Clinical trial results:
Open Label Pilot Trial in patients with recent-onset T1D to evaluate the safety, diabetes status and immune response of GAD-antigen (Diamyd®) therapy administered into lymph nodes in combination with an oral vitamin D regimen

Summary

EudraCT number	2014-001417-79
Trial protocol	SE
Global end of trial date	08 October 2019

Results information

Result version number	v1 (current)
This version publication date	07 April 2020
First version publication date	07 April 2020

Trial information

Trial identification

Sponsor protocol code	DIAGNODE-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02352974
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Linköping University
Sponsor organisation address	Div of Pediatrics, Linköping, Sweden, 581 85
Public contact	Johnny Ludvigsson, Linköping University, johnny.ludvigsson@liu.se
Scientific contact	Johnny Ludvigsson, Linköping University, johnny.ludvigsson@liu.se

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	28 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2019
Global end of trial reached?	Yes
Global end of trial date	08 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Evaluate the safety of giving Diamyd directly into lymph glands in combination with an oral vitamin D regimen
- Evaluate how the above mentioned treatments influence the immune system and endogenous insulin secretion

Protection of trial subjects:

After the injection of GAD-Alum (Diamyd) at Visits 3, 4 and 5, each patient was to remain in the vicinity of the study site for the next hour, and the injection site was examined by the investigator/study nurse 1 hour post injection.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	4
Adults (18-64 years)	8
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

20 patients were screened. All 8 screening failures were due to eligibility criteria not met. 12 patients were enrolled in the main study period and 3 of them continued in the extension period.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	GAD-Alum+Vitamin D

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Diamyd
Investigational medicinal product code	
Other name	Recombinant Human Glutamic Acid Decarboxylase (rhGAD65)
Pharmaceutical forms	Injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Intralymphatic injections of GAD-alum (Diamyd®) 4 µg on Days 30, 60 and 90.

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	Calciferol
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Vitamin D per os (2 000 IU) daily for 120 days

Number of subjects in period 1	GAD-Alum+Vitamin D
Started	12
Completed	12

Period 2	
Period 2 title	Main study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	GAD-Alum+Vitamin D
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Diamyd
Investigational medicinal product code	
Other name	Recombinant Human Glutamic Acid Decarboxylase (rhGAD65)
Pharmaceutical forms	Injection
Routes of administration	Intralymphatic use
Dosage and administration details: Intralymphatic injections of GAD-alum (Diamyd®) 4 µg on Days 30, 60 and 90.	
Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	Calciferol
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use
Dosage and administration details: Vitamin D per os (2 000 IU) daily for 120 days	

Number of subjects in period 2	GAD-Alum+Vitamin D
Started	12
Completed	12

Period 3	
Period 3 title	Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	GAD-Alum+Vitamin D
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Diamyd
Investigational medicinal product code	
Other name	Recombinant Human Glutamic Acid Decarboxylase (rhGAD65)
Pharmaceutical forms	Injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Intralymphatic injections of GAD-alum (Diamyd®) 4 µg on Days 30, 60, 90 and Month 32.

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	Calciferol
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Vitamin D per os (2 000 IU) daily for 120 days after first injection and 60 days after last injection

Number of subjects in period 3[1]	GAD-Alum+Vitamin D
Started	3
Completed	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only 3 patients of the 12 continued in to the extension period.

Baseline characteristics

Reporting groups

Reporting group title	GAD-Alum+Vitamin D

Reporting group description: -

Reporting group values	GAD-Alum+Vitamin D	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	8	8	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	18.8		
standard deviation	± 4.2	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	8	8	
Weight Units: Kilo			
arithmetic mean	64		
standard deviation	± 13.6	-	
Height Units: cm			
arithmetic mean	173.8		
standard deviation	± 9.9	-	
BMI Units: kilogram(s)/square meter			
arithmetic mean	21.1		
standard deviation	± 3.8	-	
GADA Units: (U/mL)2			
arithmetic mean	4067.1		
standard deviation	± 8491.6	-	
HbA1C Units: mmol/mol			
arithmetic mean	67.17		
standard deviation	± 28.17	-	

Average insulin dose/kg/24 h Units: IU arithmetic mean standard deviation	 0.4 ± 0.2	 -	
Weighted C-peptide Units: nmol/l arithmetic mean standard deviation	 0.55 ± 0.19	 -	
90-minute C-peptide Units: nmol/L arithmetic mean standard deviation	 0.67 ± 0.19	 -	
Fasting C-peptide Units: nmol/L arithmetic mean standard deviation	 0.27 ± 0.08	 -	
IDAA1c Units: HbA1c(%)+4*insulin dose arithmetic mean standard deviation	 9.91 ± 3.10	 -	
Type 1 diabetes duration Units: days arithmetic mean standard deviation	 65.1 ± 55.1	 -	

End points

End points reporting groups

Reporting group title	GAD-Alum+Vitamin D
Reporting group description: -	
Reporting group title	GAD-Alum+Vitamin D
Reporting group description: -	
Reporting group title	GAD-Alum+Vitamin D
Reporting group description: -	

Primary: Injection site reactions month 1

End point title	Injection site reactions month 1[1]
End point description:	
End point type	Primary
End point timeframe:	
At Month 1	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a one arm study with few patients and no formal statistical analyses have been planned or performed.

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of subjects				
Erythema	0			
Oedema	0			
Haematoma	0			
Tenderness	1			
Pain	0			
Itching	0			
Other	0			

Statistical analyses

No statistical analyses for this end point

Primary: Injection site reactions month 2

End point title	Injection site reactions month 2[2]
End point description:	
End point type	Primary

End point timeframe:

At Month 2

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a one arm study with few patients and no formal statistical analyses have been planned or performed.

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of subjects				
Erythema	0			
Oedema	0			
Haematoma	0			
Tenderness	1			
Pain	0			
Itching	0			
Other	0			

Statistical analyses

No statistical analyses for this end point

Primary: Injection site reactions month 3

End point title	Injection site reactions month 3[3]

End point description:

End point type	Primary

End point timeframe:

At Month 3

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a one arm study with few patients and no formal statistical analyses have been planned or performed.

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of subjects				
Erythema	0			
Oedema	0			
Haematoma	0			
Tenderness	2			
Pain	0			
Itching	0			
Other	0			

Statistical analyses

No statistical analyses for this end point

Primary: Injection site reactions month 32

End point title	Injection site reactions month 32[4]

End point description:

End point type	Primary

End point timeframe:

At Month 32

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a one arm study with few patients and no formal statistical analyses have been planned or performed.

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Number of subjects				
Erythema	0			
Oedema	0			
Haematoma	0			
Tenderness	0			
Pain	0			
Itching	0			
Other	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in C-peptide AUC (mean 0-120 min) from baseline to month 15

End point title	Mean change in C-peptide AUC (mean 0-120 min) from baseline to month 15

End point description:

Changes from baseline

End point type	Secondary

End point timeframe:

Baseline to Month 15

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: nmol/L				
arithmetic mean (standard deviation)	-0.11 (± 0.12)	-0.10 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in C-peptide AUC (mean 0-120 min) from baseline to month 30

End point title	Mean change in C-peptide AUC (mean 0-120 min) from baseline to month 30
End point description: Change from baseline	
End point type	Secondary
End point timeframe: Baseline to month 30	

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: nmol/L				
arithmetic mean (standard deviation)	-0.22 (± 0.16)	-0.13 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in C-peptide 90 minute values from baseline to month 15

End point title	Mean change in C-peptide 90 minute values from baseline to month 15
End point description: Change from baseline	
End point type	Secondary
End point timeframe: Baseline to month 15	

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: nmol/L				
arithmetic mean (standard deviation)	-0.16 (± 0.15)	-0.20 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in C-peptide 90-minute values from baseline to month 30

End point title	Mean change in C-peptide 90-minute values from baseline to month 30
End point description: Change from baseline	
End point type	Secondary
End point timeframe: Baseline to month 30	

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: nmol/L				
arithmetic mean (standard deviation)	-0.29 (± 0.17)	-0.17 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in C-peptide 90 minute values from baseline to month 43

End point title	Mean change in C-peptide 90 minute values from baseline to month 43
End point description:	
End point type	Secondary
End point timeframe: Baseline to Month 43	

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: nmol/L				
arithmetic mean (standard deviation)	-0.16 (± 0.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in fasting C-peptide from baseline to month 15

End point title	Mean change in fasting C-peptide from baseline to month 15

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 15

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: nmol/L				
arithmetic mean (standard deviation)	-0.03 (± 0.12)	0.00 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in fasting C-peptide from baseline to month 30

End point title	Mean change in fasting C-peptide from baseline to month 30

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 30

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: nmol/L				
arithmetic mean (standard deviation)	-0.10 (± 0.12)	-0.10 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in fasting C-peptide from baseline to month 43

End point title	Mean change in fasting C-peptide from baseline to month 43

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 43

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: nmol/L				
arithmetic mean (standard deviation)	-0.07 (± 0.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in HbA1c from baseline to month 15

End point title	Mean change in HbA1c from baseline to month 15

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 15

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: mmol/mol				
arithmetic mean (standard deviation)	-14.25 (± 18.91)	-32.00 (± 27.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in HbA1c from baseline to month 30

End point title	Mean change in HbA1c from baseline to month 30

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 30

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: mmol/mol				
arithmetic mean (standard deviation)	-10.67 (± 18.67)	-31.67 (± 20.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in HbA1c from baseline to month 43

End point title	Mean change in HbA1c from baseline to month 43

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 43

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: mmol/mol				
arithmetic mean (standard deviation)	-30.67 (± 21.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: External insulin dose at baseline

End point title	External insulin dose at baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: IU/kg/day				
arithmetic mean (standard deviation)	0.36 (± 0.13)	0.35 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: External insulin dose month 15

End point title	External insulin dose month 15

End point description:

End point type	Secondary

End point timeframe:

Month 15

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: IU/kg/day				
arithmetic mean (standard deviation)	0.34 (± 0.2)	0.16 (± 0.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: External insulin dose month 30

End point title	External insulin dose month 30

End point description:

End point type	Secondary

End point timeframe:

Month 30

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: IU/kg/day				
arithmetic mean (standard deviation)	0.44 (± 0.22)	0.35 (± 0.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: External insulin dose month 43

End point title	External insulin dose month 43

End point description:

End point type	Secondary

End point timeframe:

Month 43

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: IU/kg/day				
arithmetic mean (standard deviation)	0.25 (± 0.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: IDAA1c at baseline

End point title	IDAA1c at baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: IU/kg/day				
arithmetic mean (standard deviation)	9.00 (± 1.89)	10.34 (± 3.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: IDAA1c month 15

End point title	IDAA1c month 15

End point description:

End point type	Secondary

End point timeframe:

Month 15

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: IU/kg/day				
arithmetic mean (standard deviation)	7.64 (± 0.99)	6.63 (± 0.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: IDAA1c month 30

End point title	IDAA1c month 30

End point description:

End point type	Secondary

End point timeframe:

Month 30

End point values	GAD-Alum+Vitamin D	GAD-Alum+Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	3		
Units: IU/kg/day				
arithmetic mean (standard deviation)	8.36 (± 1.28)	7.41 (± 1.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: IDAA1c month 43

End point title	IDAA1c month 43

End point description:

End point type	Secondary

End point timeframe:

Month 43

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: IU/kg/day				
arithmetic mean (standard deviation)	7.11 (± 0.93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in C-peptide AUC (mean 0-120 min) from baseline to month 43

End point title	Mean change in C-peptide AUC (mean 0-120 min) from baseline to month 43

End point description:

End point type	Secondary

End point timeframe:

Baseline to month 43

End point values	GAD-Alum+Vitamin D			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: nmol/L				
arithmetic mean (standard deviation)	-0.13 (± 0.05)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Main study period and extension	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1
Reporting groups	
Reporting group title	GAD-Alum+Vitamin D

Reporting group description: -

Serious adverse events	GAD-Alum+Vitamin D		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	GAD-Alum+Vitamin D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Injection site pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Injection site reaction subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 3		
Pyrexia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Attention deficit/hyperactivity disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Autism spectrum disorder subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Panic disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Sleep disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Investigations Hepatic enzyme increased			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fibula fracture			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Joint dislocation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eye disorders			
Retinopathy			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Bowel movement irregularity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dysphagia			

subjects affected / exposed occurrences (all) Food poisoning subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 2 / 12 (16.67%) 2 1 / 12 (8.33%) 1 2 / 12 (16.67%) 3 1 / 12 (8.33%) 2		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Ingrowing nail subjects affected / exposed occurrences (all) Skin irritation subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Plantar fasciitis subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Infections and infestations			

Gastroenteritis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	35		
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2016	* Removed a co-investigator. * Included pediatric patients (12-18) in the study * Increased number of study patients from 5 to 9
29 August 2016	* Added a co-investigator * Increased the number of study patients from 9 to approximately 15 * Increased the number of sites from 1 to 2
22 January 2018	* Added the fourth GAD-alum (Diamyd) injection (i.e. the prolonged extension period) in 4 adult patients.
05 April 2018	* Changed the fourth GAD-alum (Diamyd) injection (i.e. the prolonged extension period) to be 3 adult patients * Fine-tuned the assessments of height for pubertal stage for pediatric patients and required insulin dose to be collected 4 days prior to each visit

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported