



## Clinical trial results:

**Proof of concept study to assess the differential effects of chronic beta-blockade (celiprolol versus bisoprolol) on cardiopulmonary outcomes at rest and during exercise in chronic obstructive pulmonary disease.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-000207-13 |
| Trial protocol           | GB             |
| Global end of trial date | 30 April 2019  |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 25 June 2021 |
| First version publication date | 25 June 2021 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 2012RC22 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02380053 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University of Dundee - NHS Tayside   |
| Sponsor organisation address | Residency Block, Level 3, Ninewells Hospital, George Pirie Way, Dundee, United Kingdom, DD1 9SY  |
| Public contact               | General Enquiries, Scottish Centre for Respiratory Research, +44 1382 383902, <a href="mailto:scrr@dundee.ac.uk">scrr@dundee.ac.uk</a> |
| Scientific contact           | General Enquiries, Scottish Centre for Respiratory Research, +44 1382 383902, <a href="mailto:scrr@dundee.ac.uk">scrr@dundee.ac.uk</a> |

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

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 30 April 2019 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 30 April 2019 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 April 2019 |
| Was the trial ended prematurely?                     | No            |

Notes:

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## General information about the trial

Main objective of the trial:

To evaluate the relative effects on heart and lung (airway) responses at rest and during exercise following beta-blocker treatment with bisoprolol versus celiprolol in COPD patients.

Protection of trial subjects:

The Sponsor carried out a study risk assessment before issuing approval. The study was approved by the East of Scotland Research Ethics Service (EoSRES) (Ref: 15/ES/0102) and full informed consent was obtained from all participants. Participants were checked against all inclusion and exclusion criteria and were only included if their COPD was stable; those with a low blood pressure or heart rate were not included. A medically-qualified person confirmed the participant's suitability to receive the study drug according to the study protocol. Participants were given a paper diary card, PiKO device and pulse oximeter for daily a-home monitoring of their lung function, heart rate and oxygen saturation. The beta-blockers (IMP) were given by slowly escalating the dose during each treatment period. Initial beta-blocker dosing started at a low dose and was titrated up halfway through each treatment period. Participants were contacted when they were due to increase their beta-blocker dose and the following items assessed: symptoms attributable to beta-blocker therapy, FEV1, and heart rate. If these were satisfactory, participants progressed to the higher beta-blocker dose for the remainder of the treatment period. Participants were contacted again within 1 week of increasing their dose to repeat the checks. Participants intolerant of higher beta-blockers doses returned to their previous maximum tolerated dose for the remainder of the treatment period. Participants unable to tolerate the minimum beta-blocker dose were withdrawn.

Participants were given an instruction leaflet with information on how to measure their lung function, heart rate and oxygen saturation, how to complete their diary cards, potential side effects of study drugs, and how to record adverse events and concomitant medications. Participants were given an out-of-hours mobile number carried by medical staff for advice if they encountered any adverse effects.

Background therapy:

Subjects remained on their usual COPD medications. The IMP was given in addition to their standard treatments.

Evidence for comparator:

Beta-blockers are underused in COPD despite evidence for reducing mortality from cardiovascular comorbidities. Beta-blockers are pharmacologically heterogeneous and the study was designed to assess the clinical consequences of different beta-blockers in COPD.

Bisoprolol (BIS) is a beta-1 selective antagonist that may cause bronchoconstriction due to dose related beta-2 blockade.

Celiprolol (CEL) is a beta-1 selective antagonist which also exhibits partial beta-2 agonist activity.

The study assessed the relative effects of both BIS and CEL in COPD patients to establish whether the proposed benefits on survival with beta-blockers in COPD are reflected in improved cardiovascular and respiratory response to exercise and exercise tolerance.

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 07 June 2016 |
| 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

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Worldwide total number of subjects   | 20                 |
| EEA total number of subjects         | 20                 |

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)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 5  |
| From 65 to 84 years                       | 15 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Subject recruitment began 7 June 2016 and the study completed on 30 April 2019. Of the 20 patients screened, 14 were randomised and 11 completed per protocol and were included in the final analysis.

### Pre-assignment

Screening details:

Males and females, 40-80 years, stable COPD (GOLD stage 2/3), post-SABA FEV1 30-80% predicted and FEV1/FVC ratio <70%, no exacerbation in the last month, no hospitalisation for exacerbation in the last 3 months,  $\geq 10$  pack-years; O2 sats  $\geq 92\%$  on room air, sinus rhythm on ECG, average resting systolic BP  $\geq 110$  mmHg, average resting HR  $\geq 55$  bpm.

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 20                |
| Number of subjects completed | 14 <sup>[1]</sup> |

### Pre-assignment subject non-completion reasons

|                            |                                    |
|----------------------------|------------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 1    |
| Reason: Number of subjects | Elective Intervention Scheduled: 1 |
| Reason: Number of subjects | Did Not meet Inclusion Criteria: 4 |

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.

Justification: 14 subjects completed run-in and attended a baseline visit.

This is a cross-over study where subjects participate in both arms during the course of the study.

Bisoprolol arm - 11 patients received at least 1 dose and are counted as participants in this arm.

Celiprolol arm - 13 subjects received at least 1 dose and are counted as participants in this arm.

11 subjects completed both arms of this cross-over trial and were able to be analysed.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |    |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Bisoprolol (BIS) |
|------------------|------------------|

Arm description: -

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Bisoprolol   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Bisoprolol 2.5 mg OD for 2 weeks, followed by 5 mg OD for 2 weeks.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Celiprolol (CEL) |
|------------------|------------------|

Arm description: -

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |            |
|--|------------|
| Investigational medicinal product name | Celiprolol |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

Celiprolol 200 mg OD for 2 weeks, followed by 400 mg OD for 2 weeks.

| <b>Number of subjects in period 1</b> | Bisoprolol (BIS) | Celiprolol (CEL) |
|---------------------------------------|------------------|------------------|
| Started                               | 11               | 13               |
| Completed                             | 11               | 11               |
| Not completed                         | 0                | 2                |
| IMP Not Tolerated                     | -                | 2                |

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

Notes:

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

Justification: The worldwide number enrolled is the number of subjects screened into the study (20).

The number of subjects in the baseline period is the number who were randomised into the study (14).

Of these 14 subjects, 11 completed both arms of the cross-over trial and were able to be analysed.

| Reporting group values                                | Overall Trial | Total |  |
|---|---------------|-------|--|
| Number of subjects                                    | 14            | 14    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0             | 0     |  |
| Children (2-11 years)                                 | 0             | 0     |  |
| Adolescents (12-17 years)                             | 0             | 0     |  |
| Adults (18-64 years)                                  | 5             | 5     |  |
| From 65-84 years                                      | 9             | 9     |  |
| 85 years and over                                     | 0             | 0     |  |
| Age continuous  |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean                                       | 69.64         |       |  |
| standard deviation                                    | ± 7.14        | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female  | 5             | 5     |  |
| Male  | 9             | 9     |  |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Bisoprolol (BIS)   |
| Reporting group description: -                                |                    |
| Reporting group title   | Celiprolol (CEL)   |
| Reporting group description: -                                |                    |
| Subject analysis set title                                    | Completed Subjects |
| Subject analysis set type                                     | Per protocol       |
| Subject analysis set description:                             |                    |
| 11 subjects who completed both arms of the study per protocol |                    |

### Primary: Inspiratory Capacity

|  |                      |
|--|----------------------|
| End point title  | Inspiratory Capacity |
| End point description:   |                      |
| End point type   | Primary              |
| End point timeframe:   |                      |
| Inspiratory Capacity was measured at baseline (pre-beta blocker) and post-beta blocker at 4 weeks. |                      |

| End point values                          | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 11                  | 11                  |  |  |
| Units: Litres                             |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 2.05 (1.72 to 2.38) | 1.77 (1.42 to 2.12) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| Statistical analysis title              | Inspiratory Capacity                |
| Comparison groups                       | Celiprolol (CEL) v Bisoprolol (BIS) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.42                              |
| Method                                  | ANOVA                               |

### Primary: DH, dynamic hyperinflation; at exercise isotime 4min

|                        |  |
|------------------------|--|
| End point title        | DH, dynamic hyperinflation; at exercise isotime 4min |
| End point description: |  |
| End point type         | Primary  |

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

| End point values                          | Bisoprolol (BIS)       | Celiprolol (CEL)       |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                        | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed               | 11                     | 11                     |  |  |
| Units: Litres                             |                        |                        |  |  |
| arithmetic mean (confidence interval 95%) | -0.42 (-0.61 to -0.23) | -0.67 (-1.12 to -0.23) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| Statistical analysis title              | Dynamic Hyperinflation              |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.52                              |
| Method                                  | ANOVA                               |

### Secondary: Borg Score (Breathing)

|  |                        |
|--|------------------------|
| End point title  | Borg Score (Breathing) |
| End point description:   |                        |
| End point type   | Secondary              |
| End point timeframe:   |                        |
| Borg Score (Breathing) was measured at baseline (pre-beta blocker) and post-beta blocker at 4 weeks. |                        |

| End point values                         | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|--|------------------|------------------|--|--|
| Subject group type                       | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed              | 11               | 11               |  |  |
| Units: units                             |                  |                  |  |  |
| geometric mean (confidence interval 95%) | 6.3 (4.8 to 8.1) | 6.6 (5.2 to 8.2) |  |  |

### Statistical analyses



|  |                                     |
|--|-------------------------------------|
| <b>Statistical analysis title</b>                                    | Borg Breathlessness                 |
| Statistical analysis description:<br>Peak Borg score breathlessness* |                                     |
| Comparison groups  | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis                              | 22                                  |
| Analysis specification   | Pre-specified                       |
| Analysis type  | superiority                         |
| P-value  | = 0.72                              |
| Method   | ANOVA                               |

### Secondary: Heart Rate recovery over 3 min n=10

|  |                                     |
|--|-------------------------------------|
| End point title  | Heart Rate recovery over 3 min n=10 |
| End point description:   |                                     |
| End point type   | Secondary                           |
| End point timeframe:   |                                     |
| Heart Rate was measured at baseline (pre-beta blocker) and post-beta blocker at 4 weeks. |                                     |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: beats/min                          |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 6.7 (5.3 to 8.0) | 4.6 (3.5 to 5.7) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Heart rate recovery                 |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.02                              |
| Method                                  | ANOVA                               |

### Secondary: Cardiac Output Peak heart rate

|                        |                                |
|------------------------|--------------------------------|
| End point title        | Cardiac Output Peak heart rate |
| End point description: |                                |
| End point type         | Secondary                      |

End point timeframe:

Cardiac Output was measured at baseline (pre-beta blocker) and post-beta blocker at 4 weeks.

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: L/min                              |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 102 (96 to 109)  | 104 (99 to 108)  |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| Statistical analysis title              | Heart rate                          |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.001                             |
| Method                                  | ANOVA                               |

### Secondary: Peak VO2, oxygen uptake

|  |                         |
|--|-------------------------|
| End point title  | Peak VO2, oxygen uptake |
| End point description:   |                         |
| End point type   | Secondary               |
| End point timeframe:   |                         |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                         |

| End point values                          | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 11                  | 11                  |  |  |
| Units: litres                             |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 1.21 (1.00 to 1.42) | 1.24 (1.02 to 1.45) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Oxygen uptake                       |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.71                              |
| Method                                  | ANOVA                               |

### Secondary: Peak VE, minute ventilation

|  |                             |
|--|-----------------------------|
| End point title  | Peak VE, minute ventilation |
| End point description:   |                             |
| End point type   | Secondary                   |
| End point timeframe:   |                             |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                             |

| End point values                          | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 11                  | 11                  |  |  |
| Units: Litres/minute                      |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 48.2 (41.0 to 55.4) | 48.3 (41.0 to 55.6) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Minute ventilation                  |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.31                              |
| Method                                  | ANOVA                               |

### Secondary: Peak RR, respiratory rate

|  |                           |
|--|---------------------------|
| End point title  | Peak RR, respiratory rate |
| End point description:   |                           |
| End point type   | Secondary                 |
| End point timeframe:   |                           |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                           |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Breaths/min                        |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 34 (30 to 38)    | 31 (28 to 34)    |  |  |

### Statistical analyses

| Statistical analysis title              | Respiratory rate                    |
|---|-------------------------------------|
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.053                             |
| Method                                  | ANOVA                               |

### Secondary: Peak O2 Sats\*, oxygen saturations

|  |                                   |
|--|-----------------------------------|
| End point title  | Peak O2 Sats*, oxygen saturations |
| End point description:   |                                   |
| End point type   | Secondary                         |
| End point timeframe:   |                                   |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                                   |

| End point values                      | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---------------------------------------|------------------|------------------|--|--|
| Subject group type                    | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed           | 11               | 11               |  |  |
| Units: Percent                        |                  |                  |  |  |
| median (inter-quartile range (Q1-Q3)) | 97 (90 to 98)    | 97 (91 to 99)    |  |  |

### Statistical analyses

| Statistical analysis title | Oxygen saturations                  |
|----------------------------|-------------------------------------|
| Comparison groups          | Celiprolol (CEL) v Bisoprolol (BIS) |

|   |               |
|---|---------------|
| Number of subjects included in analysis | 22            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.6         |
| Method                                  | ANOVA         |

### Secondary: BR, breathing reserve at peak exercise

|  |  |
|--|--|
| End point title  | BR, breathing reserve at peak exercise |
| End point description:   |  |
| End point type   | Secondary                              |
| End point timeframe:   |  |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |  |

| End point values                          | Bisoprolol (BIS)   | Celiprolol (CEL)    |  |  |
|---|--------------------|---------------------|--|--|
| Subject group type                        | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed               | 11                 | 11                  |  |  |
| Units: Percent                            |                    |                     |  |  |
| arithmetic mean (confidence interval 95%) | 1.1 (-7.8 to 10.0) | -3.5 (-14.3 to 7.2) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Breathing reserve                   |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.25                              |
| Method                                  | ANOVA                               |

### Secondary: Total exercise time (min)

|  |                           |
|--|---------------------------|
| End point title  | Total exercise time (min) |
| End point description:   |                           |
| End point type   | Secondary                 |
| End point timeframe:   |                           |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                           |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Minutes                            |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 6.5 (4.5 to 8.5) | 7.2 (5.4 to 8.9) |  |  |

### Statistical analyses

| Statistical analysis title              | Total exercise time                 |
|---|-------------------------------------|
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.83                              |
| Method                                  | ANOVA                               |

### Secondary: Peak Borg score leg discomfort\*

|  |                                 |
|--|---------------------------------|
| End point title  | Peak Borg score leg discomfort* |
| End point description:   |                                 |
| End point type   | Secondary                       |
| End point timeframe:   |                                 |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                                 |

| End point values                         | Bisoprolol (BIS)  | Celiprolol (CEL)    |  |  |
|--|-------------------|---------------------|--|--|
| Subject group type                       | Reporting group   | Reporting group     |  |  |
| Number of subjects analysed              | 11                | 11                  |  |  |
| Units: Units                             |                   |                     |  |  |
| geometric mean (confidence interval 95%) | 17 (15.8 to 18.3) | 17.4 (16.1 to 18.8) |  |  |

### Statistical analyses

| Statistical analysis title | Borg Leg Discomfort                 |
|----------------------------|-------------------------------------|
| Comparison groups          | Bisoprolol (BIS) v Celiprolol (CEL) |

|   |               |
|---|---------------|
| Number of subjects included in analysis | 22            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.16        |
| Method                                  | ANOVA         |

### Secondary: FEV1 , forced expiratory volume in 1 second

|  |   |
|--|---|
| End point title  | FEV1 , forced expiratory volume in 1 second |
| End point description:   |   |
| End point type   | Secondary                                   |
| End point timeframe:   |   |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |   |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Percentage of predicted            |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 52 (45 to 59)    | 52 (45 to 59)    |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | FEV1                                |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.9                               |
| Method                                  | ANOVA                               |

### Secondary: FVC, forced vital capacity

|  |                            |
|--|----------------------------|
| End point title  | FVC, forced vital capacity |
| End point description:   |                            |
| End point type   | Secondary                  |
| End point timeframe:   |                            |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                            |

| <b>End point values</b>                   | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Percentage of predicted            |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 102 (87 to 117)  | 100 (88 to 112)  |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | FVC                                 |
|---|-------------------------------------|
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.59                              |
| Method                                  | ANOVA                               |

### Secondary: Relaxed vital capacity

|  |                        |
|--|------------------------|
| End point title  | Relaxed vital capacity |
| End point description:   |                        |
| End point type   | Secondary              |
| End point timeframe:   |                        |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                        |

| <b>End point values</b>                   | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Percentage of predicted            |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 108 (93 to 124)  | 109 (96 to 121)  |  |  |

### Statistical analyses

| <b>Statistical analysis title</b> | Relaxed VC                          |
|-----------------------------------|-------------------------------------|
| Comparison groups                 | Bisoprolol (BIS) v Celiprolol (CEL) |



|   |               |
|---|---------------|
| Number of subjects included in analysis | 22            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.99        |
| Method                                  | ANOVA         |

### Secondary: Residual Volume/Total Lung Capacity ratio

|  |   |
|--|---|
| End point title  | Residual Volume/Total Lung Capacity ratio |
| End point description:   |   |
| End point type   | Secondary                                 |
| End point timeframe:   |   |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |   |

| End point values                          | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 11                  | 11                  |  |  |
| Units: Percent                            |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 47.7 (43.3 to 52.0) | 49.6 (44.8 to 54.3) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | RV/TLC ratio                        |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.06                              |
| Method                                  | ANOVA                               |

### Secondary: R5\*, resistance at 5 Hertz

|  |                            |
|--|----------------------------|
| End point title  | R5*, resistance at 5 Hertz |
| End point description:   |                            |
| End point type   | Secondary                  |
| End point timeframe:   |                            |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                            |

| End point values                         | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|--|------------------|------------------|--|--|
| Subject group type                       | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed              | 11               | 11               |  |  |
| Units: Percent                           |                  |                  |  |  |
| geometric mean (confidence interval 95%) | 144 (124 to 167) | 163 (149 to 179) |  |  |

### Statistical analyses

| Statistical analysis title              | R5                                  |
|---|-------------------------------------|
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.04                              |
| Method                                  | ANOVA                               |

### Secondary: Ax\*, reactance at 5 Hertz

|  |                           |
|--|---------------------------|
| End point title  | Ax*, reactance at 5 Hertz |
| End point description:   |                           |
| End point type   | Secondary                 |
| End point timeframe:   |                           |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                           |

| End point values                         | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                       | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed              | 11                  | 11                  |  |  |
| Units: Kilopascals/Litre                 |                     |                     |  |  |
| geometric mean (confidence interval 95%) | 1.98 (1.24 to 2.73) | 2.44 (1.74 to 3.13) |  |  |

### Statistical analyses

| Statistical analysis title | Ax                                  |
|----------------------------|-------------------------------------|
| Comparison groups          | Bisoprolol (BIS) v Celiprolol (CEL) |

|   |               |
|---|---------------|
| Number of subjects included in analysis | 22            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.004       |
| Method                                  | ANOVA         |

### Secondary: Oxygen pulse

|  |              |
|--|--------------|
| End point title  | Oxygen pulse |
| End point description:   |              |
| End point type   | Secondary    |
| End point timeframe:   |              |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |              |

| End point values                          | Bisoprolol (BIS)   | Celiprolol (CEL)    |  |  |
|---|--------------------|---------------------|--|--|
| Subject group type                        | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed               | 11                 | 11                  |  |  |
| Units: millilitres per beat               |                    |                     |  |  |
| arithmetic mean (confidence interval 95%) | 11.7 (9.8 to 13.5) | 11.6 (10.0 to 13.3) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Oxygen pulse                        |
| Comparison groups                       | Celiprolol (CEL) v Bisoprolol (BIS) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.001                             |
| Method                                  | ANOVA                               |

### Secondary: Peak mean arterial blood pressure

|  |                                   |
|--|-----------------------------------|
| End point title  | Peak mean arterial blood pressure |
| End point description:   |                                   |
| End point type   | Secondary                         |
| End point timeframe:   |                                   |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |                                   |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: millimetres of mercury             |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 106 (91 to 120)  | 106 (93 to 120)  |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| Statistical analysis title              | Mean arterial blood pressure        |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.03                              |
| Method                                  | ANOVA                               |

### Secondary: Cardiac Outcomes Non-Invasive Cardiac Output Monitor -peak cardiac output

|  |   |
|--|---|
| End point title  | Cardiac Outcomes Non-Invasive Cardiac Output Monitor -peak cardiac output |
| End point description:   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |   |

| End point values                          | Bisoprolol (BIS)   | Celiprolol (CEL)   |  |  |
|---|--------------------|--------------------|--|--|
| Subject group type                        | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed               | 11                 | 11                 |  |  |
| Units: Litres/minute                      |                    |                    |  |  |
| arithmetic mean (confidence interval 95%) | 11.2 (9.7 to 12.8) | 10.4 (9.4 to 11.4) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Cardiac output                      |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.7                               |
| Method                                  | ANOVA                               |

### Secondary: Cardiac Outcomes Non-Invasive Cardiac Output Monitor - Peak Stroke Volume, n=10

|                 |   |
|-----------------|---|
| End point title | Cardiac Outcomes Non-Invasive Cardiac Output Monitor - Peak Stroke Volume, n=10 |
|-----------------|---|

End point description:

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

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

|   |                  |                  |  |  |
|---|------------------|------------------|--|--|
| <b>End point values</b>                   | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: millilitres/beat                   |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 122 (102 to 142) | 105 (96 to 113)  |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Stroke volume                       |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.003                             |
| Method                                  | ANOVA                               |

### Secondary: Domiciliary Outcomes - Oxygen saturations (AM)

|                 |  |
|-----------------|--|
| End point title | Domiciliary Outcomes - Oxygen saturations (AM) |
|-----------------|--|

End point description:

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

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Percent                            |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 95 (94 to 96)    | 95 (94 to 96)    |  |  |

### Statistical analyses

| Statistical analysis title              | Oxygen saturations                  |
|---|-------------------------------------|
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.97                              |
| Method                                  | ANOVA                               |

### Secondary: Domiciliary Outcomes -oxygen saturations (PM)

|  |   |
|--|---|
| End point title  | Domiciliary Outcomes -oxygen saturations (PM) |
| End point description:   |   |
| End point type   | Secondary                                     |
| End point timeframe:   |   |
| Continuous diurnal measurement throughout the study. Mean of last 3 days of each period. |   |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Percent                            |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 94 (93 to 96)    | 95 (94 to 96)    |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Oxygen saturations                  |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.35                              |
| Method                                  | ANOVA                               |

### Secondary: Domiciliary Outcomes - Heart rate (AM)

|  |  |
|--|--|
| End point title  | Domiciliary Outcomes - Heart rate (AM) |
| End point description:   |  |
| End point type   | Secondary                              |
| End point timeframe:   |  |
| Continuous diurnal measurement throughout the study. Mean of last 3 days of each period. |  |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Beats per minute                   |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 67 (62 to 72)    | 73 (68 to 77)    |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Heart rate                          |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.001                             |
| Method                                  | ANOVA                               |

### Secondary: Domiciliary Outcomes - Heart rate (PM)

|  |  |
|--|--|
| End point title  | Domiciliary Outcomes - Heart rate (PM) |
| End point description:   |  |
| End point type   | Secondary                              |
| End point timeframe:   |  |
| Continuous diurnal measurement throughout the study. Mean of last 3 days of each period. |  |

| <b>End point values</b>                   | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Beats per minute                   |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 67 (63 to 70)    | 74 (70 to 79)    |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Heart rate                          |
|---|-------------------------------------|
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.001                             |
| Method                                  | ANOVA                               |

### Secondary: Domiciliary Outcomes - FEV1 , forced expiratory volume in 1 second (AM)

|  |   |
|--|---|
| End point title  | Domiciliary Outcomes - FEV1 , forced expiratory volume in 1 second (AM) |
| End point description:   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Continuous diurnal measurement throughout the study. Mean of last 3 days of each period. |   |

| <b>End point values</b>                   | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 11                  | 11                  |  |  |
| Units: Litres                             |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 1.24 (0.99 to 1.49) | 1.22 (0.95 to 1.49) |  |  |

### Statistical analyses



|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | FEV1                                |
| Comparison groups                       | Celiprolol (CEL) v Bisoprolol (BIS) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.46                              |
| Method                                  | ANOVA                               |

---

**Secondary: Domiciliary Outcomes - FEV1 , forced expiratory volume in 1 second (PM)**

|                 |   |
|-----------------|---|
| End point title | Domiciliary Outcomes - FEV1 , forced expiratory volume in 1 second (PM) |
|-----------------|---|

End point description:

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

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

---

| <b>End point values</b>                   | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 11                  | 11                  |  |  |
| Units: Litres                             |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 1.21 (0.96 to 1.46) | 1.22 (0.92 to 1.52) |  |  |

**Statistical analyses**

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | FEV1                                |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.33                              |
| Method                                  | ANOVA                               |

---

**Secondary: Domiciliary Outcomes - FEV1 , forced expiratory volume in 6 second (AM)**

|                 |   |
|-----------------|---|
| End point title | Domiciliary Outcomes - FEV1 , forced expiratory volume in 6 second (AM) |
|-----------------|---|

End point description:

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Continuous diurnal measurement throughout the study. Mean of last 3 days of each period. |           |

| End point values                          | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 11                  | 11                  |  |  |
| Units: Litres                             |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 2.41 (2.01 to 2.81) | 2.41 (1.96 to 2.86) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| Statistical analysis title              | FEV6                                |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.91                              |
| Method                                  | ANOVA                               |

### Secondary: Domiciliary Outcomes - FEV1 , forced expiratory volume in 6 second (PM)

|  |   |
|--|---|
| End point title  | Domiciliary Outcomes - FEV1 , forced expiratory volume in 6 second (PM) |
| End point description:   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Continuous diurnal measurement throughout the study. Mean of last 3 days of each period. |   |

| End point values                          | Bisoprolol (BIS)    | Celiprolol (CEL)    |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 11                  | 11                  |  |  |
| Units: Litres                             |                     |                     |  |  |
| arithmetic mean (confidence interval 95%) | 2.35 (1.89 to 2.80) | 2.38 (1.91 to 2.85) |  |  |

## Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | FEV6                                |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.4                               |
| Method                                  | ANOVA                               |

## Secondary: Domiciliary Outcomes - Symptoms\*\* (AM)

|  |  |
|--|--|
| End point title  | Domiciliary Outcomes - Symptoms** (AM) |
| End point description:   |  |
| End point type   | Secondary                              |
| End point timeframe:   |  |
| Continuous diurnal measurement throughout the study. Median of last 3 days of each period. |  |

|                                       |                  |                  |  |  |
|---------------------------------------|------------------|------------------|--|--|
| <b>End point values</b>               | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
| Subject group type                    | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed           | 11               | 11               |  |  |
| Units: Units (0-3)                    |                  |                  |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 1)       | 0 (0 to 1)       |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Daily symptoms                          |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL)     |
| Number of subjects included in analysis | 22                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.55                                  |
| Method                                  | Friedman's two-way analysis of variance |

## Secondary: Domiciliary Outcomes - Symptoms\*\* (PM)

|  |  |
|--|--|
| End point title  | Domiciliary Outcomes - Symptoms** (PM) |
| End point description:   |  |
| End point type   | Secondary                              |
| End point timeframe:   |  |
| Continuous diurnal measurement throughout the study. Median of last 3 days of each period. |  |

| <b>End point values</b>               | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---------------------------------------|------------------|------------------|--|--|
| Subject group type                    | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed           | 11               | 11               |  |  |
| Units: Units (0-3)                    |                  |                  |  |  |
| median (inter-quartile range (Q1-Q3)) | 1 (0 to 1)       | 1 (0 to 1)       |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Daily symptoms                          |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL)     |
| Number of subjects included in analysis | 22                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.94                                  |
| Method                                  | Friedman's two-way analysis of variance |

### Secondary: Domiciliary Outcomes - Reliever use\*\* (AM)

|  |  |
|--|--|
| End point title  | Domiciliary Outcomes - Reliever use** (AM) |
| End point description:   |  |
| End point type   | Secondary                                  |
| End point timeframe:   |  |
| Continuous diurnal measurement throughout the study. Median of last 3 days of each period. |  |

| <b>End point values</b>     | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|-----------------------------|------------------|------------------|--|--|
| Subject group type          | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed | 11               | 11               |  |  |
| Units: Number of puffs      | 0                | 0                |  |  |

### Statistical analyses

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Daily reliever use                  |
| Comparison groups                 | Bisoprolol (BIS) v Celiprolol (CEL) |

|   |   |
|---|---|
| Number of subjects included in analysis | 22                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.65                                  |
| Method                                  | Friedman's two-way analysis of variance |

### Secondary: Domiciliary Outcomes - Reliever use\*\* (PM)

|  |  |
|--|--|
| End point title  | Domiciliary Outcomes - Reliever use** (PM) |
| End point description:   |  |
| End point type   | Secondary                                  |
| End point timeframe:   |  |
| Continuous diurnal measurement throughout the study. Median of last 3 days of each period. |  |

| End point values            | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|-----------------------------|------------------|------------------|--|--|
| Subject group type          | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed | 11               | 11               |  |  |
| Units: Number of puffs      | 0                | 0                |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Daily reliever use                      |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL)     |
| Number of subjects included in analysis | 22                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.54                                  |
| Method                                  | Friedman's two-way analysis of variance |

### Secondary: Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ) GRQ Symptoms

|  |  |
|--|--|
| End point title  | Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ) GRQ Symptoms |
| End point description:   |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |  |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Units                              |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 45 (24 to 47)    | 45 (30 to 60)    |  |  |

### Statistical analyses

| Statistical analysis title              | SGRQ Symptoms                       |
|---|-------------------------------------|
| Comparison groups                       | Celiprolol (CEL) v Bisoprolol (BIS) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.19                              |
| Method                                  | ANOVA                               |

### Secondary: Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ) SGRQ Activity

|                        |   |
|------------------------|---|
| End point title        | Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ) SGRQ Activity |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Measured at            | baselines (pre-beta blocker) and post-beta blocker at 4 weeks.                      |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Units                              |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 60 (47 to 72)    | 60 (47 to 73)    |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | SGRQ Activity                       |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.96                              |
| Method                                  | ANOVA                               |

### Secondary: Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ)SGRQ Impacts

|                 |   |
|-----------------|---|
| End point title | Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ)SGRQ Impacts |
|-----------------|---|

End point description:

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

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

|   |                  |                  |  |  |
|---|------------------|------------------|--|--|
| <b>End point values</b>                   | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Units                              |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 25 (17 to 33)    | 25 (16 to 33)    |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | SGRQ Impacts                        |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.86                              |
| Method                                  | ANOVA                               |

### Secondary: Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ)SGRQ Total score

|                 |   |
|-----------------|---|
| End point title | Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ)SGRQ Total score |
|-----------------|---|

End point description:

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |           |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Units                              |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 39 (30 to 49)    | 37 (29 to 45)    |  |  |

### Statistical analyses

| Statistical analysis title              | SGRQ Total score                    |
|---|-------------------------------------|
| Comparison groups                       | Celiprolol (CEL) v Bisoprolol (BIS) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.6                               |
| Method                                  | ANOVA                               |

### Secondary: Biomarker (Venous Blood) Outcomes NT-pro-BNP\*, N-terminal pro-B-type natriuretic peptide

|  |  |
|--|--|
| End point title  | Biomarker (Venous Blood) Outcomes NT-pro-BNP*, N-terminal pro-B-type natriuretic peptide |
| End point description:   |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |  |

| End point values                          | Bisoprolol (BIS)  | Celiprolol (CEL)    |  |  |
|---|-------------------|---------------------|--|--|
| Subject group type                        | Reporting group   | Reporting group     |  |  |
| Number of subjects analysed               | 11                | 11                  |  |  |
| Units: picomoles/Litre                    |                   |                     |  |  |
| arithmetic mean (confidence interval 95%) | 6.3 (3.2 to 11.6) | 3.97 (1.55 to 8.69) |  |  |



## Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | NT-pro-BNP                          |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.01                              |
| Method                                  | ANOVA                               |

## Secondary: Biomarker (Venous Blood) Outcomes Galectin-3

|  |  |
|--|--|
| End point title  | Biomarker (Venous Blood) Outcomes Galectin-3 |
| End point description:   |  |
| End point type   | Secondary                                    |
| End point timeframe:   |  |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |  |

|   |                  |                   |  |  |
|---|------------------|-------------------|--|--|
| <b>End point values</b>                   | Bisoprolol (BIS) | Celiprolol (CEL)  |  |  |
| Subject group type                        | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed               | 11               | 11                |  |  |
| Units: nanograms/Litre                    |                  |                   |  |  |
| arithmetic mean (confidence interval 95%) | 8.0 (6.3 to 9.7) | 8.5 (7.0 to 10.0) |  |  |

## Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Galectin-3                          |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.37                              |
| Method                                  | ANOVA                               |

## Secondary: Beta-2 Adreceptor activity Creatinine kinase, n=10

|                        |  |
|------------------------|--|
| End point title        | Beta-2 Adreceptor activity Creatinine kinase, n=10 |
| End point description: |  |
| End point type         | Secondary  |

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: Units/Litre                        |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 112 (78 to 147)  | 131 (91 to 171)  |  |  |

### Statistical analyses

| Statistical analysis title              | Creatinine kinase                   |
|---|-------------------------------------|
| Comparison groups                       | Celiprolol (CEL) v Bisoprolol (BIS) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.27                              |
| Method                                  | ANOVA                               |

### Secondary: Beta-2 Adreceptor activity - Total Cholesterol

|  |  |
|--|--|
| End point title  | Beta-2 Adreceptor activity - Total Cholesterol |
| End point description:   |  |
| End point type   | Secondary                                      |
| End point timeframe:   |  |
| Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks. |  |

| End point values                          | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: millimoles/litre                   |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 4.8 (4.2 to 5.4) | 4.7 (4.2 to 5.2) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Total Cholesterol                   |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.35                              |
| Method                                  | ANOVA                               |

### Secondary: Beta-2 Adreceptor activity - Cholestrol/High Density Lipoprotein ratio

|                 |  |
|-----------------|--|
| End point title | Beta-2 Adreceptor activity - Cholestrol/High Density Lipoprotein ratio |
|-----------------|--|

End point description:

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

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

|   |                  |                  |  |  |
|---|------------------|------------------|--|--|
| <b>End point values</b>                   | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: no units                           |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 3.2 (2.8 to 3.6) | 3.0 (2.6 to 3.3) |  |  |

### Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Chol/HDL ratio                      |
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.015                             |
| Method                                  | ANOVA                               |

### Secondary: Beta-2 Adreceptor activity - Potassium

|                 |  |
|-----------------|--|
| End point title | Beta-2 Adreceptor activity - Potassium |
|-----------------|--|

End point description:

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

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

| <b>End point values</b>                   | Bisoprolol (BIS) | Celiprolol (CEL) |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 11               | 11               |  |  |
| Units: millimoles/litre                   |                  |                  |  |  |
| arithmetic mean (confidence interval 95%) | 4.5 (4.3 to 4.6) | 4.4 (4.2 to 4.6) |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Potassium                           |
|---|-------------------------------------|
| Comparison groups                       | Bisoprolol (BIS) v Celiprolol (CEL) |
| Number of subjects included in analysis | 22                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.09                              |
| Method                                  | ANCOVA                              |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were recorded from the time a participant consented to join the study until the last study visit.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Received IMP |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events                            | Received IMP   |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 13 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |

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

| Non-serious adverse events                            | Received IMP     |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 12 / 13 (92.31%) |  |  |
| Injury, poisoning and procedural complications        |                  |  |  |
| Ligament sprain                                       |                  |  |  |
| subjects affected / exposed                           | 1 / 13 (7.69%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Cardiac disorders                                     |                  |  |  |
| Palpitations  |                  |  |  |
| subjects affected / exposed                           | 1 / 13 (7.69%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Dizziness   |                  |  |  |
| subjects affected / exposed                           | 1 / 13 (7.69%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Nervous system disorders                              |                  |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 5 / 13 (38.46%)<br>7 |  |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1  |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1  |  |  |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 4 / 13 (30.77%)<br>4 |  |  |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)   | 2 / 13 (15.38%)<br>2 |  |  |
| Gait disturbance<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |
| Blood and lymphatic system disorders<br>Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)            | 1 / 13 (7.69%)<br>1  |  |  |
| Gastrointestinal disorders<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 13 (15.38%)<br>2 |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |
| Irritable bowel syndrome<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 13 (7.69%)<br>1  |  |  |
| Reproductive system and breast disorders<br>Breast pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1  |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 3 / 13 (23.08%)<br>5 |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 2 / 13 (15.38%)<br>2 |  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1  |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 13 (15.38%)<br>3 |  |  |
| Sputum increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |
| Catarrh<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1  |  |  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1  |  |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1  |  |  |
| Productive cough   |                      |  |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1   |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1   |  |  |
| Musculoskeletal and connective tissue disorders<br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all)<br><br>Swelling in Left Hallux<br>subjects affected / exposed<br>occurrences (all)<br><br>Neck pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>1<br><br>1 / 13 (7.69%)<br>1 |  |  |
| Infections and infestations<br>Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1   |  |  |



## 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