Clinical trial results:
HELIOX-DRIVEN BETA2-AGONISTS NEBULIZATION FOR CHILDREN WITH MODERATE TO SEVERE ACUTE ASTHMA: A RANDOMIZED CONTROLLED TRIAL

Summary

EudraCT number	2015-004959-50
Trial protocol	ES
Global end of trial date	18 November 2021

Results information

Result version number	v1 (current)
This version publication date	13 March 2022
First version publication date	13 March 2022
Summary attachment (see zip file)	Synopsis Heliox AP (Synopsis Heliox AP 23022022.pdf)

Trial information

Trial identification

Sponsor protocol code	Heliox-AP

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	S.E. Carburos Metálicos S.A. grupo Air Products
Sponsor organisation address	C/Qunitanavides 17 Edificio 3, Madrid, Spain, 28050
Public contact	European Regulatory Affairs Manager, S.E. Carburos Metálicos S.A. grupo Air Products, 0034 606935762, hoischv@airproducts.com
Scientific contact	European Regulatory Affairs Manager, S.E. Carburos Metálicos S.A. grupo Air Products, 0034 606935762, hoischv@airproducts.com

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	18 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2021
Global end of trial reached?	Yes
Global end of trial date	18 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of heliox (He/O2 = 78%/22%) versus Synthetic Medicinal Air (O2 22%/N2 78%) for intermittent nebulization of fast-acting beta-agonists bronchodilators (salbutamol) in children and adolescents with acute moderate to severe asthma in a pediatric ED.

Protection of trial subjects:

The study protocol and all its amendments, and the patient information sheet(s) were reviewed and approved by the appropriate independent ethics committee.

Background therapy:

Irrespective of the group to which the trial patients were randomized, they received regular treatment for this type of patients with salbutamol and oral corticosteroids

Evidence for comparator:

The comparator has the National Marketing Authorization for hypoxia prevention since January 28th 2010

Actual start date of recruitment	12 September 2016
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	Spain: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	46
Adolescents (12-17 years)	8

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Informed consent was obtained from the legal guardian of the study participants before initiation of therapy in the ED (at allocation). The details of the study were explained to the parents/guardians/child allowing them time to think and ask questions. A copy of the informed consent was given to the parents/guardians/child.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	54
Number of subjects completed	54

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Although the cylinders containing the gases (Synthetic Medicinal Air and heliox) were identical and the patients were blind to the assigned treatment group, the double-blind procedure was not possible in this specific case, because the use of heliox causes typical changes in the patients' voices ("Donald Duck voice")

Arms

Are arms mutually exclusive?	Yes
Arm title	First Arm

Arm description:

Three successive treatments (every 30 min.) of salbutamol (5 mg/30 min.) nebulized with heliox (He/O2 = 78%/22%).

Arm type	Experimental
Investigational medicinal product name	Heliox
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Patients received 3 successive treatments (every 30 min.) of salbutamol (5 mg/30 min.) nebulized with heliox (He/O2 = 78%/22%) as a carrier gas. Each treatment was applied until the nebulizer was dry, followed by a 5 to 10-minute wash-out period. Heliox was administered from the nebulizer via a non-rebreather mask at room temperature

Arm title	Second Arm

Arm description:

Three successive treatments (every 30 min.) of salbutamol (5 mg/30 min.) nebulized with Synthetic Medicinal Air.

Arm type	Active comparator

Investigational medicinal product name	Synthetic Medicinal Air
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Patients received three successive treatments (every 30 min.) of salbutamol (5 mg/30 min.) nebulized with Synthetic Medicinal Air as a carrier gas. Each treatment was applied until the nebulizer was dry, followed by a 5 to 10-minute wash-out period. Synthetic Medicinal Air was administered from the nebulizer via a non-rebreather mask at room temperature.

Number of subjects in period 1	First Arm	Second Arm
Started	27	27
Completed	26	27
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	First Arm
Reporting group description:	
Three successive treatments (every 30 min.) of salbutamol (5 mg/30 min.) nebulized with heliox (He/O2 = 78%/22%).	
Reporting group title	Second Arm
Reporting group description:	
Three successive treatments (every 30 min.) of salbutamol (5 mg/30 min.) nebulized with Synthetic Medicinal Air.	

Reporting group values	First Arm	Second Arm	Total
Number of subjects	27	27	54
Age categorical Units: Subjects			
Children (2-11 years)	24	22	46
Adolescents (12-17 years)	3	5	8
Gender categorical Units: Subjects			
Female	9	8	17
Male	18	19	37
Hospitlizations in previous years Units: Subjects			
yes	2	4	6
no	25	23	48
Maintenance treatment Units: Subjects			
yes	10	7	17
no	17	20	37
Use of corticosteroids in the previous 24 hours Units: Subjects			
yes	5	3	8
no	22	24	46
Use of B2 agonists in the previous 24 hours Units: Subjects			
yes	25	23	48
no	2	4	6
Weight Units: Kilograms			
arithmetic mean	32.9	32.1	
standard deviation	± 15.1	± 9.4	-
Height Units: centimeters			
arithmetic mean	133.7	134.1	
standard deviation	± 18.5	± 14.5	-
Duration of attack before ED presentation			

Units: hours			
arithmetic mean	31.2	30.2	
standard deviation	± 35.1	± 35.1	-
Asthma duration in years			
Units: years			
arithmetic mean	5.4	5.9	
standard deviation	± 3.0	± 2.9	-
Heart rate			
Units: bpm			
arithmetic mean	108.9	109.0	
standard deviation	± 16.8	± 21.7	-
Oxygen saturation			
Units: percentage			
arithmetic mean	94.9	94.8	
standard deviation	± 2.4	± 1.8	-
Pulmonary score			
Units: 0-9			
arithmetic mean	5.0	4.7	
standard deviation	± 1.0	± 0.8	-
Systolic pressure			
Units: mmHg			
arithmetic mean	112.3	113.7	
standard deviation	± 10.5	± 9.2	-
Diastolic Pressure			
Units: mmHg			
arithmetic mean	66.3	67.9	
standard deviation	± 6.8	± 6.9	-

End points

End points reporting groups

Reporting group title	First Arm
Reporting group description:	
Three successive treatments (every 30 min.) of salbutamol (5 mg/30 min.) nebulized with heliox (He/O2 = 78%/22%).	
Reporting group title	Second Arm
Reporting group description:	
Three successive treatments (every 30 min.) of salbutamol (5 mg/30 min.) nebulized with Synthetic Medicinal Air.	

Primary: Mean change Pulmonary Score from baseline at 30 minutes

End point title	Mean change Pulmonary Score from baseline at 30 minutes
End point description:	
The pulmonary score (PS) is a clinical score system based on respiratory rate, wheezing and the use of accessory respiratory muscles, which has been validated as a measure of the severity of asthma exacerbation in children and adolescents. The highest possible score is 9 and a PS of >3 is defined as moderate or severe disease. Pulmonary score (PS) was measure in all patients at the start of the treatment and then every 30 minutes until it ends (90 min).	
End point type	Primary
End point timeframe:	
Measured in all of the patients at the start of treatment and at 30 minutes	

End point values	First Arm	Second Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Pulmonary score units				
arithmetic mean (standard deviation)	-1.7 (± 1.1)	-1.1 (± 0.8)		

Attachments (see zip file)	Pulmonary score variation/PS variation.pdf

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis (Mean change PS)
Comparison groups	First Arm v Second Arm
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Primary: Mean change in Pulmonary Score from Baseline at 60 minutes

End point title	Mean change in Pulmonary Score from Baseline at 60 minutes

End point description:

The pulmonary score (PS) is a clinical score system based on respiratory rate, wheezing and the use of accessory respiratory muscles, which has been validated as a measure of the severity of asthma exacerbation in children and adolescents. The highest possible score is 9 and a PS of >3 is defined as moderate or severe disease. Pulmonary score (PS) was measure in all patients at the start of the treatment and then every 30 minutes until it ends (90 min).

End point type	Primary

End point timeframe:

Measured in all of the patients at the start of treatment and at 60 minutes

End point values	First Arm	Second Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	27		
Units: Pulmonary score units				
arithmetic mean (standard deviation)	-2.8 (± 1.2)	-2.0 (± 1.2)		

Attachments (see zip file)	Pulmonary score variation/PS variation.pdf

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis (Mean change PS)
Comparison groups	First Arm v Second Arm
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Primary: Mean change in Pulmonary Score from Baseline at 90 minutes

End point title	Mean change in Pulmonary Score from Baseline at 90 minutes

End point description:

The pulmonary score (PS) is a clinical score system based on respiratory rate, wheezing and the use of accessory respiratory muscles, which has been validated as a measure of the severity of asthma exacerbation in children and adolescents. The highest possible score is 9 and a PS of >3 is defined as moderate or severe disease. Pulmonary score (PS) was measure in all patients at the start of the treatment and then every 30 minutes until it ends (90 min).

End point type	Primary

End point timeframe:

Measured in all of the patients at the start of treatment and at 90 minutes

End point values	First Arm	Second Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: Pulmonary Score units				
arithmetic mean (standard deviation)	-3.6 (± 1.2)	-2.7 (± 1.3)		

Attachments (see zip file)	Pulmonary score variation/PS variation.pdf

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis (Mean change PS)
Comparison groups	First Arm v Second Arm
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Percentage of patients who require hospitalization at the end of treatment (PS ≥ 3)

End point title	Percentage of patients who require hospitalization at the end of treatment (PS ≥ 3)

End point description:

End point type	Secondary

End point timeframe:

Patients that presented with PS ≥ 3 at the end of the treatment

End point values	First Arm	Second Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	27		
Units: patients	3	4		

Statistical analyses

Statistical analysis title	Percentage of patients who require hospitalization
Statistical analysis description: A percentage comparison of hospitalized patients	
Comparison groups	First Arm v Second Arm
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Secondary: Percentage of patients who require Intensive care unit admission throughout the study

End point title	Percentage of patients who require Intensive care unit admission throughout the study
End point description:	
End point type	Secondary
End point timeframe: Throughout the study	

End point values	First Arm	Second Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: patients	0	0		

Statistical analyses

Statistical analysis title	Percentage of patients who require ICU admission
Comparison groups	First Arm v Second Arm

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Secondary: Percentage of patients who require orotracheal intubation throughout the study

End point title	Percentage of patients who require orotracheal intubation throughout the study

End point description:

End point type	Secondary

End point timeframe:

Throughout the study

End point values	First Arm	Second Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: patients	0	0		

Statistical analyses

Statistical analysis title	Percentage of patients who require intubation
Comparison groups	First Arm v Second Arm
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Secondary: Percentage of patients who died throughout the study

End point title	Percentage of patients who died throughout the study

End point description:

End point type	Secondary

End point timeframe:

Throughout the study

End point values	First Arm	Second Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: patients	0	0		

Statistical analyses

Statistical analysis title	Percentage of patients who died during study
Comparison groups	First Arm v Second Arm
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Other pre-specified: Median survival time of patients discharged due to achievement of PS < 3 throughout the treatment

End point title	Median survival time of patients discharged due to achievement of PS < 3 throughout the treatment
End point description:	
Survival analysis performed at 30, 60 and 90 minutes	
End point type	Other pre-specified
End point timeframe:	
Medians for survival time	

End point values	First Arm	Second Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: minute				
median (confidence interval 95%)	60 (51.5 to 68.4)	90 (80.9 to 99.0)		

Attachments (see zip file)	Survival analysis/Survival analysis.pdf

Statistical analyses

Statistical analysis title	Survival analysis of patients with PS<3

Statistical analysis description:

All patients enrolled in the study were analyzed. In the case of patients who were lost before the end of treatment (90 min.), the LOGRANK test was used, considering patients withdrawn due to an improvement in their pulmonary score.

Comparison groups	First Arm v Second Arm
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank
Parameter estimate	Chi-square Logrank Mantel-Cox
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All adverse events were reported on a regular basis to the sponsor as specified in the protocol	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Heliox
Reporting group description: -	
Reporting group title	Synthetic Medicinal Air
Reporting group description: -	

Serious adverse events	Heliox	Synthetic Medicinal Air	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)	3 / 27 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysnea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lack of drug effect			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 27 (7.41%)	3 / 27 (11.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Heliox	Synthetic Medicinal Air	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 27 (85.19%)	7 / 27 (25.93%)	
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Somnolence			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 27 (11.11%)	2 / 27 (7.41%)	
occurrences (all)	3	2	
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Feeling cold			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	

Gastrointestinal disorders			
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 27 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dysphonia	Additional description: The use of heliox causes typical changes in the patients' voices ("Donald Duck voice") that in this case was reported as dysphonia by investigators		
alternative assessment type: Non-systematic			
subjects affected / exposed	23 / 27 (85.19%)	0 / 27 (0.00%)	
occurrences (all)	23	0	
Psychiatric disorders			
Anxiety disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2018	The key objetive was to modify age range (from 6-16 to 5-16 years) and modify the asthma diagnosis criteria, updating them according to the international asthma guidelines (2018). Changes in PEF (Peak Flow Meter) were removed as secondary endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported