed	3 / 60 (5.00%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	placebo group	treatment group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 60 (80.00%)	42 / 56 (75.00%)	
General disorders and administration site conditions			
nasal congestion			
subjects affected / exposed	25 / 60 (41.67%)	25 / 56 (44.64%)	
occurrences (all)	63	46	
Respiratory, thoracic and mediastinal disorders			
rhinorrhea			
subjects affected / exposed	20 / 60 (33.33%)	17 / 56 (30.36%)	
occurrences (all)	45	38	
common cold or flu-like			
subjects affected / exposed	11 / 60 (18.33%)	10 / 56 (17.86%)	
occurrences (all)	15	25	
Infections and infestations			
Fever			
subjects affected / exposed	32 / 60 (53.33%)	23 / 56 (41.07%)	
occurrences (all)	50	48	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

the comparator IS might also have some effects on mucociliary clearance. use of chest CT as an outcome measure exposes the participants to ionising radiation. underestimated the volume of trapped air as exp scans were acquiredat FRC and not at RV

Notes: