



Clinical trial results:

A multicentre, randomised, double-blind, parallel group, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of benralizumab in asthmatic adults and adolescents inadequately controlled on inhaled corticosteroid plus long-acting beta2 agonist (CALIMA)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-002163-26 |
| Trial protocol | DE SE PL |
| Global end of trial date | 04 May 2016 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v2 (current) |
| This version publication date | 07 January 2017 |
| First version publication date | 24 September 2016 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D3250C00018 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01914757 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AstraZeneca AB |
| Sponsor organisation address | Vastra Malarehamnen 9, Sodertalje, Sweden, 151 85 |
| Public contact | Mitchell Goldman, AstraZeneca AB, Mitchell.Goldman@astrazeneca.com |
| Scientific contact | AZ Clinical Study Information, AstraZeneca AB, 46 855 326000, information.center@astrazeneca.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001214-PIP01-11 |
| 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 | 04 May 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 May 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 May 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the effect of two dosing regimens of benralizumab on asthma exacerbations in patients on high-dose ICS-LABA with uncontrolled asthma

Protection of trial subjects:

Data safety monitoring board (DSMB) evaluates cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. The DSMB functions independently of all other individuals associated with the conduct of the studies, including the study sponsor, AstraZeneca. The committee operates in accordance with a DSMB charter.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 21 August 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Sweden: 10 |
| Country: Number of subjects enrolled | Ukraine: 118 |
| Country: Number of subjects enrolled | United States: 171 |
| Country: Number of subjects enrolled | Philippines: 61 |
| Country: Number of subjects enrolled | Argentina: 269 |
| Country: Number of subjects enrolled | Canada: 59 |
| Country: Number of subjects enrolled | Chile: 31 |
| Country: Number of subjects enrolled | Germany: 159 |
| Country: Number of subjects enrolled | Japan: 83 |
| Country: Number of subjects enrolled | Poland: 290 |
| Country: Number of subjects enrolled | Romania: 55 |
| Worldwide total number of subjects | 1306 |
| EEA total number of subjects | 514 |

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) | 55 |
| Adults (18-64 years) | 1074 |
| From 65 to 84 years | 177 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

2505 participants signed informed consent, 2181 entered screening/run-in period, 1306 participants were randomised to receive treatment with benralizumab 30 mg Q4W, Q8W, or placebo. Of the 1306 patients randomised, all (100.0%) received treatment with study drug.

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 |
| Arm title | Benralizumab 30 mg q.4 weeks |

Arm description:

Benralizumab administered subcutaneously every 4 weeks.

| | |
|--|--|
| 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

| | |
|------------------|------------------------------|
| Arm title | Benralizumab 30 mg q.8 weeks |
|------------------|------------------------------|

Arm description:

Benralizumab administered subcutaneously every 8 weeks.

| | |
|--|--|
| 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

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo administered subcutaneously.

| | |
|--|--|
| 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

| Number of subjects in period 1 | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo |
|---------------------------------------|---------------------------------|---------------------------------|---------|
| Started | 425 | 441 | 440 |
| Completed | 389 | 390 | 402 |
| Not completed | 36 | 51 | 38 |
| Severe non-compliance to protocol | 3 | 1 | 2 |
| Adverse event, serious fatal | 2 | 2 | 1 |
| Consent withdrawn by subject | 15 | 27 | 19 |
| Eligibility criteria not fulfilled | 2 | - | 2 |
| Adverse event, non-fatal | 4 | 3 | 4 |
| Other reasons | 5 | 9 | 4 |
| Lost to follow-up | 5 | 8 | 6 |
| Study specific withdrawal criteria | - | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|------------------------------|
| Reporting group title | Benralizumab 30 mg q.4 weeks |
| Reporting group description: Benralizumab administered subcutaneously every 4 weeks. | |
| Reporting group title | Benralizumab 30 mg q.8 weeks |
| Reporting group description: Benralizumab administered subcutaneously every 8 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo administered subcutaneously. | |

| Reporting group values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo |
|---|---------------------------------|---------------------------------|---------|
| Number of subjects | 425 | 441 | 440 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 11 | 21 | 23 |
| Adults (18-64 years) | 359 | 365 | 350 |
| From 65-84 years | 55 | 55 | 67 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 50 | 49 | 48.8 |
| standard deviation | ± 13.6 | ± 14.3 | ± 15.1 |
| Gender, Male/Female Units: Participants | | | |
| Female | 270 | 273 | 264 |
| Male | 155 | 168 | 176 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 1306 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 55 | | |
| Adults (18-64 years) | 1074 | | |

| | | | |
|-------------------|-----|--|--|
| From 65-84 years | 177 | | |
| 85 years and over | 0 | | |

| | | | |
|---|-----|--|--|
| Age Continuous Units: Years arithmetic mean standard deviation | - | | |
| Gender, Male/Female Units: Participants | | | |
| Female | 807 | | |
| Male | 499 | | |

End points

End points reporting groups

| | |
|---|------------------------------|
| Reporting group title | Benralizumab 30 mg q.4 weeks |
| Reporting group description: Benralizumab administered subcutaneously every 4 weeks. | |
| Reporting group title | Benralizumab 30 mg q.8 weeks |
| Reporting group description: Benralizumab administered subcutaneously every 8 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo administered subcutaneously. | |

Primary: Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma, baseline eosinophils $\geq 300/\mu\text{L}$

| | |
|---|--|
| End point title | Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma, baseline eosinophils $\geq 300/\mu\text{L}$ |
| End point description: The annual exacerbation rate is based on unadjudicated annual exacerbation rate reported by the investigator in the eCRF. The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS | |
| End point type | Primary |
| End point timeframe: Immediately following the first administration of study drug through Study Week 56. | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--|------------------------------|------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 239 | 248 | |
| Units: events/year | | | | |
| least squares mean (confidence interval 95%) | 0.6 (0.48 to 0.74) | 0.66 (0.54 to 0.82) | 0.93 (0.77 to 1.12) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Negative Binomial Model |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |

| | |
|---|-------------------|
| Number of subjects included in analysis | 489 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | Negative Binomial |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.85 |

| | |
|---|--|
| Statistical analysis title | Negative Binomial Model |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 487 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.019 |
| Method | Negative Binomial |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.95 |

Secondary: Mean change from baseline to Week 56 in Pre-bronchodilator FEV1 (L) value for patients with baseline eosinophils $\geq 300/\mu\text{L}$

| | |
|-----------------|---|
| End point title | Mean change from baseline to Week 56 in Pre-bronchodilator FEV1 (L) value for patients with baseline eosinophils $\geq 300/\mu\text{L}$ |
|-----------------|---|

End point description:

The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56.

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 216 | 211 | 221 | |
| Units: Liter | | | | |
| arithmetic mean (standard deviation) | 0.34 (\pm 0.469) | 0.332 (\pm 0.518) | 0.206 (\pm 0.471) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.116 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.028 |
| upper limit | 0.204 |

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 437 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.125 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.037 |
| upper limit | 0.213 |

Secondary: Mean change from baseline to Week 56 asthma symptoms score for patients with baseline eosinophils $\geq 300/\mu\text{L}$

| | |
|-----------------|--|
| End point title | Mean change from baseline to Week 56 asthma symptoms score for patients with baseline eosinophils $\geq 300/\mu\text{L}$ |
|-----------------|--|

End point description:

Asthma symptoms during night time and daytime are recorded by the patient in the asthma daily diary. Symptom score values are from 0 (No asthma symptom) to 3 (unable to sleep because of asthma, or unable to do normal activities due to asthma), and total asthma symptom score is the sum of the daytime and night time score (0 to 6). Baseline is defined as the average of data collected from the evening of study day -10 to the morning of study day 1. Each time point is calculated as bi-weekly means based on daily diary data. If more than 50% of scores are missing in a 14 day period then this is considered as missing. Symptom score lower is better.

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56.

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 184 | 185 | 187 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | -1.33 (± 1.23) | -1.4 (± 1.17) | -1.2 (± 1.19) | |

Statistical analyses

| Statistical analysis title | Mixed Effect Model Repeated Measurement |
|---|---|
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 371 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.224 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.07 |

| Statistical analysis title | Mixed Effect Model Repeated Measurement |
|---|---|
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.019 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.23 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | -0.04 |

Secondary: Change in asthma rescue medication use

| | |
|--|--|
| End point title | Change in asthma rescue medication use |
| End point description: | |
| Change from Baseline to Week 56 in number of Rescue medication use (puffs/day). The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS. The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS | |
| End point type | Secondary |
| End point timeframe: | |
| Immediately following the first administration of study drug through Study Week 56. | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 184 | 185 | 187 | |
| Units: Puffs per day | | | | |
| arithmetic mean (standard deviation) | -2 (\pm 3.64) | -2.92 (\pm 3.6) | -2.65 (\pm 9.57) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 371 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.603 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.58 |
| upper limit | 0.99 |

| | |
|----------------------------|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
|----------------------------|---|

| | |
|---|--|
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.209 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.29 |
| upper limit | 0.28 |

Secondary: Home lung function assessments based on morning PEF

| | |
|------------------------|---|
| End point title | Home lung function assessments based on morning PEF |
| End point description: | Change from Baseline to Week 56 in Home lung function (morning Peak expiratory flow [PEF]). The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS |
| End point type | Secondary |
| End point timeframe: | Immediately following the first administration of study drug through Study Week 56. |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 194 | 193 | 197 | |
| Units: L/min | | | | |
| arithmetic mean (standard deviation) | 41.745 (\pm 78.534) | 43.375 (\pm 91.865) | 23.961 (\pm 71.509) | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Statistical analysis description: | Morning PEF Change from Baseline to Week 56 |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 390 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.037 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 15.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 29.64 |

| | |
|--|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Statistical analysis description: Morning PEF Change from Baseline to Week 56 | |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 391 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.029 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 15.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.59 |
| upper limit | 30.12 |

| | |
|---|---|
| Secondary: Proportion of Nights with awakening due to asthma | |
| End point title | Proportion of Nights with awakening due to asthma |
| End point description: Change from Baseline to Week 56 on Proportion of Nights with awakening due to asthma. The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS | |
| End point type | Secondary |
| End point timeframe: Immediately following the first administration of study drug through Study Week 56. | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|--------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 196 | 198 | 203 | |
| Units: Proportion of nights | | | | |
| arithmetic mean (standard deviation) | -0.373 (\pm 0.388) | -0.431 (\pm 0.4) | -0.372 (\pm 0.405) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.06 |
| upper limit | 0.03 |

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.146 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.08 |
| upper limit | 0.01 |

Secondary: Mean change from baseline to Week 56 in ACQ-6 for patients with baseline eosinophils $\geq 300/\mu\text{L}$

| | |
|-----------------|---|
| End point title | Mean change from baseline to Week 56 in ACQ-6 for patients with baseline eosinophils $\geq 300/\mu\text{L}$ |
|-----------------|---|

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. The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56.

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 192 | 185 | 197 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | -1.34 (\pm 1.13) | -1.49 (\pm 1.13) | -1.21 (\pm 1.12) | |

Statistical analyses

| Statistical analysis title | Mixed Effect Model Repeated Measurement |
|---|---|
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 389 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.043 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | -0.01 |

| Statistical analysis title | Mixed Effect Model Repeated Measurement |
|---|---|
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.008 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.25 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | -0.07 |

Secondary: Number of patients with ≥ 1 asthma exacerbation

| | |
|---|--|
| End point title | Number of patients with ≥ 1 asthma exacerbation |
| End point description: The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS | |
| End point type | Secondary |
| End point timeframe: Immediately following the first administration of study drug through Study Week 56 | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|-----------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 239 | 248 | |
| Units: Participants | 84 | 95 | 126 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Cochran-Mantel-Haenszel Test |
| Statistical analysis description: Proportion of patients with ≥ 1 asthma exacerbation | |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 489 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.31 |
| upper limit | 0.69 |

| | |
|----------------------------|------------------------------|
| Statistical analysis title | Cochran-Mantel-Haenszel Test |
|----------------------------|------------------------------|

| | |
|--|--|
| Statistical analysis description: | |
| Proportion of patients with ≥ 1 asthma exacerbation | |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 487 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.023 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.45 |
| upper limit | 0.95 |

Secondary: Annual rate of asthma exacerbation resulting emergency room visits and hospitalizations

| | |
|-----------------|---|
| End point title | Annual rate of asthma exacerbation resulting emergency room visits and hospitalizations |
|-----------------|---|

End point description:

Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization (adjudicated). The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56.

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--|------------------------------------|------------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 239 | 248 | |
| Units: events/year | | | | |
| least squares mean (confidence interval 95%) | 0.04 (0.02 to 0.06) | 0.05 (0.03 to 0.08) | 0.04 (0.02 to 0.07) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Negative Binomial |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |

| | |
|---|-------------------|
| Number of subjects included in analysis | 489 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.837 |
| Method | negative binomial |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 1.82 |

| | |
|---|--|
| Statistical analysis title | Negative Binomial |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 487 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.538 |
| Method | negative binomial |
| Parameter estimate | Rate Ratio |
| Point estimate | 1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 2.35 |

Secondary: Pharmacokinetics of benralizumab

| | |
|---|----------------------------------|
| End point title | Pharmacokinetics of benralizumab |
| End point description: | |
| Mean PK Concentration at each visit | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, Week 56, Week 60 | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|---|------------------------------------|------------------------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 425 ^[1] | 424 | 0 ^[2] | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |

| | | | | |
|-----------------------|-------------------|-------------------|----|--|
| Baseline (n=435, 419) | 0 (± 0) | 0 (± 0) | () | |
| Week 4 (n=430, 416) | 650.04 (± 154.61) | 703.16 (± 89.48) | () | |
| Week 8 (n=414, 395) | 894.86 (± 148.91) | 939.45 (± 98.99) | () | |
| Week 16 (n=390, 378) | 936.43 (± 247.46) | 252.54 (± 274.74) | () | |
| Week 24 (n=388, 361) | 827.09 (± 370.64) | 188.99 (± 308.38) | () | |
| Week 32 (n=345, 323) | 823.21 (± 362.43) | 166.53 (± 289.34) | () | |
| Week 40 (n=370, 338) | 859.69 (± 364.28) | 172.28 (± 298.6) | () | |
| Week 48 (n=355, 337) | 888.09 (± 333.98) | 186.5 (± 290.28) | () | |
| Week 56 (n=358, 344) | 763.98 (± 309.18) | 173.41 (± 235.86) | () | |
| Week 60 (n=49, 45) | 53.63 (± 1782.96) | 18.63 (± 756.47) | () | |

Notes:

[1] - Patients were treated with q.4 weeks instead of q.8 weeks, so 435 in the analysis.

[2] - No concentration of Experimental Product.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of benralizumab

| | |
|--|--------------------------------|
| End point title | Immunogenicity of benralizumab |
| End point description: | |
| Anti-drug antibodies (ADA) responses at baseline and post baseline. Persistently positive is defined as positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment. Transiently positive is defined as having at least one post-baseline ADA positive assessment and not fulfilling the conditions of persistently positive. | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-treatment until end of follow-up | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|---|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 425 ^[3] | 427 | 440 | |
| Units: Participants | | | | |
| Positive at any visit (n=438, 427, 440) | 63 | 64 | 13 | |
| Base- and post-baseline positive (n=431, 414, 430) | 5 | 5 | 5 | |
| Only post-baseline positive (n=431, 420, 436) | 55 | 57 | 8 | |
| Persistently positive (n=431, 420, 436) | 44 | 42 | 7 | |
| Transient positive (n=431, 420, 436) | 16 | 20 | 6 | |
| Only baseline positive (n=438, 421, 434) | 3 | 2 | 0 | |

Notes:

[3] - Patients were treated with q.4 rather than q.8. So 438 in the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Extent of exposure

| | |
|--|--------------------|
| End point title | Extent of exposure |
| End point description: | |
| Extent of exposure is defined as the duration of treatment in days | |
| End point type | Secondary |
| End point timeframe: | |
| Immediately following the first administration of study drug through Study Week 56 | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 425 ^[4] | 428 | 440 | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 344.14 (± 73.129) | 331.64 (± 88.839) | 336.69 (± 82.148) | |

Notes:

[4] - 13 more patients were treated with q.4 rather than q.8, so 438 in the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to Week 56 in AQLQ(S)+12

| | |
|--|--|
| End point title | Mean change from baseline to Week 56 in AQLQ(S)+12 |
| End point description: | |
| AQLQ(S)+12 overall score is defined as the average of all 32 questions in the AQLQ(S)+12 questionnaire. AQLQ(S)+12 is a 7-point scale questionnaire, ranging from 7 (no impairment) to 1 (severe impairment). Total or domain score change of ≥ 0.5 are considered clinically meaningful. The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS | |
| End point type | Secondary |
| End point timeframe: | |
| Immediately following the first administration of study drug through Study Week 56 | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 186 | 180 | 191 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | 1.44 (± 1.15) | 1.61 (± 1.24) | 1.32 (± 1.19) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Mixed Effect Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 371 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.019 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 0.45 |

| | |
|---|--|
| Statistical analysis title | Mixed Effect Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 377 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.119 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.37 |

Secondary: Change from baseline to Week 56 in EQ-5D-5L VAS

| | |
|-----------------|---|
| End point title | Change from baseline to Week 56 in EQ-5D-5L VAS |
|-----------------|---|

End point description:

EQ-5D-5L VAS is to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state. The analysis is based on the primary analysis population, ie, baseline eosinophils

>=300/uL and high-dose ICS

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Immediately following the first administration of study drug through Study Week 56 | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 183 | 179 | 191 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | 13.8 (± 21.52) | 15.5 (± 20.36) | 12.1 (± 20.13) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean work productivity loss due to asthma

| | |
|--|---|
| End point title | Mean work productivity loss due to asthma |
| End point description: | |
| WPAI+CIQ (Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire) contains 10 questions. Work productivity loss is derived by sum of percentage of missed work due to asthma and product of percentage of actual working hours times degree of asthma affecting work productivity while working. Percentage of missed work due to asthma is calculated by number of hours missed work due to asthma divided by total number of hours missed work plus number of hours actually worked. Analyses are for Week 56. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS, and is only applicable for patients employed. | |
| End point type | Secondary |
| End point timeframe: | |
| Immediately following the first administration of study drug through Study Week 56 | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 74 | 85 | |
| Units: percent of productivity loss | | | | |
| arithmetic mean (standard deviation) | 26.56 (± 25.589) | 24.44 (± 24.689) | 27.29 (± 25.802) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean productivity loss due to asthma in Classroom

| | |
|-----------------|---|
| End point title | Mean productivity loss due to asthma in Classroom |
|-----------------|---|

End point description:

WPAI+CIQ (Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire) contains 10 questions. Classroom productivity loss is derived by sum of percentage of missed classes due to asthma and product of percentage of actual hours attending classes times degree of asthma affecting classroom productivity. Percentage of missed classes due to asthma is calculated by number of hours missed classes due to asthma divided by total number of hours missed classes plus number of hours actually attending classes. Analyses are for Week 56. The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS, and patients who took classes.

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14 | 5 | 5 | |
| Units: percent of productivity loss | | | | |
| arithmetic mean (standard deviation) | 19.92 (\pm 23.765) | 14 (\pm 16.733) | 33.5 (\pm 25.593) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants that utilized health care resources

| | |
|-----------------|--|
| End point title | Number of participants that utilized health care resources |
|-----------------|--|

End point description:

The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|-------------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 239 | 248 | |
| Units: Participants | | | | |
| Hospitalizations | 11 | 14 | 12 | |
| Emergency department visits | 11 | 12 | 18 | |
| Unscheduled outpatient visits | 72 | 75 | 83 | |
| Home visits | 3 | 1 | 2 | |

| | | | | |
|----------------------|----|----|----|--|
| Telephone calls | 50 | 63 | 58 | |
| Ambulance transports | 2 | 3 | 5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient and Clinician assessment of response to treatment

| | |
|-----------------|---|
| End point title | Patient and Clinician assessment of response to treatment |
|-----------------|---|

End point description:

CGIC (clinician global impression of change), and PGIC (patient global impression of change) are overall evaluation of response to treatment, conducted separately by investigator and patient using a 7-point rating scale, ranging from 1 (Very much Improved), to 7 (Very much Worse). The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS. Due to the endpoint was implemented after the second protocol amendment, thus not all patients having data to be analyzed.

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|-----------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 239 | 248 | |
| Units: Participants | | | | |
| CGIC, Improved | 109 | 96 | 97 | |
| CGIC, Much Improved | 82 | 71 | 65 | |
| CGIC, Very Much Improved | 26 | 23 | 14 | |
| CGIC, Total | 217 | 190 | 176 | |
| PGIC, Improved | 109 | 95 | 99 | |
| PGIC, Much Improved | 83 | 80 | 66 | |
| PGIC, Very Much Improved | 34 | 30 | 17 | |
| PGIC, Total | 226 | 205 | 182 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma, baseline eosinophils $<300/\mu\text{L}$

| | |
|-----------------|--|
| End point title | Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma, baseline eosinophils $<300/\mu\text{L}$ |
|-----------------|--|

End point description:

The annual exacerbation rate is based on unadjudicated annual exacerbation rate reported by the investigator in the eCRF. The analysis is based on the analysis population of baseline eosinophils <300/uL and high-dose ICS

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56.

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|---|------------------------------------|------------------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 116 | 125 | 122 | |
| Units: events/year | | | | |
| least squares mean (confidence interval 95%) | 0.78 (0.59 to 1.02) | 0.73 (0.55 to 0.95) | 1.21 (0.96 to 1.52) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Negative binomial analysis |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | negative binomial |
| Parameter estimate | Rate ratio |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 0.86 |

| | |
|---|--|
| Statistical analysis title | Negative binomial analysis |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.015 |
| Method | Negative binomial |
| Parameter estimate | Rate ratio |
| Point estimate | 0.64 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.45 |
| upper limit | 0.92 |

Secondary: Mean change from baseline to Week 56 in Pre-bronchodilator FEV1 (L) value for patient with baseline eosinophils <300/uL

| | |
|--|---|
| End point title | Mean change from baseline to Week 56 in Pre-bronchodilator FEV1 (L) value for patient with baseline eosinophils <300/uL |
| End point description: The analysis is based on the analysis population of baseline eosinophils <300/uL and high-dose ICS | |
| End point type | Secondary |
| End point timeframe: Immediately following the first administration of study drug through Study Week 56. | |

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 101 | 98 | 99 | |
| Units: Liter | | | | |
| arithmetic mean (standard deviation) | 0.221 (± 0.441) | 0.164 (± 0.358) | 0.135 (± 0.437) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.786 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.015 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.127 |
| upper limit | 0.096 |

| | |
|----------------------------|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
|----------------------------|---|

| | |
|---|--|
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.268 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.064 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.049 |
| upper limit | 0.176 |

Secondary: Mean change from baseline to Week 56 asthma symptoms score for patient with baseline eosinophils <300/uL

| | |
|-----------------|--|
| End point title | Mean change from baseline to Week 56 asthma symptoms score for patient with baseline eosinophils <300/uL |
|-----------------|--|

End point description:

Asthma symptoms during night time and daytime are recorded by the patient in the asthma daily diary. Symptom score values are from 0 (No asthma symptom) to 3 (unable to sleep because of asthma, or unable to do normal activities due to asthma), and total asthma symptom score is the sum of the daytime and night time score (0 to 6). Baseline is defined as the average of data collected from the evening of study day -10 to the morning of study day 1. Each time point is calculated as bi-weekly means based on daily diary data. If more than 50% of scores are missing in a 14 day period then this is considered as missing. Symptom score lower is better. The analysis is based on the population of baseline eosinophils <300/uL and high-dose ICS.

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56.

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 88 | 85 | 89 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | -1.05 (± 1.14) | -0.95 (± 1.13) | -0.88 (± 1.12) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.287 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | 0.13 |

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 174 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.966 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.29 |

Secondary: Mean change from baseline to Week 56 in ACQ-6 for patients with baseline eosinophils <300/uL

| | |
|-----------------|--|
| End point title | Mean change from baseline to Week 56 in ACQ-6 for patients with baseline eosinophils <300/uL |
|-----------------|--|

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. The analysis is based on the analysis population of baseline eosinophils <300/uL and high-dose ICS

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56.

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 88 | 83 | 92 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | -1.22 (± 1.16) | -1.06 (± 1.02) | -0.83 (± 1.07) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 180 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.078 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 0.03 |

| | |
|---|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.449 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.37 |
| upper limit | 0.16 |

Secondary: Time to first asthma exacerbation

| | |
|------------------------|-----------------------------------|
| End point title | Time to first asthma exacerbation |
| End point description: | |
| End point type | Secondary |

End point timeframe:

Immediately following the first administration of study drug through Study Week 56

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|-----------------------------|------------------------------------|------------------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 241 | 239 | 248 | |
| Units: Participants | 84 | 95 | 126 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Cox regression |
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
| Number of subjects included in analysis | 489 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 0.8 |

| | |
|---|--|
| Statistical analysis title | Cox regression |
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 487 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.018 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 0.95 |

Secondary: Home lung function assessments based on evening PEF

| | |
|-----------------|---|
| End point title | Home lung function assessments based on evening PEF |
|-----------------|---|

End point description:

Change from Baseline to Week 56 in Home lung function (evening Peak expiratory flow [PEF]). The analysis is based on the primary analysis population, ie, baseline eosinophils $\geq 300/\mu\text{L}$ and high-dose ICS

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

End point timeframe:

Immediately following the first administration of study drug through Study Week 56

| End point values | Benralizumab 30 mg q.4 weeks | Benralizumab 30 mg q.8 weeks | Placebo | |
|--------------------------------------|------------------------------------|------------------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 194 | 192 | 197 | |
| Units: L/min | | | | |
| arithmetic mean (standard deviation) | 35.142 (\pm 75.489) | 39.27 (\pm 89.772) | 15.448 (\pm 78.341) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
|----------------------------|---|

Statistical analysis description:

Evening PEF Change from Baseline to Week 56

| | |
|---|--|
| Comparison groups | Benralizumab 30 mg q.8 weeks v Placebo |
| Number of subjects included in analysis | 389 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 21.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.65 |
| upper limit | 35.79 |

| | |
|----------------------------|---|
| Statistical analysis title | Mixed Effect Model Repeated Measurement |
|----------------------------|---|

Statistical analysis description:

Evening PEF Change from Baseline to Week 56

| | |
|-------------------|--|
| Comparison groups | Benralizumab 30 mg q.4 weeks v Placebo |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 391 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.018 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 17.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.07 |
| upper limit | 32 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall study period

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Benra 30 mg q.8 weeks |
|-----------------------|-----------------------|

Reporting group description:

Benralizumab administered subcutaneously event 8 weeks

| | |
|-----------------------|-----------------------|
| Reporting group title | Benra 30 mg q.4 weeks |
|-----------------------|-----------------------|

Reporting group description:

Benralizumab administered subcutaneously every 4 weeks

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

Reporting group description:

Placebo administered subcutaneously

| Serious adverse events | Benra 30 mg q.8 weeks | Benra 30 mg q.4 weeks | Placebo |
|---|-----------------------|-----------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 41 / 428 (9.58%) | 46 / 438 (10.50%) | 61 / 440 (13.86%) |
| number of deaths (all causes) | 2 | 3 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer female | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon neoplasm | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gallbladder cancer | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid adenoma | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration | | | |

| | | | |
|---|------------------|------------------|------------------|
| site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 19 / 428 (4.44%) | 21 / 438 (4.79%) | 23 / 440 (5.23%) |
| occurrences causally related to treatment / all | 1 / 27 | 0 / 25 | 0 / 38 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperventilation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal turbinate hypertrophy | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Anastomotic ulcer | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Injury | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural complication | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 2 / 440 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroduodenitis | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal polyp | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis alcoholic | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Parakeratosis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria papular | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 2 / 438 (0.46%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dupuytren's contracture | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epiphysiolysis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaw cyst | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 1 / 438 (0.23%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis haemophilus | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus hepatitis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 2 / 428 (0.47%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 2 / 438 (0.46%) | 4 / 440 (0.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 428 (0.00%) | 2 / 438 (0.46%) | 3 / 440 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas bronchitis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 1 / 438 (0.23%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 428 (0.00%) | 0 / 438 (0.00%) | 1 / 440 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Obesity | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 428 (0.23%) | 0 / 438 (0.00%) | 0 / 440 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Benra 30 mg q.8 weeks | Benra 30 mg q.4 weeks | Placebo |
|---|-----------------------|-----------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 232 / 428 (54.21%) | 244 / 438 (55.71%) | 264 / 440 (60.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 18 / 428 (4.21%) | 12 / 438 (2.74%) | 22 / 440 (5.00%) |
| occurrences (all) | 23 | 12 | 24 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 34 / 428 (7.94%) | 33 / 438 (7.53%) | 32 / 440 (7.27%) |
| occurrences (all) | 65 | 63 | 57 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 13 / 428 (3.04%) | 16 / 438 (3.65%) | 6 / 440 (1.36%) |
| occurrences (all) | 13 | 20 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 32 / 428 (7.48%) | 50 / 438 (11.42%) | 52 / 440 (11.82%) |
| occurrences (all) | 50 | 76 | 96 |
| Cough | | | |
| subjects affected / exposed | 14 / 428 (3.27%) | 10 / 438 (2.28%) | 8 / 440 (1.82%) |
| occurrences (all) | 18 | 11 | 12 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 16 / 428 (3.74%) | 21 / 438 (4.79%) | 24 / 440 (5.45%) |
| occurrences (all) | 19 | 25 | 28 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 14 / 428 (3.27%) | 8 / 438 (1.83%) | 10 / 440 (2.27%) |
| occurrences (all) | 16 | 10 | 14 |

| | | | |
|---|--------------------------|--------------------------|--------------------------|
| Back pain subjects affected / exposed occurrences (all) | 11 / 428 (2.57%) 11 | 17 / 438 (3.88%) 18 | 16 / 440 (3.64%) 20 |
| Infections and infestations | | | |
| Acute sinusitis subjects affected / exposed occurrences (all) | 5 / 428 (1.17%) 6 | 6 / 438 (1.37%) 6 | 14 / 440 (3.18%) 19 |
| Bronchitis subjects affected / exposed occurrences (all) | 45 / 428 (10.51%) 54 | 40 / 438 (9.13%) 51 | 54 / 440 (12.27%) 72 |
| Influenza subjects affected / exposed occurrences (all) | 12 / 428 (2.80%) 17 | 24 / 438 (5.48%) 27 | 25 / 440 (5.68%) 27 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 82 / 428 (19.16%) 131 | 90 / 438 (20.55%) 132 | 92 / 440 (20.91%) 147 |
| Pharyngitis subjects affected / exposed occurrences (all) | 10 / 428 (2.34%) 10 | 17 / 438 (3.88%) 21 | 8 / 440 (1.82%) 9 |
| Rhinitis subjects affected / exposed occurrences (all) | 18 / 428 (4.21%) 24 | 12 / 438 (2.74%) 13 | 17 / 440 (3.86%) 22 |
| Sinusitis subjects affected / exposed occurrences (all) | 21 / 428 (4.91%) 30 | 23 / 438 (5.25%) 31 | 39 / 440 (8.86%) 56 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 37 / 428 (8.64%) 53 | 29 / 438 (6.62%) 35 | 42 / 440 (9.55%) 53 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 13 May 2014 | addition of adolescent patient population, amended incl/exclusion criteria, additional lab measurements |
| 16 March 2015 | addition of PRO questionnaires", addition of MACE/Malignancies Adjudication, additional laboratory measurements |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported