Clinical trial results:
Open-label, non-randomized phase 2 study with safety run-in evaluating efficacy and safety of PQR309 in patients with relapsed or refractory lymphoma

Summary

EudraCT number	2014-005384-33
Trial protocol	DE
Global end of trial date	11 September 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	PQR309-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02249429
WHO universal trial number (UTN)	-
Other trial identifiers	Swissmedic ID : 2015DR2073 , EudraCT: 2015-001306-33

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	21 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2018
Global end of trial reached?	Yes
Global end of trial date	11 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the clinical efficacy of PQR309 (bimiralisib) in patients with relapsed or refractory lymphoma.
The secondary objective was to evaluate safety and pharmacokinetics of PQR309 in patients with relapsed or refractory lymphoma.

NOTE: Data from two studies, PQR309-002 (EudraCT 2014-005384-33, 54 patients enrolled) and PQR309-002A (2016-000125-38, 9 patients enrolled), were combined and analysed together. Therefore all safety and efficacy data presented in this record are from the combined analysis of both studies.

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. 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	27 August 2015
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	Switzerland: 6
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	63
EEA total number of subjects	43

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)	40
From 65 to 84 years	19
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

85 patients were screened, and 63 patients were enrolled; 54 patients under Protocol PQR309-002, and 9 under Protocol PQR309-002A. The first-patient-first-visit was on 27 Aug 2015 for PQR309-002 and 08 Jun 2016 for PQR309-002A. Patients were recruited at 17 study sites located in Switzerland, Germany, UK, Israel, USA, France, Serbia, and Bosnia.

Pre-assignment

Screening details:

Screening period: 28 days. Main inclusion criteria: confirmed relapsed or refractory lymphoma; age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance score of 0-1; signed informed consent; adequate organ system functions as determined by laboratory assessments; 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 60mg

Arm description:

bimiralisib 60mg q.d.

Arm type	Experimental
Investigational medicinal product name	bimiralisib
Investigational medicinal product code	PQR309
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

60 mg qd

Arm title	Continuous 80mg

Arm description:

bimiralisib 80mg q.d.

Arm type	Experimental
Investigational medicinal product name	bimiralisib
Investigational medicinal product code	PQR309
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

80 mg qd

Arm title	Intermittent 120mg

Arm description:

bimiralisib, 120mg intermittent schedule A

Arm type	Experimental

Investigational medicinal product name	bimiralisib
Investigational medicinal product code	PQR309
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
120 mg qd 2 days on, 5 days off

Arm title	Intermittent 140mg

Arm description:
bimiralisib, 140mg intermittent schedule A

Arm type	Experimental
Investigational medicinal product name	bimiralisib
Investigational medicinal product code	PQR309
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
140 mg qd 2 days on, 5 days off

Number of subjects in period 1	Continuous 60mg	Continuous 80mg	Intermittent 120mg
Started	8	42	6
Completed	8	42	6

Number of subjects in period 1	Intermittent 140mg
Started	7
Completed	7

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	40	
From 65-84 years	19	19	
85 years and over	4	4	
Gender categorical Units: Subjects			
Female	18	18	
Male	45	45	

End points

End points reporting groups

Reporting group title	Continuous 60mg
Reporting group description: bimiralisib 60mg q.d.	
Reporting group title	Continuous 80mg
Reporting group description: bimiralisib 80mg q.d.	
Reporting group title	Intermittent 120mg
Reporting group description: bimiralisib, 120mg intermittent schedule A	
Reporting group title	Intermittent 140mg
Reporting group description: bimiralisib, 140mg intermittent schedule A	
Subject analysis set title	The intent-to-treat (ITT) analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The intent-to-treat (ITT) analysis set: is defined as all patients who received ≥ 1 dose of bimiralisib. The intent-to-treat (ITT) analysis set was used in all safety analyses.

Primary: Response Rate (RR)

End point title	Response Rate (RR)

End point description:

The primary endpoint was response rate (RR) which was evaluated according to the revised Cheson criteria.

Data from two studies, PQR309-002 (EudraCT 2014-005384-33, 54 patients enrolled) and PQR309-002A (2016-000125-38, 9 patients enrolled), were combined and analysed together. Therefore all safety and efficacy data presented in this record are from the combined analysis of both studies.

End point type	Primary

End point timeframe:

Every 8 weeks during the first 6 months of PQR309 treatment, subsequently every 3 months up to 2 years of PQR309 treatment and every 6 months afterwards.

End point values	Continuous 60mg	Continuous 80mg	Intermittent 120mg	Intermittent 140mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	42	6	7
Units: Number of patients	1	6	0	1

Statistical analyses

Statistical analysis title	Response Rate

Statistical analysis description:

Response Rate (RR) evaluated according to the revised Cheson criteria.

Comparison groups	Continuous 80mg v Intermittent 120mg v Continuous 60mg v

	Intermittent 140mg
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	Exact test

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 60mg
Reporting group description: -	
Reporting group title	Continuous 80mg
Reporting group description: -	
Reporting group title	Intermittent 120mg
Reporting group description: -	
Reporting group title	Intermittent 140mg
Reporting group description: -	

Serious adverse events	Continuous 60mg	Continuous 80mg	Intermittent 120mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	24 / 42 (57.14%)	5 / 6 (83.33%)
number of deaths (all causes)	4	6	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pulmonary embolism			
subjects affected / exposed	1 / 8 (12.50%)	0 / 42 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 8 (0.00%)	0 / 42 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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

Disease progression			
subjects affected / exposed	2 / 8 (25.00%)	8 / 42 (19.05%)	3 / 6 (50.00%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 4	0 / 2
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	2 / 42 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	2 / 42 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 42 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 42 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 8 (0.00%)	0 / 42 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Radiation pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 42 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Wrist fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Cardiac failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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			
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 42 (7.14%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	3 / 42 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	1 / 42 (2.38%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 8 (0.00%)	2 / 42 (4.76%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus generalised			

subjects affected / exposed	0 / 8 (0.00%)	0 / 42 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Rhabdomyolysis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 42 (2.38%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 42 (0.00%)	0 / 6 (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
Escherichia sepsis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 42 (0.00%)	0 / 6 (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

Infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Lung infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 42 (0.00%)	0 / 6 (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
Rash pustular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 42 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 42 (2.38%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 42 (2.38%)	0 / 6 (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

Serious adverse events	Intermittent 140mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pulmonary embolism			

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour associated fever				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				

Dyspnoea				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Panic attack				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Weight decreased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Humerus fracture				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radiation pneumonitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal perforation			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pruritus generalised			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Rhabdomyolysis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Clostridium difficile colitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash pustular				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				

Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Continuous 60mg	Continuous 80mg	Intermittent 120mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	42 / 42 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 8 (25.00%)	9 / 42 (21.43%)	3 / 6 (50.00%)
occurrences (all)	2	9	3
Fatigue			
subjects affected / exposed	5 / 8 (62.50%)	20 / 42 (47.62%)	2 / 6 (33.33%)
occurrences (all)	5	20	2
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	5 / 42 (11.90%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Oedema peripheral			
subjects affected / exposed	1 / 8 (12.50%)	5 / 42 (11.90%)	2 / 6 (33.33%)
occurrences (all)	1	5	2
Pain			
subjects affected / exposed	2 / 8 (25.00%)	1 / 42 (2.38%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	7 / 42 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	7	1
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	2 / 6 (33.33%)
occurrences (all)	0	4	2
Dyspnoea			
subjects affected / exposed	2 / 8 (25.00%)	4 / 42 (9.52%)	1 / 6 (16.67%)
occurrences (all)	2	4	1
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Depressed mood			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Depression			
subjects affected / exposed	2 / 8 (25.00%)	7 / 42 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	7	0
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 42 (7.14%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	1 / 6 (16.67%)
occurrences (all)	0	4	1
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Weight decreased			
subjects affected / exposed	3 / 8 (37.50%)	13 / 42 (30.95%)	0 / 6 (0.00%)
occurrences (all)	3	13	0
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	1 / 6 (16.67%)
occurrences (all)	0	4	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	3 / 42 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Headache			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	1 / 6 (16.67%)
occurrences (all)	0	4	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	9 / 42 (21.43%)	1 / 6 (16.67%)
occurrences (all)	1	9	1
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	5 / 42 (11.90%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	12 / 42 (28.57%)	3 / 6 (50.00%)
occurrences (all)	0	12	3
Thrombocytopenia			
subjects affected / exposed	1 / 8 (12.50%)	10 / 42 (23.81%)	3 / 6 (50.00%)
occurrences (all)	1	10	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	6 / 42 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	6 / 42 (14.29%)	1 / 6 (16.67%)
occurrences (all)	1	6	1
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	17 / 42 (40.48%)	3 / 6 (50.00%)
occurrences (all)	1	17	3
Dry mouth			

subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	6 / 42 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Nausea			
subjects affected / exposed	4 / 8 (50.00%)	15 / 42 (35.71%)	1 / 6 (16.67%)
occurrences (all)	4	15	1
Vomiting			
subjects affected / exposed	3 / 8 (37.50%)	7 / 42 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	7	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	6 / 42 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	7 / 42 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	7	1
Rash			
subjects affected / exposed	1 / 8 (12.50%)	6 / 42 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	6	0
Rash maculo-papular			
subjects affected / exposed	1 / 8 (12.50%)	7 / 42 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	7	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	5 / 42 (11.90%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 42 (4.76%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Urinary tract infection			

subjects affected / exposed	0 / 8 (0.00%)	6 / 42 (14.29%)	2 / 6 (33.33%)
occurrences (all)	0	6	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 8 (62.50%)	10 / 42 (23.81%)	2 / 6 (33.33%)
occurrences (all)	5	10	2
Hypercreatininaemia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 42 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Hyperglycaemia			
subjects affected / exposed	5 / 8 (62.50%)	19 / 42 (45.24%)	2 / 6 (33.33%)
occurrences (all)	5	19	2
Hyperphosphatasaemia			
subjects affected / exposed	2 / 8 (25.00%)	3 / 42 (7.14%)	1 / 6 (16.67%)
occurrences (all)	2	3	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 8 (0.00%)	4 / 42 (9.52%)	2 / 6 (33.33%)
occurrences (all)	0	4	2
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	5 / 42 (11.90%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	5 / 42 (11.90%)	2 / 6 (33.33%)
occurrences (all)	0	5	2

Non-serious adverse events	Intermittent 140mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Fatigue			

subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Mucosal inflammation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Depressed mood			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Insomnia			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 3		
Dry mouth subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Rash			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypercreatininaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Hyperphosphatasaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2015	The subject selection / inclusion criteria were updated to ensure adequate contraceptive measures were in place. The dose escalation scheme and corresponding rationale for selection of the starting dose were modified. Reference to the IDSMB was removed. Section concerning handling of patients with hyperglycemia updated. Two clinical sites were added to ensure timely recruitment.
28 April 2015	Hospitalization for progressive disease was removed from table 5 (listing of exceptions to SAE definition).
22 October 2015	Imaging changed to every 8 weeks instead of every 6 weeks (4 cycles), subsequently every 2 months up to 2 years of treatment and every 6 months afterwards. Inclusion Criteria expanded to require patients to have had at least 2 prior lines of therapy instead of 1, including immune-chemotherapy. An exception was introduced for CLL, reflecting the currently available therapies in this indication. Inclusion and exclusion criteria modified to allow patients with controlled diabetes to be recruited. Exclusion criteria modified to exclude patients with concomitant medications increasing pH and those with previous AEs Grade 3 or higher on PI3K/mTOR inhibitors. Concept of "Dose Levels" was removed; actual doses remained limited to 60 and 80mg qd. The MTD for the continuous treatment schedule defined as 80 mg based on data from clinical trials in patients with solid tumors. The definition of dose limiting toxicity (DLT) was modified for clarity. This version of the protocol was not approved in Germany. As a result, new study PQR309-002A was initiated in Germany and Switzerland.
23 October 2015	The definition of dose-limiting toxicity was modified, so that it was based upon AEs "for which a causal connection to bimiralisib cannot be ruled out" as opposed to AEs "possibly, probably or definitely related to the trial drug". This amendment was to accommodate the request from US FDA. This version was only in effect in the US and sites in other countries used the previous version.
28 July 2016	Incorporation of intermittent treatment schedules (PQR309 twice weekly) into the protocol. Treatment expanded to not only include q.d. 60mg or 80mg, but also Intermittent Schedule A ("2 days on / 5 days off") and Schedule B ("Mon / Thu") starting with 120mg, increasing with 20mg or 40mg increments. DLT definition expanded with rules for the intermittent dose regimen. Both intermittent regimens were intended to reduce overall exposure compared with continuous dosing. Changes to inclusion criteria: - Specific cut-offs for liver function tests removed. Liver function parameters have to be within the same limits regardless of liver involvement. - Assessment of HbA1c removed. The HbA1c parameter does not reflect a liability for treatment with PQR309. Changes to exclusion criteria: - Expanded to exclude patients who experienced Grade 4 on PI3K/mTOR inhibitors, due to a shift in risk for these patients when being considered for treatment with PQR309. - Expanded with example (chronic active hepatitis). - HbA1c removed. Precautions: Highly effective contraception language added to align with CTFG requirements. Assessments: fasting plasma glucose, height and body weight added.

07 August 2017	The dose-escalation scheme was changed to reduce the number of patients to 3 per dose level. Three additional patients will only be enrolled if a DLT is seen in the first three patients. Exclusion criterion 7 clarified to exclude "any major surgery, chemotherapy, immunotherapy or other anticancer therapy within 21 days prior to trial treatment start." The dose reduction scheme for patients who experience AEs on intermittent dosing schemes was adjusted to clarify that patients may have their dose reduced up to two times. The use of concomitant medication was updated to reflect newly available pre-clinical and clinical data on the drug-drug interactions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 October 2016	In parallel to this study in relapsed / refractory lymphoma patients (study PQR309-002), intermittent dosing schedules were being evaluated in a separate study in patients with solid tumors (study PQR309-003), with the objective of establishing the MTD on the intermittent dosing schedule. A halt to recruitment to PQR309-002 was instigated on 4 October 2016 to allow data on dosing with the intermittent schedule from PQR309-003 to become available prior to starting step 2 of study PQR309-002. Sufficient safety data on the intermittent dosing schedules were subsequently obtained from study PQR309-003 to support restart of study PQR309-002 at 120 mg dosed intermittently on 22 March 2017.	22 March 2017
11 September 2018	The sponsor took the decision to end the study following step 1 of the expansion phase (after dose escalation with intermittent dosing on Schedule A) based on an overall review of the development program, in which it was decided to pursue future phase 2 clinical development in new studies.	-

Notes:

Limitations and caveats

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

Small number of subjects in some arms precluded comparison between groups and statistical analysis of the primary endpoint. Results from this trial (PQR309-002) have been analysed together with those of trial PQR309-002A (EudraCT ref: 2016-000125-3).

Notes: