Clinical trial results:
DIAPREV-IT Diabetes Prevention Immune Tolerance.
A double-blind, randomized investigator-initiated study to determine the safety and the effect of Diamyd® on the progression to type 1 diabetes in children with multiple islet cell autoantibodies.

Summary

EudraCT number	2008-007484-16
Trial protocol	SE
Global end of trial date	31 January 2017

Results information

Result version number	v1 (current)
This version publication date	09 April 2020
First version publication date	09 April 2020

Trial information

Trial identification

Sponsor protocol code	DIAPREV/2008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01122446
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Skåne University Hospital
Sponsor organisation address	Jan Waldenströms gata 35, hus 60, Malmö, Sweden,
Public contact	Helena Elding Larsson, Skåne University Hospital, 46 040-337676, helena.larsson@med.lu.se
Scientific contact	Helena Elding Larsson, Skåne University Hospital, 46 040-337676, helena.larsson@med.lu.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	22 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2017
Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate that Diamyd® is safe in children at risk for type 1 diabetes from 4 years of age. The subjects will be followed for 5 years.

Protection of trial subjects:

After the injection of Diamyd/placebo at visits 1 and 2, each trial participant was to remain at the study clinic for at least 1h and monitored by the study personnel. Additionally, the participants were offered to stay at the clinic for an additional 2h or contact the investigator by phone.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2009
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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	48
Adolescents (12-17 years)	2
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

55 children were screened for participation. Of those, 4 did not fulfil the inclusion criteria of positive autoantibodies to GAD65 (GADA) and at least one more islet autoantibody, or had already developed diabetes at screening. For one child, the parents changed their mind about participation and withdrew the child before the first treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Diamyd

Arm description:

ALUM-rhGAD65

Arm type	Experimental
Investigational medicinal product name	Diamyd
Investigational medicinal product code	
Other name	ALUM-rhGAD65
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 subcutaneous injections of 20 microgram each

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 injections

Number of subjects in period 1	Diamyd	Placebo
Started	25	25
Completed	25	25

Period 2	
Period 2 title	Treatment follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms	
Are arms mutually exclusive?	Yes
Arm title	Diamyd

Arm description:
ALUM-rhGAD65

Arm type	Experimental
Investigational medicinal product name	Diamyd
Investigational medicinal product code	
Other name	ALUM-rhGAD65
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
2 subcutaneous injections of 20 microgram each

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
2 subcutaneous injections

Number of subjects in period 2	Diamyd	Placebo
Started	25	25
Completed	25	25

Baseline characteristics

Reporting groups	
Reporting group title	Diamyd
Reporting group description: ALUM-rhGAD65	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Diamyd	Placebo	Total
Number of subjects	25	25	50
Age categorical Units: Subjects			
Age continuous Units: years			
median	6.0	5.0	
full range (min-max)	4.1 to 15.1	4.0 to 17.9	-
Gender categorical Units: Subjects			
Female	11	12	23
Male	14	13	27
Population source Units: Subjects			
General population	16	18	34
First degree relative	9	7	16
Stratum Units: Subjects			
2 positive antibodies	7	7	14
3-6 positive antibodies	18	18	36
GADA Units: Subjects			
Positive	25	25	50
Negative	0	0	0
Glucose tolerance Units: Subjects			
Impaired	13	13	26
Normal	12	12	24
OGTT fasting C-peptide Units: nmol/L			
arithmetic mean	0.21	0.18	
standard deviation	± 0.1	± 0.09	-
OGTT 2 hour C-peptide Units: nmol/L			
arithmetic mean	1.22	1.09	
standard deviation	± 0.46	± 0.6	-
OGTT AUC C-peptide Units: nmol/L			

arithmetic mean	146.98	134.82	
standard deviation	± 62.12	± 55.36	-
OGTT fasting glucose			
Units: mmol/L			
arithmetic mean	4.74	4.67	
standard deviation	± 0.49	± 0.56	-
OGTT 2 hour glucose			
Units: mmol/L			
arithmetic mean	6.88	6.82	
standard deviation	± 1.61	± 2.12	-
OGTT AUC glucose			
Units: mmol/L			
arithmetic mean	938.72	989.63	
standard deviation	± 190.87	± 207.07	-
HbA1c			
Units: mmol/mol			
arithmetic mean	32.76	33.84	
standard deviation	± 3.13	± 3.52	-

End points

End points reporting groups	
Reporting group title	Diamyd
Reporting group description: ALUM-rhGAD65	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Diamyd
Reporting group description: ALUM-rhGAD65	
Reporting group title	Placebo
Reporting group description: -	

Primary: Frequency of type 1 diabetes	
End point title	Frequency of type 1 diabetes
End point description:	
End point type	Primary
End point timeframe: 5 years	

End point values	Diamyd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Days	8	10		

Statistical analyses

Statistical analysis title	Progression to type 1 diabetes
Comparison groups	Diamyd v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.94

Notes:
[1] - Difference between treatment in time to type 1 diabetes

Secondary: Change from baseline in FPIR (First-phase Insulin Response)

End point title	Change from baseline in FPIR (First-phase Insulin Response)

End point description:

End point type	Secondary

End point timeframe:
5 years

End point values	Diamyd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Unknown				
arithmetic mean (standard deviation)	89.60 (± 63.60)	97.60 (± 63.15)		

Statistical analyses

Statistical analysis title	Change from baseline in FPIR
Comparison groups	Diamyd v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [2]
Method	Mixed models analysis

Notes:
[2] - Difference between the treatment groups

Secondary: Change from baseline in fasting C-peptide

End point title	Change from baseline in fasting C-peptide

End point description:

End point type	Secondary

End point timeframe:
5 years

End point values	Diamyd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Unknown				
arithmetic mean (standard deviation)	0.45 (± 0.16)	0.48 (± 0.25)		

Statistical analyses

Statistical analysis title	Change from baseline in fasting C-peptide
Comparison groups	Diamyd v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.366
Method	Mixed models analysis

Secondary: Change from baseline in 120-minutes C-peptide

End point title	Change from baseline in 120-minutes C-peptide
End point description:	

End point type	Secondary
End point timeframe:	
5 years	

End point values	Diamyd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Unknown				
arithmetic mean (standard deviation)	1.45 (± 0.5)	1.58 (± 0.7)		

Statistical analyses

Statistical analysis title	Change from baseline in 120-minutes C-peptide
Comparison groups	Diamyd v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.384 [3]
Method	Mixed models analysis

Notes:
[3] - Difference between the treatments

Secondary: Change from baseline in AUC C-peptide

End point title	Change from baseline in AUC C-peptide

End point description:

End point type	Secondary

End point timeframe:
5 years

End point values	Diamyd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Unknown				
arithmetic mean (standard deviation)	184.14 (± 65.59)	183.23 (± 64.78)		

Statistical analyses

Statistical analysis title	Change from baseline in AUC C-peptide
Comparison groups	Placebo v Diamyd
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.308 [4]
Method	Mixed models analysis

Notes:
[4] - Difference between the treatments

Secondary: Change from baseline in fasting glucose

End point title	Change from baseline in fasting glucose

End point description:

End point type	Secondary

End point timeframe:
5 years

End point values	Diamyd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: Unknown				
arithmetic mean (standard deviation)	5.36 (± 0.39)	5.29 (± 0.5)		

Statistical analyses

Statistical analysis title	Change from baseline in fasting glucose
Comparison groups	Diamyd v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5 [5]
Method	Mixed models analysis

Notes:
[5] - Difference between treatments

Secondary: Change from baseline in 120-minutes glucose

End point title	Change from baseline in 120-minutes glucose

End point description:

End point type	Secondary

End point timeframe:
5 years

End point values	Diamyd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: Unknown				
arithmetic mean (standard deviation)	7.04 (± 3.11)	6.67 (± 2.38)		

Statistical analyses

Statistical analysis title	Change from baseline in AUC glucose
Comparison groups	Diamyd v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.565 [6]
Method	Mixed models analysis

Notes:
[6] - Difference between the treatments

Secondary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

End point type	Secondary

End point timeframe:
5 years

End point values	Diamyd	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Unknown				
arithmetic mean (standard deviation)	34.00 (± 3.12)	34.56 (± 4.23)		

Statistical analyses

Statistical analysis title	Change from baseline in HbA1c
Comparison groups	Diamyd v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.151
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From randomization up to 5 year follow-up or diagnosis of type 1 diabetes.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Diamyd
Reporting group description: ALUM-rhGAD65	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	Diamyd	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 25 (8.00%)	2 / 25 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	25 / 25 (100.00%)	
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	3 / 25 (12.00%)	3 / 25 (12.00%)	
occurrences (all)	3	3	
Vaccination complication			
subjects affected / exposed	1 / 25 (4.00%)	5 / 25 (20.00%)	
occurrences (all)	1	5	
Fall			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 25 (28.00%)	6 / 25 (24.00%)	
occurrences (all)	54	17	
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
occurrences (all)	1	2	
Migraine			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
occurrences (all)	1	19	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	3	4	
Injection site reaction			
subjects affected / exposed	24 / 25 (96.00%)	23 / 25 (92.00%)	
occurrences (all)	43	43	
Malaise			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Pyrexia			
subjects affected / exposed	10 / 25 (40.00%)	19 / 25 (76.00%)	
occurrences (all)	29	43	

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 25 (12.00%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Seasonal allergy			
subjects affected / exposed	3 / 25 (12.00%)	2 / 25 (8.00%)	
occurrences (all)	6	2	
Coeliac disease			
subjects affected / exposed	2 / 25 (8.00%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	6 / 25 (24.00%)	5 / 25 (20.00%)	
occurrences (all)	10	11	
Diarrhoea			
subjects affected / exposed	3 / 25 (12.00%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	4 / 25 (16.00%)	5 / 25 (20.00%)	
occurrences (all)	5	7	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 25 (12.00%)	4 / 25 (16.00%)	
occurrences (all)	25	18	
Cough			
subjects affected / exposed	6 / 25 (24.00%)	5 / 25 (20.00%)	
occurrences (all)	16	12	
Oropharyngeal pain			
subjects affected / exposed	3 / 25 (12.00%)	3 / 25 (12.00%)	
occurrences (all)	5	5	
Musculoskeletal and connective tissue disorders			

Growing pains			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	7	
Infections and infestations			
Ear infection			
subjects affected / exposed	3 / 25 (12.00%)	6 / 25 (24.00%)	
occurrences (all)	5	11	
Enterobiasis			
subjects affected / exposed	2 / 25 (8.00%)	2 / 25 (8.00%)	
occurrences (all)	8	4	
Gastroenteritis			
subjects affected / exposed	19 / 25 (76.00%)	17 / 25 (68.00%)	
occurrences (all)	41	29	
Influenza			
subjects affected / exposed	7 / 25 (28.00%)	4 / 25 (16.00%)	
occurrences (all)	9	4	
Nasopharyngitis			
subjects affected / exposed	21 / 25 (84.00%)	21 / 25 (84.00%)	
occurrences (all)	117	92	
Otitis media			
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Scarlet fever			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Tonsillitis			
subjects affected / exposed	2 / 25 (8.00%)	7 / 25 (28.00%)	
occurrences (all)	2	10	
Upper respiratory tract infection			
subjects affected / exposed	13 / 25 (52.00%)	9 / 25 (36.00%)	
occurrences (all)	19	11	
Varicella			

subjects affected / exposed	6 / 25 (24.00%)	6 / 25 (24.00%)	
occurrences (all)	6	6	
Viral infection			
subjects affected / exposed	7 / 25 (28.00%)	2 / 25 (8.00%)	
occurrences (all)	13	3	
Conjunctivitis			
subjects affected / exposed	0 / 25 (0.00%)	4 / 25 (16.00%)	
occurrences (all)	0	4	
Otitis externa			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/2346994

http://www.ncbi.nlm.nih.gov/pubmed/25381193

http://www.ncbi.nlm.nih.gov/pubmed/29171140