



## Clinical trial results:

**A randomized, investigator-and patient-blind, placebo controlled, parallel group first in human and proof of concept study to evaluate the safety, tolerability, and efficacy of CLL442 in patients with Cutaneous Squamous Cell Carcinoma in situ (SCCis)**

### Summary

EudraCT number	2017-003495-31
Trial protocol	BE
Global end of trial date	01 November 2018

### Results information

Result version number	v1 (current)
This version publication date	24 October 2019
First version publication date	24 October 2019

### Trial information

#### Trial identification

Sponsor protocol code	CCLL442X2201
-----------------------	--------------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03333694
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals AG, +41 61 324 1111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals AG, +41 61 324 1111,

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	01 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 November 2018
Was the trial ended prematurely?	No

Notes:

---

**General information about the trial**

---

Main objective of the trial:

- To assess the safety and tolerability of CLL442 in subjects with Cutaneous Squamous Cell Carcinoma in situ (SCCis) on both lesion free skin and SCCis lesions.
- To evaluate the initial efficacy of CLL442 on reduction of lesion area in subjects with SCCis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2017
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	United States: 23
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Belgium: 5
Worldwide total number of subjects	40
EEA total number of subjects	5

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)	12

From 65 to 84 years	25
85 years and over	3

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in 8 centres across United States, Australia and Belgium.

### Pre-assignment

Screening details:

A total of 40 subjects were enrolled in the study, and all included in the Safety Population. The study consisted of two treatment periods;

Treatment Period 1 (P1): CLL442 or placebo was applied on lesion free skin for 7 days.

Treatment Period 2 (P2): CLL442 or placebo was applied on the target single SCCis lesion for a total of 84 days.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	CLL442 2.5 mg/g

Arm description:

CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).

Arm type	Experimental
Investigational medicinal product name	CLL442
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

CLL442 2.5 mg/g cutaneous cream application twice daily for 7 days on lesion free skin followed by application on target single SCCis lesion until visual clearance of the lesion and for an additional 14 days, or for a total of 84 days, whichever comes first.

<b>Arm title</b>	Placebo
------------------	---------

Arm description:

CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

CLL442-matching placebo cutaneous cream application twice daily for 7 days on lesion free skin followed by application on the target single SCCis lesion until visual clearance of the lesion and for an additional 14 days, or for a total of 84 days, whichever comes first.

<b>Number of subjects in period 1</b>	CLL442 2.5 mg/g	Placebo
Started	30	10
Completed	29	10
Not completed	1	0
Subject/Guardian Decision	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	CLL442 2.5 mg/g
-----------------------	-----------------

Reporting group description:

CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).

Reporting group values	CLL442 2.5 mg/g	Placebo	Total
Number of subjects	30	10	40
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	72.3	66.1	
standard deviation	± 9.22	± 8.60	-
Gender categorical			
Units: Subjects			
Female	17	4	21
Male	13	6	19

## End points

### End points reporting groups

Reporting group title	CLL442 2.5 mg/g
Reporting group description: CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	
Reporting group title	Placebo
Reporting group description: CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).	
Subject analysis set title	CLL442 2.5 mg/g (PK)
Subject analysis set type	Sub-group analysis
Subject analysis set description: The Pharmacokinetic (PK) analysis set included all subjects with at least one available valid (i.e., not flagged for exclusion) CLL442 concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.	

### Primary: Number of Subjects with Adverse Events (AEs), and Serious Adverse Events (SAEs)

End point title	Number of Subjects with Adverse Events (AEs), and Serious Adverse Events (SAEs) <sup>[1]</sup>
End point description: An adverse event is any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product. An SAE is any AE which is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, requires inpatient hospitalisation, etc. The safety analysis set included all subjects that received any study drug.	
End point type	Primary
End point timeframe: From First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV), up to Day 92 (End of Study (EOS))	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned for this end point.	

End point values	CLL442 2.5 mg/g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: subjects				
AEs	20	4		
SAEs	0	0		

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects with Local Tolerability Score at Day 7 or Day 84

End point title	Number of Subjects with Local Tolerability Score at Day 7 or Day 84 <sup>[2]</sup>
-----------------	--

End point description:

Local tolerability or local skin reactions (LSRs) were assessed using visual, clinical, and tactile cues at each visit after first dosing and each parameter was scored 0-3 based on severity (none, mild, moderate and severe). Overall, 8 parameters were assessed which included: edema, erosion/ulceration, erythema, flaking/scaling/dryness, itching scabbing/dryness, vesicles and weeping/exudates. The safety analysis set included all subjects that received any study drug. "n" is the number of subjects with data available for analysis at the specific time point.

End point type	Primary
----------------	---------

End point timeframe:

Period 1 (P1) Day 1 (D1) to Day 92 (EOS)

Notes:

[2] - 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: No statistical analysis was planned for this end point.

End point values	CLL442 2.5 mg/g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: subjects				
Edema(P1, D1): Mild (n=30,10)	0	0		
Edema(P1, D1): Moderate (n=30, 10)	0	0		
Edema(P1, D1): Severe (n=30,10)	0	0		
Edema(EOS): Mild (n=29,10)	5	0		
Edema(EOS): Moderate (n=29,10)	1	1		
Edema(EOS): Severe (n=29,10)	0	0		
Erosion/Ulceration(P1, D1): Mild (n=30,10)	0	0		
Erosion/Ulceration(P1, D1): Moderate (n=30,10)	0	0		
Erosion/Ulceration(P1, D1): Severe (n=30,10)	0	0		
Erosion/Ulceration(EOS): Mild (n=29,10)	2	1		
Erosion/Ulceration(EOS): Moderate (n=29,10)	0	0		
Erosion/Ulceration(EOS): Severe (n=29,10)	0	0		
Erythema(P1, D1): Mild (n=30,10)	4	0		
Erythema(P1, D1): Moderate (n=30,10)	0	0		
Erythema(P1, D1): Severe (n=30,10)	0	0		
Erythema(EOS): Mild (n=29,10)	12	3		
Erythema(EOS): Moderate (n=29,10)	5	2		
Erythema(EOS): Severe (n=29,10)	0	0		
Flaking/Scaling/Dryness(P1, D1): Mild (n=30,10)	5	0		
Flaking/Scaling/Dryness(P1, D1): Moderate (n=30,10)	0	0		
Flaking/Scaling/Dryness(P1, D1): Severe (n=30,10)	0	0		
Flaking/Scaling/Dryness(EOS): Mild (n=29,10)	11	3		
Flaking/Scaling/Dryness(EOS): Moderate (n=29,10)	4	1		



Flaking/Scaling/Dryness(EOS): Severe (n=29,10)	0	0		
Itching(P1, D1): Mild (n=30,10)	1	0		
Itching(P1, D1): Moderate (n=30,10)	0	0		
Itching(P1, D1): Severe (n=30,10)	0	0		
Itching(EOS): Mild (n=29,10)	1	1		
Itching(EOS): Moderate (n=29,10)	0	0		
Itching(EOS): Severe (n=29,10)	1	0		
Scrabbing/Dryness(P1, D1): Mild (n=30,10)	2	0		
Scrabbing/Dryness(P1, D1): Moderate (n=30,10)	0	0		
Scrabbing/Dryness(P1, D1): Severe (n=30,10)	0	0		
Scrabbing/Dryness(EOS): Mild (n=29,10)	4	2		
Scrabbing/Dryness(EOS): Moderate (n=29,10)	4	0		
Scrabbing/Dryness(EOS): Severe (n=29,10)	0	0		
Vesicles(P1, D1): Mild (n=30,10)	0	0		
Vesicles(P1, D1): Moderate (n=30,10)	0	0		
Vesicles(P1, D1): Severe (n=30,10)	0	0		
Vesicles(EOS): Mild (n=29,10)	0	0		
Vesicles(EOS): Moderate (n=29,10)	0	0		
Vesicles(EOS): Severe (n=29,10)	0	0		
Weeping/Exsudates(P1, D1): Mild (n=30,10)	0	0		
Weeping/Exsudates(P1, D1): Moderate (n=30,10)	0	0		
Weeping/Exsudates(P1, D1): Severe (n=30,10)	0	0		
Weeping/Exsudates(EOS): Mild (n=29,10)	2	0		
Weeping/Exsudates(EOS): Moderate (n=29,10)	0	0		
Weeping/Exsudates(EOS): Severe (n=29,10)	0	0		

## Statistical analyses

No statistical analyses for this end point

## Primary: Visual Analogue Scale (VAS) Score

End point title	Visual Analogue Scale (VAS) Score <sup>[3]</sup>
End point description:	
Subjects were provided a diary to assess the severity of pain (ranging from 0 = no pain at all to 10 = the worst imaginable pain) using a 10 cm VAS . The score (distance from left) on the VAS was recorded by the subject marking with a line. The safety analysis set included all subjects that received any study drug."n" is the number of subjects with data available for analysis at the specific time point.	
End point type	Primary
End point timeframe:	
P1 Day 1 to Day 92 (EOS)	

Notes:

[3] - 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: No statistical analysis was planned for this end point.

End point values	CLL442 2.5 mg/g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: score on a scale				
arithmetic mean (standard deviation)				
P1 Day 1 (n=29,10)	1.9 (± 8.90)	0.2 (± 0.63)		
P2 Day 84 (n=29,10)	0.2 (± 1.12)	1.9 (± 4.68)		
EOS (n=29,10)	0.3 (± 1.04)	1.0 (± 2.54)		

## Statistical analyses

No statistical analyses for this end point

## Primary: Change From Baseline in Lesion Area in Subjects with Squamous Cell Carcinoma in situ (SCCis) at Day 84

End point title	Change From Baseline in Lesion Area in Subjects with Squamous Cell Carcinoma in situ (SCCis) at Day 84
-----------------	--

End point description:

Area is measured by pen and ruler and standardized digital photography. Lesion tracing (planimetry) were completed on clear paper to assess lesion area. Baseline for lesion area measurement was defined at Treatment Period 2, Day 1. The Pharmacodynamic (PD) analysis set included all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

End point type	Primary
----------------	---------

End point timeframe:

Period 2 Day 1 (Baseline) and Period 2 Day 84

End point values	CLL442 2.5 mg/g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	10		
Units: square millimetre (mm <sup>2</sup> )				
arithmetic mean (confidence interval 90%)	-112.62 (-180.57 to 44.68)	-153.80 (-269.51 to 38.09)		

## Statistical analyses

Statistical analysis title	CLL442 2.5 mg/g v Placebo
Comparison groups	CLL442 2.5 mg/g v Placebo

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5984 <sup>[4]</sup>
Method	MMRM
Parameter estimate	Difference in means
Point estimate	41.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	-93.02
upper limit	175.38

Notes:

[4] - Change from baseline in lesion area was analyzed using a repeated measures mixed effects model (MMRM) which included effects for baseline lesion area, treatment, visit and treatment by visit interaction.

## Secondary: Plasma Concentration of CLL442

End point title	Plasma Concentration of CLL442
End point description:	No pharmacokinetics (PK) analysis of the concentration-time data was performed as only 3% of the collected samples had CLL442 concentrations above Lower Limit of Quantification (LLOQ).
End point type	Secondary
End point timeframe:	Day 1 through Day 84

End point values	CLL442 2.5 mg/g (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	0 <sup>[5]</sup>			
Units: picograms per millilitre(pg/mL)				
arithmetic mean (standard deviation)	( )			

Notes:

[5] - No PK analysis was done as only 3% of the collected samples had CLL442 concentrations above LLOQ.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time Required to Achieve 50% (Partial) Decrease in One Lesion Area

End point title	Time Required to Achieve 50% (Partial) Decrease in One Lesion Area
End point description:	Area is measured by pen and ruler and standardized digital photography. Lesion tracing (planimetry) were completed on clear paper to assess lesion area. The PD analysis set included all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data. 99999 indicates that the upper limit of 90% Confidence Interval was not estimable in placebo group.
End point type	Secondary
End point timeframe:	Up to Day 84

End point values	CLL442 2.5 mg/g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	10		
Units: days				
median (confidence interval 90%)	57 (55.0 to 92.0)	55.5 (8.0 to 99999)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time Required to Achieve 10% (Partial) Decrease in One Lesion Area

End point title	Time Required to Achieve 10% (Partial) Decrease in One Lesion Area
-----------------	--

End point description:

Area is measured by pen and ruler and standardized digital photography. Lesion tracing (planimetry) were completed on clear paper to assess lesion area. The PD analysis set included all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

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

End point timeframe:

Up to Day 84

End point values	CLL442 2.5 mg/g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	10		
Units: days				
median (confidence interval 90%)	28.0 (8.0 to 31.0)	41.5 (8.0 to 57.0)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time Required to Achieve Complete (100%) SCCis One Lesion Clearance at the End of the Study

End point title	Time Required to Achieve Complete (100%) SCCis One Lesion Clearance at the End of the Study
-----------------	---

End point description:

Area is measured by pen and ruler and standardized digital photography. Lesion tracing (planimetry) were completed on clear paper to assess lesion area. The PD analysis set included all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant

impact on PD data. 99999 indicates that the median time and 90% Confidence Interval required to achieve complete lesion clearance was not estimable in both CLL442 and placebo groups.

End point type	Secondary
End point timeframe:	
Day 92 (EOS)	

End point values	CLL442 2.5 mg/g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: days				
median (confidence interval 90%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Complete Clearance at the End of the Study, Assessed Visually and Histologically

End point title	Percentage of Subjects with Complete Clearance at the End of the Study, Assessed Visually and Histologically
End point description: The PD analysis set included all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.	
End point type	Secondary
End point timeframe: Day 92 (EOS)	

End point values	CLL442 2.5 mg/g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	10		
Units: percentage of subjects				
number (not applicable)	24.0	20.0		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until LPLV (up to Day 92 (EOS)).

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

### Reporting groups

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).

Reporting group title	CLL442 2.5 mg/g
-----------------------	-----------------

Reporting group description:

CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).

Serious adverse events	Placebo	CLL442 2.5 mg/g	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	CLL442 2.5 mg/g	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	20 / 30 (66.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 10 (10.00%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 30 (6.67%) 2	
General disorders and administration site conditions			
Application site erythema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Application site exfoliation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 4	
Application site oedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Application site pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 2	
Application site pruritus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 30 (6.67%) 2	
Condition aggravated subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Fatigue subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 30 (0.00%) 0	
Mucosal ulceration subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 2	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Psychiatric disorders			

Abnormal dreams subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Investigations Amylase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Electrocardiogram repolarisation abnormality subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Pancreatic enzymes increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 30 (0.00%) 0	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Gastrointestinal disorders Mouth ulceration subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 30 (3.33%) 1	
Nausea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Paraesthesia oral			



subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	3	
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle tightness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	6 / 30 (20.00%) 6	
Metabolism and nutrition disorders Polydipsia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2018	Amendment was generated in response to request from an Institutional Review Board (IRB) in the United States to add more details in the discontinuation of study treatment for increased-size lesions. Additionally, this amendment also addressed typographical errors to ensure data quality and minimize the risk of inconsistent interpretation.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported