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	v1
This version publication date	27 December 2023
First version publication date	27 December 2023

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:

7 participants were not included in the safety population as they did not receive the study drug.

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: 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 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: PFS as per Modified Response Evaluation Criteria in Solid Tumors

(Modified RECIST)

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: 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: 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:

Best overall response rate was assessed by the investigators according to the modified Response Evaluation Criteria in Solid Tumors (RECIST). 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 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:

Best overall response rate was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The assessment of BOR included post-screening RECIST assessments obtained up to: 1) disease progression, 2) death from any cause, 3) last evaluable RECIST assessment in the absence of disease progression or death, 4) start of a subsequent anti-cancer therapy; whichever occurred first.

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 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: 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.

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	1004			
Units: Months				
median (confidence interval 95%)	29.73 (21.72 to 43.30)			

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.

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	1004			
Units: Months				
median (confidence interval 95%)	27.79 (18.89 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.

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	1004			
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)			
Emotional score C19D1	4.90 (± 20.156)			
Emotional score C23D1	5.45 (± 20.057)			
Emotional score C27D1	5.94 (± 19.538)			
Emotional score C31D1	10.17 (± 19.057)			
Emotional score C35D1	8.90 (± 19.361)			
Emotional score C39D1	9.80 (± 20.883)			

Emotional score C43D1	8.22 (± 20.618)			
Emotional score C47D1	7.21 (± 19.762)			
Emotional score C51D1	9.23 (± 20.377)			
Emotional score C55D1	8.48 (± 18.359)			
Emotional score C59D1	9.88 (± 17.890)			
Emotional score C63D1	9.12 (± 16.766)			
Emotional score C67D1	8.52 (± 20.452)			
Emotional score C71D1	7.56 (± 18.345)			
Emotional score C75D1	7.33 (± 21.430)			
Emotional score C79D1	5.84 (± 22.465)			
Emotional score C83D1	8.34 (± 8.913)			
Emotional score C87D1	0.00 (± 47.235)			
Emotional score C91D1	-33.40 (± 9999999)			
Emotional score Discontinuation visit	-7.49 (± 23.771)			
Cognitive score Baseline	85.43 (± 20.943)			
Cognitive score C2D1	-1.83 (± 19.255)			
Cognitive score C3D1	-2.40 (± 18.344)			
Cognitive score C4D1	-1.58 (± 15.886)			
Cognitive score C7D1	0.00 (± 16.737)			
Cognitive score C10D1	-0.78 (± 16.763)			
Cognitive score C13D1	-0.37 (± 14.476)			
Cognitive score C16D1	0.44 (± 16.743)			
Cognitive score C19D1	-0.10 (± 17.221)			
Cognitive score C23D1	-1.27 (± 17.973)			
Cognitive score C27D1	-0.68 (± 17.324)			
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)			
Social score C43D1	5.26 (± 25.704)			
Social score C47D1	4.96 (± 27.412)			
Social score C51D1	6.34 (± 24.541)			
Social score C55D1	6.55 (± 21.946)			
Social score C59D1	8.03 (± 22.369)			
Social score C63D1	6.29 (± 22.695)			

Social score C67D1	5.80 (± 27.491)			
Social score C71D1	3.50 (± 21.995)			
Social score C75D1	10.01 (± 22.041)			
Social score C79D1	5.84 (± 28.767)			
Social score C83D1	18.75 (± 27.383)			
Social score C87D1	8.30 (± 11.738)			
Social score C91D1	33.30 (± 9999999)			
Social score Discontinuation visit	-12.20 (± 33.586)			
Fatigue score Baseline	36.04 (± 26.343)			
Fatigue score C2D1	5.58 (± 22.444)			
Fatigue score C3D1	5.01 (± 23.869)			
Fatigue score C4D1	3.27 (± 23.637)			
Fatigue score C7D1	-2.56 (± 24.879)			
Fatigue score C10D1	-3.95 (± 23.633)			
Fatigue score C13D1	-2.46 (± 23.492)			
Fatigue score C16D1	-4.97 (± 25.081)			
Fatigue score C19D1	-4.73 (± 26.358)			
Fatigue score C23D1	-3.34 (± 26.603)			
Fatigue score C27D1	-6.01 (± 24.252)			
Fatigue score C31D1	-10.09 (± 25.731)			
Fatigue score C35D1	-8.95 (± 28.738)			
Fatigue score C39D1	-9.76 (± 28.299)			
Fatigue score C43D1	-7.75 (± 28.295)			
Fatigue score C47D1	-7.95 (± 24.164)			
Fatigue score C51D1	-9.68 (± 25.102)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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) a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; 2) a visual analogue scale (VAS) that measures health state. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction.

The ITT population included all enrolled participants.

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	1004			
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)			
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)			
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)			
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 adverse events 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
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)			
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		
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			
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 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			
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			
General disorders and administration site conditions				
Asthenia				

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			
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			
Hyperpyrexia				

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		
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		
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		
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				
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			
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		
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		
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		
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		
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		
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		
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		
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			
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			
Fall				
subjects affected / exposed	3 / 997 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
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			
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			
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			
Cardiac disorders				
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			
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			
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			
Nervous system disorders				
Epilepsy				
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			
Headache				
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			
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			
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			
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			
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			
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			
Blood and lymphatic system disorders				
Pancytopenia				
subjects affected / exposed	1 / 997 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
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			
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				
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 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			
Ascites				
subjects affected / exposed	1 / 997 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
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		
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		
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		
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			
Subileus				
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			
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			
Hepatobiliary disorders				
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			
Hepatotoxicity				
subjects affected / exposed	2 / 997 (0.20%)			
occurrences causally related to treatment / all	2 / 2			
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			
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			
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			
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			
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			
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			
Skin and subcutaneous tissue disorders				
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			
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			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	19 / 997 (1.91%)			
occurrences causally related to treatment / all	0 / 20			
deaths causally related to treatment / all	0 / 2			
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			
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				
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			
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			
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			

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			
Osteoarthritis				
subjects affected / exposed	2 / 997 (0.20%)			
occurrences causally related to treatment / all	0 / 3			
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			
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			
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			
Pyelonephritis				
subjects affected / exposed	7 / 997 (0.70%)			
occurrences causally related to treatment / all	0 / 7			
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		
Pneumonia			
subjects affected / exposed	17 / 997 (1.71%)		
occurrences causally related to treatment / all	0 / 17		
deaths causally related to treatment / all	0 / 1		
Cellulitis			
subjects affected / exposed	5 / 997 (0.50%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
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		
Infection			
subjects affected / exposed	4 / 997 (0.40%)		
occurrences causally related to treatment / all	0 / 4		
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		
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			
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			
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			
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			
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			
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			
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			
Appendicitis				

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			
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			
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			
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			
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			
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			
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			
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			
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			
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			
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			
Hypercalcaemia				
subjects affected / exposed	5 / 997 (0.50%)			
occurrences causally related to treatment / all	1 / 5			
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			
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			
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			
Hypokalaemia				

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		
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		
Hypoglycaemia			
subjects affected / exposed	2 / 997 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
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			
Blood creatinine increased			
subjects affected / exposed	70 / 997 (7.02%)		
occurrences (all)	97		
Weight decreased			
subjects affected / exposed	50 / 997 (5.02%)		
occurrences (all)	53		
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		
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		
Fatigue			
subjects affected / exposed	206 / 997 (20.66%)		
occurrences (all)	257		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	182 / 997 (18.25%)		
occurrences (all)	213		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	166 / 997 (16.65%)		
occurrences (all)	219		
Constipation			
subjects affected / exposed	145 / 997 (14.54%)		
occurrences (all)	170		
Nausea			
subjects affected / exposed	130 / 997 (13.04%)		
occurrences (all)	161		
Vomiting			
subjects affected / exposed	103 / 997 (10.33%)		
occurrences (all)	124		
Abdominal pain			
subjects affected / exposed	62 / 997 (6.22%)		
occurrences (all)	67		
Respiratory, thoracic and mediastinal disorders			

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

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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported