



## Clinical trial results:

### Double-Blind, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle to Decrease the Number of Surgically Eligible Basal Cell Carcinomas in Gorlin Syndrome Patients Summary

EudraCT number	2015-004274-15
Trial protocol	GB
Global end of trial date	24 April 2017

#### Results information

Result version number	v2 (current)
This version publication date	03 July 2020
First version publication date	11 May 2018
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li><li>Revision of data set already provided</li></ul>

#### Trial information

##### Trial identification

Sponsor protocol code	Pelle-926-201
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02762084
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	PellePharm, Inc.
Sponsor organisation address	275 Middlefield Rd., Suite 100, Menlo Park, United States, CA 94025
Public contact	Alix Alderman, PellePharm, Inc, +1 510-502-6144, aalderman@pellepharm.com
Scientific contact	Alix Alderman, PellePharm, Inc, +1 510-502-6144, aalderman@pellepharm.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	24 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 April 2017
Global end of trial reached?	Yes
Global end of trial date	24 April 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of the study were to evaluate the following:

- 1.The clinical efficacy of patidegib gel 2% or 4% compared to vehicle as defined by the percent decrease in greatest diameter of Baseline treatment targeted Surgically Eligible basal cell carcinomas (SEBs) after 26 weeks of treatment. [SEBs were defined as clinically diagnosed BCCs 5 mm or greater in diameter on the face excluding the nose and periorbital skin, and 9 mm or greater at sites other than the face].
- 2.The molecular efficacy of treatment as defined by reduction in the hedgehog (HH) signaling pathway target gene GLI1 after treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 6 weeks to treatment-targeted SEBs.
- 3.The safety and tolerability of treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 26 weeks.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP, and in compliance with local regulatory requirements pertinent to safety of trial subjects.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	06 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	6
From 65 to 84 years	11
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted by 2 principal investigators at 2 clinical sites in the United Kingdom. A total of 17 subjects were randomized.

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

Number of subjects started	17
Number of subjects completed	17

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

The study drugs were packaged and labeled identically, and the study drug kits were numbered sequentially and dispensed randomly to the subjects entering the study within each investigational center. The Investigators, the site staff, PellePharm, and the Clinical Monitors were not aware of the treatment assigned to the individual study subjects. The treatment assignments for all enrolled subjects were unblinded only after the conclusion of the treatment phase of the study.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Patidegib Topical gel 2%

Arm description:

Patidegib gel 2% applied topically twice daily for 26 weeks

Arm type	Experimental
Investigational medicinal product name	Patidegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

Patidegib 2% gel applied topically twice daily for 26 weeks.

<b>Arm title</b>	Patidegib Topical gel 4%
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Arm description:

Patidegib gel 4% applied topically twice daily for 26 weeks

Arm type	Experimental
Investigational medicinal product name	Patidegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

Patidegib 4% gel applied topically twice daily for 26 weeks.

<b>Arm title</b>	Vehicle gel
Arm description: Vehicle gel applied topically twice daily for 26 weeks	
Arm type	Placebo
Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use
Dosage and administration details: Vehicle gel applied topically twice daily for 26 weeks.	

<b>Number of subjects in period 1</b>	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel
Started	6	6	5
Completed	5	6	4
Not completed	1	0	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	-	1

## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	17	17	
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)	6	6	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	60.8		
standard deviation	± 13.63	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	6	6	

## End points

### End points reporting groups

Reporting group title	Patidegib Topical gel 2%
Reporting group description: Patidegib gel 2% applied topically twice daily for 26 weeks	
Reporting group title	Patidegib Topical gel 4%
Reporting group description: Patidegib gel 4% applied topically twice daily for 26 weeks	
Reporting group title	Vehicle gel
Reporting group description: Vehicle gel applied topically twice daily for 26 weeks	
Subject analysis set title	Patidegib gel
Subject analysis set type	Full analysis
Subject analysis set description: Patidegib: 2% or 4% gel applied topically twice daily for 26 weeks	

### Primary: Clinical efficacy : Percentage change in tumor size from baseline

End point title	Clinical efficacy : Percentage change in tumor size from baseline
End point description: Percent change in tumor size of Treatment-targeted Surgically Eligible Basal Cell Carcinomas (SEBs) Tumor Size from Baseline. SEBs were defined as clinically diagnosed basal cell carcinoma (BCC) 5 millimeters (mm) or greater in diameter on the face, excluding the nose and periorbital skin, and 9-millimeter (mm) or greater at sites other than the face. The percent change in greatest diameters of treatment-targeted surgically eligible basal cell carcinomas (SEBs) from Baseline to Week 26 was calculated as follows: (sum [Baseline] - sum [Week 26] / sum [Baseline] * 100), where sum = the greatest diameters of Baseline treatment-targeted SEBs, positive Numbers to represent decrease in tumor size and negative Numbers to represent increases in tumor size. Missing values were imputed using Last-Observation Carried Forward (LOCF).	
End point type	Primary
End point timeframe: Baseline and Week 26	

End point values	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: Percentage decrease from baseline				
arithmetic mean (standard deviation)	38.82 (± 57.002)	25.57 (± 33.874)	33.00 (± 37.662)	

### Statistical analyses

Statistical analysis title	Statistical analysis 1 for Clinical Efficacy
Statistical analysis description: Percent Decrease in Baseline Treatment-targeted Surgically Eligible Basal Cell Carcinomas (SEBs) Tumor Size from Baseline	

Comparison groups	Patidegib Topical gel 2% v Vehicle gel
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.909
Method	ANCOVA

Notes:

[1] - Pairwise comparison

ANCOVA with treatment group as a factor and Baseline value as a covariate

<b>Statistical analysis title</b>	Statistical analysis 2 for Clinical Efficacy
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Statistical analysis description:

Percent Decrease in Baseline Treatment-targeted Surgically Eligible Basal Cell Carcinomas (SEBs) Tumor Size from baseline

Comparison groups	Patidegib Topical gel 4% v Vehicle gel
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	= 0.648
Method	ANCOVA

Notes:

[2] - Pairwise comparison

ANCOVA with treatment group as a factor and Baseline value as a covariate

### **Primary: Molecular efficacy: Percent Change in GLI1 mRNA levels**

End point title	Molecular efficacy: Percent Change in GLI1 mRNA levels
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End point description:

Percent change in the Hedgehog (HH) Signaling Pathway Target Gene Glioma-associated Oncogene Homolog 1 (GLI1) Messenger Ribonucleic Acid (mRNA) Levels from Baseline.

SEBs were defined as clinically diagnosed BCC 5 mm or greater in diameter on the face, excluding the nose and periorbital skin, and 9-mm or greater at sites other than the face. A single baseline SEB designated as a treatment targeted tumor at Baseline was biopsied first at Baseline and again following 6 weeks of treatment. This was used to assess percent decrease in GLI1 mRNA levels as follows: (Baseline - Week 6) / Baseline \* 100, where positive numbers to represent decrease in GL1 mRNA level, and negative Numbers to represent increase in GL1 mRNA level. Any missing values are not imputed; all available data is summarized.

End point type	Primary
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End point timeframe:

Baseline and Week 6

<b>End point values</b>	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: percentage decrease in GLI1 mRNA levels				
arithmetic mean (standard deviation)	53.83 (± 27.197)	20.69 (± 34.730)	28.53 (± 43.096)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1 for molecular efficacy
Statistical analysis description: Percent Decrease in the Hedgehog (HH) Signaling Pathway Target Gene Glioma-associated Oncogene Homolog 1 (GLI1) Messenger Ribonucleic Acid (mRNA) Levels from Baseline	
Comparison groups	Patidegib Topical gel 2% v Vehicle gel
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 0.5
Method	ANCOVA

Notes:

[3] - Pairwise comparison

With a factor of treatment group and using Baseline value as a covariate

<b>Statistical analysis title</b>	Statistical analysis 2 for molecular efficacy
Statistical analysis description: Percent Decrease in the Hedgehog (HH) Signaling Pathway Target Gene Glioma-associated Oncogene Homolog 1 (GLI1) Messenger Ribonucleic Acid (mRNA) Levels from Baseline	
Comparison groups	Patidegib Topical gel 4% v Vehicle gel
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	= 0.681
Method	ANCOVA

Notes:

[4] - Pairwise comparison

With a factor of treatment group and using Baseline value as a covariate

### **Primary: Safety and Tolerability Assessment of Treatment With Patidegib Gel: Number of Participants With a Treatment-emergent Adverse Event Causally Related to Study Drug**

End point title	Safety and Tolerability Assessment of Treatment With Patidegib Gel: Number of Participants With a Treatment-emergent Adverse Event Causally Related to Study Drug <sup>[5]</sup>
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End point description:

All serious adverse events (SAEs) and all other non-serious adverse events (AEs) regardless of causality are located in the Reported AE Module. AEs considered as related where categorized by the Investigator as either definitely related, probably related, or possibly related. Treatment-emergent AEs are those with an onset after use of study drug.

End point type	Primary
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End point timeframe:

Baseline through Week 26

Notes:

[5] - 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: Additional statistical analysis is not applicable to this endpoint.

<b>End point values</b>	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: participants	2	5	2	

## Statistical analyses

No statistical analyses for this end point

### Primary: Safety and Tolerability Assessment of Treatment With Patidegib Gel: Number of Participants With Treatment-emergent Administrative Site Skin Condition AEs Causally Related to Study Drug

End point title	Safety and Tolerability Assessment of Treatment With Patidegib Gel: Number of Participants With Treatment-emergent Administrative Site Skin Condition AEs Causally Related to Study Drug <sup>[6]</sup>
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End point description:

All SAEs and all other non-serious AEs, regardless of causality, are located in the Reported AE Module. The number of participants reporting administrative-site, skin condition treatment-emergent AEs considered related to study drug by the Investigator are presented below. Treatment-emergent AEs are those with an onset after use of study drug.

End point type	Primary
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End point timeframe:

Baseline through Week 26

Notes:

[6] - 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: Additional statistical analysis is not applicable to this endpoint.

End point values	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: Participants				
Application site alopecia	0	1	0	
Application site dermatitis	0	1	0	
Application site pain	0	1	0	
Application site rash	0	1	0	
Application site reaction	0	0	1	

## Statistical analyses

No statistical analyses for this end point

### Secondary: The Number of Participants Reporting New SEBs on the Face From Baseline for the Combined Patidegib Treatment Groups

End point title	The Number of Participants Reporting New SEBs on the Face From Baseline for the Combined Patidegib Treatment Groups <sup>[7]</sup>
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End point description:

Facial SEBs were defined as clinically diagnosed BCC 5 mm or greater in diameter on the face, excluding the nose and periorbital skin. A new facial SEB was defined as an SEB first noted on the face after Week

2 that developed at a site where there was no visible BCC of any size at Baseline or Week 2. New facial SEBs were investigated for participants on vehicle gel versus participants on patidegib 2% and 4% gel. Missing values were imputed using LOCF.

End point type	Secondary
End point timeframe:	
Baseline, Week 26	

Notes:

[7] - 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: New facial SEBs were investigated for participants on vehicle gel versus participants on patidegib 2% and 4% gel combined.

End point values	Vehicle gel	Patidegib gel		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	12		
Units: participants	3	2		

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Mean number of new SEBs on the face for the Combined Patidegib Treatment groups

End point title	The Mean number of new SEBs on the face for the Combined Patidegib Treatment groups <sup>[8]</sup>
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End point description:

Facial SEBs were defined as clinically diagnosed BCC 5 mm or greater in diameter on the face, excluding the nose and periorbital skin. A new facial SEB was defined as an SEB first noted on the face after Week 2 that developed at a site where there was no visible BCC of any size at Baseline or Week 2. New facial SEBs were investigated for participants on vehicle gel versus participants on patidegib 2% and 4% gel. Missing values were imputed using LOCF. The mean number of new SEBs (number per participant) are presented. No measure of dispersion/precision was calculated.

End point type	Secondary
End point timeframe:	
Baseline, Week 26	

Notes:

[8] - 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: New facial SEBs were investigated for participants on vehicle gel versus participants on patidegib 2% and 4% gel combined.

End point values	Vehicle gel	Patidegib gel		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	12		
Units: new SEBs				
number (not applicable)	1.4	0.4		

## Statistical analyses

No statistical analyses for this end point

### Secondary: The Mean Number of New SEBs on the Face for the Combined Patidegib Treatment Groups by Tumor Population

End point title	The Mean Number of New SEBs on the Face for the Combined Patidegib Treatment Groups by Tumor Population <sup>[9]</sup>
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End point description:

Facial SEBs were defined as clinically diagnosed BCC 5 mm or greater in diameter on the face, excluding the nose and periorbital skin. A new facial SEB was defined as an SEB first noted on the face after Week 2 that developed at a site where there was no visible BCC of any size at Baseline or Week 2. New facial SEBs were investigated for participants on vehicle gel versus participants on patidegib 2% and 4% gel. Missing values were imputed using LOCF. The mean number of new SEBs (number per participant) are presented. No measure of dispersion/precision was calculated.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

Notes:

[9] - 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: New facial SEBs were investigated for participants on vehicle gel versus participants on patidegib 2% and 4% gel combined.

End point values	Vehicle gel	Patidegib gel		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	12		
Units: new SEBs				
number (not applicable)	1.4	0.3		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change in Baseline Treatment-targeted SEBs Tumor Size From Baseline

End point title	Percent Change in Baseline Treatment-targeted SEBs Tumor Size From Baseline
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End point description:

SEBs were defined as clinically diagnosed BCC 5 mm or greater in diameter on the face, excluding the nose and periorbital skin, and 9 mm or greater at sites other than the face. The percent change in greatest diameters of Baseline treatment-targeted SEBs from Baseline to Week x (Week 6, 10, 14, 18, or 22) was calculated as follows:  $(\text{sum [Baseline]} - \text{sum [Week x]}) / \text{sum [Baseline]} * 100$ , where sum = the greatest diameters of Baseline treatment-targeted SEBs, and positive numbers to represent decrease in tumor size and negative numbers to represent increase in tumor size. Missing values were imputed using LOCF.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 6, 10, 14, 18, and 22

End point values	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: percentage decrease from Baseline				
arithmetic mean (standard deviation)				
Week 6	16.0 (± 37.07)	6.1 (± 10.41)	8.2 (± 4.55)	
Week 10	30.8 (± 39.54)	10.7 (± 12.00)	10.5 (± 5.35)	
Week 14	36.1 (± 46.45)	14.1 (± 13.18)	10.7 (± 6.26)	
Week 18	26.0 (± 73.79)	18.4 (± 26.86)	19.6 (± 21.98)	
Week 22	32.1 (± 78.71)	23.2 (± 22.87)	23.2 (± 28.03)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change in Central Facial SEBs From Baseline

End point title	Percent Change in Central Facial SEBs From Baseline
End point description:	
Central facial SEBs were defined as those located on the nose or periorbital area (eyelids) which were 3 mm or greater at Baseline. The percent change from Baseline to Week x (Week x = Weeks 6, 10, 14, 18, 22, or 26) in central facial SEBs was calculated as follows: [sum (Baseline) - sum (Week x)] / [sum (Baseline)] * 100 where sum = the greatest diameters of Baseline treatment-targeted SEBs where positive numbers to represent decrease in tumor size and negative numbers to represent increase in tumor size. Missing values were imputed using LOCF. The data presented as "99999" indicates that the standard deviation was not calculated because there was only 1 participant in the analysis population.	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 6, 10, 14, 18, 22, and 26	

End point values	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	2	2	
Units: percent decrease in central facial SEBs				
arithmetic mean (standard deviation)				
Week 6	5.9 (± 99999)	-20.0 (± 28.28)	8.0 (± 24.11)	
Week 10	5.9 (± 99999)	-10.0 (± 42.43)	12.5 (± 17.68)	
Week 14	5.9 (± 99999)	-60.0 (± 84.85)	29.5 (± 28.93)	
Week 18	5.9 (± 99999)	-70.0 (± 70.71)	17.0 (± 11.25)	
Week 22	5.9 (± 99999)	-45.0 (± 63.64)	29.5 (± 28.93)	
Week 26	5.9 (± 99999)	-65.0 (± 63.64)	20.5 (± 41.78)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Non-central Facial BCCs Increasing to $\geq 5$ mm From Baseline

End point title	Proportion of Non-central Facial BCCs Increasing to $\geq 5$ mm From Baseline
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End point description:

The proportion of non-central facial BCCs that at Baseline measured a greatest diameter of  $< 5$  mm and increased to a diameter of  $\geq 5$  mm by Week x (Week x = Weeks 6, 10, 14, 18, 22, or 26) were calculated for each participant as follows: (Number of non-central facial BCCs with greatest diameter  $\geq 5$  mm at Week x) / (Number of non-central facial BCCs with greatest diameter  $< 5$  mm at Baseline). Missing values were imputed using LOCF.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 6, 10, 14, 18, 22, and 26

End point values	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	3	
Units: proportion of BCCs				
arithmetic mean (standard deviation)				
Week 6	0.17 ( $\pm 0.289$ )	0 ( $\pm 0$ )	0.17 ( $\pm 0.289$ )	
Week 10	0 ( $\pm 0$ )	0.67 ( $\pm 0.474$ )	0.17 ( $\pm 0.289$ )	
Week 14	0 ( $\pm 0$ )	0 ( $\pm 0$ )	0 ( $\pm 0$ )	
Week 18	0 ( $\pm 0$ )	0.17 ( $\pm 0.233$ )	0 ( $\pm 0$ )	
Week 22	0 ( $\pm 0$ )	0.34 ( $\pm 0.474$ )	0 ( $\pm 0$ )	
Week 26	0 ( $\pm 0$ )	0 ( $\pm 0$ )	0.11 ( $\pm 0.191$ )	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Treatment-Targeted SEBs No Longer Classified as SEBs After 26 Weeks

End point title	Proportion of Treatment-Targeted SEBs No Longer Classified as SEBs After 26 Weeks
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End point description:

SEBs were defined as clinically diagnosed BCC 5 mm or greater in diameter on the face, excluding the nose and periorbital skin, and 9 mm or greater at sites other than the face. The proportion of Baseline treatment-targeted SEBs that at the end of 26 weeks of treatment were no longer large enough to be

classified as SEBs (that is, the proportion of Baseline treatment targeted SEBs on the face that became < 5 mm in greatest diameter and non-facial Baseline treatment targeted SEBs that became < 9 mm in greatest diameter) were calculated for each participant as follows:

(Number of Baseline treatment-targeted facial SEBs with greatest diameter < 5 mm) + (Baseline treatment targeted non-facial SEBs with greatest diameter < 9 mm) / Number of baseline treatment targeted SEBs.

Missing values were imputed using LOCF.

End point type	Secondary
End point timeframe:	
Baseline and Weeks 6, 10, 14, 18, 22, and 26	

End point values	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: Proportion of SEBs				
arithmetic mean (standard deviation)				
Week 6	0.37 (± 0.497)	0.13 (± 0.242)	0.12 (± 0.179)	
Week 10	0.40 (± 0.473)	0.13 (± 0.103)	0.16 (± 0.219)	
Week 14	0.53 (± 0.468)	0.23 (± 0.234)	0.16 (± 0.219)	
Week 18	0.57 (± 0.497)	0.23 (± 0.320)	0.28 (± 0.303)	
Week 22	0.53 (± 0.516)	0.30 (± 0.276)	0.32 (± 0.363)	
Week 26	0.53 (± 0.516)	0.30 (± 0.303)	0.36 (± 0.434)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Treatment-targeted SEBs Achieving Clear or Almost Clear on the 5-point Investigator Static Global Tumor Assessment (ISGTA) Scale

End point title	Percentage of Treatment-targeted SEBs Achieving Clear or Almost Clear on the 5-point Investigator Static Global Tumor Assessment (ISGTA) Scale
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End point description:

The ISGTA is a scale with scores ranging from 0 (clear), 1 (almost clear), 2 (minimal residual tumor), to 3 (clearly visible tumor). The Investigator assessed each Baseline treatment-targeted SEB at Weeks 6, 10, 14, 18, 22, and 26. SEBs were defined as clinically diagnosed BCC 5 mm or greater in diameter on the face, excluding the nose and periorbital skin, and 9 mm or greater at sites other than the face. The percentage of Baseline treatment-targeted SEBs evaluated as being clear or almost clear at Week x (Week x = Week 6, 10, 14, 18, 22 or 26) based on the ISGTA scale was calculated as follows: (Number of baseline treatment-targeted SEBs with ISGTA score of 0 or 1 at Week x) / (Number of Baseline treatment-targeted SEBs) \* 100. Missing data were imputed using LOCF. The percentage of responders achieving clear (0) or almost clear (1) on the ISGTA scale are presented by Week.

End point type	Secondary
End point timeframe:	
Baseline and Weeks 6, 10, 14, 18, 22, and 26	

<b>End point values</b>	Patidegib Topical gel 2%	Patidegib Topical gel 4%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5	
Units: Percentage of participants				
number (not applicable)				
Week 6	23.3	3.3	12.0	
Week 10	23.3	13.3	8.0	
Week 14	33.3	13.3	8.0	
Week 18	33.3	23.3	20.0	
Week 22	36.7	26.7	20.0	
Week 26	33.3	30.0	24.0	

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

26 weeks

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	Patidegib gel 2%
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Reporting group description:

Patidegib gel 2% applied topically twice daily for 26 weeks

Reporting group title	Patidegib gel 4%
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Reporting group description:

Patidegib gel 4% applied topically twice daily for 26 weeks

Reporting group title	Vehicle gel
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Reporting group description:

Vehicle gel applied topically twice daily for 26 weeks

Serious adverse events	Patidegib gel 2%	Patidegib gel 4%	Vehicle gel
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Pneumonia A			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
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: 0 %

<b>Non-serious adverse events</b>	Patidegib gel 2%	Patidegib gel 4%	Vehicle gel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	6 / 6 (100.00%)	3 / 5 (60.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Application site alopecia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Application site dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Application site pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Application site rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Application site reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	2 / 5 (40.00%)
occurrences (all)	2	3	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Dysphonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depressed mood			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Trigeminal neuralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Episcleritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Food poisoning			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hair growth abnormal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pruritus			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1
Rash subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Hypothyroidism subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	2 / 5 (40.00%) 2
Infections and infestations Candida infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0

Oral herpes subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0
Metabolism and nutrition disorders			
Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2016	<ul style="list-style-type: none"><li>•Section 6.1 Overall Study Design and Plan was edited to provide a rationale for the dose level and frequency of the topical gel, based on nonclinical data and the known characteristics of the oral formulation. Patidegib 2% and 4% gel applied twice daily was predicted to be effective while providing a large safety margin for both dermal and systemic safety.</li><li>•Table 2 Schedule of Assessments footnote e was expanded to specify that the following clinical laboratory tests would be performed: chemistry (AST, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, protein, sodium), hematology (WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, Red Cell Distribution Width, Platelets, Mean Platelet Volumes, Absolute/Percent Neutrophil Count, Absolute/Percent Lymphocyte count, Absolute/Percent Monocyte count, Absolute/Percent Eosinophil Count, Absolute/Percent Basophil Count), and urinalysis (including reflex microscopic examination).</li><li>•Appendix 16.4 Safety Laboratory Tests was newly added to provide a detailed list of clinical laboratory assessments to be collected.</li><li>•Section 8.3 Unblinding was edited to clarify that, in the case of a medical emergency, the Investigator could break the blind for the subject involved without first discussing the situation with the Medical Monitor.</li></ul>
02 March 2016	<ul style="list-style-type: none"><li>•Section 1 Synopsis and Section 7.1 Subject Inclusion Criteria were edited per feedback from the MHRA to specify 2 acceptable methods of contraception: 1) barrier method in association with bilateral tubal ligation, combined oral contraceptives, or implanted or injectable contraceptives with a stable dose for at least 1 month prior to Baseline; or 2) hormonal intrauterine device inserted at least 1 month prior to Baseline.</li><li>•Section 10.1.1 Screening Visit and Section 10.1.5 Week 26 were edited. Previously, subject height assessment was erroneously included at these visits; it was removed.</li><li>•Section 10.1.2 Baseline Visit (Day 1) was edited. Height and weight assessments were erroneously included in item 4; they were removed as they already were present in item 5.</li></ul>

18 August 2016	<ul style="list-style-type: none"> <li>•Synopsis/Section 7.1 Inclusion Criteria             <p>8-Female subjects must have a negative serum pregnancy test at Screening.</p> <p>9-If the subject is a male with a female sexual partner who is of childbearing potential the couple is willing to use two effective methods of birth control during the duration of the trial and for one month after the last application of the gel. A female of childbearing potential is a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy; or has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months), must agree to use two effective methods of contraception for the duration of the study and at least 1 month after the last study drug application. The two forms of birth control authorized are defined as the use of a barrier method of contraception (condom with spermicide) in association with one of the following methods of birth control: bilateral tubal ligation; combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to Baseline; hormonal intra-uterine device (IUD) inserted at least 1 month prior to Baseline.</p> </li> <li>•Synopsis/Section 7.2 Exclusion Criteria             <p>1-The subject is a woman of childbearing potential. (based on the key role of the HH pathway in embryogenesis, the known preclinical teratogenic effects of systemic cyclopamine, a naturally occurring inhibitor of SMO, and the unknown level of systemic exposure following topical application of patidegib in humans) A female of childbearing potential is a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy or has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).</p> <p>10-Female sexual partner(s) of male subjects unwilling/unable to comply with pregnancy prevention measures.</p> </li> </ul>
18 August 2016	<ul style="list-style-type: none"> <li>•Synopsis Safety Measurements /Section 10.3.1 Dermal Safety and Tolerability were amended to specify that safety and tolerability would be evaluated, and that each of the 5 baseline treatment-targeted tumor sites, as well as the face in general, would be evaluated separately for these signs and symptoms of application site reactions. Scales for assessing local skin reactions were clarified to specify that the subjects should rate the symptoms experienced at the application site(s).</li> <li>•Synopsis Statistical Methods /Section 11 Statistics were edited to add that if determined appropriate by the Sponsor, limited efficacy analysis on tumor shrinkage and biomarkers might have been performed after the last subject completed 14 weeks of treatment.</li> <li>•Table 2 Schedule of Assessments was edited to indicate that at Baseline and Week 6, a BCC was to be identified for biopsy, and that visible BCCs were to be measured at Baseline and at Weeks 2, 6, 10, 14, 18, 22, and 26/ET. Footnote f was added: Tumors to be measured and mapped included the 5 baseline treatment-targeted tumors as well as all other facial tumors including those on the eyelids and the nose. In addition, up to 10 non treatment-targeted non-facial tumors also were measured and mapped.</li> <li>•Section 10 Study Procedures and Evaluations was edited to indicate that a physician must identify the treatment targeted tumor to be biopsied.</li> </ul>

18 August 2016	<p>•Section 10.1.2 Baseline Visit (Day 1) was edited to clarify the following procedures:</p> <p>7. The Investigator will perform the clinical evaluation to identify BCCs including the 5 baseline treatment-targeted tumors, as well as, all other facial tumors (including those on the eyelids and the nose). In addition, up to 10 non treatment-targeted non facial tumors will also be clinically classified as superficial, nodular, infiltrative, morpheic or sclerosing, pigmented, or micronodular/morpheaform, circle each tumor in ink, photographed, measured, and recorded on a body diagram. The 5 baseline treatment-targeted tumors will also be evaluated based on the ISGTA.</p> <p>8. Obtain 2 mm punch biopsy from the baseline treatment targeted SEB that has been designated for biomarker evaluation. The 2 mm punch biopsies can be performed by the Investigator or designee as allowed by the clinical site's normal policies and procedures.</p> <p>9. The Investigator or designee will assess each of the areas to be treated by observations and questioning the subjects as necessary for the signs and symptoms of irritation including pain/burning, pruritus, erythema, edema, and scabbing/crusting. Each of the 5 treatment targeted-tumors, as well as the face in general, will be evaluated separately.</p>
18 August 2016	<p>•Section 10.1.3 Weeks 2, 10, 18, and 22; Section 10.1.4 Weeks 6, 14, and 26; and Section 10.1.5 Week 26 (Day 183 ± 3 Days) / Early Termination were edited to clarify the following procedures:</p> <p>-The Investigator will perform the clinical evaluation of the 5 baseline treatment targeted tumors, as well as, all other facial tumors (including those on the eyelids and the nose). In addition, up to 10 non treatment-targeted non-facial tumors will be circled in ink, photographed, measured, and recorded on a body diagram. The 5 baseline treatment-targeted tumors will be evaluated based on the ISGTA.</p> <p>-The Investigator or designee will assess each of the treated areas by observations and questioning the subjects as necessary for the signs and symptoms of irritation including pain/burning, pruritus, erythema, edema, and scabbing/crusting. Each of the 5 treatment-targeted tumors, as well as the face in general, will be evaluated separately.</p> <p>Section 10.1.4 Weeks 6, 14, and 26 was edited to clarify the following procedure:</p> <p>-Obtain a biopsy with a 2 mm punch at Week 6 from the single SEB designated as the biomarker treatment targeted tumor and previously biopsied at baseline. The 2 mm punch biopsies can be performed by the Investigator or designee as allowed by the clinical site's normal policies and procedures.</p> <p>•Section 10.1.5 Week 26 (Day 183 ± 3 Days) / Early Termination was edited to remove the 2 mm punch biopsy of non-responding tumors for subjects considered to be non responders.</p> <p>•Section 10.2 (Evaluation of Efficacy) renamed, "Evaluation of Tumors."</p> <p>•Section 11 Statistics and Section 11.6 Interim Analyses were edited to remove the sentence, "No interim analyses are planned." Text was added to Section 11.6: "If determined appropriate by the Sponsor, limited efficacy analysis on tumor shrinkage and biomarkers may be performed after the last subject completes 14 weeks of treatment."</p> <p>•Section 13 (Data Monitoring Committee) was renamed, "Data Safety Monitoring Committee."</p>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported