



Clinical trial results:

A phase III, multicenter, randomized, double blind, placebo-controlled study evaluating the efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with stages AJCC/UICC v. 8 II -IIIA and IIIB (T>5cm N2) completely resected (R0) non-small cell lung cancer (NSCLC)

Summary

| | |
|--------------------------|--|
| EudraCT number | 2017-004011-39 |
| Trial protocol | DE GR GB FR IT ES NO AT PT CZ PL BG HU SI IS IE RO |
| Global end of trial date | 07 February 2023 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 12 January 2024 |
| First version publication date | 12 January 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CACZ885T2301 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03447769 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 07 February 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 February 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the study was to compare the efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with stages II -IIIA according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) version 8 criteria and the subset of IIIB (T>5cm N2 disease) completely resected (R0) non-small cell lung cancer (NSCLC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 16 March 2018 |
| 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 | Austria: 18 |
| Country: Number of subjects enrolled | Brazil: 14 |
| Country: Number of subjects enrolled | Bulgaria: 8 |
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | Argentina: 14 |
| Country: Number of subjects enrolled | Chile: 9 |
| Country: Number of subjects enrolled | China: 100 |
| Country: Number of subjects enrolled | Colombia: 1 |
| Country: Number of subjects enrolled | Czechia: 5 |
| Country: Number of subjects enrolled | France: 99 |
| Country: Number of subjects enrolled | Georgia: 21 |
| Country: Number of subjects enrolled | Germany: 131 |
| Country: Number of subjects enrolled | Greece: 50 |
| Country: Number of subjects enrolled | Hong Kong: 13 |
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | Iceland: 5 |
| Country: Number of subjects enrolled | India: 7 |
| Country: Number of subjects enrolled | Israel: 4 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Italy: 68 |
| Country: Number of subjects enrolled | Japan: 167 |
| Country: Number of subjects enrolled | Jordan: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 58 |
| Country: Number of subjects enrolled | Lebanon: 13 |
| Country: Number of subjects enrolled | Malaysia: 19 |
| Country: Number of subjects enrolled | Norway: 13 |
| Country: Number of subjects enrolled | Panama: 4 |
| Country: Number of subjects enrolled | Peru: 3 |
| Country: Number of subjects enrolled | Philippines: 2 |
| Country: Number of subjects enrolled | Poland: 28 |
| Country: Number of subjects enrolled | Portugal: 9 |
| Country: Number of subjects enrolled | Romania: 16 |
| Country: Number of subjects enrolled | Russian Federation: 157 |
| Country: Number of subjects enrolled | Slovenia: 4 |
| Country: Number of subjects enrolled | Spain: 50 |
| Country: Number of subjects enrolled | Switzerland: 11 |
| Country: Number of subjects enrolled | Taiwan: 63 |
| Country: Number of subjects enrolled | Thailand: 39 |
| Country: Number of subjects enrolled | Türkiye: 32 |
| Country: Number of subjects enrolled | United Kingdom: 48 |
| Country: Number of subjects enrolled | United States: 50 |
| Country: Number of subjects enrolled | Viet Nam: 9 |
| Worldwide total number of subjects | 1382 |
| 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) | 0 |
| Adults (18-64 years) | 836 |
| From 65 to 84 years | 546 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 290 centers in 41 countries. A total of 1830 subjects were screened of which 1382 participants were randomized to treatment on a 1:1 basis.

Pre-assignment

Screening details:

1 participant randomized in the canakinumab arm was never treated due to subject decision. The numbers in the patient disposition table correspond to the treatment period.

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 | Canakinumab |

Arm description:

Participants receive 200mg of canakinumab subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks)

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Canakinumab |
| Investigational medicinal product code | ACZ885 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

200 mg of canakinumab administered subcutaneously on day 1 of every 21-day cycle for 18 cycles. Canakinumab solution for injection was provided by Novartis as ready-to-use pre-filled syringes to be administered by study personnel.

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

Arm description:

Participants receive canakinumab placebo subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks)

| | |
|--|------------------------|
| 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:

Placebo administered subcutaneously on day 1 of every 21-day cycle for 18 cycles. Placebo solution for injection was provided by Novartis as ready-to-use pre-filled syringes to be administered by study personnel

| Number of subjects in period 1 | Canakinumab | Placebo |
|---------------------------------------|-------------|---------|
| Started | 693 | 689 |
| Treated | 692 | 689 |
| Completed | 414 | 420 |
| Not completed | 279 | 269 |
| Adverse event, serious fatal | 2 | 7 |
| Patient decision | 27 | 27 |
| Physician decision | 13 | 5 |
| Study terminated by Sponsor | 60 | 44 |
| Adverse event, non-fatal | 34 | 31 |
| Technical problems | 1 | - |
| Protocol deviation | 4 | 6 |
| Progressive disease | 138 | 148 |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|-------------|
| Reporting group title | Canakinumab |
| Reporting group description: | |
| Participants receive 200mg of canakinumab subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks) | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants receive canakinumab placebo subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks) | |

| Reporting group values | Canakinumab | Placebo | Total |
|--|-------------|---------|-------|
| Number of subjects | 693 | 689 | 1382 |
| 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) | 0 | 0 | 0 |
| Adults (18-64 years) | 414 | 422 | 836 |
| From 65-84 years | 279 | 267 | 546 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 61.5 | 61.6 | |
| standard deviation | ± 8.90 | ± 9.00 | - |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 263 | 257 | 520 |
| Male | 430 | 432 | 862 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 393 | 391 | 784 |
| Asian | 248 | 236 | 484 |
| Black or African American | 3 | 4 | 7 |
| American Indian or Alaska Native | 0 | 5 | 5 |
| Multiple | 0 | 1 | 1 |
| Missing | 49 | 52 | 101 |

End points

End points reporting groups

| | |
|---|-------------|
| Reporting group title | Canakinumab |
| Reporting group description: | |
| Participants receive 200mg of canakinumab subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks) | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants receive canakinumab placebo subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks) | |

Primary: Disease free survival (DFS) by local investigator

| | |
|--|---|
| End point title | Disease free survival (DFS) by local investigator |
| End point description: | |
| DFS is the time from the date of randomization to the date of the first documented NSCLC disease recurrence as assessed by local investigator radiologically or death due to any cause. Disease recurrence included diagnoses of new primary lung malignancies. Clinical deterioration was not considered as a recurrence of disease. In case of non-conclusive radiological evidence, a biopsy assessment was performed to confirm NSCLC recurrence. The median DFS was estimated using the Kaplan-Meier method. DFS was censored if no DFS event was observed prior to the analysis cut-off date or subjects who received any subsequent anti-neoplastic therapy for NSCLC. The censoring date was the date of last assessment before the cut-off date or NSCLC related anti-neoplastic therapy date. 9999 indicates the value was not estimable | |
| End point type | Primary |
| End point timeframe: | |
| Up to approximately 4 years | |

| End point values | Canakinumab | Placebo | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 693 | 689 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 35.02 (28.55 to 9999) | 29.73 (23.72 to 9999) | | |

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | DFS: Canakinumab vs Placebo |
| Comparison groups | Canakinumab v Placebo |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 1382 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.258 ^[1] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 1.14 |

Notes:

[1] - 1-sided p-value

Secondary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| Overall Survival (OS) is the time from the date of randomization to the date of death due to any cause. The OS was censored at the latest date the subject was known to be alive. The OS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier medians and 95% confidence intervals of the medians were presented for each treatment group. 9999 indicates that the value was not estimable | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 4.3 years | |

| End point values | Canakinumab | Placebo | | |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 693 | 689 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 51.12 (46.95 to 9999) | 9999 (-9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in PD-L1 subgroups

| | |
|--|--|
| End point title | Overall Survival (OS) in PD-L1 subgroups |
| End point description: | |
| Overall Survival (OS) is the time from the date of randomization to the date of death due to any cause. The OS was censored at the latest date the subject was known to be alive. The OS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians were presented for each treatment group. OS analysis was performed by programmed cell death-ligand 1 (PD-L1) expression status: PD-L1 <1%, PD-L1 ≥1% and <49%, and PD-L1 ≥50%. 9999 indicates that the value was not estimable | |

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 4.3 years | |

| End point values | Canakinumab | Placebo | | |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 396 | 418 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| PD-L1 <1% (n= 211 / 203) | 9999 (-9999 to 9999) | 9999 (-9999 to 9999) | | |
| PD-L1 ≥1% and <49% (n=99 / 119) | 46.95 (22.11 to 9999) | 9999 (-9999 to 9999) | | |
| PD-L1 ≥50% (n=86 / 96) | 51.12 (-9999 to 9999) | 9999 (-9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in CD8 subgroups

| | |
|--|--|
| End point title | Overall Survival (OS) in CD8 subgroups |
| End point description: | |
| Overall Survival (OS) is the time from the date of randomization to the date of death due to any cause. The OS was censored at the latest date the subject was known to be alive. The OS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier medians and 95% confidence intervals of the medians were presented for each treatment group. OS analysis was performed by CD8 subgroups with the median of baseline CD8 expression as cut-off. 9999 indicates that the value was not estimable | |
| End point type | Secondary |
| End point timeframe: | |
| up to approximately 4.3 years | |

| End point values | Canakinumab | Placebo | | |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 429 | 449 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| CD8 < median (n= 213 / 225) | 46.95 (32.23 to 9999) | 9999 (-9999 to 9999) | | |
| CD8 ≥ median (n= 216 / 224) | 51.12 (-9999 to 9999) | 9999 (-9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Lung Cancer Specific Survival (LCSS)

| | |
|-----------------|--------------------------------------|
| End point title | Lung Cancer Specific Survival (LCSS) |
|-----------------|--------------------------------------|

End point description:

LCSS is defined as the time from date of randomization to the date of death due to lung cancer. The LCSS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier medians and 95% confidence intervals of the medians were presented for each treatment group.

9999 indicates that the value was not estimable

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

End point timeframe:

Up to approximately 4.3 years

| End point values | Canakinumab | Placebo | | |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 693 | 689 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 51.12 (44.71 to 9999) | 9999 (-9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease free survival (DFS) by local investigator in PD-L1 subgroups

| | |
|-----------------|--|
| End point title | Disease free survival (DFS) by local investigator in PD-L1 subgroups |
|-----------------|--|

End point description:

DFS is the time from the date of randomization to the date of the first documented NSCLC disease recurrence as assessed by local investigator radiologically or death due to any cause. Disease recurrence included diagnoses of new primary lung malignancies. Clinical deterioration was not considered as a recurrence of disease. In case of non-conclusive radiological evidence, a biopsy assessment was performed to confirm NSCLC recurrence.

The median DFS was estimated using the Kaplan-Meier method. DFS was censored if no DFS event was observed prior to the analysis cut-off date or subjects who received any subsequent anti-neoplastic therapy for NSCLC. The censoring date was the date of last assessment before the cut-off date or NSCLC related anti-neoplastic therapy date.

DFS analysis was performed by baseline programmed cell death-ligand 1 (PD-L1) expression status: PD-L1 <1%, PD-L1 ≥1% and <49%, and PD-L1 ≥50%.

9999 indicates that the value was not estimable

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

End point timeframe:

Up to approximately 4 years

| End point values | Canakinumab | Placebo | | |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 396 | 418 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| PD-L1 <1% (n= 211 / 203) | 30.72 (23.52 to 9999) | 9999 (23.03 to 9999) | | |
| PD-L1 ≥1% and <49% (n= 99 / 119) | 30.42 (21.42 to 9999) | 9999 (17.05 to 9999) | | |
| PD-L1 ≥50% (n = 86 / 96) | 46.95 (19.45 to 9999) | 9999 (22.31 to 9999) | | |

Statistical analyses

| Statistical analysis title | DFS in PD-L1 subgroups: Canakinumab vs Placebo |
|---|--|
| Statistical analysis description: | |
| PD-L1 <1% | |
| Comparison groups | Canakinumab v Placebo |
| Number of subjects included in analysis | 814 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.676 ^[2] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.58 |

Notes:

[2] - 1-sided p-value

| Statistical analysis title | DFS in PD-L1 subgroups: Canakinumab vs Placebo |
|---|--|
| Statistical analysis description: | |
| PD-L1 ≥50% | |
| Comparison groups | Canakinumab v Placebo |
| Number of subjects included in analysis | 814 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.823 ^[3] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 2.43 |

Notes:

[3] - 1-sided p-value

| | |
|---|--|
| Statistical analysis title | DFS in PD-L1 subgroups: Canakinumab vs Placebo |
| Statistical analysis description: | |
| PD-L1 $\geq 1\%$ and $< 49\%$ | |
| Comparison groups | Canakinumab v Placebo |
| Number of subjects included in analysis | 814 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.036 [4] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.34 |
| upper limit | 1.05 |

Notes:

[4] - 1-sided p-value

Secondary: Disease free survival (DFS) by local investigator in CD8 subgroups

| | |
|---|--|
| End point title | Disease free survival (DFS) by local investigator in CD8 subgroups |
| End point description: | |
| <p>DFS is the time from the date of randomization to the date of the first documented NSCLC disease recurrence as assessed by local investigator radiologically or death due to any cause. Disease recurrence included diagnoses of new primary lung malignancies. Clinical deterioration was not considered as a recurrence of disease. In case of non-conclusive radiological evidence, a biopsy assessment was performed to confirm NSCLC recurrence.</p> <p>The median DFS was estimated using the Kaplan-Meier method. DFS was censored if no DFS event was observed prior to the analysis cut-off date or subjects who received any subsequent anti-neoplastic therapy for NSCLC. The censoring date was the date of last assessment before the cut-off date or NSCLC related anti-neoplastic therapy date.</p> <p>DFS analysis was performed by CD8 subgroups with the median of baseline CD8 expression as cut-off. 9999 indicates that the value was not estimable</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 4 years | |

| End point values | Canakinumab | Placebo | | |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 429 | 449 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| CD8 < median (n= 213 / 225) | 26.58 (20.67 to 9999) | 9999 (25.03 to 9999) | | |
| CD8 \geq median (n= 216 / 224) | 46.95 (28.81 to 9999) | 9999 (23.89 to 9999) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | DFS in CD8 subgroups: Canakinumab vs Placebo |
| Statistical analysis description: CD8 \geq median | |
| Comparison groups | Canakinumab v Placebo |
| Number of subjects included in analysis | 878 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.303 ^[5] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.33 |

Notes:

[5] - 1-sided p-value

| | |
|---|--|
| Statistical analysis title | DFS in CD8 subgroups: Canakinumab vs Placebo |
| Statistical analysis description: CD8 < median | |
| Comparison groups | Canakinumab v Placebo |
| Number of subjects included in analysis | 878 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.872 ^[6] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.72 |

Notes:

[6] - 1-sided p-value

Secondary: Canakinumab serum concentrations

| | |
|-----------------|---|
| End point title | Canakinumab serum concentrations ^[7] |
|-----------------|---|

End point description:

Serum concentrations of canakinumab were determined using an ELISA method.

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

End point timeframe:

Cycle 1 on day 1 (pre-dose), day 8 and 15; Cycle 2, 4, 6, 9 and 12 on day 1 (pre-dose). Cycle=21 days

Notes:

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

Justification: Only participants who received canakinumab were included in this analysis

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Canakinumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 664 | | | |
| Units: ug/ml | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n= 664) | 0 (± 0) | | | |
| Cycle 1 Day 8 (n= 569) | 18.1 (± 6.53) | | | |
| Cycle 1 Day 15 (n= 611) | 16.9 (± 5.43) | | | |
| Cycle 2 Day 1 (n= 636) | 15.0 (± 4.91) | | | |
| Cycle 4 Day 1 (n= 611) | 29.7 (± 10.3) | | | |
| Cycle 6 Day 1 (n= 559) | 34.7 (± 13.0) | | | |
| Cycle 9 Day 1 (n=530) | 37.1 (± 14.5) | | | |
| Cycle 12 Day 1 (n=502) | 38.6 (± 15.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Canakinumab Anti-drug Antibody (ADA) prevalence at baseline

| | |
|-----------------|--|
| End point title | Canakinumab Anti-drug Antibody (ADA) prevalence at |
|-----------------|--|

End point description:

Canakinumab ADA prevalence at baseline was calculated as the percentage of participants who had an ADA positive result at baseline

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

End point timeframe:

Baseline

Notes:

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

Justification: Only participants who received canakinumab were included in this analysis

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Canakinumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 692 | | | |
| Units: Participants | 8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Canakinumab ADA incidence

| | |
|---|--|
| End point title | Canakinumab ADA incidence ^[9] |
| End point description: Canakinumab ADA incidence on-treatment was calculated as the percentage of participants who were treatment-induced ADA positive (post-baseline ADA positive with ADA-negative sample at baseline) and treatment-boosted ADA positive (post-baseline ADA positive with titer that was at least the fold titer change greater than the ADA-positive baseline titer) | |
| End point type | Secondary |
| End point timeframe: From baseline up to 130 days after end of treatment, assessed up to approx. 1.5 years | |
| Notes: [9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only participants who received canakinumab were included in this analysis | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Canakinumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 692 | | | |
| Units: Participants | 7 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive 10 point deterioration symptom scores of pain,cough and dyspnea per European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ)- Lung cancer (LC) 13 questionnaire

| | |
|---|--|
| End point title | Time to definitive 10 point deterioration symptom scores of pain,cough and dyspnea per European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ)- Lung cancer (LC) 13 questionnaire |
| End point description: The Lung Cancer module of the EORTC's quality of life questionnaire (EORTC QLQ-LC13) was used in conjunction with the EORTC QLQ-C30 and provided information on an additional 13 items specifically related to lung cancer. The lung cancer module incorporated one multi-item scale to assess dyspnea, and 9 single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. All of the domain scores ranged from 0 to 100. A high score indicated a high level of symptoms. The time to definitive 10 point deterioration symptom scores of pain, cough and dyspnea was defined as the time from the date of randomization to the date of event, which was defined as at least 10 points relative to baseline worsening of the EORTC QLQ-LC13 symptom score with no later change below this threshold or death due to any cause, whichever occurred earlier. 9999 indicates that the value was not estimable | |
| End point type | Secondary |
| End point timeframe: From baseline up to approximately 4 years | |

| End point values | Canakinumab | Placebo | | |
|----------------------------------|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 693 | 689 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Pain | 9999 (35.45 to 9999) | 9999 (-9999 to 9999) | | |
| Cough | 9999 (35.06 to 9999) | 9999 (34.99 to 9999) | | |
| Dyspnea | 28.88 (23.10 to 34.96) | 34.99 (23.13 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive 10 point deterioration of global health status/quality of life (QoL), shortness of breath and pain per EORTC QLQ-C30 questionnaire

| | |
|-----------------|---|
| End point title | Time to definitive 10 point deterioration of global health status/quality of life (QoL), shortness of breath and pain per EORTC QLQ-C30 questionnaire |
|-----------------|---|

End point description:

The EORTC QLQ-C30 was a questionnaire developed to assess the health-related quality of life of cancer participants. It assessed 15 domains consisting of 5 functional domains and 9 symptom domains and a global health status/QoL scale. All domain scores ranged from 0 to 100. A high score for the functional or global health status scales indicated a high level of functioning or QoL; a high score for a symptom scale indicated a high level of symptoms.

The time to definitive 10 point deterioration of global health status/QoL, shortness of breath and pain was defined as the time from the date of randomization to the date of event, which was defined as at least 10 points relative to baseline worsening of the score with no later change below this threshold or death due to any cause, whichever occurred earlier.

9999 indicates that the value was not estimable

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

End point timeframe:

From baseline up to approximately 4 years

| End point values | Canakinumab | Placebo | | |
|----------------------------------|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 693 | 689 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Global health status/QoL | 34.99 (29.93 to 9999) | 35.15 (35.15 to 9999) | | |
| Shortness of breath | 9999 (-9999 to 9999) | 35.15 (34.99 to 9999) | | |
| Pain | 29.93 (28.29 to 35.22) | 36.44 (34.99 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first 10 point deterioration for symptom scores of pain, cough and dyspnea per EORTC QLQ-LC13 questionnaire

| | |
|-----------------|---|
| End point title | Time to first 10 point deterioration for symptom scores of pain, cough and dyspnea per EORTC QLQ-LC13 questionnaire |
|-----------------|---|

End point description:

The Lung Cancer module of the EORTC's quality of life questionnaire (EORTC QLQ-LC13) was used in conjunction with the EORTC QLQ-C30 and provided information on an additional 13 items specifically related to lung cancer. The lung cancer module incorporated one multi-item scale to assess dyspnea, and 9 single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. All of the domain scores ranged from 0 to 100. A high score indicated a high level of symptoms.

The time to first 10 point deterioration symptom scores of pain, cough and dyspnea was defined as the time from the date of randomization to the first onset of at least 10 points absolute increase from baseline (worsening) in symptoms scores or death due to any cause, whichever occurred earlier.

9999 indicates that the value was not estimable

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

End point timeframe:

From baseline up to approximately 4 years

| End point values | Canakinumab | Placebo | | |
|----------------------------------|------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 693 | 689 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Pain | 35.15 (26.58 to 9999) | 9999 (23.06 to 9999) | | |
| Cough | 15.44 (10.38 to 23.06) | 15.01 (9.69 to 9999) | | |
| Dyspnea | 4.17 (3.42 to 5.55) | 4.86 (3.48 to 6.97) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first 10 point deterioration of global health status/QoL, shortness of breath and pain per EORTC QLQ-C30 questionnaire

| | |
|-----------------|--|
| End point title | Time to first 10 point deterioration of global health status/QoL, shortness of breath and pain per EORTC QLQ-C30 questionnaire |
|-----------------|--|

End point description:

The EORTC QLQ-C30 was a questionnaire developed to assess the health-related quality of life of cancer participants. It assessed 15 domains consisting of 5 functional domains (physical, role, emotional, cognitive, social) and 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and a global health status/QoL scale. All domain scores ranged from 0 to 100. A high score for the functional or global health status scales indicated a high level of functioning or QoL; a high score for a symptom scale indicated a high level of symptoms.

The time to first 10 point deterioration of global health status/QoL, shortness of breath and pain scores

was defined as the time from the date of randomization to the first onset of at least 10 points absolute increase from baseline (worsening) in symptoms scores or death due to any cause, whichever occurred earlier.

9999 indicates that the value was not estimable

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From baseline up to approximately 4 years | |

| End point values | Canakinumab | Placebo | | |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 693 | 689 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Global health status/QoL | 9.23 (7.10 to 11.76) | 9.07 (7.62 to 11.76) | | |
| Shortness of breath | 29.14 (23.03 to 9999) | 9999 (23.13 to 9999) | | |
| Pain | 5.49 (4.21 to 6.90) | 5.62 (4.17 to 7.62) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the utility scores of the EuroQoL- 5 dimension- 5 level (EQ-5D-5L)

| | |
|-----------------|--|
| End point title | Change from baseline in the utility scores of the EuroQoL- 5 dimension- 5 level (EQ-5D-5L) |
|-----------------|--|

End point description:

EQ-5D-5L was a standardized participant completed questionnaire that measured health-related QoL and translated that score into an index value or utility score. EQ-5D-5L consisted of two components: a health state profile and a visual analogue scale (VAS). EQ-5D health state profile was comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension had 5 levels: from 1= no problems to 5= extreme problems. Higher scores indicated greater levels of problems across each of the five dimensions. A negative change from baseline indicated improvement. This endpoint was assessed throughout the study, including safety and efficacy follow-up (FU) visits. Safety FU visits: every 4 weeks after end of treatment up to 130 days post-last dose. Efficacy FU visits: at 18, 24, 30, 36 and 48 months post-randomization (if no recurrence observed during treatment or safety FU).

9999 indicates that the value was not estimable

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

End point timeframe:

Baseline, every 3 weeks for 14 months; end of treatment; every 4 weeks up to 130 days post-treatment; at 18,24,30,36 and 48 months post-randomization (if no recurrence); 7 and 28 days post-disease progression, up to approx. 4 years.

| End point values | Canakinumab | Placebo | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 643 | 630 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 3 (n= 643 /630) | 0.9 (± 14.67) | 0.6 (± 9.91) | | |
| Week 6 (n= 626 /615) | 0.9 (± 10.80) | 0.6 (± 10.35) | | |
| Week 9 (n= 619 /603) | 1.0 (± 11.45) | 0.4 (± 11.35) | | |
| Week 12 (n= 619 /604) | 0.8 (± 11.23) | 0.6 (± 11.35) | | |
| Week 15 (n= 565 /555) | 1.1 (± 11.75) | 1.1 (± 11.21) | | |
| Week 18 (n= 534 /529) | 1.5 (± 12.76) | 1.5 (± 12.08) | | |
| Week 21 (n= 517 /520) | 1.0 (± 12.53) | 1.4 (± 11.76) | | |
| Week 24 (n=505 /505) | 1.2 (± 12.56) | 1.3 (± 11.34) | | |
| Week 27 (n= 468/479) | 1.9 (± 11.89) | 1.7 (± 11.75) | | |
| Week 30 (n=455/450) | 1.6 (± 14.96) | 1.6 (± 11.71) | | |
| Week 33 (n=437/444) | 1.4 (± 12.84) | 1.8 (± 11.81) | | |
| Week 36 (n=423/431) | 0.5 (± 12.94) | 1.4 (± 11.94) | | |
| Week 39 (n=394/407) | 1.2 (± 12.99) | 1.2 (± 12.23) | | |
| Week 42 (n=377/389) | 1.1 (± 14.19) | 1.3 (± 12.42) | | |
| Week 45 (371/368) | 1.5 (± 13.60) | 1.0 (± 12.45) | | |
| Week 48 (n=348/353) | 1.7 (± 13.77) | 1.4 (± 12.17) | | |
| Week 51 (n=315/336) | 1.8 (± 13.49) | 1.6 (± 13.47) | | |
| Week 54 (n=11/10) | -0.4 (± 20.75) | 13.5 (± 19.98) | | |
| Week 57 (n=0/1) | 9999 (± 9999) | 16.0 (± 9999) | | |
| Week 60 (n=0/1) | 9999 (± 9999) | 10.0 (± 9999) | | |
| Safety FU 1 (n=302/323) | 1.9 (± 14.00) | 1.2 (± 13.16) | | |
| Safety FU 2 (n=280/295) | 1.9 (± 13.99) | 1.4 (± 12.79) | | |
| Safety FU 3 (n=269/271) | 1.8 (± 14.36) | 0.5 (± 12.72) | | |
| Safety FU 4 (n=239/250) | 3.0 (± 13.90) | 0.7 (± 13.94) | | |
| Safety FU 5 (n=229/228) | 2.5 (± 14.31) | 1.6 (± 12.36) | | |
| Efficacy FU 1 (n=172/173) | 1.7 (± 13.56) | 0.8 (± 12.10) | | |
| Efficacy FU 2 (n=132/125) | 1.3 (± 13.41) | 2.2 (± 12.20) | | |
| Efficacy FU 3 (n=74/66) | 1.8 (± 15.56) | 2.2 (± 15.18) | | |
| Efficacy FU 4 (n=30/25) | 2.6 (± 16.57) | 5.4 (± 16.49) | | |
| Efficacy FU 5 (n=1/0) | 2.0 (± 9999) | 9999 (± 9999) | | |
| 7 days post disease progression (n=26/19) | -5.0 (± 17.50) | -9.2 (± 16.87) | | |
| 28 days post disease progression (n=79/62) | -9.0 (± 15.86) | -6.5 (± 16.11) | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

| | |
|-----------------|----------------------|
| End point title | All collected deaths |
|-----------------|----------------------|

End point description:

Pre-treatment deaths were collected from day of participant's informed consent to the day before first dose of study medication.

On-treatment deaths were collected from start of treatment to 130 days after last dose.

Post-treatment follow-up deaths were collected from day 131 after last dose of study treatment to end of study.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Pre-treatment: Up to 28 days prior to treatment. On-treatment: Up to approx. 1.5 years. Post-treatment follow-up: Up to approx. 4.3 years

| End point values | Canakinumab | Placebo | | |
|---------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 693 | 689 | | |
| Units: Participants | | | | |
| Pre-treatment deaths | 0 | 0 | | |
| On-treatment deaths | 9 | 17 | | |
| Post-treatment follow-up deaths | 53 | 51 | | |
| All deaths | 62 | 68 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment to 130 days after last dose of study medication (on-treatment), up to approx. 1.5 years.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Canakinumab |
|-----------------------|-------------|

Reporting group description:

Canakinumab

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

Reporting group description:

Placebo

| Serious adverse events | Canakinumab | Placebo | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 141 / 692 (20.38%) | 146 / 689 (21.19%) | |
| number of deaths (all causes) | 9 | 17 | |
| number of deaths resulting from adverse events | 0 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 3 / 692 (0.43%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm swelling | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer stage 0 | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|-----------------|--|
| Asthenia | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (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 | | | |
| Cough | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 3 / 689 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 7 / 692 (1.01%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 692 (0.43%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 3 / 692 (0.43%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 692 (0.43%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord polyp | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Schizophrenia | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 3 / 689 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram T wave amplitude decreased | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Influenza A virus test positive subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SARS-CoV-2 test positive subjects affected / exposed | 3 / 692 (0.43%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Head injury subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| 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 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pneumothorax subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Spinal compression fracture subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents subjects affected / exposed | 0 / 692 (0.00%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac disorders | | | |
| Acute coronary syndrome subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Angina pectoris subjects affected / exposed | 3 / 692 (0.43%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation subjects affected / exposed | 2 / 692 (0.29%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 4 / 689 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pericarditis constrictive | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Peripheral nerve palsy | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 4 / 692 (0.58%) | 4 / 689 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulnar nerve palsy | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic cerebral infarction | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |

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|---|-----------------|-----------------|--|
| Vertigo | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal tear | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhegmatogenous retinal detachment | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 692 (0.43%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal pain | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar hernia | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic cyst | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (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 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder obstruction | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis acute | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 3 / 689 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |

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|---|-----------------|-----------------|--|
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal haemorrhage | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue | | | |

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|---|------------------|------------------|--|
| disorders | | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 3 / 689 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tenosynovitis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 48 / 692 (6.94%) | 48 / 689 (6.97%) | |
| occurrences causally related to treatment / all | 0 / 50 | 2 / 50 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asymptomatic COVID-19 | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Bronchitis | | | |
| subjects affected / exposed | 2 / 692 (0.29%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 4 / 689 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronavirus infection | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection parasitic | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 13 / 692 (1.88%) | 9 / 689 (1.31%) | |
| occurrences causally related to treatment / all | 1 / 13 | 2 / 10 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 692 (0.00%) | 2 / 689 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 0 / 689 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 692 (0.14%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 692 (0.00%) | 1 / 689 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Canakinumab | Placebo | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 465 / 692 (67.20%) | 455 / 689 (66.04%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 65 / 692 (9.39%) | 49 / 689 (7.11%) | |
| occurrences (all) | 102 | 68 | |
| Amylase increased | | | |
| subjects affected / exposed | 52 / 692 (7.51%) | 51 / 689 (7.40%) | |
| occurrences (all) | 83 | 70 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 53 / 692 (7.66%) | 37 / 689 (5.37%) | |
| occurrences (all) | 76 | 45 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 35 / 692 (5.06%) | 18 / 689 (2.61%) | |
| occurrences (all) | 93 | 30 | |
| Weight increased | | | |
| subjects affected / exposed | 63 / 692 (9.10%) | 48 / 689 (6.97%) | |
| occurrences (all) | 90 | 68 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 45 / 692 (6.50%) | 13 / 689 (1.89%) | |
| occurrences (all) | 105 | 23 | |
| Lipase increased | | | |
| subjects affected / exposed | 47 / 692 (6.79%) | 47 / 689 (6.82%) | |
| occurrences (all) | 68 | 79 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 35 / 692 (5.06%) | 24 / 689 (3.48%) | |
| occurrences (all) | 40 | 27 | |
| Nervous system disorders | | | |
| Paraesthesia | | | |
| subjects affected / exposed | 29 / 692 (4.19%) | 44 / 689 (6.39%) | |
| occurrences (all) | 32 | 48 | |
| Headache | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 31 / 692 (4.48%) 37 | 60 / 689 (8.71%) 72 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 46 / 692 (6.65%) 57 | 50 / 689 (7.26%) 56 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) | 70 / 692 (10.12%) 92 28 / 692 (4.05%) 30 47 / 692 (6.79%) 61 | 60 / 689 (8.71%) 84 43 / 689 (6.24%) 47 33 / 689 (4.79%) 38 | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 34 / 692 (4.91%) 38 57 / 692 (8.24%) 84 46 / 692 (6.65%) 63 | 42 / 689 (6.10%) 56 48 / 689 (6.97%) 66 51 / 689 (7.40%) 61 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) | 67 / 692 (9.68%) 80 89 / 692 (12.86%) 117 | 50 / 689 (7.26%) 55 108 / 689 (15.67%) 143 | |
| Skin and subcutaneous tissue disorders Pruritus | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 35 / 692 (5.06%) 43 | 34 / 689 (4.93%) 37 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 74 / 692 (10.69%) | 88 / 689 (12.77%) | |
| occurrences (all) | 83 | 108 | |
| Back pain | | | |
| subjects affected / exposed | 61 / 692 (8.82%) | 56 / 689 (8.13%) | |
| occurrences (all) | 64 | 68 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 44 / 692 (6.36%) | 33 / 689 (4.79%) | |
| occurrences (all) | 49 | 38 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 37 / 692 (5.35%) | 31 / 689 (4.50%) | |
| occurrences (all) | 45 | 36 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 11 December 2018 | Included a biomarker sub-study which collected pre- and post- resection surgery blood samples. Central ECG collection was replaced by local ECG at screening and as clinically indicated. Updated dose interruption schedule related to Drug Induced Liver Injury (DILI). Updated the contraception language. Reduced number of C1D2 and C1D3 pharmacokinetics samples. Made clarifications, editorial and typographic changes |
| 05 February 2020 | Allowed sites the flexibility to perform hematology, chemistry, and coagulation based on local laboratory results allowed for same-day safety evaluations. The remaining blood specimens collected as part of safety monitoring (e.g., HIV screen, HbsAg, HCV antibody) continued to be performed by central laboratory. Additional minor protocol language clarification updates were made throughout the amendment. |
| 03 February 2022 | Second DFS IA removal. Inclusion as a secondary endpoint the comparison between the canakinumab and placebo arms of DFS by investigator local assessment and OS in subgroups defined respectively by PD-L1 and CD8 expression Time to first 10-point deterioration addition for symptoms and global health status/QoL as a secondary patient-reported outcomes variable of interest Disruption proofing language addition |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported