Clinical trial results:
A pilot study on safety, feasibility and insulin-promotion by intra-inguinal lymph node injections of glutamic acid decarboxylase (GAD) in patients with LADA type of diabetes.

Summary

EudraCT number	2019-002692-34
Trial protocol	NO SE
Global end of trial date	05 May 2022

Results information

Result version number	v1 (current)
This version publication date	24 June 2023
First version publication date	24 June 2023

Trial information

Trial identification

Sponsor protocol code	GADinLADA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04262479
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NTNU, Dept of Clinical and Molecular Medicine, Gastrosenteret
Sponsor organisation address	Postboks 8905, Trondheim, Norway, 7491
Public contact	Ingrid K Hals, NTNU, Dep of Clinical and Molecular Medicine, Gastrosenteret , ingrid.hals@ntnu.no
Scientific contact	Ingrid K Hals, NTNU, Dep of Clinical and Molecular Medicine, Gastrosenteret , ingrid.hals@ntnu.no

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	05 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2022
Global end of trial reached?	Yes
Global end of trial date	05 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the trial is to evaluate the effects of 3 intra-nodal injections of GAD-alum in a population of LADA patients with high GADA titers. The primary objective is to evaluate safety and feasibility of this treatment regimen.

The pilot study will be performed in order to support the launch of a larger placebo controlled clinical trial in the LADA population.

Protection of trial subjects:

Regional ethical committees, drug administration agencies and data protection authorities in Norway and Sweden approved the proposed trial. Informed consent was obtained from all study participants.

Background therapy:

Vitamin D 1 tablet/day, total daily dose of 2000 IE given per os from day -30 through day 90.

Evidence for comparator: -

Actual start date of recruitment	07 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Sweden: 8
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	0

Adults (18-64 years)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment	
Recruitment details: -	
Pre-assignment	
Screening details: -	
Pre-assignment period milestones	
Number of subjects started	14
Number of subjects completed	14

Period 1	
Period 1 title	Baseline (month 0)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Arm title	rhGAD65
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	rhGAD65
Investigational medicinal product code	
Other name	Diamyd (R)
Pharmaceutical forms	Solution for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Drug: recombinant human glutamic acid dehydrogenase (rhGAD65), formulated in aluminium hydrogel
3 intra-inguinal injections (into the lymph nodes) of GAD-alum one month apart.

Number of subjects in period 1	rhGAD65
Started	14
Completed	14

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

Arms

Arm title	rhGAD65
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	rhGAD65
Investigational medicinal product code	
Other name	Diamyd (R)
Pharmaceutical forms	Solution for injection
Routes of administration	Intralymphatic use

Dosage and administration details:

Drug: recombinant human glutamic acid dehydrogenase (rhGAD65), formulated in aluminium hydrogel
3 intra-inguinal injections (into the lymph nodes) of GAD-alum one month apart.

Number of subjects in period 2	rhGAD65
Started	14
Completed	14

Baseline characteristics

Reporting groups

Reporting group title	Baseline (month 0)

Reporting group description: -

Reporting group values	Baseline (month 0)	Total	
Number of subjects	14	14	
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)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	46.6		
full range (min-max)	30 to 62	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	7	7	
BMI (kg/m^2) Units: Subjects			
Non-obese (BMI<=30)	10	10	
Obese (BMI >30)	4	4	
HLA characterization Units: Subjects			
DR3-DQ2+	7	7	
DR3-DQ2-	7	7	
Time from diagnosis			
Time from diagnosis to informed consent			
Units: month			
arithmetic mean	5.3		
standard deviation	± 3.8	-	

Subject analysis sets

Subject analysis set title	TP
Subject analysis set type	Full analysis

Subject analysis set description:

Total population set will include all patients who receive at least 1 dose of GAD-alum regardless of

withdrawal.

Reporting group values	TP		
Number of subjects	14		
Age categorical 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)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	14		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	46.6		
full range (min-max)	30 to 62		
Gender categorical Units: Subjects			
Female	7		
Male	7		
BMI (kg/m^2) Units: Subjects			
Non-obese (BMI<=30)	10		
Obese (BMI >30)	4		
HLA characterization Units: Subjects			
DR3-DQ2+	7		
DR3-DQ2-	7		
Time from diagnosis			
Time from diagnosis to informed consent			
Units: month			
arithmetic mean	5.3		
standard deviation	± 3.8		

End points

End points reporting groups

Reporting group title	rhGAD65
Reporting group description: -	
Reporting group title	rhGAD65
Reporting group description: -	
Subject analysis set title	TP
Subject analysis set type	Full analysis
Subject analysis set description:	
Total population set will include all patients who receive at least 1 dose of GAD-alum regardless of withdrawal.	

Primary: Change in GAD65A titer serum levels

End point title	Change in GAD65A titer serum levels
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to month 12	

End point values	rhGAD65	rhGAD65	TP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	14	14	
Units: unit(s)/millilitre				
arithmetic mean (standard deviation)	180406.14 (± 634160.18)	163356.07 (± 457735.54)	-17050.07 (± 178422.15)	

Statistical analyses

Statistical analysis title	Change from baseline to Month 12
Comparison groups	rhGAD65 v rhGAD65
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0002
Method	Wilcoxon Signed Rank test

Notes:

[1] - Pairwise comparison of change from baseline (14 subjects are included in the analysis with baseline and month 12 values)

Secondary: Change in HbA1c

End point title	Change in HbA1c
End point description:	
End point type	Secondary

End point timeframe:

Change from baseline to Month 12

End point values	rhGAD65	rhGAD65	TP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	14	14	
Units: mmol/mol				
arithmetic mean (standard deviation)	43.00 (± 6.03)	48.07 (± 12.27)	5.07 (± 7.51)	

Statistical analyses

Statistical analysis title	Change from baseline to Month 12
Comparison groups	rhGAD65 v rhGAD65
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0024
Method	Wilcoxon Signed Rank test

Notes:

[2] - Pairwise comparison of change from baseline (14 subjects are included in the analysis with baseline and month 12 values)

Secondary: Change in maximum C-peptide during MMTT

End point title	Change in maximum C-peptide during MMTT

End point description:

Maximum C-peptide during Mixed meal tolerance test

End point type	Secondary

End point timeframe:

Change from baseline to month 12

End point values	rhGAD65	rhGAD65	TP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	14	14	
Units: nmol/l				
arithmetic mean (standard deviation)	2.04 (± 0.51)	1.78 (± 0.52)	-0.26 (± 0.38)	

Statistical analyses

Statistical analysis title	Change from baseline to Month 12
Comparison groups	rhGAD65 v rhGAD65

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0437
Method	Wilcoxon Signed Rank test

Notes:

[3] - Pairwise comparison of change from baseline (14 subjects are included in the analysis with baseline and month 12 values)

Secondary: Change in fasting glucose

End point title	Change in fasting glucose

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to month 12

End point values	rhGAD65	rhGAD65	TP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	14	14	
Units: mmol/mol				
arithmetic mean (standard deviation)	6.92 (± 1.49)	7.16 (± 1.62)	0.24 (± 1.03)	

Statistical analyses

Statistical analysis title	Change from baseline to Month 12
Comparison groups	rhGAD65 v rhGAD65
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.7209
Method	Wilcoxon Signed Rank test

Notes:

[4] - Pairwise comparison of change from baseline (14 subjects are included in the analysis with baseline and month 12 values)

Secondary: Change in AUC C-peptide

End point title	Change in AUC C-peptide

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to month 12

End point values	rhGAD65	rhGAD65	TP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	14	14	
Units: ug/ml				
arithmetic mean (standard deviation)	5.36 (± 1.21)	5.51 (± 1.24)	1.03 (± 1.13)	

Statistical analyses

Statistical analysis title	Change from baseline to Month 12
Comparison groups	rhGAD65 v rhGAD65
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.5
Method	Wilcoxon Signed Rank test

Notes:

[5] - Pairwise comparison of change from baseline (14 subjects are included in the analysis with baseline and month 12 values)

Secondary: Change in Fasting C-Peptide

End point title	Change in Fasting C-Peptide

End point description:

End point type	Secondary

End point timeframe:

Baseline and Month 12 (6 min)

End point values	rhGAD65	rhGAD65	TP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	14	14	
Units: mmol/L				
arithmetic mean (standard deviation)	0.71 (± 0.37)	0.64 (± 0.33)	-0.06 (± 0.10)	

Statistical analyses

Statistical analysis title	Change from baseline to Month 12
Comparison groups	rhGAD65 v rhGAD65
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0313
Method	Wilcoxon Signed Rank test

Notes:

[6] - Pairwise comparison of change from baseline (14 subjects are included in the analysis with baseline and month 12 values)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening to end of study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26

Reporting groups	
Reporting group title	Total Population
Reporting group description:	
Total population will include all patients who receive at least 1 dose of GAD-alum regardless of withdrawal	

Serious adverse events	Total Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Muscle rupture			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)		
Investigations			

Blood glucose increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Procedural dizziness			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Wrong product administered			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injection site erythema			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Injection site haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Pyrexia			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) Vertigo positional subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Social circumstances Menopause subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Pancreatic cystadenoma subjects affected / exposed occurrences (all)	 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1		
Hepatobiliary disorders Biliary colic subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all) Throat irritation subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Psychiatric disorders Nightmare subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 3		
Infections and infestations			

COVID-19 subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2019	Study participants (with vitamin D levels <100 nmol/L) will receive oral supplementation of vitamin D in addition to the investigational medicinal product
10 July 2020	Changes in inclusion criteria stated in item 2 in Section 6.3.
29 January 2021	Specification regarding total number of trial subjects in Section 3.6, and change in exclusion criteria, item 4 in Section 6.3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported