Clinical trial results:
Etude de la dose-réponse au bronchodilatateur puis recherche de dose du bronchodilatateur par la technique de l'interruption du débit chez l'enfant siffleur âgé de 2,5 à 6 ans - Etude DORESI.

Summary

EudraCT number	2011-002261-38
Trial protocol	FR
Global end of trial date	23 January 2014

Results information

Result version number	v1 (current)
This version publication date	21 September 2023
First version publication date	21 September 2023
Summary attachment (see zip file)	Article (10NBN-Doresi_PedPulmo2018Beydon_2018xxxx_XXX.pdf)

Trial information

Trial identification

Sponsor protocol code	P100504

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01470755
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Assistance Publique – Hôpitaux de Paris (AP-HP)
Sponsor organisation address	1, avenue Claude Vellefaux, Paris, France, 75010
Public contact	Dr BEYDON Nicole, Assistance Publique – Hôpitaux de Paris, nicole.beydon@aphp.fr
Scientific contact	Dr BEYDON Nicole, Assistance Publique – Hôpitaux de Paris, nicole.beydon@aphp.fr

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	06 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2014
Global end of trial reached?	Yes
Global end of trial date	23 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Estimer la relation dose-effet du bronchodilatateur chez le jeune enfant siffleur par la technique de l'interruption du débit aérien.

Protection of trial subjects:

Children recruited only with their consent and with their parents consents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 106
Worldwide total number of subjects	106
EEA total number of subjects	106

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)	106
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:

Start of recruitment : 25/01/2012
End of recruitment : 23/01/2014
recruitment centers : Hôpital Armand Trousseau – Paris, Hôpital Robert Debré – Paris, Hôpital Arnaud de Villeneuve - Montpellier

Pre-assignment

Screening details:

Any patient aged 2 years 6 months and 6 years 11 months referred for a pulmonary function test with bronchodilator test, because of recurrent wheezing on at least 3 occasions in the past year. Absence of BD intake in the 12 hours before the examination. Parents who gave signed consent for the study

Period 1

Period 1 title	Inclusion/randomization (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The children included will receive 2 successive doses of bronchodilator (BD) at 30 minutes interval, with a Rint measurement between 20 and 30 minutes after each dose. Two doses per child will be tested according to 4 designs that will be randomized. These doses will be evaluated blind to the person measuring the Rint.

Arms

Are arms mutually exclusive?	Yes
Arm title	400 µg Salbutamol (100+300)

Arm description:

Rint was measured at baseline, and after random assignment to a first dose (100µg) and a second dose (cumulative dose: 400)

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

Dosage and administration details:

Rint was measured at baseline, and after random assignment to a first dose (100 or 200µg) and a second dose (cumulative dose: 400, 600, or 800µg) of salbutamol.

Arm title	600 µg Salbutamol (100+500)

Arm description:

Rint was measured at baseline, and after random assignment to a first dose (100µg) and a second dose (cumulative dose: 600)

Arm type	Experimental
Investigational medicinal product name	Salbutamol
Investigational medicinal product code	
Other name	Ventoline
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

Rint was measured at baseline, and after random assignment to a first dose (100 or 200µg) and a second dose (cumulative dose: 400, 600, or 800µg) of salbutamol.

Arm title	800 µg Salbutamol

Arm description:

Rint was measured at baseline, and after random assignment to a first dose (200µg) and a second dose (cumulative dose: 800)

Arm type	Experimental
Investigational medicinal product name	Salbutamol
Investigational medicinal product code	
Other name	Ventoline
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

Rint was measured at baseline, and after random assignment to a first dose (100 or 200µg) and a second dose (cumulative dose: 400, 600, or 800µg) of salbutamol.

Arm title	400 µg Salbutamol

Arm description:

Rint was measured at baseline, and after random assignment to a first dose (200µg) and a second dose (cumulative dose: 400)

Arm type	Experimental
Investigational medicinal product name	Salbutamol
Investigational medicinal product code	
Other name	Ventoline
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

The dosage schedules − first and second doses of salbutamol received 30 min apart − were as follows: 100 + 300, 100 + 500, 200 + 200, and 200 + 600 µg (Figure 1), delivered via a new valve-holding chamber (Vortex®, Pari, Starnberg, Germany). At baseline and 30 min after each dose, pulse oximetry (oxygen saturation [SpO2] and heart rate) and Rint measurements during expiration (MicroRint, Micro Medical Ltd,
Rochester, UK, or SpiroDyn'R, Dyn'R Ltd, Aix-en-Provence, France) were recorded by an investigator blinded to the doses received by the child.

Number of subjects in period 1	400 µg Salbutamol (100+300)	600 µg Salbutamol (100+500)	800 µg Salbutamol
Started	27	26	28
Completed	26	22	26
Not completed	1	4	2
Didn't complete Rint measurements	1	4	1
Protocol deviation	-	-	1

Number of subjects in period 1	400 µg Salbutamol
Started	25
Completed	25
Not completed	0
Didn't complete Rint measurements	-
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Inclusion/randomization

Reporting group description: -

Reporting group values	Inclusion/randomization	Total	
Number of subjects	106	106	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	106	106	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	4.8		
inter-quartile range (Q1-Q3)	3.1 to 6.9	-	
Gender categorical Units: Subjects			
Female	43	43	
Male	63	63	

Subject analysis sets

Subject analysis set title	Method
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Rint was measured at baseline, and after random assignment to a first dose (100 or 200 µg) and a second dose (cumulative dose: 400, 600, or 800 µg) of salbutamol. Data were analyzed using mixed modeling approach with an inhibitory maximal effect (Imax) model, to account for a sparse sampling design. Simulations were performed to predict the percentage of children with significant Rint reversibility at several doses.

Reporting group values	Method		
Number of subjects	99		
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)	99		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median	4.8		
inter-quartile range (Q1-Q3)	3.1 to 6.9		
Gender categorical			
Units: Subjects			
Female	38		
Male	61		

End points

End points reporting groups

Reporting group title	400 µg Salbutamol (100+300)
Reporting group description:	
Rint was measured at baseline, and after random assignment to a first dose (100µg) and a second dose (cumulative dose: 400)	
Reporting group title	600 µg Salbutamol (100+500)
Reporting group description:	
Rint was measured at baseline, and after random assignment to a first dose (100µg) and a second dose (cumulative dose: 600)	
Reporting group title	800 µg Salbutamol
Reporting group description:	
Rint was measured at baseline, and after random assignment to a first dose (200µg) and a second dose (cumulative dose: 800)	
Reporting group title	400 µg Salbutamol
Reporting group description:	
Rint was measured at baseline, and after random assignment to a first dose (200µg) and a second dose (cumulative dose: 400)	
Subject analysis set title	Method
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Rint was measured at baseline, and after random assignment to a first dose (100 or 200 µg) and a second dose (cumulative dose: 400, 600, or 800 µg) of salbutamol. Data were analyzed using mixed modeling approach with an inhibitory maximal effect (Imax) model, to account for a sparse sampling design. Simulations were performed to predict the percentage of children with significant Rint reversibility at several doses.	

Primary: Rint reversibility

End point title	Rint reversibility
End point description:	
End point type	Primary
End point timeframe:	
after random assignment to a first dose (100 or 200 µg) and a second dose (cumulative dose: 400, 600, or 800 µg) of salbutamol.	

End point values	400 µg Salbutamol (100+300)	600 µg Salbutamol (100+500)	800 µg Salbutamol	400 µg Salbutamol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	22	26	25
Units: binary				
Positive response (decrease of at least 35%)	9	8	9	10

End point values	Method			

Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: binary				
Positive response (decrease of at least 35%)	36			

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Repeated Rint measurements were simultaneously analyzed in all patients by mixed effect modeling approach which can
compensate for the lack of individual information by borrowing strength from the whole data, and therefore, allow for precise
parameter estimation even with sparse sampling design.Each parameter was composed of two parts: a fixed effect which
represented the median value of this parameter in the study population;a random effect which accounted for the interindividual variability

Comparison groups	400 µg Salbutamol (100+300) v 600 µg Salbutamol (100+500) v 800 µg Salbutamol v 400 µg Salbutamol
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	Mixed models analysis

Notes:

[1] - dose-response

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
During all the study period (25/01/2012 - 23/01/2014)	
Adverse event reporting additional description:	
No Adverse event has been reported to the sponsor during the study duration.	
Assessment type	Systematic

Dictionary used	
Dictionary name	Internal document
Dictionary version	1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There are no non-serious adverse events reported in this study

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2012	Addition of beta2-adrenergic receptor genotyping study as a source of variation in bronchodilator dose-response
21 March 2013	Participation of the Physiology-Functional Explorations Department of the Robert Debré Hospital in Paris in the genetic study complementary to the DORESI study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported