Clinical trial results:
Efficacy of Intermittent Tiotropium in Early Childhood Wheezing
Summary

EudraCT number	2015-002985-22
Trial protocol	FI
Global end of trial date	18 November 2020

Results information

Result version number	v1 (current)
This version publication date	22 January 2023
First version publication date	22 January 2023

Trial information

Trial identification

Sponsor protocol code	TFS01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03199976
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mika J. Mäkelä
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Scientific contact	Paediatric Unit -- Trials, Department of Allergology, Helsinki University Hospital, +358 94711,

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	14 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2020
Global end of trial reached?	Yes
Global end of trial date	18 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary AIM of the study is

1) to find out the effect of intermittent tiotropium bromide and salbutamol as needed (TBS) versus intermittent fluticasone propionate and salbutamol as needed (FPS), or solely, salbutamol as needed (SA) on episode-free days in infants and toddlers with recurrent episodes of wheeze and/or shortness of breath.

Episode-free days are defined as those days during which there are no symptoms of wheeze and/or shortness of breath, no unscheduled medical visits for wheeze and/or shortness of breath, and no use of rescue or supplementary controller medications.

Protection of trial subjects:

Most of the study visits took place as part of routine outpatient control visits at the nearest hospital, and the study laboratory tests were taken as part of routine laboratory tests during the routine outpatient visits. Occurrence of drug-related adverse events was attempted to be minimized by including the conditions that may increase the risk for drug-related adverse events in the exclusion criteria.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 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	Finland: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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	53

months)	
Children (2-11 years)	27
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:

The first patient was recruited to the study on April 20, 2016, and the last patient on December 16, 2019. All participants were recruited in the coordinating center, and the coordinating subinvestigator recruited 98% of the study subjects.

Pre-assignment

Screening details:

170 patients were screened for eligibility -- 4 of those did not meet inclusion criteria and 44 had at least 1 exclusion criterion. 122 children were considered eligible, and 80 of them were enrolled and randomized. Because the interventions were intermittent, the trial did not include a run-in period.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tiotropium Bromide & Salbutamol

Arm description:

Inhaled tiotropium bromide 5 ug once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

Arm type	Experimental
Investigational medicinal product name	Spiriva Respimat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2.5 ug two doses once a day via an AeroChamber spacer device, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed

Investigational medicinal product name	Ventoline Evohaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

0.1 mg 2 doses 4 to 6 times a day via an AeroChamber spacer device as needed for wheeze and shortness of breath

Arm title	Fluticasone Propionate & Salbutamol

Arm description:

Inhaled fluticasone propionate 125 ug twice a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

Arm type	Active comparator

Investigational medicinal product name	Flixotide Evohaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

125 ug twice a day via a Babyhaler spacer device, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed

Investigational medicinal product name	Ventoline Evohaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

0.1 mg 2 doses 4 to 6 times a day via a Babyhaler spacer device as needed for wheeze and shortness of breath

Arm title	Salbutamol

Arm description:

Inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

Arm type	Active comparator
Investigational medicinal product name	Ventoline Evohaler
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

0.1 mg 2 doses 4 to 6 times a day via a Babyhaler spacer device as needed for wheeze and shortness of breath

Number of subjects in period 1	Tiotropium Bromide & Salbutamol	Fluticasone Propionate & Salbutamol	Salbutamol
Started	27	25	28
Completed	23	18	14
Not completed	4	7	14
Consent withdrawn by subject	1	-	-
Lost to follow-up	-	1	1
Lack of efficacy	3	6	13

Baseline characteristics

Reporting groups	
Reporting group title	Tiotropium Bromide & Salbutamol
Reporting group description:	
Inhaled tiotropium bromide 5 ug once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath	
Reporting group title	Fluticasone Propionate & Salbutamol
Reporting group description:	
Inhaled fluticasone propionate 125 ug twice a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath	
Reporting group title	Salbutamol
Reporting group description:	
Inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath	

Reporting group values	Tiotropium Bromide & Salbutamol	Fluticasone Propionate & Salbutamol	Salbutamol
Number of subjects	27	25	28
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: months			
arithmetic mean	21.4	20.0	22.1
standard deviation	± 7.0	± 6.8	± 6.0
Gender categorical			
Units: Subjects			
Female	9	9	10
Male	18	16	18
Allergic sensitization			
Defined as a specific IgE level of >=0.70 kU/l to food allergens (i.e. milk, egg, wheat, soy bean, cod, peanut), a specific IgE level of >=0.35 kU/l to aeroallegens (i.e. birch, timothy, mugwort, cat, dog, horse, Dermatophagoides pteronyssinus, Cladosporium herbarum), or in case there was no blood specimen drawn, as an earlier skin prick test result with a wheal diameter of >=3 mm to aeroallergens.			
Units: Subjects			
Sensitized	8	12	5
Not sensitized	19	13	23
Short-course glucocorticoid treatment in previous 2 weeks			
Short-course glucocorticoid treatment in previous 2 weeks, i.e. per oral for 1 to 3 days, or inhaled for 1			

to 2 weeks.			
Units: Subjects			
Present	3	10	8
Not present	24	15	20
Physician-confirmed episodes of wheeze and/or shortness of breath			
Units: Number of episodes			
median	2	3	3
inter-quartile range (Q1-Q3)	2 to 3	2 to 3	2 to 3

Reporting group values	Total		
Number of subjects	80		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	28		
Male	52		
Allergic sensitization			
Defined as a specific IgE level of >=0.70 kU/l to food allergens (i.e. milk, egg, wheat, soy bean, cod, peanut), a specific IgE level of >=0.35 kU/l to aeroallegens (i.e. birch, timothy, mugwort, cat, dog, horse, Dermatophagoides pteronyssinus, Cladosporium herbarum), or in case there was no blood specimen drawn, as an earlier skin prick test result with a wheal diameter of >=3 mm to aeroallergens.			
Units: Subjects			
Sensitized	25		
Not sensitized	55		
Short-course glucocorticoid treatment in previous 2 weeks			
Short-course glucocorticoid treatment in previous 2 weeks, i.e. per oral for 1 to 3 days, or inhaled for 1 to 2 weeks.			
Units: Subjects			
Present	21		
Not present	59		
Physician-confirmed episodes of wheeze and/or shortness of breath			
Units: Number of episodes			
median			
inter-quartile range (Q1-Q3)	-		

End points

End points reporting groups

Reporting group title	Tiotropium Bromide & Salbutamol
Reporting group description:	
Inhaled tiotropium bromide 5 ug once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath	
Reporting group title	Fluticasone Propionate & Salbutamol
Reporting group description:	
Inhaled fluticasone propionate 125 ug twice a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath	
Reporting group title	Salbutamol
Reporting group description:	
Inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath	

Primary: Proportion of episode-free days

End point title	Proportion of episode-free days
End point description:	
Episode-free days were defined as the days with no symptoms of wheeze and/or shortness of breath, no unscheduled medical visits for wheeze and/or shortness of breath, and no use of rescue or supplementary controller medications.	
End point type	Primary
End point timeframe:	
Up to 48 weeks	

End point values	Tiotropium Bromide & Salbutamol	Fluticasone Propionate & Salbutamol	Salbutamol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26[1]	25[2]	26[3]	
Units: percent				
median (inter-quartile range (Q1-Q3))	97 (93 to 99)	87 (78 to 93)	88 (79 to 95)	

Notes:

[1] - Subjects with diary data available were included in the intention-to treat analysis.

[2] - Subjects with diary data available were included in the intention-to treat analysis.

[3] - Subjects with diary data available were included in the intention-to treat analysis.

Statistical analyses

Statistical analysis title	Primary outcome analysis -- Episode-free days
Statistical analysis description:	
The primary outcome was efficacy, assessed as intention-to treat by comparing the proportion of episode-free days between the treatment groups. Early termination of recruitment lead to re-calculation of power by replacing an assumed SD of 27% with an observed SD of 17% for episode-free days in the Salbutamol group. Calculations allowing a 20% drop-out rate yielded a sample size of 25 children per group; a total number of 80 recruited subjects was considered sufficient for data analyses.	
Comparison groups	Tiotropium Bromide & Salbutamol v Fluticasone Propionate & Salbutamol v Salbutamol

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.05 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Bonferroni correction was applied in pairwise analyses by multiplying each P value by 3.

[5] - P=0.002 between Tiotropium Bromide & Salbutamol and Fluticasone Propionate & Salbutamol groups.
P=0.003 between Tiotropium Bromide & Salbutamol and Salbutamol group.

Secondary: Unscheduled physician visits for wheeze

End point title	Unscheduled physician visits for wheeze

End point description:

Effect of intervention on the number of unscheduled physician visits for episodes of wheeze and/or shortness of breath.

End point type	Secondary

End point timeframe:

Up to 48 weeks

End point values	Tiotropium Bromide & Salbutamol	Fluticasone Propionate & Salbutamol	Salbutamol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27[6]	25[7]	28[8]	
Units: Number of participants				
Unscheduled physician visits for wheeze	10	10	14	
No unscheduled physician visits for wheeze	17	15	14	

Notes:

[6] - Analysis performed as intention to treat.

[7] - Analysis performed as intention to treat.

[8] - Analysis performed as intention to treat.

Statistical analyses

Statistical analysis title	Secondary outcome analysis -- Unscheduled visits

Statistical analysis description:

Bonferroni correction was applied in pairwise analyses by multiplying each P-value by 3.

Comparison groups	Tiotropium Bromide & Salbutamol v Fluticasone Propionate & Salbutamol v Salbutamol
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Chi-squared

Secondary: Rescue Medication

End point title	Rescue Medication

End point description:

Effect of intervention on the need for salbutamol.

End point type	Secondary

End point timeframe:

Up to 48 weeks

End point values	Tiotropium Bromide & Salbutamol	Fluticasone Propionate & Salbutamol	Salbutamol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26[9]	25[10]	26[11]	
Units: Percentage of days				
median (inter-quartile range (Q1-Q3))	2 (0 to 7)	13 (6 to 21)	12 (6 to 20)	

Notes:

[9] - Subjects with diary data available were included in the intention-to-treat analysis.

[10] - Subjects with diary data available were included in the intention-to-treat analysis.

[11] - Subjects with diary data available were included in the intention-to-treat analysis.

Statistical analyses

Statistical analysis title	Secondary outcome analysis -- Rescue medication

Statistical analysis description:

Bonferroni correction was applied in pairwise analyses by multiplying each P-value by 3.

Comparison groups	Tiotropium Bromide & Salbutamol v Fluticasone Propionate & Salbutamol v Salbutamol
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - P<0.001 between Tiotropium Bromide & Salbutamol and Fluticasone Propionate groups.
P<0.001 between Tiotropium Bromide & Salbutamol and Salbutamol groups.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 48 weeks

Adverse event reporting additional description:

Adverse events were charted by collecting data from daily diaries and by reviewing the medical records.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD coding
Dictionary version	10

Reporting groups

Reporting group title	Tiotropium Bromide & Salbutamol

Reporting group description:

Inhaled tiotropium bromide 5 ug once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

Reporting group title	Flixotide Propionate & Salbutamol

Reporting group description:

Inhaled fluticasone propionate 125 ug twice a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

Reporting group title	Salbutamol

Reporting group description:

Inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

Serious adverse events	Tiotropium Bromide & Salbutamol	Flixotide Propionate & Salbutamol	Salbutamol
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 27 (14.81%)	3 / 25 (12.00%)	3 / 28 (10.71%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylactic reaction to cashew nut		
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Enteritis infectious			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	3 / 27 (11.11%)	3 / 25 (12.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tiotropium Bromide & Salbutamol	Flixotide Propionate & Salbutamol	Salbutamol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 27 (70.37%)	22 / 25 (88.00%)	23 / 28 (82.14%)
Injury, poisoning and procedural complications			
Contusion	Additional description: Minor trauma		
subjects affected / exposed	2 / 27 (7.41%)	3 / 25 (12.00%)	2 / 28 (7.14%)
occurrences (all)	2	4	2
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 27 (3.70%)	3 / 25 (12.00%)	1 / 28 (3.57%)
occurrences (all)	1	3	1
Exanthema			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	2 / 28 (7.14%)
occurrences (all)	1	2	2
Infections and infestations			
Otitis media			
subjects affected / exposed	16 / 27 (59.26%)	9 / 25 (36.00%)	12 / 28 (42.86%)
occurrences (all)	18	16	20
Upper respiratory tract infection			
subjects affected / exposed	13 / 27 (48.15%)	13 / 25 (52.00%)	9 / 28 (32.14%)
occurrences (all)	20	16	16

Wheezing			
subjects affected / exposed	7 / 27 (25.93%)	7 / 25 (28.00%)	12 / 28 (42.86%)
occurrences (all)	10	12	19
Enteritis infectious			
subjects affected / exposed	3 / 27 (11.11%)	3 / 25 (12.00%)	2 / 28 (7.14%)
occurrences (all)	3	4	3
Pharyngitis			
subjects affected / exposed	2 / 27 (7.41%)	0 / 25 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	2
Tonsillitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 25 (4.00%)	3 / 28 (10.71%)
occurrences (all)	1	1	3
Conjunctivitis			
subjects affected / exposed	4 / 27 (14.81%)	1 / 25 (4.00%)	7 / 28 (25.00%)
occurrences (all)	5	1	8
Laryngitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 25 (4.00%)	1 / 28 (3.57%)
occurrences (all)	1	1	1

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.

Early termination leading to small numbers of subjects analyzed.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35942814