



Clinical trial results:

A randomised, double-blind, double-dummy, multi-site, phase III, single dose, 4-way cross-over pharmacodynamic study evaluating the efficacy of Bricanyl Turbuhaler M3 compared to Bricanyl Turbuhaler M2 by studying the protective effect on methacholine induced bronchoconstriction in patients with stable, mild to moderate asthma

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-001457-16 |
| Trial protocol | SE NL |
| Global end of trial date | 05 November 2015 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 02 October 2016 |
| First version publication date | 02 October 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D4711C00001 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AstraZeneca R&D Gothenburg |
| Sponsor organisation address | SE-431 83, Mölndal, Sweden, |
| Public contact | Göran Eckerwall, MD, PhD, AstraZeneca R&D, goran.eckerwall@astrazeneca.com |
| Scientific contact | Göran Eckerwall, MD, PhD, AstraZeneca R&D, goran.eckerwall@astrazeneca.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 | 25 April 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate therapeutic equivalence between Bricanyl Turbuhaler M3 and Bricanyl Turbuhaler M2 using bronchoprotective effect as outcome measure.

Outcome measurements: PC20 (Methacholine provocative concentration causing a 20% drop in FEV1)

Protection of trial subjects:

Prior methacholine challenge a stable asthma condition was ensured by FEV1 at every visit. Signs and symptoms were recorded and the challenge stopped after a 20% fall in FEV1 was reached. Ipratropium was given post challenge.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 10 March 2015 |
| 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 | Canada: 35 |
| Country: Number of subjects enrolled | Netherlands: 10 |
| Country: Number of subjects enrolled | Sweden: 15 |
| Worldwide total number of subjects | 60 |
| EEA total number of subjects | 25 |

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) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 60 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

Patients with stable, mild to moderate asthma were enrolled. The first patient entered the study on 10 March 2015 and the last patient completed the study on 5 November 2015. Subjects were recruited from: Site 1001 and 1002 in Canada, Site 7201 in Sweden, and Site 5001 in the Netherlands.

Pre-assignment

Screening details:

Of the 95 patients enrolled 34 were screen failures mainly due to not fulfilling specific randomization criteria on stability in asthma or sensitivity to methacholine challenge; 1 was withdrawal by subject; 72 entered run in period. A total of 60 patients were randomized to the 4 single-dose treatments with terbutaline in a crossover design.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Visit 3 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | M2 0.5 mg |

Arm description:

0.5 mg terbutaline sulphate administered via Turbuhaler M2

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M2 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

0.5 mg M2 Turbuhaler

| | |
|------------------|-----------|
| Arm title | M2 1.5 mg |
|------------------|-----------|

Arm description:

1.5 mg terbutaline sulphate administered via Turbuhaler M2

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M2 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

1.5 mg M2 Turbuhaler

| | |
|------------------|-----------|
| Arm title | M3 0.5 mg |
|------------------|-----------|

Arm description:

0.5 mg terbutaline sulphate administered via Turbuhaler M3

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--|
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M3 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 0.5 mg M3 Turbuhaler | |
| Arm title | M3 1.5 mg |

Arm description:

1.5 mg terbutaline sulphate administered via Turbuhaler M3

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M3 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

1.5 mg M3 Turbuhaler

| Number of subjects in period 1 | M2 0.5 mg | M2 1.5 mg | M3 0.5 mg |
|---------------------------------------|-----------|-----------|-----------|
| Started | 15 | 15 | 14 |
| Completed | 15 | 15 | 14 |

| Number of subjects in period 1 | M3 1.5 mg |
|---------------------------------------|-----------|
| Started | 16 |
| Completed | 16 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Visit 4 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|--|
| Arm title | M2 0.5 mg |
| Arm description: 0.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M2 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: 0.5 mg M2 Turbuhaler | |
| Arm title | M2 1.5 mg |
| Arm description: 1.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M2 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: 1.5 mg M2 Turbuhaler | |
| Arm title | M3 0.5 mg |
| Arm description: 0.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M3 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: 0.5 mg M3 Turbuhaler | |
| Arm title | M3 1.5 mg |
| Arm description: 1.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M3 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: 1.5 mg M3 Turbuhaler | |

| Number of subjects in period 2 | M2 0.5 mg | M2 1.5 mg | M3 0.5 mg |
|--------------------------------|-----------|-----------|-----------|
| Started | 15 | 14 | 16 |
| Completed | 15 | 14 | 16 |

| Number of subjects in period 2 | M3 1.5 mg |
|--------------------------------|-----------|
| Started | 15 |
| Completed | 15 |

Period 3

| | |
|------------------------------|---|
| Period 3 title | Visit 5 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | M2 0.5 mg |

Arm description:

0.5 mg terbutaline sulphate administered via Turbuhaler M2

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M2 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

0.5 mg M2 Turbuhaler

| | |
|------------------|-----------|
| Arm title | M2 1.5 mg |
|------------------|-----------|

Arm description:

1.5 mg terbutaline sulphate administered via Turbuhaler M2

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M2 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

1.5 mg M2 Turbuhaler

| | |
|------------------|-----------|
| Arm title | M3 0.5 mg |
|------------------|-----------|

Arm description:

0.5 mg terbutaline sulphate administered via Turbuhaler M3

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--|
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M3 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| 0.5 mg M3 Turbuhaler | |
| Arm title | M3 1.5 mg |

Arm description:

1.5 mg terbutaline sulphate administered via Turbuhaler M3

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M3 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

1.5 mg M3 Turbuhaler

| Number of subjects in period 3 | M2 0.5 mg | M2 1.5 mg | M3 0.5 mg |
|---------------------------------------|-----------|-----------|-----------|
| Started | 16 | 15 | 15 |
| Completed | 16 | 15 | 15 |

| Number of subjects in period 3 | M3 1.5 mg |
|---------------------------------------|-----------|
| Started | 14 |
| Completed | 14 |

Period 4

| | |
|------------------------------|---|
| Period 4 title | Visit 6 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|--|--|
| Arm title | M2 0.5 mg |
| Arm description: 0.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M2 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: 0.5 mg M2 Turbuhaler | |
| Arm title | M2 1.5 mg |
| Arm description: 1.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M2 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: 1.5 mg M2 Turbuhaler | |
| Arm title | M3 0.5 mg |
| Arm description: 0.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M3 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: 0.5 mg M3 Turbuhaler | |
| Arm title | M3 1.5 mg |
| Arm description: 1.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Arm type | Active comparator |
| Investigational medicinal product name | terbutaline sulphate via Turbuhaler M3 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: 1.5 mg M3 Turbuhaler | |

| Number of subjects in period 4 | M2 0.5 mg | M2 1.5 mg | M3 0.5 mg |
|---------------------------------------|-----------|-----------|-----------|
| Started | 14 | 16 | 15 |
| Completed | 14 | 16 | 15 |

| Number of subjects in period 4 | M3 1.5 mg |
|---------------------------------------|-----------|
| Started | 15 |
| Completed | 15 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Visit 3 |
|-----------------------|---------|

| |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

| Reporting group values | Visit 3 | Total | |
|--|----------|-------|--|
| Number of subjects | 60 | 60 | |
| 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) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 60 | 60 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age Continuous | | | |
| Units: years | | | |
| median | 26 | | |
| full range (min-max) | 18 to 64 | - | |
| Gender, Male/Female | | | |
| Gender | | | |
| Units: Participants | | | |
| Female | 40 | 40 | |
| Male | 20 | 20 | |
| Race/Ethnicity, Customized | | | |
| Race | | | |
| Units: Subjects | | | |
| White | 57 | 57 | |
| Black or African American | 1 | 1 | |
| Asian | 2 | 2 | |

Subject analysis sets

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Efficacy Analysis Set |
|----------------------------|-----------------------|

| | |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

| |
|-----------------------------------|
| Subject analysis set description: |
|-----------------------------------|

| |
|--|
| All patients who have at least two values of the primary endpoints in the efficacy analysis set. |
|--|

| Reporting group values | Efficacy Analysis Set | | |
|------------------------|-----------------------|--|--|
| Number of subjects | 60 | | |
| 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) | 60 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Units: years | | | |
| median | 26 | | |
| full range (min-max) | 18 to 64 | | |
| Gender, Male/Female | | | |
| Gender | | | |
| Units: Participants | | | |
| Female | 40 | | |
| Male | 20 | | |
| Race/Ethnicity, Customized | | | |
| Race | | | |
| Units: Subjects | | | |
| White | 57 | | |
| Black or African American | 1 | | |
| Asian | 2 | | |

End points

End points reporting groups

| | |
|--|-----------|
| Reporting group title | M2 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M2 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M3 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M3 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M2 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M2 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M3 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M3 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M2 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M2 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M3 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M3 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M2 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M2 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M3 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M3 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M2 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M2 1.5 mg |
| Reporting group description: 1.5 mg terbutaline sulphate administered via Turbuhaler M2 | |
| Reporting group title | M3 0.5 mg |
| Reporting group description: 0.5 mg terbutaline sulphate administered via Turbuhaler M3 | |
| Reporting group title | M3 1.5 mg |

Reporting group description:

1.5 mg terbutaline sulphate administered via Turbuhaler M3

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Efficacy Analysis Set |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

All patients who have at least two values of the primary endpoints in the efficacy analysis set.

Primary: PC20

| | |
|-----------------|------|
| End point title | PC20 |
|-----------------|------|

End point description:

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

End point timeframe:

During treatment period from Visit 3 to Visit 6

| End point values | M2 0.5 mg | M2 0.5 mg | M2 0.5 mg | M2 0.5 mg |
|---|----------------------|-----------------------|-----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 15 | 16 | 14 |
| Units: mg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 5.43 (\pm 302.49) | 10.03 (\pm 185.14) | 11.21 (\pm 160.36) | 23.06 (\pm 341.4) |

| End point values | M2 1.5 mg | M2 1.5 mg | M2 1.5 mg | M2 1.5 mg |
|---|-----------------------|-----------------------|-----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 14 | 15 | 16 |
| Units: mg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 22.76 (\pm 255.89) | 37.39 (\pm 306.96) | 10.99 (\pm 164.29) | 18.01 (\pm 132.9) |

| End point values | M3 0.5 mg | M3 0.5 mg | M3 0.5 mg | M3 0.5 mg |
|---|----------------------|----------------------|--------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 15 | 15 |
| Units: mg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 17.8 (\pm 319.32) | 8.63 (\pm 106.66) | 12 (\pm 237.01) | 5.44 (\pm 215.56) |

| End point values | M3 1.5 mg | M3 1.5 mg | M3 1.5 mg | M3 1.5 mg |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 16 | 15 | 14 | 15 |
| Units: mg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 19.34 (\pm | 10.22 (\pm | 29.04 (\pm | 17.93 (\pm |

| | | | | |
|---------------|---------|--------|--------|--------|
| of variation) | 178.83) | 199.6) | 253.8) | 250.8) |
|---------------|---------|--------|--------|--------|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | PC20 mixed effect model analysis: M2 1.5 vs M2 0.5 |
| Statistical analysis description: | |
| A linear mixed effect model based on restricted maximum likelihood analysis is used to estimate the treatment effect. PC20 in natural log scale is the response variable, treatment and period are the fixed effects, and patient within sequence is a random effect. | |
| Comparison groups | M2 0.5 mg v M2 1.5 mg v M2 0.5 mg v M2 1.5 mg v M2 0.5 mg v M2 1.5 mg v M2 0.5 mg v M2 1.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated mean ratio |
| Point estimate | 1.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.52 |
| upper limit | 2.29 |

| | |
|---|---|
| Statistical analysis title | PC20 mixed effect model analysis: M3 1.5 vs M3 0.5 |
| Statistical analysis description: | |
| A linear mixed effect model based on restricted maximum likelihood analysis is used to estimate the treatment effect. PC20 in natural log scale is the response variable, treatment and period are the fixed effects, and patient within sequence is a random effect. | |
| Comparison groups | M3 0.5 mg v M3 1.5 mg v M3 0.5 mg v M3 1.5 mg v M3 0.5 mg v M3 1.5 mg v M3 0.5 mg v M3 1.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated mean ratio |
| Point estimate | 1.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.46 |
| upper limit | 2.2 |

| | |
|---|---|
| Statistical analysis title | PC20 mixed effect model analysis: M3 0.5 vs M2 0.5 |
| Statistical analysis description: | |
| A linear mixed effect model based on restricted maximum likelihood analysis is used to estimate the treatment effect. PC20 in natural log scale is the response variable, treatment and period are the fixed effects, and patient within sequence is a random effect. | |
| Comparison groups | M2 0.5 mg v M3 0.5 mg v M2 0.5 mg v M3 0.5 mg v M2 0.5 mg v M3 0.5 mg v M2 0.5 mg v M3 0.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Method | Mixed models analysis |
| Parameter estimate | Estimated mean ratio |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.13 |

| | |
|---|---|
| Statistical analysis title | PC20 mixed effect model analysis: M3 1.5 vs M2 1.5 |
| Statistical analysis description: | |
| A linear mixed effect model based on restricted maximum likelihood analysis is used to estimate the treatment effect. PC20 in natural log scale is the response variable, treatment and period are the fixed effects, and patient within sequence is a random effect. | |
| Comparison groups | M2 1.5 mg v M3 1.5 mg v M2 1.5 mg v M3 1.5 mg v M2 1.5 mg v M3 1.5 mg v M2 1.5 mg v M3 1.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Method | Mixed models analysis |
| Parameter estimate | Estimated mean ratio |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.08 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During randomized treatment period from Visit 3 to Visit 6

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
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|--------------------|------|
| Dictionary version | 18.1 |
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Reporting groups

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|-----------------------|-----------|
| Reporting group title | M2 0.5 mg |
|-----------------------|-----------|

Reporting group description:

0.5 mg terbutaline sulphate administered via Turbuhaler M2

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|-----------------------|-----------|
| Reporting group title | M3 0.5 mg |
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Reporting group description:

0.5 mg terbutaline sulphate administered via Turbuhaler M3

| | |
|-----------------------|-----------|
| Reporting group title | M3 1.5 mg |
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Reporting group description:

1.5 mg terbutaline sulphate administered via Turbuhaler M3

| | |
|-----------------------|-----------|
| Reporting group title | M2 1.5 mg |
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Reporting group description:

1.5 mg terbutaline sulphate administered via Turbuhaler M2

| Serious adverse events | M2 0.5 mg | M3 0.5 mg | M3 1.5 mg |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 60 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | M2 1.5 mg | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | M2 0.5 mg | M3 0.5 mg | M3 1.5 mg |
|---|------------------|-----------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 60 (20.00%) | 7 / 60 (11.67%) | 13 / 60 (21.67%) |
| Injury, poisoning and procedural complications | | | |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 2 / 60 (3.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | 5 / 60 (8.33%) | 7 / 60 (11.67%) |
| occurrences (all) | 6 | 5 | 7 |
| Headache | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 60 (1.67%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 1 | 1 |
| Sciatica | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 60 (1.67%) | 5 / 60 (8.33%) |
| occurrences (all) | 2 | 1 | 5 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Pyrexia | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 60 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 2 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | M2 1.5 mg | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 60 (16.67%) | | |
| Injury, poisoning and procedural complications | | | |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |

| | | | |
|--|-----------------|--|--|
| Palpitations | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | | |
| occurrences (all) | 6 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tremor | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| occurrences (all) | 3 | | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|--|--|--|
| Dry mouth subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | | |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | | |
| Psychiatric disorders Restlessness subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 | | |

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

None reported