Clinical trial results:
A Phase IIb, 2-Arm, Randomized, Double-blind, Placebo-Controlled, Multicentre Study to Optimize Diamyd® Therapy Administered into Lymph Nodes Combined with Oral Vitamin D to Investigate the Impact on the Progression of Type 1 diabetes

Summary

EudraCT number	2017-001861-25
Trial protocol	SE CZ ES NL
Global end of trial date	27 April 2021

Results information

Result version number	v1 (current)
This version publication date	13 October 2021
First version publication date	13 October 2021

Trial information

Trial identification

Sponsor protocol code	DIAGNODE-2 (D/P2/17/6)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03345004
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Diamyd Medical AB
Sponsor organisation address	Kungsgatan 29, Stockholm, Sweden, SE-111 56
Public contact	Clinical Study Director, Diamyd Medical AB, clinicaltrials@diamyd.com
Scientific contact	Clinical Study Director, Diamyd Medical AB, clinicaltrials@diamyd.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000609-PIP01-09
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	27 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2021
Global end of trial reached?	Yes
Global end of trial date	27 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of Diamyd, administered into lymph nodes in combination with an oral vitamin D regimen, compared to placebo in terms of preserving endogenous insulin secretion as measured by C-peptide.

Protection of trial subjects:

The final study protocol, including any substantial amendments and the final version of the subject information and consent form, were reviewed and approved by an Independent Ethics Committee and Competent Authorities prior to inclusion of subjects. The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association. The investigator was responsible for giving the patients and his/her parents/caregivers full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. Patients and, if applicable, his/her parents/caregivers were also notified that they were free to withdraw from the study at any time. The patients and parents/caregivers had reasonable time to read and understand the information before signing. The investigator was responsible for obtaining signed informed consent from all patients before including the patient in any study related procedures.

Background therapy:

Standard of care

Evidence for comparator: -

Actual start date of recruitment	17 December 2017
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	Netherlands: 2
Country: Number of subjects enrolled	Spain: 43
Country: Number of subjects enrolled	Sweden: 31
Country: Number of subjects enrolled	Czech Republic: 33
Worldwide total number of subjects	109
EEA total number of subjects	109

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	75
Adults (18-64 years)	34
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 18 sites in total, in Spain, Sweden, Czech Republic and the Netherlands. Patients were recruited from 07 December 2017 and the last patient's last visit was on 24 April 2021.

Pre-assignment

Screening details:

Inclusion: Patients aged 12-24 with type-1 diabetes diagnosed for at least 6 months with fasting C-peptide over 0.12 nmol/L and positive for GAD65A (<50,000 IU/mL) with adequate contraception. Exclusion: patients using immunosuppressants, anti-inflammatory drugs, anti-diabetics (other than insulin), vitamin D, with history of anaemia or epilepsy.

Period 1

Period 1 title	Main Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	No
Arm title	Diamyd + vitamin D (FAS, Main Study)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Diamyd® intralymphatic injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

4 ug administered in the inguinal lymph node on Day 30, 60 and 90.

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	D-vitaminolja ACO orala droppar, lösning, 80 IE/droppe
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

2000 IU/day (25 drops á 80 IE/drop) from Day 1 to Day 120.

Arm title	Placebo (FAS, Main Study)

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo intralymphatic injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Administered in the inguinal lymph node on Day 30, 60 and 90.

Investigational medicinal product name	Placebo oral drops
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Administered daily from Day 1 to Day 120.

Arm title	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Diamyd® intralymphatic injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

4 ug administered in the inguinal lymph node on Day 30, 60 and 90.

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	D-vitaminolja ACO orala droppar, lösning, 80 IE/droppe
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

2000 IU/day (25 drops á 80 IE/drop) from Day 1 to Day 120.

Arm title	Placebo (HLA DR3-DQ2, Main Study)

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo intralymphatic injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Administered in the inguinal lymph node on Day 30, 60 and 90.

Investigational medicinal product name	Placebo oral drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Administered daily from Day 1 to Day 120.

Number of subjects in period 1	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)
Started	57	52	29
Completed	56	51	28
Not completed	1	1	1
Physician decision	1	-	1

Consent withdrawn by subject	-	1	-

Number of subjects in period 1	Placebo (HLA DR3-DQ2, Main Study)
Started	19
Completed	18
Not completed	1
Physician decision	-
Consent withdrawn by subject	1

Period 2

Period 2 title	Extension Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	No
Arm title	Diamyd + vitamin D (Extension)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Diamyd® intralymphatic injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

4 ug administered in the inguinal lymph node on Day 30, 60 and 90.

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	D-vitaminolja ACO orala droppar, lösning, 80 IE/droppe
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

2000 IU/day (25 drops á 80 IE/drop) from Day 1 to Day 120.

Arm title	Placebo (Extension)

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo intralymphatic injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Administered in the inguinal lymph node on Day 30, 60 and 90.

Investigational medicinal product name	Placebo oral drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Administered daily from Day 1 to Day 120.

Arm title	Diamyd + vitamin D (HLA DR3-DQ2, Extension)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Diamyd® intralymphatic injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

4 ug administered in the inguinal lymph node on Day 30, 60 and 90.

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	D-vitaminolja ACO orala droppar, lösning, 80 IE/droppe
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

2000 IU/day (25 drops á 80 IE/drop) from Day 1 to Day 120.

Arm title	Placebo (HLA DR3-DQ2, Extension)

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo intralymphatic injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Administered in the inguinal lymph node on Day 30, 60 and 90.

Investigational medicinal product name	Placebo oral drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Administered daily from Day 1 to Day 120.

Number of subjects in period 2	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)
Started	30	23	15
Completed	28	22	15
Not completed	2	1	0
Lost to follow-up	2	1	-

Number of subjects in period 2	Placebo (HLA DR3-DQ2, Extension)
Started	8
Completed	8
Not completed	0
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Main Study

Reporting group description: -

Reporting group values	Main Study	Total	
Number of subjects	109	109	
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)	75	75	
Adults (18-64 years)	34	34	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	16.4		
standard deviation	± 4.1	-	
Gender categorical Units: Subjects			
Female	47	47	
Male	62	62	

End points

End points reporting groups	
Reporting group title	Diamyd + vitamin D (FAS, Main Study)
Reporting group description: -	
Reporting group title	Placebo (FAS, Main Study)
Reporting group description: -	
Reporting group title	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)
Reporting group description: -	
Reporting group title	Placebo (HLA DR3-DQ2, Main Study)
Reporting group description: -	
Reporting group title	Diamyd + vitamin D (Extension)
Reporting group description: -	
Reporting group title	Placebo (Extension)
Reporting group description: -	
Reporting group title	Diamyd + vitamin D (HLA DR3-DQ2, Extension)
Reporting group description: -	
Reporting group title	Placebo (HLA DR3-DQ2, Extension)
Reporting group description: -	

Primary: Change in C-peptide area under the curve (AUC)	
End point title	Change in C-peptide area under the curve (AUC)
End point description:	
Data is unitless as it is back-transformed from log scale.	
End point type	Primary
End point timeframe:	
Change between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).	

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	48	29	17
Units: unitless				
arithmetic mean (standard deviation)	0.551 (± 1.715)	0.506 (± 2.163)	0.663 (± 1.511)	0.425 (± 2.436)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	22	15	8

Units: unitless				
arithmetic mean (standard deviation)	0.376 (± 1.738)	0.453 (± 1.914)	0.449 (± 1.642)	0.381 (± 1.706)

Statistical analyses

Statistical analysis title	MMRM of change in C-peptide AUC
Comparison groups	Diamyd + vitamin D (FAS, Main Study) v Placebo (FAS, Main Study)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5009
Method	Mixed models analysis
Parameter estimate	Estimated ratio
Point estimate	1.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.845
upper limit	1.408

Statistical analysis title	MMRM of change in C-peptide AUC: HLA DR3-DQ2
Comparison groups	Diamyd + vitamin D (HLA DR3-DQ2, Main Study) v Placebo (HLA DR3-DQ2, Main Study)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078
Method	Mixed models analysis
Parameter estimate	Estimated ratio
Point estimate	1.557
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.126
upper limit	2.153

Statistical analysis title	MMRM of change in C-peptide AUC: Extension
Comparison groups	Diamyd + vitamin D (Extension) v Placebo (Extension)

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2215
Method	Mixed models analysis
Parameter estimate	Estimated ratio
Point estimate	0.807
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.569
upper limit	1.143

Statistical analysis title	MMRM of change in C-peptide AUC: Extension DR3-DQ2
Comparison groups	Diamyd + vitamin D (HLA DR3-DQ2, Extension) v Placebo (HLA DR3-DQ2, Extension)
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4038
Method	Mixed models analysis
Parameter estimate	Estimated ratio
Point estimate	1.197
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.781
upper limit	1.834

Secondary: Change in Insulin-dose-adjusted HbA1c (IDAA1c)

End point title	Change in Insulin-dose-adjusted HbA1c (IDAA1c)

End point description:

End point type	Secondary

End point timeframe:

Change between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	44	28	15
Units: unitless				
arithmetic mean (standard deviation)	0.757 (± 1.851)	0.377 (± 2.183)	0.663 (± 1.627)	0.667 (± 2.788)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	22	13	8
Units: unitless				
arithmetic mean (standard deviation)	1.327 (± 2.187)	1.195 (± 1.881)	1.402 (± 1.619)	0.803 (± 2.481)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HbA1c

End point title	Change in HbA1c

End point description:

End point type	Secondary

End point timeframe:

Change between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	51	29	18
Units: mmol/mol haemoglobin				
arithmetic mean (standard deviation)	1.04 (± 15.87)	0.53 (± 14.57)	0.87 (± 14.34)	-0.98 (± 18.75)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2,	Placebo (HLA DR3-DQ2, Extension)

			Extension)	
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	22	15	8
Units: mmol/mol haemoglobin				
arithmetic mean (standard deviation)	3.94 (± 13.51)	4.29 (± 14.40)	6.00 (± 11.60)	1.36 (± 21.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in daily exogenous insulin consumption

End point title	Change in daily exogenous insulin consumption

End point description:

End point type	Secondary

End point timeframe:

Change between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	44	28	15
Units: IU/kg/24h				
arithmetic mean (standard deviation)	0.183 (± 0.285)	0.094 (± 0.342)	0.143 (± 0.196)	0.153 (± 0.399)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	22	13	8
Units: IU/kg/24h				
arithmetic mean (standard deviation)	0.256 (± 0.342)	0.201 (± 0.275)	0.233 (± 0.317)	0.173 (± 0.247)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in glycaemic variability

End point title	Change in glycaemic variability

End point description:

End point type	Secondary

End point timeframe:

Change between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	39	25	12
Units: per day				
arithmetic mean (standard deviation)				
70-180 mg/dL (hours)	-2.479 (± 4.638)	-2.451 (± 4.012)	-1.724 (± 3.346)	-3.920 (± 4.090)
50-70 mg/dL (hours)	-0.035 (± 2.416)	0.197 (± 1.961)	0.034 (± 2.992)	0.581 (± 1.057)
<50 mg/dL (minutes)	15.7 (± 46.4)	9.0 (± 88.4)	16.7 (± 59.3)	48.1 (± 107.0)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	16	13	6
Units: per day				
arithmetic mean (standard deviation)				
70-180 mg/dL (hours)	-3.104 (± 2.859)	-2.598 (± 4.295)	-2.643 (± 3.305)	-4.270 (± 4.420)
50-70 mg/dL (hours)	-0.041 (± 2.142)	-0.185 (± 2.150)	-0.325 (± 2.529)	0.159 (± 1.697)
<50 mg/dL (minutes)	13.6 (± 47.2)	18.6 (± 97.0)	11.2 (± 56.0)	46.7 (± 72.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with IDAA1c ≤ 9

End point title	Proportion of patients with IDAA1c ≤ 9

End point description:

End point type	Secondary

End point timeframe:

Proportion of patients at Month 15 (Main Study reporting groups) and at Month 24 (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	44	28	15
Units: percent				
number (confidence interval 95%)	62.7 (48.1 to 75.9)	61.4 (45.5 to 75.6)	78.6 (59.0 to 91.7)	40.0 (16.3 to 67.7)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	22	13	8
Units: percent				
number (confidence interval 95%)	60.9 (38.5 to 80.3)	54.5 (32.2 to 75.6)	69.2 (38.6 to 90.9)	62.5 (24.5 to 91.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with stimulated maximum C-peptide above 0.2 nmol/L

End point title	Proportion of patients with stimulated maximum C-peptide above 0.2 nmol/L

End point description:

End point type	Secondary

End point timeframe:

Proportion of patients at Month 15 (Main Study reporting groups) and at Month 24 (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	49	29	17
Units: percent				
number (confidence interval 95%)	92.7 (82.4 to 98.0)	75.5 (61.1 to 86.7)	96.6 (82.2 to 99.9)	70.6 (44.0 to 89.7)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	22	15	8
Units: percent				
number (confidence interval 95%)	75.0 (55.1 to 89.3)	72.7 (49.8 to 89.3)	80.0 (51.9 to 95.7)	62.5 (24.5 to 91.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with stimulated 90-minute C-peptide above 0.2 nmol/L

End point title	Proportion of patients with stimulated 90-minute C-peptide above 0.2 nmol/L

End point description:

End point type	Secondary

End point timeframe:

Proportion of patients at Month 15 (Main Study reporting groups) and at Month 24 (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	49	29	17
Units: percent				
number (confidence interval 95%)	87.3 (75.5 to 94.7)	71.4 (56.7 to 83.4)	96.6 (82.2 to 99.9)	64.7 (38.3 to 85.8)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	22	14	8
Units: percent				
number (confidence interval 95%)	70.4 (49.8 to 86.2)	68.2 (45.1 to 86.1)	71.4 (41.9 to 91.6)	62.5 (24.5 to 91.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of self-reported episodes of severe hypoglycaemia

End point title	Number of self-reported episodes of severe hypoglycaemia

End point description:

End point type	Secondary

End point timeframe:

Between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	52	29	19
Units: episodes	0	6	0	0

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	23	15	8
Units: episodes	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with at least 1 severe hypoglycaemic event

End point title	Number of patients with at least 1 severe hypoglycaemic event

End point description:

End point type	Secondary

End point timeframe:

Between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	52	29	19
Units: patients	0	1	0	0

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	23	15	8
Units: patients	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change in maximum C-peptide during MMTT

End point title	Change in maximum C-peptide during MMTT

End point description:

End point type	Secondary

End point timeframe:

Change between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	49	29	17
Units: nmol/L				
arithmetic mean (standard deviation)	-0.350 (± 0.463)	-0.300 (± 0.350)	-0.257 (± 0.400)	-0.277 (± 0.349)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2, Extension)	Placebo (HLA DR3-DQ2, Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	22	15	8
Units: nmol/L				
arithmetic mean (standard deviation)	-0.546 (± 0.295)	-0.403 (± 0.306)	-0.557 (± 0.319)	-0.520 (± 0.364)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting C-peptide

End point title	Change in fasting C-peptide

End point description:

End point type	Secondary

End point timeframe:

Change between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	49	29	17
Units: nmol/L				
arithmetic mean (standard deviation)	-0.115 (± 0.148)	-0.106 (± 0.169)	-0.081 (± 0.100)	-0.095 (± 0.190)

End point values	Diamyd + vitamin D (Extension)	Placebo (Extension)	Diamyd + vitamin D (HLA DR3-DQ2,	Placebo (HLA DR3-DQ2, Extension)

			Extension)	
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	22	15	8
Units: nmol/L				
arithmetic mean (standard deviation)	-0.144 (± 0.160)	-0.139 (± 0.122)	-0.082 (± 0.119)	-0.150 (± 0.107)

Statistical analyses

No statistical analyses for this end point

Secondary: C-peptide measured at 30, 60, 90 and 120 minutes during MMTT

End point title	C-peptide measured at 30, 60, 90 and 120 minutes during MMTT

End point description:

End point type	Secondary

End point timeframe:

At Month 15.

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (HLA DR3-DQ2, Main Study)	Placebo (HLA DR3-DQ2, Main Study)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	49	29	19
Units: nmol/L				
arithmetic mean (standard deviation)				
30 min	0.376 (± 0.295)	0.374 (± 0.330)	0.659 (± 0.352)	0.580 (± 0.282)
60 min	0.536 (± 0.383)	0.495 (± 0.411)	0.911 (± 0.393)	0.715 (± 0.308)
90 min	0.645 (± 0.495)	0.562 (± 0.438)	1.016 (± 0.451)	0.717 (± 0.318)
120 min	0.691 (± 0.542)	0.590 (± 0.444)	1.065 (± 0.430)	0.728 (± 0.317)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight and BMI

End point title	Change in body weight and BMI[1]

End point description:

End point type	Secondary

End point timeframe:

Change between baseline and 15 months (Main Study reporting groups) or between baseline and 24 months (Extension Study reporting groups).

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was summarised overall only, not further split by HLA subgroup.

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (Extension)	Placebo (Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	51	28	22
Units: unit(s)				
arithmetic mean (standard deviation)				
Body weight (kg)	4.3 (± 5.0)	5.6 (± 5.4)	6.5 (± 6.9)	6.8 (± 6.8)
Body mass index (kg/m2)	0.8 (± 1.4)	1.3 (± 1.6)	1.2 (± 1.9)	1.9 (± 2.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Injection site reactions

End point title	Injection site reactions[2]

End point description:

End point type	Secondary

End point timeframe:

Change between baseline and 15 months (Main Study reporting groups)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was summarised overall only, not further split by HLA subgroup.

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	52		
Units: severe injection site reactions	10	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory assessments

End point title	Laboratory assessments[3]

End point description:

Clinically significant abnormal results from laboratory measurements (haematology and clinical chemistry) and urinalysis.

End point type	Secondary

End point timeframe:

From Screening until 15 months (Main Study reporting groups) or from Screening until 24 months (Extension Study reporting groups)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was summarised overall only, not further split by HLA subgroup.

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (Extension)	Placebo (Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	52	30	23
Units: clinically significant abnormal results	11	3	3	3

Statistical analyses

No statistical analyses for this end point

Secondary: Physical and neurological examination

End point title	Physical and neurological examination[4]

End point description:

End point type	Secondary

End point timeframe:

From Screening until 15 months (Main Study reporting groups) or from Screening until 24 months (Extension Study reporting groups)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was summarised overall only, not further split by HLA subgroup.

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (Extension)	Placebo (Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	52	30	23
Units: clinically significant abnormal results				
Physical examination	15	9	10	1
Neurological examination	4	0	4	0

Statistical analyses

No statistical analyses for this end point

Secondary: GAD65A titer

End point title	GAD65A titer[5]

End point description:

Last assessment corresponds to Month 15 for the Main Study reporting groups and Month 24 for the Extension Study reporting groups

End point type	Secondary

End point timeframe:

At baseline and 15 months (Main Study reporting groups) or at Baseline and 24 months (Extension Study reporting groups)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was summarised overall only, not further split by HLA subgroup.

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (Extension)	Placebo (Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	52	30	23
Units: IU/mL				
arithmetic mean (standard deviation)				
Baseline	731.3 (± 2302.9)	627.3 (± 1829.9)	677.8 (± 2060.8)	168.0 (± 283.5)
Last assessment	19941.2 (± 23083.6)	19197.7 (± 22218.7)	18972.5 (± 21432.4)	18253.7 (± 21199.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs (blood pressure)

End point title	Vital signs (blood pressure)[6]

End point description:

End point type	Secondary

End point timeframe:

From Screening until 15 months (Main Study reporting groups) or from Screening until 24 months (Extension Study reporting groups)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was summarised overall only, not further split by HLA subgroup.

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (Extension)	Placebo (Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	52	30	23
Units: clinically significant abnormal results				
Systolic blood pressure	0	0	0	0
Diastolic blood pressure	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life: EQ-5D-5L

End point title	Quality of life: EQ-5D-5L[7]

End point description:

Last assessment corresponds to Month 15 for the Main Study reporting groups and Month 24 for the Extension Study reporting groups

End point type	Secondary

End point timeframe:

At baseline and 15 months (Main Study reporting groups) or at Baseline and 24 months (Extension Study reporting groups)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was summarised overall only, not further split by HLA subgroup.

End point values	Diamyd + vitamin D (FAS, Main Study)	Placebo (FAS, Main Study)	Diamyd + vitamin D (Extension)	Placebo (Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	47	26	21
Units: unitless				
median (inter-quartile range (Q1-Q3))				
Baseline	1.000 (0.922 to 1.000)	1.000 (0.919 to 1.000)	1.000 (0.922 to 1.000)	1.000 (0.919 to 1.000)
Last assessment	1.000 (0.919 to 1.000)	1.000 (1.000 to 1.000)	1.000 (0.919 to 1.000)	1.000 (0.919 to 1.000)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent adverse events, from start of Diamyd/Placebo treatment until Month 24.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Diamyd + vitamin D
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Diamyd + vitamin D	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 57 (0.00%)	3 / 52 (5.77%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Jaw fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 57 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Diamyd + vitamin D	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 57 (31.58%)	12 / 52 (23.08%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 57 (5.26%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 57 (5.26%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 57 (17.54%)	10 / 52 (19.23%)	
occurrences (all)	13	17	
Viral infection			
subjects affected / exposed	4 / 57 (7.02%)	0 / 52 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2017	Amendment 1 included: • Addition of new inclusion criterion • Clarification on all visits timing • Specification of c-peptid concentration at screening visit • Clarification on the physical examination outcome • Clarification on the lymph node injection side • Clarification on the relationship to study medication
21 August 2017	Amendment 4 included: • Patients taking Vitamin D before screening had to stop it during trial (new exclusion criterion)
28 June 2018	Amendment 5 included: • Addition of 2 sites in The Netherlands (new country) • Increase the number of total patients 106 instead of 80 • Increase the recruitment period in 4 months (16 in total) • ICFs were updated
18 June 2019	Amendment 6 included: • All patients that were ongoing, were asked to participate in the Extension Study Period which included Visit 8 at month 24. • Exploratory endpoints included all data collected at the 24-month follow-up visit • ICFs were updated for the patients that approved to participate in the Extension Study
15 May 2020	Amendment 7 included: • Addition of key secondary endpoints to evaluate diabetic status • Correction of secondary endpoints and addition of new ones (body weight, body mass index and serological test for Covid-19) • Upgrade of analysis sets for statistical analysis • Upgrade of primary endpoint variable analysis; secondary efficacy endpoint variables analysis; secondary variables of diabetic status analysis; and exploratory endpoints variables analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported