



## Clinical trial results:

### **B.R.E.A.T.H.E. Bronchiolitis RCT: Emergency Assisted Therapy with Heliox - an Evaluation.**

**A Prospective, Double-Blinded, Randomised, Controlled Clinical Trial to assess the effect of helium-oxygen gas mixtures during the management of bronchiolitis.**

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2005-003007-36 |
| Trial protocol           | GB             |
| Global end of trial date | 31 August 2007 |

## Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 22 January 2020 |
| First version publication date | 22 January 2020 |

## Trial information

### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | HP002A |
|-----------------------|--------|

### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN18238432 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

## Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Imperial College London  |
| Sponsor organisation address | South Kensington Campus, London, United Kingdom, SW7 2AZ                                     |
| Public contact               | Professor Parviz Habibi, Imperial College London, +44 020 3312 7683, p.habibi@imperial.ac.uk |
| Scientific contact           | Professor Parviz Habibi, Imperial College London, +44 020 3312 7683, p.habibi@imperial.ac.uk |

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:

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**Results analysis stage**

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|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 29 August 2008 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 31 August 2007 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 31 August 2007 |
| Was the trial ended prematurely?                     | No             |

Notes:

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**General information about the trial**

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Main objective of the trial:

The main objective of this trial is to determine the efficacy of helium-oxygen mixtures in the management of bronchiolitis.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 03 October 2005 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 319 |
| Worldwide total number of subjects   | 319                 |
| EEA total number of subjects         | 319                 |

Notes:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 319 |
| Children (2-11 years)                     | 0   |
| 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:

A total of 361 patients with clinically diagnosed bronchiolitis were considered for eligibility. Consent was obtained for 319 subjects who were randomized and enrolled in the study.

### Pre-assignment

Screening details:

Infants presenting with any respiratory signs or symptoms were screened between the period of 2005 to 2008.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Allocation              |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

Blinding implementation details:

The BREATHE study is the largest phase III, multicenter, double-blinded RCT of Heliox in bronchiolitis. It attempted to resolve the challenges of blinding. The use of special hosing material, identical in appearance for Heliox and Airox ensured that there was no difference in sound generation that could have alerted the investigator to identify the study gas.

### Arms

|                              |        |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes    |
| Arm title                    | Heliox |

Arm description:

Participants received treatment with Heliox gas

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Heliox21  |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Gas and solvent for dispersion for injection/infusion |
| Routes of administration               | Inhalation use  |

Dosage and administration details:

The intervention with additional oxygen titrated via Y-connection tubing, resulting in gas mixes with additional oxygen. Gas delivery was by a tight-fitting 3-valve, nonrebreathing facemask (FM; 1192; Intersurgical) or a nasal cannula (NC; BC 2745-20; Fisher & Paykel Healthcare) if the subject was FM intolerant. Gas drove the continuous positive airway pressure (CPAP) device (EME infant flow driver; CareFusion).

|           |       |
|-----------|-------|
| Arm title | AirOX |
|-----------|-------|

Arm description:

Participants received a mixture of 21% oxygen + 79% nitrogen.

|  |   |
|--|---|
| Arm type                               | Active comparator                                     |
| Investigational medicinal product name | Medical Air   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Gas and solvent for dispersion for injection/infusion |
| Routes of administration               | Inhalation use  |

Dosage and administration details:

Treatment is a mixture of 21% oxygen + 79% nitrogen.

The intervention with additional oxygen titrated via Y-connection tubing, resulting in gas mixes with additional oxygen. Gas delivery was by a tight-fitting 3-valve, nonrebreathing facemask (FM; 1192; Intersurgical) or a nasal cannula (NC; BC 2745-20; Fisher & Paykel Healthcare) if the subject was FM

intolerant. Gas drove the continuous positive airway pressure (CPAP) device (EME infant flow driver; CareFusion).

| <b>Number of subjects in period 1</b> | Heliox | AirOX |
|---------------------------------------|--------|-------|
| Started                               | 160    | 159   |
| Completed                             | 140    | 141   |
| Not completed                         | 20     | 18    |
| Consent withdrawn by subject          | 3      | 6     |
| Physician decision                    | 1      | -     |
| screening failure                     | 4      | 8     |
| therapy prematurely disrupted         | 8      | -     |
| Protocol deviation                    | 4      | 4     |

## Period 2

|                              |                    |
|------------------------------|--------------------|
| Period 2 title               | Follow up          |
| Is this the baseline period? | Yes <sup>[1]</sup> |
| Allocation method            | Not applicable     |
| Blinding used                | Not blinded        |

## Arms

|                              |        |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes    |
| <b>Arm title</b>             | Heliox |

Arm description:

Participants received treatment with Heliox gas

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Heliox21  |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Gas and solvent for dispersion for injection/infusion |
| Routes of administration               | Inhalation use  |

Dosage and administration details:

The intervention with additional oxygen titrated via Y-connection tubing, resulting in gas mixes with additional oxygen. Gas delivery was by a tight-fitting 3-valve, nonrebreathing facemask (FM; 1192; Intersurgical) or a nasal cannula (NC; BC 2745-20; Fisher & Paykel Healthcare) if the subject was FM intolerant. Gas drove the continuous positive airway pressure (CPAP) device (EME infant flow driver; CareFusion).

|                  |       |
|------------------|-------|
| <b>Arm title</b> | AirOX |
|------------------|-------|

Arm description:

Participants received a mixture of 21% oxygen + 79% nitrogen.

|  |   |
|--|---|
| Arm type                               | Active comparator                                     |
| Investigational medicinal product name | Medical Air   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Gas and solvent for dispersion for injection/infusion |
| Routes of administration               | Inhalation use  |

Dosage and administration details:

Treatment is a mixture of 21% oxygen + 79% nitrogen.

The intervention with additional oxygen titrated via Y-connection tubing, resulting in gas mixes with additional oxygen. Gas delivery was by a tight-fitting 3-valve, nonrebreathing facemask (FM; 1192; Intersurgical) or a nasal cannula (NC; BC 2745-20; Fisher & Paykel Healthcare) if the subject was FM intolerant. Gas drove the continuous positive airway pressure (CPAP) device (EME infant flow driver; CareFusion).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristic provided only for participants that completed the study.

| <b>Number of subjects in period 2<sup>[2]</sup></b> | Heliox | AirOX |
|---|--------|-------|
| Started   | 140    | 141   |
| Completed   | 140    | 141   |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristic provided only for participants that completed the study.

## Baseline characteristics

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | Heliox |
|-----------------------|--------|

Reporting group description:

Participants received treatment with Heliox gas

|                       |       |
|-----------------------|-------|
| Reporting group title | AirOX |
|-----------------------|-------|

Reporting group description:

Participants received a mixture of 21% oxygen + 79% nitrogen.

| Reporting group values                | Heliox       | AirOX      | Total |
|---------------------------------------|--------------|------------|-------|
| Number of subjects                    | 140          | 141        | 281   |
| Age categorical                       |              |            |       |
| Units: Subjects                       |              |            |       |
| Infants                               | 140          | 141        | 281   |
| Age continuous                        |              |            |       |
| Units: weeks                          |              |            |       |
| median                                | 39           | 40         |       |
| inter-quartile range (Q1-Q3)          | 38 to 40     | 38 to 40   | -     |
| Gender categorical                    |              |            |       |
| Units: Subjects                       |              |            |       |
| Female                                | 86           | 85         | 171   |
| Male                                  | 54           | 56         | 110   |
| Weight at presentation                |              |            |       |
| Units: kilogram(s)                    |              |            |       |
| median                                | 5.65         | 5.7        |       |
| inter-quartile range (Q1-Q3)          | 4.34 to 7.70 | 4.4 to 7.7 | -     |
| Modified Wood`s Clinical Asthma Score |              |            |       |
| Maximum score 11.                     |              |            |       |
| Units: score                          |              |            |       |
| median                                | 3            | 3          |       |
| inter-quartile range (Q1-Q3)          | 2 to 3       | 2 to 4     | -     |

## End points

### End points reporting groups

|   |        |
|---|--------|
| Reporting group title   | Heliox |
| Reporting group description:                                  |        |
| Participants received treatment with Heliox gas               |        |
| Reporting group title   | AirOX  |
| Reporting group description:                                  |        |
| Participants received a mixture of 21% oxygen + 79% nitrogen. |        |
| Reporting group title   | Heliox |
| Reporting group description:                                  |        |
| Participants received treatment with Heliox gas               |        |
| Reporting group title   | AirOX  |
| Reporting group description:                                  |        |
| Participants received a mixture of 21% oxygen + 79% nitrogen. |        |

### Primary: Total length of treatment (LoT)

|                        |                                 |
|------------------------|---------------------------------|
| End point title        | Total length of treatment (LoT) |
| End point description: |                                 |
|                        |                                 |
| End point type         | Primary                         |
| End point timeframe:   |                                 |
| 1 week                 |                                 |

| End point values                      | Heliox             | AirOX               |  |  |
|---------------------------------------|--------------------|---------------------|--|--|
| Subject group type                    | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed           | 140                | 141                 |  |  |
| Units: days                           |                    |                     |  |  |
| median (inter-quartile range (Q1-Q3)) | 1.9 (1.08 to 3.17) | 1.87 (1.11 to 3.34) |  |  |

### Statistical analyses

|   |                         |
|---|-------------------------|
| Statistical analysis title              | LoT                     |
| Comparison groups                       | Heliox v AirOX          |
| Number of subjects included in analysis | 281                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.41                  |
| Method                                  | Wilcoxon (Mann-Whitney) |

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**Primary: Total length of treatment (LoT) for facemask tolerant participants**

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|                 |  |
|-----------------|--|
| End point title | Total length of treatment (LoT) for facemask tolerant participants |
|-----------------|--|

End point description:

Heliox - 44 participants, Aieox - 40 participants were facemask tolerant, used a nasal cannula

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

1 week

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| End point values                      | Heliox              | AirOX               |  |  |
|---------------------------------------|---------------------|---------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed           | 44                  | 40                  |  |  |
| Units: day                            |                     |                     |  |  |
| median (inter-quartile range (Q1-Q3)) | 1.46 (0.85 to 1.95) | 2.01 (0.93 to 2.86) |  |  |

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**Statistical analyses**

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | LoT with facemask tolerant |
|-----------------------------------|----------------------------|

Statistical analysis description:

Heliox - 44 participants, Aieox - 40 participants were facemask tolerant, used nasal cannula

|                   |                |
|-------------------|----------------|
| Comparison groups | Heliox v AirOX |
|-------------------|----------------|

|   |    |
|---|----|
| Number of subjects included in analysis | 84 |
|---|----|

|                        |          |
|------------------------|----------|
| Analysis specification | Post-hoc |
|------------------------|----------|

|               |             |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

|         |        |
|---------|--------|
| P-value | = 0.03 |
|---------|--------|

|        |                         |
|--------|-------------------------|
| Method | Wilcoxon (Mann-Whitney) |
|--------|-------------------------|

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**Secondary: Proportion of cases progressing to CPAP (continuous positive airway pressure)**

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|                 |   |
|-----------------|---|
| End point title | Proportion of cases progressing to CPAP (continuous positive airway pressure) |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 week

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| <b>End point values</b>     | Heliox          | AirOX           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 140             | 141             |  |  |
| Units: percent              | 17              | 19              |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | CPAP            |
|---|-----------------|
| Comparison groups                       | Heliox v AirOX  |
| Number of subjects included in analysis | 281             |
| Analysis specification                  | Post-hoc        |
| Analysis type                           | superiority     |
| Parameter estimate                      | Odds ratio (OR) |
| Point estimate                          | 0.87            |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.47            |
| upper limit                             | 1.6             |

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

1 week

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |   |
|--------------------|---|
| Dictionary version | 5 |
|--------------------|---|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

Reporting group description: -

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: It was no reported any non-serious adverse event.

| Serious adverse events                            | Overall trial   |  |  |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events |                 |  |  |
| subjects affected / exposed                       | 6 / 319 (1.88%) |  |  |
| number of deaths (all causes)                     | 0               |  |  |
| number of deaths resulting from adverse events    | 0               |  |  |
| Respiratory, thoracic and mediastinal disorders   |                 |  |  |
| Intubation  |                 |  |  |
| subjects affected / exposed                       | 6 / 319 (1.88%) |  |  |
| occurrences causally related to treatment / all   | 0 / 6           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Overall trial   |  |  |
|---|-----------------|--|--|
| Total subjects affected by non-serious adverse events |                 |  |  |
| subjects affected / exposed                           | 0 / 319 (0.00%) |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23509160>