



Clinical trial results:

An Open Label, Single Arm, Multicenter, Safety Study of Atezolizumab in Locally Advanced or Metastatic Urothelial or Non-urothelial Carcinoma of the Urinary Tract

Summary

| | |
|--------------------------|---|
| EudraCT number | 2016-002625-11 |
| Trial protocol | GR EE LT DE HU IE DK CZ PT GB BG NL PL ES BE SK HR IT |
| Global end of trial date | 12 December 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v3 (current) |
| This version publication date | 22 March 2024 |
| First version publication date | 27 December 2023 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | MO29983 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02928406 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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 | 12 December 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 December 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the safety of atezolizumab as second- to fourth-line treatment for participants with locally advanced or metastatic urothelial or non-urothelial cancer of the urinary tract in addition to evaluating the efficacy of atezolizumab and potential tumor biomarkers associated with atezolizumab.

Protection of trial subjects:

All study subjects were required to read and sign and Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 30 November 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Argentina: 8 |
| Country: Number of subjects enrolled | Australia: 58 |
| Country: Number of subjects enrolled | Austria: 17 |
| Country: Number of subjects enrolled | Belgium: 20 |
| Country: Number of subjects enrolled | Brazil: 32 |
| Country: Number of subjects enrolled | Bulgaria: 3 |
| Country: Number of subjects enrolled | Canada: 17 |
| Country: Number of subjects enrolled | China: 3 |
| Country: Number of subjects enrolled | Colombia: 8 |
| Country: Number of subjects enrolled | Croatia: 12 |
| Country: Number of subjects enrolled | Czechia: 10 |
| Country: Number of subjects enrolled | Denmark: 20 |
| Country: Number of subjects enrolled | Estonia: 3 |
| Country: Number of subjects enrolled | Germany: 55 |
| Country: Number of subjects enrolled | Greece: 40 |
| Country: Number of subjects enrolled | Hungary: 33 |
| Country: Number of subjects enrolled | India: 11 |
| Country: Number of subjects enrolled | Ireland: 15 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Italy: 270 |
| Country: Number of subjects enrolled | Lebanon: 5 |
| Country: Number of subjects enrolled | Lithuania: 11 |
| Country: Number of subjects enrolled | Netherlands: 34 |
| Country: Number of subjects enrolled | Poland: 20 |
| Country: Number of subjects enrolled | Portugal: 14 |
| Country: Number of subjects enrolled | Romania: 20 |
| Country: Number of subjects enrolled | Russian Federation: 10 |
| Country: Number of subjects enrolled | Saudi Arabia: 5 |
| Country: Number of subjects enrolled | Slovakia: 9 |
| Country: Number of subjects enrolled | Spain: 170 |
| Country: Number of subjects enrolled | Switzerland: 25 |
| Country: Number of subjects enrolled | Taiwan: 6 |
| Country: Number of subjects enrolled | United Kingdom: 40 |
| Worldwide total number of subjects | 1004 |
| EEA total number of subjects | 776 |

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) | 378 |
| From 65 to 84 years | 613 |
| 85 years and over | 13 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 172 centers in 32 countries

Pre-assignment

Screening details: -

Pre-assignment period milestones

| | |
|----------------------------|------|
| Number of subjects started | 1004 |
|----------------------------|------|

| | |
|------------------------------|-----|
| Number of subjects completed | 997 |
|------------------------------|-----|

Pre-assignment subject non-completion reasons

| | |
|----------------------------|------------------------------------|
| Reason: Number of subjects | Did not receive study treatment: 7 |
|----------------------------|------------------------------------|

Period 1

| | |
|----------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
|----------------|--------------------------------|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|-----------------------------|
| Allocation method | Non-randomised - controlled |
|-------------------|-----------------------------|

| | |
|---------------|-------------|
| Blinding used | Not blinded |
|---------------|-------------|

Arms

| | |
|-----------|--------------|
| Arm title | Atezolizumab |
|-----------|--------------|

Arm description:

Participants received atezolizumab every 3 weeks (Q3W) until investigator assessed loss of clinical benefit, unacceptable toxicity, investigator or participant decision to withdraw from therapy, or death (whichever occurred first).

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------|
| Investigational medicinal product name | Atezolizumab |
|--|--------------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|-----------|
| Other name | MPDL3280A |
|------------|-----------|

| | |
|----------------------|----------|
| Pharmaceutical forms | Infusion |
|----------------------|----------|

| | |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

Atezolizumab 1200 milligrams (mg) was administered by intravenous (IV) infusion Q3W.

| Number of subjects in period 1 ^[1] | Atezolizumab |
|---|--------------|
| Started | 997 |
| Completed | 0 |
| Not completed | 997 |
| Consent withdrawn by subject | 40 |
| Physician decision | 1 |
| Death | 775 |
| Non-compliance | 1 |

| | |
|-----------------------------|----|
| Study terminated by sponsor | 57 |
| Various reasonse | 72 |
| Progressive disease | 3 |
| Lost to follow-up | 48 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: This number is based on the safety population, that is those participants who were enrolled and received at least one dose of study treatment

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Atezolizumab |
|-----------------------|--------------|

Reporting group description:

Participants received atezolizumab every 3 weeks (Q3W) until investigator assessed loss of clinical benefit, unacceptable toxicity, investigator or participant decision to withdraw from therapy, or death (whichever occurred first).

| Reporting group values | Atezolizumab | Total | |
|--|--------------|-------|--|
| Number of subjects | 997 | 997 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 375 | 375 | |
| From 65-84 years | 609 | 609 | |
| 85 years and over | 13 | 13 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 66.6 | | |
| standard deviation | ± 10.00 | - | |
| Gender Categorical | | | |
| Units: Participants | | | |
| Female | 225 | 225 | |
| Male | 772 | 772 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 11 | 11 | |
| Asian | 30 | 30 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 4 | 4 | |
| White | 920 | 920 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 32 | 32 | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 112 | 112 | |
| Not Hispanic or Latino | 820 | 820 | |
| Unknown or Not Reported | 65 | 65 | |

End points

End points reporting groups

| | |
|---|-----------------------|
| Reporting group title | Atezolizumab |
| Reporting group description: Participants received atezolizumab every 3 weeks (Q3W) until investigator assessed loss of clinical benefit, unacceptable toxicity, investigator or participant decision to withdraw from therapy, or death (whichever occurred first). | |
| Subject analysis set title | Intent to Treat (ITT) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: This is the ITT population | |

Primary: Percentage of Participants With Adverse Events (AEs)

| | |
|--|---|
| End point title | Percentage of Participants With Adverse Events (AEs) ^[1] |
| End point description: AEs were defined as any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of causal attribution. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. New disease, exacerbation of existing disease, recurrence of an intermittent medical condition not present at baseline, any deterioration in a laboratory value or other clinical test associated with symptoms or leading to a change in study/concomitant treatment or discontinuation from study drug as well as events related to protocol-mandated interventions are considered AEs. The safety population included all enrolled participants who received at least one dose of study medication. | |
| End point type | Primary |
| End point timeframe: Baseline up to end of study (up to approximately 6 years) | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The incidence of AEs are summarized by frequency tables. Corresponding 95% Clopper-Pearson confidence intervals (CIs) are also presented, as applicable. Complicated statistical methods for AEs analysis are rarely used, and there is a reliance on simple approaches to display information such as in frequency tables and descriptive statistics.

| | | | | |
|-----------------------------------|-----------------|--|--|--|
| End point values | Atezolizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 900 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 90.3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

| | |
|-----------------|---|
| End point title | Progression Free Survival (PFS) as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) |
|-----------------|---|

End point description:

PFS was defined as the date of first occurrence of tumor progression (earliest of the dates of the RECIST component indicating tumor progression) or date of death (in the absence of tumor progression) by any cause, whichever occurred first, or date of censoring minus date of start of study treatment plus 1.

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

End point timeframe:

Randomization up to disease progression or death from any cause, whichever occurred first (up to approximately 6 years)

| End point values | Intent to Treat (ITT) | | | |
|----------------------------------|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1004 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.20 (2.14 to 2.40) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as per Modified Response Evaluation Criteria in Solid Tumors (Modified RECIST)

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|-----------------|--|
| End point title | PFS as per Modified Response Evaluation Criteria in Solid Tumors (Modified RECIST) |
|-----------------|--|

End point description:

PFS as per Modified RECIST was defined as:

- date of first occurrence of tumor progression after a modified confirmed response if the participant was a responder according to modified RECIST or
 - date of first occurrence of tumor progression in case the participant was not a responder according to modified RECIST or
 - date of death (in the absence of tumor progression) by any cause, or
 - date of censoring
- whichever occurred first, minus date of start of study treatment plus 1

The ITT population included all enrolled participants.

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

End point timeframe:

Randomization up to disease progression or death from any cause, whichever occurred first (up to approximately 6 years)

| End point values | Intent to Treat (ITT) | | | |
|----------------------------------|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1004 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.79 (2.37 to 3.45) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as date of death (due to any cause) or censoring minus date of start of study treatment plus 1.

The intent-to-treat (ITT) population included all enrolled participants.

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

End point timeframe:

Randomization until death from any cause (up to approximately 6 years)

| End point values | Intent to Treat (ITT) | | | |
|----------------------------------|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1004 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.57 (7.75 to 9.72) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Best Overall Response (BOR) as Assessed by RECIST v1.1

| | |
|-----------------|--|
| End point title | Percentage of Participants With Best Overall Response (BOR) as Assessed by RECIST v1.1 |
|-----------------|--|

End point description:

BOR was assessed by the investigators according to the RECIST v1.1. BOR was defined as a complete response (CR) or partial response (PR) determined on two consecutive investigator assessments ≥ 4 weeks apart in participants with measurable disease at baseline. CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 millimeters (mm); PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Progressive Disease (PD) = At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must have demonstrated an absolute increase of at least 5 mm. Stable Disease (SD) = Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study.

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

End point timeframe:

Randomization up to disease progression or death from any cause, whichever occurred first (up to approximately 6 years)

| | | | | |
|-----------------------------------|-----------------------|--|--|--|
| End point values | Intent to Treat (ITT) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1004 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 15.7 (13.5 to 18.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With BOR as Assessed by Modified RECIST

| | |
|-----------------|--|
| End point title | Percentage of Participants With BOR as Assessed by Modified RECIST |
|-----------------|--|

End point description:

BOR was assessed by the investigators according to the modified RECIST. BOR was defined as complete response (CR) or partial response (PR). CR includes complete disappearance of all tumor lesions and no new measurable or unmeasurable lesions confirmed by a consecutive assessment ≥ 4 weeks from the first documented date. PR is a decrease in the sum of the diameters of all target and all new measurable lesions $\geq 30\%$, relative to baseline, in the absence of CR confirmed by a consecutive assessment ≥ 4 weeks from the first documented date. The assessment of BOR included post-screening RECIST assessments obtained up to: 1) death from any cause, 2) last evaluable RECIST assessment in the absence of death, 3) start of a subsequent anti-cancer therapy, whichever occurred first. The ITT population included all enrolled participants.

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

End point timeframe:

Randomization up to disease progression or death from any cause, whichever occurred first (up to approximately 6 years)

| | | | | |
|-----------------------------------|-----------------------|--|--|--|
| End point values | Intent to Treat (ITT) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1004 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 16.4 (14.2 to 18.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control as Assessed by RECIST v1.1

| | |
|-----------------|--|
| End point title | Percentage of Participants With Disease Control as Assessed by RECIST v1.1 |
|-----------------|--|

End point description:

Disease control was determined separately on disease status using RECIST v1.1 by the investigator. Disease control rate was defined as the sum of the complete response, partial response, and stable disease rates. The ITT population included all enrolled participants.

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

End point timeframe:

Randomization up to disease progression or death from any cause, whichever occurred first (up to approximately 6 years)

| | | | | |
|-----------------------------------|-----------------------|--|--|--|
| End point values | Intent to Treat (ITT) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1004 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 39.9 (36.9 to 43.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control as Assessed by Modified RECIST

| | |
|-----------------|--|
| End point title | Percentage of Participants With Disease Control as Assessed by Modified RECIST |
|-----------------|--|

End point description:

Disease control was determined separately on disease status using modified RECIST by the investigator. Disease control rate was defined as the sum of the complete response, partial response, and stable disease rates. The ITT population included all enrolled participants.

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

End point timeframe:

Randomization up to disease progression or death from any cause, whichever occurred first (up to approximately 6 years)

| | | | | |
|-----------------------------------|-----------------------|--|--|--|
| End point values | Intent to Treat (ITT) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1004 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 46.0 (42.9 to 49.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Assessed by RECIST v1.1

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) as Assessed by RECIST v1.1 |
|-----------------|---|

End point description:

Duration of response was determined separately on disease status using RECIST v1.1 by the investigator. For overall responders, DoR was defined as the time from the date of first occurrence of a confirmed response (complete response or partial response) to date of tumor progression or death from any cause, or to censoring date: 1) end of response coincided with the date of tumor progression or death (in the absence of tumor progression) used for the PFS endpoint, 2) for a participant without disease progression or death following a response, the censored end of response coincided with the PFS censoring date (that was latest RECIST assessment or start of subsequent cancer therapy, whichever occurred first). The ITT population included all enrolled participants. Only participants with a response were analyzed for this outcome measure.

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

End point timeframe:

Time from first occurrence of a documented response to disease progression or death from any cause, whichever occurred first (up to approximately 6 years)

| End point values | Intent to Treat (ITT) | | | |
|----------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 158 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 27.79 (18.89 to 43.30) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as Assessed by Modified RECIST

| | |
|-----------------|------------------------------------|
| End point title | DOR as Assessed by Modified RECIST |
|-----------------|------------------------------------|

End point description:

DOR was determined separately on disease status using modified RECIST by the investigator. For overall responders, DoR was defined as the time from the date of first occurrence of a confirmed response (complete response or partial response) to date of tumor progression following that confirmed response or death from any cause, or to censoring date: 1) end of response was the date of tumor progression after that confirmed response or death (in the absence of tumor progression), 2) for a participant without disease progression or death following a response, the censored end of response was the latest RECIST assessment or start of subsequent cancer therapy, whichever occurred first. The ITT population included all enrolled participants. Only participants with a response were analyzed for this outcome measure.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Time from first occurrence of a documented response to disease progression or death from any cause, whichever occurred first (up to approximately 6 years) | |

| | | | | |
|----------------------------------|------------------------|--|--|--|
| End point values | Intent to Treat (ITT) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 165 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 29.73 (21.72 to 43.30) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-Related Quality of Life (HRQoL), as Assessed Using European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) Score

| | |
|-----------------|--|
| End point title | Change From Baseline in Health-Related Quality of Life (HRQoL), as Assessed Using European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) Score |
|-----------------|--|

End point description:

The EORTC QLQ-C30 included global health status, functional scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain) and single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Most questions used a 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale [1 'very poor' to 7 'Excellent']). Scores were averaged and transformed to 0 - 100 scale. Higher scores on the global health status and functional scales indicated better health status/function. Higher scores on the symptoms scales and symptom items indicated greater symptom burden. The ITT population included all enrolled participants who completed the questionnaire at baseline and had 1 post-baseline assessment.

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

Baseline, Day 1 of Cycles 1, 2, 3 and thereafter every 9 weeks for 54 weeks from study treatment start; and then every 12 weeks until progression/study discontinuation (up to approximately 6 years) (Cycle length = 21 days)

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Intent to Treat (ITT) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 964 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical score Baseline | 70.62 (± 23.784) | | | |
| Physical score Cycle(C) 2 Day(D) 1 | -3.43 (± 16.923) | | | |

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| Physical score C3D1 | -3.98 (± 18.854) | | | |
| Physical score C4D1 | -2.01 (± 18.647) | | | |
| Physical score C7D1 | 1.72 (± 19.408) | | | |
| Physical score C10D1 | 3.10 (± 17.494) | | | |
| Physical score C13D1 | 3.32 (± 16.829) | | | |
| Physical score C16D1 | 3.62 (± 19.790) | | | |
| Physical score C19D1 | 3.27 (± 20.591) | | | |
| Physical score C23D1 | 4.16 (± 19.298) | | | |
| Physical score C27D1 | 4.90 (± 20.032) | | | |
| Physical score C31D1 | 6.50 (± 20.053) | | | |
| Physical score C35D1 | 4.95 (± 24.876) | | | |
| Physical score C39D1 | 7.33 (± 22.307) | | | |
| Physical score C43D1 | 6.06 (± 19.840) | | | |
| Physical score C47D1 | 6.56 (± 19.682) | | | |
| Physical score C51D1 | 4.85 (± 22.585) | | | |
| Physical score C55D1 | 4.93 (± 19.110) | | | |
| Physical score C59D1 | 5.69 (± 21.916) | | | |
| Physical score C63D1 | 7.64 (± 18.894) | | | |
| Physical score C67D1 | 8.66 (± 23.154) | | | |
| Physical score C71D1 | 3.50 (± 19.652) | | | |
| Physical score C75D1 | 6.67 (± 17.914) | | | |
| Physical score C79D1 | 1.00 (± 18.245) | | | |
| Physical score C83D1 | -4.15 (± 7.908) | | | |
| Physical score C87D1 | -10.00 (± 14.142) | | | |
| Physical score C91D1 | -20.00 (± 9999999) | | | |
| Physical score Discontinuation visit | -13.87 (± 26.541) | | | |
| Role score Baseline | 67.29 (± 31.545) | | | |
| Role score C2D1 | -5.38 (± 25.918) | | | |
| Role score C3D1 | -4.31 (± 27.800) | | | |
| Role score C4D1 | -1.45 (± 29.012) | | | |
| Role score C7D1 | 1.81 (± 29.762) | | | |

| | | | | |
|----------------------------------|--------------------|--|--|--|
| Role score C10D1 | 3.25 (± 27.060) | | | |
| Role score C13D1 | 5.73 (± 26.659) | | | |
| Role score C16D1 | 4.10 (± 28.314) | | | |
| Role score C19D1 | 2.28 (± 28.10) | | | |
| Role score C23D1 | 2.70 (± 32.535) | | | |
| Role score C27D1 | 6.56 (± 30.725) | | | |
| Role score C31D1 | 9.18 (± 31.951) | | | |
| Role score C35D1 | 4.86 (± 34.899) | | | |
| Role score C39D1 | 10.81 (± 33.457) | | | |
| Role score C43D1 | 6.58 (± 31.276) | | | |
| Role score C47D1 | 7.21 (± 31.464) | | | |
| Role score C51D1 | 6.91 (± 31.914) | | | |
| Role score C55D1 | 5.06 (± 21.136) | | | |
| Role score C59D1 | 8.03 (± 23.736) | | | |
| Role score C63D1 | 5.66 (± 24.664) | | | |
| Role score C67D1 | 2.90 (± 34.116) | | | |
| Role score C71D1 | 4.65 (± 29.171) | | | |
| Role score C75D1 | 5.57 (± 22.335) | | | |
| Role score C79D1 | 4.18 (± 31.934) | | | |
| Role score C83D1 | -4.16 (± 14.743) | | | |
| Role score C87D1 | -8.30 (± 11.738) | | | |
| Role score C91D1 | -16.60 (± 9999999) | | | |
| Role score Discontinuation visit | -17.61 (± 35.664) | | | |
| Emotional score Baseline | 75.89 (± 22.274) | | | |
| Emotional score C2D1 | 0.79 (± 18.975) | | | |
| Emotional score C3D1 | 1.55 (± 18.868) | | | |
| Emotional score C4D1 | 1.04 (± 19.530) | | | |
| Emotional score C7D1 | 3.05 (± 18.978) | | | |
| Emotional score C10D1 | 4.39 (± 17.733) | | | |
| Emotional score C13D1 | 3.96 (± 17.669) | | | |
| Emotional score C16D1 | 5.79 (± 20.044) | | | |

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|---------------------------------------|-------------------------|--|--|--|
| Emotional score C19D1 | 4.90 (\pm 20.156) | | | |
| Emotional score C23D1 | 5.45 (\pm 20.057) | | | |
| Emotional score C27D1 | 5.94 (\pm 19.538) | | | |
| Emotional score C31D1 | 10.17 (\pm 19.057) | | | |
| Emotional score C35D1 | 8.90 (\pm 19.361) | | | |
| Emotional score C39D1 | 9.80 (\pm 20.883) | | | |
| Emotional score C43D1 | 8.22 (\pm 20.618) | | | |
| Emotional score C47D1 | 7.21 (\pm 19.762) | | | |
| Emotional score C51D1 | 9.23 (\pm 20.377) | | | |
| Emotional score C55D1 | 8.48 (\pm 18.359) | | | |
| Emotional score C59D1 | 9.88 (\pm 17.890) | | | |
| Emotional score C63D1 | 9.12 (\pm 16.766) | | | |
| Emotional score C67D1 | 8.52 (\pm 20.452) | | | |
| Emotional score C71D1 | 7.56 (\pm 18.345) | | | |
| Emotional score C75D1 | 7.33 (\pm 21.430) | | | |
| Emotional score C79D1 | 5.84 (\pm 22.465) | | | |
| Emotional score C83D1 | 8.34 (\pm 8.913) | | | |
| Emotional score C87D1 | 0.00 (\pm 47.235) | | | |
| Emotional score C91D1 | -33.40 (\pm 9999999) | | | |
| Emotional score Discontinuation visit | -7.49 (\pm 23.771) | | | |
| Cognitive score Baseline | 85.43 (\pm 20.943) | | | |
| Cognitive score C2D1 | -1.83 (\pm 19.255) | | | |
| Cognitive score C3D1 | -2.40 (\pm 18.344) | | | |
| Cognitive score C4D1 | -1.58 (\pm 15.886) | | | |
| Cognitive score C7D1 | 0.00 (\pm 16.737) | | | |
| Cognitive score C10D1 | -0.78 (\pm 16.763) | | | |
| Cognitive score C13D1 | -0.37 (\pm 14.476) | | | |
| Cognitive score C16D1 | 0.44 (\pm 16.743) | | | |
| Cognitive score C19D1 | -0.10 (\pm 17.221) | | | |
| Cognitive score C23D1 | -1.27 (\pm 17.973) | | | |
| Cognitive score C27D1 | -0.68 (\pm 17.324) | | | |

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|---------------------------------------|------------------|--|--|--|
| Cognitive score C31D1 | 1.38 (± 14.715) | | | |
| Cognitive score C35D1 | 0.32 (± 15.112) | | | |
| Cognitive score C39D1 | -1.46 (± 15.238) | | | |
| Cognitive score C43D1 | -2.19 (± 16.623) | | | |
| Cognitive score C47D1 | -0.68 (± 14.702) | | | |
| Cognitive score C51D1 | -0.23 (± 16.051) | | | |
| Cognitive score C55D1 | 1.79 (± 14.791) | | | |
| Cognitive score C59D1 | -0.31 (± 17.271) | | | |
| Cognitive score C63D1 | -1.25 (± 15.615) | | | |
| Cognitive score C67D1 | -3.98 (± 16.909) | | | |
| Cognitive score C71D1 | -5.42 (± 13.946) | | | |
| Cognitive score C75D1 | -6.67 (± 15.951) | | | |
| Cognitive score C79D1 | -8.34 (± 13.792) | | | |
| Cognitive score C83D1 | -6.24 (± 12.382) | | | |
| Cognitive score C87D1 | 0.00 (± 0.00) | | | |
| Cognitive score C91D1 | 0.00 (± 9999999) | | | |
| Cognitive score Discontinuation visit | -9.76 (± 23.884) | | | |
| Social score Baseline | 74.56 (± 26.597) | | | |
| Social score C2D1 | -1.25 (± 26.277) | | | |
| Social score C3D1 | -0.02 (± 24.058) | | | |
| Social score C4D1 | -0.38 (± 25.568) | | | |
| Social score C7D1 | 0.24 (± 26.865) | | | |
| Social score C10D1 | 3.78 (± 25.930) | | | |
| Social score C13D1 | 4.43 (± 23.550) | | | |
| Social score C16D1 | 3.99 (± 23.579) | | | |
| Social score C19D1 | 24.45 (± 25.186) | | | |
| Social score C23D1 | 1.65 (± 28.106) | | | |
| Social score C27D1 | 4.24 (± 24.482) | | | |
| Social score C31D1 | 7.65 (± 28.007) | | | |
| Social score C35D1 | 5.02 (± 26.279) | | | |
| Social score C39D1 | 6.96 (± 26.070) | | | |

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|------------------------------------|------------------------|--|--|--|
| Social score C43D1 | 5.26 (\pm 25.704) | | | |
| Social score C47D1 | 4.96 (\pm 27.412) | | | |
| Social score C51D1 | 6.34 (\pm 24.541) | | | |
| Social score C55D1 | 6.55 (\pm 21.946) | | | |
| Social score C59D1 | 8.03 (\pm 22.369) | | | |
| Social score C63D1 | 6.29 (\pm 22.695) | | | |
| Social score C67D1 | 5.80 (\pm 27.491) | | | |
| Social score C71D1 | 3.50 (\pm 21.995) | | | |
| Social score C75D1 | 10.01 (\pm 22.041) | | | |
| Social score C79D1 | 5.84 (\pm 28.767) | | | |
| Social score C83D1 | 18.75 (\pm 27.383) | | | |
| Social score C87D1 | 8.30 (\pm 11.738) | | | |
| Social score C91D1 | 33.30 (\pm 9999999) | | | |
| Social score Discontinuation visit | -12.20 (\pm 33.586) | | | |
| Fatigue score Baseline | 36.04 (\pm 26.343) | | | |
| Fatigue score C2D1 | 5.58 (\pm 22.444) | | | |
| Fatigue score C3D1 | 5.01 (\pm 23.869) | | | |
| Fatigue score C4D1 | 3.27 (\pm 23.637) | | | |
| Fatigue score C7D1 | -2.56 (\pm 24.879) | | | |
| Fatigue score C10D1 | -3.95 (\pm 23.633) | | | |
| Fatigue score C13D1 | -2.46 (\pm 23.492) | | | |
| Fatigue score C16D1 | -4.97 (\pm 25.081) | | | |
| Fatigue score C19D1 | -4.73 (\pm 26.358) | | | |
| Fatigue score C23D1 | -3.34 (\pm 26.603) | | | |
| Fatigue score C27D1 | -6.01 (\pm 24.252) | | | |
| Fatigue score C31D1 | -10.09 (\pm 25.731) | | | |
| Fatigue score C35D1 | -8.95 (\pm 28.738) | | | |
| Fatigue score C39D1 | -9.76 (\pm 28.299) | | | |
| Fatigue score C43D1 | -7.75 (\pm 28.295) | | | |
| Fatigue score C47D1 | -7.95 (\pm 24.164) | | | |
| Fatigue score C51D1 | -9.68 (\pm 25.102) | | | |

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|-------------------------------------|-------------------|--|--|--|
| Fatigue score C55D1 | -7.73 (± 24.710) | | | |
| Fatigue score C59D1 | -9.46 (± 21.528) | | | |
| Fatigue score C63D1 | -7.13 (± 21.259) | | | |
| Fatigue score C67D1 | -6.76 (± 28.838) | | | |
| Fatigue score C71D1 | -5.42 (± 23.187) | | | |
| Fatigue score C75D1 | -3.70 (± 26.146) | | | |
| Fatigue score C79D1 | -6.66 (± 23.200) | | | |
| Fatigue score C83D1 | -4.18 (± 13.215) | | | |
| Fatigue score C87D1 | -5.55 (± 39.386) | | | |
| Fatigue score C91D1 | 22.30 (± 9999999) | | | |
| Fatigue score Discontinuation visit | 13.35 (± 28.962) | | | |
| Nausea/Vomiting score Baseline | 6.94 (± 14.538) | | | |
| Nausea/Vomiting score C2D1 | 3.53 (± 16.328) | | | |
| Nausea/Vomiting score C3D1 | 2.43 (± 15.445) | | | |
| Nausea/Vomiting score C4D1 | 1.77 (± 14.485) | | | |
| Nausea/Vomiting score C7D1 | 0.81 (± 14.300) | | | |
| Nausea/Vomiting score C10D1 | -0.36 (± 12.603) | | | |
| Nausea/Vomiting score C13D1 | -0.52 (± 11.533) | | | |
| Nausea/Vomiting score C16D1 | -1.06 (± 12.109) | | | |
| Nausea/Vomiting score C19D1 | -0.72 (± 10.436) | | | |
| Nausea/Vomiting score C23D1 | 0.13 (± 10.880) | | | |
| Nausea/Vomiting score C27D1 | -0.14 (± 11.838) | | | |
| Nausea/Vomiting score C31D1 | -1.53 (± 8.939) | | | |
| Nausea/Vomiting score C35D1 | -2.91 (± 9.461) | | | |
| Nausea/Vomiting score C39D1 | -2.93 (± 10.421) | | | |
| Nausea/Vomiting score C43D1 | -3.29 (± 8.614) | | | |
| Nausea/Vomiting score C47D1 | -2.93 (± 8.879) | | | |
| Nausea/Vomiting score C51D1 | -2.86 (± 8.960) | | | |
| Nausea/Vomiting score C55D1 | -3.03 (± 9.123) | | | |
| Nausea/Vomiting score C59D1 | -2.47 (± 9.388) | | | |
| Nausea/Vomiting score C63D1 | -3.46 (± 9.446) | | | |

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|---|--------------------|--|--|--|
| Nausea/Vomiting score C67D1 | -2.90 (± 9.494) | | | |
| Nausea/Vomiting score C71D1 | -2.33 (± 8.587) | | | |
| Nausea/Vomiting score C75D1 | -2.09 (± 5.642) | | | |
| Nausea/Vomiting score C79D1 | -2.51 (± 6.118) | | | |
| Nausea/Vomiting score C83D1 | 0.00 (± 0.000) | | | |
| Nausea/Vomiting score C87D1 | 8.30 (± 11.738) | | | |
| Nausea/Vomiting score C91D1 | 0.00 (± 4.69) | | | |
| Nausea/Vomiting score Discontinuation visit | 19.358 (± 9999999) | | | |
| Pain score Baseline | 33.97 (± 31.221) | | | |
| Pain score C2D1 | 0.06 (± 23.064) | | | |
| Pain score C3D1 | 1.54 (± 26.411) | | | |
| Pain score C4D1 | -0.13 (± 27.312) | | | |
| Pain score C7D1 | -2.61 (± 30.687) | | | |
| Pain score C10D1 | -3.90 (± 26.146) | | | |
| Pain score C13D1 | -4.02 (± 25.814) | | | |
| Pain score C16D1 | -5.74 (± 29.692) | | | |
| Pain score C19D1 | -6.83 (± 27.035) | | | |
| Pain score C23D1 | -5.98 (± 28.577) | | | |
| Pain score C27D1 | -9.29 (± 26.684) | | | |
| Pain score C31D1 | -10.10 (± 25.864) | | | |
| Pain score C35D1 | -9.71 (± 33.050) | | | |
| Pain score C39D1 | -11.54 (± 30.400) | | | |
| Pain score C43D1 | -8.56 (± 29.125) | | | |
| Pain score C47D1 | -10.36 (± 29.157) | | | |
| Pain score C51D1 | -6.58 (± 29.875) | | | |
| Pain score C55D1 | -8.04 (± 26.779) | | | |
| Pain score C59D1 | -8.96 (± 27.033) | | | |
| Pain score C63D1 | -5.04 (± 30.238) | | | |
| Pain score C67D1 | -5.80 (± 32.632) | | | |
| Pain score C71D1 | -8.54 (± 29.178) | | | |
| Pain score C75D1 | -12.01 (± 30.999) | | | |
| Pain score C79D1 | -6.67 (± 32.628) | | | |

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|----------------------------------|-------------------|--|--|--|
| Pain score C83D1 | -8.35 (± 30.876) | | | |
| Pain score C87D1 | -16.70 (± 23.617) | | | |
| Pain score C91D1 | 33.30 (± 9999999) | | | |
| Pain score Discontinuation visit | 9.53 (± 33.994) | | | |
| Dyspnoea score Baseline | 16.23 (± 24.815) | | | |
| Dyspnoea score C2D1 | 1.03 (± 22.912) | | | |
| Dyspnoea score C3D1 | 3.29 (± 24.647) | | | |
| Dyspnoea score C4D1 | 0.88 (± 22.962) | | | |
| Dyspnoea score C7D1 | -0.57 (± 23.661) | | | |
| Dyspnoea score C10D1 | -1.09 (± 22.079) | | | |
| Dyspnoea score C13D1 | -0.30 (± 23.616) | | | |
| Dyspnoea score C16D1 | -1.06 (± 22.042) | | | |
| Dyspnoea score C19D1 | -0.21 (± 22.650) | | | |
| Dyspnoea score C23D1 | -0.26 (± 24.014) | | | |
| Dyspnoea score C27D1 | 1.10 (± 25.791) | | | |
| Dyspnoea score C31D1 | -3.98 (± 24.725) | | | |
| Dyspnoea score C35D1 | -4.20 (± 23.647) | | | |
| Dyspnoea score C39D1 | -3.30 (± 22.794) | | | |
| Dyspnoea score C43D1 | -2.63 (± 24.798) | | | |
| Dyspnoea score C47D1 | -3.19 (± 23.669) | | | |
| Dyspnoea score C51D1 | -2.90 (± 23.379) | | | |
| Dyspnoea score C55D1 | -2.97 (± 20.366) | | | |
| Dyspnoea score C59D1 | -1.24 (± 21.421) | | | |
| Dyspnoea score C63D1 | -1.26 (± 20.616) | | | |
| Dyspnoea score C67D1 | -3.62 (± 23.530) | | | |
| Dyspnoea score C71D1 | -3.88 (± 22.066) | | | |
| Dyspnoea score C75D1 | 0.00 (± 27.800) | | | |
| Dyspnoea score C79D1 | 1.67 (± 25.301) | | | |
| Dyspnoea score C83D1 | 12.50 (± 17.252) | | | |
| Dyspnoea score C87D1 | 50.00 (± 23.617) | | | |
| Dyspnoea score C91D1 | 66.70 (± 9999999) | | | |

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|--------------------------------------|-------------------|--|--|--|
| Dyspnoea score Discontinuation visit | 8.71 (± 29.191) | | | |
| Insomnia score Baseline | 27.26 (± 30.907) | | | |
| Insomnia score C2D1 | -1.35 (± 28.522) | | | |
| Insomnia score C3D1 | -1.59 (± 29.084) | | | |
| Insomnia score C4D1 | -2.09 (± 30.102) | | | |
| Insomnia score C7D1 | -5.92 (± 31.614) | | | |
| Insomnia score C10D1 | -5.70 (± 28.263) | | | |
| Insomnia score C13D1 | -3.87 (± 30.033) | | | |
| Insomnia score C16D1 | -6.88 (± 33.594) | | | |
| Insomnia score C19D1 | -6.62 (± 28.337) | | | |
| Insomnia score C23D1 | -5.64 (± 29.969) | | | |
| Insomnia score C27D1 | -6.28 (± 29.791) | | | |
| Insomnia score C31D1 | -12.54 (± 30.360) | | | |
| Insomnia score C35D1 | -9.39 (± 33.797) | | | |
| Insomnia score C39D1 | -10.26 (± 33.217) | | | |
| Insomnia score C43D1 | -4.83 (± 34.298) | | | |
| Insomnia score C47D1 | -4.57 (± 31.091) | | | |
| Insomnia score C51D1 | -4.28 (± 28.901) | | | |
| Insomnia score C55D1 | -2.38 (± 33.548) | | | |
| Insomnia score C59D1 | -4.94 (± 27.784) | | | |
| Insomnia score C63D1 | -1.89 (± 29.540) | | | |
| Insomnia score C67D1 | -4.35 (± 31.901) | | | |
| Insomnia score C71D1 | -9.30 (± 31.972) | | | |
| Insomnia score C75D1 | -6.95 (± 29.451) | | | |
| Insomnia score C79D1 | -6.95 (± 29.451) | | | |
| Insomnia score C83D1 | -16.69 (± 35.646) | | | |
| Insomnia score C87D1 | -0.05 (± 47.164) | | | |
| Insomnia score C91D1 | 33.30 (± 9999999) | | | |
| Insomnia score Discontinuation visit | 8.07 (± 33.114) | | | |
| Appetite Loss score Baseline | 21.21 (± 30.066) | | | |
| Appetite Loss score C2D1 | 7.36 (± 27.805) | | | |

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|---|-------------------|--|--|--|
| Appetite Loss score C3D1 | 6.15 (± 26.405) | | | |
| Appetite Loss score C4D1 | 1.97 (± 28.206) | | | |
| Appetite Loss score C7D1 | -1.14 (± 29.837) | | | |
| Appetite Loss score C10D1 | -2.89 (± 26.152) | | | |
| Appetite Loss score C13D1 | -3.72 (± 27.719) | | | |
| Appetite Loss score C16D1 | -4.94 (± 26.392) | | | |
| Appetite Loss score C19D1 | -3.73 (± 23.565) | | | |
| Appetite Loss score C23D1 | -1.02 (± 24.532) | | | |
| Appetite Loss score C27D1 | -3.28 (± 25.136) | | | |
| Appetite Loss score C31D1 | -5.20 (± 23.643) | | | |
| Appetite Loss score C35D1 | -7.77 (± 28.847) | | | |
| Appetite Loss score C39D1 | -6.96 (± 26.064) | | | |
| Appetite Loss score C43D1 | -5.26 (± 22.473) | | | |
| Appetite Loss score C47D1 | -3.15 (± 23.515) | | | |
| Appetite Loss score C51D1 | -4.29 (± 21.919) | | | |
| Appetite Loss score C55D1 | -4.16 (± 27.749) | | | |
| Appetite Loss score C59D1 | -6.92 (± 23.892) | | | |
| Appetite Loss score C63D1 | -4.40 (± 25.347) | | | |
| Appetite Loss score C67D1 | -7.24 (± 19.765) | | | |
| Appetite Loss score C71D1 | -3.10 (± 20.328) | | | |
| Appetite Loss score C75D1 | -1.39 (± 6.797) | | | |
| Appetite Loss score C79D1 | -3.34 (± 23.929) | | | |
| Appetite Loss score C83D1 | 0.03 (± 35.639) | | | |
| Appetite Loss score C87D1 | 16.65 (± 23.547) | | | |
| Appetite Loss score C91D1 | 33.30 (± 9999999) | | | |
| Appetite Loss score Discontinuation visit | 14.68 (± 32.487) | | | |
| Constipation score Baseline | 24.98 (± 31.584) | | | |
| Constipation score C2D1 | 0.74 (± 26.700) | | | |
| Constipation score C3D1 | -1.41 (± 29.876) | | | |
| Constipation score C4D1 | -3.48 (± 27.560) | | | |
| Constipation score C7D1 | -3.91 (± 29.908) | | | |

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|--|-------------------|--|--|--|
| Constipation score C10D1 | -4.95 (± 29.467) | | | |
| Constipation score C13D1 | -6.40 (± 30.010) | | | |
| Constipation score C16D1 | -7.05 (± 28.513) | | | |
| Constipation score C19D1 | -5.38 (± 25.523) | | | |
| Constipation score C23D1 | -5.64 (± 26.619) | | | |
| Constipation score C27D1 | -6.01 (± 29.384) | | | |
| Constipation score C31D1 | -12.53 (± 27.131) | | | |
| Constipation score C35D1 | -12.30 (± 28.388) | | | |
| Constipation score C39D1 | -10.25 (± 29.267) | | | |
| Constipation score C43D1 | -8.77 (± 27.953) | | | |
| Constipation score C47D1 | -9.46 (± 27.868) | | | |
| Constipation score C51D1 | -9.52 (± 30.108) | | | |
| Constipation score C55D1 | -8.33 (± 25.624) | | | |
| Constipation score C59D1 | -9.87 (± 22.079) | | | |
| Constipation score C63D1 | -9.43 (± 22.052) | | | |
| Constipation score C67D1 | -8.69 (± 20.408) | | | |
| Constipation score C71D1 | -8.52 (± 23.112) | | | |
| Constipation score C75D1 | -4.16 (± 14.933) | | | |
| Constipation score C79D1 | -8.33 (± 30.334) | | | |
| Constipation score C83D1 | -12.49 (± 17.234) | | | |
| Constipation score C87D1 | 0.00 (± 0.00) | | | |
| Constipation score C91D1 | 0.00 (± 9999999) | | | |
| Constipation score Discontinuation visit | 4.13 (± 33.230) | | | |
| Diarrhoea score Baseline | 6.84 (± 16.552) | | | |
| Diarrhoea score C2D1 | 1.23 (± 18.840) | | | |
| Diarrhoea score C3D1 | 0.33 (± 19.495) | | | |
| Diarrhoea score C4D1 | -0.32 (± 18.847) | | | |
| Diarrhoea score C7D1 | 0.38 (± 18.060) | | | |
| Diarrhoea score C10D1 | 1.57 (± 21.110) | | | |
| Diarrhoea score C13D1 | 1.81 (± 20.267) | | | |
| Diarrhoea score C16D1 | 0.71 (± 15.774) | | | |

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|---------------------------------------|------------------|--|--|--|
| Diarrhoea score C19D1 | 1.45 (± 19.838) | | | |
| Diarrhoea score C23D1 | -0.25 (± 18.251) | | | |
| Diarrhoea score C27D1 | -1.37 (± 15.677) | | | |
| Diarrhoea score C31D1 | -0.31 (± 15.374) | | | |
| Diarrhoea score C35D1 | 1.29 (± 19.755) | | | |
| Diarrhoea score C39D1 | -2.56 (± 14.252) | | | |
| Diarrhoea score C43D1 | -1.31 (± 12.684) | | | |
| Diarrhoea score C47D1 | -2.25 (± 15.915) | | | |
| Diarrhoea score C51D1 | -1.41 (± 15.356) | | | |
| Diarrhoea score C55D1 | -1.19 (± 10.933) | | | |
| Diarrhoea score C59D1 | -1.85 (± 13.595) | | | |
| Diarrhoea score C63D1 | -1.26 (± 11.240) | | | |
| Diarrhoea score C67D1 | -1.45 (± 13.964) | | | |
| Diarrhoea score C71D1 | -2.32 (± 13.390) | | | |
| Diarrhoea score C75D1 | -1.33 (± 15.138) | | | |
| Diarrhoea score C79D1 | -3.33 (± 14.892) | | | |
| Diarrhoea score C83D1 | 4.16 (± 21.341) | | | |
| Diarrhoea score C87D1 | 0.00 (± 0.00) | | | |
| Diarrhoea score C91D1 | 0.00 (± 9999999) | | | |
| Diarrhoea score Discontinuation visit | 0.30 (± 22.379) | | | |
| Financial difficulties score Baseline | 17.34 (± 27.147) | | | |
| Financial difficulties score C2D1 | -1.86 (± 21.216) | | | |
| Financial difficulties score C3D1 | -1.42 (± 22.408) | | | |
| Financial difficulties score C4D1 | -1.54 (± 22.497) | | | |
| Financial difficulties score C7D1 | -4.14 (± 24.057) | | | |
| Financial difficulties score C10D1 | -3.88 (± 24.021) | | | |
| Financial difficulties score C13D1 | -4.06 (± 22.615) | | | |
| Financial difficulties score C16D1 | -2.84 (± 25.172) | | | |
| Financial difficulties score C19D1 | -4.14 (± 26.023) | | | |
| Financial difficulties score C23D1 | -5.35 (± 24.042) | | | |
| Financial difficulties score C27D1 | -5.19 (± 23.867) | | | |

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|--|-------------------|--|--|--|
| Financial difficulties score C31D1 | -9.48 (± 26.489) | | | |
| Financial difficulties score C35D1 | -3.96 (± 25.517) | | | |
| Financial difficulties score C39D1 | -4.76 (± 25.615) | | | |
| Financial difficulties score C43D1 | -2.63 (± 22.942) | | | |
| Financial difficulties score C47D1 | -0.90 (± 25.869) | | | |
| Financial difficulties score C51D1 | -5.63 (± 25.191) | | | |
| Financial difficulties score C55D1 | -4.76 (± 26.541) | | | |
| Financial difficulties score C59D1 | -6.79 (± 24.551) | | | |
| Financial difficulties score C63D1 | -6.92 (± 22.984) | | | |
| Financial difficulties score C67D1 | -6.52 (± 24.693) | | | |
| Financial difficulties score C71D1 | -6.98 (± 17.154) | | | |
| Financial difficulties score C75D1 | -14.68 (± 23.740) | | | |
| Financial difficulties score C79D1 | -1.68 (± 20.157) | | | |
| Financial difficulties score C83D1 | -4.18 (± 33.028) | | | |
| Financial difficulties score C87D1 | -16.70 (± 23.617) | | | |
| Financial difficulties score C91D1 | 0.00 (± 9999999) | | | |
| Financial difficulties score Discontinuation visit | 2.41 (± 27.481) | | | |
| Global health status Baseline | 59.01 (± 22.821) | | | |
| Global health status C2D1 | -1.48 (± 19.541) | | | |
| Global health status C3D1 | -0.27 (± 19.770) | | | |
| Global health status C4D1 | 0.82 (± 20.587) | | | |
| Global health status C7D1 | 3.64 (± 20.564) | | | |
| Global health status C10D1 | 3.63 (± 19.943) | | | |
| Global health status C13D1 | 6.01 (± 19.679) | | | |
| Global health status C16D1 | 5.76 (± 21.404) | | | |
| Global health status C19D1 | 4.88 (± 20.838) | | | |
| Global health status C23D1 | 5.21 (± 21.759) | | | |
| Global health status C27D1 | 6.22 (± 24.016) | | | |
| Global health status C31D1 | 8.10 (± 22.827) | | | |
| Global health status C35D1 | 11.17 (± 22.555) | | | |
| Global health status C39D1 | 8.52 (± 23.857) | | | |

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|--|-------------------|--|--|--|
| Global health status C43D1 | 8.56 (± 22.846) | | | |
| Global health status C47D1 | 5.30 (± 24.608) | | | |
| Global health status C51D1 | 7.51 (± 20.985) | | | |
| Global health status C55D1 | 8.49 (± 20.309) | | | |
| Global health status C59D1 | 9.57 (± 18.900) | | | |
| Global health status C63D1 | 8.34 (± 19.604) | | | |
| Global health status C67D1 | 7.43 (± 22.369) | | | |
| Global health status C71D1 | 9.30 (± 21.904) | | | |
| Global health status C75D1 | 10.67 (± 19.301) | | | |
| Global health status C79D1 | 10.43 (± 16.196) | | | |
| Global health status C83D1 | 10.44 (± 15.292) | | | |
| Global health status C87D1 | 4.20 (± 17.678) | | | |
| Global health status C91D1 | -8.30 (± 9999999) | | | |
| Global health status Discontinuation visit | -10.94 (± 27.334) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Quality of Life (EuroQoL) Group 5-Dimension 5-Level (EQ-5D-5L) Self Report Questionnaire Health Utility Score

| | |
|-----------------|--|
| End point title | Change from Baseline in European Quality of Life (EuroQoL) Group 5-Dimension 5-Level (EQ-5D-5L) Self Report Questionnaire Health Utility Score |
|-----------------|--|

End point description:

The EuroQol 5-Dimension Questionnaire (EQ-5D-5L) is a self-report health status questionnaire that consists of 6 questions used to calculate a health utility score for use in health economic analysis. There are two components to the EuroQol EQ-5D: 1) five health dimensions that assess mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; 2) a visual analogue scale (VAS) that measures health state. There are 5 response levels for each dimension (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems) with the highest level representing the worst outcome. The VAS is scored on a scale from 0 to 100, with 0 representing the worst imaginable health and 100 representing the best imaginable health. The ITT population included all enrolled participants who completed the questionnaire at baseline and had 1 post-baseline assessment.

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

End point timeframe:

Baseline, Day 1 of Cycles 1, 2, 3 and thereafter every 9 weeks for 54 weeks from study treatment start; and then every 12 weeks until progression/study discontinuation (up to approximately 6 years) (Cycle length = 21 days)

| End point values | Intent to Treat (ITT) | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 960 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mobility Baseline | 1.9 (± 1.03) | | | |
| Mobility C2D1 | 0.1 (± 0.90) | | | |
| Mobility C3D1 | 0.2 (± 0.90) | | | |
| Mobility C4D1 | 0.1 (± 0.88) | | | |
| Mobility C7D1 | 0.0 (± 0.93) | | | |
| Mobility C10D1 | -0.1 (± 0.90) | | | |
| Mobility C13D1 | -0.1 (± 0.80) | | | |
| Mobility C16D1 | -0.2 (± 0.91) | | | |
| Mobility C19D1 | -0.1 (± 0.92) | | | |
| Mobility C23D1 | -0.1 (± 0.91) | | | |
| Mobility C27D1 | -0.2 (± 0.84) | | | |
| Mobility C31D1 | -0.2 (± 0.88) | | | |
| Mobility C35D1 | -0.1 (± 1.05) | | | |
| Mobility C39D1 | -0.2 (± 0.92) | | | |
| Mobility C43D1 | -0.2 (± 1.04) | | | |
| Mobility C47D1 | -0.2 (± 0.84) | | | |
| Mobility C51D1 | -0.3 (± 0.89) | | | |
| Mobility C55D1 | -0.1 (± 0.79) | | | |
| Mobility C59D1 | -0.2 (± 0.99) | | | |
| Mobility C63D1 | -0.2 (± 1.00) | | | |
| Mobility C67D1 | -0.2 (± 0.93) | | | |
| Mobility C71D1 | -0.1 (± 0.85) | | | |
| Mobility C75D1 | -0.1 (± 0.67) | | | |
| Mobility C79D1 | 0.00 (± 0.97) | | | |
| Mobility C83D1 | -0.1 (± 0.83) | | | |
| Mobility C87D1 | 1.0 (± 1.41) | | | |
| Mobility C91D1 | 2.0 (± 9999999) | | | |
| Mobility Discontinuation visit | 0.5 (± 1.19) | | | |
| Self-Care Baseline | 1.4 (± 0.81) | | | |
| Self-Care C2D1 | 0.1 (± 0.72) | | | |
| Self-Care C3D1 | 0.2 (± 0.77) | | | |
| Self-Care C4D1 | 0.1 (± 0.69) | | | |
| Self-Care C7D1 | 0.0 (± 0.72) | | | |
| Self-Care C10D1 | 0.0 (± 0.68) | | | |
| Self-Care C13D1 | 0.0 (± 0.62) | | | |
| Self-Care C16D1 | -0.1 (± 0.57) | | | |
| Self-Care C19D1 | 0.0 (± 0.68) | | | |
| Self-Care C23D1 | 0.0 (± 0.67) | | | |
| Self-Care C27D1 | 0.0 (± 0.63) | | | |
| Self-Care C31D1 | -0.1 (± 0.62) | | | |
| Self-Care C35D1 | -0.1 (± 0.69) | | | |
| Self-Care C39D1 | -0.1 (± 0.69) | | | |
| Self-Care C43D1 | -0.1 (± 0.83) | | | |
| Self-Care C47D1 | -0.1 (± 0.72) | | | |
| Self-Care C51D1 | -0.1 (± 0.84) | | | |

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| Self-Care C55D1 | -0.1 (± 0.66) | | | |
| Self-Care C59D1 | -0.1 (± 0.82) | | | |
| Self-Care C63D1 | -0.1 (± 0.76) | | | |
| Self-Care C67D1 | -0.1 (± 0.75) | | | |
| Self-Care C71D1 | 0.0 (± 0.60) | | | |
| Self-Care C75D1 | 0.0 (± 0.20) | | | |
| Self-Care C79D1 | 0.1 (± 0.45) | | | |
| Self-Care C83D1 | -0.3 (± 0.46) | | | |
| Self-Care C87D1 | 0.0 (± 0.00) | | | |
| Self-Care C91D1 | 1.0 (± 9999999) | | | |
| Self-Care Discontinuation visit | 0.4 (± 1.04) | | | |
| Usual Activities Baseline | 2.0 (± 1.08) | | | |
| Usual Activities C2D1 | 0.2 (± 0.92) | | | |
| Usual Activities C3D1 | 0.2 (± 0.99) | | | |
| Usual Activities C4D1 | 0.1 (± 0.90) | | | |
| Usual Activities C7D1 | 0.0 (± 0.93) | | | |
| Usual Activities C10D1 | -0.1 (± 0.92) | | | |
| Usual Activities C13D1 | -0.2 (± 0.86) | | | |
| Usual Activities C16D1 | -0.1 (± 1.04) | | | |
| Usual Activities C19D1 | 0.0 (± 0.98) | | | |
| Usual Activities C23D1 | -0.1 (± 0.93) | | | |
| Usual Activities C27D1 | -0.2 (± 0.92) | | | |
| Usual Activities C31D1 | -0.3 (± 0.96) | | | |
| Usual Activities C35D1 | -0.2 (± 1.10) | | | |
| Usual Activities C39D1 | -0.2 (± 0.96) | | | |
| Usual Activities C43D1 | -0.1 (± 0.93) | | | |
| Usual Activities C47D1 | -0.2 (± 0.86) | | | |
| Usual Activities C51D1 | -0.3 (± 0.91) | | | |
| Usual Activities C55D1 | -0.2 (± 0.91) | | | |
| Usual Activities C59D1 | -0.3 (± 0.95) | | | |
| Usual Activities C63D1 | -0.2 (± 0.85) | | | |
| Usual Activities C67D1 | -0.3 (± 0.80) | | | |
| Usual Activities C71D1 | -0.2 (± 0.68) | | | |
| Usual Activities C75D1 | -0.1 (± 0.49) | | | |
| Usual Activities C79D1 | 0.0 (± 0.65) | | | |
| Usual Activities C83D1 | 0.1 (± 0.64) | | | |
| Usual Activities C87D1 | 0.0 (± 0.00) | | | |
| Usual Activities C91D1 | 0.0 (± 9999999) | | | |
| Usual Activities Discontinuation visit | 0.6 (± 1.23) | | | |
| Pain/Discomfort Baseline | 2.3 (± 1.08) | | | |
| Pain/Discomfort C2D1 | 0.0 (± 0.82) | | | |
| Pain/Discomfort C3D1 | 0.1 (± 0.98) | | | |
| Pain/Discomfort C4D1 | 0.0 (± 0.94) | | | |
| Pain/Discomfort C7D1 | 0.0 (± 1.04) | | | |
| Pain/Discomfort C10D1 | -0.2 (± 0.96) | | | |
| Pain/Discomfort C13D1 | -0.2 (± 0.96) | | | |
| Pain/Discomfort C16D1 | -0.3 (± 1.02) | | | |
| Pain/Discomfort C19D1 | -0.2 (± 1.04) | | | |
| Pain/Discomfort C23D1 | -0.2 (± 1.04) | | | |
| Pain/Discomfort C27D1 | -0.3 (± 1.03) | | | |

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|--|-----------------|--|--|--|
| Pain/Discomfort C31D1 | -0.3 (± 0.96) | | | |
| Pain/Discomfort C35D1 | -0.3 (± 1.05) | | | |
| Pain/Discomfort C39D1 | -0.4 (± 1.05) | | | |
| Pain/Discomfort C43D1 | -0.4 (± 0.98) | | | |
| Pain/Discomfort C47D1 | -0.4 (± 1.03) | | | |
| Pain/Discomfort C51D1 | -0.3 (± 1.07) | | | |
| Pain/Discomfort C55D1 | -0.4 (± 1.00) | | | |
| Pain/Discomfort C59D1 | -0.4 (± 1.05) | | | |
| Pain/Discomfort C63D1 | -0.3 (± 1.04) | | | |
| Pain/Discomfort C67D1 | -0.2 (± 1.20) | | | |
| Pain/Discomfort C71D1 | -0.2 (± 1.09) | | | |
| Pain/Discomfort C75D1 | -0.3 (± 1.11) | | | |
| Pain/Discomfort C79D1 | -0.3 (± 1.02) | | | |
| Pain/Discomfort C83D1 | 0.0 (± 0.93) | | | |
| Pain/Discomfort C87D1 | -1.0 (± 0.00) | | | |
| Pain/Discomfort C91D1 | 0.0 (± 9999999) | | | |
| Pain/Discomfort Discontinuation visit | 0.3 (± 1.18) | | | |
| Anxiety/Depression Baseline | 1.7 (± 0.87) | | | |
| Anxiety/Depression C2D1 | 0.0 (± 0.75) | | | |
| Anxiety/Depression C3D1 | 0.0 (± 0.81) | | | |
| Anxiety/Depression C4D1 | 0.0 (± 0.87) | | | |
| Anxiety/Depression C7D1 | -0.1 (± 0.81) | | | |
| Anxiety/Depression C10D1 | -0.2 (± 0.74) | | | |
| Anxiety/Depression C13D1 | -0.2 (± 0.78) | | | |
| Anxiety/Depression C16D1 | -0.2 (± 0.78) | | | |
| Anxiety/Depression C19D1 | -0.1 (± 0.78) | | | |
| Anxiety/Depression C23D1 | -0.1 (± 0.88) | | | |
| Anxiety/Depression C27D1 | -0.2 (± 0.73) | | | |
| Anxiety/Depression C31D1 | -0.3 (± 0.75) | | | |
| Anxiety/Depression C35D1 | -0.3 (± 0.74) | | | |
| Anxiety/Depression C39D1 | -0.2 (± 0.78) | | | |
| Anxiety/Depression C43D1 | -0.3 (± 0.80) | | | |
| Anxiety/Depression C47D1 | -0.3 (± 0.77) | | | |
| Anxiety/Depression C51D1 | -0.2 (± 0.78) | | | |
| Anxiety/Depression C55D1 | -0.2 (± 0.73) | | | |
| Anxiety/Depression C59D1 | -0.1 (± 0.68) | | | |
| Anxiety/Depression C63D1 | -0.1 (± 0.82) | | | |
| Anxiety/Depression C67D1 | -0.1 (± 0.76) | | | |
| Anxiety/Depression C71D1 | -0.1 (± 0.78) | | | |
| Anxiety/Depression C75D1 | -0.3 (± 0.82) | | | |
| Anxiety/Depression C79D1 | -0.5 (± 1.00) | | | |
| Anxiety/Depression C83D1 | -0.4 (± 0.74) | | | |
| Anxiety/Depression C87D1 | 0.0 (± 1.41) | | | |
| Anxiety/Depression C91D1 | 1.0 (± 9999999) | | | |
| Anxiety/Depression Discontinuation visit | 0.3 (± 1.03) | | | |
| Visual Analog Scale (VAS) Baseline | 64.7 (± 20.37) | | | |
| VAS C2D1 | -0.6 (± 14.76) | | | |
| VAS C3D1 | -0.3 (± 17.21) | | | |
| VAS C4D1 | 0.3 (± 18.02) | | | |
| VAS C7D1 | 3.7 (± 17.47) | | | |

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|---------------------------|-----------------|--|--|--|
| VAS C10D1 | 3.5 (± 17.88) | | | |
| VAS C13D1 | 5.8 (± 17.46) | | | |
| VAS C16D1 | 6.4 (± 17.87) | | | |
| VAS C19D1 | 5.9 (± 16.49) | | | |
| VAS C23D1 | 7.7 (± 17.14) | | | |
| VAS C27D1 | 8.9 (± 17.99) | | | |
| VAS C31D1 | 8.9 (± 17.99) | | | |
| VAS C35D1 | 11.0 (± 19.13) | | | |
| VAS C39D1 | 9.0 (± 19.31) | | | |
| VAS C43D1 | 8.9 (± 17.59) | | | |
| VAS C47D1 | 9.0 (± 16.08) | | | |
| VAS C51D1 | 7.4 (± 18.85) | | | |
| VAS C55D1 | 8.7 (± 18.10) | | | |
| VAS C59D1 | 5.3 (± 16.15) | | | |
| VAS C63D1 | 18.5 (± 17.08) | | | |
| VAS C67D1 | 6.8 (± 18.89) | | | |
| VAS C71D1 | 7.7 (± 18.48) | | | |
| VAS C75D1 | 8.3 (± 14.89) | | | |
| VAS C79D1 | 7.2 (± 13.47) | | | |
| VAS C83D1 | 9.0 (± 10.74) | | | |
| VAS C87D1 | 7.5 (± 10.61) | | | |
| VAS C91D1 | 0.0 (± 9999999) | | | |
| VAS Discontinuation visit | -8.0 (± 22.60) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (up to approximately 6 years)

Adverse event reporting additional description:

Serious and other AEs were reported based on the safety population, which included all randomized participants who received any amount of study treatment, regardless of whether a full or partial dose was received. This population was evaluated after the initiation of study treatment.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Atezolizumab |
|-----------------------|--------------|

Reporting group description:

Participants received atezolizumab every 3 weeks (Q3W) until investigator assessed loss of clinical benefit, unacceptable toxicity, investigator or participant decision to withdraw from therapy, or death (whichever occurred first).

| Serious adverse events | Atezolizumab | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 380 / 997 (38.11%) | | |
| number of deaths (all causes) | 775 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Haemangioma of skin | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal adenocarcinoma | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of the oral cavity | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour pain | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 6 / 997 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic stenosis | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Intermittent claudication | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Hyperpyrexia | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 15 / 997 (1.50%) | | | |
| occurrences causally related to treatment / all | 7 / 18 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death | | | | |
| subjects affected / exposed | 8 / 997 (0.80%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 8 | | | |
| Fatigue | | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | | |
| occurrences causally related to treatment / all | 3 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chest pain | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pain | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Asthenia | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Complication of device insertion | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular device occlusion | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Systemic immune activation | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sarcoidosis | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Female genital tract fistula | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrotal inflammation | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spermatocele | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 11 / 997 (1.10%) | | |
| occurrences causally related to treatment / all | 11 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 997 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 2 / 2 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 5 / 997 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | | |
|---|-----------------|--|--|--|
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 1 / 2 | | | |
| Bronchopneumopathy | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoxia | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune-mediated lung disease | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary oedema | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary thrombosis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Hepatic enzyme increased subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial necrosis marker increased | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Craniocerebral injury | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral neck fracture | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip fracture | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incisional hernia | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Joint injury | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular procedure complication | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract stoma complication | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Traumatic haemothorax | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seroma | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular dysfunction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic valve disease | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 5 / 997 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pericardial haemorrhage | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral atrophy | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Corneal degeneration | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 16 / 997 (1.60%) | | |
| occurrences causally related to treatment / all | 1 / 17 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 997 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 997 (0.70%) | | |
| occurrences causally related to treatment / all | 3 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 6 / 997 (0.60%) | | |
| occurrences causally related to treatment / all | 5 / 6 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Vomiting | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 6 / 997 (0.60%) | | |
| occurrences causally related to treatment / all | 1 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune colitis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspepsia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterovesical fistula | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subileus | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Large intestinal obstruction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proctitis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Biliary obstruction | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute hepatic failure | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Hepatic cyst | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gallbladder obstruction | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Immune-mediated dermatitis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pemphigoid | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 16 / 997 (1.60%) | | |
| occurrences causally related to treatment / all | 0 / 16 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 5 / 997 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 5 / 997 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephritis | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder tamponade | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary bladder haemorrhage | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 19 / 997 (1.91%) | | |
| occurrences causally related to treatment / all | 0 / 20 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophysitis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 6 / 997 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Flank pain | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Compartment syndrome | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 997 (0.60%) | | |
| occurrences causally related to treatment / all | 1 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 59 / 997 (5.92%) | | |
| occurrences causally related to treatment / all | 0 / 86 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Urosepsis | | | |
| subjects affected / exposed | 19 / 997 (1.91%) | | |
| occurrences causally related to treatment / all | 0 / 20 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 997 (1.71%) | | |
| occurrences causally related to treatment / all | 0 / 17 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory tract infection | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 5 / 997 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pyelonephritis | | | | |
| subjects affected / exposed | 7 / 997 (0.70%) | | | |
| occurrences causally related to treatment / all | 0 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 5 / 997 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 12 / 997 (1.20%) | | | |
| occurrences causally related to treatment / all | 1 / 12 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Infection | | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Soft tissue infection | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Device related infection | | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erysipelas | | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 3 / 997 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative wound infection | | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cystitis | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Encephalitis | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocarditis | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Febrile infection | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis acute | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Scrotal abscess | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic Shock | | | | |
| subjects affected / exposed | 4 / 997 (0.40%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Urinary tract infection bacterial | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular device infection | | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Abdominal infection | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal sepsis | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Acute hepatitis B | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anal abscess | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chlamydial infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis infective | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Candida sepsis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin infection | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epididymitis | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia sepsis | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected cyst | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infective aneurysm | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Kidney infection | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Klebsiella bacteraemia | | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung abscess | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural sepsis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory moniliasis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dengue fever | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stoma site infection | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection pseudomonal | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 6 / 997 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 6 / 997 (0.60%) | | |
| occurrences causally related to treatment / all | 1 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 5 / 997 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Atezolizumab | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 888 / 997 (89.07%) | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 50 / 997 (5.02%) | | |
| occurrences (all) | 53 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 70 / 997 (7.02%) | | |
| occurrences (all) | 97 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 52 / 997 (5.22%) | | |
| occurrences (all) | 61 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|--------------------|--|--|
| Asthenia | | | |
| subjects affected / exposed | 211 / 997 (21.16%) | | |
| occurrences (all) | 270 | | |
| Fatigue | | | |
| subjects affected / exposed | 206 / 997 (20.66%) | | |
| occurrences (all) | 257 | | |
| Pyrexia | | | |
| subjects affected / exposed | 156 / 997 (15.65%) | | |
| occurrences (all) | 212 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 64 / 997 (6.42%) | | |
| occurrences (all) | 74 | | |
| Pain | | | |
| subjects affected / exposed | 57 / 997 (5.72%) | | |
| occurrences (all) | 58 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 182 / 997 (18.25%) | | |
| occurrences (all) | 213 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 62 / 997 (6.22%) | | |
| occurrences (all) | 67 | | |
| Vomiting | | | |
| subjects affected / exposed | 103 / 997 (10.33%) | | |
| occurrences (all) | 124 | | |
| Nausea | | | |
| subjects affected / exposed | 130 / 997 (13.04%) | | |
| occurrences (all) | 161 | | |
| Constipation | | | |
| subjects affected / exposed | 145 / 997 (14.54%) | | |
| occurrences (all) | 170 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 166 / 997 (16.65%) | | |
| occurrences (all) | 219 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|---------------------------|--|--|
| Dyspnoea subjects affected / exposed occurrences (all) | 72 / 997 (7.22%) 80 | | |
| Cough subjects affected / exposed occurrences (all) | 104 / 997 (10.43%) 124 | | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 125 / 997 (12.54%) 170 | | |
| Rash subjects affected / exposed occurrences (all) | 72 / 997 (7.22%) 99 | | |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 76 / 997 (7.62%) 96 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 67 / 997 (6.72%) 70 | | |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 64 / 997 (6.42%) 68 | | |
| Back pain subjects affected / exposed occurrences (all) | 120 / 997 (12.04%) 139 | | |
| Arthralgia subjects affected / exposed occurrences (all) | 132 / 997 (13.24%) 180 | | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 152 / 997 (15.25%) 240 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------------|--|--|
| Decreased appetite subjects affected / exposed occurrences (all) | 185 / 997 (18.56%) 212 | | |
|--|---------------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 May 2017 | The following updates were made to the protocol: [1] The term "immune-mediated" was changed to "immune-related" throughout the protocol; [2] The term "antitherapeutic antibody" was replaced with "anti-drug antibody;" [3] Updates were made to the eligibility criteria; [4] Language was updated to match current recommendations for atezolizumab administration; [5] Tumor response evaluations were revised; [6] Language for HBV serology was updated; [7] Language was added that clarified the use of biomarker samples after participant withdrew consent; [8] Language for electrocardiogram assessments was updated; [9] The list of AESI's was updated; [10] Correction to the reporting of infusion-related reactions; [11] The definition of abnormal liver function tests was revised; [12] Specific details related to the reporting of deaths was revised; [13] Language related to hospitalization or prolonged hospitalization was revised; [14] Two additional subgroup analyses were added; [15] Language related to protocol deviations was revised; [16] Link to the Roche Global Policy on Sharing of Clinical Trials was updated; [17] Appendices 1, 8 and 9 were updated; [18] Appendix 10 was added; [19] Additional minor changes were made to improve clarity and consistency. |
| 22 February 2018 | The following updates were made to the protocol: [1] Addition of appendix 11. |
| 08 October 2018 | The following updates were made to the protocol: [1] Appendix 11 was updated to include the changes made to the TECENTRIQ® International Brochure versions 12 and 13. |
| 22 October 2019 | The following updates were made to the protocol: [1] The Medical Monitor changed; [2] The interruption period of atezolizumab changed; [3] "Immune-related" was changed to "immune-mediated;" [4] Quality tolerance limits were introduced. |
| 03 March 2021 | The following updates were made to the protocol: [1] Text was added to describe the potential consequences of COVID-19 on atezolizumab therapy; [2] text was added to indicate that sites could confirm that appropriate temperature conditions had been maintained during Investigational Medicinal Product (IMP) transit; [3] text was added to clarify what were considered potential risks for atezolizumab; [4] the list of adverse events of special interest (AESIs) were updated; [5] reporting requirements for IRRs were updated; [6] |

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| 17 December 2021 | The following updates were made to the protocol: [1] Benefit-risk assessment and guidance on concomitant administration of coronavirus disease 2019 vaccines with atezolizumab was added; [2] Language was added to indicate that sites could confirm that appropriate temperature conditions had been maintained during IMP transit; [3] Public information source could be used to obtain information about survival status about participants who withdrew; [4] The protocol was updated to align with the current Roche Atezolizumab protocol template; [5] The Roche Global Policy on Continued Access to Investigational Medicinal Product was added; [6] The responsibilities of the Principal Investigator and the role of the Medical Monitor were clarified; [7] The serious adverse events and adverse events of special interest reporting timelines were corrected; [8] Language clarified that study adverse event reports would not be derived from patient reported outcome (PRO) data by the Sponsor; [9] Additional language regarding Roche's data retention policy, study compliance with applicable laws and study data management, sharing and application was added; [10] The language regarding the informed consent form revision and the re-consenting in accordance with local applicable laws and IRB/EC policy was clarified; [11] The guidelines for management of suspected anaphylactic reaction were updated; [12] The term "primary biliary cholangitis" replaced "primary biliary cirrhosis;" [13] Adverse Event management guidelines were updated; [14] The study synopsis was simplified; [15] Additional minor changes were made to improve clarity and consistency. |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported