Clinical trial results:
An open label, non-randomized, multicenter phase 1/2b study investigating safety and efficacy of PQR309 and eribulin combination in patients with locally advanced or metastatic HER2 negative and triple-negative breast cancer

Summary

EudraCT number	2015-004225-14
Trial protocol	ES GB
Global end of trial date	03 October 2018

Results information

Result version number	v1 (current)
This version publication date	16 November 2019
First version publication date	16 November 2019

Trial information

Trial identification

Sponsor protocol code	PQR309-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02723877
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PIQUR Therapeutics AG
Sponsor organisation address	Hochbergerstrasse 60C, Basel, Switzerland, 4057
Public contact	Chief Medical Officer, PIQUR Therapeutics AG, +41 615512050, info@piqur.com
Scientific contact	Chief Medical Officer, PIQUR Therapeutics AG, +41 615512050, info@piqur.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	23 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2018
Global end of trial reached?	Yes
Global end of trial date	03 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary Objectives:
-For the escalation part: To identify maximum tolerated dose (MTD) of PQR309 (bimiralisib) administered in combination with standard dose of eribulin.
-For the dose expansion part: To evaluate the clinical efficacy of PQR309 in combination with eribulin at the treatment schedule established in the escalation part.

Secondary Objectives:
-To assess overall safety and tolerability of PQR309 in combination with eribulin.
-To assess the pharmacokinetics (PK) of PQR309 in combination with eribulin and to investigate the potential effect of PQR309 on eribulin PK.

Protection of trial subjects:

The study processes, potential benefits and any risks (known and potentially unknown) of participating in the study were explained to each patient. Patients were continuously monitored by the clinical investigators via regular study visits throughout the duration of the study. In addition, if the study drug needed to be stopped for safety, then the responsible investigator would continue to monitor the patient`s health and determine what treatment should be given (if any) until the symptoms or findings had resolved or until a satisfactory conclusion was reached.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2016
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	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 9
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	34
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

59 patients were screened, and 41 patients were enrolled. The first-patient-first-visit was on 28-Mar-2016. Patients were recruited at 5 study sites located in Spain and United Kingdom.

Pre-assignment

Screening details:

Screening period: 28 days. Main inclusion criteria: female ≥ 18 years, confirmed diagnosis of HER2 negative breast cancer, received ≥ 2 & ≤ 5 prior chemotherapeutic regimens, ECOG Performance Score of 0-2, signed informed consent, adequate bone marrow and organ function, ability and willingness to swallow and retain oral medication.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Continuous Schedule

Arm description:

Continous daily dosing with PQR309

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

Dosage and administration details:

60 mg qd or 80 mg qd, orally.

Investigational medicinal product name	eribulin (Halaven)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Standard eribulin mesylate dosing 1.4 mg/m2 intravenously, on Day 1 and Day 8 in the 21-day cycle.

Arm title	Intermittent A Schedule

Arm description:

Intermittent dosing consisting of weekly treatment "two days on / 5 days off" with PQR309

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

Dosage and administration details:

60 mg, 80 mg, 100 mg or 120 mg administered orally each week for 2 days on, 5 days off.

Investigational medicinal product name	eribulin (Halaven)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Standard eribulin mesylate dosing 1.4 mg/m2 intravenously, on Day 1 and Day 8 in the 21-day cycle.

Arm title	Intermittent B Schedule

Arm description:

Intermittent dosing consisting of weekly treatment twice weekly "Monday / Thursday" with PQR309

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

Dosage and administration details:

60 mg, 80 mg or 100 mg administered orally, weekly on Mondays and Thursdays.

Investigational medicinal product name	eribulin (Halaven)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Standard eribulin mesylate dosing 1.4 mg/m2 intravenously, on Day 1 and Day 8 in the 21-day cycle.

Number of subjects in period 1	Continuous Schedule	Intermittent A Schedule	Intermittent B Schedule
Started	9	20	12
Completed	9	20	12

Baseline characteristics

Reporting groups	
Reporting group title	Continuous Schedule
Reporting group description:	
Continous daily dosing with PQR309	
Reporting group title	Intermittent A Schedule
Reporting group description:	
Intermittent dosing consisting of weekly treatment "two days on / 5 days off" with PQR309	
Reporting group title	Intermittent B Schedule
Reporting group description:	
Intermittent dosing consisting of weekly treatment twice weekly "Monday / Thursday" with PQR309	

Reporting group values	Continuous Schedule	Intermittent A Schedule	Intermittent B Schedule
Number of subjects	9	20	12
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)	8	18	8
From 65-84 years	1	2	4
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	9	20	12
Male	0	0	0

Reporting group values	Total		
Number of subjects	41		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	34		
From 65-84 years	7		
85 years and over	0		

Gender categorical Units: Subjects			
Female	41		
Male	0		

End points

End points reporting groups

Reporting group title	Continuous Schedule
Reporting group description: Continous daily dosing with PQR309	
Reporting group title	Intermittent A Schedule
Reporting group description: Intermittent dosing consisting of weekly treatment "two days on / 5 days off" with PQR309	
Reporting group title	Intermittent B Schedule
Reporting group description: Intermittent dosing consisting of weekly treatment twice weekly "Monday / Thursday" with PQR309	

Primary: Maximum tolerated dose (MTD) in combination with eribulin

End point title	Maximum tolerated dose (MTD) in combination with

End point description:

MTD was evaluated according to a traditional 3 + 3 dose escalation scheme. Patients were followed to observe if they experienced any dose-limiting toxicity (DLT) during the first treatment cycle. Up to three (3) patients were first included in the dosing schedule at dose level 1. If one DLT was observed, three additional patients were enrolled to the cohort to determine the number of total DLTs observed in six patients.

Results: the MTD for continuous dosing was established as 60mg. The MTD for intermittent schedule A was not reached, with 120mg intermittent A being the highest dose under this regimen without any DLT. The MTD for intermittent schedule B was not reached, with the highest dose being 100mg with one DLT observed.

End point type	Primary

End point timeframe:

First treatment cycle.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary safety endpoint was to determine MTD based on number of dose limiting toxicity (DLT) events and therefore no statistical analysis was used.
[2] - 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: The MTD was only determined for the continuous dosing schedule. MTD was not reached for Intermittent Schedule A or Intermittent Schedule B; highest doses administered were intermittent doses of 120mg and 100mg, respectively.

End point values	Continuous Schedule			
Subject group type	Reporting group			
Number of subjects analysed	9[3]			
Units: mg				
number (not applicable)				
MTD	60			

Notes:

[3] - 7 patients received 60 mg and 2 patients received 80 mg.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose until 30 days after the last dose	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Continuous
Reporting group description: -	
Reporting group title	Intermittent A
Reporting group description: -	
Reporting group title	Intermittent B
Reporting group description: -	

Serious adverse events	Continuous	Intermittent A	Intermittent B
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	9 / 20 (45.00%)	5 / 12 (41.67%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Vascular disorders			
Peripheral venous disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Radiculopathy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 9 (22.22%)	4 / 20 (20.00%)	3 / 12 (25.00%)
occurrences causally related to treatment / all	2 / 2	4 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 9 (0.00%)	4 / 20 (20.00%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Continuous	Intermittent A	Intermittent B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	20 / 20 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Peripheral venous disease			

subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 9 (44.44%)	6 / 20 (30.00%)	5 / 12 (41.67%)
occurrences (all)	4	6	5
Pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Mucosal inflammation			
subjects affected / exposed	3 / 9 (33.33%)	7 / 20 (35.00%)	2 / 12 (16.67%)
occurrences (all)	3	7	2
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	2 / 20 (10.00%)	3 / 12 (25.00%)
occurrences (all)	2	2	3
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)	8 / 20 (40.00%)	5 / 12 (41.67%)
occurrences (all)	0	8	5
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General physical health deterioration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	0 / 9 (0.00%)	3 / 20 (15.00%)	2 / 12 (16.67%)
occurrences (all)	0	3	2
Axillary pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Chills			

subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Disease progression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Generalised oedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Breast inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Productive cough			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Catarrh			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 9 (0.00%)	3 / 20 (15.00%)	2 / 12 (16.67%)
occurrences (all)	0	3	2
Dysphonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	3 / 12 (25.00%)
occurrences (all)	0	1	3
Pharyngeal inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pulmonary artery thrombosis			

subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dyspnoea at rest			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Anhedonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Persistent depressive disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Abnormal dreams			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Affect lability			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 9 (66.67%)	5 / 20 (25.00%)	3 / 12 (25.00%)
occurrences (all)	6	5	3
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 9 (77.78%)	5 / 20 (25.00%)	2 / 12 (16.67%)
occurrences (all)	7	5	2
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 9 (11.11%)	3 / 20 (15.00%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 9 (33.33%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	1
Amylase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Blood sodium decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Radiation injury			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Toxicity to various agents			

subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Atrial fibrillation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 9 (33.33%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Dysgeusia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Neuropathy peripheral			
subjects affected / exposed	1 / 9 (11.11%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	1	2	2
Encephalopathy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 9 (0.00%)	5 / 20 (25.00%)	1 / 12 (8.33%)
occurrences (all)	0	5	1
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Neurotoxicity			
subjects affected / exposed	0 / 9 (0.00%)	4 / 20 (20.00%)	4 / 12 (33.33%)
occurrences (all)	0	4	4
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Radiculopathy			

subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Cerebral disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Neuralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 9 (33.33%)	6 / 20 (30.00%)	3 / 12 (25.00%)
occurrences (all)	3	6	3
Febrile neutropenia			
subjects affected / exposed	2 / 9 (22.22%)	4 / 20 (20.00%)	3 / 12 (25.00%)
occurrences (all)	2	4	3
Neutropenia			
subjects affected / exposed	9 / 9 (100.00%)	13 / 20 (65.00%)	10 / 12 (83.33%)
occurrences (all)	9	13	10
Leukopenia			
subjects affected / exposed	0 / 9 (0.00%)	3 / 20 (15.00%)	2 / 12 (16.67%)
occurrences (all)	0	3	2
Lymphopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Thrombocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Neutrophilia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Tinnitus			

subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Eye disorders			
Cataract			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Lacrimation increased			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Blepharitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	1 / 9 (11.11%)	2 / 20 (10.00%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Abdominal pain upper			

subjects affected / exposed	3 / 9 (33.33%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	3	2	2
Constipation			
subjects affected / exposed	2 / 9 (22.22%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	2	2	2
Diarrhoea			
subjects affected / exposed	6 / 9 (66.67%)	8 / 20 (40.00%)	6 / 12 (50.00%)
occurrences (all)	6	8	6
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)	6 / 20 (30.00%)	3 / 12 (25.00%)
occurrences (all)	1	6	3
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 9 (44.44%)	1 / 20 (5.00%)	3 / 12 (25.00%)
occurrences (all)	4	1	3
Haemorrhoids			
subjects affected / exposed	2 / 9 (22.22%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	4 / 9 (44.44%)	11 / 20 (55.00%)	7 / 12 (58.33%)
occurrences (all)	4	11	7
Odynophagia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Stomatitis			
subjects affected / exposed	1 / 9 (11.11%)	3 / 20 (15.00%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Vomiting			
subjects affected / exposed	2 / 9 (22.22%)	6 / 20 (30.00%)	4 / 12 (33.33%)
occurrences (all)	2	6	4
Abdominal pain lower			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mouth ulceration			

subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 9 (22.22%)	3 / 20 (15.00%)	3 / 12 (25.00%)
occurrences (all)	2	3	3
Dermatitis acneiform			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 9 (11.11%)	2 / 20 (10.00%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Pruritus			
subjects affected / exposed	3 / 9 (33.33%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Psoriasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	2 / 9 (22.22%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	2	2	2
Rash maculo-papular			
subjects affected / exposed	2 / 9 (22.22%)	0 / 20 (0.00%)	3 / 12 (25.00%)
occurrences (all)	2	0	3
Rash papular			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blister			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin ulcer			

subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Micturition disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Bladder spasm			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Micturition urgency			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urinary incontinence			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 9 (11.11%)	3 / 20 (15.00%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	3 / 12 (25.00%)
occurrences (all)	0	2	3
Muscle spasms			

subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	3 / 20 (15.00%)	2 / 12 (16.67%)
occurrences (all)	0	3	2
Osteonecrosis of jaw			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	3 / 20 (15.00%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Pain in jaw			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pathological fracture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 9 (11.11%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Febrile infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Haemorrhoid infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	2 / 9 (22.22%)	3 / 20 (15.00%)	2 / 12 (16.67%)
occurrences (all)	2	3	2

Cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Erysipelas			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Oral herpes			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Viral infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Appendicitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eye infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Fungal skin infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pyuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 9 (33.33%)	9 / 20 (45.00%)	5 / 12 (41.67%)
occurrences (all)	3	9	5
Hyperglycaemia			
subjects affected / exposed	7 / 9 (77.78%)	6 / 20 (30.00%)	3 / 12 (25.00%)
occurrences (all)	7	6	3
Hyperinsulinaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hyperlipasaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hyperphosphatasaemia			
subjects affected / exposed	3 / 9 (33.33%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hypokalaemia			

subjects affected / exposed	1 / 9 (11.11%)	1 / 20 (5.00%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Hypophosphataemia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 20 (10.00%)	1 / 12 (8.33%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2016	Inclusion criteria: - phosphate within normal limits (WNL) added to prevent any patients being enrolled with electrolyte imbalance; Dose modification guidelines for haematological AEs updated to align with eribulin prescribing information: - for "Thrombocytopenia CTC grade 4 and 3 (requiring blood transfusion)" changed from: "Interrupt administration until ANC ≥ 1 x 109 /L (see section 12)" to "Interrupt administration until ANC ≥ 1 x 109 /L and platelet count ≥ 75,000 mm3", and - for "Thrombocytopenia CTC grade 3 " changed from: "Interrupt administration until ANC ≥ 1 x 109 /L (see section 12)" to "Interrupt administration until platelet count ≥ 75,000 mm3". Guidelines for management of hyperglycaemia modified to provide additional clarity on dose modifications for both PQR309 and eribulin for second occurence of Grade 3 hyperglycaemia. Clarification was made that fasting glucose would be collected before food intake at each PK sampling timepoint, and as part of the blood chemistry panel at visits where PK sampling is not required.

05 September 2016	4.2.4 "Non-clinical pharmacokinetics and metabolism" and 4.3 "Clinical experience" updated based on clinical experience with PQR309. PQR309 40 mg dose added as a back-up dose. The expansion part will apply a Simon's MinMax design instead of a Simon's optimum design. The calculation of Clinical Benefit Rate (CBR) has been clarified (CBR = CR+PR+ SD ≥ 6 months), impacting the primary endpoint. Additional safety parameters / assessments added: Additional blood sample at baseline as safety baseline sample; C-reactive protein assessment on Day 1 of each cycle; assessment of ketones and erythrocytes as part of urinanayses; HbA1c assessment frequency changed to every 3 weeks. 10.7.9.3 "Guideline for the management of GI adverse events" updated to include more detailed guidance for diarrhea, nausea and vomiting. List of "Prohibited QT prolonging drugs with a known risk of Torsades de Pointes" updated Additional guidance provided (in 11.1.2.2) that drugs metabolised by CYP450 enzymes should only be used with caution. 11.1.3.8 "Gastric protection agents" expanded to specify wash-out periods prior to PQR309 treatment start and introduce option to use acid reducing agents in a regulated manner. Dose interruptions for haematological AEs modified to allow shorter / less frequent interruptions since PQR309 has not been associated with haematologic AEs. Now treatment will be interrupted following Grade 4 neutropenia until the event resolves to Grade 3; treatment following Grade 3 neutropenia will not be interrupted. Guidance on use of haematopoietic growth factors updated allowing use according to local standard practice. Dosing modification/delay section updated allowing treatment with PQR309 to be resumed earlier once AEs related to eribulin have resolved. Inclusion criteria: specific cut-offs for liver function in patients with liver metastases removed. Inclusion/exclusion criteria: HbA1c removed; fasting glucose must still be in normal range.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 October 2018	After the escalation part ended, the sponsor decided not to pursue the expansion part in triple negative breast cancer patients.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was interrupted prior to starting the expansion part and therefore the primary efficacy endpoint was unevaluable.

Notes: