





Precision Medicine for Autoimmune Diabetes in Pivotal Phase 3



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TARGETING AUTOIMMUNE AND INSULIN DEFICIENT DIABETES



Leading clinical stage pipeline

- First-in-class disease modifying therapies Diamyd® and Remygen®
- Pivotal program with a precision medicine approach, R&D partnership with JDRF

De-risked development program • Responder nations identified



- Responder patients identified for Diamyd®, significantly increasing likelihood for success in pivotal program with a precision medicine approach
- Excellent safety profile and simple procedure support successful commercialization

Strong growth opportunity



- Multibillion dollar market and label expansion opportunities
- **Pivotal program** in Type 1 Diabetes (Diamyd®), **Prevention program** Type 1 Diabetes (Diamyd®), establishing **GMP biomanufacturing facility**

Experienced team



- Significant operational experience in clinical development within diabetes
- Access to world leading scientists and clinical experts





AUTOIMMUNE DIABETES

Significant unmet medical need and health economic burden

Type 1 Diabetes

~ 500,000 new cases every year*

184,100 children and adolescents (0-19 years of age) and 329,000 adults are diagnosed with type 1 diabetes every year. It is more prevalent in western countries with the highest incidence in the Nordic countries.

The disease is characterized by life-long dependence on exogenous insulin therapy and blood glucose monitoring and the disease is associated with severe short and long-term complications that lead to shorter life-expectancy, decreased quality of life and significant health economic costs.

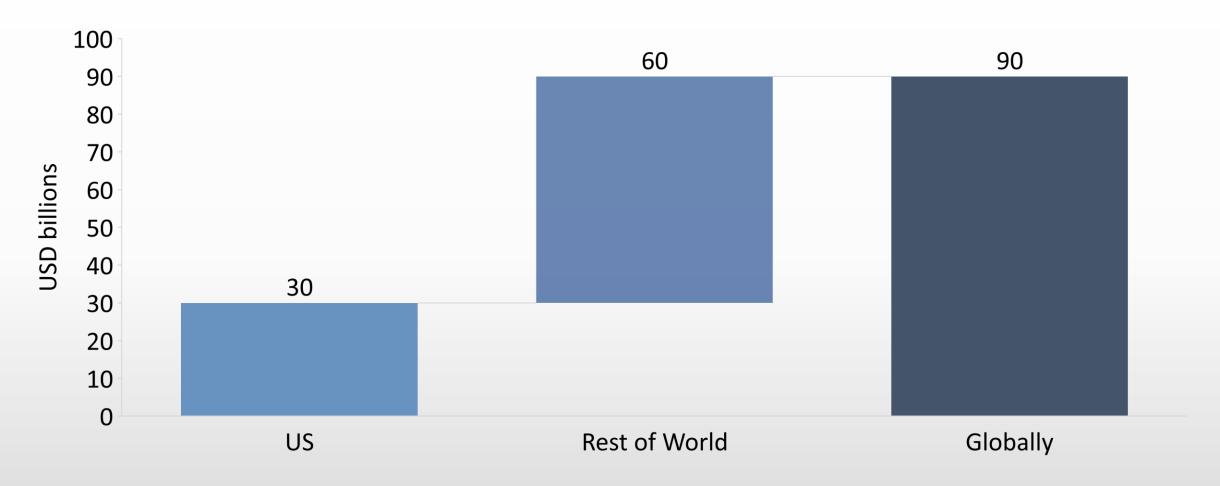
LADA (Latent Autoimmune Diabetes in Adults)

>2 million new cases every year

It is estimated that up to 10% of all type 2 diabetes patients have autoimmune diabetes characterized by autoantibodies against GAD and faster progression to insulin dependence. While type 1 diabetes is rare in many non-western countries, LADA is a prevalent form not only in western countries but also in India, China and Japan.

The disease is today (mis)treated as type 2 diabetes and no disease modifying therapies are available. It is associated with severe short and long-term complications that lead to shorter life-expectancy, decreased quality of life and significant health economic costs.

SIGNIFICANT ANNUAL ECONOMIC BURDEN OF TYPE 1 DIABETES



Disease modifying therapies for T1D are predicted to have a multibillion-dollar economic impact in the US alone

Leading pipeline targeting autoimmune diabetes

Product	Indication	Sample size	Sponsor	Development Phase				Chahua
				Preclinical	ı	II	III	Status
Diamyd®	Recently-diagnosed clinical (Stage 3) T1D	330 (target)	Diamyd Medical	DIAGNODE-3				Ongoing in Europe, approved to start in the US Topline H2 2026
	Recently-diagnosed Clinical (Stage 3) T1D	6	Linköping University	DIAGNODE-B				Ongoing Topline Q4 2023
	Latent Autoimmune Diabetes in Adults (LADA)	15	NTNU, Trondheim	GADinLADA				Completed*
	Prevention of T1D in at-risk (Stage 1 & 2) individuals	15 (target)	Diamyd Medical	DiaPrecise				Approved to start
Remygen®	Long-term Clinical (stage 3) T1D	36	Uppsala University	ReGenerate-:	1			Fully recruited Topline Q1 2023

^{*}Presented at EASD 2022 in Stockholm. Met primary endpoint of safety and tolerability, supports benefit for C-peptide preservation in HLA DR3-DQ2 individuals.



Diamyd®

Recombinant GAD65 Formulated in Alum (rhGAD65/alum)

Primary Indication

New-onset (stage 3) Type 1 Diabetes with HLA type DR3-DQ2

Label Expansion

Type 1 Diabetes prevention (stage 1 & 2), LADA

Mechanism of Action

Induce immunological tolerance against GAD65

Clinical Effect and Benefit

Preserve the endogenous insulin production, reduce short- and long-term complications

Mode of Administration

Three intranodal injections one month apart

Development Status

Phase III — Stage 3 T1D Phase I/II — Stage 1&2 T1D Phase I/II - LADA

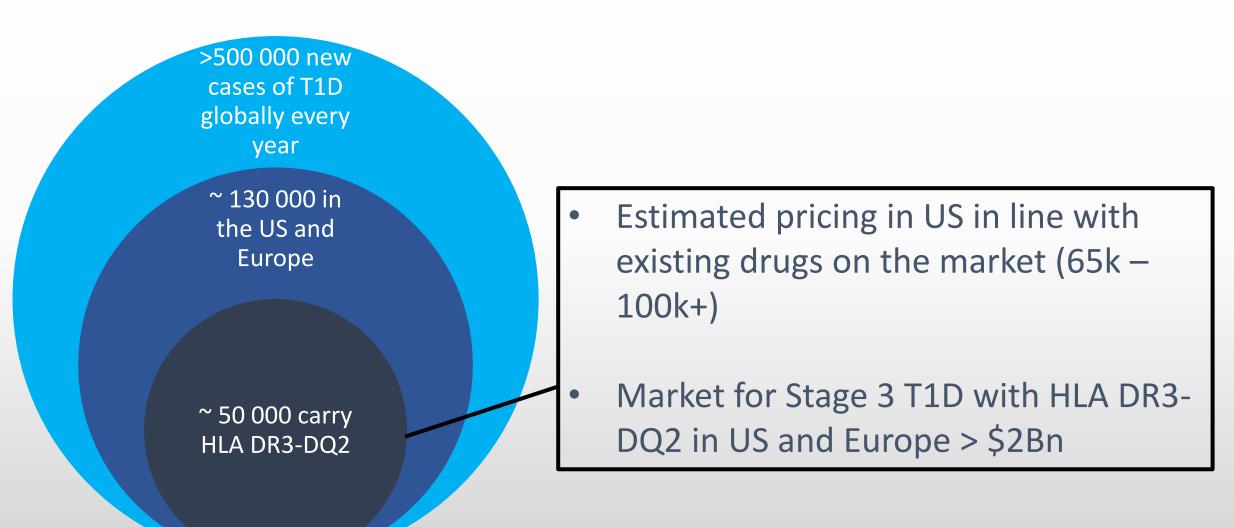
Licensing Status

Global rights available





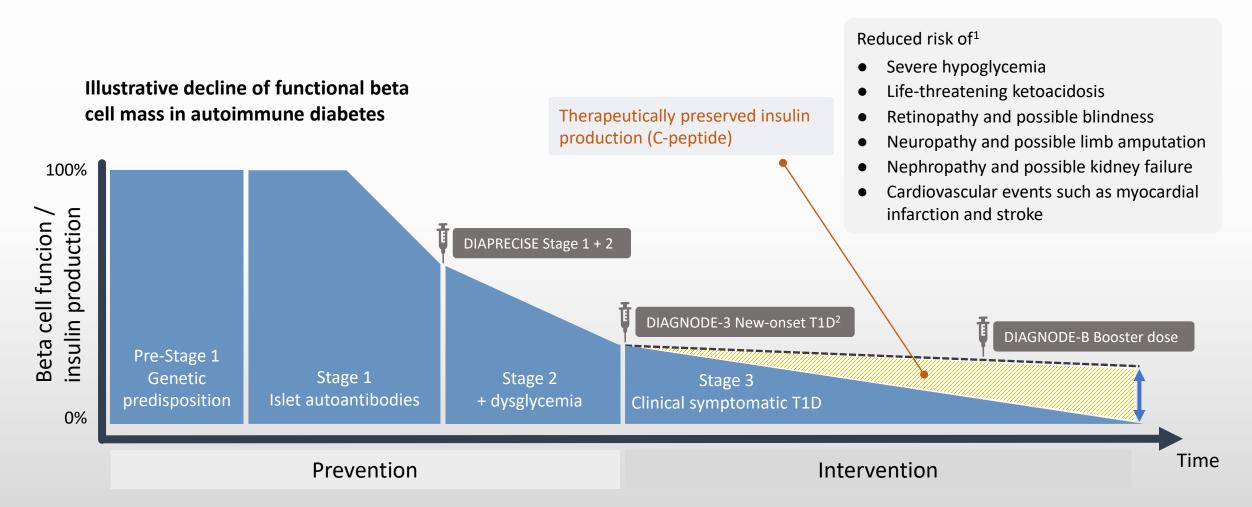
Multibillion total addressable market for Diamyd®

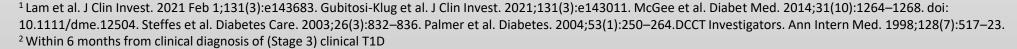




Focus on preemptive medicine

Diamyd[®] is designed to prevent diabetes complications and improve glucose control by stopping the autoimmune destruction of beta cells

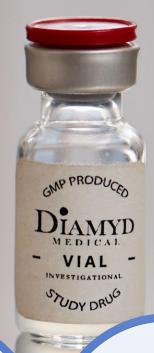












Stage 3 T1D Stage 1&2 T1D

LADA

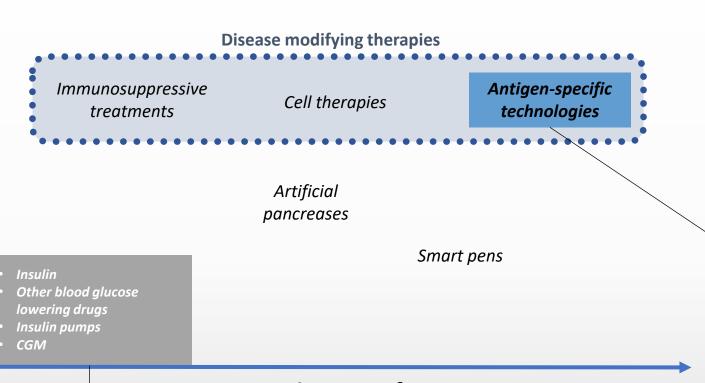
Boosters

Combinations



POSITION DIAMYD® TO MAXIMIZE EFFICACY, SAFETY, CONVENIENCE





Antigen-specific immunotherapy with Diamyd® targets the body's immune system by reprogramming it to stop attacking the insulin-producing cells. This treatment has the potential for long-term efficacy. Compared with other technologies under development often requiring hospitalization, the diabetes vaccine Diamyd® displays an excellent safety profile and is a fast and easy treatment.

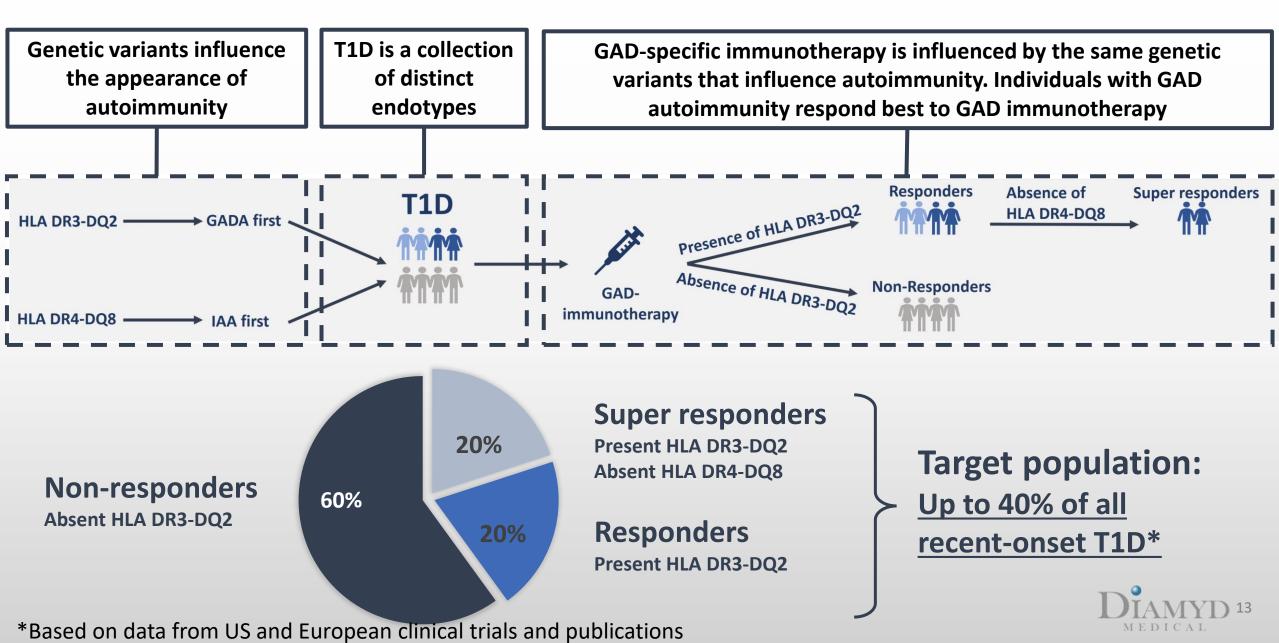
Convenience, Safety

Added value compared to standard of care

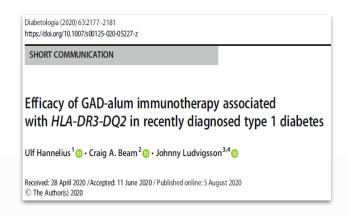
The current **standard treatment** for type 1 diabetes is life-sustaining, subcutaneous deliveries of insulin by injection or pump therapy, combined with continuous glucose monitoring (CGM). In addition to non-insulin anti-diabetic drugs and aids, such as artificial pancreases and smart insulin pens to help patients manage their condition, therapies targeting the underlying causes of the disease are also being developed.

New-onset (Stage 3) Type 1 Diabetes with HLA type DR3-DQ2

RESPONDERS TO DIAMYD® TREATMENT



CRUCIAL RESEARCH ADVANCES IN PRECISION MEDICINE FOR TYPE 1 DIABETES





Intralymphatic Glutamic Acid
Decarboxylase With Vitamin D
Supplementation in Recent-Onset
Type 1 Diabetes: A Double-Blind,
Randomized, Placebo-Controlled

Diabetes Care Volume 44, July 2021

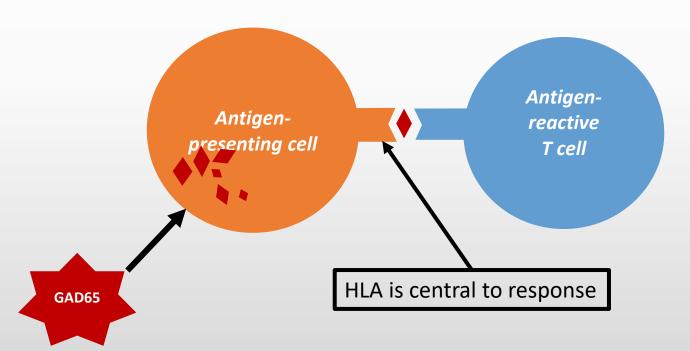
Diabetes Care 2021;44:1-9 | https://doi.org/10.2337/dc21-0318

Phase IIb Trial

Johany Ludvigsson, ¹. Zdenek Sumnik, ²
Terzie Pelikanova, ² Lia Nattero Chover, ⁴
Elena Lundbergi Zhtsos Rica, ²
Maria A. Martinez-Brocca, ²
Maris A. Martinez-Brocca, ³
Anastasia Katsarou, ³⁸ Ragnar Hanas, ¹¹
Cristina Henamade, ¹²
Maria Clemente León, ¹²
Maria Clemente León, ¹³
Ana Gómez-Gia, ³⁸ Marcus Lind, ^{15,16}
Marta Ferrer Lotono, ¹² Theo Sas, ³⁸
Ulf Samuelsson, ³ Sepanka Pruhova, ²
Fobricia Dietrich, ¹⁸ Sara Puente Marin, ¹⁹
Anders Nordlund, ³⁰ Ulf Hannelius, ²¹ and
Rossura Casas, ³⁰
Rossura Casas, ³⁰









Significant treatment effects on:

- 1. Preservation of endogenous insulin production
- 2. Improved HbA1c
- 3. Less glycemic variability
- 4. More time spent in optimal glucose range
- Less time spent in hyperglycemia

HLA INFLUENCES EFFECT OF DIAMYD®

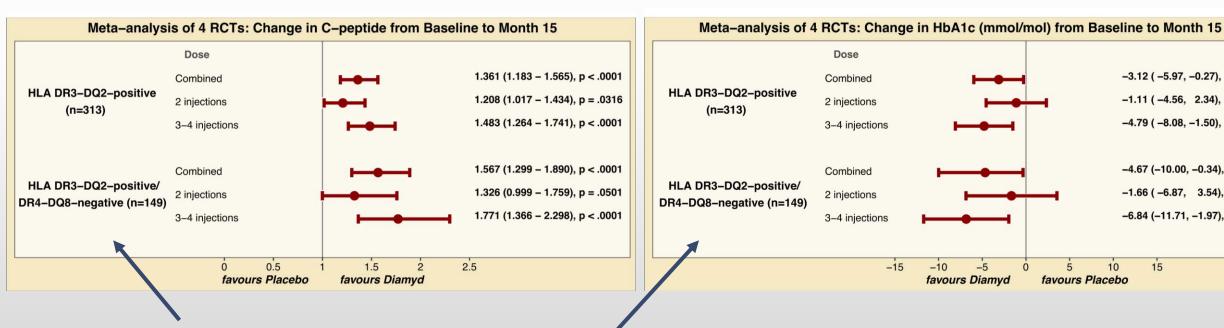
Significant and dose-dependent treatment effect of Diamyd® (GAD-alum) in HLA DR3-DQ2 positive individuals on preservation of own insulin production and HbA1c

Meta-analysis with >600 recent-onset T1D patients

4 RCTs (Phase III EUR, Phase II SWE, Phase II US, Phase IIb EUR)

C-peptide

HbA1c



High responder group lacking **HLA DR4-DQ8**



15

-3.12 (-5.97, -0.27), p = .032

-1.11 (-4.56, 2.34), p = .527

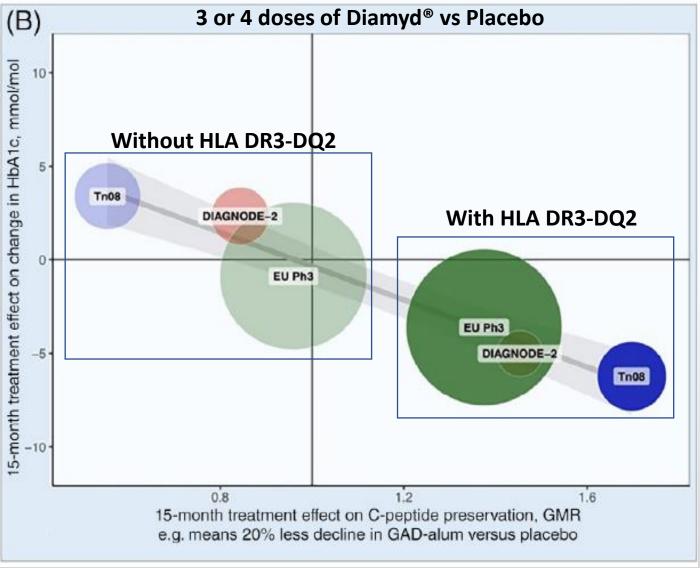
-4.79 (-8.08, -1.50), p = .004

-4.67 (-10.00, -0.34), p = .035

-1.66 (-6.87, 3.54), p = .529

-6.84(-11.71, -1.97), p = .006

CORRELATED TREATMENT EFFECTS (CHANGE FROM BASELINE TO MONTH 15 VERSUS PLACEBO) ON C-PEPTIDE AND HBA1C



DIABETES, OBESITY AND METABOLISM

Association between treatment effect on C-peptide preservation and HbA1c in meta-analysis of GAD-alum immunotherapy in recent-onset Type 1 diabetes

Christoph Nowak, Ulf Hannelius, Johnny Ludvigsson

First published: 17 April 2022 | https://doi.org/10.1111/dom.14720

Sensitivity analyses, including adjustment for insulin dose, confirm robust effect





The first ever precision medicine Phase III trial in Type 1 Diabetes

- Diamyd[®] in individuals recently diagnosed with type 1 diabetes and positive for the HLA DR3-DQ2 haplotype
- Ongoing in 8 European countries, approved to start in the US
- Partnership with JDRF, the leading global type 1 diabetes research and advocacy organization

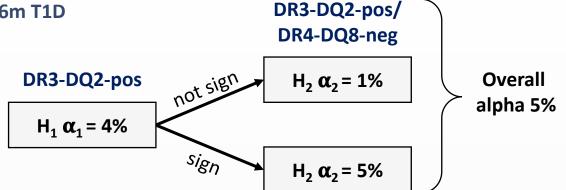


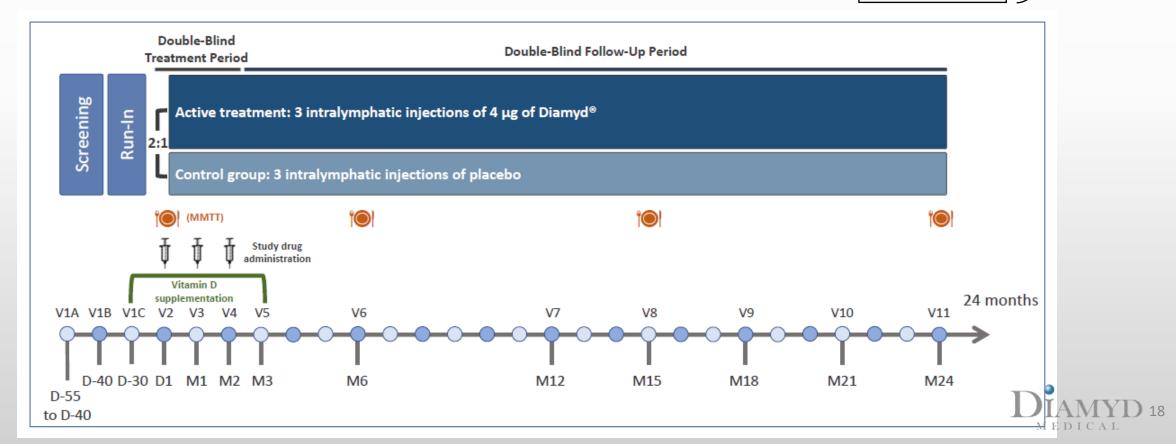
Diagnode-3
study

www.diagnode-3.com

RESULTS SUPPORT DESIGN OF PIVOTAL, GLOBAL PHASE III TRIAL DIAGNODE-3

- Responder population HLA DR3-DQ2 (40-50%) with GADA, 12-28 yr, <6m T1D
- Intralympatic injections (superior to subcutaneous injections)
- 3 monthly injections (superior to 2 injections)
- Co-primary endpoints C-peptide and HbA1c (baseline to Month 24)
- Total n = 330





Latent Autoimmune Diabetes in Adults (LADA)*

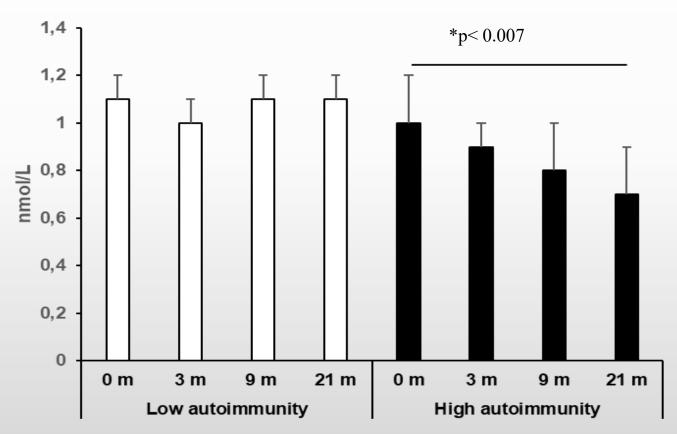


^{*}Also called Slowly progressing Autoimmune Diabetes (SAID) or Slowly progressing insulindependent diabetes mellitus (SPIDDM)

Background

In highly autoimmune LADA individuals: treatment that directly targets autoimmunity is needed

Glucagon-stimulated C-peptide (mean ± SEM)

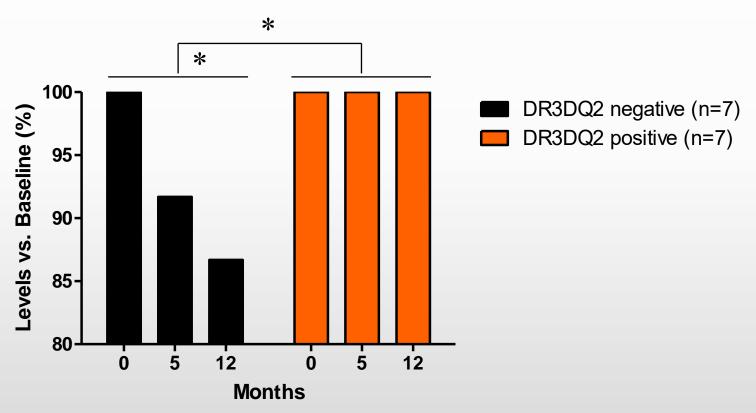


Hals IK, Fiskvik Fleiner H, Reimers N, Astor MC, Filipsson K, Ma Z, Grill V, Björklund A. Investigating optimal β-cell-preserving treatment in latent autoimmune diabetes in adults: Results from a 21-month randomized trial. Diabetes Obes Metab. 2019 Oct

Glucagon-stimulated C-peptide levels unchanged at 12 months vs Baseline (0 months) in the HLA-DR3DQ2 positive subgroup

Phase 2 trial with Diamyd in up to 70 year-old LADA patients

Glucagon-stimulated C-peptide



^{*}p< 0.03 for median 13.3% reduction at 12 months vs. Baseline (0 months) in the DR3DQ2 negative subgroup (n=7).

^{*}p< 0.04 for difference between HLA subgroups in change at 12 months vs. Baseline (0 months).

Conclusions

- Treatment with intralymphatic GAD is well tolerated in LADA individuals no safety concerns
- GAD-induced immune responses appear compatible with those in studies with type 1 diabetes
- Results on C-peptide suggest an HLA-dependent beneficial effect akin to type 1 diabetes

Also see

- Latent Autoimmune Diabetes in Adults: Background, Safety and Feasibility of an Ongoing Pilot Study With Intra-Lymphatic Injections of GAD-Alum and Oral Vitamin D, Björklund et al, Front Endocrinol, 2022
- Press release: Updated results from clinical trial with Diamyd® presented today at diabetes conference

Type 1 Diabetes prevention (Stage 1 & 2)

DIAMYD MEDICAL COORDINATES THE ASSET MILIEU

A T1D Forum to drive precision medicine, prevention and screening



ABOUT ASSET

The innovation milieu ASSET (AI for Sustainable Prevention of Autoimmunity in the Society – www.asset.healthcare) will develop and evaluate new algorithms based on AI to be able to assess the individual risk of developing Type 1 Diabetes (T1D), and the likelihood of responding to different treatments. Data from cohort studies such as TEDDY (The Environmental Determinants of Diabetes in the Young), from Diamyd Medical's clinical trials with Diamyd® and from sources such as the National Diabetes Registry will consitute the initial training dataset for the algorithm. T1D will form the pilot project for the program, but the goal is extend the functionality to other indications including other autoimmune diseases that are strongly linked to T1D such as celiac disease (gluten intolerance) and autoimmune thyroiditis (inflammatory disease of the thyroid gland). The prediction algorithm will be evaluated in clinical prevention trials where individuals at high risk for type 1 diabetes will be treated preventively with the diabetes vaccine Diamyd[®]. In parallel, ASSET will study organizational, economic, and legal prerequisites and consequences of applying the approach as a tool for precision health in the Swedish health care system. The project has a duration of five years and is financed via the Swedish innovation agency VINNOVA.









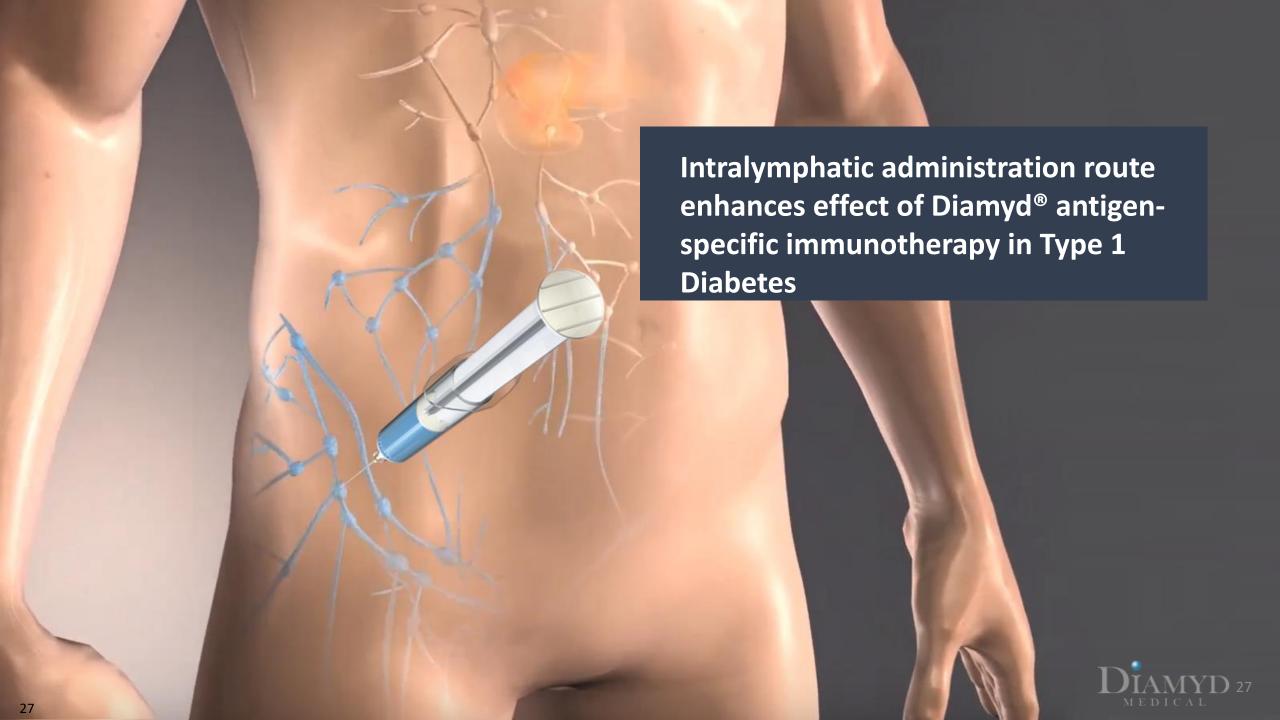






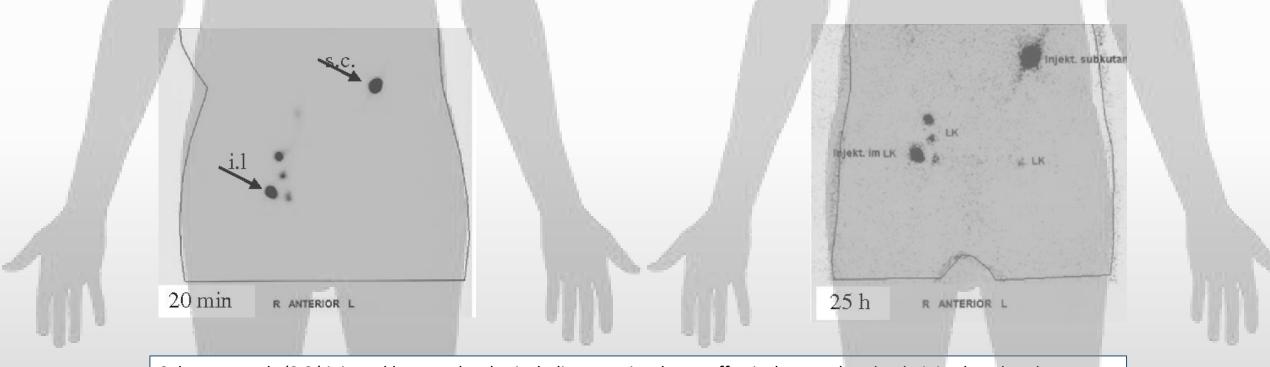
Safety and administration of Diamyd®





MORE EFFICIENT UPTAKE IN AND DRAINAGE TO LYMPH NODES FOLLOWING INTRALYMPHATIC COMPARED TO SUBCUTANEOUS ADMINISTRATION

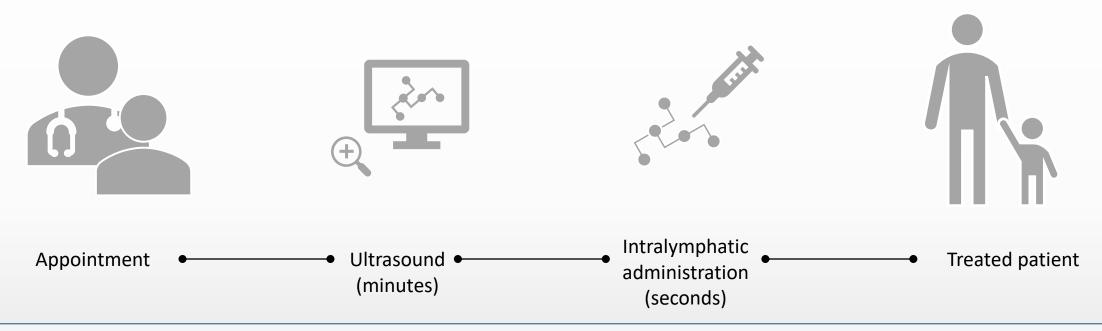
Lessons Learned from Allergy Immunotherapy Trials



Subcutaneously (S.C.) injected large molecules including proteins do not effectively spread to the draining lymphnodes. Intranodal (I.L.) injections lead to immediate spreading to deeper lymphnodes. The image depicts radio tracing of labeled IgG at 20 minutes and 25 hours after subcutaneous and intranodal injection in a healthy human volunteer.

CONVENIENT OUTPATIENT PROCEDURE ENHANCES VALUE PROPOSITION FOR DIAMYD®

Potential to reach patients outside specialized clinics and avoiding costs related to hospitalization

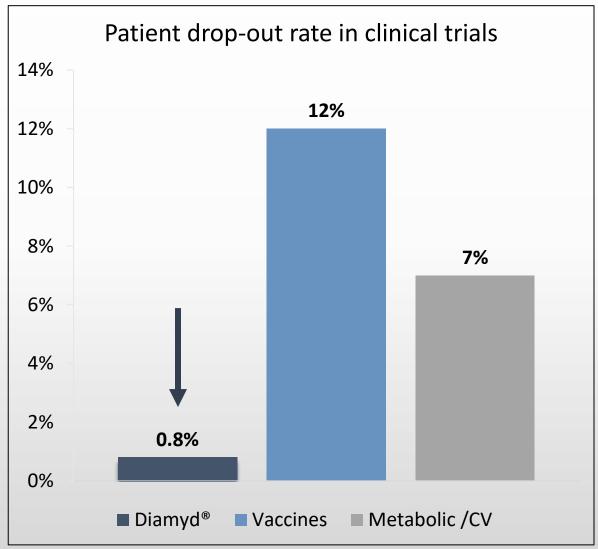


The procedure is performed by a radiologist by way of ultrasound guided injections that are given three times, one month apart. Clinical results and safety support the addition of annual booster injections in the pivotal trial.

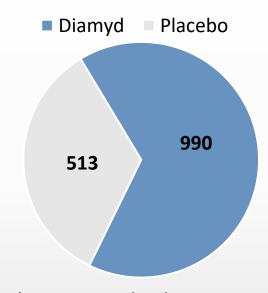
Confirmed* by interviews and questionnaires involving radiologists and study nurses taking part in the ongoing Phase IIb program, the procedure is simple and convenient, and can be performed using hand-held ultrasound devices. Non-radiologists could be educated to perform the procedure.

^{*} Evaluation of the Feasibility of Intralymphatic Injection of Diamyd®, Selam Fessehaye 2019, Master Thesis, Uppsala University

SUPERIOR SAFETY PROFILE



Total patient exposure



Most commonly reported adverse events:

- tenderness, injection site edema, injection site pain and injection site reaction.
- no difference in the rate of occurrence of the adverse events between active Diamyd[®] treatment and placebo

Manufacturing and Market Exclusivity of Diamyd®









Biomanufacturing – control and predictability

- 20,000 square feet site comprising clean rooms, laboratory facilities and office space
- In-house manufacturing of recombinant GAD65 (active pharmaceutical ingredient in the antigen-specific immunotherapy Diamyd®)
- Independent of third parties
- Goal to be production ready in 2023



DIAMYD® (rhGAD65/ALUM) MANUFACTURING

Upstream process:



Baculovirus expression system & Insect cells



Downstream process:





Clarification
Capture
Polish
Nanofiltration

DP formulation



DIAMYD® IP & MARKET EXCLUSIVITY



Core Intellectual Property

- Substance of matter in the US until 2032
- Intralymphatic administration of Diamyd® in Europe, Japan, China, Australia and Russia, additional countries pending, expiry 2035.
- Intralymphatic administration of additional betacell antigens (proinsulin, preproinsulin etc) approved in Australia, additional countries pending.
- **Precision medicine patent** based on HLA subgroups approved in Europe and Eurasia, expiry **2035**, additional countries pending.



Regulatory exclusivity

- US BLA approval provides 12 years exclusivity
- US orphan designation provides **7 years exclusivity** from approval
- European approval provides 10 years of exclusivity
- Accelerated approval pathways are being evaluated



Modified Release GABA

Primary Indication

Type 1 diabetes

Label expansion

LADA, Insulin-deficient type 2 diabetes

Mechanism of Action

Activate GABA-receptors in the pancreas

Clinical Effect

- Regenerate endogenous insulin production, reduce shortand long-term complications
- Prevention of hypoglycemia

Mode of Administration

Oral

Development status

Phase Ib/IIa ongoing

Licensing Status

Global rights available

Remygen®





CLINICAL RESULTS WITH ATTRACTIVE PATH TO MARKET FOR REMYGEN®

- Ongoing clinical Phase IIa trial*
 - ReGenerate-1 at the University of Uppsala where Remygen® (proprietary formulation of GABA) alone and in combination with low-dose alprazolam (GABA receptor modulator to enhance effect, see next slide) are being evaluated in longstanding type 1 diabetes patients
- Clinical effects (dose-escalation) from ReGenerate-1 shown on preventing hypoglycemia by correcting the counter regulatory hormone response and increasing time-in-range in long-term type 1 diabetes*
- Clinical effects of GABA shown on decreasing glucagon secretion in recent-onset type 1 diabetes**
- Preclinical effects on insulin secretion, glucagon secretion and beta cell regeneration
- Endogenous substance with very good safety profile***



^{*}Favorable clinical effects following dose-escalation communicated in November 2019

^{**}Preliminary results presented at EASD 2019 by Professor Kenneth McCormick, University of Alabama at Birmingham

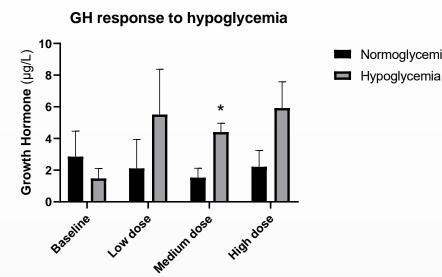
^{***}Favorable safety review following dose-escalation in November 2019 and combination with Alprazolam in January 2021

BMJ Open Diabetes Research & Care

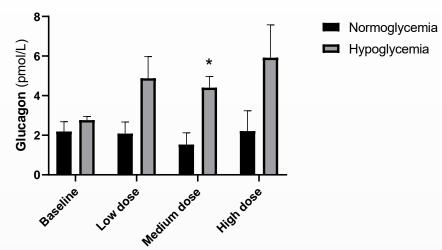
GABA induces a hormonal counterregulatory response in subjects with long-standing type 1 diabetes

Daniel Espes , 1,2 Hanna Liljebäck, 4 Henrik Hill, Andris Elksnis, José Caballero-Corbalan, Per-Ola Carlsson, Andris Elksnis,

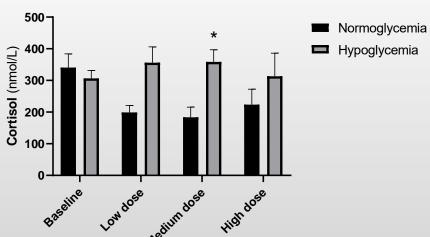
GABA TREATMENT IMPROVES THE HORMONAL RESPONSE TO HYPOGLYCEMIA



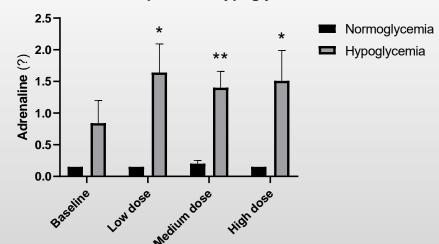
Glucagon response to hypoglycemia



Cortisol response to hypoglycemia



Adrenaline response to hypoglycemia

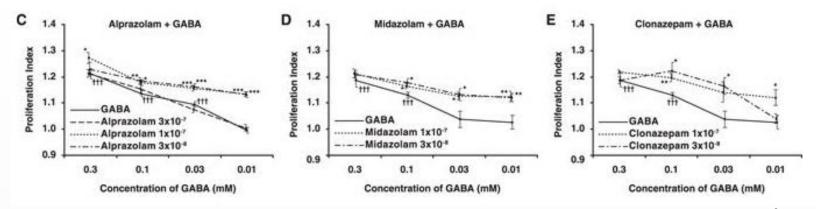


Comparisions between noro- and hypoglycemia for the respective group using a multiple T-test with pvalues corrected for multiple testing using the Holm-Sidak method. * denotes p<0.05, ** <0.01 Values are given as mean±SEM



Normoglycemia

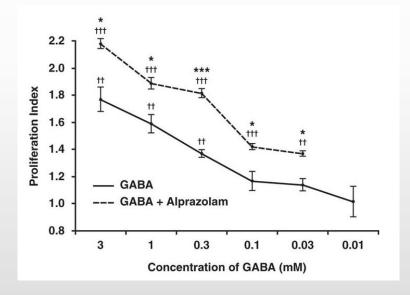
Positive allosteric modulators enhance GABA:s beta cell regenerative effects*



Effect of PAMs on INS-1 cell proliferation. INS-1 cells were cultured with the indicated PAM at a dose range of 10^{-9} to 10^{-6} M and assessed for their proliferation. Data shown are the average rate of proliferation relative to that of cultures with media alone (designated as 1).

Alprazolam enhances GABA's ability to promote human islet cell replication. Human islets were incubated with a dose range of GABA together with alprazolam (100 ng/ml) for 4 days in the presence of 3H thymidine. Data shown are the average rate of proliferation relative to that of cultures with medium alone (designated as 1) in a representative study. N = two independent studies with triplicate cultures. The results were very similar in both studies. $^{++}p < 0.01$ and $^{+++}p < 0.001$ for GABA, or GABA + alprazolam vs. control medium alone; $^{+}p < 0.05$ and $^{+++}P < 0.01$ for GABA + alprazolam vs. GABA alone, determined by Student T-test.

→ Potential to safely enhance GABA:s regenerative effects on beta cells by using a small (sub-CNS) dose of benzodiazepines



^{*}Clinically applicable GABA receptor positive allosteric modulators promote ß-cell replication. Sci Rep. 2017 Mar 23

REMYGEN® MARKET EXCLUSIVITY AND MANUFACTURING



Core Intellectual Property

- Exclusive license from UCLA on treating diabetes and other inflammatory diseases with GABA
- **Formulation patent** application (Remygen®). Application in national phase.
- Exclusive license from UCLA on GABA in combination with GABA receptor modulators to enhance the regenerative and immunomodulatry effect. Application in national phase.



Regulatory exclusivity

• 505(b)(2) regulatory pathway in the US provides potentially faster time to market at reduced cost

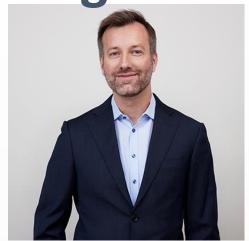


Manufacturing

• GMP drug substance (GABA) and drug product (Remygen®) manufacturing in place



Management



Ulf Hannelius

Chief Executive Officer



Martina Widman

Chief Operating Officer



Anna Styrud

Chief Financial Officer



Anton Lindqvist

Chief Scientific Officer



Maja Johansson
Site Manager, Umeå



Eva Karlström

Chief Regulatory Affairs

Officer



Christoph Nowak
Chief Medical and
Business Officer



Board of Directors



Erik Nerpin Chairman



Anders Essen-Möller



Maria-Teresa Essen-Möller



Torbjörn Bäckström



Mark A. Atkinson



Karin Hehenberger



Karin Rosén Adjunct member



TOP WORLDWIDE EXPERTS

Covering the areas of clinical practice and scientific excellence in Type 1 Diabetes and



Prof. Johnny Ludvigsson

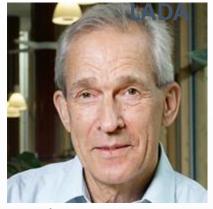
Professor of Pediatrics. First in the world to use immune intervention in children and teenagers with newly diagnosed T1D, and in collaboration with others

64kD was found. An alumformulation of GAD was developed (Diamyd®), used as a treatment in an effort to deviate the immune system and create tolerance.



Prof. David Leslie

Professor of Diabetes and Autoimmunity. Professor Leslie has been Director of the British Diabetic Twin Study since 1982, the world's largest twin study of its type and Principal Investigator of the European Action LADA consortium. By studying twins, Professor Leslie has been able to show the possibilities for predicting and preventing autoimmune diabetes.



Prof. Åke Lernmark

Professor in Experimental
Diabetes Research, Professor
Lernmark has focused his
research on diabetes and at an
early stage identified the
antigen that later proved to be
GAD. He and his colleagues
were the first to clone GAD65
from human islets using
biochemical methods and was
thus the first to define
autoantibodies against GAD65
in patients with type 1 diabetes.



Prof. Daniel Kaufman

Professor Kaufman's research is focused on studies in the field of autoimmunity, particularly type 1 diabetes (T1D) and understanding the disease mechanisms in order to develop novel therapeutics in mouse models that could potentially be translated to clinical use. Using preclinical models, Dr. Kaufman's lab helped to develop some of the GAD and GABA-based diagnostics and therapeutics for T1D that are in clinical use or are being tested in clinical trials.



Prof. Mark A. Atkinson

Professor of Diabetes Research, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, USA. American Diabetes Association Eminent Scholar for Diabetes Research. Director, UF Diabetes Institute, University of Florida. Independent of the Company and its principal owners.

Diamyd Medical Board member.





DIAMYD MEDICAL

- Swedish clinical phase pharmaceutical company, founded 1994
- NASDAQ First North Growth Market, ticker DMYD B

FINANCES

- Market Cap Apr 13, 2023 ~ MSEK 1 432
- Cash Feb 28, 2022: MSEK 102

INDICATIONS

- Diabetes
- Autoimmunity

PRODUCT CANDIDATES

- Diamyd® (Phase III)
- Remygen® (Phase Ib/IIa)

INVESTMENTS

- NextCell Pharma (Stockholm, Sweden)
- MainlyAl (Stockholm, Sweden)



Diamyd Medical

www.diamyd.com





