Clinical trial results:
A Multi-center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Effects of Intra-Erythrocyte Dexamethasone Sodium Phosphate on Neurological Symptoms in Patients with Ataxia Telangiectasia

Summary

EudraCT number	2015-005241-31
Trial protocol	DE BE NO ES PL IT
Global end of trial date	13 May 2021

Results information

Result version number	v1 (current)
This version publication date	24 March 2024
First version publication date	24 March 2024

Trial information

Trial identification

Sponsor protocol code	IEDAT-02-2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02770807
WHO universal trial number (UTN)	-
Other trial identifiers	US IND: 115929

Notes:

Sponsors

Sponsor organisation name	EryDel S.p.A.
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2021
Global end of trial reached?	Yes
Global end of trial date	13 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Initial Double-Blind Treatment Period (0 to 6 Months)
Evaluate the effect of EryDex at two dose levels (low dose and high dose DSP/infusion), compared to placebo, on central nervous system (CNS) symptoms measured by the change in the Modified International Cooperative Ataxia Rating Scale (mICARS) from baseline to Month 6 (Visit 9) in patients with ataxia telangiectasia (A-T).

Extension Treatment Period (6-12 Months):
Evaluate the efficacy of EryDex at two dose levels (low dose and high dose DSP/infusion) compared to placebo, in treating CNS symptoms in A-T patients during longer-term treatment (up to 12 months), as measured by the mICARS.

Protection of trial subjects:

The study was conducted under the provision of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator:

This was a multi-center, one-year, randomized, prospective, double-blind, placebo-controlled, phase III study.
This study was divided into three periods: Screening (Days -30 to -1), 6-month Initial Treatment Period (Months 1-6; Visits 1-9), and 6-month Extension Treatment Period (Months 7-12; Visits 10-15).
A total of 175 patients (pts), of the 180 planned, met all selection criteria at baseline, and were randomized in a 1:1:1 fashion to one of the two EDS-EP dose levels or placebo.
These pts were randomly assigned to receive one of the two doses of EDS-EP or placebo, as follows:
• Group 1: EDS-EP dose range of ~5-10 mg DSP/infusion (low dose), 59 pts
• Group 2: EDS-EP dose range of ~14-22 mg DSP/infusion (high dose), 57 pts
• Group 3: Placebo EDS infusion, 59 pts
The initial 6-month treatment period was considered complete when the endpoint assessment (at Visit 9/Month 6 or at early discontinuation) was performed for all pts.
All pts who completed the assessments over the initial 6 months were eligible to continue in an additional 6-month, double-blind, placebo-controlled extension, designed to collect infos on the longer-term safety and efficacy of the trial treatments.
Following completion of the 6-month Initial Treatment Period, patients that met all entry criteria were re-randomized and treated as follows:
• pts originally randomized to one of the two dose levels of EryDex (low or high dose; Groups 1 or 2) continued in the same treatment arm.
• Pts originally randomized to the Placebo were re-allocated as defined at the initial randomization in equal proportions (1:1) and received either the EryDex low dose or high dose as follows:
• After 6 months, 1/3 of the placebo pts were switched to treatment with EryDex, as described above.
• After 9 months, another third of the placebo pts were switched to treatment with EryDex, as described above.
At 12 months, all remaining placebo pts were eligible to switch to open-label treatment with Erydex as above

Actual start date of recruitment	02 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Tunisia: 8
Country: Number of subjects enrolled	India: 66
Worldwide total number of subjects	175
EEA total number of subjects	63

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)	141
Adolescents (12-17 years)	28
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

176 patients were randomized, and 175 patients received study drug (Safety Population or ITT). There were 164 patients in the mITT and 107 patients in the PP population. Of the 164 patients in the mITT, 54 were randomized to placebo, 56 to low dose, and 54 to high dose EryDex.

Pre-assignment

Screening details:

Patients (pts) were randomly assigned to one of the 3 treatment groups (1:1:1). After 6 months of treatment, one third of the placebo pts were switched to treatment with EryDex low dose or high dose. After 9 months, another third of the placebo pts were switched to treatment with EryDex low or high dose.

Period 1

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

Blinding implementation details:

This was a randomized, double-blind study; therefore, the Sponsor, Investigator, site staff, and patients were not aware of the treatment assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	EryDex Low Dose DSP (SAF)

Arm description:

EDS-EP dose range of ~5-10 mg DSP/infusion. This study treatment was to be administered by IV infusion, once per month, for 12 consecutive months (6 months Initial Treatment Period + 6 months Extension Treatment Period).
Before the study treatment, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).

Arm type	Experimental
Investigational medicinal product name	EryDex Low dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Patients were treated with EryDex as indicated in the arm description.

Arm title	EryDex High Dose DSP (SAF)

Arm description:

EDS-EP dose range of ~14-22 mg DSP/infusion.
Before starting the study treatment, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).

Arm type	Experimental

Investigational medicinal product name	EryDex High dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Patients were treated with EryDex prepared as described in the arm description.

Arm title	Pooled Placebo (SAF)

Arm description:

Patients were treated with EDS processed autologous erythrocytes using a placebo solution (5 mL of 0.372% sodium chloride [NaCl] solution), plus 11 mL sterile water for injection in the same syringe, for a total of 16 mL.
Before starting placebo, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).

Arm type	Placebo
Investigational medicinal product name	Placebo Comparator
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Placebo was to be administered by IV infusion, once per month, for 12 consecutive months (6 months Initial Treatment Period + 6 months Extension Treatment Period).

Number of subjects in period 1	EryDex Low Dose DSP (SAF)	EryDex High Dose DSP (SAF)	Pooled Placebo (SAF)
Started	59	57	59
Completed	34	38	36
Not completed	25	19	23
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	7	3	4
Physician decision	-	-	1
Covid-related Treatment/Visit Delay	15	13	17
Adverse event, non-fatal	3	3	-

Baseline characteristics

Reporting groups	
Reporting group title	EryDex Low Dose DSP (SAF)
Reporting group description:	
EDS-EP dose range of ~5-10 mg DSP/infusion. This study treatment was to be administered by IV infusion, once per month, for 12 consecutive months (6 months Initial Treatment Period + 6 months Extension Treatment Period). Before the study treatment, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).	
Reporting group title	EryDex High Dose DSP (SAF)
Reporting group description:	
EDS-EP dose range of ~14-22 mg DSP/infusion. Before starting the study treatment, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).	
Reporting group title	Pooled Placebo (SAF)
Reporting group description:	
Patients were treated with EDS processed autologous erythrocytes using a placebo solution (5 mL of 0.372% sodium chloride [NaCl] solution), plus 11 mL sterile water for injection in the same syringe, for a total of 16 mL. Before starting placebo, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).	

Reporting group values	EryDex Low Dose DSP (SAF)	EryDex High Dose DSP (SAF)	Pooled Placebo (SAF)
Number of subjects	59	57	59
Age categorical			
The Safety Population (SAF), which consisted of all patients who received any amount of randomized treatment (also referred to as the ITT).			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	50	47	44
Adolescents (12-17 years)	7	8	13
Adults (18-64 years)	2	2	2
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	9.5	10.2	10.3
standard deviation	± 3.16	± 4.86	± 4.02
Gender categorical			
Units: Subjects			
Female	30	30	30
Male	29	27	29

Reporting group values	Total		
Number of subjects	175		

Age categorical			
The Safety Population (SAF), which consisted of all patients who received any amount of randomized treatment (also referred to as the ITT).			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	141		
Adolescents (12-17 years)	28		
Adults (18-64 years)	6		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	90		
Male	85		

Subject analysis sets

Subject analysis set title	EryDex Low Dose DSP - mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intention to Treat population - mITT: all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment of the primary efficacy variable.

Subject analysis set title	EryDex High Dose DSP - mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intention to Treat population - mITT: all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment of the primary efficacy variable.

Subject analysis set title	Pooled Placebo - mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intention to Treat population - mITT: all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment of the primary efficacy variable.

Reporting group values	EryDex Low Dose DSP - mITT	EryDex High Dose DSP - mITT	Pooled Placebo - mITT
Number of subjects	56	54	54
Age categorical			
The Safety Population (SAF), which consisted of all patients who received any amount of randomized treatment (also referred to as the ITT).			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	9.6	10.4	10.3
standard deviation	± 3.22	± 4.96	± 4.18
Gender categorical Units: Subjects			
Female	27	26	26
Male	29	28	28

End points

End points reporting groups

Reporting group title	EryDex Low Dose DSP (SAF)

Reporting group description:

EDS-EP dose range of ~5-10 mg DSP/infusion. This study treatment was to be administered by IV infusion, once per month, for 12 consecutive months (6 months Initial Treatment Period + 6 months Extension Treatment Period).
Before the study treatment, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).

Reporting group title	EryDex High Dose DSP (SAF)

Reporting group description:

EDS-EP dose range of ~14-22 mg DSP/infusion.
Before starting the study treatment, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).

Reporting group title	Pooled Placebo (SAF)

Reporting group description:

Patients were treated with EDS processed autologous erythrocytes using a placebo solution (5 mL of 0.372% sodium chloride [NaCl] solution), plus 11 mL sterile water for injection in the same syringe, for a total of 16 mL.
Before starting placebo, each patient underwent a 30-day Screening Period, during which any previous treatments with other corticosteroid compounds were withdrawn (washout from previous treatment).

Subject analysis set title	EryDex Low Dose DSP - mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intention to Treat population - mITT: all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment of the primary efficacy variable.

Subject analysis set title	EryDex High Dose DSP - mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intention to Treat population - mITT: all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment of the primary efficacy variable.

Subject analysis set title	Pooled Placebo - mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intention to Treat population - mITT: all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment of the primary efficacy variable.

Primary: Change from baseline in Modified International Cooperative Ataxia Rating Scale (mICARS)

End point title	Change from baseline in Modified International Cooperative Ataxia Rating Scale (mICARS)

End point description:

The International Cooperative Ataxia Rating Scale (ICARS) was an assessment of the degree of impairment in patients with cerebellar ataxia and was administered in its entirety; however, the primary efficacy assessment was based on the modified (m)ICARS, which excluded the Oculomotor domain (items 17 to 19) and items 8 to 12 of the Kinetic Functions domain of the ICARS.
The mICARS was a 54 points maximum score (min 0) questionnaire divided into 3 sections:
• Posture and Gait Disturbance section-7 items (min score 0, max score 34)
• Kinetic Function-2 items (min score 0, max score 12)
• Speech Disorder- 2 items (min score 0, max score 8).
The assessment was designed to be completed within 30 minutes, and higher scores - both for total and subscores - indicate a higher level of disease impairment. The subscores were added to give the total score.

End point type	Primary
End point timeframe: to Month 6 (Visit 9)	

End point values	EryDex Low Dose DSP - mITT	EryDex High Dose DSP - mITT	Pooled Placebo - mITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	56	54	54	
Units: Score on a scale				
arithmetic mean (standard deviation)	0.8 (± 3.56)	1.0 (± 3.32)	2.3 (± 5.03)	

Statistical analyses

Statistical analysis title	EryDex Low Dose DSP - mITT, Placebo - mITT
Statistical analysis description: Least squares means, and p-values are derived from a mixed model repeated measures analysis with baseline modified ICARS value as covariate and the fixed effects of treatment, age, sex, region and visit and the interaction term treatment-by-visit.	
Comparison groups	EryDex Low Dose DSP - mITT v Pooled Placebo - mITT
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0847
Method	Mixed models analysis
Parameter estimate	Last squares mean difference
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.932
upper limit	0.19

Statistical analysis title	EryDex High Dose DSP - mITT, Placebo - mITT
Statistical analysis description: Least squares means, and p-values are derived from a mixed model repeated measures analysis with baseline modified ICARS value as covariate and the fixed effects of treatment, age, sex, region and visit and the interaction term treatment-by-visit.	
Comparison groups	EryDex High Dose DSP - mITT v Pooled Placebo - mITT
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0765
Method	Mixed models analysis
Parameter estimate	Last squares mean difference
Point estimate	-1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.957
upper limit	0.152

Secondary: Number of Patients With Improving, Stable or Worsening Score Using a Clinical Global Impression of Change (CGI-C)

End point title	Number of Patients With Improving, Stable or Worsening Score Using a Clinical Global Impression of Change (CGI-C)

End point description:

The CGI-C scale assesses the change in the patient's clinical status from baseline using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. Clinicians were required to conduct a full clinical interview and examination of the patient.
The interview and examination assessed various aspects of the patient's appearance (grooming, evidence of falls, etc.), ataxia, cognition (orientation, calculation ability, language, ability to follow commands, memory, etc.), apraxia, dysarthria, extrapyramidal motor symptoms, activities of daily living, and mood. The higher the score the worse the outcome.

End point type	Secondary

End point timeframe:

to Month 6 (Visit 9)

End point values	EryDex Low Dose DSP - mITT	EryDex High Dose DSP - mITT	Pooled Placebo - mITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	56	54	54	
Units: Number of patients				
Improvement (Scores 1-3)	19	27	19	
Stable or Worsening (Scores 4-7)	37	27	35	

Statistical analyses

Statistical analysis title	EryDex Low Dose DSP - mITT, Placebo - mITT
Comparison groups	EryDex Low Dose DSP - mITT v Pooled Placebo - mITT
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.8919
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.946
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.426
upper limit	2.099

Notes:

[1] - Logistic regression modeling (0/1), where 0 = No change or worsening and 1= improvement, with age (at 2 levels: <10 years, ≥10 years), sex, treatment, region as fixed effects.

Statistical analysis title	EryDex High Dose DSP - mITT, Placebo - mITT
Comparison groups	EryDex High Dose DSP - mITT v Pooled Placebo - mITT
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.1255
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.848
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.842
upper limit	4.053

Notes:

[2] - Logistic regression modeling (0/1), where 0 = No change or worsening and 1= improvement, with age (at 2 levels: <10 years, ≥10 years), sex, treatment, and region as fixed effects.

Secondary: Number of Patients With None to Severe (0 to 4) Scores in Clinical Global Impression of Severity (CGI-S)-Structured of Neurological Symptoms of AT

End point title	Number of Patients With None to Severe (0 to 4) Scores in Clinical Global Impression of Severity (CGI-S)-Structured of Neurological Symptoms of AT

End point description:

The CGI-S scale measures global severity of illness at a given point in time, and is usually rated on a 7-point, Likert-type scale ranging from 1 (normal, not ill at all) to 7 (among the most extremely ill patients). No version of the CGI-S exists which has been specifically adapted for use in patients with A-T; therefore, a 5-point version was developed that considered the severity of the following symptoms of A-T: ataxia (walking), dysarthria, dysmetria, extrapyramidal symptoms (chorea, myoclonus, dystonia, and tremor), and eye movements. Ratings of none (0), mild (1), moderate (2), severe (3), and very severe (4) were selected based on the level of symptomatology. The higher the score the worse the outcome.

End point type	Secondary

End point timeframe:

to Visit 9 (Month 6)

End point values	EryDex Low Dose DSP - mITT	EryDex High Dose DSP - mITT	Pooled Placebo - mITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	56	54	54	
Units: Number of patients				
CGI-S Score - 0	0	0	0	
CGI-S Score - 1	15	16	17	
CGI-S Score - 2	29	26	24	
CGI-S Score - 3	12	12	13	
CGI-S Score - 4	0	0	0	

Statistical analyses

Statistical analysis title	EryDex Low Dose DSP - mITT, Placebo - mITT

Statistical analysis description:

Odds ratio, confidence limits, and p-value derived using a proportional odds ordinal logistic regression analysis, with age (at 2 levels: <10 years, ≥10 years), sex, treatment, region, visit, baseline CGI-S score, and treatment-by-visit interaction as fixed effects.

Comparison groups	EryDex Low Dose DSP - mITT v Pooled Placebo - mITT
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4583
Method	Ordinal Logistic Regression Analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.369
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.597
upper limit	3.144

Statistical analysis title	EryDex High Dose DSP - mITT, Placebo - mITT

Statistical analysis description:

Odds ratio, confidence limits, and p-value derived using a proportional odds ordinal logistic regression analysis, with age (at 2 levels: <10 years, ≥10 years), sex, treatment, region, visit, baseline CGI-S score, and treatment-by- visit interaction as fixed effects.

Comparison groups	EryDex High Dose DSP - mITT v Pooled Placebo - mITT
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4585
Method	Ordinal Logistic Regression Analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.371
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.595
upper limit	3.16

Secondary: Change from baseline of Vineland Adaptive Behavior Scale (VABS-II)

scores - Last Observation Carried Forward (LOCF)	
End point title	Change from baseline of Vineland Adaptive Behavior Scale (VABS-II) scores - Last Observation Carried Forward (LOCF)

End point description:

VABS-II was a questionnaire to assess adaptive behavior. It contained 4 domains each with 2-3 subdomains, every subdomain contained various items (questions):
A) communication (receptive, expressive, written)
B) daily living skills (personal, domestic, community)
C) socialization (interpersonal relationships, play and leisure time, coping skills)
D) motor skills (gross motor, fine motor).
The expanded version of the VABS consisted of 540 items, 261 of which were used in this study.
The possible score for each item was from 0 to 4 based on whether the patient performed that activity "never", "rarely", "sometimes", "often" or "almost always".
At the end of each domain section, a total score (the sum of the score for each item) was calculated.
Range for domain A: 0-572. Range for domain B: 0-800. Domain C: 0-580. Domain D: 0-424. A grand total score (sum of A+B+C+D scores) was provided.
The lower the score the higher the disability at all levels (domains, subdomains, total)

End point type	Secondary

End point timeframe:

to Visit 9 (Month 6)

End point values	EryDex Low Dose DSP - mITT	EryDex High Dose DSP - mITT	Pooled Placebo - mITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	56	52	52	
Units: Score on a scale				
arithmetic mean (standard deviation)	42.6 (± 125.95)	-26.5 (± 214.52)	573.5 (± 200.37)	

Statistical analyses

Statistical analysis title	EryDex Low Dose DSP - mITT, Placebo - mITT
Comparison groups	EryDex Low Dose DSP - mITT v Pooled Placebo - mITT
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.7029
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	-13.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.261
upper limit	55.601

Notes:

[3] - Least squares mean difference, associated statistics, and p-values derived using ANCOVA, with age (at 2 levels: <10 years, >=10 years), sex, treatment, region, and baseline VABS score as fixed effects.

Statistical analysis title	EryDex High Dose DSP - mITT, Placebo - mITT

Comparison groups	EryDex High Dose DSP - mITT v Pooled Placebo - mITT
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0328
Method	ANCOVA
Parameter estimate	Last squares mean difference
Point estimate	-77.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-148.201
upper limit	-6.421

Notes:

[4] - Least squares mean difference, associated statistics, and p-values derived using ANCOVA, with age (at 2 levels: <10 years, >=10 years), sex, treatment, region, and baseline VABS score as fixed effects.

Secondary: Number of Patients With at Least One Treatment-Emergent Adverse Event (TEAE) up to Month 6

End point title	Number of Patients With at Least One Treatment-Emergent Adverse Event (TEAE) up to Month 6

End point description:

TEAE = Treatment Emergent Adverse Events were any AEs started on or after the day of the first infusion through the day just prior to the day of the Visit 9 ("Month 6") infusion, or <=60 days after last dose if the subject never continued past this period.

End point type	Secondary

End point timeframe:

to Visit 9 (Month 6)

End point values	EryDex Low Dose DSP (SAF)	EryDex High Dose DSP (SAF)	Pooled Placebo (SAF)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59[5]	57[6]	59[7]	
Units: Number of patients				
Patients With Pre- treatment AE	14	16	14	
Patients With Any TEAE	43	47	43	
Patients With Any Treatment-related TEAE	15	21	15	
Patients With Any Serious TEAE	6	7	7	
Patients With Any Serious Treatment-related TEAE	0	1	0	
Patients With Any TEAE Leading to Discontinuation	0	2	0	
Patients With Any TEAE Leading to Death	0	0	0	

Notes:

[5] - Safety Population (SAF): all patients who received any amount of randomized treatment

[6] - Safety Population (SAF): all patients who received any amount of randomized treatment

[7] - Safety Population (SAF): all patients who received any amount of randomized treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With at Least One Treatment-Emergent Adverse Event (TEAE) up to month 12

End point title	Number of Patients With at Least One Treatment-Emergent Adverse Event (TEAE) up to month 12

End point description:

TEAE = Treatment Emergent Adverse Events were any AEs started on or after the day of the first infusion through the day just prior to the day of the Visit 15 (“Month 12”) infusion.
Please note that placebo patients who switched to EryDex treatment at 6 and 9 months were not added to the Extension Treatment Period safety data, so that the results reported are for those patients who remained under placebo from the start of the study (N=19).

End point type	Secondary

End point timeframe:

to Visit 15 (Month 12)

End point values	EryDex Low Dose DSP (SAF)	EryDex High Dose DSP (SAF)	Pooled Placebo (SAF)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59[8]	57[9]	19[10]	
Units: Number of patients				
Patients With Any TEAE	45	50	15	
Patients With Any Treatment-related TEAE	19	25	5	
Patients With Any Serious TEAE	8	9	4	
Patients With Any Serious Treatment-related TEAE	1	1	1	
Patients With Any TEAE Leading to Discontinuation	1	2	0	
Patients With Any TEAE Leading to Death	0	0	0	

Notes:

[8] - Safety Population: all patients who received any amount of randomized treatment

[9] - Safety Population: all patients who received any amount of randomized treatment

[10] - Non-switch placebo: Placebo patients who didn't switched to EryDex treatment at 6 and 9 months.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were reported up to the end of the Extension Treatment Period (Month 12).

Adverse event reporting additional description:

TEAEs included all AEs with an onset date on or after the start of the first infusion through 60 days after the last dose. A patient with more than 1 event with the same system organ class is counted once at that level.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	EryDex Low Dose DSP - SAF

Reporting group description:

Safety Population (SAF): all patients who received any amount of randomized treatment (also referred to as the ITT population).

Reporting group title	EryDex High Dose DSP - SAF

Reporting group description:

Safety Population (SAF): all patients who received any amount of randomized treatment (also referred to as the ITT population).

Reporting group title	Non-switch Placebo - SAF

Reporting group description:

Safety Population (SAF): all patients who received any amount of randomized treatment (also referred to as the ITT population). Placebo patients who switched to EryDex treatment at 6 and 9 months were not added to the Extension Treatment Period safety data so that the results reported are for those patients who remained on placebo from the start of the study (N=19).

Reporting group title	Placebo Patients Switch to Low Dose - Month 6 - SAF

Reporting group description:

Patients originally randomized to the Placebo group (Pooled Placebo) re-allocated in EryDex low dose at Month 6 - Visit 9. (N=9)

Reporting group title	Placebo Patients Switch to High Dose - Month 6 - SAF

Reporting group description:

Patients originally randomized to the Placebo group (Pooled Placebo) re-allocated in EryDex High dose at Month 6 - Visit 9. (N=9)

Reporting group title	Placebo patients switch to Low Dose - Month 9 - SAF

Reporting group description:

Patients originally randomized to the Placebo group (Pooled Placebo) re-allocated in EryDex low dose at Month 9 - Visit 12 . (N=11)

Reporting group title	Placebo patients switch to High Dose - Month 9 - SAF

Reporting group description:

Patients originally randomized to the Placebo group (Pooled Placebo) re-allocated in EryDex low dose at Month 9 - Visit 12. (N=11)

Serious adverse events	EryDex Low Dose DSP - SAF	EryDex High Dose DSP - SAF	Non-switch Placebo - SAF
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 59 (13.56%)	9 / 57 (15.79%)	4 / 19 (21.05%)
number of deaths (all causes)	0	0	1
number of deaths resulting from	0	0	0

adverse events			
Investigations			
Bacterial test positive			
subjects affected / exposed	4 / 59 (6.78%)	6 / 57 (10.53%)	3 / 19 (15.79%)
occurrences causally related to treatment / all	2 / 4	0 / 6	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	0 / 19 (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
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	0 / 19 (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
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dystonia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	0 / 19 (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			
Anemia			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	0 / 19 (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
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	0 / 19 (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			
Vomiting			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	0 / 19 (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
Musculoskeletal and connective tissue disorders			
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
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			
Herpes zoster			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	0 / 19 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	0 / 19 (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			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	0 / 19 (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
Sepsis			

subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	0 / 19 (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

Serious adverse events	Placebo Patients Switch to Low Dose - Month 6 - SAF	Placebo Patients Switch to High Dose - Month 6 - SAF	Placebo patients switch to Low Dose - Month 9 - SAF
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	1 / 11 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Bacterial test positive			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dystonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	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	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (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			
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo patients switch to High Dose - Month 9 - SAF		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Bacterial test positive			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Dystonia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lower respiratory tract infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	EryDex Low Dose DSP - SAF	EryDex High Dose DSP - SAF	Non-switch Placebo - SAF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 59 (76.27%)	50 / 57 (87.72%)	15 / 19 (78.95%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	1 / 19 (5.26%)
occurrences (all)	0	3	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Extravasation			

subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	4 / 59 (6.78%)	3 / 57 (5.26%)	0 / 19 (0.00%)
occurrences (all)	4	3	0
Malaise			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	15 / 59 (25.42%)	19 / 57 (33.33%)	3 / 19 (15.79%)
occurrences (all)	15	19	3
Swelling			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Gynaecomastia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	10 / 59 (16.95%)	13 / 57 (22.81%)	6 / 19 (31.58%)
occurrences (all)	10	13	6
Epistaxis			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Nasal congestion			

subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Oropharyngeal pain			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Productive cough			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	6 / 59 (10.17%)	4 / 57 (7.02%)	3 / 19 (15.79%)
occurrences (all)	6	4	3
Psychiatric disorders			
Affect lability			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Emotional poverty			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Enuresis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	3	0	1
Mood altered			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Bacterial test positive			
subjects affected / exposed	10 / 59 (16.95%)	10 / 57 (17.54%)	4 / 19 (21.05%)
occurrences (all)	10	10	4
Blood bilirubin increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood iron decreased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood potassium increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Bone density decreased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Chest expansion decreased			

subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Platelet count increased			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Respiratory rate increased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Vitamin D decreased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Fall			

subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	3	0	1
Incision site haemorrhage			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Scar			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin laceration			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Talipes			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Balance disorder			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Decreased vibratory sense			

subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Dystonia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	8 / 59 (13.56%)	5 / 57 (8.77%)	2 / 19 (10.53%)
occurrences (all)	8	5	2
Lethargy			
subjects affected / exposed	1 / 59 (1.69%)	3 / 57 (5.26%)	0 / 19 (0.00%)
occurrences (all)	1	3	0
Myoclonus			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Parkinsonism			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Pineal gland cyst			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Otorrhoea			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Tympanic membrane scarring			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Eye movement disorder			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Papilloedema			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 59 (0.00%)	4 / 57 (7.02%)	1 / 19 (5.26%)
occurrences (all)	0	4	1
Abdominal pain upper			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Abnormal faeces			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Anal pruritus			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Constipation			

subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	8 / 59 (13.56%)	6 / 57 (10.53%)	5 / 19 (26.32%)
occurrences (all)	8	6	5
Dyspepsia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Enterocolitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	4 / 59 (6.78%)	4 / 57 (7.02%)	0 / 19 (0.00%)
occurrences (all)	4	4	0
Salivary hypersecretion			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Teething			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	13 / 59 (22.03%)	11 / 57 (19.30%)	3 / 19 (15.79%)
occurrences (all)	13	11	3
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Acanthosis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Cold sweat			

subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Eczema			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Erythema			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Granuloma skin			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Macule			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	3 / 59 (5.08%)	10 / 57 (17.54%)	0 / 19 (0.00%)
occurrences (all)	3	10	0
Rash papular			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Costochondritis			

subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Foot deformity			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Muscle atrophy			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 59 (0.00%)	4 / 57 (7.02%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
Scoliosis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	4 / 59 (6.78%)	2 / 57 (3.51%)	1 / 19 (5.26%)
occurrences (all)	4	2	1

Conjunctivitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Croup infectious			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	3 / 59 (5.08%)	5 / 57 (8.77%)	2 / 19 (10.53%)
occurrences (all)	3	5	2
Gastroenteritis viral			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 59 (0.00%)	4 / 57 (7.02%)	1 / 19 (5.26%)
occurrences (all)	0	4	1
Laryngitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Molluscum contagiosum			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Nasopharyngitis			
subjects affected / exposed	10 / 59 (16.95%)	11 / 57 (19.30%)	5 / 19 (26.32%)
occurrences (all)	10	11	5
Oral herpes			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Otitis externa			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	3	0	1
Sinusitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	8 / 59 (13.56%)	9 / 57 (15.79%)	1 / 19 (5.26%)
occurrences (all)	8	9	1
Urinary tract infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Varicella			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Wound infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Insulin resistance			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	6 / 59 (10.17%)	5 / 57 (8.77%)	1 / 19 (5.26%)
occurrences (all)	6	5	1

Non-serious adverse events	Placebo Patients Switch to Low Dose - Month 6 - SAF	Placebo Patients Switch to High Dose - Month 6 - SAF	Placebo patients switch to Low Dose - Month 9 - SAF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	8 / 9 (88.89%)	7 / 11 (63.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Catheter site pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Extravasation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	3 / 9 (33.33%)	2 / 9 (22.22%)	4 / 11 (36.36%)
occurrences (all)	3	2	4
Swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gynaecomastia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 9 (11.11%)	4 / 9 (44.44%)	3 / 11 (27.27%)
occurrences (all)	1	4	3

Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
Psychiatric disorders			
Affect lability			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Emotional poverty			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Enuresis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Mood altered			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Mood swings			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Bacterial test positive			
subjects affected / exposed	1 / 9 (11.11%)	2 / 9 (22.22%)	1 / 11 (9.09%)
occurrences (all)	1	2	1
Blood bilirubin increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood iron decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood potassium increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood triglycerides increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Body temperature increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Bone density decreased			

subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Chest expansion decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Low density lipoprotein increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Platelet count increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Respiratory rate increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vitamin D decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
White blood cell count increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Contusion			

subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Incision site haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Joint injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Scar			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Talipes			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Balance disorder			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Decreased vibratory sense			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dystonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Lethargy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Myoclonus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Parkinsonism			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pineal gland cyst			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0

Lymphadenopathy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Otorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tympanic membrane scarring			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye movement disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Papilloedema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Abnormal faeces			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Anal pruritus			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Enterocolitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Teething			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acanthosis			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cold sweat			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Granuloma skin			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Macule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Rash pruritic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Costochondritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Foot deformity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Muscle atrophy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Osteopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Scoliosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acarodermatitis			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Croup infectious			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Molluscum contagiosum			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Oral herpes			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Otitis externa			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Wound infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Insulin resistance			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo patients switch to High Dose - Month 9 - SAF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Hypotension			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Extravasation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Swelling			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gynaecomastia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Aphonia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Psychiatric disorders			
Affect lability			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Emotional poverty			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Enuresis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Irritability			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Mood altered			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Bacterial test positive			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Blood bilirubin increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood cholesterol increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood iron decreased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood potassium increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood triglycerides increased			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Body temperature increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Bone density decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Chest expansion decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Low density lipoprotein increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Platelet count increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Respiratory rate increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vitamin D decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural			

complications			
Arthropod sting			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Incision site haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Scar			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin laceration			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Talipes			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Ataxia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Balance disorder			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Decreased vibratory sense			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dystonia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Myoclonus			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Parkinsonism			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pineal gland cyst			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Lymphadenopathy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Ear pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Otorrhoea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Tympanic membrane scarring			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Eye movement disorder			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Papilloedema			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			

subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Abnormal faeces			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anal pruritus			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Enterocolitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Salivary hypersecretion			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Teething			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Hepatobiliary disorders			

Liver disorder subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Skin and subcutaneous tissue disorders Acanthosis subjects affected / exposed occurrences (all) Cold sweat subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Granuloma skin subjects affected / exposed occurrences (all) Macule subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash papular subjects affected / exposed occurrences (all) Rash pruritic subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0		
Renal and urinary disorders			

Pollakiuria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Costochondritis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Foot deformity			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Juvenile idiopathic arthritis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Muscle atrophy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Osteopenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Scoliosis			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Croup infectious			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Impetigo			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Laryngitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Molluscum contagiosum				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Oral herpes				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Otitis externa				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Otitis media acute				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Varicella subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Wound infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Increased appetite subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Insulin resistance subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Iron deficiency subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2015	Expected lower dose decreased from 8 to 12 mg to 5 to 10 mg DSP. Update d for mICARS to be the sole primary efficacy measure, and CGI-C updated to be a key secondary objective. Updated minimization procedure to ensure balanced groups. Added exclusion criteria for patients with renal or hepatic impairment, or who are exposed to CYP3A4 inducers/inhibitors.
01 February 2016	Clinical diagnosis update to be based on the presence of neurological signs, diagnosis confirmed by genetic tests. Updated version of QoL scale used. Additional guidelines for rater of primary and key secondary endpoints to not have access to other efficacy measures.
28 April 2016	Criterion for inclusion of women of childbearing potential was modified based on a request made during the VHP review. Monthly urine pregnancy tests were added before EryDex administration. Tanner Scale for assessment was added.
25 May 2016	Criterion for inclusion of women of childbearing potential that was modified based on a request made during the VHP review. This change was applicable for Belgium, Germany, Italy, Norway, Poland, Spain, and UK.
29 November 2016	Addition of sterility testing to the study protocol to ensure that the sterility of the product was maintained throughout the process. Consolidated exclusion criteria for women of childbearing potential for the US and the Rest of World countries. Procedures for assessment of adrenal insufficiency were added. BMD procedure modified so measurements were performed on spine and total body.
20 September 2017	Site Specific: Implemented exploratory assessment of A-T NEST at selected sites that agreed to participate.
29 September 2017	Added description of the procedure that was followed to ensure that the blind is maintained for patients continuing in the 6-month, double blind, Extension Treatment Period of the study.
13 March 2018	Implemented changes requested by the FDA, introduced to revise the study procedures to ensure sterility is maintained throughout collection of autologous blood cells, processing, administration and testing (rapid testing, gram stain and culture) of EryDex.
26 March 2018	Addition of unscheduled visits between Visit 14 and Visit 15/Month 12, to allow patients to continue treatment while the Study IEDAT-03-2015 is not yet approved by local IRB/IEC.
23 April 2018	Addition of unscheduled visits between Visit 14 and Visit 15/Month 12, to allow patients to continue treatment while the Study IEDAT-03-2015 is not yest approved by local IRB/IEC.

24 October 2018	Country Specific (Germany): Sites in Germany were not allowed to perform DXA scans given concerns regarding the risk of exposing A-T patients to ionizing radiation for assessing BMD.
11 April 2019	To consolidate in a unique document all the temporary changes that have been implemented as a result of the COVID-19 pandemic, and update of date of first patient in and last patient in, plus last patient last visit date.
16 April 2019	Removal of Rapid Microbial Staining test as it was not sensitive enough to detect contamination. Defined modification to exclusion criteria for patients >6 years with a CD4+ lymphocyte count less than 200 mm3.
24 June 2020	Included all temporary changes implemented as a result of COVID-19 pandemic including remote safety contacts, local testing of any required lab parameter and additional safety assessments.

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.

Many study centers experienced delays in activating the OLE-IEDAT study and so, for this reason, 45 patients continued treatment in the ATTeST trial in their respective randomization group longer than the original schedule.

Notes: