Clinical trial results:
A Phase 2B/3 Prospective, Randomized, Double-Blind, Sham-Controlled Trial of VTS-270 (2-hydroxypropyl--cyclodextrin) in Subjects with Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease

Summary

EudraCT number	2015-002548-15
Trial protocol	DE GB ES IT
Global end of trial date	11 April 2022

Results information

Result version number	v1 (current)
This version publication date	08 April 2023
First version publication date	08 April 2023

Trial information

Trial identification

Sponsor protocol code	VTS301 (Part C)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04958642
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mandos, LLC
Sponsor organisation address	9200 Sunset Blvd, Suite 1010, West Hollywood, CA, United States, 90069
Public contact	Executive Vice President, Regulatory Affairs, Mandos, LLC, 001 (619) 905-0489, jspinella@mandoshealth.com
Scientific contact	Executive Vice President, Regulatory Affairs, Mandos, LLC, 001 (619) 905-0489, jspinella@mandoshealth.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	11 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2022
Global end of trial reached?	Yes
Global end of trial date	11 April 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the longer-term safety and tolerability of VTS-270.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonization (ICH) Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 December 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	United Kingdom: 8
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United States: 38
Worldwide total number of subjects	66
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	27
Adolescents (12-17 years)	21
Adults (18-64 years)	18

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This is an open-label extension phase of study VTS301 (Parts A/B) (NCT02534844). Participants who completed Part B and participants who completed National Institutes of Health (NIH) phase 1 study (Protocol 13-CH-0001) were eligible to participate in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Naive

Arm description:

Treatment-naive participants received adrabetadex 900 milligrams (mg) administered intrathecal (IT) via lumbar puncture (LP) infusion every 2 weeks until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.

Arm type	Experimental
Investigational medicinal product name	Adrabetadex
Investigational medicinal product code	VTS-270
Other name	2-hydroxypropyl-β-cyclodextrin, Cyclodextrin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intrathecal use

Dosage and administration details:

Adrabetadex was administered per dose and schedule specified in the arm description.

Arm title	Previously Treated in Phase I

Arm description:

Rollover participants from Study 13-CH-0001 received adrabetadex at an amended dose and/or regimen after prior written authorization from the sponsor. The treatment was continued until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.

Arm type	Experimental
Investigational medicinal product name	Adrabetadex
Investigational medicinal product code	VTS-270
Other name	2-hydroxypropyl-β-cyclodextrin, Cyclodextrin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intrathecal use

Dosage and administration details:

Adrabetadex was administered per dose and schedule specified in the arm description.

Arm title	Previously Treated in Part A/B

Arm description:

Participants continuing from Part B of the study received adrabetadex 900 mg administered IT via LP infusion every 2 weeks until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.

Arm type	Experimental

Investigational medicinal product name	Adrabetadex
Investigational medicinal product code	VTS-270
Other name	2-hydroxypropyl-β-cyclodextrin, Cyclodextrin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intrathecal use

Dosage and administration details:

Adrabetadex was administered per dose and schedule specified in the arm description.

Number of subjects in period 1	Treatment Naive	Previously Treated in Phase I	Previously Treated in Part A/B
Started	18	13	35
Received at least 1 dose of study drug	18	13	35
Completed	0	0	0
Not completed	18	13	35
Transferred to OLEX program	3	-	5
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	4	9	13
Investigator's Decision	-	-	1
Adverse event, non-fatal	1	-	1
Termination by Sponsor/Regulatory Authorities	8	4	13
Lost to follow-up	1	-	-
Transferred to Expanded Access Program	1	-	-
Transferred to EAP following study termination	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Naive
Reporting group description:	
Treatment-naive participants received adrabetadex 900 milligrams (mg) administered intrathecal (IT) via lumbar puncture (LP) infusion every 2 weeks until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	
Reporting group title	Previously Treated in Phase I
Reporting group description:	
Rollover participants from Study 13-CH-0001 received adrabetadex at an amended dose and/or regimen after prior written authorization from the sponsor. The treatment was continued until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	
Reporting group title	Previously Treated in Part A/B
Reporting group description:	
Participants continuing from Part B of the study received adrabetadex 900 mg administered IT via LP infusion every 2 weeks until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	

Reporting group values	Treatment Naive	Previously Treated in Phase I	Previously Treated in Part A/B
Number of subjects	18	13	35
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	13.2	17.5	14.1
standard deviation	± 5.07	± 6.16	± 5.60
Gender categorical			
Units: Subjects			
Female	10	7	15
Male	8	6	20
Race			
Units: Subjects			
Asian	1	0	4
Black or African American	0	0	1
White	16	13	29
Multiple	0	0	1
Other	1	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	1	2
Not Hispanic or Latino	15	11	29
Not Reported	0	1	4

Reporting group values	Total		
Number of subjects	66		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	32		
Male	34		
Race Units: Subjects			
Asian	5		
Black or African American	1		
White	58		
Multiple	1		
Other	1		
Ethnicity Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	55		
Not Reported	5		

End points

End points reporting groups

Reporting group title	Treatment Naive
Reporting group description:	
Treatment-naive participants received adrabetadex 900 milligrams (mg) administered intrathecal (IT) via lumbar puncture (LP) infusion every 2 weeks until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	
Reporting group title	Previously Treated in Phase I
Reporting group description:	
Rollover participants from Study 13-CH-0001 received adrabetadex at an amended dose and/or regimen after prior written authorization from the sponsor. The treatment was continued until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	
Reporting group title	Previously Treated in Part A/B
Reporting group description:	
Participants continuing from Part B of the study received adrabetadex 900 mg administered IT via LP infusion every 2 weeks until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	

Primary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1]
End point description:	
An AE was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious adverse events (SAEs) were defined as death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized participant and required medical intervention to prevent 1 of the outcomes listed in this definition. A TEAE was defined as an AE with onset on or after the start of adrabetadex treatment. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section.	
End point type	Primary
End point timeframe:	
Baseline up to 5 years	
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: The endpoint was descriptive in nature.	

End point values	Treatment Naive	Previously Treated in Phase I	Previously Treated in Part A/B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	13	35	
Units: participants				
Any TEAEs	18	13	34	
SAEs	9	7	20	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 5 years	
Adverse event reporting additional description:	
The Open-label population included participants who received at least 1 dose of adrabetadex during Part C.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Treatment Naive
Reporting group description:	
Treatment-naive participants received adrabetadex 900 milligrams (mg) administered intrathecal (IT) via lumbar puncture (LP) infusion every 2 weeks until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	
Reporting group title	Previously Treated in Phase I
Reporting group description:	
Rollover participants from Study 13-CH-0001 received adrabetadex at an amended dose and/or regimen after prior written authorization from the sponsor. The treatment was continued until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	
Reporting group title	Previously Treated in Part A/B
Reporting group description:	
Participants continuing from Part B of the study received adrabetadex 900 mg administered IT via LP infusion every 2 weeks until the investigator considered adrabetadex to no longer be beneficial to the participant, or the development program was discontinued.	

Serious adverse events	Treatment Naive	Previously Treated in Phase I	Previously Treated in Part A/B
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 18 (50.00%)	7 / 13 (53.85%)	20 / 35 (57.14%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Catheter site inflammation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	0 / 35 (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
Respiratory failure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Sleep apnoea syndrome			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mania			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional medical device removal by patient			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access complication			

subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Chorea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplegia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Encephalopathy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Headache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			

subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Paraesthesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Seizure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure cluster			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Spinal subarachnoid haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal subdural haematoma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deafness neurosensory			

subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deafness unilateral			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	4 / 35 (11.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive oesophagitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Pneumoperitoneum			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior mesenteric artery syndrome			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Drug eruption			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
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			
Back pain			
subjects affected / exposed	3 / 18 (16.67%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myosclerosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (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	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex pharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Implant site infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infectious mononucleosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis staphylococcal			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 13 (15.38%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (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
Sepsis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site cellulitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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
Urinary tract infection			

subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Food intolerance			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (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	Treatment Naive	Previously Treated in Phase I	Previously Treated in Part A/B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)	13 / 13 (100.00%)	34 / 35 (97.14%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Haematoma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	1	0	3
Hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	1	0	4
Orthostatic hypotension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1

Application site rash			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Asthenia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	2	0	2
Catheter site haematoma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Catheter site swelling			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Cyst			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Discomfort			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	8 / 18 (44.44%)	5 / 13 (38.46%)	13 / 35 (37.14%)
occurrences (all)	101	11	146
Gait disturbance			
subjects affected / exposed	2 / 18 (11.11%)	6 / 13 (46.15%)	10 / 35 (28.57%)
occurrences (all)	4	10	55
Infusion site extravasation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	1 / 35 (2.86%)
occurrences (all)	0	3	1
Oedema peripheral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
Pain			
subjects affected / exposed	1 / 18 (5.56%)	2 / 13 (15.38%)	3 / 35 (8.57%)
occurrences (all)	2	3	4

Peripheral swelling			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	6 / 18 (33.33%)	9 / 13 (69.23%)	17 / 35 (48.57%)
occurrences (all)	13	48	36
Swelling			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	2	0	4
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Drug hypersensitivity			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Seasonal allergy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	8
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	2 / 35 (5.71%)
occurrences (all)	0	2	4
Choking			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	0	1	3
Cough			
subjects affected / exposed	5 / 18 (27.78%)	6 / 13 (46.15%)	15 / 35 (42.86%)
occurrences (all)	13	15	29

Dysphonia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	2 / 18 (11.11%)	4 / 13 (30.77%)	9 / 35 (25.71%)
occurrences (all)	3	4	45
Hypoxia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Increased upper airway secretion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Interstitial lung disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Laryngeal haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Laryngeal inflammation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract congestion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Nasal congestion			
subjects affected / exposed	2 / 18 (11.11%)	3 / 13 (23.08%)	6 / 35 (17.14%)
occurrences (all)	6	3	12
Oropharyngeal pain			
subjects affected / exposed	3 / 18 (16.67%)	2 / 13 (15.38%)	2 / 35 (5.71%)
occurrences (all)	3	2	2
Pleural effusion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Pneumonia aspiration			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	0	1	2

Productive cough			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	1 / 35 (2.86%)
occurrences (all)	0	3	1
Respiratory distress			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	1	1	2
Respiratory tract oedema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 18 (5.56%)	4 / 13 (30.77%)	0 / 35 (0.00%)
occurrences (all)	1	5	0
Sinus congestion			
subjects affected / exposed	2 / 18 (11.11%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	4	1	2
Sleep apnoea syndrome			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Sneezing			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Tachypnoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Upper-airway cough syndrome			
subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Wheezing			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	2 / 35 (5.71%)
occurrences (all)	0	3	3
Psychiatric disorders			
Aggression			

subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Anxiety			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Communication disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Daydreaming			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	5	0	0
Depressed mood			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Dyssomnia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Inappropriate affect			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Initial insomnia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 18 (5.56%)	3 / 13 (23.08%)	2 / 35 (5.71%)
occurrences (all)	1	3	3
Irritability			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Restlessness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			

subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Suicidal ideation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	4
Device malfunction			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Body temperature increased			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Electroencephalogram abnormal			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Mean cell volume decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
PO2 decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	1	0	3
Prothrombin time prolonged			

subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Respiratory rate increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
SARS-CoV-2 test positive			
subjects affected / exposed	3 / 18 (16.67%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	4	0	0
Vitamin D decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Weight increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Administration related reaction			
subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	1
Ankle fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	3
Arthropod bite			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Bone contusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	2 / 18 (11.11%)	7 / 13 (53.85%)	5 / 35 (14.29%)
occurrences (all)	10	17	29
Eye contusion			

subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	1	3	2
Face injury			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	5 / 18 (27.78%)	7 / 13 (53.85%)	16 / 35 (45.71%)
occurrences (all)	37	42	117
Head injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	5 / 35 (14.29%)
occurrences (all)	0	1	10
Injection related reaction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Joint dislocation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Ligament sprain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	1	1	1
Limb injury			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	5 / 35 (14.29%)
occurrences (all)	1	1	5
Lip injury			
subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	1
Nail injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Oral contusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Post procedural complication			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Procedural complication			

subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	3	0	33
Procedural hypotension			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	10
Procedural pain			
subjects affected / exposed	3 / 18 (16.67%)	1 / 13 (7.69%)	5 / 35 (14.29%)
occurrences (all)	6	1	15
Sedation complication			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	3
Skin abrasion			
subjects affected / exposed	2 / 18 (11.11%)	6 / 13 (46.15%)	11 / 35 (31.43%)
occurrences (all)	9	15	33
Skin laceration			
subjects affected / exposed	3 / 18 (16.67%)	2 / 13 (15.38%)	4 / 35 (11.43%)
occurrences (all)	3	2	7
Soft tissue injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Stoma site pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Wound complication			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Wound dehiscence			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	1 / 18 (5.56%)	3 / 13 (23.08%)	2 / 35 (5.71%)
occurrences (all)	1	3	3

Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Ataxia			
subjects affected / exposed	9 / 18 (50.00%)	2 / 13 (15.38%)	8 / 35 (22.86%)
occurrences (all)	21	7	78
Atonic seizures			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Balance disorder			
subjects affected / exposed	1 / 18 (5.56%)	2 / 13 (15.38%)	8 / 35 (22.86%)
occurrences (all)	1	3	15
Cataplexy			
subjects affected / exposed	3 / 18 (16.67%)	1 / 13 (7.69%)	5 / 35 (14.29%)
occurrences (all)	3	1	7
Coordination abnormal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Diplegia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 18 (11.11%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	2	2	4
Dysarthria			
subjects affected / exposed	3 / 18 (16.67%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	18	3	64
Dyskinesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Dystonia			
subjects affected / exposed	2 / 18 (11.11%)	4 / 13 (30.77%)	2 / 35 (5.71%)
occurrences (all)	2	5	3
Epilepsy			

subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	5	0	3
Headache			
subjects affected / exposed	9 / 18 (50.00%)	9 / 13 (69.23%)	12 / 35 (34.29%)
occurrences (all)	29	34	79
Hypoaesthesia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	3 / 35 (8.57%)
occurrences (all)	0	1	4
Hypotonia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Intracranial pressure increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	3 / 18 (16.67%)	1 / 13 (7.69%)	4 / 35 (11.43%)
occurrences (all)	3	4	11
Memory impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	0	1	4
Migraine			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Movement disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Muscle spasticity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Petit mal epilepsy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Repetitive speech			

subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	1 / 18 (5.56%)	4 / 13 (30.77%)	8 / 35 (22.86%)
occurrences (all)	3	34	14
Seizure cluster			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	1 / 18 (5.56%)	2 / 13 (15.38%)	0 / 35 (0.00%)
occurrences (all)	1	2	0
Tremor			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	1	1	1
Visual field defect			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	2
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Deafness neurosensory			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Ear pain			

subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	3 / 35 (8.57%)
occurrences (all)	0	2	3
External ear inflammation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Hypoacusis			
subjects affected / exposed	9 / 18 (50.00%)	4 / 13 (30.77%)	9 / 35 (25.71%)
occurrences (all)	20	7	12
Neurosensory hypoacusis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Otorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	6 / 18 (33.33%)	2 / 13 (15.38%)	5 / 35 (14.29%)
occurrences (all)	72	5	5
Vestibular disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Eye pruritus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Eye swelling			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Periorbital oedema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	1	0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 18 (22.22%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	5	1	2
Anal incontinence			
subjects affected / exposed	2 / 18 (11.11%)	2 / 13 (15.38%)	2 / 35 (5.71%)
occurrences (all)	5	10	6
Constipation			
subjects affected / exposed	3 / 18 (16.67%)	2 / 13 (15.38%)	9 / 35 (25.71%)
occurrences (all)	3	2	15
Dental caries			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	9 / 18 (50.00%)	6 / 13 (46.15%)	14 / 35 (40.00%)
occurrences (all)	19	14	28
Dry mouth			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	4 / 18 (22.22%)	6 / 13 (46.15%)	6 / 35 (17.14%)
occurrences (all)	4	6	10
Faeces soft			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Gastrointestinal disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Malpositioned teeth			

subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Mouth haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	4 / 18 (22.22%)	4 / 13 (30.77%)	6 / 35 (17.14%)
occurrences (all)	6	13	10
Oral disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Retained deciduous tooth			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Retching			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Salivary hypersecretion			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Toothache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	12 / 18 (66.67%)	9 / 13 (69.23%)	16 / 35 (45.71%)
occurrences (all)	26	24	25
Hepatobiliary disorders			
Hepatosplenomegaly			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Decubitus ulcer			

subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Dermatitis contact			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	1
Erythema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Excessive granulation tissue			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
Ingrowing nail			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	1	1	1
Ingrown hair			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Papule			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	1 / 18 (5.56%)	3 / 13 (23.08%)	3 / 35 (8.57%)
occurrences (all)	1	4	5
Rash maculo-papular			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	1	1	1
Rosacea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Skin irritation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Skin lesion			

subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	1
Skin mass			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Skin striae			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Haematuria			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Incontinence			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Micturition urgency			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Nephrolithiasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Proteinuria			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Urinary incontinence			
subjects affected / exposed	1 / 18 (5.56%)	2 / 13 (15.38%)	2 / 35 (5.71%)
occurrences (all)	1	9	4

Urinary retention			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Urine abnormality			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Perineal rash			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Allergic respiratory symptom			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Apnoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 18 (11.11%)	2 / 13 (15.38%)	3 / 35 (8.57%)
occurrences (all)	4	2	3
Back pain			
subjects affected / exposed	8 / 18 (44.44%)	9 / 13 (69.23%)	18 / 35 (51.43%)
occurrences (all)	36	74	142
Coccydynia			
subjects affected / exposed	0 / 18 (0.00%)	4 / 13 (30.77%)	1 / 35 (2.86%)
occurrences (all)	0	14	1
Foot deformity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Haemarthrosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Mobility decreased			

subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	5
Muscular weakness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	2 / 35 (5.71%)
occurrences (all)	0	16	5
Musculoskeletal discomfort			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal pain			
subjects affected / exposed	2 / 18 (11.11%)	3 / 13 (23.08%)	1 / 35 (2.86%)
occurrences (all)	18	10	1
Musculoskeletal stiffness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Myositis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 18 (5.56%)	2 / 13 (15.38%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Pain in extremity			
subjects affected / exposed	6 / 18 (33.33%)	3 / 13 (23.08%)	7 / 35 (20.00%)
occurrences (all)	7	7	12
Plantar fasciitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Rotator cuff syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Scoliosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Abscess limb			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Bronchitis			
subjects affected / exposed	1 / 18 (5.56%)	3 / 13 (23.08%)	0 / 35 (0.00%)
occurrences (all)	1	3	0
COVID-19			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Conjunctivitis			
subjects affected / exposed	1 / 18 (5.56%)	3 / 13 (23.08%)	2 / 35 (5.71%)
occurrences (all)	1	4	3
Cystitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 18 (0.00%)	3 / 13 (23.08%)	2 / 35 (5.71%)
occurrences (all)	0	3	2
Folliculitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	2 / 18 (11.11%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
Gastroenteritis viral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Genital infection fungal			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0

Gingivitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Influenza			
subjects affected / exposed	3 / 18 (16.67%)	3 / 13 (23.08%)	0 / 35 (0.00%)
occurrences (all)	3	5	0
Laryngitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 18 (16.67%)	3 / 13 (23.08%)	7 / 35 (20.00%)
occurrences (all)	10	6	13
Oral herpes			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Otitis externa			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Otitis media			
subjects affected / exposed	1 / 18 (5.56%)	3 / 13 (23.08%)	1 / 35 (2.86%)
occurrences (all)	2	6	1
Otitis media acute			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Pharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Pharyngitis streptococcal			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	0 / 35 (0.00%)
occurrences (all)	0	4	0

Pilonidal cyst			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	4 / 13 (30.77%)	1 / 35 (2.86%)
occurrences (all)	3	4	1
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	2
Rhinitis			
subjects affected / exposed	3 / 18 (16.67%)	0 / 13 (0.00%)	7 / 35 (20.00%)
occurrences (all)	4	0	7
Sinusitis			
subjects affected / exposed	0 / 18 (0.00%)	3 / 13 (23.08%)	2 / 35 (5.71%)
occurrences (all)	0	4	3
Skin infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Tonsillitis			
subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	1
Tooth infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	11 / 18 (61.11%)	7 / 13 (53.85%)	10 / 35 (28.57%)
occurrences (all)	34	27	24
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	2 / 13 (15.38%)	0 / 35 (0.00%)
occurrences (all)	1	3	0
Varicella			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0

Viral infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Polydipsia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Dehydration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Iron deficiency			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 35 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2019	The following major changes were made to the protocol: • Incorporation of Administrative Letter 4 (01 July 2019): The protocol states that participants who transition into Part C would receive treatment with adrabetadex for up to 3.5 years or until the investigator considered adrabetadex to no longer be beneficial to the participant, adrabetadex received marketing authorization, or the development program was discontinued". Although participants may have discontinued upon reaching 3.5 years of treatment, the adrabetadex program was continuing. As this milestone was reached, the reasons for ending participant participation were: − The Investigator considered adrabetadex to no longer be beneficial to the participant. − Adrabetadex received marketing authorization. − The development program was discontinued. • For all participants that reached Week 156 in Part C and were continuing in the study, sites were to follow the same general schedule as listed in in the protocol. A new table (for Beyond Week 182 Visit Number 92) was added and subsequent tables were renumbered. Additional follow-up visits were added for participants who terminated early in Part C; these were 2, 12, and 24 weeks after last dose of study drug. The follow-up visits used the same procedures as listed in protocol in addition to AEs collection and audiologic testing. Medical monitor specifics were removed and referenced to the Study Manual. • In Part C, an independent data monitoring committee (DMC) was to be re-convened to monitor safety on an ongoing basis. Details of the re-convened independent DMC constituency and remit can be found in the DMC charter.
10 October 2019	The following major change was made to the protocol: For participants who experienced an increase in hearing loss from their baseline evaluation, information on unscheduled audiologic evaluation visits was added.
10 February 2021	The following major changes were made to the protocol: • Auditory brainstem response testing was removed, as this procedure often required sedation and the risks were outweighed by any potential benefit. • Efficacy assessments (NPC-SS, Clinician CGIC) and self-reported outcomes (EuroQol 5 Dimension, 3-Level [EQ-FD-3L] questionnaire) would not be collected in order to decrease participant burden. Sections regarding the efficacy evaluations were deleted. • The sponsor had made a determination of a negative benefit/risk balance for adrabetadex. Participants in this study were to be allowed to continue treatment until 20 October 2021 to allow time to start alternative treatment unless there were additional time restrictions mandated by an Institutional Review Board (IRB)/Ethics Committee or health authority. Following the last dose of adrabetadex, participants would be asked to return to the clinic for a follow-up safety visit. • Collection of cerebrospinal fluid (CSF) samples for trough 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) concentrations would not be done. • The Schedule of Assessments was updated to align with the changes noted

23 June 2021	The following major changes were made to the protocol: • For participants continuing in the study after 21 June 2021, the investigator had to assess whether the participant was benefiting from treatment with intrathecal adrabetadex. • For those participants who appeared to benefit from treatment, the investigator must have reviewed with them the risks associated with adrabetadex, including hearing loss, and the data from the randomized, controlled trial that demonstrated no significant differences between participants treated with adrabetadex and sham-treated participants on any efficacy measures. • After 21 June 2021, participants must have been discontinued from the study if the investigator either did not consider them to be benefiting from treatment and/or they did not understand the risks associated with adrabetadex, including hearing loss. • This discussion was to be documented in the participant's medical record and only those participants (or legally authorized representative) who demonstrated an understanding of the risk/benefit of adrabetadex treatment were to be permitted to continue in the study.

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.

The development program for adrabetadex was discontinued and Part C of the study was terminated by the Sponsor.

Notes: