Clinical trial results:
A Phase 2, 2-Stage, 2-Cohort Study of Talazoparib (BMN 673) Administered to Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer

Summary

EudraCT number	2013-003076-12
Trial protocol	GB ES
Global end of trial date	31 October 2018

Results information

Result version number	v2 (current)
This version publication date	07 September 2019
First version publication date	17 September 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	673-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02034916
WHO universal trial number (UTN)	-
Other trial identifiers	Alias Study Number: C3441008

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	02 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the objective response rate (ORR) for each cohort treated with talazoparib as a single agent. The ORR would be based on confirmed responses as defined by Response Evaluation Criteria in Solid Tumors (RECIST).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	84
EEA total number of subjects	59

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	70
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In this study, enrollment of subjects was to be done in 2 stages for each of the 2 cohorts. Sufficient responses in each cohort were observed such that enrollment could proceed to Stage 2 for both cohorts. However, due to Sponsor decision, enrollment in the overall trial was terminated early.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Talazoparib 1 mg

Arm description:

Subjects who responded to a prior platinum-containing treatment for metastatic breast cancer, received talazoparib 1.0 milligram (mg) orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Arm type	Experimental
Investigational medicinal product name	Talazoparib
Investigational medicinal product code	
Other name	BMN 673, MDV3800
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Talazoparib 1 mg was administered orally, once daily.

Arm title	Cohort 2: Talazoparib 1 mg

Arm description:

Subjects with more than 2 prior non-platinum chemotherapy treatment for metastatic breast cancer, received talazoparib 1.0 mg orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. Prior adjuvant or neo-adjuvant therapy with a platinum was allowed if first disease recurrence was for more than 6 months since last dose of adjuvant/neo-adjuvant platinum treatment. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Arm type	Experimental
Investigational medicinal product name	Talazoparib
Investigational medicinal product code	
Other name	BMN 673, MDV3800
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Talazoparib 1 mg was administered orally, once daily.

Number of subjects in period 1	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg
Started	49	35
Treated	48	35
Completed	0	0
Not completed	49	35
Consent withdrawn by subject	2	1
Death	39	28
Study terminated by sponsor	4	5
Lost to follow-up	4	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: Talazoparib 1 mg

Reporting group description:

Subjects who responded to a prior platinum-containing treatment for metastatic breast cancer, received talazoparib 1.0 milligram (mg) orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Reporting group title	Cohort 2: Talazoparib 1 mg

Reporting group description:

Subjects with more than 2 prior non-platinum chemotherapy treatment for metastatic breast cancer, received talazoparib 1.0 mg orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. Prior adjuvant or neo-adjuvant therapy with a platinum was allowed if first disease recurrence was for more than 6 months since last dose of adjuvant/neo-adjuvant platinum treatment. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Reporting group values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg	Total
Number of subjects	49	35	84
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	28	70
From 65-84 years	7	7	14
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	50.1	53.4	
standard deviation	± 11.48	± 11.05	-
Gender, Male/Female Units: Subjects			
Female	48	34	82
Male	1	1	2

Subject analysis sets

Subject analysis set title	All Subjects: Talazoparib 1 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects, who either responded to a prior platinum-containing treatment for metastatic breast cancer or had more than 2 prior non-platinum chemotherapy treatment for metastatic breast cancer, received talazoparib 1.0 mg orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. For the subjects with non-

platinum chemotherapy, prior adjuvant or neo-adjuvant therapy with a platinum was allowed if first disease recurrence was for more than 6 months since last dose of adjuvant/neo-adjuvant platinum treatment. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Reporting group values	All Subjects: Talazoparib 1 mg		
Number of subjects	83		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: years			
arithmetic mean	51.5		
standard deviation	± 11.35		
Gender, Male/Female			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Cohort 1: Talazoparib 1 mg

Reporting group description:

Subjects who responded to a prior platinum-containing treatment for metastatic breast cancer, received talazoparib 1.0 milligram (mg) orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Reporting group title	Cohort 2: Talazoparib 1 mg

Reporting group description:

Subjects with more than 2 prior non-platinum chemotherapy treatment for metastatic breast cancer, received talazoparib 1.0 mg orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. Prior adjuvant or neo-adjuvant therapy with a platinum was allowed if first disease recurrence was for more than 6 months since last dose of adjuvant/neo-adjuvant platinum treatment. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Subject analysis set title	All Subjects: Talazoparib 1 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects, who either responded to a prior platinum-containing treatment for metastatic breast cancer or had more than 2 prior non-platinum chemotherapy treatment for metastatic breast cancer, received talazoparib 1.0 mg orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. For the subjects with non-platinum chemotherapy, prior adjuvant or neo-adjuvant therapy with a platinum was allowed if first disease recurrence was for more than 6 months since last dose of adjuvant/neo-adjuvant platinum treatment. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

ORR: Percentage of subjects with a confirmed best overall complete response (CR) or partial response (PR) according to response evaluation criteria in solid tumors version 1.1 (RECIST 1.1), evaluated by an independent radiology facility (IRF). CR: Disappearance of all non-nodal target and non-target lesions, including target and non-target lymph nodes reduction to less than 10 millimeter (mm) in short axis. PR: Greater than or equal to (>=) 30 percent (%) decrease in sum of diameters of target lesions, compared to the sum at baseline. Tumor-evaluable population (TEP) included all treated subjects who had a baseline and at least 1 post-baseline tumor assessment or who discontinued the study before first scheduled post-baseline tumor scan plus (+) 1 week window.

End point type	Primary

End point timeframe:

From randomization until data cutoff date (01 Sep 2016)

Notes:

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

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: percentage of subjects				
number (confidence interval 95%)	20.8 (10.47 to 34.99)	37.1 (21.47 to 55.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate-24 (CBR-24)

End point title	Clinical Benefit Rate-24 (CBR-24)

End point description:

CBR24: Percentage of subjects with a best overall response of confirmed CR, confirmed PR or stable disease (SD) sustained for at least 24 weeks, as assessed by IRF using RECIST 1.1. CR: Disappearance of all non-nodal target and non-target lesions, including target and non-target lymph nodes reduction to less than 10 mm in short axis. PR: >=30% decrease in sum of diameters of target lesions, compared to the sum at baseline. SD: Neither PR nor progression of disease (PD) criteria met. SD follow PR only when sum increases by less than 20% from the nadir, but previously seen 30% decrease from baseline no longer hold. PD: >=20% increase (>=5 mm absolute increase) in the sum of target lesion measurements, compared to the smallest sum on study (including baseline), or unequivocal progression of non-target lesions, evaluated as a whole, such that it is clear that treatment has failed and disease is progressing, regardless of the status of the target lesions. Analysis was done on TEP.

End point type	Secondary

End point timeframe:

From randomization until data cutoff date (01 Sep 2016)

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: percentage of subjects				
number (confidence interval 95%)	27.1 (15.28 to 41.85)	45.7 (28.83 to 63.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR: Time from first documentation of CR or PR, to PD by IRF using RECIST 1.1, or to death (any cause), whichever occurred first. CR: Disappearance of all non-nodal target, non-target lesions (lymph nodes reduction to less than (<) 10 mm in short axis). PR: >=30% decrease in sum of diameters of target lesions, compared baseline sum. PD: >=20% increase (>=5 mm absolute increase) in sum of target lesion, compared to smallest sum, or unequivocal progression of non-target lesions, regardless target lesions. Subjects with no PD or death were censored at last tumor assessment prior to on or before of new anticancer therapy or before data cutoff. Analysis was done on TEP. Here 'Number of subjects analyzed' signifies subjects evaluable for this endpoint and '99999' signifies data not available

as upper limit of 95% confidence interval (CI) was not reached due to very less number of subjects and insufficient events at data cutoff.

End point type	Secondary

End point timeframe:

From first documentation of CR or PR until PD, last tumor assessment without PD before new anticancer treatment initiation or death due to any cause, whichever occurred first (up to the data cutoff date [01 Sep 2016])

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	13		
Units: months				
median (confidence interval 95%)	5.8 (2.8 to 99999)	3.8 (2.8 to 10.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS: Time, in months, from the first dose of study drug to the first documentation of PD by investigator assessment using RECIST 1.1 or death due to any cause on or before the data cutoff date, whichever occurred first. PD: >=20% increase (>=5 mm absolute increase) in the sum of target lesion measurements, compared to the smallest sum on study (including baseline), or unequivocal progression of non-target lesions, evaluated as a whole, such that it is clear that treatment has failed and disease is progressing, regardless of the status of the target lesions. Subjects with no PFS event at the analysis were censored at last tumor assessment date prior to data cutoff or date of new anticancer treatment initiation, whichever occurred first. ITT population involved all enrolled subjects including subjects who were not treated.

End point type	Secondary

End point timeframe:

From first dose of study drug until PD, last tumor assessment without PD before new anticancer treatment initiation or death due to any cause, whichever occurred first (up to the data cutoff date [01 Sep 2016])

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	35		
Units: months				
median (confidence interval 95%)	4.0 (2.8 to 5.4)	5.6 (5.5 to 7.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from first dose of study drug to death due to any cause. For subjects without a death date at the time of data cutoff or permanently lost to follow-up, OS was right-censored at the date the subject was last known to be alive on or before the data cutoff date. ITT population. Here '99999' signifies data not available due to insufficient number of events at data cutoff.

End point type	Secondary

End point timeframe:

From first dose of study drug until death due to any cause (up to the data cutoff date [01 Sep 2016])

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	35		
Units: months				
median (confidence interval 95%)	11.8 (8.8 to 15.0)	16.5 (10.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; an important medical event or reaction, including events requiring medical intervention to prevent worsening to any of the previously noted seriousness criteria. A treatment emergent AE was defined as an event that emerged during the treatment period that was absent before treatment, or worsened during the treatment period relative to the pretreatment state. AEs included both serious and non-serious AEs. Safety population included all subjects who received at least 1 dose of talazoparib.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to a maximum duration of 42.8 months): based on data cutoff date (31 Oct 2018)

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: subjects				
AEs	47	34		
SAEs	16	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

A treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. A treatment-related SAE was a treatment-related AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; an important medical event or reaction, including events requiring medical intervention to prevent worsening to any of the previously noted seriousness criteria. Safety population included all subjects who received at least 1 dose of talazoparib. Related TEAEs are TEAEs that were judged by the investigators as possibly, probably, or definitely related to study drug. AEs included both SAES and non SAES.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to a maximum duration of 42.8 months): based on data cutoff date (31 Oct 2018)

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: subjects				
AEs	46	33		
SAEs	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Outcome in Response to Adverse Events (AEs)

End point title	Number of Subjects With Outcome in Response to Adverse Events (AEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Outcome of an AE was response to a question answered by the investigator: 'Is the AE leading to study discontinuation or death?' as 'yes'. Safety population included all subjects who received at least 1 dose of talazoparib.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to a maximum duration of 42.8 months): based on data cutoff date (31 Oct 2018)

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: subjects				
AEs leading to study drug discontinuation	4	1		
AEs leading to death	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Toxicity Grades Increase of 2 or More in Laboratory Parameter (Hematology Parameter)

End point title	Number of Subjects With Toxicity Grades Increase of 2 or More in Laboratory Parameter (Hematology Parameter)

End point description:

Laboratory tests included hematology (hemoglobin [low], leucocytes [low], lymphocytes [low], neutrophils [low], platelets [low]). Toxicity grades were evaluated based on national cancer institute-common terminology criteria for adverse events (NCI-CTCAE) version 4.03. Number of subjects with increase of 2 or more CTCAE toxicity grades above baseline, for hematology laboratory parameter is reported in this endpoint. Safety population included all subjects who received at least 1 dose of talazoparib.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to a maximum duration of 42.8 months): based on data cutoff date (31 Oct 2018)

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: subjects				
Hemoglobin (low)	19	16		
Leukocytes (low)	16	15		
Lymphocytes (low)	15	4		
Neutrophils (low)	20	17		
Platelets (low)	21	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Toxicity Grades Increase of 2 or More in Laboratory Parameter (Chemistry Parameter)

End point title	Number of Subjects With Toxicity Grades Increase of 2 or More in Laboratory Parameter (Chemistry Parameter)

End point description:

Laboratory tests included serum chemistry (alanine aminotransferase [high], albumin [low], alkaline phosphatase [high], aspartate aminotransferase [high], bilirubin [high], calcium [low], glucose [high], magnesium [low], phosphate [low], potassium [high], potassium [low], sodium [high], sodium [low]). Toxicity grades were evaluated based on national cancer institute- common terminology criteria for adverse events (NCI-CTCAE) version 4.03. Number of subjects with increase of 2 or more CTCAE toxicity grades above baseline, for chemistry laboratory parameter is reported in this endpoint. Safety population included all subjects who received at least 1 dose of talazoparib.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after the last dose of study drug or before initiation of a new anticancer treatment, whichever occurred first (up to data cutoff date [01 Sep 2016])

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: subjects				
Alanine aminotransferase (high)	3	2		
Albumin (low)	3	0		
Alkaline phosphatase (high)	1	1		
Aspartate aminotransferase (high)	2	1		
Bilirubin (high)	2	0		
Calcium (low)	4	1		
Glucose (high)	1	1		
Magnesium (low)	1	0		
Phosphate (low)	6	2		
Potassium (high)	1	0		
Potassium (low)	2	0		

Sodium (high)	1	0		
Sodium (low)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Vital Signs

End point title	Number of Subjects With Clinically Significant Change From Baseline in Vital Signs

End point description:

Criteria for clinically significant vital signs changes: 1) Blood pressure: systolic blood pressure (SBP): greater than or equal to (>=30) millimeters of mercury (mmHg) increase from baseline, diastolic blood pressure (DBP): >=20 mmHg decrease from baseline; 2) Heart rate (HR): absolute HR greater than (>) 120 beats per minute (bpm) and >30 bpm increase from baseline, absolute HR less than (<) 50 bpm and >20 bpm decrease from baseline; 3) Weight: >10 percent (%) decrease from baseline. Number of subjects with any clinically significant change from baseline for blood pressure, heart rate and weight are reported in this endpoint. Safety population included all subjects who received at least 1 dose of talazoparib.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to a maximum duration of 42.8 months): based on data cutoff date (31 Oct 2018)

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: subjects				
Blood pressure (SBP or DBP)	20	18		
HR	2	0		
Weight	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Physical Findings

End point title	Number of Subjects With Clinically Significant Change From Baseline in Physical Findings

End point description:

Physical examination included examination of the head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The examination assessed the subjects for any potential changes in general appearance, the respiratory and

cardiovascular systems, as well as towards subject reported symptoms. Findings were considered to be clinically significant based on investigator's decision. Safety population included all subjects who received at least 1 dose of talazoparib.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to a maximum duration of 42.8 months): based on data cutoff date (31 Oct 2018)

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With At Least 1 Concomitant Medication

End point title	Number of Subjects With At Least 1 Concomitant Medication

End point description:

Number of subjects taking any non-study medications, therapies, including herbal supplements during the treatment-emergent period for the management of an adverse event or for the treatment of any other disease. Safety population included all subjects who received at least 1 dose of talazoparib.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to a maximum duration of 42.8 months): based on data cutoff date (31 Oct 2018)

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	35		
Units: subjects	48	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration Versus Time Summary of Talazoparib

End point title	Trough Concentration Versus Time Summary of Talazoparib

End point description:

Concentrations below the limit of quantitation values less than or equal to (<=) 25 picogram per milliliter (pg/mL) were set as zero. Pharmacokinetic (PK) analysis was not done separately for each reporting arm and cohorts were combined for PK analysis. PK population included all subjects who received at least 1 dose of talazoparib and had evaluable PK assessments. Here 'n' signifies subjects evaluable for each specified categories.

End point type	Secondary

End point timeframe:

Predose on Day 1 of Cycle 1, 2, 3, and 4 (data cutoff date: 01 Sep 2016)

End point values	All Subjects: Talazoparib 1 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	83			
Units: pg/mL				
arithmetic mean (standard deviation)				
Day 1 of Cycle 1 (n = 82)	10.3 (± 93.3)			
Day 1 of Cycle 2 (n = 63)	4340 (± 2360)			
Day 1 of Cycle 3 (n = 44)	4510 (± 2720)			
Day 1 of Cycle 4 (n = 33)	3660 (± 1690)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Deterioration in Global Health Status/Quality of Life (QOL) and Functional Status as Assessed by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)

End point title	Time to Deterioration in Global Health Status/Quality of Life (QOL) and Functional Status as Assessed by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)

End point description:

Time to deterioration was defined as the time from baseline to day to death, first occurrence of progression, or a >=10 point change from baseline in any of the functional status score and global health status/QOL score based on the EORTC-QLQ-C30, whichever occurred first. EORTC-QLQ-C30 questionnaire is a standardized instrument developed to assess the quality of life of people with cancer. EORTC-QLQ-C30 functional subscale includes 5 items: physical, role, emotional, cognitive, and social functioning. All of the single items of functional status subscale measures and global health status/QOL subscale range from 0 to 100, where higher scores represent a better level of functioning/quality of life. ITT population involved all enrolled subjects including subjects who were not treated.

End point type	Other pre-specified

End point timeframe:

Baseline up to death, disease progression or end of treatment (30 days after last dose of study drug or before initiation of a new anticancer therapy, whichever occurred first [up to data cutoff date: 01 Sep 2016])

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	35		
Units: months				
median (confidence interval 95%)				
Global Health Status/QOL	2.8 (2.1 to 3.0)	5.5 (4.2 to 5.7)		
Physical Functioning	3.1 (2.1 to 4.6)	5.6 (5.3 to 7.7)		
Role Functioning	2.1 (1.4 to 2.8)	4.2 (2.1 to 5.5)		
Emotional Functioning	2.7 (2.0 to 2.8)	5.5 (4.3 to 5.6)		
Cognitive Functioning	2.7 (1.6 to 3.2)	4.2 (2.8 to 5.5)		
Social Functioning	2.2 (1.4 to 2.9)	5.3 (4.1 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Deterioration in Disease Specific Symptoms as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module (EORTC-QLQ-BR23)

End point title	Time to Deterioration in Disease Specific Symptoms as Assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module (EORTC-QLQ-BR23)

End point description:

Time to deterioration was defined as the time from baseline to day to death, first occurrence of progression, or a >=10 point change from baseline in any of the symptom score based on the EORTC-QLQ-BR23, whichever occurred first. EORTC-QLQ-BR23 is a disease-specific module for breast cancer developed as a supplement for the EORTC-QLQ-C30 to assess the quality of life of subjects with breast cancer. EORTC-QLQ-BR23 symptoms subscale includes 4 items: systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss. Each item is rated by choosing 1 of 4 possible responses that record the level of intensity (1= not at all, 2= a little, 3= quite a bit, and 4= very much) within each scale. ITT population involved all enrolled subjects including subjects who were not treated.

End point type	Other pre-specified

End point timeframe:

Baseline up to death, disease progression or end of treatment (30 days after last dose of study drug or before initiation of a new anticancer therapy, whichever occurred first [up to data cutoff date: 01 Sep 2016])

End point values	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	35		
Units: months				
median (confidence interval 95%)				
Systemic Therapy Side Effects	2.8 (2.3 to 4.0)	5.5 (4.1 to 5.6)		
Breast Symptoms	3.1 (2.5 to 4.6)	5.6 (5.3 to 7.7)		
Arm Symptoms	2.6 (2.0 to 3.7)	4.2 (2.8 to 5.5)		
Upset by Hair Loss	4.0 (2.7 to 5.4)	5.6 (5.3 to 7.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (up to maximum duration of 42.8 months)

Adverse event reporting additional description:

Same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study. AEs and SAEs were collected for safety population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Cohort 1: Talazoparib 1 mg

Reporting group description:

Subjects who responded to a prior platinum-containing treatment for metastatic breast cancer, received talazoparib 1.0 mg orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Reporting group title	Cohort 2: Talazoparib 1 mg

Reporting group description:

Subjects with more than 2 prior non-platinum chemotherapy treatment for metastatic breast cancer, received talazoparib 1.0 mg orally, once daily for 21 days in repeated 21-day cycles until disease progression, occurrence of unacceptable toxicity or permanent treatment discontinuation. Prior adjuvant or neo-adjuvant therapy with a platinum was allowed if first disease recurrence was for more than 6 months since last dose of adjuvant/neo-adjuvant platinum treatment. Subjects were followed-up for survival and new anticancer treatment at every 60 days after the last dose of study drug for the first year, every 90 days thereafter.

Serious adverse events	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 48 (33.33%)	7 / 35 (20.00%)	
number of deaths (all causes)	5	1	
number of deaths resulting from adverse events			
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			

subjects affected / exposed	3 / 48 (6.25%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 1	
Breast cancer metastatic			
subjects affected / exposed	2 / 48 (4.17%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Silicon granuloma			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (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			
Transfusion reaction			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Lipoinjection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophorectomy	Additional description: Gender specific event.		
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (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	1 / 48 (2.08%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 48 (10.42%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	4 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 48 (4.17%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (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 / 48 (6.25%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 48 (4.17%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			

subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 48 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (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			
Arthralgia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (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			
Neutropenic sepsis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza			
subjects affected / exposed	0 / 48 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 35 (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: 5 %

Non-serious adverse events	Cohort 1: Talazoparib 1 mg	Cohort 2: Talazoparib 1 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 48 (97.92%)	34 / 35 (97.14%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	3 / 48 (6.25%)	3 / 35 (8.57%)	
occurrences (all)	3	3	
Lymphoedema			
subjects affected / exposed	3 / 48 (6.25%)	2 / 35 (5.71%)	
occurrences (all)	3	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 48 (6.25%)	10 / 35 (28.57%)	
occurrences (all)	7	31	
Axillary pain			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	4	
Fatigue			
subjects affected / exposed	29 / 48 (60.42%)	8 / 35 (22.86%)	
occurrences (all)	37	15	
Mucosal inflammation			
subjects affected / exposed	4 / 48 (8.33%)	2 / 35 (5.71%)	
occurrences (all)	5	2	
Non-cardiac chest pain			
subjects affected / exposed	3 / 48 (6.25%)	0 / 35 (0.00%)	
occurrences (all)	7	0	
Oedema peripheral			

subjects affected / exposed	1 / 48 (2.08%)	6 / 35 (17.14%)	
occurrences (all)	1	10	
Pyrexia			
subjects affected / exposed	1 / 48 (2.08%)	5 / 35 (14.29%)	
occurrences (all)	1	9	
Chills			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 48 (18.75%)	7 / 35 (20.00%)	
occurrences (all)	9	12	
Dyspnoea			
subjects affected / exposed	9 / 48 (18.75%)	9 / 35 (25.71%)	
occurrences (all)	11	22	
Epistaxis			
subjects affected / exposed	2 / 48 (4.17%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Nasal congestion			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Pleural effusion			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	3	
Rhinorrhoea			
subjects affected / exposed	0 / 48 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Oropharyngeal pain			
subjects affected / exposed	2 / 48 (4.17%)	3 / 35 (8.57%)	
occurrences (all)	2	3	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Insomnia			

subjects affected / exposed	5 / 48 (10.42%)	3 / 35 (8.57%)	
occurrences (all)	5	4	
Anxiety			
subjects affected / exposed	2 / 48 (4.17%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 48 (2.08%)	3 / 35 (8.57%)	
occurrences (all)	3	6	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 48 (8.33%)	2 / 35 (5.71%)	
occurrences (all)	4	5	
Neutrophil count decreased			
subjects affected / exposed	5 / 48 (10.42%)	5 / 35 (14.29%)	
occurrences (all)	11	16	
Platelet count decreased			
subjects affected / exposed	7 / 48 (14.58%)	5 / 35 (14.29%)	
occurrences (all)	29	16	
Weight decreased			
subjects affected / exposed	3 / 48 (6.25%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
White blood cell count decreased			
subjects affected / exposed	3 / 48 (6.25%)	5 / 35 (14.29%)	
occurrences (all)	13	12	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 48 (12.50%)	2 / 35 (5.71%)	
occurrences (all)	7	2	
Dysgeusia			
subjects affected / exposed	1 / 48 (2.08%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Headache			

subjects affected / exposed	9 / 48 (18.75%)	11 / 35 (31.43%)	
occurrences (all)	14	26	
Neuralgia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Neuropathy peripheral			
subjects affected / exposed	2 / 48 (4.17%)	4 / 35 (11.43%)	
occurrences (all)	2	5	
Presyncope			
subjects affected / exposed	0 / 48 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 48 (47.92%)	19 / 35 (54.29%)	
occurrences (all)	67	89	
Leukopenia			
subjects affected / exposed	7 / 48 (14.58%)	6 / 35 (17.14%)	
occurrences (all)	17	21	
Lymphopenia			
subjects affected / exposed	2 / 48 (4.17%)	4 / 35 (11.43%)	
occurrences (all)	3	8	
Neutropenia			
subjects affected / exposed	10 / 48 (20.83%)	12 / 35 (34.29%)	
occurrences (all)	36	36	
Thrombocytopenia			
subjects affected / exposed	18 / 48 (37.50%)	9 / 35 (25.71%)	
occurrences (all)	49	34	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Abdominal distension			
subjects affected / exposed	1 / 48 (2.08%)	3 / 35 (8.57%)	
occurrences (all)	1	4	
Abdominal pain			

subjects affected / exposed	7 / 48 (14.58%)	7 / 35 (20.00%)	
occurrences (all)	8	14	
Abdominal pain upper			
subjects affected / exposed	2 / 48 (4.17%)	6 / 35 (17.14%)	
occurrences (all)	3	13	
Constipation			
subjects affected / exposed	9 / 48 (18.75%)	6 / 35 (17.14%)	
occurrences (all)	10	15	
Diarrhoea			
subjects affected / exposed	18 / 48 (37.50%)	10 / 35 (28.57%)	
occurrences (all)	26	18	
Dry mouth			
subjects affected / exposed	0 / 48 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	5 / 48 (10.42%)	3 / 35 (8.57%)	
occurrences (all)	5	4	
Nausea			
subjects affected / exposed	20 / 48 (41.67%)	15 / 35 (42.86%)	
occurrences (all)	24	22	
Stomatitis			
subjects affected / exposed	3 / 48 (6.25%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Toothache			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	10 / 48 (20.83%)	8 / 35 (22.86%)	
occurrences (all)	19	15	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	11 / 48 (22.92%)	6 / 35 (17.14%)	
occurrences (all)	11	6	
Dry skin			
subjects affected / exposed	1 / 48 (2.08%)	4 / 35 (11.43%)	
occurrences (all)	1	5	

Erythema			
subjects affected / exposed	0 / 48 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	4	
Pruritus			
subjects affected / exposed	1 / 48 (2.08%)	3 / 35 (8.57%)	
occurrences (all)	1	4	
Hyperhidrosis			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 48 (16.67%)	9 / 35 (25.71%)	
occurrences (all)	10	14	
Back pain			
subjects affected / exposed	12 / 48 (25.00%)	8 / 35 (22.86%)	
occurrences (all)	13	11	
Bone pain			
subjects affected / exposed	0 / 48 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	4 / 48 (8.33%)	5 / 35 (14.29%)	
occurrences (all)	4	5	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 48 (6.25%)	2 / 35 (5.71%)	
occurrences (all)	4	2	
Musculoskeletal pain			
subjects affected / exposed	1 / 48 (2.08%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Neck pain			
subjects affected / exposed	1 / 48 (2.08%)	3 / 35 (8.57%)	
occurrences (all)	1	15	
Pain in extremity			
subjects affected / exposed	2 / 48 (4.17%)	3 / 35 (8.57%)	
occurrences (all)	2	4	
Myalgia			

subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	4	
Infections and infestations			
Gingivitis			
subjects affected / exposed	0 / 48 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Influenza			
subjects affected / exposed	3 / 48 (6.25%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Lower respiratory tract infection			
subjects affected / exposed	3 / 48 (6.25%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	0 / 48 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	4	
Pharyngitis			
subjects affected / exposed	0 / 48 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	4	
Sinusitis			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	4 / 48 (8.33%)	2 / 35 (5.71%)	
occurrences (all)	4	3	
Upper respiratory tract infection			
subjects affected / exposed	3 / 48 (6.25%)	5 / 35 (14.29%)	
occurrences (all)	3	6	
Oral herpes			
subjects affected / exposed	0 / 48 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Viral upper respiratory tract infection			
subjects affected / exposed	11 / 48 (22.92%)	3 / 35 (8.57%)	
occurrences (all)	14	4	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	12 / 48 (25.00%)	10 / 35 (28.57%)	
occurrences (all)	13	14	
Hyperglycaemia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 35 (5.71%)	
occurrences (all)	2	4	
Hypomagnesaemia			
subjects affected / exposed	3 / 48 (6.25%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Hyponatraemia			
subjects affected / exposed	1 / 48 (2.08%)	2 / 35 (5.71%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2015	To add liver safety monitoring guidelines in accordance with United States Food and Drug Administration (US FDA) Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009). To update the dose modification guidelines taking into consideration the type of toxicity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported