A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of Diamyd® to Preserve Endogenous Beta Cell Function in Adolescents and Adults with Recently Diagnosed Type 1 Diabetes, Carrying the Genetic HLA DR3-DQ2 Haplotype

Published: 21-10-2021
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This study has been transitioned to CTIS with ID 2024-513304-33-00 check the CTIS register for the current data. The primary objective is to assess the effect of three doses of Diamyd compared to a placebo in terms of (1) beta cell function; and (2…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON54104

Source
ToetsingOnline

Brief title
DIAGNODE-3 (4515/0012)

Condition

- Diabetic complications

Synonym
HLA DR3-DQ2 Haplotype, Type 1 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: ICON Clinical Research
Source(s) of monetary or material Support: The study sponsor as indicated in B7.

Intervention

Keyword: Adolescents and Adults, Diabetes Type 1, Diamyd®, HLA DR3-DQ2 Haplotype

Outcome measures

Primary outcome

Treatment: Intralymphatic injections of 4 µg Diamyd or placebo.

Target population: Study participants diagnosed with T1D who carry the HLA

DR3-DQ2 haplotype and have antibodies against GAD65.

Variable: Change from baseline to Month 24 in C peptide area under the curve

(AUC)mean 0-120 min during a 2-hour mixed meal tolerance test (MMTT)

Intercurrent event strategy:

1. Study drug discontinuation due to any cause, patient does not withdraw

consent: treatment policy strategy.

2. Study drug discontinuation due to any cause, patient withdraws consent:

hypothetical strategy.

3. Study drug non-adherence (missing doses) or drug administration error:

treatment policy strategy.

4. Prohibited medications and substances, including additional medication (oral

or non-insulin injectable therapies) for glycemic control (Sponsor*s Medical

Experts will take decision if patient can continue or should be discontinued):

hypothetical (if patient is discontinued), or treatment policy (if patient

continues in the study) strategy.

Population level summary: The geometric mean ratio (Diamyd/placebo) of the

change from baseline in C-peptide AUCmean 0-120 min.

Secondary outcome

Treatment: as above.

Target population: as above.

Variable: Change from baseline to Month 24 in hemoglobin A1c (HbA1c).

Intercurrent event strategy: as above.

Population level summary: Mean difference in change from baseline.

Study description

Background summary

Type-1 diabetes (T1D) is an autoimmune disorder in which the immune system attacks the insulin producing beta cells in the pancreas. As of 2019, an estimated 463 million people had diabetes worldwide, of which T1D accounts for between 7% to 12%, including over 1.1 million children with T1D1.

By the time an individual is diagnosed with T1D, 70 to 90% of the pancreatic islet beta cell function, i.e., the production and secretion of insulin, has been lost due to autoimmune responses against specific beta cell antigens. Over time the ability to produce endogenous insulin is reduced even further.

The destruction of the pancreatic beta cells in T1D is associated with cellular immune responses towards 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)2. The development of T1D autoantibodies often precedes the clinical onset of the disease. Autoantibodies directed against glutamic acid decarboxylase (GAD) with a molecular mass 65 kDa (GAD65A), insulinoma-associated protein 2 (IA-2A), insulin or zinc transporter antigen T8

(ZnT8A) are widely recognized as diagnostic markers for autoimmune beta cell destruction and as predictive markers for the disease. Susceptibility to T1D also has a strong genetic component with the strongest risk attributable to genes that encode the classical human leukocyte antigens (HLA).

Acute and long-term T1D complications
Currently, T1D treatment consists of lifelong administration of exogenous insulin, a replacement disease management therapy that does not satisfactorily prevent neither acute nor serious complications. The disease has a devastating impact on the quality of life (QoL) of the patient due to the constant stress of adjusting blood sugar and the common acute and deadly side effects of imperfect control, diabetic ketoacidosis (DKA) and hypoglycaemia. In addition to this, patients later suffer from both macro- and microvascular complications affecting the heart, nerves, eyes and kidneys.

DKA is the most common cause of death in children, teenagers, and young adults with diabetes, accounting for approximately 50% of all deaths in diabetic individuals younger than 24 years old and more than 160,000 hospital admissions per year in the United States (US). The risk of ketoacidosis in established T1D is 1% to 10% per patient per year and a recent study from Scotland showed a worrying increase in mortality due to DKA in T1D patients between 2004 and 2018. Cerebral injury is the major cause of mortality and 10% to 25% of survivors of cerebral edema have significant residual morbidity.

Clinical development program of Diamyd
Diamyd has been studied in numerous clinical trials over the years comprising over 1,500 patients in total (active or placebo), evaluating both subcutaneous (SC) and intralymphatic administration routes. More than 900 patients have been treated with active Diamyd as a SC injection (in doses up to 500 µg) and at least 82 patients with intralymphatically administered active Diamyd (4 µg/dose).
All clinical trials supported a favorable safety profile, with the Diamyd treatment being well tolerated. However, several Phase II and III trials performed in 2004 to 2011 evaluating subcutaneous Diamyd administration were inconclusive in terms of clinical efficacy in the full trial population.

For more information, please refer to the Protocol section 6.1.

Study objective

This study has been transitioned to CTIS with ID 2024-513304-33-00 check the CTIS register for the current data.

The primary objective is to assess the effect of three doses of Diamyd compared to a placebo in terms of (1) beta cell function; and (2) control of blood glucose levels in adolescents and adults recently diagnosed with type 1 diabetes (T1D) and who are carriers of human leukocyte antigen (HLA) haplotype

DR3 DQ2 and have antibodies against glutamic acid decarboxylase with molecular mass 65 kDa (GAD65).
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Study design

DIAGNODE-3 is a Phase III randomized, double-blind, placebo-controlled, multicenter, parallel-arm, 24-month trial in adolescents and adults with recently diagnosed T1D, carrying the HLA DR3-DQ2 haplotype. Patients will have the HLA genotyping performed at the first Screening visit (Visit 1A) after preliminary eligibility is confirmed based on appropriate assessments performed. If the results indicate the patient is carrying the HLA DR3-DQ2 haplotype, then the patient will attend the second Screening visit (Visit 1B) to perform the remaining Screening procedures. After V1C, patients deemed eligible will undergo CGM for 14 days, receive diabetes education and collect self reported diabetes information in their eDiary. Patients with a Screening Vitamin D level <100 nmol/L (40 ng/mL) will start receiving oral Vitamin D supplementation (2000 IU daily) beginning at Visit 1C, 30 days prior to randomization. Insulin doses will be collected 7 days after each study visit starting from Visit 1C. At Visit 2, patients will be randomized 2:1 to one of the following two treatment groups: Treatment Group 1: 3 intralymphatic injections of 4 µg (0.1 mL) of Diamyd administered on Days 0, 30 and 60 Treatment Group 2: 3 intralymphatic injections of 0.1 mL placebo administered on Days 0, 30 and 60 Randomization will be stratified by HLA subgroup (presence or absence of HLA DR4-DQ8) and by region. The maximum number of adult (>18 years old) patients recruited into the trial is 160. Diamyd or placebo injections will be administered in the inguinal lymph node by qualified personnel with the help of ultrasound. To the extent possible, study drug should be injected into the same lymph node; when this is not feasible, injection into another lymph node will be acceptable. Vitamin D levels will be monitored throughout the trial. Vitamin D oral supplementation (2000 IU daily) will be administered from Day -30 (Visit 1C) through Day 90 (Visit 5) for a total of 120 days for patients with a level <100 nmol/L (40 ng/mL) at Screening. A 2-hour MMTT following an overnight fast (>10 hours) will be performed at baseline (Visit 2) and at 6 (Visit 6), 15 (Visit 8), and 24 (Visit 11, end of study [EoS]) months. Meal stimulated plasma glucose and C-peptide levels will be assessed throughout the MMTT. Fasting C-peptide, HbA1c, fasting plasma glucose, and GAD65 antibody levels will be monitored throughout the trial. CGM will be performed for 14 days following Visit 1C and after the 6 (Visit 6), 15 (Visit 8), and 24-month (Visit 11, EoS) visits.
Patient/caregivers will complete QoL questionnaires to assess the impact of study drug on their lives at baseline (Visit 2) and at 6 (Visit 6), 15 (Visit 8), and 24 (Visit 11, EoS) months. Safety will be assessed via physical examinations, neurological assessments, vital signs, clinical laboratory assessments, monitoring of injection site reactions, and adverse events (AEs). Information concerning episodes of mild/moderate hypoglycemia will be collected in the eDiary for 14 day periods after Visit 1C (Run-In) and at 6 (Visit 6), 15

(Visit 8) and 24 (Visit 11, EoS) months. All episodes of severe hypoglycemia will be collected in the eDiary from Visit 1C and reported at each study visit starting from Visit 2. Hospitalization due to DKA will be recorded in the eDiary from Visit 1C and reported at each study visit starting from Visit 2. The investigator will determine if the DKA event is a true event after reviewing the patient*s medical journal and available laboratory parameters (if possible) and/or the hospital discharge letter and enter the DKA event in the eCRF. The co-primary efficacy endpoints and secondary endpoints will be analyzed after all randomized patients have completed the 24-month study visit (unless early termination prior to this visit). All patients/caregivers and site personnel will remain blinded until database lock has been performed at the end of the study.

Intervention

At Visit 2, patients will be randomized 2:1 to one of the following two treatment groups:
Treatment Group 1: 3 intralymphatic injections of 4 µg (0.1 mL) of Diamyd administered on Days 0, 30 and 60
Treatment Group 2: 3 intralymphatic injections of 0.1 mL placebo administered on Days 0, 30 and 60

Study burden and risks

There is a great unmet medical need for the preservation of beta cell function in T1D. Efforts to delay or halt disease progression have been ongoing for several decades, but clinical intervention trials with recent-onset T1D patients have thus far shown no or limited efficacy, which highlights the complexity of the disease and the difficulty in translating treatment from animal models to human T1D. Antigen-specific immunotherapy, such as Diamyd, intends to treat the underlying causes of the disease and specifically to modulate the immune system to ultimately shut down the degeneration of the insulin producing beta cells. Diamyd has presented a favorable safety profile in all 15 clinical trials initiated to date and intralymphatic therapy appears to be as well tolerated as SC therapy. In order to safeguard the patients, a Data and Safety Monitoring Board (DSMB) will review data from the study twice a year.

Diamyd is one of the first potential precision medicine based treatments for T1D, with the genetically defined patient subpopulation carrying the HLA DR3-DQ2 haplotype likely to benefit the most from the therapy. Given a favorable safety profile and clinical efficacy in individuals with HLA DR3-DQ2, it is considered that the potential benefits of Diamyd treatment clearly outweigh any potential risks.

Contacts

Public
ICON Clinical Research

Van Swietenlaan 6
Groningen 9728 NZ
NL
Scientific
ICON Clinical Research

Van Swietenlaan 6
Groningen 9728 NZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

1. Must be capable of providing written, signed, and dated informed consent; and for patients who are minors, age-appropriate assent (performed according to local regulations) and parent/caregiver consent.
2. Males and females aged >=12 and <=29 years old at the time of Screening. (V1A)
3. Diagnosed with T1D (according to the American Diabetes Association [ADA] classification) <=6 months at the time of Screening. (V1A)
4. Possess the HLA DR3-DQ2 haplotype (all patients will be tested; prior genetic testing results will not be accepted).
5. Fasting C-peptide >=0.12 nmol/L (>=0.36 ng/mL) on at least one occasion (maximum two tests on different days during the Screening period).
6. Possess detectable circulating GAD65 antibodies (lowest level of detection

defined by the method used by the central laboratory).
7. Possess HbA1c levels between 35 to 80 mmol/mol (5.4 to 9.5%) on at least one occasion prior to randomization (maximum one additional test within one month from V1B).
8. Be on a stable insulin dose or insulin dosing regimen for one month prior to inclusion with limited fluctuation of daily insulin requirement based on investigator*s assessment. For example, if the average insulin dose/kg/24h over a 7-day period compared to the previous 7day period does not vary more than approximately 15% and/or if the daily insulin dose does not vary more than 0.1 U/kg/24h, the dose can be considered stable. Individuals that are diagnosed with T1D according to the ADA classification but are not taking insulin are eligible to participate.
9. (i). Females of childbearing potential (FOCBP) must agree to avoid pregnancy and have a negative pregnancy test performed at the required study visits. FOCBP must agree to use highly effective contraception, during treatment and, until 90 days after the last administration of study medication. Birth control methods, which may be considered as highly effective (e.g., a failure rate of less than 1% per year when used consistently and correctly) include:
• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
o Oral.
o Intravaginal.
o Transdermal.
• Progestogen-only hormonal contraception associated with inhibition of ovulation:
o Oral.
o Injectable.
o Implantable.
• Intrauterine device.
• Intrauterine hormone-releasing system.
• Bilateral tubal occlusion.
• Vasectomized partner (vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the FOCBP trial patient and that the vasectomized partner has received medical assessment of the surgical success).
• Sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient).
9. (ii). Male patients must agree to remain abstinent from heterosexual sex during treatment and for 90 days after treatment or, if sexually active, to use two effective methods of birth control (e.g., male uses a condom and female uses contraception) during and for 90 days after treatment. Acceptable male contraception is as follows:
• Condom (male).
• Abstinence from heterosexual intercourse.

• Vasectomy.
The agreement to remain abstinent or use two effective methods of birth control will be clearly defined in the informed consent; the patient or legally authorized representatives (e.g., parents, caregivers, or legal guardians) must sign this specific section.

Exclusion criteria

1. Participation in any other trial aimed to influence beta cell function from time of diagnosis of T1D. 2. Treatment with any oral or non-insulin injectable anti-diabetic medication within 3 months prior to Randomization. 3. History of maturity-onset diabetes of the young (MODY). 4. Pancreatic surgery, chronic pancreatitis, or other pancreatic disorders that could result in decreased beta cell capacity. 5. Occurrence of DKA or severe hypoglycemia requiring hospitalization in the period of 90 days prior to Randomization. 6. Signs or symptoms suggesting very poorly controlled diabetes e.g., ongoing weight loss, polyuria or polydipsia. 7. Hematologic condition that would make HbA1c uninterpretable including: a) Hemoglobinopathy, with the exception of sickle cell trait or thalassemia minor; or chronic or recurrent hemolysis. b) Donation of blood or blood products to a blood bank, blood transfusion or participation in a clinical study requiring withdrawal of >400 mL of blood during the 8 weeks prior to the Screening (V1B) visit. c) Significant iron deficiency anemia. d) Heart malformations or vaso-occlusive crisis (VOC) leading to increased turnover of erythrocytes. 8. Treatment with marketed or over-the-counter Vitamin D at the time of Screening (V1C) and unwilling to abstain from such medication during the 120 days when the patient will be supplemented with the study-provided Vitamin D. A patient currently taking Vitamin D at the time of Screening (V1C) must be willing to switch to the study-provided Vitamin D treatment and to administer it per the study requirements. 9. Any clinically significant history of an acute reaction to a vaccine or its constituents (e.g., Alhydrogel). 10. Treatment with any (live or inactive) vaccine, including influenza vaccine and Coronavirus Disease 2019 (COVID-19) vaccine, within 4 weeks prior to planned first study dose of study drug; or planned treatment with any vaccine up to 4 weeks after the last injection with study drug. 11. Any acute or chronic skin infection or condition that would preclude intralymphatic injection. 12. Recent (past 12 months) or current treatment with immunosuppressant therapy, including chronic use of glucocorticoid therapy. Inhaled, topical, and intranasal steroid use is acceptable. Short courses (e.g., <=5 days) of oral or intra-articular injections of steroids will be permitted on trial. 13. Continuous/chronic treatment with prescribed or over-the-counter anti-inflammatory therapies. Short-term use (e.g., <7 days) is permissible, for example to treat a headache or in connection with a fever. 14. Known or suspected acute infection, including COVID-19 or influenza, at the time of Randomization or within 4 weeks prior to Randomization. 15. A history of epilepsy, head trauma or cerebrovascular accident, or clinical features of

continuous motor unit activity in proximal muscles. 16. Known diagnosis of human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection. Patients with previous hepatitis C infection that is now cured may be eligible. 17. Any clinically significant concomitant medical condition, including but not limited to other autoimmune diseases, cardiovascular, gastrointestinal, hematological, immune, renal including a history of renal transplantation, neurological (including Batten disease), significant diabetes complication, any underlying conditions or receiving treatments that could affect red blood cell turnover or other diseases that in the opinion of the investigator would interfere with trial participation or procedures. Celiac disease with adequate diet before diagnosis or discovered by increased autoantibodies at Screening (V1B) will be permitted. 18. History of significant hepatic disease or Screening alanine aminotransferase (ALT) >2.5 x upper limit of normal (ULN) or aspartate aminotransferase (AST) 3 x ULN and/or total bilirubin >2 x ULN. Patients with documented Gilbert syndrome and total bilirubin level >=2 x ULN due to unconjugated hyperbilirubinemia, without other hepatic impairment, are permitted. 19. Estimated glomerular filtration rate (eGFR) calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) for those >18 years old, and by the Schwartz equation for those 12 to 18 years old, <90 mL/min per 1.73 m or rapidly progressing renal disease. 20. Patients with hypothyroidism or hyperthyroidism must be on stable treatment for at least 3 months prior to Randomization (with normal free thyroxine [T4] levels if hypothyroid). Refer to protocol other exclusion criteria.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-09-2022

Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Diamyd
Generic name:	rhGAD65

Ethics review

Approved WMO Date:	21-10-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-12-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-07-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-10-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-10-2022

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-01-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-10-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-03-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	23-05-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
EU-CTR	CTIS2024-513304-33-00
EudraCT	EUCTR2021-002731-32-NL
CCMO	NL78794.100.21