



Clinical trial results:

Open-label, non-randomized, phase 2 study evaluating efficacy and safety of PQR309 in patients with relapsed or refractory primary CNS lymphoma

Summary

EudraCT number	2015-001306-33
Trial protocol	ES BE GB
Global end of trial date	12 January 2018

Results information

Result version number	v1 (current)
This version publication date	20 April 2019
First version publication date	20 April 2019

Trial information

Trial identification

Sponsor protocol code	PQR309-005
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02669511
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 127078

Notes:

Sponsors

Sponsor organisation name	PIQR Therapeutics AG
Sponsor organisation address	Hochbergerstrasse, 60C, Basel, Switzerland, 4057
Public contact	Chief Operating Officer, PIQR Therapeutics AG, +41 615512050, melanie.rolli@piqr.com
Scientific contact	Chief Operating Officer, PIQR Therapeutics AG, +41 615512050, melanie.rolli@piqr.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	25 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2018
Global end of trial reached?	Yes
Global end of trial date	12 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy (ORR) of PQR309 in the treatment of patients with relapsed or refractory primary CNS lymphoma.

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. 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	12 November 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	France: 1
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	21
EEA total number of subjects	14

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)	7
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between November 12th 2015 and January 12th 2018, 21 patients were included into the trial at 9 centers, 1 in France, 4 in Germany, 2 in USA, 1 in Spain and 1 in UK.

Pre-assignment

Screening details:

Screening period:28 days. Main inclusion criteria:Confirmed relapsed or refractory PCNSL, Age \geq 18 years, Presence of at least one lesion of bi-dimensionally measurable disease, Signed informed consent, Karnofsky Performance Score \geq 70%, No Secondary CNS lymphoma or chronic immunosuppression-associated CNS lymphoma, No Fasting glucose $>$ 7.0 mmol/dL

Pre-assignment period milestones

Number of subjects started	21
Number of subjects completed	21

Period 1

Period 1 title	Screening 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/80mg
------------------	----------------------

Arm description: -

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:

60mg/80mg qd

Arm title	Intermittent 140mg
------------------	--------------------

Arm description: -

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 2 days on, 5 days off

Number of subjects in period 1	Continuous 60mg/80mg	Intermittent 140mg
Started	14	7
Completed	14	7

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	Continuous 60mg/80mg
------------------	----------------------

Arm description: -

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:

60mg/80mg qd

Arm title	Intermittent 140mg
------------------	--------------------

Arm description: -

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 2 days on, 5 days off

Number of subjects in period 2	Continuous 60mg/80mg	Intermittent 140mg
Started	14	7
Completed	14	7

Baseline characteristics

Reporting groups

Reporting group title	Screening period
-----------------------	------------------

Reporting group description: -

Reporting group values	Screening period	Total	
Number of subjects	21	21	
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)	7	7	
From 65-84 years	14	14	
85 years and over	0	0	
Age continuous			
Units: years			
median	75		
full range (min-max)	42 to 83	-	
Gender categorical			
Units: Subjects			
Female	12	12	
Male	9	9	

End points

End points reporting groups

Reporting group title	Continuous 60mg/80mg
Reporting group description: -	
Reporting group title	Intermittent 140mg
Reporting group description: -	
Reporting group title	Continuous 60mg/80mg
Reporting group description: -	
Reporting group title	Intermittent 140mg
Reporting group description: -	
Subject analysis set title	The intent-to-treat (ITT) analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intent-to-treat (ITT) analysis set: is defined as all patients who received ≥ 1 dose of bimiralisib.	
Subject analysis set title	The intent-to-treat (ITT) analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The intent-to-treat (ITT) analysis set was used in all safety analyses.	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description: Objective response rate (ORR) was evaluated according to the Response Criteria of the International Primary CNS Lymphoma Collaborative Group. For purposes of determining the ORR, tumor response was based on the best overall response recorded for each patient since baseline. The best overall response was the best response recorded from the start of the study treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the study treatment started). If a response recorded at one scheduled MRI did not persist at the next regular scheduled MRI, the response would still be recorded based on the prior scan, but would be designated as a non-sustained (unconfirmed) response. If the response was sustained i.e. still present on the subsequent MRI taken 4 weeks apart, it would be recorded as a confirmed response, lasting until the time of tumor progression.	
End point type	Primary
End point timeframe: Every 4 weeks	

End point values	Continuous 60mg/80mg	Intermittent 140mg	The intent-to-treat (ITT) analysis set	The intent-to-treat (ITT) analysis set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	14	7	14	7
Units: N/A	1	0	1	0

Statistical analyses

Statistical analysis title	Statistical Analysis Plan
Comparison groups	The intent-to-treat (ITT) analysis set v The intent-to-treat

	(ITT) analysis set
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.2
Method	Simon's two-stage minimax design

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
End point type	Secondary
End point timeframe:	
Complete Treatment Duration	

End point values	Continuous 60mg/80mg	Intermittent 140mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Days	87	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)
End point description:	
End point type	Secondary
End point timeframe:	
Complete Treatment Duration	

End point values	Continuous 60mg/80mg	Intermittent 140mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Days	41	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title | Duration of Response (DOR)

End point description:

End point type | Secondary

End point timeframe:

Complete Treatment Duration

End point values	Continuous 60mg/80mg	Intermittent 140mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0 ^[1]		
Units: Days	644			

Notes:

[1] - Not analysed for other patients

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure (TTF)

End point title | Time to treatment failure (TTF)

End point description:

End point type | Secondary

End point timeframe:

Complete Treatment Duration

End point values	Continuous 60mg/80mg	Intermittent 140mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Days	88	36		

Statistical analyses

No statistical analyses for this end point

Secondary: 1-year survival rate

End point title | 1-year survival rate

End point description:

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

End point timeframe:

Complete Treatment Duration

End point values	Continuous 60mg/80mg	Intermittent 140mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	0 ^[2]		
Units: Number of patients	1			

Notes:

[2] - Not analysed

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	21.1
--------------------	------

Reporting groups

Reporting group title	Continuous 60mg/80mg
-----------------------	----------------------

Reporting group description: -

Reporting group title	Intermittent 140mg
-----------------------	--------------------

Reporting group description: -

Serious adverse events	Continuous 60mg/80mg	Intermittent 140mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	5 / 7 (71.43%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	6 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system lymphoma			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysarthria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 14 (0.00%)	2 / 7 (28.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 14 (14.29%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 7 (28.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancytopenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	2 / 14 (14.29%)	4 / 7 (57.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 1	
General physical health deterioration			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	6 / 7	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
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 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (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			
Lung infection			

subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	10 / 10	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Continuous 60mg/80mg	Intermittent 140mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	7 / 7 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	4 / 14 (28.57%)	2 / 7 (28.57%)	
occurrences (all)	4	2	
Gait inability			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	3 / 14 (21.43%)	1 / 7 (14.29%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	2 / 14 (14.29%)	2 / 7 (28.57%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Wheezing			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Disorientation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Tension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 14 (42.86%)	1 / 7 (14.29%)	
occurrences (all)	6	1	
C-reactive protein increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Fall subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Tongue injury subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Traumatic haemorrhage subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Cardiac disorders Pericarditis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Ventricular arrhythmia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Nervous system disorders Altered state of consciousness subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Clonus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Epilepsy subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Facial paralysis			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Headache subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	1 / 7 (14.29%) 1	
Polyneuropathy subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Speech disorder subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Vasogenic cerebral oedema subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Lymphopenia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Eye disorders Cataract subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Eye pruritus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Gastrointestinal disorders Cheilitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Constipation			

subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oral discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Exfoliative rash			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Pain of skin			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pruritus			

subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 5	0 / 7 (0.00%) 0	
Pruritus generalised subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Rash generalised subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Rash maculo-papular subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Rash pruritic subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Renal and urinary disorders			
Leukocyturia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Proteinuria subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Renal failure subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Urinary incontinence subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Urinary retention subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Bone pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Muscle tightness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Gingivitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Lip infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Staphylococcal infection			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	
Dehydration subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Hypercreatininaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Hyperinsulinaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Hyperlactacidaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Hypernatraemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Hyperphosphatasaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	

Hypokalaemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2016	<p>New exclusion criterion (#14) and section 11.2.2.8 Gastric protection agents of Concomitant medication added to restrict patient population based on use of medicinal products that increase the pH (reduce acidity) of the upper gastrointestinal tract and define their washout period prior to study treatment starts.</p> <p>Added as Gastric Protection Agents interfere with the solubility and absorption of PQR309 and consequently its bioavailability.</p>
30 September 2016	<p>Reduction of starting dose to 60mg Bimiralisib daily, Introduction of intermittent dosing schedules, The inclusion criterion #5 has been modified, from "Maximum one prior system therapy regimen" to "Maximum two prior system therapy regimens excluding high dose chemotherapy at first relapse". The exclusion criterion #18 has been modified to remove HbA1c as a parameter for exclusion, A treatment delay of >14 days due to AE of hyperglycemia will not automatically lead to withdrawal from the study.</p> <p>Changes made as a response to the observation that the 80 mg daily dosing is not adequately tolerated in the long term in PCNSL. Intermittent schedules: In the initial phase of PQR309 early clinical development, continuous daily administration of PQR309 was evaluated to determine the maximum tolerated dose (MTD) and to establish the safety and pharmacokinetics of continuous administration. It was shown that at a dose of 80 mg per day PQR309 reaches plasma concentrations that were expected to be pharmacologically active based on pre-clinical experiments with most of adverse events (AEs) of CTC AE grade 1 or 2. This dose and regimen was therefore chosen for further evaluation of clinical anticancer activity. However, pre-clinical data with PQR309 suggest that it might not be necessary to inhibit PI3K/mTOR continuously to achieve full efficacy. Therefore, additional intermittent dosing regimens will be explored in this study if continuous daily dosing with 60mg is not adequately tolerated or is inefficacious.</p>
23 May 2017	<p>Dose-escalation scheme: The dose-escalation scheme has been 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.</p> <p>Inclusion criterion #5: The term "high dose chemotherapy" has been replaced by the more appropriate term "myeloablative therapy": Maximum of two prior systemic therapy regimens excluding myeloablative therapy at first relapse Patients who have previously received whole brain radiotherapy (WBRT) may be enrolled if they were free of WBRT-associated symptoms. Consequently, exclusion criterion #3 has been modified as follows: "Patients with persisting symptoms from previous whole brain radiation (WBRT)"</p> <p>Concomitant Medications: The use of concomitant medication has been updated to reflect newly available pre-clinical and clinical data on the drug-drug interaction potential of PQR309. In this context, exclusion criterion #7 and #8 have been removed. A dedicated separate summary-of-changes describing these changes has been provided.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported.

Notes: