



## Clinical trial results:

### A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Onset of Effect and Time Course of Change in Lung Function with Benralizumab in Severe, Uncontrolled Asthma Patients with Eosinophilic Inflammation

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-002094-36 |
| Trial protocol           | HU DE          |
| Global end of trial date | 30 August 2018 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 26 July 2019 |
| First version publication date | 26 July 2019 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | D3250C00038 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02869438 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | AstraZeneca AB  |
| Sponsor organisation address | Vastra Malarehamnen 9, So dertalje, Sweden, 151 85  |
| Public contact               | Ubaldo Martin, Global Clinical Lead Benralizumab, AstraZeneca AB, Ubaldo.Martin@astrazeneca.com |
| Scientific contact           | Clinical Study Information, AstraZeneca AB, 46 855 32600, information.center@astrazeneca.com    |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 30 August 2018 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 30 August 2018 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 30 August 2018 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study is to determine the effect of Benralizumab on the time course of change (onset and maintenance of effect) on lung function

Protection of trial subjects:

The study is performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological samples. Each PI is responsible for providing the ECs/institutional review boards (IRBs) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca provides this information to the PI so that he/she can meet these reporting requirements. During the study, AstraZeneca representative have regular contacts with the study site, ie, monitoring the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 09 November 2017 |
| 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 | Chile: 38                                  |
| Country: Number of subjects enrolled | Germany: 36                                |
| Country: Number of subjects enrolled | Hungary: 41                                |
| Country: Number of subjects enrolled | Philippines: 37                            |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 40 |
| Country: Number of subjects enrolled | United States: 41                          |
| Worldwide total number of subjects   | 233  |
| EEA total number of subjects         | 77   |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|  |     |
|--|-----|
| Infants and toddlers (28 days-23 months) | 0   |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 195 |
| From 65 to 84 years                      | 38  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

721 patients enrolled into D3250C00038 (Solana). 233 participants were randomized to receive treatment with benralizumab 30 mg or placebo. Of the 233 patients randomised, all (100.0%) received treatment with study drug. 118 (50.6%) patients received benralizumab 30 mg and 115 (49.4%) patients received placebo.

### Period 1

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

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Benra 30 mg |

Arm description:

12-week treatment period and receive Benra 30 mg at Day 0, Day 28 ( $\pm 3$  days), and Day 56 ( $\pm 3$  days).

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Benralizumab                                 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

30 mg

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

Arm description:

12-week treatment period and receive Placebo at Day 0, Day 28 ( $\pm 3$  days), and Day 56 ( $\pm 3$  days).

|  |  |
|--|--|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

30 mg

| <b>Number of subjects in period 1</b> | Benra 30 mg | Placebo |
|---------------------------------------|-------------|---------|
| Started                               | 118         | 115     |
| Completed                             | 115         | 113     |
| Not completed                         | 3           | 2       |
| Consent withdrawn by subject          | 1           | 2       |
| Adverse event, non-fatal              | 1           | -       |
| Lost to follow-up                     | 1           | -       |

## Baseline characteristics

### Reporting groups

|  |             |
|--|-------------|
| Reporting group title  | Benra 30 mg |
| Reporting group description:<br>12-week treatment period and receive Benra 30 mg at Day 0, Day 28 ( $\pm 3$ days), and Day 56 ( $\pm 3$ days). |             |
| Reporting group title  | Placebo     |
| Reporting group description:<br>12-week treatment period and receive Placebo at Day 0, Day 28 ( $\pm 3$ days), and Day 56 ( $\pm 3$ days).     |             |

| Reporting group values  | Benra 30 mg         | Placebo             | Total |
|---|---------------------|---------------------|-------|
| Number of subjects  | 118                 | 115                 | 233   |
| Age categorical<br>Units: Subjects                                      |                     |                     |       |
| Adults (18-64 years)  | 97                  | 98                  | 195   |
| From 65-84 years  | 21                  | 17                  | 38    |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 51.9<br>$\pm 13.62$ | 50.9<br>$\pm 12.34$ | -     |
| Sex: Female, Male<br>Units: Subjects                                    |                     |                     |       |
| Female  | 74                  | 83                  | 157   |
| Male  | 44                  | 32                  | 76    |
| Race/Ethnicity, Customized<br>Units: Subjects                           |                     |                     |       |
| White   | 69                  | 67                  | 136   |
| Black or African American   | 3                   | 4                   | 7     |
| Asian   | 39                  | 40                  | 79    |
| Other   | 7                   | 4                   | 11    |

## End points

### End points reporting groups

|  |             |
|--|-------------|
| Reporting group title  | Benra 30 mg |
| Reporting group description:<br>12-week treatment period and receive Benra 30 mg at Day 0, Day 28 ( $\pm 3$ days), and Day 56 ( $\pm 3$ days). |             |
| Reporting group title  | Placebo     |
| Reporting group description:<br>12-week treatment period and receive Placebo at Day 0, Day 28 ( $\pm 3$ days), and Day 56 ( $\pm 3$ days).     |             |

### Primary: Change from baseline (visit 4) to Day 28 (Visit 8), Day 56 (Visit 9), and Day 84 (Visit 10) in pre-BD FEV1

|  |  |
|--|--|
| End point title  | Change from baseline (visit 4) to Day 28 (Visit 8), Day 56 (Visit 9), and Day 84 (Visit 10) in pre-BD FEV1 |
| End point description:<br>The average over the mean differences between benralizumab and placebo for change from baseline in pre-BD FEV1 is used to determine if the study is positive and to determine maintenance of effect. The first post baseline time point where the p-value for the mean difference between benralizumab and placebo is less than or equal to 0.05 is used to determine time to onset of effect. |  |
| End point type   | Primary  |
| End point timeframe:<br>From first IP dose to Day 84   |  |

| End point values                     | Benra 30 mg           | Placebo               |  |  |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed          | 118                   | 115                   |  |  |
| Units: Liter                         |                       |                       |  |  |
| arithmetic mean (standard deviation) |                       |                       |  |  |
| Day 28                               | 0.21 ( $\pm 0.335$ )  | 0.132 ( $\pm 0.316$ ) |  |  |
| Day 56                               | 0.22 ( $\pm 0.367$ )  | 0.203 ( $\pm 0.349$ ) |  |  |
| Day 84                               | 0.209 ( $\pm 0.344$ ) | 0.149 ( $\pm 0.366$ ) |  |  |

### Statistical analyses

|                            |                               |
|----------------------------|-------------------------------|
| Statistical analysis title | Repeated measurement analyses |
| Comparison groups          | Benra 30 mg v Placebo         |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[1]</sup>     |
| P-value                                 | = 0.0707                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.077                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.007                         |
| upper limit                             | 0.161                          |

Notes:

[1] - For Day 28

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[2]</sup>     |
| P-value                                 | = 0.7747                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.013                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.077                         |
| upper limit                             | 0.104                          |

Notes:

[2] - For Day 56

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[3]</sup>     |
| P-value                                 | = 0.0969                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.079                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.014                         |
| upper limit                             | 0.173                          |

Notes:

[3] - For Day 84

|                                   |                               |
|-----------------------------------|-------------------------------|
| <b>Statistical analysis title</b> | Repeated measurement analyses |
|-----------------------------------|-------------------------------|



|   |                                |
|---|--------------------------------|
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[4]</sup>     |
| P-value                                 | = 0.1558                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.057                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.022                         |
| upper limit                             | 0.135                          |

Notes:

[4] - For average of Day 28, 56, 84

### Primary: Change from baseline (Visit 4) to end of treatment Day 84 (Visit 10) in Residual volume (RV)

|                        |  |
|------------------------|--|
| End point title        | Change from baseline (Visit 4) to end of treatment Day 84 (Visit 10) in Residual volume (RV)   |
| End point description: | Body plethysmography was performed for sub-study patients. Lung volume subdivisions measures were performed by the investigator or qualified designee according to ATS/ERS guidelines. |
| End point type         | Primary  |
| End point timeframe:   | From first IP dose to Day 84   |

| End point values                     | Benra 30 mg      | Placebo          |  |  |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 18               | 22               |  |  |
| Units: Liter                         |                  |                  |  |  |
| arithmetic mean (standard deviation) | -0.415 (± 0.609) | -0.208 (± 0.528) |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 40                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[5]</sup>     |
| P-value                                 | = 0.2847                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.176                         |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.505  |
| upper limit         | 0.153   |

Notes:

[5] - For Day 84

### Secondary: Percent change from baseline to end of treatment in eosinophils counts

|  |  |
|--|--|
| End point title  | Percent change from baseline to end of treatment in eosinophils counts |
| End point description:<br>Percent change from baseline to Day 84 |  |
| End point type   | Secondary  |
| End point timeframe:<br>From first IP dose to Day 84             |  |

| End point values                       | Benra 30 mg            | Placebo                |  |  |
|--|------------------------|------------------------|--|--|
| Subject group type                     | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed            | 118                    | 115                    |  |  |
| Units: cell/uL                         |                        |                        |  |  |
| arithmetic mean (full range (min-max)) | -88.55 (-100 to -12.5) | 11.55 (-91.4 to 833.3) |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title              | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[6]</sup>     |
| P-value                                 | < 0.0001                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -101                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -118.9                         |
| upper limit                             | -83.06                         |

Notes:

[6] - For Day 84

### Secondary: Change from baseline (Visit 4) to post baseline visits in pre-BD FEV1

|                 |   |
|-----------------|---|
| End point title | Change from baseline (Visit 4) to post baseline visits in pre-BD FEV1 |
|-----------------|---|

End point description:

Post baseline visits include Day 3, Day 7, Day 14, Day 28, Day 56, Day 84. [Note: Day 28, 56, 84 are presented in the Primary measure.]

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

End point timeframe:

From first IP dose to Day 84

| End point values                     | Benra 30 mg     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 118             | 115             |  |  |
| Units: Liter                         |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Day 3                                | 0.104 (± 0.223) | 0.081 (± 0.269) |  |  |
| Day 7                                | 0.125 (± 0.229) | 0.081 (± 0.263) |  |  |
| Day 14                               | 0.126 (± 0.3)   | 0.1 (± 0.287)   |  |  |

## Statistical analyses

| Statistical analysis title              | Repeated measurement analyses  |
|---|--------------------------------|
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[7]</sup>     |
| P-value                                 | = 0.6384                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.015                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.049                         |
| upper limit                             | 0.08                           |

Notes:

[7] - For Day 3

| Statistical analysis title              | Repeated measurement analyses  |
|---|--------------------------------|
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[8]</sup>     |
| P-value                                 | = 0.148                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.046                          |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.016  |
| upper limit         | 0.109   |

Notes:

[8] - For Day 7

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[9]</sup>     |
| P-value                                 | = 0.4959                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.026                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.049                         |
| upper limit                             | 0.101                          |

Notes:

[9] - For Day 14

### Secondary: Change from baseline to post baseline for pre-BD FVC

|  |  |
|--|--|
| End point title  | Change from baseline to post baseline for pre-BD FVC |
| End point description:   |  |
| Post baseline visits include Day 3, Day 7, Day 14, Day 28, Day 56, and Day 84. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| From first IP dose to Day 84   |  |

| End point values                     | Benra 30 mg     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 118             | 115             |  |  |
| Units: Liter                         |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Day 3                                | 0.122 (± 0.247) | 0.11 (± 0.267)  |  |  |
| Day 7                                | 0.138 (± 0.277) | 0.099 (± 0.292) |  |  |
| Day 14                               | 0.126 (± 0.331) | 0.111 (± 0.312) |  |  |
| Day 28                               | 0.21 (± 0.347)  | 0.134 (± 0.34)  |  |  |
| Day 56                               | 0.211 (± 0.404) | 0.187 (± 0.369) |  |  |
| Day 84                               | 0.213 (± 0.376) | 0.131 (± 0.359) |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[10]</sup>    |
| P-value                                 | = 0.8667                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.006                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.062                         |
| upper limit                             | 0.073                          |

Notes:

[10] - For Day 3

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[11]</sup>    |
| P-value                                 | = 0.2734                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.041                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.033                         |
| upper limit                             | 0.115                          |

Notes:

[11] - For Day 7

|                                   |                               |
|-----------------------------------|-------------------------------|
| <b>Statistical analysis title</b> | Repeated measurement analyses |
| Comparison groups                 | Benra 30 mg v Placebo         |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[12]</sup>    |
| P-value                                 | = 0.7252                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.015                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.068                         |
| upper limit                             | 0.098                          |

Notes:

[12] - For Day 14

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[13]</sup>    |
| P-value                                 | = 0.0976                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.075                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.014                         |
| upper limit                             | 0.164                          |

Notes:

[13] - For Day 28

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[14]</sup>    |
| P-value                                 | = 0.6536                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.023                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.077                         |
| upper limit                             | 0.122                          |

Notes:

[14] - For Day 56

|                                   |                               |
|-----------------------------------|-------------------------------|
| <b>Statistical analysis title</b> | Repeated measurement analyses |
|-----------------------------------|-------------------------------|

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[15]</sup>    |
| P-value                                 | = 0.0595                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.092                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.004                         |
| upper limit                             | 0.188                          |

Notes:

[15] - For Day 84

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[16]</sup>    |
| P-value                                 | = 0.1377                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.063                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.02                          |
| upper limit                             | 0.147                          |

Notes:

[16] - For average of Day 28, 56, 84

### Secondary: Percentage of pre-BD FEV1 responder

|  |                                     |
|--|-------------------------------------|
| End point title  | Percentage of pre-BD FEV1 responder |
| End point description:   |                                     |
| Pre-BD FEV1 responder is defined as change from baseline in FEV1 $\geq$ 100 ml |                                     |
| End point type   | Secondary                           |
| End point timeframe:   |                                     |
| From first IP dose to Day 84   |                                     |

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Benra 30 mg     | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 118             | 115             |  |  |
| Units: Percentage           |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Day 3                       | 48.2            | 37.4            |  |  |

|        |      |      |  |  |
|--------|------|------|--|--|
| Day 7  | 48.3 | 42.0 |  |  |
| Day 14 | 50.0 | 38.9 |  |  |
| Day 28 | 57.6 | 46.9 |  |  |
| Day 56 | 62.1 | 55.8 |  |  |
| Day 84 | 57.9 | 51.8 |  |  |

## Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Logistic Regression analyses |
| Comparison groups                       | Benra 30 mg v Placebo        |
| Number of subjects included in analysis | 233                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority <sup>[17]</sup>  |
| P-value                                 | = 0.1604                     |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Odds ratio (OR)              |
| Point estimate                          | 1.49                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.85                         |
| upper limit                             | 2.58                         |

Notes:

[17] - For Day 3

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Logistic Regression analyses |
| Comparison groups                       | Benra 30 mg v Placebo        |
| Number of subjects included in analysis | 233                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority <sup>[18]</sup>  |
| P-value                                 | = 0.34                       |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Odds ratio (OR)              |
| Point estimate                          | 1.29                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.76                         |
| upper limit                             | 2.19                         |

Notes:

[18] - For Day 7

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Logistic Regression analyses |
| Comparison groups                 | Benra 30 mg v Placebo        |



|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 233                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[19]</sup> |
| P-value                                 | = 0.0924                    |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.58                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.93                        |
| upper limit                             | 2.7                         |

Notes:

[19] - For Day 14

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Logistic Regression analyses |
| Comparison groups                       | Benra 30 mg v Placebo        |
| Number of subjects included in analysis | 233                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority <sup>[20]</sup>  |
| P-value                                 | = 0.1052                     |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Odds ratio (OR)              |
| Point estimate                          | 1.57                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.91                         |
| upper limit                             | 2.71                         |

Notes:

[20] - For Day 28

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Logistic Regression analyses |
| Comparison groups                       | Benra 30 mg v Placebo        |
| Number of subjects included in analysis | 233                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority <sup>[21]</sup>  |
| P-value                                 | = 0.3271                     |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Odds ratio (OR)              |
| Point estimate                          | 1.3                          |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.77                         |
| upper limit                             | 2.21                         |

Notes:

[21] - For Day 56

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Logistic Regression analyses |
|-----------------------------------|------------------------------|

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Benra 30 mg v Placebo       |
| Number of subjects included in analysis | 233                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[22]</sup> |
| P-value                                 | = 0.3017                    |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.33                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.77                        |
| upper limit                             | 2.29                        |

Notes:

[22] - For Day 84

## Secondary: Change from baseline in ACQ-6

|  |                               |
|--|-------------------------------|
| End point title  | Change from baseline in ACQ-6 |
| End point description:   |                               |
| ACQ-6 contains one bronchodilator question and 5 symptom questions. Questions are rated from 0 (totally controlled) to 6 (severely uncontrolled). Mean ACQ-6 score is the average of the responses. Mean scores of ≤0.75 indicates well-controlled asthma, scores between 0.75 to ≤1.5 indicate partly controlled asthma, and >1.5 indicates not well controlled asthma. |                               |
| End point type   | Secondary                     |
| End point timeframe:   |                               |
| From first IP dose to Day 84   |                               |

| End point values                     | Benra 30 mg      | Placebo          |  |  |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 118              | 115              |  |  |
| Units: Score on a scale              |                  |                  |  |  |
| arithmetic mean (standard deviation) |                  |                  |  |  |
| Day 14                               | -0.989 (± 0.901) | -0.665 (± 0.837) |  |  |
| Day 28                               | -1.126 (± 0.947) | -0.693 (± 0.869) |  |  |
| Day 56                               | -1.164 (± 1.132) | -0.827 (± 1.023) |  |  |
| Day 84                               | -1.355 (± 1.146) | -0.867 (± 1.114) |  |  |

## Statistical analyses

|                            |                               |
|----------------------------|-------------------------------|
| Statistical analysis title | Repeated measurement analyses |
| Comparison groups          | Benra 30 mg v Placebo         |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[23]</sup>    |
| P-value                                 | = 0.0024                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.293                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.481                         |
| upper limit                             | -0.105                         |

Notes:

[23] - For Day 14

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[24]</sup>    |
| P-value                                 | = 0.0002                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.402                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.609                         |
| upper limit                             | -0.195                         |

Notes:

[24] - For Day 28

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[25]</sup>    |
| P-value                                 | = 0.0117                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.312                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.554                         |
| upper limit                             | -0.07                          |

Notes:

[25] - For Day 56

|                                   |                               |
|-----------------------------------|-------------------------------|
| <b>Statistical analysis title</b> | Repeated measurement analyses |
|-----------------------------------|-------------------------------|

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[26]</sup>    |
| P-value                                 | = 0.0004                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.472                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.731                         |
| upper limit                             | -0.213                         |

Notes:

[26] - For Day 84

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[27]</sup>    |
| P-value                                 | = 0.0002                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.395                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.603                         |
| upper limit                             | -0.188                         |

Notes:

[27] - For average of Day 28, 56, 84

### **Secondary: Change from baseline in St. George's Respiratory Questionnaire (SGRQ)**

|                              |  |
|------------------------------|--|
| End point title              | Change from baseline in St. George's Respiratory Questionnaire (SGRQ)  |
| End point description:       | The SGRQ is designed to measure health impairment in patients with asthma and COPD. It contains two parts: Part 1 (Questions 1 to 8) covers the patients' recollection of their symptoms over a preceding 4 weeks; Part 2, 42 items, relates to the daily activity and psychosocial impacts of the individual's respiratory condition. Total score is presented as a percentage of overall impairment, in which 100 represents the worst possible health status, while 0 indicates the best. |
| End point type               | Secondary  |
| End point timeframe:         |  |
| From first IP dose to Day 84 |  |

| End point values                     | Benra 30 mg             | Placebo                 |  |  |
|--------------------------------------|-------------------------|-------------------------|--|--|
| Subject group type                   | Reporting group         | Reporting group         |  |  |
| Number of subjects analysed          | 118                     | 115                     |  |  |
| Units: Score on a scale              |                         |                         |  |  |
| arithmetic mean (standard deviation) |                         |                         |  |  |
| Day 28                               | -16.956 ( $\pm$ 15.51)  | -9.444 ( $\pm$ 14.136)  |  |  |
| Day 56                               | -19.941 ( $\pm$ 21.528) | -13.802 ( $\pm$ 16.705) |  |  |
| Day 84                               | -23.343 ( $\pm$ 20.302) | -14.385 ( $\pm$ 18.836) |  |  |

## Statistical analyses

| Statistical analysis title              | Repeated measurement analyses  |
|---|--------------------------------|
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[28]</sup>    |
| P-value                                 | = 0.0001                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -7.229                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -10.832                        |
| upper limit                             | -3.626                         |

Notes:

[28] - For Day 28

| Statistical analysis title              | Repeated measurement analyses  |
|---|--------------------------------|
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[29]</sup>    |
| P-value                                 | = 0.0115                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -5.942                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -10.538                        |
| upper limit                             | -1.346                         |

Notes:

[29] - For Day 56

| Statistical analysis title | Repeated measurement analyses |
|----------------------------|-------------------------------|
|----------------------------|-------------------------------|

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[30]</sup>    |
| P-value                                 | = 0.0004                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -8.599                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -13.3                          |
| upper limit                             | -3.898                         |

Notes:

[30] - For Day 84

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[31]</sup>    |
| P-value                                 | = 0.0003                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -7.257                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -11.133                        |
| upper limit                             | -3.38                          |

Notes:

[31] - For average of Day 28, 56, 84

## Secondary: Change from baseline to end of treatment in FeNO

|                        |   |
|------------------------|---|
| End point title        | Change from baseline to end of treatment in FeNO  |
| End point description: | Airway inflammation was evaluated via fractional exhaled nitric oxide (FeNO) measurement. |
| End point type         | Secondary   |
| End point timeframe:   | From first IP dose to Day 84  |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | Benra 30 mg     | Placebo         |  |  |
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 118             | 115             |  |  |
| Units: ppb                           |                 |                 |  |  |
| arithmetic mean (standard deviation) | 5.92 (± 45.295) | 0.05 (± 27.634) |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[32]</sup>    |
| P-value                                 | = 0.2825                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 5.414                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -4.492                         |
| upper limit                             | 15.321                         |

Notes:

[32] - For Day 84

## Secondary: Change from baseline to end of treatment in total lung capacity (TLC) for sub-study patients

|                 |  |
|-----------------|--|
| End point title | Change from baseline to end of treatment in total lung capacity (TLC) for sub-study patients |
|-----------------|--|

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

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

End point timeframe:

From first IP dose to Day 84

|                                      |                  |                  |  |  |
|--------------------------------------|------------------|------------------|--|--|
| <b>End point values</b>              | Benra 30 mg      | Placebo          |  |  |
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 18               | 22               |  |  |
| Units: Liter                         |                  |                  |  |  |
| arithmetic mean (standard deviation) | -0.276 (± 0.677) | -0.175 (± 0.418) |  |  |

## Statistical analyses

No statistical analyses for this end point

---

**Secondary: Change from baseline to end of treatment in ratio of residual volume (RV) and total lung capacity (TLC) for sub-study patients**

---

|                 |  |
|-----------------|--|
| End point title | Change from baseline to end of treatment in ratio of residual volume (RV) and total lung capacity (TLC) for sub-study patients |
|-----------------|--|

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

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

End point timeframe:

From first IP dose to Day 84

---

| End point values                     | Benra 30 mg     | Placebo          |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 18              | 22               |  |  |
| Units: ratio                         |                 |                  |  |  |
| arithmetic mean (standard deviation) | -0.05 (± 0.056) | -0.026 (± 0.087) |  |  |

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Change from baseline to end of treatment in inspiratory capacity (IC) for sub-study patients**

---

|                 |  |
|-----------------|--|
| End point title | Change from baseline to end of treatment in inspiratory capacity (IC) for sub-study patients |
|-----------------|--|

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

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

End point timeframe:

From first IP dose to Day 84

---

| End point values                     | Benra 30 mg     | Placebo          |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 18              | 22               |  |  |
| Units: Liter                         |                 |                  |  |  |
| arithmetic mean (standard deviation) | 0.119 (± 0.447) | -0.268 (± 0.603) |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to end of treatment in functional residual capacity (FRC) for sub-study patients

|                 |   |
|-----------------|---|
| End point title | Change from baseline to end of treatment in functional residual capacity (FRC) for sub-study patients |
|-----------------|---|

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

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

End point timeframe:

From first IP dose to Day 84

|                                      |                       |                      |  |  |
|--------------------------------------|-----------------------|----------------------|--|--|
| <b>End point values</b>              | Benra 30 mg           | Placebo              |  |  |
| Subject group type                   | Reporting group       | Reporting group      |  |  |
| Number of subjects analysed          | 18                    | 22                   |  |  |
| Units: Liter                         |                       |                      |  |  |
| arithmetic mean (standard deviation) | -0.394 ( $\pm$ 0.783) | 0.093 ( $\pm$ 0.466) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to end of treatment in vital capacity (VC) for sub-study patients

|                 |  |
|-----------------|--|
| End point title | Change from baseline to end of treatment in vital capacity (VC) for sub-study patients |
|-----------------|--|

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

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

End point timeframe:

From first IP dose to Day 84

| End point values                     | Benra 30 mg          | Placebo              |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 18                   | 22                   |  |  |
| Units: Liter                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0.139 ( $\pm$ 0.245) | 0.033 ( $\pm$ 0.676) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of IP administration

|  |                               |
|--|-------------------------------|
| End point title  | Duration of IP administration |
| End point description:<br>Duration of IP administration is last IP dose date - first IP dose +1. |                               |
| End point type   | Secondary                     |
| End point timeframe:<br>From first IP to last IP   |                               |

| End point values                     | Benra 30 mg        | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 118                | 115                |  |  |
| Units: Days                          |                    |                    |  |  |
| arithmetic mean (standard deviation) | 55.9 ( $\pm$ 7.83) | 56.2 ( $\pm$ 7.61) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Serum concentration of Benralizumab

|  |   |
|--|---|
| End point title  | Serum concentration of Benralizumab <sup>[33]</sup> |
| End point description:<br>PK sample was collected pre-dose at each visit |   |
| End point type   | Other pre-specified                                 |
| End point timeframe:<br>From first IP dose to end of treatment           |   |

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is serum concentration with benralizumab, so is only applicable for the active treatment arm

|   |                    |  |  |  |
|---|--------------------|--|--|--|
| <b>End point values</b>                             | Benra 30 mg        |  |  |  |
| Subject group type                                  | Reporting group    |  |  |  |
| Number of subjects analysed                         | 117                |  |  |  |
| Units: ng/mL  |                    |  |  |  |
| geometric mean (geometric coefficient of variation) |                    |  |  |  |
| Baseline  | 1.95 (± 0)         |  |  |  |
| Day 3   | 1266.78 (± 199.59) |  |  |  |
| Day 7   | 1449.47 (± 125.02) |  |  |  |
| Day 14  | 1317.92 (± 79.53)  |  |  |  |
| Day 28  | 738.47 (± 80.77)   |  |  |  |
| Day 56  | 1015.72 (± 59.74)  |  |  |  |
| Day 84  | 1079.22 (± 73.24)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: PK parameter of Benralizumab (Cmax)

|  |   |
|--|---|
| End point title  | PK parameter of Benralizumab (Cmax) <sup>[34]</sup> |
| End point description:   |   |
| PK parameters are derived in patients with at least three qualifiable serum PK concentrations post first dose (collected on Day 3, 7, and either 14, or 28)  |   |
| End point type   | Other pre-specified                                 |
| End point timeframe:   |   |
| From first IP dose to end of treatment   |   |
| Notes:   |   |
| [34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. |   |
| Justification: This endpoint is serum concentration with benralizumab, so is only applicable for the active treatment arm  |   |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| <b>End point values</b>                             | Benra 30 mg     |  |  |  |
| Subject group type                                  | Reporting group |  |  |  |
| Number of subjects analysed                         | 117             |  |  |  |
| Units: ng/mL  |                 |  |  |  |
| geometric mean (geometric coefficient of variation) | 1729.6 (± 36.8) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

**Other pre-specified: Anti-drug antibody responses**

|                 |                              |
|-----------------|------------------------------|
| End point title | Anti-drug antibody responses |
|-----------------|------------------------------|

End point description:

Anti-drug antibody responses at baseline and post baseline, including nAb responses

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From first IP dose to end of treatment

| End point values                         | Benra 30 mg     | Placebo         |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 118             | 115             |  |  |
| Units: Participants                      |                 |                 |  |  |
| ADA prevalence                           | 7               | 2               |  |  |
| nAb prevalence                           | 2               | 0               |  |  |
| Both baseline and post baseline positive | 1               | 2               |  |  |
| Only post baseline positive              | 5               | 0               |  |  |
| Only baseline positive                   | 1               | 0               |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: Change from baseline to end of treatment in PGI-S**

|                 |   |
|-----------------|---|
| End point title | Change from baseline to end of treatment in PGI-S |
|-----------------|---|

End point description:

The patient global impression of severity (PGI-S) is a single item designed to capture the patient's perception of overall symptom severity at the time of the completion using a 6-point categorical response scale (no symptom [0] to very severe symptom [5])

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From first IP dose to Day 84

| End point values                     | Benra 30 mg     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 118             | 115             |  |  |
| Units: Score on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -1.2 (± 1.31)   | -0.8 (± 1.21)   |  |  |

**Statistical analyses**

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Repeated measurement analyses  |
| Comparison groups                       | Benra 30 mg v Placebo          |
| Number of subjects included in analysis | 233                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[35]</sup>    |
| P-value                                 | = 0.012                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.365                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.649                         |
| upper limit                             | -0.081                         |

Notes:

[35] - For Day 84

### Other pre-specified: Change from baseline to end of treatment in CGI-C

|   |   |
|---|---|
| End point title   | Change from baseline to end of treatment in CGI-C |
| End point description:  |   |
| Clinician global impression of change (CGI-C) is used for an overall evaluation of response to treatment. The investigator is asked to rate the degree of change in overall asthma status compare to the start of treatment. A 7-point rating scale is used from 1=very much improved to 7=very much worse. |   |
| End point type  | Other pre-specified                               |
| End point timeframe:  |   |
| From first IP dose to Day 84  |   |

| End point values            | Benra 30 mg     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 118             | 115             |  |  |
| Units: Participants         |                 |                 |  |  |
| Very much improved          | 18              | 10              |  |  |
| Much improved               | 39              | 36              |  |  |
| Minimally improved          | 39              | 28              |  |  |
| No change                   | 17              | 28              |  |  |
| Minimally worse             | 0               | 7               |  |  |
| Much worse                  | 0               | 1               |  |  |
| Very much worse             | 0               | 0               |  |  |
| Missing                     | 5               | 5               |  |  |

### Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>   | Logistic regression analyses |
| Statistical analysis description:   |                              |
| Responder analysis: responder is defined as Very much improved, improved, and minimally improved. |                              |
| Comparison groups   | Benra 30 mg v Placebo        |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 233                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[36]</sup> |
| P-value                                 | = 0.0018                    |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 2.97                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.5                         |
| upper limit                             | 5.88                        |

Notes:

[36] - For Day 84

### Other pre-specified: Change from baseline to end of treatment in PGI-C

|  |   |
|--|---|
| End point title  | Change from baseline to end of treatment in PGI-C |
| End point description:   |   |
| Patient global impression of change (PGI-C) is used for an overall evaluation of response to treatment. The patient is asked to rate the degree of change in overall asthma status compare to the start of treatment. A 7-point rating scale is used from 1=very much improved to 7=very much worse. |   |
| End point type   | Other pre-specified                               |
| End point timeframe:   |   |
| From first IP dose to Day 84   |   |

| End point values            | Benra 30 mg     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 118             | 115             |  |  |
| Units: Participants         |                 |                 |  |  |
| Very much improved          | 32              | 17              |  |  |
| Much improved               | 42              | 35              |  |  |
| Minimally improved          | 23              | 29              |  |  |
| No change                   | 14              | 27              |  |  |
| Minimally worse             | 1               | 4               |  |  |
| Much worse                  | 1               | 1               |  |  |
| Very much worse             | 1               | 0               |  |  |
| Missing                     | 4               | 2               |  |  |

### Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title  | Logistic regression analyses |
| Statistical analysis description:   |                              |
| Responder analysis: responder is defined as Very much improved, improved, and minimally improved. |                              |
| Comparison groups   | Benra 30 mg v Placebo        |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 233                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[37]</sup> |
| P-value                                 | = 0.0107                    |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 2.51                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.24                        |
| upper limit                             | 5.09                        |

Notes:

[37] - For Day 84

### Other pre-specified: Change from baseline to end of treatment in specific airway resistance (SGaw) for sub-study patients

|                 |  |
|-----------------|--|
| End point title | Change from baseline to end of treatment in specific airway resistance (SGaw) for sub-study patients |
|-----------------|--|

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From first IP dose to Day 84

| End point values                     | Benra 30 mg     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 18              | 22              |  |  |
| Units: 1/(kPa*sec)                   |                 |                 |  |  |
| arithmetic mean (standard deviation) | -0.05 (± 0.146) | 0.052 (± 0.224) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Change from baseline to end of treatment in airway resistance (Raw) for sub-study patients

|                 |  |
|-----------------|--|
| End point title | Change from baseline to end of treatment in airway resistance (Raw) for sub-study patients |
|-----------------|--|

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

---

End point timeframe:

From first IP dose to Day 84

---

|                                      |                  |                 |  |  |
|--------------------------------------|------------------|-----------------|--|--|
| <b>End point values</b>              | Benra 30 mg      | Placebo         |  |  |
| Subject group type                   | Reporting group  | Reporting group |  |  |
| Number of subjects analysed          | 18               | 22              |  |  |
| Units: kPa/L/sec                     |                  |                 |  |  |
| arithmetic mean (standard deviation) | -0.233 (± 1.509) | -0.2 (± 0.532)  |  |  |

### Statistical analyses

---

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From informed consent form was signed to end of study.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

12-week treatment period and receive Placebo at Day 0, Day 28 ( $\pm 3$  days), and Day 56 ( $\pm 3$  days).

|                       |             |
|-----------------------|-------------|
| Reporting group title | Benra 30 mg |
|-----------------------|-------------|

Reporting group description:

12-week treatment period and receive Benra 30 mg at Day 0, Day 28 ( $\pm 3$  days), and Day 56 ( $\pm 3$  days).

| Serious adverse events                            | Placebo         | Benra 30 mg     |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 7 / 115 (6.09%) | 1 / 118 (0.85%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    |                 |                 |  |
| Cardiac disorders                                 |                 |                 |  |
| Coronary artery disease                           |                 |                 |  |
| subjects affected / exposed                       | 1 / 115 (0.87%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                          |                 |                 |  |
| Generalised tonic-clonic seizure                  |                 |                 |  |
| subjects affected / exposed                       | 1 / 115 (0.87%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Migraine  |                 |                 |  |
| subjects affected / exposed                       | 1 / 115 (0.87%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Immune system disorders                           |                 |                 |  |
| Drug hypersensitivity                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 2 / 115 (1.74%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 115 (1.74%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Placebo           | Benra 30 mg       |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 30 / 115 (26.09%) | 28 / 118 (23.73%) |  |
| Respiratory, thoracic and mediastinal disorders       |                   |                   |  |
| Asthma  |                   |                   |  |
| subjects affected / exposed                           | 18 / 115 (15.65%) | 11 / 118 (9.32%)  |  |
| occurrences (all)                                     | 22                | 11                |  |
| Infections and infestations                           |                   |                   |  |
| Bronchitis  |                   |                   |  |
| subjects affected / exposed                           | 3 / 115 (2.61%)   | 6 / 118 (5.08%)   |  |
| occurrences (all)                                     | 3                 | 6                 |  |
| Nasopharyngitis                                       |                   |                   |  |
| subjects affected / exposed                           | 6 / 115 (5.22%)   | 8 / 118 (6.78%)   |  |
| occurrences (all)                                     | 7                 | 9                 |  |
| Upper respiratory tract infection                     |                   |                   |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 115 (5.22%) | 6 / 118 (5.08%) |  |
| occurrences (all)           | 8               | 7               |  |

## **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