



## Clinical trial results:

### A Pragmatic Proof of Concept Study to Evaluate the Effect of Benralizumab on Mannitol Challenge in Severe Eosinophilic Asthma Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-003763-22 |
| Trial protocol           | GB             |
| Global end of trial date | 01 July 2022   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 15 December 2022 |
| First version publication date | 15 December 2022 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 1.027.19 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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               | Anna Forber, General enquiries<br>Scottish Centre for Respiratory Research<br>01382 383 902<br>scrr@dundee.ac.uk, 01382 383902, scrr@dundee.ac.uk |
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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                       | 01 July 2022 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 01 July 2022 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 01 July 2022 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To assess the effect of benralizumab on airway hyper-responsiveness (AHR), after 3 months of treatment, measured by mannitol challenge as the provocative dose causing a 10% fall in forced expiratory volume in 1 second (FEV1) (PD10 Mannitol), from post-run-in baseline in severe eosinophilic asthma.

Protection of trial subjects:

The provocative dose of mannitol required to drop a subject's FEV1 by 10% (PD10) was chosen as this was a cohort of severe asthma patients and therefore we opted for a safer cut point than other studies that have traditionally used PD15. We monitored patients 1 on 1 for the entirety of the mannitol challenges to minimise distress.

Background therapy:

Subjects were maintained on their usual inhaler and oral therapy for asthma control to ensure safety. This meant that benralizumab was used as an additional medication on top of their usual standard of care.

Evidence for comparator:

There was no comparison in this trial as large Phase III trials have shown good efficacy for benralizumab in the treatment of severe eosinophilic asthma. Our study was a single arm open label trial as we felt it was unethical to give patients placebo when there is established evidence that benralizumab improves clinical outcomes.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 16 December 2020 |
| 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 | United Kingdom: 21 |
| Worldwide total number of subjects   | 21                 |
| EEA total number of subjects         | 0                  |

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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 13 |
| From 65 to 84 years       | 8  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

21 severe eosinophilic asthma patients were recruited between 16/12/20 and 15/12/21 from Dundee, Scotland, UK.

### Pre-assignment

Screening details:

Key inclusion criteria included patients aged 18 - 75 with severe GINA defined asthma taking a medium to high dose of ICS/LABA. Patients also had to have uncontrolled asthma ( $ACQ \geq 1.5$ ), mannitol PD10  $\leq 635$ mg at visit 1 and eosinophilic asthma. There was a 4 week run-in period between screen and visit 1. In total 34 patients were screened.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | overall trial               |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|  |  |
|--|--|
| Arm title                              | Baseline                                 |
| Arm description: -                     |  |
| Arm type                               | Single arm open label                    |
| Investigational medicinal product name | Benralizumab                             |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

30mg every 4 weeks for 3 doses

| Number of subjects in period 1 | Baseline |
|--------------------------------|----------|
| Started                        | 21       |
| Completed                      | 21       |

### Period 2

|                              |                |
|------------------------------|----------------|
| Period 2 title               | none           |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

### Arms

|   |      |
|---|------|
| <b>Arm title</b>  | none |
| Arm description: -  |      |
| Arm type  | none |
| No investigational medicinal product assigned in this arm |      |

|   |      |
|---|------|
| <b>Number of subjects in period 2<sup>[1]</sup></b> | none |
| Started   | 1    |
| Completed   | 1    |

---

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Our study was a single arm open label study. However the system does not allow submission of the form unless there are two arms so we have created one with zero values to facilitate form submission.

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | overall trial |
| Reporting group description: - |               |

| Reporting group values  | overall trial | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 21            | 21    |  |
| Age categorical   |               |       |  |
| Units: Subjects   |               |       |  |
| In utero  |               | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                 |               | 0     |  |
| Newborns (0-27 days)  |               | 0     |  |
| Infants and toddlers (28 days-23<br>months)                           |               | 0     |  |
| Children (2-11 years)   |               | 0     |  |
| Adolescents (12-17 years)   |               | 0     |  |
| Adults (18-64 years)  |               | 0     |  |
| From 65-84 years  |               | 0     |  |
| 85 years and over   |               | 0     |  |
| Age continuous  |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean   | 53            |       |  |
| standard deviation  | ± 16          | -     |  |
| Gender categorical  |               |       |  |
| Units: Subjects   |               |       |  |
| Female  | 9             | 9     |  |
| Male  | 12            | 12    |  |
| Body mass index   |               |       |  |
| Units: kg/m2  |               |       |  |
| arithmetic mean   | 30            |       |  |
| standard deviation  | ± 5.5         | -     |  |
| Inhaled corticosteroid beclomethasone<br>dipropionate equivalent dose |               |       |  |
| Units: mcg  |               |       |  |
| arithmetic mean   | 1895          |       |  |
| standard deviation  | ± 273         | -     |  |
| Peripheral blood eosinophils  |               |       |  |
| Units: cells/microlitre   |               |       |  |
| arithmetic mean   | 439           |       |  |
| standard deviation  | ± 316         | -     |  |
| Asthma control questionnaire (6 point)                                |               |       |  |
| Units: points   |               |       |  |
| arithmetic mean   | 2.6           |       |  |
| standard deviation  | ± 0.9         | -     |  |
| mini Asthma Quality of Life<br>Questionnaire                          |               |       |  |
| Units: points   |               |       |  |
| arithmetic mean   | 3.6           |       |  |

|  |                     |   |  |
|--|---------------------|---|--|
| standard deviation   | ± 1.3               | - |  |
| Forced expiratory volume in 1 second<br>Units: litre(s)<br>arithmetic mean<br>standard deviation                               | 2.37<br>± 1.00      | - |  |
| Forced expiratory flow rate between 25 and 75% of forced vital capacity<br>Units: L/s<br>arithmetic mean<br>standard deviation | 1.48<br>± 0.90      | - |  |
| Fractional exhaled nitric oxide<br>Units: ppb<br>arithmetic mean<br>standard deviation   | 51<br>± 42          | - |  |
| Forced vital capacity<br>Units: litre(s)<br>arithmetic mean<br>standard deviation  | 3.62<br>± 1.42      | - |  |
| FEV1/FVC ratio<br>Units: unit(s)<br>arithmetic mean<br>standard deviation  | 65.5<br>± 9.4       | - |  |
| R5-R20<br>Units: kPa/L/s<br>arithmetic mean<br>standard deviation  | 0.14<br>± 0.12      | - |  |
| X5<br>Units: kPa/L/s<br>arithmetic mean<br>standard deviation  | -0.28<br>± 0.22     | - |  |
| AX<br>Units: kPa/L<br>arithmetic mean<br>standard deviation  | 2.77<br>± 2.83      | - |  |
| Mannitol PD10<br>Units: mg<br>log mean<br>standard deviation   | 1.8278<br>± 0.66186 | - |  |
| R5<br>Units: kPa/L/s<br>arithmetic mean<br>standard deviation  | 0.53<br>± 0.18      | - |  |
| R20<br>Units: kPa/L/s<br>arithmetic mean<br>standard deviation   | 0.39<br>± 0.10      | - |  |
| Fres<br>Units: Hz<br>arithmetic mean<br>standard deviation   | 22.32<br>± 6.57     | - |  |
| Eosinophil derived neurotoxin<br>Units: ng/ml  |                     |   |  |

|   |                |   |  |
|---|----------------|---|--|
| arithmetic mean<br>standard deviation   | 65.6<br>± 26.6 | - |  |
| Diary card peak flow<br>Units: litre(s)<br>arithmetic mean<br>standard deviation                | 357<br>± 130   | - |  |
| Diary card symptoms<br>Units: units<br>arithmetic mean<br>standard deviation                    | 1.7<br>± 0.6   | - |  |
| Diary card reliever use<br>Units: number of puffs used<br>arithmetic mean<br>standard deviation | 3.4<br>± 3.1   | - |  |



## End points

### End points reporting groups

|                                |          |
|--------------------------------|----------|
| Reporting group title          | Baseline |
| Reporting group description: - |          |
| Reporting group title          | none     |
| Reporting group description: - |          |

### Primary: Mannitol PD10

|                        |               |
|------------------------|---------------|
| End point title        | Mannitol PD10 |
| End point description: |               |
| End point type         | Primary       |
| End point timeframe:   |               |
| 12 weeks               |               |

| End point values                         | Baseline        | none            |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 21              | 1               |  |  |
| Units: milligram(s)                      |                 |                 |  |  |
| geometric mean (confidence interval 95%) | 67 (34 to 135)  | 0 (0 to 0)      |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Geometric mean fold difference at 12 weeks |
| Comparison groups                       | Baseline v none                            |
| Number of subjects included in analysis | 22   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | other <sup>[1]</sup>                       |
| P-value                                 | < 0.01 <sup>[2]</sup>                      |
| Method                                  | ANOVA                                      |

Notes:

[1] - Single arm open label

[2] - Bonferroni corrected

### Secondary: Mannitol RDR

|                        |              |
|------------------------|--------------|
| End point title        | Mannitol RDR |
| End point description: |              |
| End point type         | Secondary    |
| End point timeframe:   |              |
| 12 weeks               |              |

| End point values                         | Baseline         | none            |  |  |
|--|------------------|-----------------|--|--|
| Subject group type                       | Reporting group  | Reporting group |  |  |
| Number of subjects analysed              | 21               | 1               |  |  |
| Units: geometric mean fold difference    |                  |                 |  |  |
| geometric mean (confidence interval 95%) | 0.2 (0.1 to 0.5) | 0 (0 to 0)      |  |  |

### Statistical analyses

| Statistical analysis title              | Geometric mean fold difference in RDR at 12 weeks |
|---|---|
| Comparison groups                       | Baseline v none                                   |
| Number of subjects included in analysis | 22  |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | other <sup>[3]</sup>                              |
| P-value                                 | < 0.01 <sup>[4]</sup>                             |
| Method                                  | ANOVA   |

Notes:

[3] - Single arm open label

[4] - Bonferroni corrected

### Secondary: FEV1

|                        |           |
|------------------------|-----------|
| End point title        | FEV1      |
| End point description: |           |
| End point type         | Secondary |
| End point timeframe:   |           |
| 12 weeks               |           |

| End point values                          | Baseline             | none            |  |  |
|---|----------------------|-----------------|--|--|
| Subject group type                        | Reporting group      | Reporting group |  |  |
| Number of subjects analysed               | 21                   | 1               |  |  |
| Units: litre(s)                           |                      |                 |  |  |
| arithmetic mean (confidence interval 95%) | 0.12 (-0.15 to 0.39) | 0 (0 to 0)      |  |  |

### Statistical analyses

| Statistical analysis title | Change in FEV1 at 12 weeks |
|----------------------------|----------------------------|
| Comparison groups          | Baseline v none            |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 22                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other <sup>[5]</sup>  |
| P-value                                 | > 0.05 <sup>[6]</sup> |
| Method                                  | ANOVA                 |

Notes:

[5] - Single arm open label

[6] - Bonferroni corrected

### Secondary: FEF25-75

|                        |          |
|------------------------|----------|
| End point title        | FEF25-75 |
| End point description: |          |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 12 weeks             |           |

| End point values                          | Baseline             | none            |  |  |
|---|----------------------|-----------------|--|--|
| Subject group type                        | Reporting group      | Reporting group |  |  |
| Number of subjects analysed               | 21                   | 1               |  |  |
| Units: litres/second                      |                      |                 |  |  |
| arithmetic mean (confidence interval 95%) | 0.05 (-0.27 to 0.37) | 0 (0 to 0)      |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Change in FEF25-75 at 12 weeks |
| Comparison groups                       | Baseline v none                |
| Number of subjects included in analysis | 22                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other <sup>[7]</sup>           |
| P-value                                 | > 0.05 <sup>[8]</sup>          |
| Method                                  | ANOVA                          |

Notes:

[7] - Single arm open label

[8] - Bonferroni corrected

### Secondary: FVC

|                        |     |
|------------------------|-----|
| End point title        | FVC |
| End point description: |     |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 12 weeks             |           |

|   |                      |                 |  |  |
|---|----------------------|-----------------|--|--|
| <b>End point values</b>                   | Baseline             | none            |  |  |
| Subject group type                        | Reporting group      | Reporting group |  |  |
| Number of subjects analysed               | 21                   | 1               |  |  |
| Units: litres                             |                      |                 |  |  |
| arithmetic mean (confidence interval 95%) | 0.16 (-0.05 to 0.37) | 0 (0 to 0)      |  |  |

### Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | Change in FVC at 12 weeks |
| Comparison groups                       | Baseline v none           |
| Number of subjects included in analysis | 22                        |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other <sup>[9]</sup>      |
| P-value                                 | > 0.05 <sup>[10]</sup>    |
| Method                                  | ANOVA                     |

Notes:

[9] - Single arm open label

[10] - Bonferroni corrected

### Secondary: FEV1/FVC

|                 |          |
|-----------------|----------|
| End point title | FEV1/FVC |
|-----------------|----------|

End point description:

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

End point timeframe:

12 weeks

|   |                   |                 |  |  |
|---|-------------------|-----------------|--|--|
| <b>End point values</b>                   | Baseline          | none            |  |  |
| Subject group type                        | Reporting group   | Reporting group |  |  |
| Number of subjects analysed               | 21                | 1               |  |  |
| Units: ratio                              |                   |                 |  |  |
| arithmetic mean (confidence interval 95%) | 1.0 (-1.9 to 3.9) | 0 (0 to 0)      |  |  |

### Statistical analyses

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | Change in FEV1/FVC at 12 weeks |
| Comparison groups                 | Baseline v none                |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 22                     |
| Analysis specification                  | Pre-specified          |
| Analysis type                           |                        |
| P-value                                 | > 0.05 <sup>[11]</sup> |
| Method                                  | ANOVA                  |

Notes:

[11] - Bonferroni corrected

## Secondary: R5-R20

|                        |           |
|------------------------|-----------|
| End point title        | R5-R20    |
| End point description: |           |
| End point type         | Secondary |
| End point timeframe:   |           |
| 12 weeks               |           |

| End point values                          | Baseline             | none            |  |  |
|---|----------------------|-----------------|--|--|
| Subject group type                        | Reporting group      | Reporting group |  |  |
| Number of subjects analysed               | 21                   | 1               |  |  |
| Units: kPa/L/s                            |                      |                 |  |  |
| arithmetic mean (confidence interval 95%) | 0.00 (-0.04 to 0.04) | 0 (0 to 0)      |  |  |

## Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title              | Change in R5-R20 at 12 weeks |
| Comparison groups                       | none v Baseline              |
| Number of subjects included in analysis | 22                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other <sup>[12]</sup>        |
| P-value                                 | > 0.05 <sup>[13]</sup>       |
| Method                                  | ANOVA                        |

Notes:

[12] - Single arm open label

[13] - Bonferroni corrected

## Secondary: X5

|                        |           |
|------------------------|-----------|
| End point title        | X5        |
| End point description: |           |
| End point type         | Secondary |
| End point timeframe:   |           |
| 12 weeks               |           |

| End point values                          | Baseline             | none            |  |  |
|---|----------------------|-----------------|--|--|
| Subject group type                        | Reporting group      | Reporting group |  |  |
| Number of subjects analysed               | 21                   | 1               |  |  |
| Units: kPa/L/s                            |                      |                 |  |  |
| arithmetic mean (confidence interval 95%) | 0.04 (-0.04 to 0.12) | 0 (0 to 0)      |  |  |

## Statistical analyses

| Statistical analysis title              | Change in X5 at 12 weeks |
|---|--------------------------|
| Comparison groups                       | Baseline v none          |
| Number of subjects included in analysis | 22                       |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[14]</sup>    |
| P-value                                 | > 0.05 <sup>[15]</sup>   |
| Method                                  | ANOVA                    |

Notes:

[14] - Single arm open label

[15] - Bonferroni corrected

## Secondary: AX

|                        |           |
|------------------------|-----------|
| End point title        | AX        |
| End point description: |           |
| End point type         | Secondary |
| End point timeframe:   |           |
| 12 weeks               |           |

| End point values                          | Baseline              | none            |  |  |
|---|-----------------------|-----------------|--|--|
| Subject group type                        | Reporting group       | Reporting group |  |  |
| Number of subjects analysed               | 21                    | 1               |  |  |
| Units: kPa/L                              |                       |                 |  |  |
| arithmetic mean (confidence interval 95%) | -0.46 (-1.43 to 0.50) | 0 (0 to 0)      |  |  |

## Statistical analyses

| Statistical analysis title | Change in AX at 12 weeks |
|----------------------------|--------------------------|
| Comparison groups          | Baseline v none          |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 22                     |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | other <sup>[16]</sup>  |
| P-value                                 | > 0.05 <sup>[17]</sup> |
| Method                                  | ANOVA                  |

Notes:

[16] - Single arm open label

[17] - Bonferroni corrected

### Secondary: Peripheral blood eosinophils

|                        |                              |
|------------------------|------------------------------|
| End point title        | Peripheral blood eosinophils |
| End point description: |                              |

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

End point timeframe:

12 weeks

| End point values                          | Baseline            | none            |  |  |
|---|---------------------|-----------------|--|--|
| Subject group type                        | Reporting group     | Reporting group |  |  |
| Number of subjects analysed               | 21                  | 1               |  |  |
| Units: cells/microlitre                   |                     |                 |  |  |
| arithmetic mean (confidence interval 95%) | -426 (-574 to -277) | 0 (0 to 0)      |  |  |

### Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | Change in PBE at 12 weeks |
| Comparison groups                       | Baseline v none           |
| Number of subjects included in analysis | 22                        |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other <sup>[18]</sup>     |
| P-value                                 | < 0.0001 <sup>[19]</sup>  |
| Method                                  | ANOVA                     |

Notes:

[18] - Single arm open label

[19] - Bonferroni corrected

### Secondary: Eosinophil derived neurotoxin

|                        |                               |
|------------------------|-------------------------------|
| End point title        | Eosinophil derived neurotoxin |
| End point description: |                               |

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

End point timeframe:

12 weeks

| End point values                          | Baseline               | none            |  |  |
|---|------------------------|-----------------|--|--|
| Subject group type                        | Reporting group        | Reporting group |  |  |
| Number of subjects analysed               | 21                     | 1               |  |  |
| Units: ng/ml                              |                        |                 |  |  |
| arithmetic mean (confidence interval 95%) | -50.3 (-62.2 to -38.5) | 0 (0 to 0)      |  |  |

### Statistical analyses

| Statistical analysis title              | Change in EDN at 12 weeks |
|---|---------------------------|
| Comparison groups                       | none v Baseline           |
| Number of subjects included in analysis | 22                        |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other <sup>[20]</sup>     |
| P-value                                 | < 0.0001 <sup>[21]</sup>  |
| Method                                  | ANOVA                     |

Notes:

[20] - Single arm open label

[21] - Bonferroni corrected

### Secondary: Fractional exhaled nitric oxide

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Fractional exhaled nitric oxide |
|-----------------|---------------------------------|

End point description:

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

End point timeframe:

12 weeks

| End point values                          | Baseline        | none            |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                        | Reporting group | Reporting group |  |  |
| Number of subjects analysed               | 21              | 1               |  |  |
| Units: Parts per billion                  |                 |                 |  |  |
| arithmetic mean (confidence interval 95%) | 8 (-11 to 28)   | 0 (0 to 0)      |  |  |

### Statistical analyses

| Statistical analysis title | Change in FeNO at 12 weeks |
|----------------------------|----------------------------|
| Comparison groups          | Baseline v none            |



|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 22                     |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | other <sup>[22]</sup>  |
| P-value                                 | > 0.05 <sup>[23]</sup> |
| Method                                  | ANOVA                  |

Notes:

[22] - Single arm open label

[23] - Bonferroni corrected

### Secondary: Asthma Control Questionnaire 6

|                        |                                |
|------------------------|--------------------------------|
| End point title        | Asthma Control Questionnaire 6 |
| End point description: |                                |

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

End point timeframe:

12 weeks

| End point values                          | Baseline            | none            |  |  |
|---|---------------------|-----------------|--|--|
| Subject group type                        | Reporting group     | Reporting group |  |  |
| Number of subjects analysed               | 21                  | 1               |  |  |
| Units: units                              |                     |                 |  |  |
| arithmetic mean (confidence interval 95%) | -1.5 (-2.0 to -1.1) | 0 (0 to 0)      |  |  |

### Statistical analyses

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Change in ACQ6 at 12 weeks |
| Comparison groups                       | Baseline v none            |
| Number of subjects included in analysis | 22                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other <sup>[24]</sup>      |
| P-value                                 | < 0.0001 <sup>[25]</sup>   |
| Method                                  | ANOVA                      |

Notes:

[24] - Single arm open label

[25] - Bonferroni corrected

### Secondary: Mini Asthma Quality of Life Questionnaire

|                        |   |
|------------------------|---|
| End point title        | Mini Asthma Quality of Life Questionnaire |
| End point description: |   |

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

End point timeframe:

12 weeks

| End point values                          | Baseline         | none            |  |  |
|---|------------------|-----------------|--|--|
| Subject group type                        | Reporting group  | Reporting group |  |  |
| Number of subjects analysed               | 21               | 1               |  |  |
| Units: units                              |                  |                 |  |  |
| arithmetic mean (confidence interval 95%) | 1.7 (1.1 to 2.3) | 0 (0 to 0)      |  |  |

### Statistical analyses

| Statistical analysis title              | Change in mii-AQLQ at 12 weeks |
|---|--------------------------------|
| Comparison groups                       | Baseline v none                |
| Number of subjects included in analysis | 22                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other <sup>[26]</sup>          |
| P-value                                 | < 0.0001 <sup>[27]</sup>       |
| Method                                  | ANOVA                          |

Notes:

[26] - Single arm open label

[27] - Bonferroni corrected

### Secondary: Diary card peak expiratory flow

| End point title        | Diary card peak expiratory flow |
|------------------------|---------------------------------|
| End point description: |                                 |
| End point type         | Secondary                       |
| End point timeframe:   |                                 |
| 12 weeks               |                                 |

| End point values                          | Baseline        | none            |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                        | Reporting group | Reporting group |  |  |
| Number of subjects analysed               | 21              | 1               |  |  |
| Units: litres/minute                      |                 |                 |  |  |
| arithmetic mean (confidence interval 95%) | 48 (21 to 74)   | 0 (0 to 0)      |  |  |

### Statistical analyses

| Statistical analysis title | Change in PEF at 12 weeks |
|----------------------------|---------------------------|
| Comparison groups          | Baseline v none           |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 22                     |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | other <sup>[28]</sup>  |
| P-value                                 | < 0.01 <sup>[29]</sup> |
| Method                                  | ANOVA                  |

Notes:

[28] - Single arm open label

[29] - Bonferroni corrected

### Secondary: Diary card symptoms

|                        |                     |
|------------------------|---------------------|
| End point title        | Diary card symptoms |
| End point description: |                     |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 12 weeks             |           |

| End point values                          | Baseline            | none            |  |  |
|---|---------------------|-----------------|--|--|
| Subject group type                        | Reporting group     | Reporting group |  |  |
| Number of subjects analysed               | 21                  | 1               |  |  |
| Units: units                              |                     |                 |  |  |
| arithmetic mean (confidence interval 95%) | -0.7 (-0.9 to -0.5) | 0 (0 to 0)      |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change in diary card symptoms at 12 weeks |
| Comparison groups                       | Baseline v none                           |
| Number of subjects included in analysis | 22  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | other <sup>[30]</sup>                     |
| P-value                                 | < 0.0001 <sup>[31]</sup>                  |
| Method                                  | ANOVA                                     |

Notes:

[30] - Single arm open label

[31] - Bonferroni corrected

### Secondary: Diary card reliever use

|                        |                         |
|------------------------|-------------------------|
| End point title        | Diary card reliever use |
| End point description: |                         |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 12 weeks             |           |

|   |                 |                 |  |  |
|---|-----------------|-----------------|--|--|
| <b>End point values</b>                   | Baseline        | none            |  |  |
| Subject group type                        | Reporting group | Reporting group |  |  |
| Number of subjects analysed               | 21              | 1               |  |  |
| Units: units                              |                 |                 |  |  |
| arithmetic mean (confidence interval 95%) | -2 (-3 to 0)    | 0 (0 to 0)      |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change in diary card reliever use at 12 weeks |
| Comparison groups                       | Baseline v none                               |
| Number of subjects included in analysis | 22  |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | other <sup>[32]</sup>                         |
| P-value                                 | < 0.05 <sup>[33]</sup>                        |
| Method                                  | ANOVA   |

Notes:

[32] - Single arm open label

[33] - Bonferroni corrected

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From study enrolment to last patient last visit

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

### Reporting groups

|                       |      |
|-----------------------|------|
| Reporting group title | BISA |
|-----------------------|------|

Reporting group description: -

| Serious adverse events                            | BISA   |  |  |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 1 / 21 (4.76%)                                   |  |  |
| number of deaths (all causes)                     | 0  |  |  |
| number of deaths resulting from adverse events    |  |  |  |
| Respiratory, thoracic and mediastinal disorders   |  |  |  |
| Hospitalisation                                   | Additional description: Coronavirus disease 2019 |  |  |
| subjects affected / exposed                       | 1 / 21 (4.76%)                                   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |

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

| Non-serious adverse events                            | BISA             |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 18 / 21 (85.71%) |  |  |
| Nervous system disorders                              |                  |  |  |
| Headache  |                  |  |  |
| subjects affected / exposed                           | 4 / 21 (19.05%)  |  |  |
| occurrences (all)                                     | 20               |  |  |
| General disorders and administration site conditions  |                  |  |  |
| Sinusitis   |                  |  |  |
| subjects affected / exposed                           | 4 / 21 (19.05%)  |  |  |
| occurrences (all)                                     | 7                |  |  |

|  |   |  |  |
|--|---|--|--|
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 3 / 21 (14.29%)<br>3  |  |  |
| Mechanical fall<br>subjects affected / exposed<br>occurrences (all)  | 2 / 21 (9.52%)<br>2   |  |  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 21 (4.76%)<br>2   |  |  |
| Gastrointestinal disorders<br>Heartburn<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 1 / 21 (4.76%)<br>2<br><br>2 / 21 (9.52%)<br>2<br><br>2 / 21 (9.52%)<br>3     |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Breathlessness<br>subjects affected / exposed<br>occurrences (all)<br><br>Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Exacerbation of asthma<br>subjects affected / exposed<br>occurrences (all) | 3 / 21 (14.29%)<br>12<br><br>4 / 21 (19.05%)<br>5<br><br>5 / 21 (23.81%)<br>5 |  |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)   | 2 / 21 (9.52%)<br>2   |  |  |
| Musculoskeletal and connective tissue disorders  |   |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all)                              | 3 / 21 (14.29%)<br>4 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 4 / 21 (19.05%)<br>5 |  |  |
| Allergic rhinitis<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 21 (9.52%)<br>4  |  |  |
| Infections and infestations<br>Coronavirus disease 2019<br>subjects affected / exposed<br>occurrences (all) | 7 / 21 (33.33%)<br>7 |  |  |
| Flu-like illness<br>subjects affected / exposed<br>occurrences (all)  | 2 / 21 (9.52%)<br>2  |  |  |

## 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? Yes

| Date            | Interruption  | Restart date  |
|-----------------|---|---------------|
| 01 January 2021 | Government mandated lockdown in response to coronavirus disease 2019 pandemic | 13 April 2021 |

Notes:

### Limitations and caveats

None reported