



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/O ₂ = 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 |
| Hospitalizations 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 standard deviation | 31.2 ± 35.1 | 30.2 ± 35.1 | - |
| Asthma duration in years Units: years arithmetic mean standard deviation | 5.4 ± 3.0 | 5.9 ± 2.9 | - |
| Heart rate Units: bpm arithmetic mean standard deviation | 108.9 ± 16.8 | 109.0 ± 21.7 | - |
| Oxygen saturation Units: percentage arithmetic mean standard deviation | 94.9 ± 2.4 | 94.8 ± 1.8 | - |
| Pulmonary score Units: 0-9 arithmetic mean standard deviation | 5.0 ± 1.0 | 4.7 ± 0.8 | - |
| Systolic pressure Units: mmHg arithmetic mean standard deviation | 112.3 ± 10.5 | 113.7 ± 9.2 | - |
| Diastolic Pressure Units: mmHg arithmetic mean standard deviation | 66.3 ± 6.8 | 67.9 ± 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/O ₂ = 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 occurrences (all) Vomiting alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Abdominal pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) | 0 / 27 (0.00%) | |
| | 1 | 0 | |
| | 0 / 27 (0.00%) | 3 / 27 (11.11%) | |
| | 0 | 3 | |
| | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| | 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 objective 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