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

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Primary objective:The primary objective is 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-...

Ethical review	Approved WMO
Status	Completed
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON49006

Source
ToetsingOnline

Brief title
DIAGNODE-2

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Type 1 diabetes; Diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Diamyd Medical AB
Source(s) of monetary or material Support: Diamyd Medical AB

Intervention

Keyword: GAD65, Type 1 diabetes, Vitamin D

Outcome measures

Primary outcome

Change in C-peptide (Area Under the Curve [AUC]mean 0-120 min) during a Mixed Meal Tolerance Test (MMTT) between baseline to 15 months.

Secondary outcome

Key secondary endpoints:

• Change in insulin-dose-adjusted HbA1c (IDAA1c) between baseline and 15 months

• Change in Hemoglobin A1c (HbA1c) between baseline and 15 months

• Change in daily exogenous insulin consumption between baseline and 15 months.

Secondary endpoints;

• Other variables that indicate Diabetes Status such as plasma C-peptide, variability of blood sugar, and number of self-reported hypoglycemia.

• Variables that indicate treatment safety such as occurrence of adverse events (AEs), physical examinations, hematology, urine analysis, injection site reactions, GAD65A titer, vital signs and clinical chemistry.

• Variables that indicate effects on the immune system such as serum autoantibodies (and isotypes) to GAD65, serum cytokine levels, secretion of

cytokines by immune cells in response to GAD65 stimulation, and proportions of

immune cells in blood.

• Measurements of patient QoL by questionnaire.

Study description

Background summary

Type 1 diabetes is an autoimmune disease in which beta cells in the pancreas - the cells in the body that create insulin - are broken down by the patient*s own immune system (white blood cells). Although today patients with type 1 diabetes are intensively treated with insulin, it can still be difficult to maintain a good sugar balance. This can lead to serious acute complications such as unconsciousness due to low blood sugar (insulin shock) or acidosis (diabetic coma). In the long term, an unsatisfactory blood sugar balance can lead to serious damage to the kidneys, eyes, nerves and heart. Therefore, it would be valuable if a treatment could be found that was able to stop the degradation of the beta cells by the patient*s own immune system. Preserving insulin production may make treatment easier and improve blood sugar balance, which in turn may reduce the risk of acute and later complications.

The destruction of the pancreatic beta cells in T1D is associated with cellular immune responses to the pancreatic islet cells, genetic susceptibility involving genes thought to modulate the immune response, and the presence of autoantibodies against several islet beta cell components (i.e., autoantigens) , In addition, as these T1D-associated autoantibodies often precede the clinical onset of disease, GAD65A, i.e. autoantibodies directed against glutamic acid decarboxylase (GAD) with a molecular weight of 65 kDa (GAD65A), insulinoma-associated protein 2 (IA-2A), insulin (IAA) or zinc T8 (ZnT8A) are widely recognized not only as diagnostic markers for autoimmune beta cell destruction, but as predictive markers for the disease.

Diamyd is an investigational drug composed of the recombinant human GAD65 (rhGAD65) protein formulated in a sterile, non-pyrogenic phosphate buffered saline containing the aluminum hydroxide (alum) adjuvant, Alhydrogel. Diamyd therapy aims at intervening in this destructive process by modulating the immune system in a discrete, antigen-specific fashion to prevent the destruction of beta cells. Thus, the goal of Diamyd therapy would be to slow down or halt the ongoing autoimmune destruction of pancreatic islet beta cells in order to preserve the largest possible amount of endogenous insulin production. In the proposed treatment regimen, exogenous oral Vitamin D treatment may improve the efficacy both via effects on the immune system and

mechanism directly on the beta cells to increase beta cell function and limit the autoimmune reaction. This may improve blood sugar control and at the same create a fertile field for Diamyd to induce long term tolerability.

The hypothesis is that the proposed treatment regime will rebalance islet cell interactions and the pancreatic immune environment to increase beta cell function and limit the autoimmune reaction. This will improve blood sugar control and at the same create a more fertile field for the GAD65 antigen specific immunotherapy Diamyd to induce long term tolerability.

Study objective

Primary objective:
The primary objective is 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.

Secondary objectives:
The secondary objectives are to compare Diamyd, administered into lymph nodes in combination with an oral vitamin D regimen and placebo treatment with respect to the effects on the diabetes status, treatment safety, immune system and quality of life (QoL) of the patients.

Study design

The study is a 2-arm, randomized, double-blind, placebo-controlled, multicenter, clinical trial. Eligible patients will receive injections of Diamyd/placebo into an inguinal lymph gland at three occasions, with one month intervals in combination with an oral vitamin D/placebo regimen (starting 1 month ahead of injections) during 4 months. All patients will continue to receive intensive insulin treatment from their personal physicians during the whole study period. The patients will be followed in a blinded manner for a total of 15 months. All patients that are ongoing, i.e. have not performed Visit 7 (15 months visit) when protocol version 7 is approved and implemented, will be asked to participate in the Extension Study
Period which include Visit 8 at month 24.

Intervention

The patients will be assessed for eligibility at the screening visit (Visit 1) 2 to 4 weeks prior to start of oral treatment with vitamin D. On Visit 2 (Day 1), patients eligible for the study will be randomized to 1 of 2 treatment groups:
• Approximately 53 patients will be assigned to receive i) three (3) intralymphatic injections with 4µg Diamyd on Days 30, 60, and 90 and; ii) oral vitamin D 2000 IE daily for 4 months (from Day 1 through Day 120)

• Approximately 53 patients will be assigned to receive i) three (3) intralymphatic injections of Placebo for Diamyd on Days 30, 60, and 90 and; ii) oral Placebo for vitamin D once a day for 4 months (from Day 1 through Day 120)

Study burden and risks

Giving a blood sample can cause discomfort such as bruising and tenderness. It can also be perceived as difficult to be fasting before the visits during which blood samples will be taken.

Treatment with the Diamyd® vaccine does not cause any known side effects or risks of particular severity or seriousness anticipated based on the toxicological data in animals or prior studies in humans, except that patients have reported injection site reactions, such as e.g. itching, edema, tenderness, bruises, and pain. Previous studies have shown that Diamyd® is safe and patients who have received the vaccine have tolerated it well. Patients treated for allergies by injection into a lymph node have experienced the stick of the needle in the lymph node as less unpleasant than having a blood sample taken from the arm, and patients injected with Diamyd® in a lymph node in the groin have not stated that they experienced significant discomfort.

There are no anticipated risks of vitamin D supplementation at the dose to be administered in this study, although toxic levels may induce hypercalcemia with symptoms such as tiredness, euphoria, nausea, drowsiness, weight loss, thirst, polyuria, nefrocalcinosis and renal failure. Additional symptoms of vitamin D toxicity include electrocardigraph changes, arrhythmia and pancreatitis.

As Diamyd has proven to be well tolerated in a large number of patients in previous studies, the possibility of therapeutic benefit outweighs the risks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Informed consent given by patients and/or patient*s parent(s) or legal acceptable representative(s) (guardian(s)) according to national regulations
2. T1D according to the ADA classification diagnosed <=6 months at the time of screening
3. Age: >=12 and <25 years old
4. Fasting C-peptide >=0.12 nmol/L
5. Positive for GAD65A but < 50 000 IU/ml
6. Females must agree to avoid pregnancy and have a negative urine pregnancy test.
Patients of childbearing potential must agree to use adequate contraception, until one (1) year after the last administration of Diamyd. Adequate contraception is as follows:
For females of childbearing potential:
a. oral (except low*dose gestagen (lynestrenol and norestisteron)), injectable, or implanted hormonal contraceptives
b. combined (estrogen and progestogen containing)
c. oral, intravaginal or transdermal progesterone hormonal contraception associated with inhibition of ovulation
d. intrauterine device
e. intrauterine hormone-releasing system (for example, progestin*releasing coil)
f. bilateral tubal occlusion
g. vasectomized male (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate)
h. male partner using condom
i. abstinence from heterosexual intercourse , For males of childbearing potential:

a. condom (male)
b. abstinence from heterosexual intercourse

Exclusion criteria

1. Previous or current treatment with immunosuppressant therapy (although topical or inhaled steroids are accepted)
2. Continuous treatment with anti-inflammatory drug (sporadic treatment e.g. because of headache or in connection with fever a few days will be accepted)
3. Treatment with any oral or injected anti-diabetic medications other than insulin
4. Treatment with Vitamin D, marketed or not, or unwilling to abstain from such medication during the trial
5. A history of anemia or significantly abnormal hematology results at screening
6. A history of epilepsy, head trauma or cerebrovascular accident, or clinical features of continuous motor unit activity in proximal muscles
7. Clinically significant history of acute reaction to vaccines or other drugs in the past
8. Treatment with any vaccine, including influenza vaccine, within 4 months prior to planned first study drug dose or planned treatment with any vaccine up to 4 months after the last injection with study drug.
9. Participation in other clinical trials with a new chemical entity within the previous 3 months
10. Inability or unwillingness to comply with the provisions of this protocol
11. A history of alcohol or drug abuse
12. A significant illness other than diabetes within 2 weeks prior to first dosing
13. Known HIV or hepatitis
14. Females who are lactating or pregnant (the possibility of pregnancy must be excluded by urine βHCG on-site within 24 hours prior to the Diamyd/placebo treatment)
15. Presence of associated serious disease or condition, including active skin infections that preclude intralymphatic injection, which in the opinion of the investigator makes the patient non-eligible for the study
16. Deemed by the investigator not being able to follow instructions and/or follow the study protocol

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-04-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Diamyd
Generic name:	rhGAD65 formulated in alum (GADalum)

Ethics review

Approved WMO Date:	13-09-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	31-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-001861-25-NL
ClinicalTrials.gov	NCT03345004

Register	ID
CCMO	NL66896.078.18

Study results

Date completed:	21-04-2021
Results posted:	24-09-2021
Actual enrolment:	2

First publication
14-09-2021