Clinical trial results:
An open label phase II study of Sirolimus in patients with segmental overgrowth syndrome

Summary

EudraCT number	2015-005416-15
Trial protocol	DE
Global end of trial date	19 July 2023

Results information

Result version number	v1 (current)
This version publication date	07 February 2025
First version publication date	07 February 2025

Trial information

Trial identification

Sponsor protocol code	SIPA-SOS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00010085

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
Public contact	Coordinating investigator: Dr. med. Friedrich Kapp, Medical Center – University of Freiburg, Center for Pediatrics, +49 761270-43000, friedrich.kapp@uniklinik-freiburg.de
Scientific contact	Coordinating investigator: Dr. med. Friedrich Kapp, Medical Center – University of Freiburg, Center for Pediatrics, +49 761270-43000, friedrich.kapp@uniklinik-freiburg.de

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 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2023
Global end of trial reached?	Yes
Global end of trial date	19 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of sirolimus to reduce the size of defined target lesions in patients with segmental overgrowth syndromes.

Protection of trial subjects:

Before enrolment in the clinical trial, the patient/legal representative was informed that participation in the clinical trial is voluntary and that he/she may withdraw from the clinical trial at any time without having to give reasons and without penalty or loss of benefits to which the patient is otherwise entitled. The treating physician provided the patient/legal representative with information about the treatment methods and the possible risks involved. At the same time, the nature, significance, implications, expected benefits and potential risks of the clinical trial and alternative treatments were explained to the patient/legal representative. During the informed consent discussion, the patient was also informed about the insurance cover that exists and the insured's obligations. The patient/legal representative was given ample time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the patient and/or his/her legal representative. In addition, the patient/legal representative was given a patient information sheet that contains all the important information in writing.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2021
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	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	7
Adolescents (12-17 years)	5
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	18
Number of subjects completed	18

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable, as this was an open-label study.

Arms

Arm title	Sirolimus

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	Rapamune
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Strength: 0.5 mg, 1 mg, 1 mg/mL; Dose: Recommended starting dose of sirolimus: 1.6 mg/m2 (divided in two doses if patients age < 16 years)

Number of subjects in period 1	Sirolimus
Started	18
Completed	14
Not completed	4
Switch to other clinical trial, week 39	1
Lack of compliance, week 13	1
Progressive complaints after Sirolimus cessation	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	18	18	
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)	7	7	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	6	6	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	15.8		
standard deviation	± 8.5	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	6	6	

End points

End points reporting groups

Reporting group title	Sirolimus

Reporting group description: -

Primary: Best response: Complete Remission (CR) or Partial Remission (PR)

End point title	Best response: Complete Remission (CR) or Partial Remission (PR)[1]

End point description:

End point type	Primary

End point timeframe:

until 6 months after baseline (start of study therapy)

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: A statistical test of the null hypothesis that the probability of best response CR or PR until 6 months after start of treatment was <=2% was tested at a one-sided sign. level of 5%. This null hypothesis can be rejected, if the number of patients with a best response CR or PR until 6 months after start of treatment is >=2 out of 18 patients. As none of the 18 patients had CR or PR at month 6 after start of treatment, according to this decision rule, sirolimus cannot be considered as effective.

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Morphological changes in disfigurement compared to baseline by using a scale for external validation documented by photography

End point title	Morphological changes in disfigurement compared to baseline by using a scale for external validation documented by photography

End point description:

The response scale for patients without progression ranged from 0 (no response compared to screening) to 100 (complete response compared to screening)

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[2]			
Units: Response scale				
arithmetic mean (standard deviation)				
month 3	7.4 (± 7.2)			
month 6	8.3 (± 13.9)			
month 9	7.4 (± 8.3)			

Notes:

[2] - month 3: n=17 patients, month 6: n=16 patients, month 9: n=12 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Neuropsychological tests, Strengths and Difficulties Questionnaire, SDQ parents

End point title	Neuropsychological tests, Strengths and Difficulties Questionnaire, SDQ parents

End point description:

For each of the two patient groups a total difficulty score exists, each containing the subscales emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationship problems. Each subscale ranged from 0-10 points, summing up to a total of 0-40 points for the total difficulty score, where 0 is "perfect" health and 40 is “worst”. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[3]			
Units: Total difficulty score [0-40 points]				
arithmetic mean (confidence interval 95%)				
Month 3	-0.9 (-3.1 to 1.3)			
Month 6	-1.7 (-5.5 to 2.2)			
Month 9	-2.3 (-5.8 to 1.2)			

Notes:

[3] - Day 0, Month 3, Month 6: n=10; Month 9: n=8

Statistical analyses

No statistical analyses for this end point

Secondary: Pain assessment

End point title	Pain assessment

End point description:

Changes in pain compared to baseline by visual pain scales for adults and children. Two age-adapted pain scales for adults/teenagers (≥ 14 years) and children (3-13 years) were used. Both pain scales ranged from 0 (no pain) to 10 (worst pain you can imagine).

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[4]			
Units: Pain scale [0-10 points]				
arithmetic mean (confidence interval 95%)				
Month 3	-0.3 (-1.5 to 0.9)			
Month 6	-0.5 (-1.5 to 0.6)			
Month 9	0.5 (-0.5 to 1.5)			

Notes:

[4] - Day 0: n=18; Month 3: n=18; Month 6: n=17; Month 9: n=14

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, WHOQOL-BREF Questionnaire, Physical health

End point title	Quality of life, WHOQOL-BREF Questionnaire, Physical health

End point description:

Changes in quality of life compared to baseline. The WHOQOL-BREF questionnaire was to be answered only by the 6 patients aged ≥ 18 years at baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	6[5]			
Units: Domain score [0-100 points]				
arithmetic mean (confidence interval 95%)				
Month 3	1.8 (-10.2 to 13.8)			
Month 6	9.3 (-0.9 to 19.5)			
Month 9	4.8 (-8.8 to 18.3)			

Notes:

[5] - Month 3: n=6; Month 6: n=5; Month 9: n=3

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker IGF-1

End point title	Biomarker IGF-1

End point description:

Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[6]			
Units: IGF-1 [ng/mL]				
arithmetic mean (confidence interval 95%)				
Month 3	9.3 (-3.8 to 22.5)			
Month 6	2.7 (-23.3 to 28.6)			
Month 9	1.0 (-17.4 to 19.4)			

Notes:

[6] - Day 0, Month 3: n=18; Month 6: n=17; Month 9: n=14

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, WHOQOL-BREF Questionnaire, Scocial relationships

End point title	Quality of life, WHOQOL-BREF Questionnaire, Scocial relationships

End point description:

The WHOQOL-BREF questionnaire was to be answered only by the 6 patients aged ≥ 18 years at baseline. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	9[7]			
Units: Domain score [0-100 points]				
arithmetic mean (confidence interval 95%)				
Month 3	-4.2 (-16.2 to 7.9)			
Month 6	0.0 (-12.7 to 12.7)			
Month 9	5.6 (-26.1 to 37.2)			

Notes:

[7] - Month 3: n=6; Month 6: n=5; Month 9: n=3

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, WHOQOL-BREF Questionnaire, Psychological

End point title	Quality of life, WHOQOL-BREF Questionnaire, Psychological

End point description:

The WHOQOL-BREF questionnaire was to be answered only by the 6 patients aged ≥ 18 years at baseline. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	6[8]			
Units: Domain score [0-100 points]				
arithmetic mean (confidence interval 95%)				
Month 3	1.4 (-24.1 to 26.8)			
Month 6	9.2 (0.7 to 17.7)			
Month 9	4.2 (-6.2 to 14.5)			

Notes:

[8] - Month 3: n=6; Month 6: n=5; Month 9: n=3

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, WHOQOL-BREF Questionnaire, Environment

End point title	Quality of life, WHOQOL-BREF Questionnaire, Environment

End point description:

The WHOQOL-BREF questionnaire was to be answered only by the 6 patients aged ≥ 18 years at baseline. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	6[9]			
Units: Domain score [0-100 points] Day				
arithmetic mean (confidence interval 95%)				
Month 3	2.1 (-2.4 to 6.6)			
Month 6	-0.6 (-9.9 to 8.6)			
Month 9	3.1 (-17.4 to 23.7)			

Notes:

[9] - Month 3: n=6; Month 6: n=5; Month 9: n=3

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, KINDL Questionnaire, KINDL® parents

End point title	Quality of life, KINDL Questionnaire, KINDL® parents

End point description:

The KINDL questionnaire is available in 3 versions and was to be answered by/for patients aged < 18 years at baseline (KINDL® parents), for toddlers aged 3-6 years, and for children and teenager aged 7-17 years. Difference to baseline.

End point type	Secondary

End point timeframe:

At Month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[10]			
Units: Total score [0-100 points]				
arithmetic mean (confidence interval 95%)				
Month 3	-9.0 (-16.4 to -1.7)			
Month 6	-1.0 (-9.4 to 7.3)			

Month 9	-0.7 (-7.4 to 6.1)			

Notes:

[10] - Day 0: n=12; Month 3: n=9; Month 6: n=7; Month 9: n=8

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, Karnofsky Scale, Performance status

End point title	Quality of life, Karnofsky Scale, Performance status

End point description:

For the assessment of the performance status of the patients the Lansky/Karnofsky scales were used. Both scales run from 100% to 0%, where 100% is "perfect" health and 0% is death, with standard intervals of 10%. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[11]			
Units: Scale [0-100 %]				
arithmetic mean (confidence interval 95%)				
Month 3	2.2 (-1.2 to 5.6)			
Month 6	2.5 (-1.4 to 6.4)			
Month 9	5.0 (-0.7 to 10.7)			

Notes:

[11] - Day 0: n=9; Month 3: n=10; Month 6: n=9; Month 9: n=6

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, KINDL Questionnaire, KINDL® toddlers

End point title	Quality of life, KINDL Questionnaire, KINDL® toddlers

End point description:

The KINDL questionnaire is available in 3 versions and was to be answered by/for patients aged < 18 years at baseline (KINDL® parents), for toddlers aged 3-6 years, and for children and teenager aged 7-17 years. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9. Only month 3 reported here, because only the result of one participant available at month 6 and 9.

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[12]			
Units: Total score [0-100 points]				
arithmetic mean (confidence interval 95%)				
Month 3	5.6 (-26.1 to 37.2)			

Notes:

[12] - month 3: n=3

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, KINDL Questionnaire, KINDL® children and teenager

End point title	Quality of life, KINDL Questionnaire, KINDL® children and teenager

End point description:

The KINDL questionnaire is available in 3 versions and was to be answered by/for patients aged < 18 years at baseline (KINDL® parents), for toddlers aged 3-6 years, and for children and teenager aged 7-17 years. Difference to baseline.

End point type	Secondary

End point timeframe:

At Month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[13]			
Units: Total score [0-100 points]				
arithmetic mean (confidence interval 95%)				
Month 3	0.2 (-4.2 to 4.5)			
Month 6	-1.0 (-7.4 to 5.3)			
Month 9	1.3 (-2.8 to 5.3)			

Notes:

[13] - Day 0: n=7; Month 3: n=7; Month 6: n=6; Month 9: n=7

Statistical analyses

No statistical analyses for this end point

Secondary: Neuropsychological tests, Strengths and Difficulties Questionnaire, SDQ

children (≥ 11 years)	
End point title	Neuropsychological tests, Strengths and Difficulties Questionnaire, SDQ children (≥ 11 years)

End point description:

For each of the two patient groups a total difficulty score exists, each containing the subscales emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationship problems. Each subscale ranged from 0-10 points, summing up to a total of 0-40 points for the total difficulty score, where 0 is "perfect" health and 40 is “worst”. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[14]			
Units: Total difficulty score [0-40 points]				
arithmetic mean (confidence interval 95%)				
Month 3	1.5 (-0.8 to 3.8)			
Month 6	0.3 (-1.8 to 2.4)			
Month 9	-1.1 (-3.9 to 1.6)			

Notes:

[14] - Day 0: n=11; Month 3: n=12; Month 6: n=11; Month 9: n=9

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, Lansky/Karnofsky scale combined, Performance status	
End point title	Quality of life, Lansky/Karnofsky scale combined, Performance status

End point description:

For the assessment of the performance status of the patients the Lansky/Karnofsky scales were used. Both scales run from 100% to 0%, where 100% is "perfect" health and 0% is death, with standard intervals of 10%. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[15]			
Units: Scale [0-100 %]				
arithmetic mean (confidence interval 95%)				
Month 3	2.8 (0.5 to 5.1)			
Month 6	3.5 (1.0 to 6.1)			
Month 9	5.7 (2.7 to 8.7)			

Notes:

[15] - Day 0: n=18; Month 3: n=18; Month 6: n=17; Month 9: n=14

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life, Lansky scale, Performance status

End point title	Quality of life, Lansky scale, Performance status

End point description:

For the assessment of the performance status of the patients the Lansky/Karnofsky scales were used. Both scales run from 100% to 0%, where 100% is "perfect" health and 0% is death, with standard intervals of 10%. Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[16]			
Units: Scale [0-100 %]				
arithmetic mean (confidence interval 95%)				
Month 3	3.8 (-0.6 to 8.1)			
Month 6	5.0 (0.5 to 9.5)			
Month 9	6.3 (1.9 to 10.6)			

Notes:

[16] - Day 0: n=9; Month 3: n=8; Month 6: n=8; Month 9: n=8

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker IGFBP-3

End point title	Biomarker IGFBP-3

End point description:

Difference to baseline.

End point type	Secondary

End point timeframe:

At month 3, 6 and 9

End point values	Sirolimus			
Subject group type	Reporting group			
Number of subjects analysed	18[17]			
Units: IGFBP-3 [µg/mL]				
arithmetic mean (confidence interval 95%)				
Month 3	0.5 (0.2 to 0.8)			
Month 6	0.3 (-0.1 to 0.8)			
Month 9	0.2 (-0.2 to 0.7)			

Notes:

[17] - Day 0, Month 3: n=18; Month 6: n=17; Month 9: n=14

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Complete study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	Sirolimus
Reporting group description: 1,6 mg/m² sirolimus daily over 6 months	

Serious adverse events	Sirolimus		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (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	Sirolimus		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Fatigue			

subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 4		
Feeling abnormal subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Malaise subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Pain subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 5		
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Pyrexia subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 7		
Vaccination site reaction subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Epistaxis subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Oropharyngeal pain			

subjects affected / exposed occurrences (all) Vocal cord inflammation subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 4 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all) Mood altered subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Injury, poisoning and procedural complications Arthropod sting subjects affected / exposed occurrences (all) Muscle rupture subjects affected / exposed occurrences (all) Sunburn subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all) Extrasystoles subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Nervous system disorders			

Headache			
subjects affected / exposed	10 / 18 (55.56%)		
occurrences (all)	19		
Peroneal nerve palsy			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Eye disorders			
Dyschromatopsia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Eye inflammation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	5		
Aphthous ulcer			
subjects affected / exposed	9 / 18 (50.00%)		
occurrences (all)	17		
Abdominal pain upper			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		
Faeces soft			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Lip dry			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	7		
Swollen tongue			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Photosensitivity reaction			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Skin disorder			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	6		
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	3		
Hordeolum			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Nasopharyngitis			
subjects affected / exposed	9 / 18 (50.00%)		
occurrences (all)	12		
Pharyngitis			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	8		
Scarlet fever			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Subcutaneous abscess			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Viral sinusitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2020	CTP version V5.0: The main changes of the substantial amendment applied to the following items: • Primary purpose was a better definition of inclusion/exclusion criteria, objectives and endpoints • Most importantly, stable disease (SD) has been removed as successful treatment outcome, obviating the need for the observation period before therapy start • There were administrative modifications (including change of the coordinating investigator and project manager, redistribution of responsibilities for the conduct of the study, update of addresses, introduction of data monitoring committee (DMC), some wording specifications, and use of the CTCAE version 5.0 instead off 4.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported