



## Clinical trial results:

### Exploratory study of the efficacy and safety of topical bimiralisib in an inflammatory and hyperproliferative skin condition

#### Summary

EudraCT number	2019-001189-14
Trial protocol	FR
Global end of trial date	16 March 2020

#### Results information

Result version number	v1 (current)
This version publication date	09 October 2020
First version publication date	09 October 2020

#### Trial information

##### Trial identification

Sponsor protocol code	PQR309-401
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	PIQUR Therapeutics AG
Sponsor organisation address	Hochbergerstrasse 60C, Basel, Switzerland, CH-4057
Public contact	Clinical Program Leader, PIQUR Therapeutics AG, info@piqur.com
Scientific contact	Clinical Program Leader, PIQUR Therapeutics AG, 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	18 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2020
Global end of trial reached?	Yes
Global end of trial date	16 March 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of three concentrations of topical bimiralisib compared to matching vehicle and two approved topical medications (Daivobet® and Daivonex®) applied once daily to distinct 2 cm diameter treatment mini-zones on each patient.

Protection of trial subjects:

The study processes, potential benefits and any risks 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:

Not applicable.

Evidence for comparator:

Two active comparators were used: Daivobet ointment and Daivonex ointment. Daivobet contains two active substances: calcipotriol and betamethasone. The vitamin D derivative, Calcipotriol, acts through receptors prevent skin proliferation that causes the scaly patches in psoriasis. Betamethasone is an anti-inflammatory that helps reduce the inflammation and itching that occur with psoriasis. Daivonex contains only calcipotriol. Both medicinal products have been approved for over 15 years for topical treatment of plaque psoriasis and have previously been used as positive comparators in the established 4-week Psoriasis Plaque Test (PPT), which formed the basis of the current study.

Actual start date of recruitment	12 November 2019
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: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	21
From 65 to 84 years	3
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from 12-Nov-2019 until 15-Jan-2020 to one clinical site in Nice, France.

### Pre-assignment

Screening details:

In total 26 patients were screened, of which 24 were enrolled in the study. Two patients were not enrolled because they did not meet inclusion criteria (07 and 09, respectively).

### Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator <sup>[1]</sup>

Blinding implementation details:

The study was not double-blinded as the two commercially-available active comparators were distinguishable from the other IMPs. However, the study was considered investigator-blinded since IMP applications were performed out of sight of the investigator/evaluator.

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Vehicle

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Vehicle (non-aqueous gel)
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

50 µL vehicle was administered once daily for six consecutive days per week for four weeks (24 applications) on a 2-cm diameter mini-zone.

<b>Arm title</b>	Bimiralisib 0.5% (w/w)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	bimiralisib 0.5% (w/w) gel
Investigational medicinal product code	PQR309
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

50 µL bimiralisib 0.5% (w/w) non-aqueous gel was administered once daily for six consecutive days per week for four weeks (24 applications) on a 2-cm diameter mini-zone.

<b>Arm title</b>	Bimiralisib 2.0% (w/w)
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	bimiralisib 2.0% (w/w) gel
Investigational medicinal product code	PQR309
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

50 µL bimiralisib 2.0% (w/w) non-aqueous gel was administered once daily for six consecutive days per week for four weeks (24 applications) on a 2-cm diameter mini-zone.

<b>Arm title</b>	Bimiralisib 6.3% (w/w)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	bimiralisib 6.3% (w/w) gel
Investigational medicinal product code	PQR309
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

50 µL bimiralisib 6.3% (w/w) non-aqueous gel was administered once daily for six consecutive days per week for four weeks (24 applications) on a 2-cm diameter mini-zone.

<b>Arm title</b>	Daivobet
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Daivobet ointment
Investigational medicinal product code	
Other name	Betamethasone (as dipropionate) 0.5mg/g + Calcipotriol 50µg/g
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

50 µL Daivobet ointment (betamethasone (as dipropionate) 0.5mg/g + calcipotriol 50µg/g) was administered once daily for six consecutive days per week for four weeks (24 applications) on a 2-cm diameter mini-zone.

<b>Arm title</b>	Daivonex
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Daivonex ointment
Investigational medicinal product code	
Other name	Calcipotriol 50µg/g
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

50 µL Daivonex ointment (calcipotriol 50µg/g) was administered once daily for six consecutive days per week for four weeks (24 applications) on a 2-cm diameter mini-zone.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The study was designed as an investigator-blinded, within-patient randomised, intra-individual comparison of treatments. Hence each patient received all study treatments which were randomly allocated to one of six mini-zones selected on psoriasis plaques of identical severity. During the study, the patient and person dispensing IMP were instructed not to discuss study products with the investigator who performed evaluations.

<b>Number of subjects in period 1</b>	Vehicle	Bimiralisib 0.5% (w/w)	Bimiralisib 2.0% (w/w)
Started	24	24	24
Completed	24	24	24

<b>Number of subjects in period 1</b>	Bimiralisib 6.3% (w/w)	Daivobet	Daivonex
Started	24	24	24
Completed	24	24	24

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment Period
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Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	24	24	
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)	21	21	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous			
Units: years			
median	56.5		
full range (min-max)	32 to 79	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	17	17	
Skin type			
Skin type according to Fitzpatrick's classification			
Units: Subjects			
Type II	2	2	
Type III	20	20	
Type IV	2	2	

## End points

### End points reporting groups

Reporting group title	Vehicle
Reporting group description: -	
Reporting group title	Bimiralisib 0.5% (w/w)
Reporting group description: -	
Reporting group title	Bimiralisib 2.0% (w/w)
Reporting group description: -	
Reporting group title	Bimiralisib 6.3% (w/w)
Reporting group description: -	
Reporting group title	Daivobet
Reporting group description: -	
Reporting group title	Daivonex
Reporting group description: -	

### Primary: AUEC of Total Clinical Score

End point title	AUEC of Total Clinical Score
End point description:	The primary efficacy endpoint was the Area Under the Effect Curve (AUEC) of Total Clinical Score (TCS) calculated from Day 1 to Day 29 using the trapezoidal rule. The lower the AUEC1-29, the stronger is the activity of the drug. TCS was defined in the protocol as the sum of psoriasis severity index scores of erythema, scaling and induration.
End point type	Primary
End point timeframe:	From Day 1 to Day 29

End point values	Vehicle	Bimiralisib 0.5% (w/w)	Bimiralisib 2.0% (w/w)	Bimiralisib 6.3% (w/w)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	24	24
Units: Score				
arithmetic mean (standard deviation)	170.69 (± 33.51)	157.65 (± 44.04)	160.92 (± 31.46)	171.31 (± 37.66)

End point values	Daivobet	Daivonex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Score				
arithmetic mean (standard deviation)	58.31 (± 19.00)	92.52 (± 27.05)		



## Statistical analyses

<b>Statistical analysis title</b>	Analysis of AUEC1-29 of the TCS
Statistical analysis description: The AUEC1-29 of the TCS was analyzed using a mixed-effect model. This model included treatment as fixed effect and subject as random effect. The treatments were compared using the Tukey Kramer multiple comparison test performed at a 5% two-sided significance level.	
Comparison groups	Vehicle v Bimimalisib 0.5% (w/w) v Bimimalisib 2.0% (w/w) v Bimimalisib 6.3% (w/w) v Daivobet v Daivonex
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$\leq 0.05$
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The analysis of adverse events (AEs) is based on treatment emergent adverse events (TEAEs), defined as all AEs occurring or worsening after first dose of IMP.

Adverse event reporting additional description:

Safety assessments were conducted for all patients at the screening visit (following ICF signature) and at every subsequent visit. Safety parameters were: 1) Local tolerance assessed twice weekly using a 4-point scale for each mini-zone, and 2) Monitoring and recording of AEs.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Safety Population
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Reporting group description:

All randomized patients who received at least one dose of the study products (i.e. either test or reference products).

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 24 (16.67%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Infections and infestations			

Paronychia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

This study involved an intra-individual comparison of treatments therefore each patient received each of the five IMPs randomized to five treatment mini-zones. The total number of patients in the analysis was thus 24 (and not 144).
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Notes: