



Clinical trial results:

A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to assess the efficacy and safety of Olaparib Monotherapy versus Physician's Choice Single Agent Chemotherapy in the Treatment of Platinum Sensitive Relapsed Ovarian Cancer in Patients carrying germline BRCA1/2 Mutations

Summary

EudraCT number	2014-003438-20
Trial protocol	HU BE CZ ES IT
Global end of trial date	19 July 2022

Results information

Result version number	v1 (current)
This version publication date	21 September 2022
First version publication date	21 September 2022

Trial information

Trial identification

Sponsor protocol code	D0816C00010
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02282020
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Global Clinical Leader, AstraZeneca AB, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Leader, AstraZeneca AB, +1 877-240-9479, information.center@astrazeneca.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	16 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of olaparib vs. physician's choice single agent chemotherapy by assessment of Objective Response Rate (ORR) using blinded independent central review (BICR).

Protection of trial subjects:

The study used an external IDMC to perform interim reviews of accumulating study safety data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Korea, Republic of: 33
Country: Number of subjects enrolled	Poland: 32
Country: Number of subjects enrolled	Czechia: 21
Country: Number of subjects enrolled	Mexico: 21
Country: Number of subjects enrolled	Brazil: 19
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Argentina: 3
Worldwide total number of subjects	266
EEA total number of subjects	128

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	186
From 65 to 84 years	79
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 678 patients were screened (gave informed consent) at 94 centres in 13 countries. Of the 678 patients screened, 266 patients were randomised from 78 sites in 13 countries worldwide.

A wash-out period of up to 5 weeks was required for participants who have previously taken potent inhibitors or CYP3A4/5 inducers.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio between olaparib and single agent chemotherapy. Of the 266 patients randomised, 178 patients were in the olaparib arm and 88 in the chemotherapy arm.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Olaparib 300mg BID

Arm description:

Participants received olaparib twice daily as a 300 mg tablet.

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablet taken twice daily.

Arm title	Single Agent Chemotherapy
------------------	---------------------------

Arm description:

Participants received physician's choice of chemotherapy, out of weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine.

Arm type	Active comparator
Investigational medicinal product name	Physicians choice of paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered dose and schedule as required for physicians choice of chemotherapy.

Number of subjects in period 1	Olaparib 300mg BID	Single Agent Chemotherapy
Started	178	88
Received Treatment	178	76
Completed	19	0
Not completed	159	88
Severe Non-compliance to Protocol	1	-
Consent withdrawn by subject	7	10
Objective Disease Progression	128	30
Adverse event, non-fatal	18	15
Developed Discontinuation Criteria	-	2
Miscellaneous	5	19
Withdrew Consent Prior to Dosing	-	12

Baseline characteristics

Reporting groups

Reporting group title	Olaparib 300mg BID
Reporting group description:	
Participants received olaparib twice daily as a 300 mg tablet.	
Reporting group title	Single Agent Chemotherapy
Reporting group description:	
Participants received physician's choice of chemotherapy, out of weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine.	

Reporting group values	Olaparib 300mg BID	Single Agent Chemotherapy	Total
Number of subjects	178	88	266
Age categorical			
Units: Subjects			
Adults (18-50 years)	31	15	46
From 50-65 years	101	39	140
65 years and over	46	34	80
Age Continuous			
Units: Years			
arithmetic mean	58.5	60.4	
standard deviation	± 9.3	± 9.9	-
Sex: Female, Male			
Units: Participants			
Female	178	88	266
Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
White	148	75	223
Black Or African American	1	1	2
Asian	24	10	34
American Indian Or Alaska Native	4	2	6
Other	1	0	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	31	16	47
Not Hispanic or Latino	146	72	218
Unknown or Not Reported	1	0	1

Subject analysis sets

Subject analysis set title	Olaparib 300 mg BID
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received olaparib twice daily as a 300 mg tablet.	
Subject analysis set title	Selected Chemotherapy
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received physician's choice of chemotherapy, out of weekly paclitaxel, topotecan, pegylated	

Reporting group values	Olaparib 300 mg BID	Selected Chemotherapy	
Number of subjects	178	88	
Age categorical Units: Subjects			
Adults (18-50 years)	31	15	
From 50-65 years	101	39	
65 years and over	46	34	
Age Continuous Units: Years			
arithmetic mean	58.5	60.4	
standard deviation	± 9.3	± 9.9	
Sex: Female, Male Units: Participants			
Female	178	88	
Male	0	0	
Race/Ethnicity, Customized Units: Subjects			
White	148	75	
Black Or African American	1	1	
Asian	24	10	
American Indian Or Alaska Native	4	2	
Other	1	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	31	16	
Not Hispanic or Latino	146	72	
Unknown or Not Reported	1	0	

End points

End points reporting groups

Reporting group title	Olaparib 300mg BID
Reporting group description: Participants received olaparib twice daily as a 300 mg tablet.	
Reporting group title	Single Agent Chemotherapy
Reporting group description: Participants received physician's choice of chemotherapy, out of weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine.	
Subject analysis set title	Olaparib 300 mg BID
Subject analysis set type	Full analysis
Subject analysis set description: Participants received olaparib twice daily as a 300 mg tablet.	
Subject analysis set title	Selected Chemotherapy
Subject analysis set type	Full analysis
Subject analysis set description: Participants received physician's choice of chemotherapy, out of weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine.	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description: To determine the efficacy of olaparib vs. physician's choice single agent chemotherapy by assessment of Objective Response Rate (ORR) using blinded independent central review (BICR) Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria was used by a Blinded Independent Central Review (BICR) to assess participant response to treatment ORR is the number of participants with Complete Response (CR) or Partial Response (PR) in the Measurable Disease Analysis Set (MDAS). MDAS includes all participants in the FAS with measurable disease at baseline (as per RECIST 1.1), determined using BICR. Complete response is declared when all lesions have disappeared or all lesions have disappeared and all nodal disease is < 10 mm each. Partial response is declared when there is a decrease in sum of diameters of target lesions \geq 30%.	
End point type	Primary
End point timeframe: RECIST follow-up assessments performed every 8 weeks (\pm 1 week), up to 48 weeks, then every 12 weeks (\pm 1 week) from randomisation, assessed from date of first patient randomised to data cut off: 10Oct2018 (approx. 3 years 8 months)	

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	72		
Units: Count of Participants	109	37		

Statistical analyses

Statistical analysis title	ORR based by BICR, adjusted logistic regression
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	4.58

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by progression free survival (PFS) using BICR assessment according to RECIST 1.1 criteria	
PFS is defined as the time from randomization until the date of objective radiological disease progression according to RECIST 1.1 or death (by any cause in the absence of disease progression) regardless of whether the participant withdrew from randomized therapy or received another anti-cancer therapy prior to disease progression (i.e., date of RECIST progression/death or censoring – date of randomization +1).	
End point type	Secondary
End point timeframe:	
RECIST follow-up assessments performed every 8 weeks (± 1 week), up to 48 weeks, then every 12 weeks (± 1 week) from randomisation, assessed from date of first patient randomised to data cut off: 10Oct2018 (approx. 3 years 8 months)	

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	88		
Units: Months				
median (confidence interval 95%)	13.4 (10.9 to 14.1)	9.2 (7.6 to 11.2)		

Statistical analyses

Statistical analysis title	rPFS by BICR, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.91

Notes:

[1] - Determined using a log-rank test with a factor for time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Time from Randomisation to Second Progression (PFS2)

End point title	Time from Randomisation to Second Progression (PFS2)
-----------------	--

End point description:

To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by second progression (PFS2).

Time from randomization to PFS2 is defined as the time from the date of randomization to the earliest of the progression events subsequent to first progression or death. The date of second progression was recorded by the investigator and defined according to local standard clinical practice, and could involve objective radiological, clinical, cancer antigen-125 (CA-125) progression or death. CA-125 progression was assessed per Gynecological Cancer Intergroup (GCIG) criteria.

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

End point timeframe:

Visits to occur every 12 weeks from the date of first progression, assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	88		
Units: Months				
median (confidence interval 95%)	23.6 (19.2 to 26.0)	19.6 (16.9 to 21.8)		

Statistical analyses

Statistical analysis title	PFS2, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.15

Notes:

[2] - Determined using a log-rank test with a factor for time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by overall survival (OS).	
Overall survival is defined as the time from the date of randomisation until death due to any cause.	
End point type	Secondary
End point timeframe:	
Visits to occur every 12 weeks from the date of first progression, assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)	

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	88		
Units: Months				
median (confidence interval 95%)	34.9 (30.0 to 39.2)	32.9 (23.5 to 43.2)		

Statistical analyses

Statistical analysis title	OS, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.714 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.49

Notes:

[3] - Determined using a log-rank test with a factor for time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Time To Earliest Progression By RECIST 1.1 Or Cancer Antigen (CA) -125 Or Death

End point title	Time To Earliest Progression By RECIST 1.1 Or Cancer Antigen (CA) -125 Or Death
-----------------	---

End point description:

To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by time to earliest progression by RECIST 1.1 or CA-125 or death.

Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria was used to assess participant response to treatment. CA-125 progression was assessed per Gynecological Cancer Intergroup (GCIG).

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

End point timeframe:

RECIST and CA-125 follow-up assessments performed every 8 weeks (± 1 week), up to 48 weeks, then every 12 weeks (± 1 week) from randomisation, assessed from date of first patient randomised to data cut off: 10Oct2018 (approx. 3 years 8 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	88		
Units: Months				
median (confidence interval 95%)	11.1 (9.7 to 13.8)	7.9 (6.9 to 9.4)		

Statistical analyses

Statistical analysis title	Earliest progression, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.85

Notes:

[4] - Determined using a log-rank test with a factor for time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Time From Randomization To First Subsequent Therapy Or Death (TFST)

End point title	Time From Randomization To First Subsequent Therapy Or Death (TFST)
-----------------	---

End point description:

To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by time from randomisation to first subsequent therapy or death (TFST)

TFST is defined as the time from the date of randomisation to the earlier of first subsequent chemotherapy start date or death.

Anti-cancer treatments include chemotherapy and targeted agents.

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

End point timeframe:

Anti-cancer treatments initiated post discontinuation of study treatment and investigator's opinion of response and date of progression recorded, assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	88		
Units: Months				
median (confidence interval 95%)	15.4 (13.5 to 17.6)	10.9 (9.2 to 14.2)		

Statistical analyses

Statistical analysis title	TFST, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.69

Notes:

[5] - Model included factors for number of prior chemotherapy regimens received for ovarian cancer (2 or 3 prior lines vs 4 or more lines) and time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Time From Randomization To Second Subsequent Therapy Or Death

(TSST)

End point title	Time From Randomization To Second Subsequent Therapy Or Death (TSST)
-----------------	--

End point description:

To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by time from randomisation to second subsequent therapy or death (TSST)

TSST was defined as the time from the date of randomisation to the earlier of second subsequent chemotherapy start date or death.

Anti-cancer treatments include chemotherapy and targeted agents.

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

End point timeframe:

Anti-cancer treatments initiated post discontinuation of study treatment and investigator's opinion of response and date of progression recorded, assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	88		
Units: Months				
median (confidence interval 95%)	25.2 (21.3 to 27.8)	19.9 (18.0 to 24.2)		

Statistical analyses

Statistical analysis title	TSST, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.05

Notes:

[6] - Model included factors for number of prior chemotherapy regimens received for ovarian cancer (2 or 3 prior lines vs 4 or more lines) and time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Time From Randomization To Study Treatment Discontinuation Or Death (TDT)

End point title	Time From Randomization To Study Treatment Discontinuation Or Death (TDT)
-----------------	---

End point description:

To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by time to study treatment discontinuation or death (TDT)

TDT was defined as the time from randomization to the earlier of the date of study treatment discontinuation or death.

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

End point timeframe:

Patients randomised to Olaparib administer their tablets orally at a dose of 300 mg twice daily and continue Olaparib until objective disease progression. Assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	88		
Units: Months				
median (confidence interval 95%)	13.1 (10.2 to 14.6)	5.1 (4.7 to 6.5)		

Statistical analyses

Statistical analysis title	TDT, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.29

Notes:

[7] - Model included factors for number of prior chemotherapy regimens received for ovarian cancer (2 or 3 prior lines vs 4 or more lines) and time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
-----------------	----------------------------

End point description:

To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by duration of response (DoR) by BICR using RECIST 1.1 criteria for evaluable patients, in MDAS. MDAS includes all participants in the FAS with measurable disease at baseline (as per RECIST 1.1), determined using BICR.

Duration of response is the time from the first documentation of complete response (CR) or partial response (PR) until the date of progression or death, or the last evaluable RECIST assessment for participants that do not progress or progress after 2 missed assessments. Response Evaluation Criteria

In Solid Tumors (RECIST) 1.1 criteria was used to assess participant response to treatment.

End point type	Secondary
End point timeframe:	
RECIST follow-up assessments performed every 8 weeks (± 1 week), up to 48 weeks, then every 12 weeks (± 1 week) from randomisation, assessed from date of first patient randomised to data cut off: 10Oct2018 (approx. 3 years 8 months)	

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	37		
Units: Months				
median (inter-quartile range (Q1-Q3))	9.4 (5.6 to 25.7)	10.2 (5.5 to 15.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)
End point description:	
To determine the efficacy of single agent olaparib vs. physician's choice single agent chemotherapy by time to response (TTR) by BICR using RECIST 1.1 criteria for evaluable patients, in MDAS. MDAS includes all participants in the FAS with measurable disease at baseline (as per RECIST 1.1), determined using BICR.	
TTR was defined as the time from randomization until the date of first documented response by Blinded independent central review (BICR) assessment.	
End point type	Secondary
End point timeframe:	
RECIST follow-up assessments performed every 8 weeks (± 1 week), up to 48 weeks, then every 12 weeks (± 1 week) from randomisation, assessed from date of first patient randomised to data cut off: 10Oct2018 (approx. 3 years 8 months)	

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	37		
Units: Months				
median (inter-quartile range (Q1-Q3))	2.0 (1.8 to 3.9)	3.5 (1.8 to 3.7)		

Statistical analyses

Secondary: Mean Change From Baseline In Trial Outcome Index (TOI) Score

End point title	Mean Change From Baseline In Trial Outcome Index (TOI) Score
-----------------	--

End point description:

To compare the efficacy of single agent olaparib versus physician's choice single agent chemotherapy on the Health-related Quality of Life (HRQoL) as measured by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)

The TOI score was derived from the sum of the scores of the 25 items included in the physical well-being (7 items), functional well-being (7 items), and additional concerns ovarian cancer subscale (11 items) of the FACT-O questionnaire Version 4. TOI score ranges from 0 to 100, a higher score indicates a higher HRQoL. A negative change in score from baseline indicated a worsening in symptoms.

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

End point timeframe:

Baseline (Day 1) to Week 48 (± 1 week). DCO: 10Oct2018

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	62		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-2.4 (± 11.1)	-3.6 (± 9.8)		

Statistical analyses

Statistical analysis title	Change from baseline in TOI, MMRM
Comparison groups	Olaparib 300mg BID v Single Agent Chemotherapy
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	5.5

Secondary: Number of Participants Who Show an Improvement in TOI Score

End point title	Number of Participants Who Show an Improvement in TOI Score
-----------------	---

End point description:

To compare the efficacy of single agent olaparib versus physician's choice single agent chemotherapy on the Health-related Quality of Life (HRQoL) as measured by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O)

The TOI score was derived from the sum of the scores of the 25 items included in the physical well-being (7 items), functional well-being (7 items), and additional concerns ovarian cancer subscale (11 items) of the FACT-O questionnaire Version 4. TOI score ranges from 0 to 100, a higher score indicates a higher health-related quality of life (HRQoL). A change in at least 10 points was considered clinically relevant.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Week 48 (±1 week). DCO: 100Oct2018	

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	69		
Units: Count of Participants	25	5		

Statistical analyses

Statistical analysis title	Improvement in TOI, adjusted logistic regression
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092 ^[8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	6.86

Notes:

[8] - Estimated from an unadjusted logistic regression model

Secondary: Objective Response Rate (ORR) in Breast Cancer Susceptibility (BRCA) Gene Population by Blinded Independent Central Review (BICR)

End point title	Objective Response Rate (ORR) in Breast Cancer Susceptibility (BRCA) Gene Population by Blinded Independent Central Review (BICR)
-----------------	---

End point description:

BRCA gene population includes participants identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (eg, gene sequencing and large rearrangement analysis).

The number of participants with complete or partial response per Response Evaluation Criteria In Solid

Tumors (RECIST) 1.1 criteria. Partial response is declared when there is a decrease in sum of target disease $\geq 30\%$. Complete response is declared when all lesions have disappeared or all lesions have disappeared and all nodal disease is < 10 mm each.

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

End point timeframe:

RECIST follow-up assessments performed every 8 weeks (± 1 week), up to 48 weeks, then every 12 weeks (± 1 week) from randomisation, assessed from date of first patient randomised to data cut off: 10Oct2018 (approx. 3 years 8 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	70		
Units: Count of Participants	103	36		

Statistical analyses

Statistical analysis title	ORR in BRCA by BICR, adjusted logistic regression
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	4.39

Notes:

[9] - Determined using a log-rank test with a factor for time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Number of Participants who Experienced Disease Progression or Death in BRCA Gene Population by Blinded Independent Central Review (BICR)

End point title	Number of Participants who Experienced Disease Progression or Death in BRCA Gene Population by Blinded Independent Central Review (BICR)
-----------------	--

End point description:

BRCA gene population includes participants identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (eg, gene sequencing and large rearrangement analysis).

Progressive disease was defined as at least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

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

End point timeframe:

RECIST follow-up assessments performed every 8 weeks (± 1 week), up to 48 weeks, then every 12

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Count of Participants	105	48		

Statistical analyses

Statistical analysis title	PFS in BRCA by BICR, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014 ^[10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.91

Notes:

[10] - Determined using a log-rank test with a factor for time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Number of Participants who Experienced Second Progression or Death (PFS2) in BRCA Gene Population

End point title	Number of Participants who Experienced Second Progression or Death (PFS2) in BRCA Gene Population
-----------------	---

End point description:

BRCA gene population includes participants identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (eg, gene sequencing and large rearrangement analysis).

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

End point timeframe:

Visits to occur every 12 weeks from the date of first progression, assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Count of Participants	110	48		

Statistical analyses

Statistical analysis title	PFS2 in BRCA, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.213 ^[11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.14

Notes:

[11] - Determined using a log-rank test with a factor for time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Overall Survival (OS) in BRCA Gene Population

End point title	Overall Survival (OS) in BRCA Gene Population
-----------------	---

End point description:

BRCA gene population includes participants identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (eg, gene sequencing and large rearrangement analysis).

OS in BRCA gene population was measured by the number of participants who died due to any cause.

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

End point timeframe:

Visits to occur every 12 weeks from the date of first progression, assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Count of Participants	111	45		

Statistical analyses

Statistical analysis title	OS in BRCA, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.699 ^[12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.51

Notes:

[12] - Determined using a log-rank test with a factor for time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Number of Participants who Discontinued Study Treatment or Died in BRCA Gene Population

End point title	Number of Participants who Discontinued Study Treatment or Died in BRCA Gene Population
-----------------	---

End point description:

BRCA gene population includes participants identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (eg, gene sequencing and large rearrangement analysis).

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

End point timeframe:

Patients randomised to Olaparib administer their tablets orally at a dose of 300 mg twice daily and continue Olaparib until objective disease progression. Assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Count of Participants	151	76		

Statistical analyses

Statistical analysis title	TDT in BRCA, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.27

Notes:

[13] - Model included factors for number of prior chemotherapy regimens received for ovarian cancer (2 or 3 prior lines vs 4 or more lines) and time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Number of Participants who Received Subsequent Chemotherapy or Died in BRCA Gene Population

End point title	Number of Participants who Received Subsequent Chemotherapy or Died in BRCA Gene Population
-----------------	---

End point description:

BRCA gene population includes participants identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (eg, gene sequencing and large rearrangement analysis).

Anti-cancer treatments include chemotherapy and targeted agents.

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

End point timeframe:

Anti-cancer treatments initiated post discontinuation of study treatment and investigator's opinion of response and date of progression recorded, assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Count of Participants	138	66		

Statistical analyses

Statistical analysis title	TFST in BRCA, stratified log rank test
Comparison groups	Olaparib 300mg BID v Single Agent Chemotherapy
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.66

Notes:

[14] - Model included factors for number of prior chemotherapy regimens received for ovarian cancer (2 or 3 prior lines vs 4 or more lines) and time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Number of Participants who Received Second Subsequent Chemotherapy or Died in BRCA Gene Population

End point title	Number of Participants who Received Second Subsequent Chemotherapy or Died in BRCA Gene Population
-----------------	--

End point description:

BRCA gene population includes participants identified as having a deleterious or suspected deleterious variant in either of the BRCA genes using variants identified with current and future BRCA mutation assays (eg, gene sequencing and large rearrangement analysis).

Anti-cancer treatments include chemotherapy and targeted agents.

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

End point timeframe:

Anti-cancer treatments initiated post discontinuation of study treatment and investigator's opinion of response and date of progression recorded, assessed from date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Count of Participants	127	56		

Statistical analyses

Statistical analysis title	TSST, stratified log rank test
Comparison groups	Single Agent Chemotherapy v Olaparib 300mg BID
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055 ^[15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.01

Notes:

[15] - Model included factors for number of prior chemotherapy regimens received for ovarian cancer (2 or 3 prior lines vs 4 or more lines) and time to disease progression after the end of last platinum based chemotherapy (6-12 months vs > 12 months).

Secondary: Geometric Mean Plasma Concentration of Olaparib

End point title	Geometric Mean Plasma Concentration of Olaparib ^[16]
-----------------	---

End point description:

Summary of plasma concentrations (ug/mL) of olaparib

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

End point timeframe:

Day 1, 1 hour post-dose and Day 29 pre-dose. DCO: 10Oct2018

Notes:

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

Justification: Endpoint only applies to experimental arm

End point values	Olaparib 300mg BID			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Day 1, 1 hour post-dose	4.76 (± 112.93)			
Day 29, pre-dose	1.78 (± 100.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experience at Least One Adverse Event (AE)

End point title	Number of Participants Who Experience at Least One Adverse Event (AE)
-----------------	---

End point description:

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

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

End point timeframe:

Safety Follow-up 30 days after last dose of IP, assessed from the date of first patient randomised to data cut off: 16Apr2021 (approx. 6 years 2 months)

End point values	Olaparib 300mg BID	Single Agent Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	76		
Units: Count of Participants	175	73		

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days following date of last dose

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

Dictionary used

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

Dictionary version	24.0
--------------------	------

Reporting groups

Reporting group title	Olaparib 300mg BID
-----------------------	--------------------

Reporting group description:

Participants received olaparib twice daily as a 300 mg tablet.

Reporting group title	Single Agent Chemotherapy
-----------------------	---------------------------

Reporting group description:

Participants received physician's choice of chemotherapy, out of weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine.

Serious adverse events	Olaparib 300mg BID	Single Agent Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 178 (25.84%)	14 / 76 (18.42%)	
number of deaths (all causes)	116	46	
number of deaths resulting from adverse events	6	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myeloid leukaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema peripheral			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 178 (1.12%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	3 / 178 (1.69%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 178 (3.37%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			
subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 178 (1.12%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 178 (1.69%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic nephropathy			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract obstruction			

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Periarthritis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Corneal abscess			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Device related infection			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Olaparib 300mg BID	Single Agent Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	175 / 178 (98.31%)	73 / 76 (96.05%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			

subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 178 (1.69%)	2 / 76 (2.63%)	
occurrences (all)	3	3	
Embolism			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Deep vein thrombosis			
subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences (all)	2	1	
Hot flush			
subjects affected / exposed	4 / 178 (2.25%)	1 / 76 (1.32%)	
occurrences (all)	4	1	
Hyperaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	5 / 178 (2.81%)	3 / 76 (3.95%)	
occurrences (all)	5	3	
Hypotension			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Lymphoedema			
subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences (all)	2	1	
Peripheral venous disease			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	

Thrombophlebitis superficial subjects affected / exposed occurrences (all)	2 / 178 (1.12%) 2	0 / 76 (0.00%) 0	
Venous thrombosis subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Thrombosis subjects affected / exposed occurrences (all)	0 / 178 (0.00%) 0	1 / 76 (1.32%) 1	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	35 / 178 (19.66%) 52	12 / 76 (15.79%) 16	
Fatigue subjects affected / exposed occurrences (all)	66 / 178 (37.08%) 91	20 / 76 (26.32%) 26	
Influenza like illness subjects affected / exposed occurrences (all)	7 / 178 (3.93%) 8	4 / 76 (5.26%) 5	
Mucosal inflammation subjects affected / exposed occurrences (all)	5 / 178 (2.81%) 5	10 / 76 (13.16%) 11	
Oedema peripheral subjects affected / exposed occurrences (all)	16 / 178 (8.99%) 24	10 / 76 (13.16%) 16	
Pyrexia subjects affected / exposed occurrences (all)	21 / 178 (11.80%) 28	8 / 76 (10.53%) 10	
Application site pain subjects affected / exposed occurrences (all)	0 / 178 (0.00%) 0	1 / 76 (1.32%) 1	
Catheter site erythema subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Catheter site pain			

subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	2
Catheter site rash		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Chest discomfort		
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	3
Chest pain		
subjects affected / exposed	2 / 178 (1.12%)	2 / 76 (2.63%)
occurrences (all)	3	3
Chills		
subjects affected / exposed	7 / 178 (3.93%)	1 / 76 (1.32%)
occurrences (all)	9	1
Face oedema		
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	2
Illness		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	7	0
General physical health deterioration		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Feeling hot		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Infusion site extravasation		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Injection site bruising		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Injection site reaction		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Malaise		

subjects affected / exposed	5 / 178 (2.81%)	0 / 76 (0.00%)	
occurrences (all)	14	0	
Localised oedema			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Oedema			
subjects affected / exposed	1 / 178 (0.56%)	2 / 76 (2.63%)	
occurrences (all)	2	2	
Medical device pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)	
occurrences (all)	3	0	
Pain			
subjects affected / exposed	5 / 178 (2.81%)	2 / 76 (2.63%)	
occurrences (all)	5	2	
Swelling face			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Drug hypersensitivity			
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)	
occurrences (all)	0	2	
Hypersensitivity			
subjects affected / exposed	3 / 178 (1.69%)	1 / 76 (1.32%)	
occurrences (all)	3	1	
Seasonal allergy			
subjects affected / exposed	4 / 178 (2.25%)	3 / 76 (3.95%)	
occurrences (all)	4	3	

Reproductive system and breast disorders			
Atrophic vulvovaginitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Breast pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Intermenstrual bleeding			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Dyspareunia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	2	
Vaginal haemorrhage			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	3	
Vaginal discharge			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Vulvovaginal dryness			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Vulvovaginal erythema			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal inflammation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Cough		
subjects affected / exposed	18 / 178 (10.11%)	10 / 76 (13.16%)
occurrences (all)	24	10
Dyspnoea		
subjects affected / exposed	22 / 178 (12.36%)	8 / 76 (10.53%)
occurrences (all)	26	8
Epistaxis		
subjects affected / exposed	0 / 178 (0.00%)	5 / 76 (6.58%)
occurrences (all)	0	6
Chronic obstructive pulmonary disease		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Dysphonia		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Dyspnoea exertional		
subjects affected / exposed	2 / 178 (1.12%)	2 / 76 (2.63%)
occurrences (all)	3	2
Hiccups		
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)
occurrences (all)	4	0
Hypoxia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Nasal dryness		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Nasal congestion		
subjects affected / exposed	3 / 178 (1.69%)	1 / 76 (1.32%)
occurrences (all)	3	1
Laryngeal inflammation		
subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)
occurrences (all)	4	0
Obstructive airways disorder		

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	5 / 178 (2.81%)	1 / 76 (1.32%)	
occurrences (all)	5	1	
Productive cough			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Pulmonary embolism			
subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences (all)	2	1	
Respiratory fatigue			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Pulmonary mass			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)	
occurrences (all)	3	0	
Rhinorrhoea			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Sinus congestion			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Throat irritation			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	3	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Psychiatric disorders			

Depression			
subjects affected / exposed	9 / 178 (5.06%)	2 / 76 (2.63%)	
occurrences (all)	9	2	
Insomnia			
subjects affected / exposed	17 / 178 (9.55%)	5 / 76 (6.58%)	
occurrences (all)	18	5	
Anxiety			
subjects affected / exposed	4 / 178 (2.25%)	6 / 76 (7.89%)	
occurrences (all)	6	6	
Confusional state			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Delusion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Nervousness			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences (all)	3	0	
Product issues			
Thrombosis in device			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	5 / 178 (2.81%) 7	4 / 76 (5.26%) 4
Neutrophil count decreased subjects affected / exposed occurrences (all)	16 / 178 (8.99%) 34	10 / 76 (13.16%) 36
Blood creatinine increased subjects affected / exposed occurrences (all)	14 / 178 (7.87%) 25	1 / 76 (1.32%) 1
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	6 / 178 (3.37%) 8	4 / 76 (5.26%) 4
White blood cell count decreased subjects affected / exposed occurrences (all)	18 / 178 (10.11%) 34	9 / 76 (11.84%) 22
Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0
Amylase increased subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 178 (1.69%) 5	3 / 76 (3.95%) 3
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	3 / 178 (1.69%) 3	1 / 76 (1.32%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	4 / 178 (2.25%) 7	0 / 76 (0.00%) 0
Blood calcium decreased subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0
Blood creatine increased		

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Blood culture positive		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Blood lactate dehydrogenase increased		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Blood potassium increased		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Blood pressure increased		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Blood urine present		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Blood triglycerides increased		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Haematocrit decreased		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Glomerular filtration rate decreased		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Body temperature increased		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Haemoglobin decreased		
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)
occurrences (all)	3	0
International normalised ratio increased		

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Lipase increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Lymphocyte count decreased			
subjects affected / exposed	6 / 178 (3.37%)	1 / 76 (1.32%)	
occurrences (all)	10	4	
Mean cell haemoglobin increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Mean cell volume abnormal			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Mean cell volume increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	8 / 178 (4.49%)	3 / 76 (3.95%)	
occurrences (all)	26	6	
Weight decreased			
subjects affected / exposed	5 / 178 (2.81%)	2 / 76 (2.63%)	
occurrences (all)	7	3	
Transaminases increased			
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)	
occurrences (all)	0	2	
Red blood cell count decreased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Animal bite		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Concussion		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Head injury		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Fall		
subjects affected / exposed	5 / 178 (2.81%)	2 / 76 (2.63%)
occurrences (all)	7	2
Contusion		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Humerus fracture		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Injury		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Joint injury		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Meniscus injury		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Procedural pain		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Radius fracture		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Skin abrasion		

subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	1 / 76 (1.32%) 1	
Spinal compression fracture subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Urostomy complication subjects affected / exposed occurrences (all)	0 / 178 (0.00%) 0	1 / 76 (1.32%) 1	
Spinal fracture subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Cardiac disorders			
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 178 (0.00%) 0	1 / 76 (1.32%) 1	
Palpitations subjects affected / exposed occurrences (all)	5 / 178 (2.81%) 6	0 / 76 (0.00%) 0	
Arrhythmia subjects affected / exposed occurrences (all)	0 / 178 (0.00%) 0	1 / 76 (1.32%) 1	
Tachycardia subjects affected / exposed occurrences (all)	2 / 178 (1.12%) 2	1 / 76 (1.32%) 1	
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Nervous system disorders			
Neuropathy peripheral subjects affected / exposed occurrences (all)	5 / 178 (2.81%) 6	8 / 76 (10.53%) 8	
Dizziness subjects affected / exposed occurrences (all)	25 / 178 (14.04%) 65	6 / 76 (7.89%) 6	
Headache			

subjects affected / exposed	29 / 178 (16.29%)	9 / 76 (11.84%)
occurrences (all)	79	11
Dysgeusia		
subjects affected / exposed	13 / 178 (7.30%)	6 / 76 (7.89%)
occurrences (all)	16	6
Paraesthesia		
subjects affected / exposed	7 / 178 (3.93%)	5 / 76 (6.58%)
occurrences (all)	8	6
Ageusia		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Balance disorder		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Burning sensation		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Head titubation		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	3	0
Epilepsy		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Hypoaesthesia		
subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)
occurrences (all)	4	0
Neuralgia		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Memory impairment		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Lethargy		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Neurotoxicity		

subjects affected / exposed	0 / 178 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	6
Parosmia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Peripheral sensory neuropathy		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Presyncope		
subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)
occurrences (all)	4	0
Polyneuropathy		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Retinal migraine		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Restless legs syndrome		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Sciatica		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Sinus headache		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Sensory loss		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Seizure		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	2	0
Somnolence		
subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)
occurrences (all)	4	0
Transient ischaemic attack		

subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Taste disorder subjects affected / exposed occurrences (all)	8 / 178 (4.49%) 8	0 / 76 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	3 / 178 (1.69%) 3	1 / 76 (1.32%) 1	
Tremor subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	87 / 178 (48.88%) 163	19 / 76 (25.00%) 22	
Neutropenia subjects affected / exposed occurrences (all)	29 / 178 (16.29%) 41	22 / 76 (28.95%) 37	
Leukopenia subjects affected / exposed occurrences (all)	13 / 178 (7.30%) 24	6 / 76 (7.89%) 6	
Thrombocytopenia subjects affected / exposed occurrences (all)	16 / 178 (8.99%) 20	6 / 76 (7.89%) 11	
Lymphopenia subjects affected / exposed occurrences (all)	4 / 178 (2.25%) 7	1 / 76 (1.32%) 1	
Macrocytosis subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Neutrophilia subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Ear and labyrinth disorders			
Hyperacusis			

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Ear congestion			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Deafness			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Ototoxicity			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences (all)	3	1	
Vertigo			
subjects affected / exposed	6 / 178 (3.37%)	1 / 76 (1.32%)	
occurrences (all)	17	1	
Eye disorders			
Conjunctival discolouration			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Cataract			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Corneal disorder			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Eye disorder			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	

Lacrimation increased			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Macular oedema			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Periorbital oedema			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Photophobia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Scleral disorder			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	11 / 178 (6.18%)	1 / 76 (1.32%)	
occurrences (all)	12	1	
Abdominal pain			
subjects affected / exposed	41 / 178 (23.03%)	11 / 76 (14.47%)	
occurrences (all)	80	15	
Abdominal pain upper			
subjects affected / exposed	21 / 178 (11.80%)	4 / 76 (5.26%)	
occurrences (all)	36	4	
Diarrhoea			

subjects affected / exposed	52 / 178 (29.21%)	13 / 76 (17.11%)
occurrences (all)	149	16
Constipation		
subjects affected / exposed	24 / 178 (13.48%)	17 / 76 (22.37%)
occurrences (all)	28	23
Dyspepsia		
subjects affected / exposed	19 / 178 (10.67%)	7 / 76 (9.21%)
occurrences (all)	26	8
Flatulence		
subjects affected / exposed	1 / 178 (0.56%)	4 / 76 (5.26%)
occurrences (all)	1	5
Nausea		
subjects affected / exposed	115 / 178 (64.61%)	24 / 76 (31.58%)
occurrences (all)	240	47
Gastrooesophageal reflux disease		
subjects affected / exposed	10 / 178 (5.62%)	2 / 76 (2.63%)
occurrences (all)	10	2
Stomatitis		
subjects affected / exposed	8 / 178 (4.49%)	14 / 76 (18.42%)
occurrences (all)	11	28
Vomiting		
subjects affected / exposed	66 / 178 (37.08%)	14 / 76 (18.42%)
occurrences (all)	165	20
Abdominal pain lower		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Abdominal discomfort		
subjects affected / exposed	3 / 178 (1.69%)	1 / 76 (1.32%)
occurrences (all)	5	1
Anal incontinence		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Anorectal discomfort		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	2	0
Aphthous ulcer		

subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)
occurrences (all)	5	0
Aptyalism		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Ascites		
subjects affected / exposed	2 / 178 (1.12%)	2 / 76 (2.63%)
occurrences (all)	4	3
Colitis		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	2	0
Dental caries		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Dry mouth		
subjects affected / exposed	4 / 178 (2.25%)	1 / 76 (1.32%)
occurrences (all)	8	1
Dysphagia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Faeces soft		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Gastric mucosal hypertrophy		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Food poisoning		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Gastric ulcer		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Gastritis		
subjects affected / exposed	5 / 178 (2.81%)	0 / 76 (0.00%)
occurrences (all)	6	0
Gastrointestinal disorder		

subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Gastrointestinal fistula		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Gastrointestinal wall thickening		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Gastrointestinal pain		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Gingival pain		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Haemorrhoids		
subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)
occurrences (all)	5	0
Odynophagia		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	2
Irritable bowel syndrome		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Hyperaesthesia teeth		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Oesophageal pain		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Oesophagitis		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Oral pain		
subjects affected / exposed	0 / 178 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	3
Pneumatosis intestinalis		

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Proctitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 178 (0.56%)	2 / 76 (2.63%)	
occurrences (all)	1	2	
Tooth loss			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	3 / 178 (1.69%)	1 / 76 (1.32%)	
occurrences (all)	5	1	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Hepatic pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 178 (0.00%)	4 / 76 (5.26%)	
occurrences (all)	0	4	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 178 (0.56%)	27 / 76 (35.53%)	
occurrences (all)	1	42	
Skin hyperpigmentation			
subjects affected / exposed	1 / 178 (0.56%)	4 / 76 (5.26%)	
occurrences (all)	1	5	
Pruritus			

subjects affected / exposed	5 / 178 (2.81%)	5 / 76 (6.58%)
occurrences (all)	8	6
Rash		
subjects affected / exposed	13 / 178 (7.30%)	9 / 76 (11.84%)
occurrences (all)	17	14
Rash maculo-papular		
subjects affected / exposed	1 / 178 (0.56%)	4 / 76 (5.26%)
occurrences (all)	1	4
Alopecia		
subjects affected / exposed	11 / 178 (6.18%)	12 / 76 (15.79%)
occurrences (all)	11	12
Erythema		
subjects affected / exposed	2 / 178 (1.12%)	4 / 76 (5.26%)
occurrences (all)	2	4
Nail discolouration		
subjects affected / exposed	0 / 178 (0.00%)	4 / 76 (5.26%)
occurrences (all)	0	4
Nail disorder		
subjects affected / exposed	1 / 178 (0.56%)	6 / 76 (7.89%)
occurrences (all)	1	8
Butterfly rash		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Blister		
subjects affected / exposed	0 / 178 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	3
Decubitus ulcer		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Dermatitis		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Dermatitis bullous		
subjects affected / exposed	0 / 178 (0.00%)	3 / 76 (3.95%)
occurrences (all)	0	3
Dermatitis contact		

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Ecchymosis		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Eczema		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Eczema asteatotic		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Hair disorder		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Erythema nodosum		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Hyperhidrosis		
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)
occurrences (all)	3	0
Hand dermatitis		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Hyperkeratosis		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Miliaria		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Ingrowing nail		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Nail pigmentation		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Onychalgia		

subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Onychoclasia		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Onycholysis		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Pain of skin		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Onychomadesis		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Papule		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Panniculitis		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Pigmentation disorder		
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	2
Psoriasis		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Rash erythematous		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	2
Skin erosion		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Skin discolouration		
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	2
Skin exfoliation		

subjects affected / exposed	2 / 178 (1.12%)	1 / 76 (1.32%)	
occurrences (all)	2	1	
Skin fissures			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Skin induration			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Skin irritation			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Skin mass			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Skin tightness			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Skin toxicity			
subjects affected / exposed	0 / 178 (0.00%)	3 / 76 (3.95%)	
occurrences (all)	0	3	
Skin ulcer			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Calculus urinary			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Acute kidney injury			
subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)	
occurrences (all)	4	0	

Cystitis noninfective		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Dysuria		
subjects affected / exposed	8 / 178 (4.49%)	1 / 76 (1.32%)
occurrences (all)	9	1
Haematuria		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Hydronephrosis		
subjects affected / exposed	3 / 178 (1.69%)	1 / 76 (1.32%)
occurrences (all)	3	1
Hydroureter		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Leukocyturia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Micturition urgency		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Pollakiuria		
subjects affected / exposed	1 / 178 (0.56%)	2 / 76 (2.63%)
occurrences (all)	1	2
Nephrolithiasis		
subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)
occurrences (all)	4	0
Renal colic		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Renal failure		
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)
occurrences (all)	3	0
Ureteric obstruction		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1

Urinary incontinence subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	1 / 76 (1.32%) 1	
Urinary tract disorder subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Urinary tract obstruction subjects affected / exposed occurrences (all)	2 / 178 (1.12%) 2	0 / 76 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	17 / 178 (9.55%) 28	3 / 76 (3.95%) 3	
Arthralgia subjects affected / exposed occurrences (all)	18 / 178 (10.11%) 35	6 / 76 (7.89%) 10	
Muscle spasms subjects affected / exposed occurrences (all)	12 / 178 (6.74%) 21	0 / 76 (0.00%) 0	
Muscular weakness subjects affected / exposed occurrences (all)	2 / 178 (1.12%) 2	4 / 76 (5.26%) 4	
Myalgia subjects affected / exposed occurrences (all)	9 / 178 (5.06%) 18	2 / 76 (2.63%) 3	
Pain in extremity subjects affected / exposed occurrences (all)	10 / 178 (5.62%) 13	6 / 76 (7.89%) 7	
Arthritis subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 76 (0.00%) 0	
Bone pain subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	3 / 76 (3.95%) 3	
Flank pain			

subjects affected / exposed	4 / 178 (2.25%)	3 / 76 (3.95%)
occurrences (all)	5	3
Extremity contracture		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Groin pain		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	2	0
Joint stiffness		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Musculoskeletal pain		
subjects affected / exposed	3 / 178 (1.69%)	1 / 76 (1.32%)
occurrences (all)	3	1
Musculoskeletal chest pain		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Joint swelling		
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)
occurrences (all)	3	0
Neck pain		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Osteopenia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Periarthritis		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Osteoporosis		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Spinal pain		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Rotator cuff syndrome		

subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Tendonitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	16 / 178 (8.99%)	8 / 76 (10.53%)	
occurrences (all)	19	9	
Urinary tract infection			
subjects affected / exposed	21 / 178 (11.80%)	4 / 76 (5.26%)	
occurrences (all)	26	4	
Bronchitis			
subjects affected / exposed	10 / 178 (5.62%)	2 / 76 (2.63%)	
occurrences (all)	12	2	
Acute sinusitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Catheter site infection			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 178 (0.56%)	2 / 76 (2.63%)	
occurrences (all)	1	3	
Cellulitis			
subjects affected / exposed	1 / 178 (0.56%)	2 / 76 (2.63%)	
occurrences (all)	1	2	
Diverticulitis			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Cystitis			
subjects affected / exposed	5 / 178 (2.81%)	1 / 76 (1.32%)	
occurrences (all)	5	2	

Ear infection		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Eye infection		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	2	0
Escherichia infection		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Erysipelas		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Folliculitis		
subjects affected / exposed	1 / 178 (0.56%)	2 / 76 (2.63%)
occurrences (all)	1	2
Fungal infection		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Gastroenteritis viral		
subjects affected / exposed	4 / 178 (2.25%)	0 / 76 (0.00%)
occurrences (all)	4	0
Gastrointestinal infection		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Gingivitis		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	4	0
Herpes simplex		
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	2
Herpes simplex reactivation		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0

Herpes virus infection		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Influenza		
subjects affected / exposed	8 / 178 (4.49%)	0 / 76 (0.00%)
occurrences (all)	8	0
Infected bite		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Herpes zoster		
subjects affected / exposed	1 / 178 (0.56%)	2 / 76 (2.63%)
occurrences (all)	1	3
Mastitis		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Localised infection		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	2
Lice infestation		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Mucosal infection		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Nail infection		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	2
Nasopharyngitis		
subjects affected / exposed	8 / 178 (4.49%)	2 / 76 (2.63%)
occurrences (all)	10	2
Oesophageal candidiasis		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Oral herpes		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1

Oral candidiasis		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Onychomycosis		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Paronychia		
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	2
Pharyngitis		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Pneumonia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	3	0
Rash pustular		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Pyuria		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Rhinitis		
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	1
Respiratory tract infection		
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)
occurrences (all)	2	0
Sinusitis		
subjects affected / exposed	5 / 178 (2.81%)	0 / 76 (0.00%)
occurrences (all)	6	0
Tooth infection		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Tooth abscess		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0

Skin infection			
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)	
occurrences (all)	0	2	
Vaginal infection			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 178 (14.61%)	9 / 76 (11.84%)	
occurrences (all)	30	9	
Hypoalbuminaemia			
subjects affected / exposed	10 / 178 (5.62%)	4 / 76 (5.26%)	
occurrences (all)	13	4	
Hypokalaemia			
subjects affected / exposed	12 / 178 (6.74%)	3 / 76 (3.95%)	
occurrences (all)	16	4	
Hypomagnesaemia			
subjects affected / exposed	10 / 178 (5.62%)	1 / 76 (1.32%)	
occurrences (all)	19	1	
Hyponatraemia			
subjects affected / exposed	9 / 178 (5.06%)	2 / 76 (2.63%)	
occurrences (all)	14	2	
Diabetes mellitus			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Dehydration			
subjects affected / exposed	2 / 178 (1.12%)	3 / 76 (3.95%)	
occurrences (all)	4	4	
Appetite disorder			
subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)	
occurrences (all)	1	1	
Glucose tolerance impaired			

subjects affected / exposed	1 / 178 (0.56%)	1 / 76 (1.32%)
occurrences (all)	1	2
Hypercalcaemia		
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)
occurrences (all)	4	0
Hyperamylasaemia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Gout		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	3	0
Hyperkalaemia		
subjects affected / exposed	2 / 178 (1.12%)	2 / 76 (2.63%)
occurrences (all)	3	3
Hyperglycaemia		
subjects affected / exposed	5 / 178 (2.81%)	0 / 76 (0.00%)
occurrences (all)	7	0
Hypercreatininaemia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Hypermagnesaemia		
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	1
Hypernatraemia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Hyperphosphataemia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Hypertriglyceridaemia		
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)
occurrences (all)	1	0
Hyperuricaemia		
subjects affected / exposed	0 / 178 (0.00%)	2 / 76 (2.63%)
occurrences (all)	0	2
Hypocalcaemia		

subjects affected / exposed	5 / 178 (2.81%)	1 / 76 (1.32%)	
occurrences (all)	6	1	
Hypochloraemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 76 (0.00%)	
occurrences (all)	4	0	
Vitamin D deficiency			
subjects affected / exposed	2 / 178 (1.12%)	0 / 76 (0.00%)	
occurrences (all)	2	0	
Steroid diabetes			
subjects affected / exposed	0 / 178 (0.00%)	1 / 76 (1.32%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	3 / 178 (1.69%)	0 / 76 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2017	Primary objective and endpoint changed from PFS to ORR and recruitment changed to close once a minimum of 250 patients were randomized instead of 411 as initially planned.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported