Clinical trial results:
An open-label multi-part first-in-human study of oral LMI070 in infants with Type 1 spinal muscular atrophy.

Summary

EudraCT number	2014-002053-19
Trial protocol	DK IT DE BE NL CZ PL HU BG
Global end of trial date	29 December 2022

Results information

Result version number	v1 (current)
This version publication date	14 July 2023
First version publication date	14 July 2023

Trial information

Trial identification

Sponsor protocol code	CLMI070X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02268552
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1: Determine the safety and tolerability of ascending weekly doses and estimate the maximum tolerated dose (MTD) of branaplam in infants with Type 1 SMA.
Part 2: Evaluate the safety and tolerability of 2 doses of branaplam administered weekly for 52 weeks in subjects with Type 1 SMA.
Part 3: Assess long term safety and tolerability of extended, once a week branaplam treatment in subjects with Type 1 SMA who have had at least 52 weeks of treatment in either Part 1 or 2 of this protocol.

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	02 April 2015
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	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Russian Federation: 17
Worldwide total number of subjects	38
EEA total number of subjects	21

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	38
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There was a screening period of 1 week to assess eligibility and a baseline period of 1 week to review baseline safety evaluation results prior to dosing.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part 1 LMI070 Overall

Arm description:

Enteral route via feeding tube or oral. There were 5 cohorts: 0.3125, 0.625, 1.25, 2.5, 3.125 mg/kg weekly doses for 2 weeks

Arm type	Experimental
Investigational medicinal product name	branaplam
Investigational medicinal product code	LMI070
Other name	
Pharmaceutical forms	Gastroenteral solution, Oral solution
Routes of administration	Enteral use , Oral use

Dosage and administration details:

Branaplam in a dose strength of 3.5 mg/mL administered by the enteral route or orally depending ability to swallow

Arm title	Part 2 LMI070 0.625 mg/kg

Arm description:

LMI070 0.625 mg/kg by enteral route via feeding tube or oral

Arm type	Experimental
Investigational medicinal product name	branaplam
Investigational medicinal product code	LMI070
Other name	
Pharmaceutical forms	Gastroenteral solution, Oral solution
Routes of administration	Enteral use , Oral use

Dosage and administration details:

Branaplam in a dose strength of 3.5 mg/mL administered by the enteral route or orally depending ability to swallow

Arm title	Part 2 LMI070 2.5 mg/kg

Arm description:

LMI070 2.5 mg/kg by enteral route via feeding tube or oral

Arm type	Experimental
Investigational medicinal product name	branaplam
Investigational medicinal product code	LMI070
Other name	
Pharmaceutical forms	Gastroenteral solution, Oral solution
Routes of administration	Enteral use , Oral use

Dosage and administration details:

Branaplam in a dose strength of 3.5 mg/mL administered by the enteral route or orally depending ability to swallow

Arm title	Parts 1 & 3 Overall

Arm description:

Participants who completed 52 weeks of treatment in Part 1 could have continued on same dose or moved to optimal dose (2.5 mg/kg) in Part 3

Arm type	Experimental
Investigational medicinal product name	branaplam
Investigational medicinal product code	LMI070
Other name	
Pharmaceutical forms	Gastroenteral solution, Oral solution
Routes of administration	Enteral use , Oral use

Dosage and administration details:

Branaplam in a dose strength of 3.5 mg/mL administered by the enteral route or orally depending ability to swallow

Arm title	Parts 2 & 3 Overall

Arm description:

Participants who completed 52 weeks of treatment in Part 2 could have continued on same dose or could have moved to optimal dose (2.5 mg/kg) in Part 3

Arm type	Experimental
Investigational medicinal product name	branaplam
Investigational medicinal product code	LMI070
Other name	
Pharmaceutical forms	Gastroenteral solution, Oral solution
Routes of administration	Enteral use , Oral use

Dosage and administration details:

Branaplam in a dose strength of 3.5 mg/mL administered by the enteral route or orally depending ability to swallow

Number of subjects in period 1	Part 1 LMI070 Overall	Part 2 LMI070 0.625 mg/kg	Part 2 LMI070 2.5 mg/kg
Started	13	10	15
Completed	7	10	12
Not completed	6	0	3
Adverse event, serious fatal	5	-	2
Early termination of trial	-	-	-
Did not complete, reason not stated	-	-	-
Subject/guardian decision	1	-	1

Number of subjects in period 1	Parts 1 & 3 Overall	Parts 2 & 3 Overall
Started	13	25
Completed	0	0
Not completed	13	25
Adverse event, serious fatal	5	7

Early termination of trial	7	15
Did not complete, reason not stated	-	1
Subject/guardian decision	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	38	38	
Age Continuous Units: months			
arithmetic mean	4.04		
standard deviation	± 1.331	-	
Sex: Female, Male Units: participants			
Female	22	22	
Male	16	16	
Race/Ethnicity, Customized Units: Subjects			
Asian	1	1	
Caucasian	35	35	
Other	2	2	

Subject analysis sets	
Subject analysis set title	Part 1 LMI070 Overall BL
Subject analysis set type	Full analysis

Subject analysis set description:

Enteral route via feeding tube or oral. There were 5 cohorts: 0.3125, 0.625, 1.25, 2.5, 3.125 mg/kg weekly doses for 2 weeks for Baseline

Subject analysis set title	Part 2 LMI070 0.625 BL
Subject analysis set type	Full analysis

Subject analysis set description:

LMI070 0.625 mg/kg by enteral route via feeding tube or oral for Baseline

Subject analysis set title	Part 2 LMI070 2.5 mg/kg BL
Subject analysis set type	Full analysis

Subject analysis set description:

LMI070 2.5 mg/kg by enteral route via feeding tube or oral for Baseline

Reporting group values	Part 1 LMI070 Overall BL	Part 2 LMI070 0.625 BL	Part 2 LMI070 2.5 mg/kg BL
Number of subjects	13	10	15
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	13	10	15

Age Continuous Units: months arithmetic mean standard deviation	±	±	±
Sex: Female, Male Units: participants			
Female	8	5	9
Male	5	5	6
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	1
Caucasian	11	10	14
Other	2	0	0

End points

End points reporting groups

Reporting group title	Part 1 LMI070 Overall
Reporting group description:	
Enteral route via feeding tube or oral. There were 5 cohorts: 0.3125, 0.625, 1.25, 2.5, 3.125 mg/kg weekly doses for 2 weeks	
Reporting group title	Part 2 LMI070 0.625 mg/kg
Reporting group description:	
LMI070 0.625 mg/kg by enteral route via feeding tube or oral	
Reporting group title	Part 2 LMI070 2.5 mg/kg
Reporting group description:	
LMI070 2.5 mg/kg by enteral route via feeding tube or oral	
Reporting group title	Parts 1 & 3 Overall
Reporting group description:	
Participants who completed 52 weeks of treatment in Part 1 could have continued on same dose or moved to optimal dose (2.5 mg/kg) in Part 3	
Reporting group title	Parts 2 & 3 Overall
Reporting group description:	
Participants who completed 52 weeks of treatment in Part 2 could have continued on same dose or could have moved to optimal dose (2.5 mg/kg) in Part 3	
Subject analysis set title	Part 1 LMI070 Overall BL
Subject analysis set type	Full analysis
Subject analysis set description:	
Enteral route via feeding tube or oral. There were 5 cohorts: 0.3125, 0.625, 1.25, 2.5, 3.125 mg/kg weekly doses for 2 weeks for Baseline	
Subject analysis set title	Part 2 LMI070 0.625 BL
Subject analysis set type	Full analysis
Subject analysis set description:	
LMI070 0.625 mg/kg by enteral route via feeding tube or oral for Baseline	
Subject analysis set title	Part 2 LMI070 2.5 mg/kg BL
Subject analysis set type	Full analysis
Subject analysis set description:	
LMI070 2.5 mg/kg by enteral route via feeding tube or oral for Baseline	

Primary: Number of participants with dose limiting toxicities (DLT) in Part 1 - Safety analysis set (SAS)

End point title	Number of participants with dose limiting toxicities (DLT) in Part 1 - Safety analysis set (SAS)[1][2]
End point description:	
A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant therapies that occurs within the first 14 days of treatment with LMI070 and meets any of the criteria for blood and lymphatic system disorders, gastrointestinal disorders, investigations and other toxicities considered clinically significant.	
End point type	Primary
End point timeframe:	
Baseline up to 2 weeks for Part 1	

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 analysis was done

[2] - 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: No analysis was done

End point values	Part 1 LMI070 Overall			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with treatment emergent adverse events (TEAEs) and serious adverse events -SAS

End point title	Number of participants with treatment emergent adverse events (TEAEs) and serious adverse events -SAS[3][4]

End point description:

TEAEs are defined as adverse events starting on or after the first dose of study treatment that were absent pre-treatment, or events present prior to the first dose but increased in severity after the first dose. Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post last treatment.

End point type	Primary

End point timeframe:

Baseline up to approximately 83 months

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 analysis was done

[4] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: participants				
Participants with adverse events (AEs)	13	25		
Participants with AEs causing study drug discont	1	2		
Participants with serious adverse events (SAEs)	13	19		
Participants with SAEs causing study drug discont	1	2		
Deaths	9	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma pharmacokinetic (PK) parameter area under the curve (AUC) after a single dose - Part 1 - Pharmacokinetics analysis set (PAS)

End point title	Summary of plasma pharmacokinetic (PK) parameter area

	under the curve (AUC) after a single dose - Part 1 - Pharmacokinetics analysis set (PAS)[5]

End point description:

The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume)

End point type	Secondary

End point timeframe:

Post single dose

Notes:

[5] - 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: No analysis was done

End point values	Part 1 LMI070 Overall			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
0.321 mg/kg - Actual	378 (± 31.9)			
0.654 mg/kg - Actual	892 (± 12.3)			
1.39 mg/kg - Actual	1820 (± 999)			
2.49 mg/kg - Actual	3310 (± 1340)			
2.94 mg/kg - Actual	3800 (± 1590)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma pharmacokinetic (PK) parameter area under the curve (AUC) for all observation periods - Part 1 - PAS

End point title	Summary of plasma pharmacokinetic (PK) parameter area under the curve (AUC) for all observation periods - Part 1 - PAS[6]

End point description:

AUC is the area under the curve for branaplan in plasma after a single dose. AUC values used for comparison are combined from AUCinf values after single dose and AUC 0–168-hour values after repeated administration.

End point type	Secondary

End point timeframe:

Post single dose, hours 1,2,4,8,24,48,96,168

Notes:

[6] - 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: No analysis was done

End point values	Part 1 LMI070 Overall			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
0.299 mg/kg - Actual	413 (± 98.3)			

0.644 mg/kg - Actual	761 (± 170)			
1.30 mg/kg - Actual	1340 (± 381)			
2.52 mg/kg - Actual	3310 (± 850)			
2.99 mg/kg - Actual	4280 (± 1030)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma pharmacokinetic (PK) parameter Cmax after a single dose - Part 1 - PAS

End point title	Summary of plasma pharmacokinetic (PK) parameter Cmax after a single dose - Part 1 - PAS[7]

End point description:

The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume)

End point type	Secondary

End point timeframe:

Post single dose

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: No analysis was done

End point values	Part 1 LMI070 Overall			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/mL				
arithmetic mean (standard deviation)				
0.321 mg/kg - Actual	9.10 (± 1.22)			
0.654 mg/kg - Actual	18.6 (± 1.63)			
1.39 mg/kg - Actual	55.6 (± 999)			
2.49 mg/kg - Actual	53.2 (± 9.50)			
2.94 mg/kg - Actual	72.4 (± 16.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma pharmacokinetic (PK) parameter Cmax for all observation periods - Part 1 - PAS

End point title	Summary of plasma pharmacokinetic (PK) parameter Cmax for all observation periods - Part 1 - PAS[8]

End point description:

The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume

End point type	Secondary

End point timeframe:

Post single dose, hours 1,2,4,8,24,48,96,168

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: No analysis was done

End point values	Part 1 LMI070 Overall			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
arithmetic mean (standard deviation)				
0.299 mg/kg - Actual	8.84 (± 3.58)			
0.644 mg/kg - Actual	15.3 (± 4.10)			
1.30 mg/kg - Actual	37.8 (± 12.8)			
2.51 mg/kg - Actual	69.1 (± 15.7)			
2.99 mg/kg - Actual	96.5 (± 32.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma pharmacokinetic (PK) parameter area under the curve (AUC) after a single dose - Part 2 - PAS

End point title	Summary of plasma pharmacokinetic (PK) parameter area under the curve (AUC) after a single dose - Part 2 - PAS[9]

End point description:

The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume)

End point type	Secondary

End point timeframe:

Post single dose

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: No analysis was done

End point values	Part 2 LMI070 0.625 mg/kg	Part 2 LMI070 2.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: h*ng/mL				
arithmetic mean (standard deviation)	1150 (± 357)	4060 (± 734)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma pharmacokinetic (PK) parameter area under the curve (AUC) for all observation periods - Part 2 - PAS

End point title	Summary of plasma pharmacokinetic (PK) parameter area under the curve (AUC) for all observation periods - Part 2 - PAS[10]

End point description:

The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume). AUC values used for comparison are combined from AUCinf values after single dose and AUC 0–168-hour values after repeated administration.

End point type	Secondary

End point timeframe:

Post single dose, hours 1,2,4,8,24,48,96,168

Notes:

[10] - 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: No analysis was done

End point values	Part 2 LMI070 0.625 mg/kg	Part 2 LMI070 2.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[11]	15[12]		
Units: h*ng/mL				
arithmetic mean (standard deviation)	1020 (± 278)	3470 (± 909)		

Notes:

[11] - The number of subjects analyzed was 10 and number of observations was 28

[12] - The number of subjects analyzed was 15 and number of observations was 29

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma pharmacokinetic (PK) parameter Cmax for a single dose - Part 2 - PAS

End point title	Summary of plasma pharmacokinetic (PK) parameter Cmax for a single dose - Part 2 - PAS[13]

End point description:

The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume)

End point type	Secondary

End point timeframe:

Post single dose

Notes:

[13] - 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: No analysis was done

End point values	Part 2 LMI070 0.625 mg/kg	Part 2 LMI070 2.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: ng/mL				
arithmetic mean (standard deviation)	22.0 (± 5.70)	82.0 (± 22.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of plasma pharmacokinetic (PK) parameter Cmax for all observation periods - Part 2 - PAS

End point title	Summary of plasma pharmacokinetic (PK) parameter Cmax for all observation periods - Part 2 - PAS[14]

End point description:

The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume)

End point type	Secondary

End point timeframe:

Post single dose, hours 1,2,4,8,24,48,96,168

Notes:

[14] - 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: No analysis was done

End point values	Part 2 LMI070 0.625 mg/kg	Part 2 LMI070 2.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[15]	15[16]		
Units: ng/mL				
arithmetic mean (standard deviation)	21.7 (± 5.71)	77.4 (± 27.5)		

Notes:

[15] - The number of subjects analyzed was 10 and number of observations was 29

[16] - The number of subjects analyzed was 15 and number of observations was 38

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in growth parameters: chest circumference, body length and chest circumference - FAS

End point title	Change from baseline in growth parameters: chest circumference, body length and chest circumference - FAS[17]

End point description:

To evaluate the effect of branaplam on length, head circumference and chest circumference

End point type	Secondary

End point timeframe:

Baseline up to Part 3, Month 6

Notes:

[17] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: cm				
arithmetic mean (standard deviation)				
Chest - Week 52	4.68 (± 2.4769)	5.656 (± 3.0167)		
Chest - P3 Month 6	14.750 (± 5.0548)	8.582 (± 2.7423)		
Head -Week 52	5.030 (± 1.1235)	5.111 (± 1.3407)		
Head - P3 Month 6	9.717 (± 1.8766)	6.359 (± 1.2971)		
Length - Week 52	16.950 (± 3.7825)	16.942 (± 4.5806)		
Length - P3 Month 6	52.140 (± 9.8766)	22.944 (± 3.7686)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in growth parameter: body weight - FAS

End point title	Change from baseline in growth parameter: body weight -

End point description:

To evaluate the effect of branaplam on weight

End point type	Secondary

End point timeframe:

Baseline up to Part 3, Month 6

Notes:

[18] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: kg				
arithmetic mean (standard deviation)				
Week 52	2.739 (± 1.3545)	3.145 (± 1.5089)		
P3 Month 6	9.546 (± 3.5069)	4.402 (± 1.3250)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in respiratory function: Pulse oximetry - FAS

End point title	Change from baseline in respiratory function: Pulse oximetry - FAS[19]

End point description:

To evaluate the effect of branaplam on pulse oximetry in percentage (%) of oxygen saturation.

End point type	Secondary

End point timeframe:

Baseline up to Part 3, Month 6

Notes:

[19] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: percentage				
arithmetic mean (standard deviation)				
Week 52	-0.8 (± 2.59)	-0.1 (± 1.56)		
P3 Month 6	-0.7 (± 2.58)	0.0 (± 1.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in respiratory function: Respiratory rate - FAS

End point title	Change from baseline in respiratory function: Respiratory rate - FAS[20]

End point description:

To evaluate the effect of branaplam on respiratory rate

End point type	Secondary

End point timeframe:

Baseline up to Part 3, Month 6

Notes:

[20] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	25		
Units: breaths per minute				
arithmetic mean (standard deviation)				
Week 52	41.3 (± 7.57)	40.5 (± 13.46)		
P3 Month 6	29.2 (± 6.59)	37.2 (± 8.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in respiratory function: Chest circumference during quiet breathing - end of inspiration and expiration - FAS

End point title	Change from baseline in respiratory function: Chest circumference during quiet breathing - end of inspiration and expiration - FAS[21]

End point description:

To evaluate the effect of branaplam on chest circumference during quiet breathing or sleep at the end of inspiration.

End point type	Secondary

End point timeframe:

Baseline, Week 52 and Part 3 Month 6

Notes:

[21] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	18		
Units: cm				
arithmetic mean (standard deviation)				
Week 52 - end of inspiration	999 (± 999)	5.964 (± 3.6345)		
P3 Month 6 - end of inspiration	999 (± 999)	8.535 (± 3.3083)		
Week 52 - end of expiration	999 (± 999)	6.033 (± 3.9466)		
P3 Month 6 - end of expiration	999 (± 999)	9.147 (± 3.5755)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with presence of paradoxical breathing - FAS

End point title	Number of participants with presence of paradoxical breathing - FAS[22]

End point description:

A paradoxical breathing occurs when one compartment moves out of phase compared to another one. In SMA type I, paradoxical breathing is often a sign of breathing problems where the pulmonary ribcage moves inward during inspiration rather than outward while the abdomen expands.

End point type	Secondary

End point timeframe:

Baseline up to Part 3, Month 6

Notes:

[22] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: participants				
Week 52	5	15		
P3 Month 6	4	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of CHOP INTEND total score - Parts 1 and 3 and Parts 2 and 3 - FAS

End point title	Summary of CHOP INTEND total score - Parts 1 and 3 and Parts 2 and 3 - FAS[23]

End point description:

CHOP INTEND is a motor test measure for SMA Type 1 and similarly weak infants with neuromuscular disease. The CHOP INTEND provides a useful measure of motor skills and strength in this population. It is a 16 item, 64 point scale. Each item (motor skill) is given a score from zero to 4: zero indicates can't complete the movement, 1 to 3 indicates partial performance and a 4 indicates person can complete the movement on their own without assistance. These scores are added up to a possible total score of 64 and higher scores indicate better outcomes.

End point type	Secondary

End point timeframe:

Baseline up to Part 3, Month 6

Notes:

[23] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	18		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 52	38.1 (± 8.69)	43.6 (± 6.79)		
Part 3, Month 6	26.0 (± 999)	44.7 (± 8.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants fed orally or by feeding tube for Parts 1 and 3 and Parts 2 and 3 - FAS

End point title	Number of participants fed orally or by feeding tube for Parts 1 and 3 and Parts 2 and 3 - FAS[24]

End point description:

To evaluate the efficacy of branaplam on preservation of oral feeding

End point type	Secondary

End point timeframe:

Baseline up to Part 3, Month 6

Notes:

[24] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: participants				
Only exclusively orally fed	3	18		
Only exclusively tube fed	0	0		
Started on orally fed, switched to tube fed	0	2		
Started on tube fed, switched to orally fed	0	0		
Other (mixture of both tube and oral feeding)	8	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants and HINE Motor subscale milestones (ability to sit, stand or walk without support) - FAS

End point title	Number of participants and HINE Motor subscale milestones (ability to sit, stand or walk without support) - FAS[25]

End point description:

HINE Section 2 is a standardized evaluation of motor function. It evaluates 8 items; grasp, head control, kicking, rolling over, sitting up, crawling, standing and walking. Motor skills are assigned a score of 0 to 3 to 5 points and zero means the child lacks that motor skill. The maximum score is 26 which is dependent on age, level of development and severity of disease. A higher score is a better outcome. This assessment was added with amendment 6, therefore no baseline was available.

End point type	Secondary

End point timeframe:

Baseline up to Part 3, Month 6

Notes:

[25] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: participants				
Week 52 Sitting	1	1		
Week 52 Standing	0	2		
Week 52: Walking	0	1		
Part 3, Month 6: Sitting	0	4		
Part 3, Month 6: Standing	0	5		
Part 3, Month 6: Walking	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Ventilation use for Parts 1 and 3 and Parts 2 and 3 - FAS

End point title	Ventilation use for Parts 1 and 3 and Parts 2 and 3 - FAS[26]

End point description:

BiBAP (bilevel positive airway pressure) ventilation is a 2 level breathing support which has a tube that connects to a mask. It provides a different level of air pressure for inhalation vs. exhalation, whereas a CPAP (continuous positive airway pressure) only pumps one level of air pressure but is also non-invasiive. Invasive ventilation is delivered via an endotracheal or tracheostomy tube.

End point type	Secondary

End point timeframe:

Baselline up 168 weeks

Notes:

[26] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25		
Units: participants				
Non-invasive ventilation - BiPAP	9	18		
Non-invasive ventilation - CPAP	3	2		
Invasive ventilation	4	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Hammersmith Infant Neurologic Examination Section 2 (HINE-2) - FAS

End point title	Summary of Hammersmith Infant Neurologic Examination Section 2 (HINE-2) - FAS[27]

End point description:

HINE Section 2 is a standardized evaluation of motor function. It evaluates 8 items; grasp, head control, kicking, rolling over, sitting up, crawling, standing and walking. Motor skills are assigned a score of 0 to 3 to 5 points and zero means the child lacks that motor skill. The maximum score is 26 which is dependent on age, level of development and severity of disease. A higher score is a better outcome. This assessment was added with amendment 6, therefore no baseline was available.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

Notes:

[27] - 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: No analysis was done

End point values	Parts 1 & 3 Overall	Parts 2 & 3 Overall		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	25		
Units: total scores				
arithmetic mean (standard deviation)				
Week 52	3.3 (± 2.31)	4.9 (± 3.44)		
Part 3 Month 6	3.0 (± 2.12)	7.7 (± 4.82)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post last treatment up a maximum of 83 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Parts 1 and 3
Reporting group description:	
Parts 1 and 3	
Reporting group title	Parts 2 and 3 LMI070 2.5
Reporting group description:	
Parts 2 and 3 LMI070 2.5	
Reporting group title	Parts 2 and 3 LMI070 0.625
Reporting group description:	
Parts 2 and 3 LMI070 0.625	

Serious adverse events	Parts 1 and 3	Parts 2 and 3 LMI070 2.5	Parts 2 and 3 LMI070 0.625
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	11 / 15 (73.33%)	8 / 10 (80.00%)
number of deaths (all causes)	9	2	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	5 / 13 (38.46%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Apnoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	5 / 13 (38.46%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchostenosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngospasm			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	5 / 13 (38.46%)	2 / 15 (13.33%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 8	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 0
Tachypnoea			

subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus test positive			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Rotavirus test positive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella test positive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ultrasound kidney abnormal			

subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	4 / 13 (30.77%)	0 / 15 (0.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body in gastrointestinal tract			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shunt malfunction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Left ventricular hypertrophy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thrombocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hypercalciuria			

subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 15 (13.33%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovirus infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea infectious			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	3 / 13 (23.08%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 13 (0.00%)	2 / 15 (13.33%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	9 / 13 (69.23%)	7 / 15 (46.67%)	4 / 10 (40.00%)
occurrences causally related to treatment / all	0 / 18	0 / 13	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	3 / 13 (23.08%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Parts 1 and 3	Parts 2 and 3 LMI070 2.5	Parts 2 and 3 LMI070 0.625
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	15 / 15 (100.00%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cyanosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Diastolic hypertension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	5
Hypotension			

subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Therapy cessation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tracheostomy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Catheter site haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Discomfort			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Granuloma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Hyperthermia			
subjects affected / exposed	1 / 13 (7.69%)	4 / 15 (26.67%)	0 / 10 (0.00%)
occurrences (all)	2	7	0
Malaise			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Medical device pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Medical device site granuloma			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	11 / 13 (84.62%)	6 / 15 (40.00%)	7 / 10 (70.00%)
occurrences (all)	58	16	19
Hyperpyrexia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Drug hypersensitivity			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Immunisation reaction			
subjects affected / exposed	6 / 13 (46.15%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	7	0	0
Multiple allergies			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Genital rash			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal rash			

subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Aspiration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Atelectasis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Bronchospasm			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Respiratory distress			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Chronic respiratory failure			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	3 / 13 (23.08%)	4 / 15 (26.67%)	3 / 10 (30.00%)
occurrences (all)	10	6	3
Dysphonia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Epistaxis			

subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Hypoxia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 15 (13.33%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Increased bronchial secretion			
subjects affected / exposed	3 / 13 (23.08%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Increased upper airway secretion			
subjects affected / exposed	4 / 13 (30.77%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	10	0	0
Lung disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nasal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nasal obstruction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Obstructive airways disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Pulmonary fibrosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory depression			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Respiratory disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Choking			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Respiratory failure			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	3	1	2
Rhinorrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sputum discoloured			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Tachypnoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
Vasomotor rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory tract inflammation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Behaviour disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Agitation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Irritability			
subjects affected / exposed	3 / 13 (23.08%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Restlessness			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Investigations			
Fungal test positive			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 13 (23.08%)	0 / 15 (0.00%)	5 / 10 (50.00%)
occurrences (all)	4	0	9
Blood albumin decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 13 (0.00%)	2 / 15 (13.33%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood creatinine decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	3 / 10 (30.00%)
occurrences (all)	0	1	3
Blood iron decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	1	1	2

Blood parathyroid hormone decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood potassium increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Body temperature increased			
subjects affected / exposed	3 / 13 (23.08%)	2 / 15 (13.33%)	0 / 10 (0.00%)
occurrences (all)	3	5	0
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Crystal urine present			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Electrocardiogram P pulmonale			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	5 / 10 (50.00%)
occurrences (all)	2	0	5
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
White blood cell count decreased			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	4	2	1
Heart rate decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Heart rate increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Nerve conduction studies abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Oxygen saturation decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Platelet count increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Red blood cell count decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
Reticulocyte count decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	0	1	1

Troponin T increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Troponin increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Ultrasound kidney abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Urine phosphorus increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Urine uric acid increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Vitamin D decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	4 / 13 (30.77%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	6	0	1
Haematocrit decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	4
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Exposure to SARS-CoV-2			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Femur fracture			

subjects affected / exposed	2 / 13 (15.38%)	3 / 15 (20.00%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Fibula fracture			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Humerus fracture			
subjects affected / exposed	3 / 13 (23.08%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Joint dislocation			
subjects affected / exposed	3 / 13 (23.08%)	2 / 15 (13.33%)	1 / 10 (10.00%)
occurrences (all)	3	2	1
Lower limb fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Subdural haematoma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Subdural haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Tibia fracture			
subjects affected / exposed	4 / 13 (30.77%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
Tracheostomy malfunction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Upper limb fracture			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic			

disorders			
Cryptorchism			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dacryostenosis congenital			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Developmental hip dysplasia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Phimosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Plagiocephaly			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Atrial tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Bradycardia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Cardiac failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Myocarditis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pericardial effusion			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Right ventricular hypertrophy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sinus node dysfunction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 15 (13.33%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Supraventricular extrasystoles			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Supraventricular tachycardia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Sinus bradycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cerebral atrophy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Complex regional pain syndrome			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Facial paresis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0

Glossopharyngeal nerve disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Hydrocephalus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Monocytosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Lymphopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	0	1	3
Leukocytosis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 15 (13.33%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Iron deficiency anaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Anaemia			
subjects affected / exposed	2 / 13 (15.38%)	3 / 15 (20.00%)	0 / 10 (0.00%)
occurrences (all)	3	5	0
White blood cell disorder			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Thrombocytosis			

subjects affected / exposed	1 / 13 (7.69%)	3 / 15 (20.00%)	4 / 10 (40.00%)
occurrences (all)	2	8	8
Thrombocytopenia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Polycythaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pancytopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	3 / 10 (30.00%)
occurrences (all)	1	3	10
Reticulocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	9	0	0
Tympanic membrane hyperaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Heterophoria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Astigmatism			
subjects affected / exposed	3 / 13 (23.08%)	3 / 15 (20.00%)	1 / 10 (10.00%)
occurrences (all)	3	3	1
Blepharitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Chalazion			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hypermetropia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Optic atrophy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Strabismus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Myopia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Anal fissure			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Aphthous ulcer			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0

Constipation			
subjects affected / exposed	6 / 13 (46.15%)	3 / 15 (20.00%)	7 / 10 (70.00%)
occurrences (all)	19	5	7
Dental cyst			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	7 / 13 (53.85%)	2 / 15 (13.33%)	2 / 10 (20.00%)
occurrences (all)	19	3	3
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
Dysphagia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Erosive oesophagitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Faecaloma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Food poisoning			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal pain			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Gingival pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Gingival swelling			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Haematochezia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hiatus hernia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Inguinal hernia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Malocclusion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Oesophagitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Oesophagitis haemorrhagic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Regurgitation			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Salivary hypersecretion			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Teething			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1
Tongue disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Vomiting			
subjects affected / exposed	10 / 13 (76.92%)	2 / 15 (13.33%)	2 / 10 (20.00%)
occurrences (all)	40	10	3
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypertransaminasaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 13 (30.77%)	3 / 15 (20.00%)	1 / 10 (10.00%)
occurrences (all)	7	8	1
Blister			
subjects affected / exposed	3 / 13 (23.08%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Decubitus ulcer			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Dermatitis atopic			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Dermatitis diaper			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Drug eruption			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eczema			

subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	1	1	2
Hyperhidrosis			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Keratosis pilaris			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Papule			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Perioral dermatitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	3 / 13 (23.08%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	4	1	2
Urticaria			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hypercalciuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Ketonuria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	3 / 10 (30.00%)
occurrences (all)	0	2	7
Leukocyturia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Nephrocalcinosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nephrolithiasis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nephroptosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pyelocaliectasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Urinary retention			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Deformity thorax			

subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Foot deformity			
subjects affected / exposed	3 / 13 (23.08%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	3	1	1
Fracture pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Joint contracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	4 / 13 (30.77%)	0 / 15 (0.00%)	2 / 10 (20.00%)
occurrences (all)	10	0	2
Osteolysis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Osteopenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Rib deformity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Scoliosis			
subjects affected / exposed	5 / 13 (38.46%)	3 / 15 (20.00%)	4 / 10 (40.00%)
occurrences (all)	5	3	4
Musculoskeletal chest pain			

subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 13 (7.69%)	8 / 15 (53.33%)	5 / 10 (50.00%)
occurrences (all)	6	10	9
Asymptomatic COVID-19			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Bacterial disease carrier			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Bacterial rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis norovirus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis viral			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Hordeolum			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infected bite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
Infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Klebsiella infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Bronchitis bacterial			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	1 / 13 (7.69%)	2 / 15 (13.33%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Candida infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	2 / 13 (15.38%)	3 / 15 (20.00%)	2 / 10 (20.00%)
occurrences (all)	2	5	2
Cystitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Cytomegalovirus infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dermatitis infected			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	3 / 13 (23.08%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	8	1	1
Ear infection viral			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Eye infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Fungal skin infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	5 / 13 (38.46%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	6	0	0
Medical device site infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Staphylococcal infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Oral fungal infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Otitis externa			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Otitis media			
subjects affected / exposed	4 / 13 (30.77%)	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	6	1	1
Otitis media acute			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 15 (13.33%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	5 / 13 (38.46%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	8	2	0
Pseudomonas infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Pyuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rash pustular			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	4 / 13 (30.77%)	3 / 15 (20.00%)	3 / 10 (30.00%)
occurrences (all)	17	3	3
Respiratory tract infection viral			
subjects affected / exposed	2 / 13 (15.38%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	2	1	2
Rhinitis			
subjects affected / exposed	6 / 13 (46.15%)	4 / 15 (26.67%)	2 / 10 (20.00%)
occurrences (all)	13	12	2
Rhinovirus infection			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
Roseola			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin bacterial infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	5 / 13 (38.46%)	6 / 15 (40.00%)	0 / 10 (0.00%)
occurrences (all)	9	8	0
Tonsillitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1

Upper respiratory tract infection			
subjects affected / exposed	7 / 13 (53.85%)	3 / 15 (20.00%)	4 / 10 (40.00%)
occurrences (all)	34	5	11
Urethritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	6 / 13 (46.15%)	2 / 15 (13.33%)	2 / 10 (20.00%)
occurrences (all)	20	2	6
Varicella			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Viral infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Vulvitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Feeding disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Failure to thrive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Feeding intolerance			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Fluid intake reduced			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
Hyponatraemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Hypophagia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Iron deficiency			
subjects affected / exposed	0 / 13 (0.00%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Malnutrition			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Decreased appetite			
subjects affected / exposed	2 / 13 (15.38%)	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2014	Clarified the phases of the study, the sequential enrollment of subjects into the cohorts. Provided clariication on the safety monitoring of the subjects after they received their first dose of study treatment. Correction of the study phase from Phase II to Phase I/II
27 February 2015	Clarifed the exclusion criteria, the dose limiting toxicities and the provisional dose levels. Revised the criteria for interruption and re-initiation of branaplam treatment based on the revision of the dose limiting toxicity (DLT) criteria.
30 November 2015	Iimplemented additional safety measures following an urgent safety measures (USM). Ophthalmologic monitoring was added as part of the safety monitoring plan. Implemented requests for modification from the independent data monitoring committee (DMC) following their review of the clinical safety data. Added a different and much less burdensome assessment to evaluate respiratory function, measurement of chest circumference during quiet breathing. Plans to increase the total number of subjects to be enrolled in Part 1 of the study up to approximately 30.
31 March 2016	Implemented additional cardiac monitoring following a second USM. Exclusion criterion #10 was expanded to exclude a broader range of cardiac disease. Dose modification rules were added for cardiac disorders and hypertension. Two higher dose levels (120 mg/m2 and 240 mg/m2), which exceeded the available preclinical toxicology exposure were removed. Measurement of quadriceps muscle thickness by ultrasound and the evaluation of exploratory biomarkers in hair and in urine were removed.
31 August 2016	Implemented additional safety monitoring following a third USM. Reduction of the Weekly dose of branaplam administered to all subjects having completed the initial 13 Weeks of treatment to 6 mg/m2. Addition of two following safety endpoints: neurologic examination and neurophysiologic examination to the primary objective. Correction of a discrepancy in secondary objective which indicated that branaplam pharmacokinetics were evaluated in serum instead of plasma samples. The CMAP which used to be optional was amended as mandatory for all subjects enrolled in the study.
28 April 2017	Implemented to allow resumption of enrollment in the ongoing study as agreed by the independent DMC. Part 2 of the study was modified to obtain additional safety and efficacy data with oral administration of up to 3 dose levels of branaplam, already tested in Part 1. Part 2 was to enroll approximately 30 subjects. The age of subjects at screening was restricted to 180 days of age. A minimum CHOP INTEND score of 15 was required at baseline and subjects were required to be able to feed orally for all nutritional needs and be greater than the 2nd percentile for weight on the standard growth curves for the country of origin.
29 December 2017	Implemented in all countries where the study was being conducted the changes made based on the request of the German Health Authority during their review of the Amended Protocol version v06.Added criteria used to decide interrupting and re-initiating treatment with branaplam in the event of thrombocytosis. The name of the Novartis department where serious adverse events (SAEs) need to be sent was changed. Updated Appendix 16.1.1-Protocol-Table 6-2 to include the dose conversion from BSA to weight for doses in Part 1 of the study.

31 October 2018	Ensured that the studied doses were clinically distinguishable and more efficiently investigated the branaplam dose-response relationship in conjunction with the data generated in Part 1. Several modifications to the inclusion and exclusion criteria. Clarified that Part 1 subjects followed the Extended treatment Schedule of Assessment and subjects enrolled in Part 2 could receive study treatment in a separate protocol.
30 April 2019	Provided subjects from Part 1 and Part 2 of this protocol the possibility for continuous treatment and long-term safety and efficacy follow up in the newly added Part 3 of the study. Study description for Part 3 provided. Eliminated assessments that were present in Parts 1 and 2 and which were not necessary for Part 3. Revised efficacy endpoints (CHOP INTEND to be collected up to 3 years of age, i.e. 36 months). Clarified and simplified the process of branaplam administration at home.
28 February 2020	Clarified the frequency of ophthalmology assessments in Part 3 of the study. Updated the possibility to have a dose increase to 2.5 mg/kg in Part 3 for subjects treated with 0.625 mg/kg dose from Part 2, if no further improvement becomes evident, or in case of disease progression at the discretion of investigator and after consultation with the sponsor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Notes: