



Clinical trial results:

A Multicentre, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma (NAVIGATOR)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-003078-15 |
| Trial protocol | GB DE FR AT |
| Global end of trial date | 12 November 2020 |

Results information

| | |
|--------------------------------|-------------|
| Result version number | v1 |
| This version publication date | 28 May 2021 |
| First version publication date | 28 May 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D5180C00007 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03347279 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name | AstraZeneca AB |
| Sponsor organisation address | 151 85, Sodertalje, Sweden, |
| Public contact | Global Clinical Head, AstraZeneca, information.center@astrazeneca.com |
| Scientific contact | AstraZeneca Clinical Study Information, AstraZeneca, 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-001613-PIP01-14 |
| 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 | 12 November 2020 |
| Is this the analysis of the primary completion data? | No |
| <hr/> | |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 November 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe uncontrolled asthma compared with placebo

Protection of trial subjects:

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure (IB), and other relevant documents (eg, advertisements) were submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study was initiated.

The Investigator or his/her representative explained the nature of the study to the subject or his/her legally authorised representative and answered all questions regarding the study. Subjects were informed that their participation was voluntary. Subjects or their legally authorised representative were required to sign a statement of informed consent that met the requirements of 21 CFR 31.27, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

For subjects under the age of majority (adolescent subjects), the subject's legal guardian provided their informed consent in addition to the subject's informed consent. The medical record must have included a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must have also signed the ICF.

Subjects must have been re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) was provided to the subject or the subject's legally authorised representative.

Background therapy:

Subjects who had received a physician-prescribed asthma controller medication with medium- or high-dose ICS as per GINA guideline (GINA 2017) for at least 12 months prior to Visit 1.

Documented treatment with a total daily dose of either medium or high-dose ICS ($\geq 500\mu\text{g}$ fluticasone propionate dry powder formulation equivalent total daily dose) for at least 3 months prior to Visit 1. The ICS could be contained within an ICS/LABA combination product.

At least one additional maintenance asthma controller medication was required according to standard practice of care. Use of additional asthma controller medications must have been documented for at least 3 months prior to Visit 1.

Evidence for comparator: -

| | |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment | 23 November 2017 |
| 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 | Korea, Republic of: 126 |
| Country: Number of subjects enrolled | Japan: 97 |
| Country: Number of subjects enrolled | Vietnam: 20 |
| Country: Number of subjects enrolled | Taiwan: 9 |
| Country: Number of subjects enrolled | United States: 186 |
| Country: Number of subjects enrolled | Canada: 36 |
| Country: Number of subjects enrolled | Brazil: 93 |
| Country: Number of subjects enrolled | Argentina: 81 |
| Country: Number of subjects enrolled | Germany: 103 |
| Country: Number of subjects enrolled | France: 41 |
| Country: Number of subjects enrolled | Australia: 19 |
| Country: Number of subjects enrolled | Austria: 8 |
| Country: Number of subjects enrolled | South Africa: 109 |
| Country: Number of subjects enrolled | Israel: 47 |
| Country: Number of subjects enrolled | Saudi Arabia: 7 |
| Country: Number of subjects enrolled | Russian Federation: 51 |
| Country: Number of subjects enrolled | Ukraine: 26 |
| Worldwide total number of subjects | 1059 |
| EEA total number of subjects | 152 |

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) | 82 |
| Adults (18-64 years) | 807 |
| From 65 to 84 years | 170 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 2420 subjects were enrolled at 297 centres in 18 countries;

Pre-assignment

Screening details:

1061 subjects were randomised to receive treatment with tezepelumab 210mg Q4W or placebo. Of the 1061 randomised, 1059 (99.8%) subjects received treatment. 82 (7.7%) of the subjects randomised and treated were adolescents.

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, Carer, Data analyst, Assessor |

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Tezepelumab 210mg Q4W |

Arm description:

Tezepelumab administered every 4 weeks subcutaneously

| | |
|----------------------------------------|-------------------------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tezepelumab administered every 4 weeks subcutaneously |
| Investigational medicinal product code | |
| Other name | Tezepelumab |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

210 mg Q4W

| | |
|------------------|---------|
| 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 |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Q4W

| Number of subjects in period 1 | Tezepelumab 210mg Q4W | Placebo |
|---------------------------------------|--------------------------|---------|
| Started | 528 | 531 |
| Completed | 513 | 509 |
| Not completed | 15 | 22 |
| Adverse event, serious fatal | - | 2 |
| Consent withdrawn by subject | 8 | 15 |
| Other reasons | 2 | 3 |
| Lost to follow-up | 5 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Tezepelumab 210mg Q4W |
|-----------------------|-----------------------|

Reporting group description:

Tezepelumab administered every 4 weeks subcutaneously

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

Reporting group description:

Placebo administered subcutaneously

| Reporting group values | Tezepelumab 210mg Q4W | Placebo | Total |
|----------------------------------------------------|-----------------------|---------|-------|
| Number of subjects | 528 | 531 | 1059 |
| 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) | 41 | 41 | 82 |
| Adults (18-64 years) | 391 | 416 | 807 |
| From 65-84 years | 96 | 74 | 170 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 49.9 | 49.0 | |
| standard deviation | ± 16.3 | ± 15.9 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 335 | 337 | 672 |
| Male | 193 | 194 | 387 |

End points

End points reporting groups

| | |
|-------------------------------------------------------|-----------------------|
| Reporting group title | Tezepelumab 210mg Q4W |
| Reporting group description: | |
| Tezepelumab administered every 4 weeks subcutaneously | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo administered subcutaneously | |

Primary: Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| End point title | Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma |
| 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 population (Full Analysis Set) | |
| End point type | Primary |
| End point timeframe: | |
| From randomisation to Study Week 52. | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------------------------|-----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: annual rate of event over time at risk | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least squares means (95% confidence interval) | 0.93 (0.80 to 1.07) | 2.10 (1.84 to 2.39) | | |

Statistical analyses

| | |
|-----------------------------------------|---------------------------------|
| Statistical analysis title | Negative binomial analysis |
| Comparison groups | Tezepelumab 210mg Q4W v Placebo |
| Number of subjects included in analysis | 1059 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Negative Binomial |
| Parameter estimate | Rate ratio |
| Point estimate | 0.44 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 0.53 |

Primary: Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma in subjects with baseline eosinophils < 300 cells/uL

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma in subjects with baseline eosinophils < 300 cells/uL |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

From randomisation to Study Week 52.

| | | | | |
|-----------------------------------------------|-----------------------|---------------------|--|--|
| End point values | Tezepelumab 210mg Q4W | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 309 | 309 | | |
| Units: Annual rate of event over time at risk | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least squares means (95% confidence interval) | 1.02 (0.84 to 1.23) | 1.73 (1.46 to 2.05) | | |

Statistical analyses

| | |
|-----------------------------------------|---------------------------------|
| Statistical analysis title | Negative Binomial model |
| Comparison groups | Tezepelumab 210mg Q4W v Placebo |
| Number of subjects included in analysis | 618 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Negative Binomial |
| Parameter estimate | Rate ratio |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 0.75 |

Secondary: Mean change from baseline at Week 52 in pre-bronchodilator FEV1 (L) (key secondary endpoint)

| | |
|-----------------|----------------------------------------------------------------------------------------------|
| End point title | Mean change from baseline at Week 52 in pre-bronchodilator FEV1 (L) (key secondary endpoint) |
|-----------------|----------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 471 | 453 | | |
| Units: Litre | | | | |
| least squares mean (standard error) | | | | |
| Least square means (standard error) | 0.23 (± 0.018) | 0.10 (± 0.018) | | |

Statistical analyses

| | |
|-----------------------------------------|---------------------------------|
| Statistical analysis title | Repeated measures model |
| Comparison groups | Tezepelumab 210mg Q4W v Placebo |
| Number of subjects included in analysis | 924 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.08 |
| upper limit | 0.18 |

Secondary: Mean change from baseline at Week 52 in ACQ-6 (key secondary endpoint)

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|-----------------|------------------------------------------------------------------------|
| End point title | Mean change from baseline at Week 52 in ACQ-6 (key secondary endpoint) |
|-----------------|------------------------------------------------------------------------|

End point description:

| | |
|-------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 485 | 472 | | |
| Units: Scale of score | | | | |
| least squares mean (standard error) | | | | |
| Least squares mean (standard error) | -1.53 (\pm 0.045) | -1.20 (\pm 0.046) | | |

Statistical analyses

| | |
|-----------------------------------------|---------------------------------|
| Statistical analysis title | Repeated measures model |
| Comparison groups | Tezepelumab 210mg Q4W v Placebo |
| Number of subjects included in analysis | 957 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | -0.2 |

Secondary: Mean change from baseline at Week 52 in AQLQ(S)+12 total score (key secondary endpoint)

| | |
|-------------------------------------|-----------------------------------------------------------------------------------------|
| End point title | Mean change from baseline at Week 52 in AQLQ(S)+12 total score (key secondary endpoint) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|-----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 480 | 467 | | |
| Units: Scale of score | | | | |
| least squares mean (standard error) | | | | |
| Least squares mean (standard error) | 1.48 (\pm 0.049) | 1.14 (\pm 0.049) | | |

Statistical analyses

| Statistical analysis title | Repeated measures model |
|-----------------------------------------|---------------------------------|
| Comparison groups | Tezepelumab 210mg Q4W v Placebo |
| Number of subjects included in analysis | 947 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 0.47 |

Secondary: Mean change from baseline at Week 52 in Asthma Symptom Diary (key secondary endpoint)

| | |
|-------------------------------------|---------------------------------------------------------------------------------------|
| End point title | Mean change from baseline at Week 52 in Asthma Symptom Diary (key secondary endpoint) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 374 | 355 | | |
| Units: Scale of score | | | | |
| least squares mean (standard error) | | | | |
| Least squares mean (standard error) | -0.70 (\pm 0.027) | -0.59 (\pm 0.027) | | |

Statistical analyses

| | |
|-----------------------------------------|---------------------------------|
| Statistical analysis title | Repeated measures model |
| Comparison groups | Tezepelumab 210mg Q4W v Placebo |
| Number of subjects included in analysis | 729 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.19 |
| upper limit | -0.04 |

Secondary: Annual asthma exacerbation rate resulting in emergency room visit or hospitalisation

| | |
|-------------------------------------|--------------------------------------------------------------------------------------|
| End point title | Annual asthma exacerbation rate resulting in emergency room visit or hospitalisation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From randomisation to Study Week 52 | |

| | | | | |
|-----------------------------------------------|-----------------------|---------------------|--|--|
| End point values | Tezepelumab 210mg Q4W | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Annual rate of event over time at risk | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least squares mean (95% confidence interval) | 0.06 (0.04 to 0.09) | 0.28 (0.20 to 0.39) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annual asthma exacerbations associated with hospitalisations

End point title Annual asthma exacerbations associated with hospitalisations

End point description:

End point type Secondary

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Annual rate of event over time at risk | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least squares mean (95% Confidence interval) | 0.03 (0.01 to 0.06) | 0.19 (0.12 to 0.30) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annual asthma exacerbation rate using adjudicated data

End point title Annual asthma exacerbation rate using adjudicated data

End point description:

End point type Secondary

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Annual rate of event over time at risk | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least squares mean (95% confidence interval) | 0.94 (0.81 to 1.09) | 2.14 (1.88 to 2.44) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annual asthma exacerbation rate associated with emergency room visit or hospitalisation using adjudicated data

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Annual asthma exacerbation rate associated with emergency room visit or hospitalisation using adjudicated data |
|-----------------|----------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

From randomisation to Study Week 52.

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Annual rate of event over time at risk | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least squares mean (95% confidence interval) | 0.08 (0.05 to 0.12) | 0.31 (0.22 to 0.42) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with ≥ 1 asthma exacerbation and time to first asthma exacerbation

| | |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Proportion of subjects with ≥ 1 asthma exacerbation and time to first asthma exacerbation |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|------------------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Count | | | | |
| Number of subjects with ≥ 1 asthma exacerbation | 231 | 319 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with ≥ 1 asthma exacerbation associated with emergency room visit or hospitalisation and time to first asthma exacerbation associated with emergency room visit or hospitalisation

| | |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Proportion of subjects with ≥ 1 asthma exacerbation associated with emergency room visit or hospitalisation and time to first asthma exacerbation associated with emergency room visit or hospitalisation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|----------------------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Count | | | | |
| Number of subjects with ≥ 1 event | 25 | 65 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who had no asthma exacerbations

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title | Proportion of subjects who had no asthma exacerbations |
| End point description: | |
| The proportion of subjects with no exacerbations is defined as subjects who meet both the following criteria: (1) completed the 52 week treatment period and (2) did not report an exacerbation during this period. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Number of subjects | | | | |
| Number of subjects with no asthma exacerbations | 286 | 205 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with no asthma exacerbations associated with emergency room visit or hospitalisation.

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Proportion of subjects with no asthma exacerbations associated with emergency room visit or hospitalisation. |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

The proportion of subjects with no exacerbations associated with emergency room visit or hospitalisation. is defined as subjects who meet both the following criteria: (1) completed the 52 week treatment period and (2) did not report an exacerbation associated with emergency room visit or hospitalisation.during this period.

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

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Number of subjects | | | | |
| Number of subjects with no events | 488 | 452 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline at Week 52 in clinic FeNO (ppb)

| | |
|-----------------|-----------------------------------------------------------|
| End point title | Mean change from baseline at Week 52 in clinic FeNO (ppb) |
|-----------------|-----------------------------------------------------------|

End point description:

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

End point timeframe:
From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 440 | 426 | | |
| Units: ppb | | | | |
| least squares mean (standard error) | | | | |
| Least squares mean (SE) | -17.29 (\pm 1.156) | -3.46 (\pm 1.165) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline at Week 52 in Eosinophils (cells/uL)

| | |
|------------------------|----------------------------------------------------------------|
| End point title | Mean change from baseline at Week 52 in Eosinophils (cells/uL) |
| End point description: | |

| | |
|-------------------------------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: From randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 458 | 451 | | |
| Units: cells/uL | | | | |
| least squares mean (standard error) | -170.02 (\pm 9.222) | -40.15 (\pm 9.254) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline at Week 52 in IgE (IU/mL)

| | |
|------------------------|-----------------------------------------------------|
| End point title | Mean change from baseline at Week 52 in IgE (IU/mL) |
| End point description: | |

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

End point timeframe:
From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 482 | 471 | | |
| Units: IU/mL | | | | |
| least squares mean (standard error) | -164.38 (\pm 34.414) | 43.61 (\pm 34.542) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in daily rescue medication use at Week 52

| | |
|-----------------|---------------------------------------------------------------------|
| End point title | Mean change from baseline in daily rescue medication use at Week 52 |
|-----------------|---------------------------------------------------------------------|

End point description:

Daily rescue medication use is defined as: Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of daytime inhaler puffs + 2 x [number of day nebulizer times].

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

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 439 | 428 | | |
| Units: weekly mean use | | | | |
| least squares mean (standard error) | -2.53 (\pm 0.137) | -2.36 (\pm 0.137) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in night time awakenings due to asthma at Week 52

| | |
|-----------------|---------------------------------------------------------------|
| End point title | Mean change in night time awakenings due to asthma at Week 52 |
|-----------------|---------------------------------------------------------------|

End point description:

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

End point timeframe:
From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|---------------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 418 | 395 | | |
| Units: percentage of nights with awakenings | | | | |
| least squares mean (standard error) | -33.51 (\pm 1.381) | -30.22 (\pm 1.387) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in home based morning PEF (L/min) at Week 52

| | |
|-----------------|----------------------------------------------------------|
| End point title | Mean change in home based morning PEF (L/min) at Week 52 |
|-----------------|----------------------------------------------------------|

End point description:

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

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 414 | 391 | | |
| Units: Weekly mean (L/min) | | | | |
| least squares mean (standard error) | 34.57 (\pm 3.051) | 18.01 (\pm 3.074) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in home based evening PEF (L/min) at Week 52

| | |
|-----------------|----------------------------------------------------------|
| End point title | Mean change in home based evening PEF (L/min) at Week 52 |
|-----------------|----------------------------------------------------------|

End point description:

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

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 405 | 390 | | |
| Units: weekly mean (L/min) | | | | |
| least squares mean (standard error) | 23.87 (\pm 3.075) | 9.01 (\pm 3.094) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinicians global impression of change at Week 52

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| End point title | Clinicians global impression of change at Week 52 |
| End point description: CGIC (Clinical global impression of change), is an overall evaluation of response to treatment, conducted by investigator using 7-point rating scale, ranging from 1 (very much improved), to 7 (very much worse) | |
| End point type | Secondary |
| End point timeframe: From randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 483 | 477 | | |
| Units: Number of subjects | | | | |
| Very much improved | 96 | 60 | | |
| Much improved | 199 | 132 | | |
| Minimally Improved | 98 | 131 | | |
| No change | 77 | 130 | | |
| Minimally worse | 11 | 19 | | |
| Much worse | 2 | 4 | | |
| Very much worse | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patients global impression of change at Week 52

| | |
|-----------------|-------------------------------------------------|
| End point title | Patients global impression of change at Week 52 |
|-----------------|-------------------------------------------------|

End point description:

PGIC (Patient global impression of change) is an overall evaluation of response to treatment, conducted by the patient using 7-point rating scale, ranging from 1 (very much improved), to 7 (very much worse).

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

End point timeframe:

From randomisation to Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 479 | 466 | | |
| Units: Number of subjects | | | | |
| Very much Improved | 255 | 182 | | |
| Much improved | 103 | 94 | | |
| Minimally improved | 71 | 76 | | |
| No Change | 39 | 99 | | |
| Minimally worse | 6 | 8 | | |
| Much worse | 4 | 6 | | |
| Very much worse | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patients global impression of severity at Week 52

| | |
|-----------------|---------------------------------------------------|
| End point title | Patients global impression of severity at Week 52 |
|-----------------|---------------------------------------------------|

End point description:

PGI-S (Patient global impression of severity) is an overall evaluation of patient's perception of overall symptom severity using a 6-point rating scale, ranging from 0 = No symptoms, 1=Very mild symptoms, 2=Mild symptoms, 3=Moderate symptoms, 4=Severe symptoms, 5=Very severe symptoms

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

End point timeframe:

At Study Week 52

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 479 | 466 | | |
| Units: Number of subjects | | | | |
| No symptoms | 118 | 78 | | |
| Very mild symptoms | 138 | 128 | | |
| Mild symptoms | 110 | 128 | | |
| Moderate symptoms | 99 | 111 | | |
| Severe symptoms | 14 | 19 | | |

| | | | | |
|----------------------|---|---|--|--|
| Very severe symptoms | 0 | 2 | | |
|----------------------|---|---|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of healthcare utilization over 52 weeks

| | |
|-------------------------------------|------------------------------------------------|
| End point title | Number of healthcare utilization over 52 weeks |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| From randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|---------------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 531 | | |
| Units: Number of subjects | | | | |
| Hospitalisation | 17 | 37 | | |
| Emergency room visit | 23 | 50 | | |
| Unscheduled visit to specialist | 187 | 231 | | |
| Home visit | 9 | 10 | | |
| Telephone call | 101 | 133 | | |
| Ambulance transport | 4 | 12 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in work productivity loss due to asthma at Week 52

| | |
|--------------------------------------------|------------------------------------------------------------------------------|
| End point title | Mean change from baseline in work productivity loss due to asthma at Week 52 |
| End point description: | |
| WPAI+CIQ work productivity loss at Week 52 | |
| End point type | Secondary |
| End point timeframe: | |
| From randomisation to Study Week 52 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|--------------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 185 | 177 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -20.16 (± 30.31) | -16.58 (± 29.46) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in class productivity loss due to asthma at Week 52

| | |
|------------------------|--------------------------------------------------------------------------------|
| End point title | Mean change from baseline in class productivity loss due to asthma at Week 52 |
| End point description: | WPAI+CIQ productivity loss at Week 52 for subjects currently attending school. |
| End point type | Secondary |
| End point timeframe: | From randomisation to study week 52 |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|--------------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 19 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -14.03 (± 33.00) | -24.72 (± 26.48) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Activity impairment at Week 52

| | |
|------------------------|-------------------------------------|
| End point title | Activity impairment at Week 52 |
| End point description: | WPAI+CIQ activity impairment |
| End point type | Secondary |
| End point timeframe: | From randomisation to Study Week 52 |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|--------------------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 207 | 196 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -20.0 (± 28.6) | -17.9 (± 27.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of tezepelumab

| | |
|---------------------------------------------------------------|---------------------------------|
| End point title | Pharmacokinetics of tezepelumab |
| End point description: | |
| Mean serum trough PK concentrations at each visit | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 4, Week 12, Week 24, Week 36, Week 52, Week 64 | |

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-----------------------------------------------------|--------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 528 | 0 ^[1] | | |
| Units: ug/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Baseline (n=524) | 0 (± 0) | () | | |
| Week 4 (n=514) | 10.1573 (± 74.51) | () | | |
| Week 12 (n=491) | 18.7396 (± 48.53) | () | | |
| Week 24 (n=461) | 20.1924 (± 51.77) | () | | |
| Week 36 (n=464) | 19.5246 (± 55.58) | () | | |
| Week 52 (n=452) | 19.8894 (± 70.04) | () | | |
| Week 64 (n=72) | 1.7675 (± 171.86) | () | | |

Notes:

[1] - Not applicable since it is not the experimental product.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of tezepelumab

| | |
|-----------------|-------------------------------|
| End point title | Immunogenicity of tezepelumab |
|-----------------|-------------------------------|

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 the first and the 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. Treatment boosted ADA defined as baseline positive ADA that was boosted to a 4 fold or higher level following treatment. Treatment emergent ADA defined as sum of treatment induced ADA and treatment boosted ADA.

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

End point timeframe:

Baseline, and from time of first dose to end of study

| End point values | Tezepelumab 210mg Q4W | Placebo | | |
|-------------------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 527 | 530 | | |
| Units: Number of subjects | | | | |
| ADA positive at baseline and/or post-baseline | 26 | 44 | | |
| Any baseline ADA positive | 17 | 25 | | |
| Only baseline ADA positive | 14 | 8 | | |
| Any post-baseline ADA positive | 12 | 36 | | |
| Both baseline and ≥ 1 post-baseline ADA positive | 3 | 17 | | |
| Treatment induced ADA positive | 9 | 18 | | |
| Treatment boosted ADA positive | 1 | 2 | | |
| Treatment emergent ADA positive | 10 | 20 | | |
| ADA persistently positive | 4 | 18 | | |
| ADA transiently positive | 8 | 18 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline at Week 52 in EQ-5D-5L VAS

| | |
|-----------------|------------------------------------------------------|
| End point title | Mean change from baseline at Week 52 in EQ-5D-5L VAS |
|-----------------|------------------------------------------------------|

End point description:

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

End point timeframe:

At Study Week 52

| | | | | |
|-------------------------------------|--------------------------|--------------------|--|--|
| End point values | Tezepelumab 210mg Q4W | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 448 | 435 | | |
| Units: scale of score | | | | |
| least squares mean (standard error) | 14.64 (± 0.708) | 11.86 (± 0.712) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until last study visit

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Placebo administered subcutaneously

| | |
|-----------------------|-----------------|
| Reporting group title | Teze 210 mg Q4W |
|-----------------------|-----------------|

Reporting group description:

Tezepelumab administered every 4 weeks subcutaneously

| Serious adverse events | Placebo | Teze 210 mg Q4W | |
|---------------------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 75 / 531 (14.12%) | 55 / 528 (10.42%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | 2 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 531 (0.38%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign neoplasm of thyroid gland | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon adenoma | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial cancer | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 2 / 528 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of the oral cavity | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 2 / 528 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|------------------------------------------------------|------------------|------------------|--|
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 42 / 531 (7.91%) | 16 / 528 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 91 | 2 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eosinophilic pneumonia | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal polyps | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incisional hernia | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 2 / 528 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Hypertrophic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Cardiac disorders | | | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 2 / 528 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cubital tunnel syndrome | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Idiopathic generalised epilepsy | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelopathy | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uveitis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticular perforation | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal achalasia | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis necrotising | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Bone cyst | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle necrosis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyarthritis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal stenosis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|--|
| Infections and infestations Anal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 531 (0.00%) 0 / 0 0 / 0 | 1 / 528 (0.19%) 0 / 1 0 / 0 | |
| Atypical pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 531 (0.00%) 0 / 0 0 / 0 | 1 / 528 (0.19%) 0 / 1 0 / 0 | |
| Breast abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 531 (0.00%) 0 / 0 0 / 0 | 1 / 528 (0.19%) 0 / 1 0 / 0 | |
| COVID-19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 531 (0.00%) 0 / 0 0 / 0 | 1 / 528 (0.19%) 0 / 1 0 / 0 | |
| Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 531 (0.38%) 0 / 2 0 / 0 | 0 / 528 (0.00%) 0 / 0 0 / 0 | |
| Diverticulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 531 (0.38%) 0 / 2 0 / 0 | 1 / 528 (0.19%) 0 / 1 0 / 0 | |
| Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 531 (0.38%) 0 / 2 0 / 0 | 1 / 528 (0.19%) 0 / 1 0 / 0 | |
| Gastroenteritis salmonella subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 531 (0.00%) 0 / 0 0 / 0 | 1 / 528 (0.19%) 0 / 1 0 / 0 | |
| Gastroenteritis viral | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster oticus | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 2 / 531 (0.38%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 2 / 528 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 531 (0.38%) | 2 / 528 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 531 (0.00%) | 1 / 528 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 531 (0.19%) | 0 / 528 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Teze 210 mg Q4W | |
|-------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 432 / 531 (81.36%) | 404 / 528 (76.52%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 22 / 531 (4.14%) | 23 / 528 (4.36%) | |
| occurrences (all) | 29 | 27 | |
| Nervous system disorders | | | |

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--|
| Headache subjects affected / exposed occurrences (all) | 48 / 531 (9.04%) 73 | 44 / 528 (8.33%) 102 | |
| General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) | 23 / 531 (4.33%) 27 | 20 / 528 (3.79%) 22 | |
| Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all) | 50 / 531 (9.42%) 61 17 / 531 (3.20%) 25 | 38 / 528 (7.20%) 43 16 / 528 (3.03%) 19 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 14 / 531 (2.64%) 15 16 / 531 (3.01%) 17 8 / 531 (1.51%) 9 | 23 / 528 (4.36%) 29 22 / 528 (4.17%) 27 16 / 528 (3.03%) 17 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Bronchitis bacterial subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis | 34 / 531 (6.40%) 37 18 / 531 (3.39%) 21 15 / 531 (2.82%) 17 | 27 / 528 (5.11%) 41 25 / 528 (4.73%) 27 17 / 528 (3.22%) 18 | |

| | | |
|-----------------------------------------|--------------------|--------------------|
| subjects affected / exposed | 118 / 531 (22.22%) | 115 / 528 (21.78%) |
| occurrences (all) | 195 | 174 |
| Pharyngitis | | |
| subjects affected / exposed | 17 / 531 (3.20%) | 17 / 528 (3.22%) |
| occurrences (all) | 19 | 18 |
| Rhinitis | | |
| subjects affected / exposed | 19 / 531 (3.58%) | 15 / 528 (2.84%) |
| occurrences (all) | 40 | 19 |
| Sinusitis | | |
| subjects affected / exposed | 40 / 531 (7.53%) | 21 / 528 (3.98%) |
| occurrences (all) | 57 | 26 |
| Upper respiratory tract infection | | |
| subjects affected / exposed | 92 / 531 (17.33%) | 60 / 528 (11.36%) |
| occurrences (all) | 133 | 98 |
| Urinary tract infection | | |
| subjects affected / exposed | 23 / 531 (4.33%) | 23 / 528 (4.36%) |
| occurrences (all) | 27 | 36 |
| Viral upper respiratory tract infection | | |
| subjects affected / exposed | 13 / 531 (2.45%) | 17 / 528 (3.22%) |
| occurrences (all) | 21 | 21 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 November 2017 | Inclusion of St George's Respiratory Questionnaire, clarifications on outcomes of secondary endpoints, amended inclusion/exclusion criteria, changes to concomitant medication |
| 16 March 2018 | Change in collection times of SNOT-22, added details regarding enrolment in separate extension study, clarification on adjudication committee, amended inclusion/exclusion criteria, clarification on concomitant/prohibited medication |
| 15 April 2019 | Neutralizing antibodies moved to exploratory endpoint, additional of baseline eosinophils <300/uL subgroup into the confirmatory hierarchical testing strategy, revised inclusion/exclusion criteria, clarification on dose preparation/administration, clarification on laboratories requiring treatment information for sample analyses, addition of a primary database lock, clarification on procedures for discontinuation of IP, |
| 14 May 2020 | Added appendix with guidance for changes related to the COVID-19 pandemic, clarification on subjects enrolling into long term extension study can continue with follow-up visits until an on-site visit is possible, clarification on schedule of assessments due to the COVID-19 pandemic, secondary endpoint proportion of subjects with ≥ 1 asthma exacerbation updated to proportion of subjects who did not experience an asthma exacerbation, clarification that pulmonology, cardiology, neurology and oncology specialists will form part of the independent adjudication committee, safety reporting period updated from post-treatment to on-study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported