LEVICURE

REVERSE THE IRREVERSIBLE

Proprietary Disease-Modifying Treatment to Promote Remission Through ß-cells Regeneration in Type 1 Diabetes

INNODIA EASD Symposium

STARTUP +HEALTH

T1D Moonshot
Fellowship recipient

Levicure is developing a breakthrough disease-modifying treatment to promote remission through ß-cell regeneration in patients with recent-onset Type 1 Diabetes (T1D)

DPP-4i

GABA*

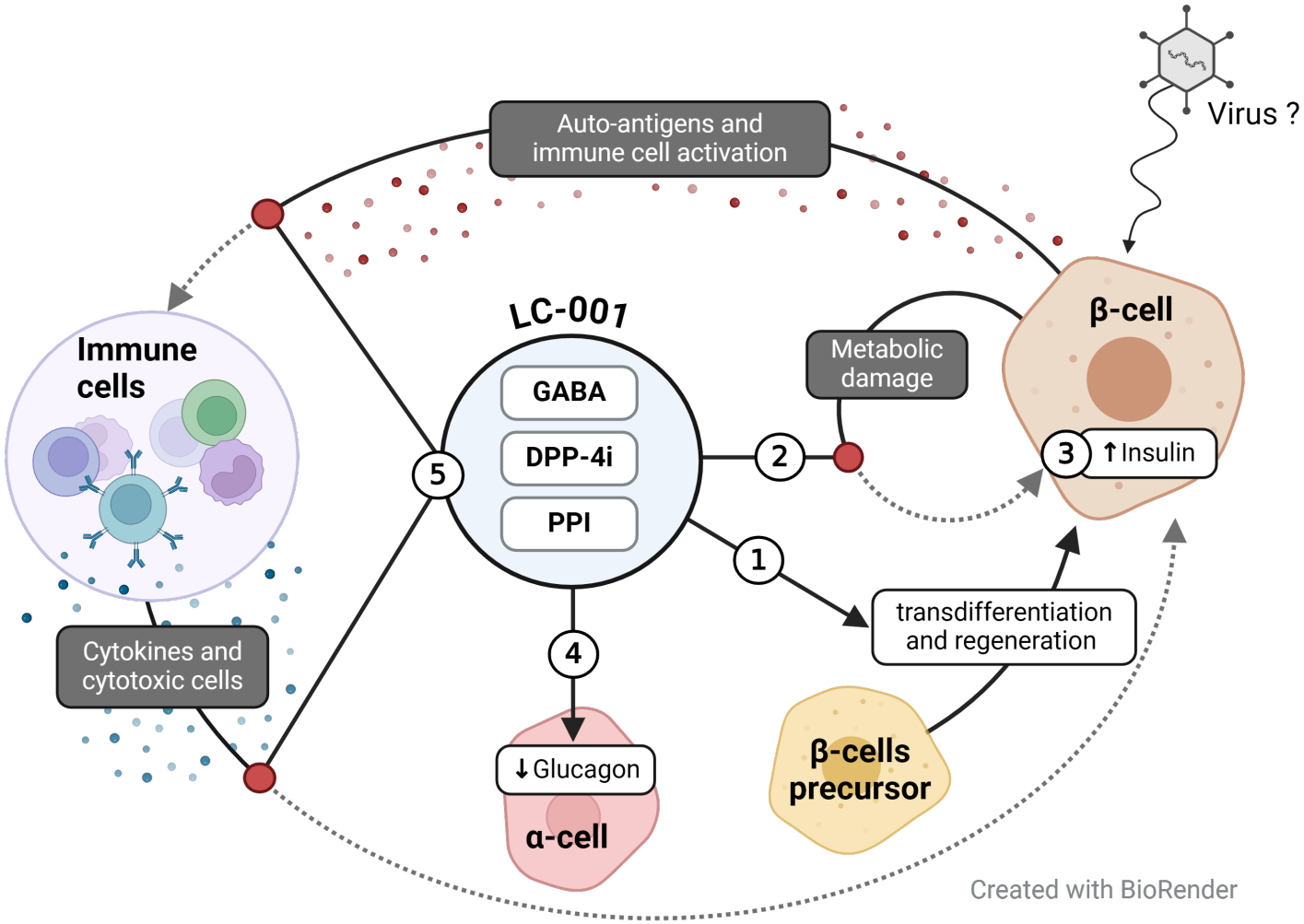
PPI

- Regenerate ß-cells
- Eliminate or reduce the need for additional insulin therapy
- Sustain normal blood glucose levels
- Reduce short and long-term T1D complications
- Once-a-day treatment

*extended-release gastro-retentive (ER/GR)

Mechanism of Action: GABA + DPP-4i + PPI treatment simultaneously synergistically focuses on regeneration of ß-cells and inhibition of autoimmunity

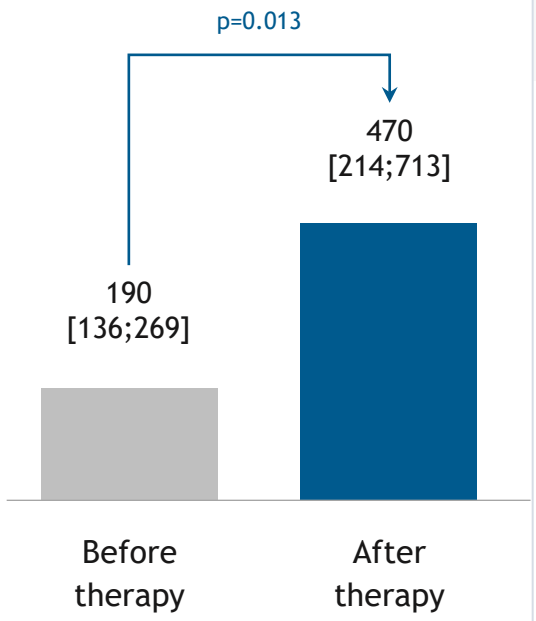
1. Initiates the transdifferentiation of duct cells and regeneration of ß-cells
2. Stops metabolic self-damage of ß-cells (downregulates TxNIP)
3. Increases insulin secretion
4. Inhibits glucagon secretion
5. Inhibits autoimmunity to ß-cells



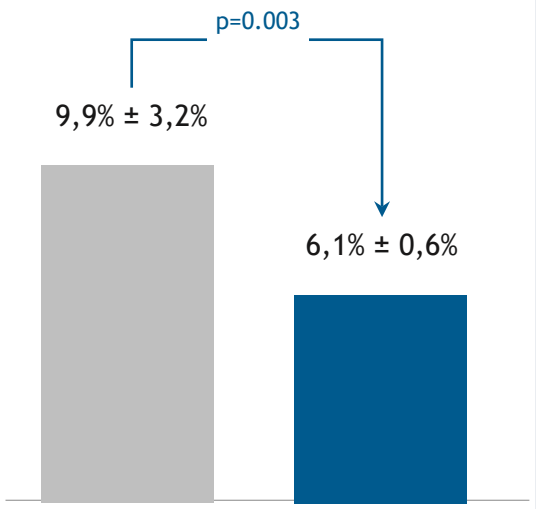
Our published retrospective study of prospectively treated patients shows significant outcomes in recent-onset adult Stage 3 T1D patients after 32 weeks of treatment with GABA, DPP-4i and PPI

Rabinovitch et al., Frontiers in Endocrinology, 2023

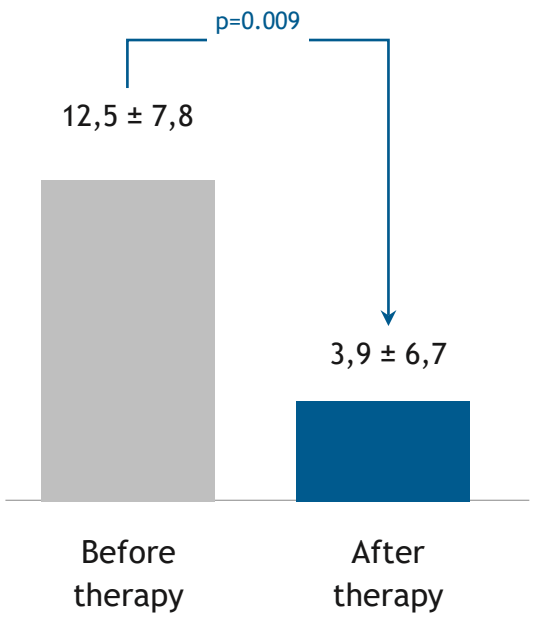
+147% C-peptide (pmol/L)



-38% HbA1c (%)



-69% Daily insulin dose (Units/Day)

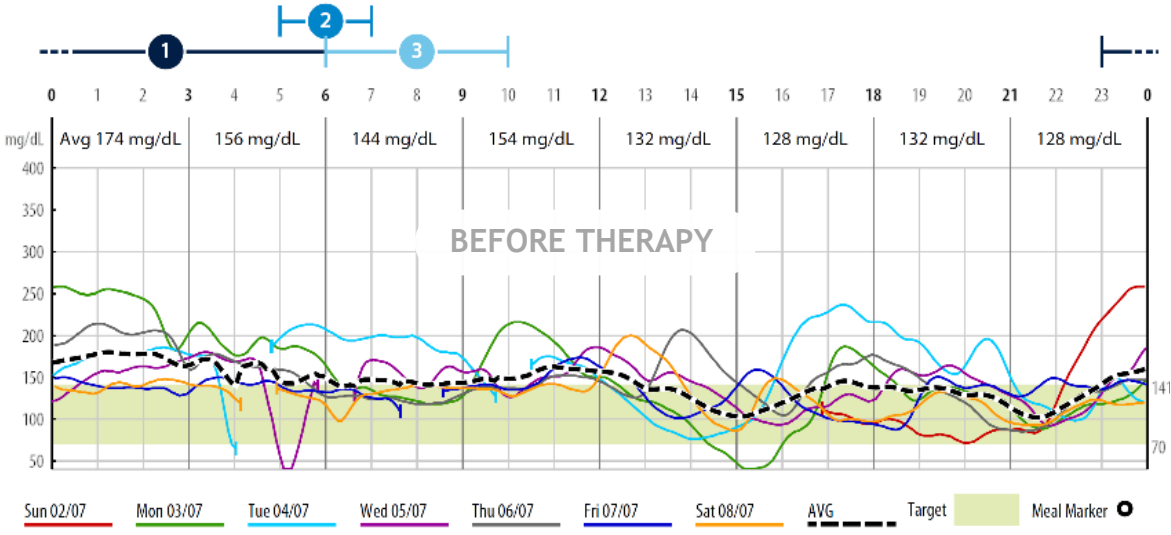


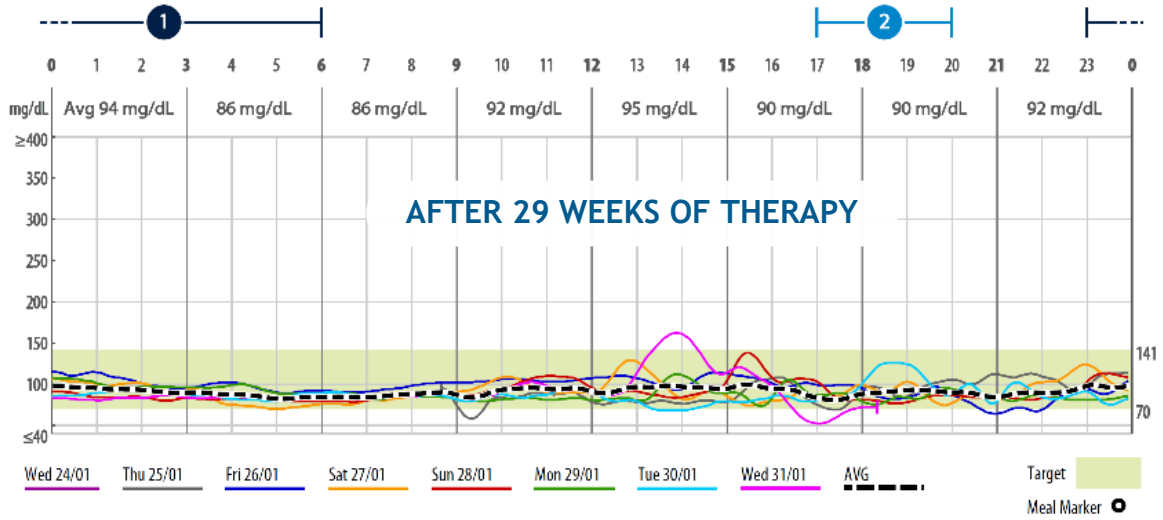
70%

of 10 recent-onset T1D patients (<12 months from diagnosis) stopped insulin injections and maintained normoglycemia within 32 weeks of treatment

Example: Patient 29-week results demonstrate significant improvement with Levicure Combination Therapy

OUR PATIENT	Age – 18 years	BMI - 19.8	GAD65 – Positive	Ketoacidosis on manifestation	Hospitalization on manifestation





Poor glycemic control

Insulin	12 units
HbA1c	8.5%
Fasting BG	130 (mg/dl)

Results within the healthy person reference range

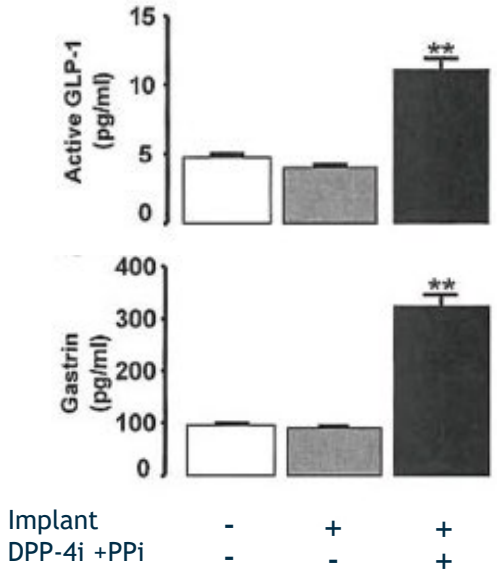
Insulin	0 units
HbA1c	5.2%
Fasting BG	100 (mg/dl)

DPP-4i + PPI induced ß-cell neogenesis from human pancreatic duct cells increasing the number of insulin-producing cells by 1300% via GLP-1 and gastrin elevation

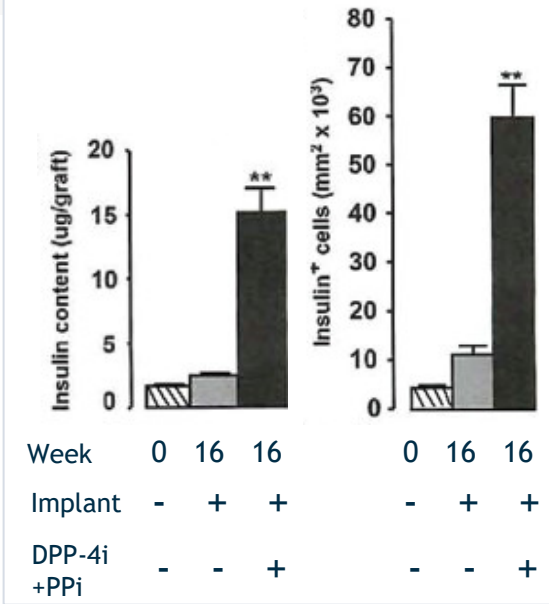
CELL TRANSPLANTATION

W. L. Suarez-Pinzon et al., Cell Transplantation, 2011

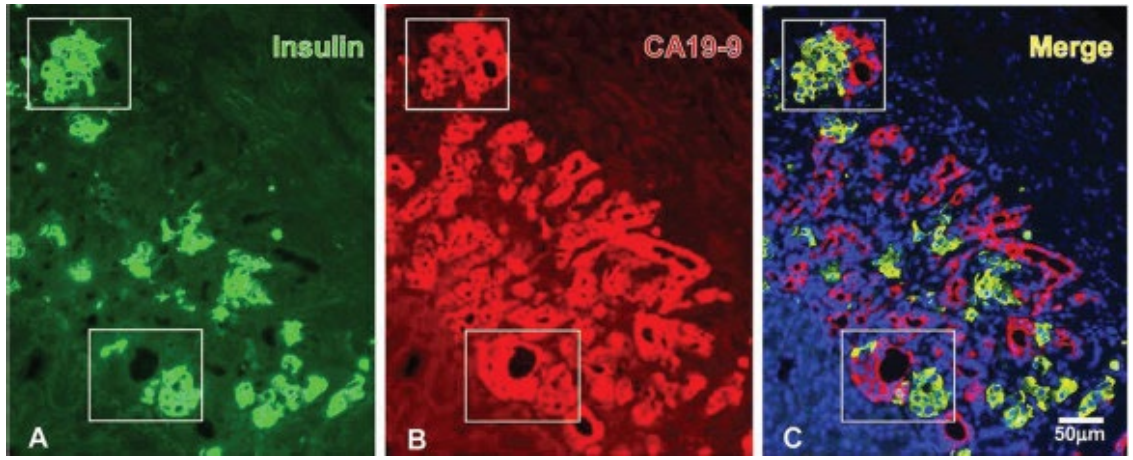
DPP-4i and PPI increased levels of GLP-1 and gastrin



DPP-4i and PPI increased insulin content and number of insulin producing cells by 1300%



All insulin-positive cells were colocalized with CA19-9-positive duct cells, with the double positive cells appearing yellow in the merged photomicrograph (Neogenesis)



Insulin+ cells | Duct+ cells | Insulin+ Duct+ cells

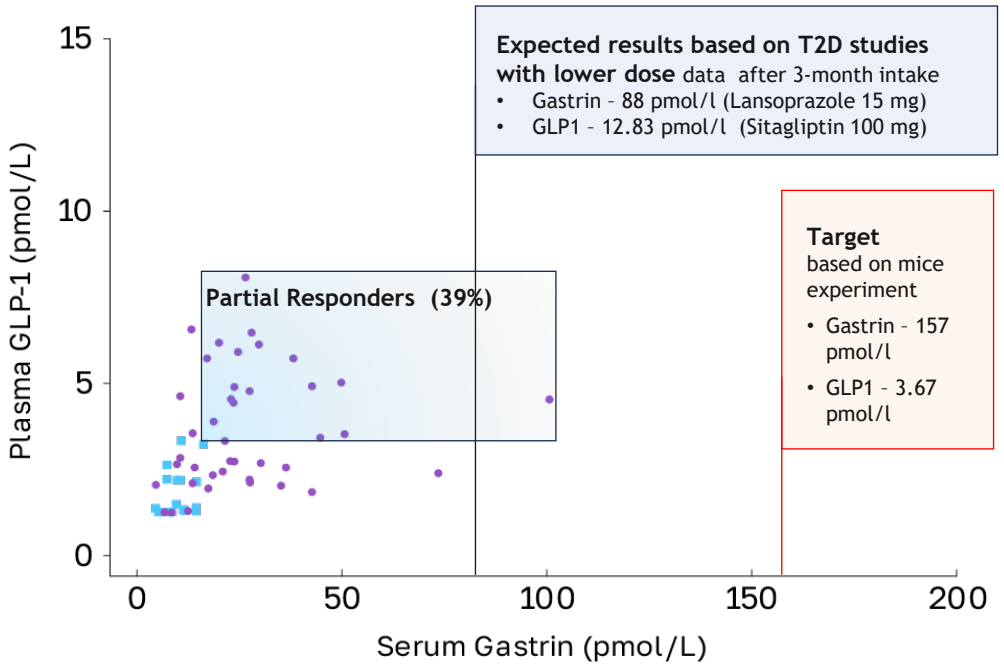
REPAIR T1D study: DPP-4i and PPI failed to increase GLP-1 and gastrin to expected levels in all recent-onset T1D patients and did not meet clinical endpoints

THE LANCET Diabetes & Endocrinology | Griffin et al., Lancet, 2014

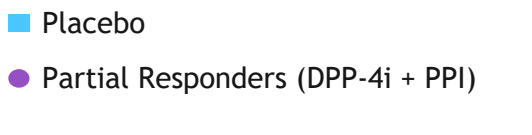
Even partial elevation of GLP-1 and gastrin in 39% of patients showed trends for improvement in clinical trial endpoints

Sitagliptin and Lansoprazole failed to the induce increases of GLP1 and gastrin to the level of planned effect in all patients

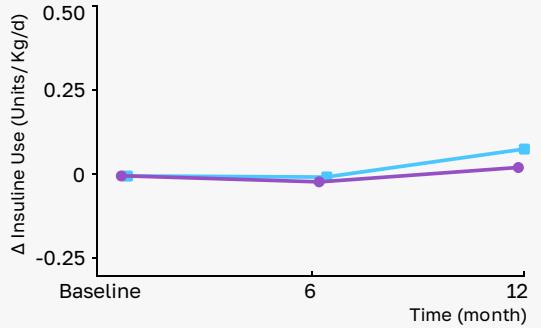
Study dose: Sitagliptin >18 years - 100 mg; <18 - 50 mg Lansoprazole >18 - 60 mg, <18 - 30 mg



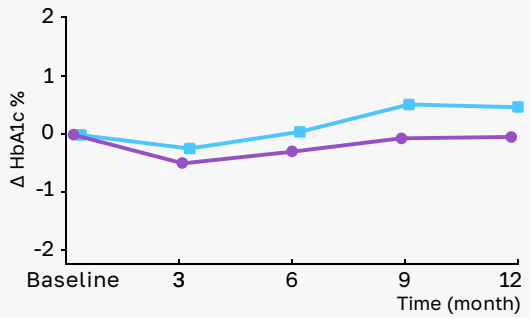
Partial responders showed trend for reduction of HbA1c, insulin dose and preservation of C-peptide response to MMTT



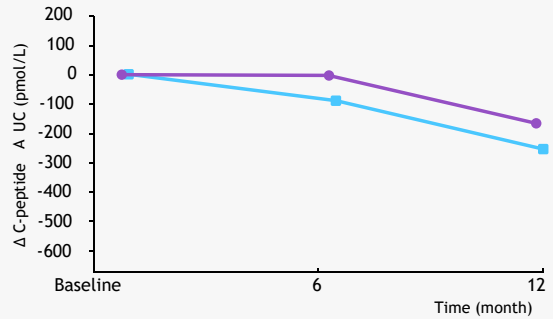
Delta insulin use (Units/kg/d)



Delta HbA1c, %



Delta C-peptide AUC (pmol/L)

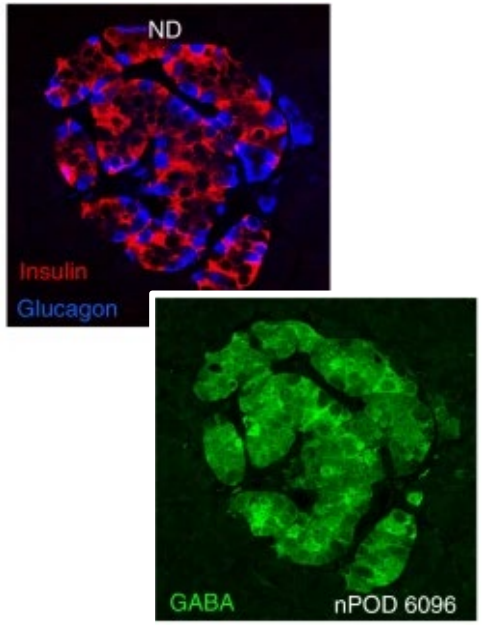


ß-cells are the main source of GABA in the islets. Loss of GABA is observed in all T1D donor islets affecting normal ß- and α-cell function

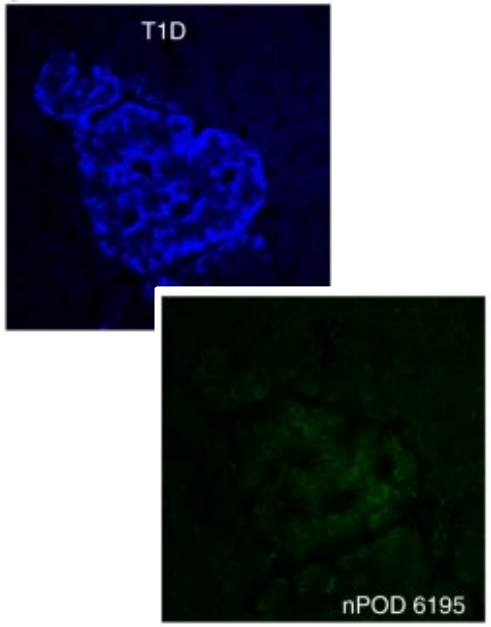
nature metabolism | Menegaz, D., Hagan, D.W., et al. Nature metabolism, 2019

Cytosolic pools of GABA are depleted in all type 1 diabetic islets

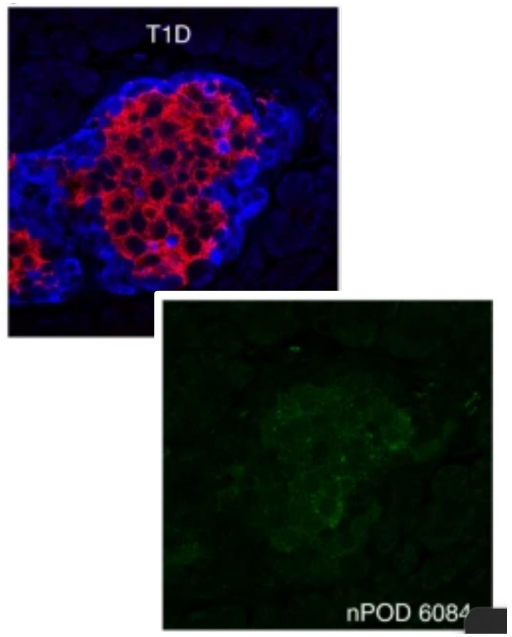
Healthy donor



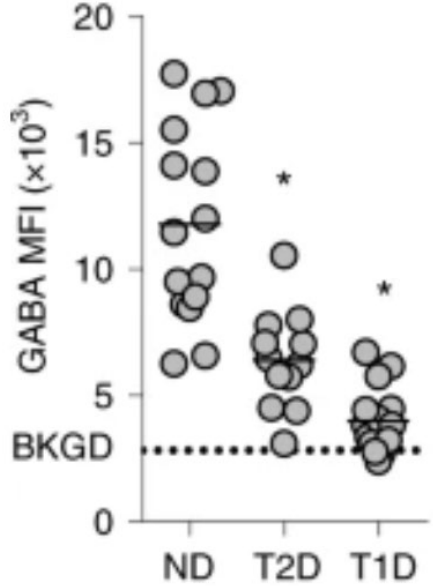
T1D Donor
(devoid of ß-cells)



T1D Donor
(with residual ß-cells)



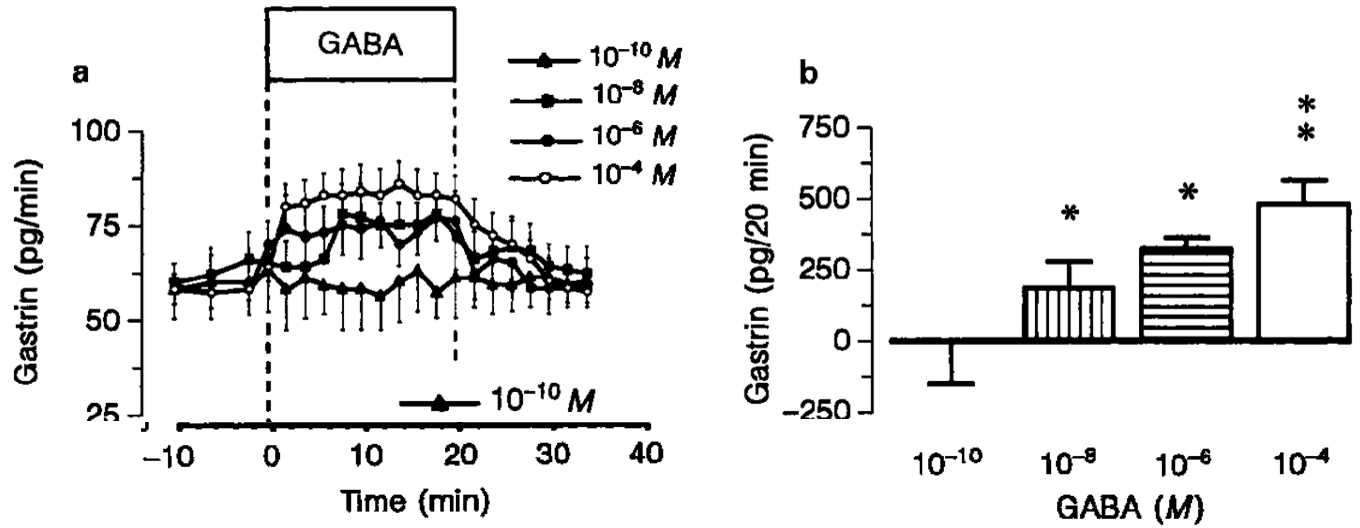
GABA content in T1D ß-cells is lower in comparison to healthy controls and T2D patients



Addition of GABA to the combination of DDP-4i and PPI is needed to ensure GLP-1 and gastrin elevation in all T1D patients

GABA stimulates secretion of Gastrin

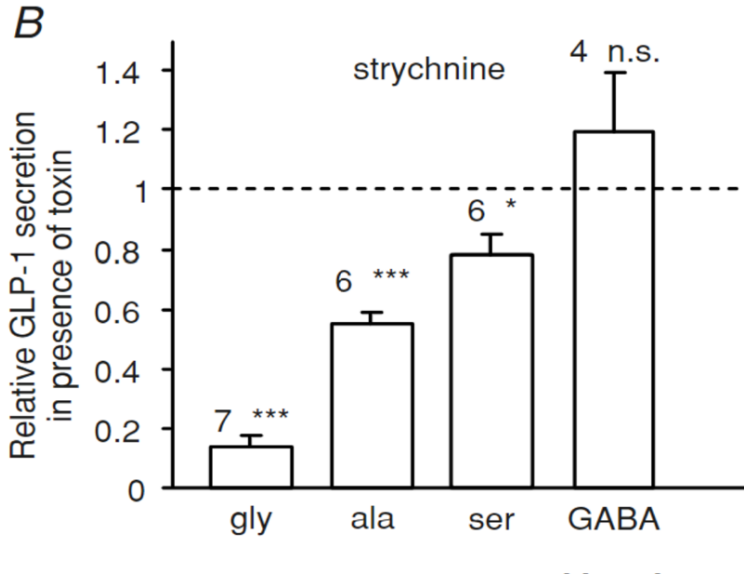
Perfused rat stomachs, Digestion, Weigert et al,1998



GABA stimulates secretion of GLP1

The Journal of Physiology

L-cell model GLUTag cells, Journal of Physiology, A. Gamiero, et al., 2005

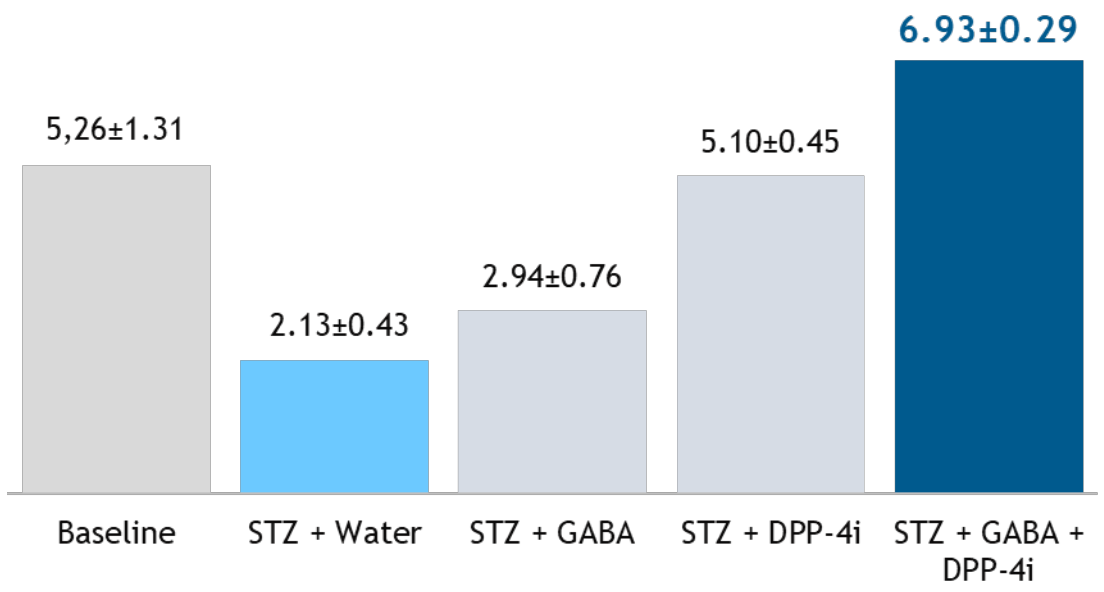


GABA and DPP-4i synergistically stimulate the secretion of GLP-1, promote β-cell proliferation and reduce the expression of pro-apoptotic TxNIP

Combined effect of GABA and DPP-4i was able to synergistically increase GLP-1

frontiers in Pharmacology

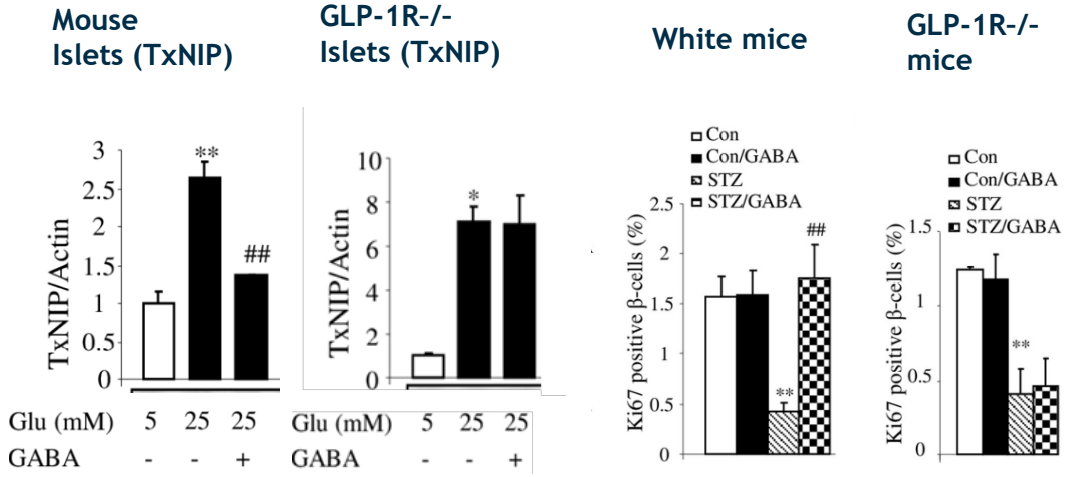
STZ mice, Liu W. et al., Frontiers in Pharmacology, 2017



GABA requires GLP-1 signaling to reduce the expression of TxNIP and promote proliferation

Journal of Endocrinology

WT mice and GLP1-1R-/- mice, Weijuan Shao et al., Journal of Endocrinology, 2020

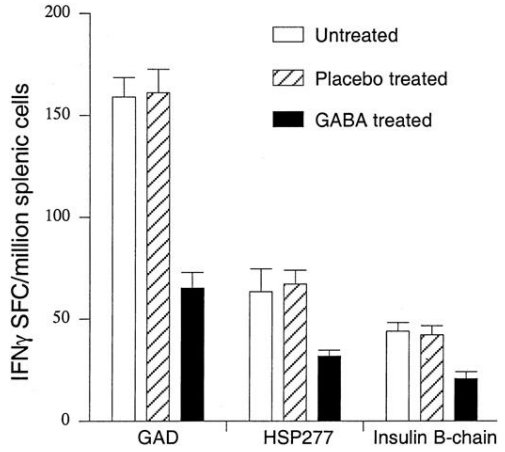


GABA and DPP-4i inhibits inflammatory immune response in T1D

GABA inhibits T cell autoimmunity and inflammatory cytokine responses in T1D

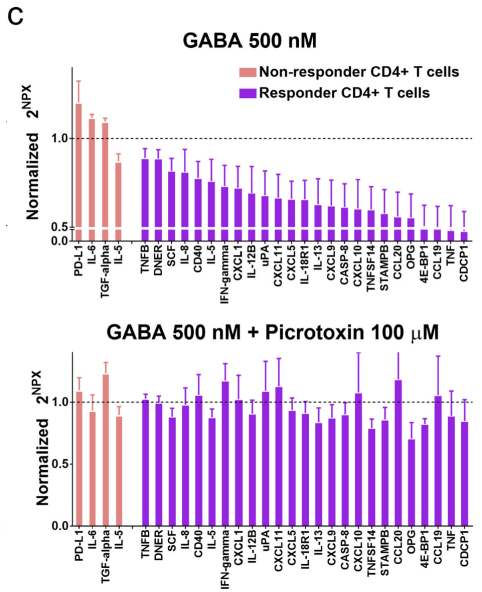
The Journal of Immunology

NOD mice, Tian J. et al., The Journal of Immunology, 2004



EBioMedicine
Published by THE LANCET

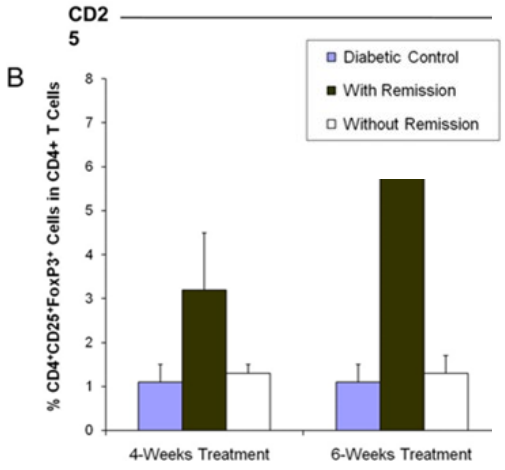
T1D patients, A. K. Bhandage et al., eBioMedicine, 2018



DPP-4i increases CD4+ regulatory T cells and decrease CD4+ proinflammatory T cells

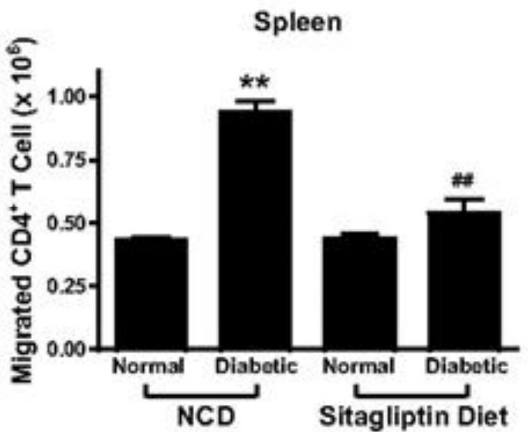
ENDOCRINOLOGY

NOD Mice, Tian L. et al., Endocrinology, 2010



diabetes

NOD Mice, S. J. Kim. et al, Diabetes, 2010

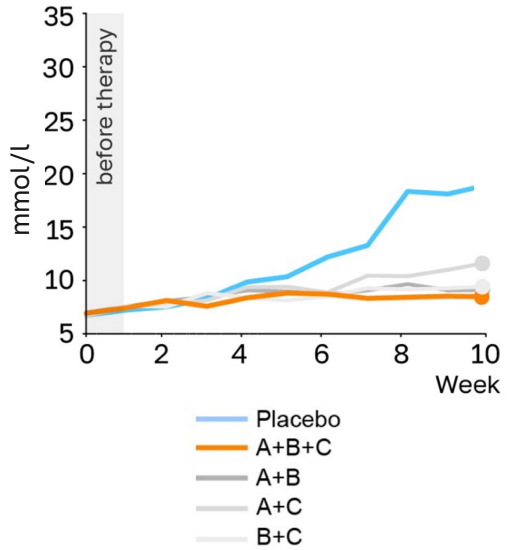


Triple Therapy showed a superior synergistic effect to reverse Stage 3 T1D in insulin-dependent hyperglycemic NOD mice
A - GABA, B - sitagliptin, C - omeprazole

frontiers | Lagunas-Rangel et al., Frontiers in Endocrinology, 2022

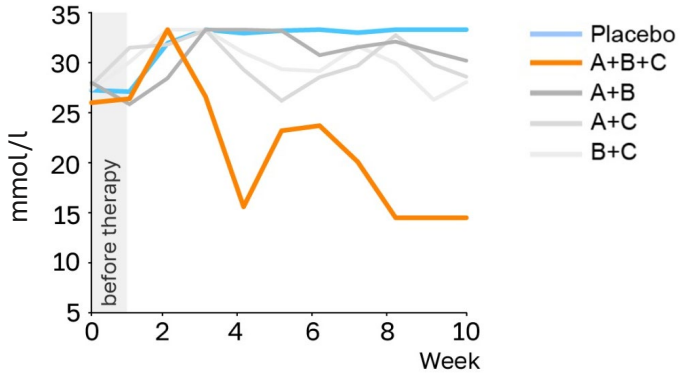
Pre-diabetic Stage 2 NOD mice

Blood glucose level (mmol/l)

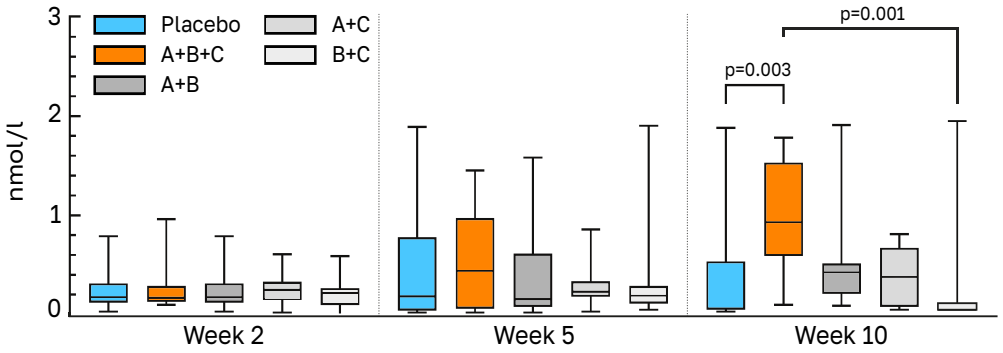


Hyperglycemic insulin-dependent Stage 3 NOD mice (up to 6 weeks after diagnosis)

Blood glucose level (mmol/l)



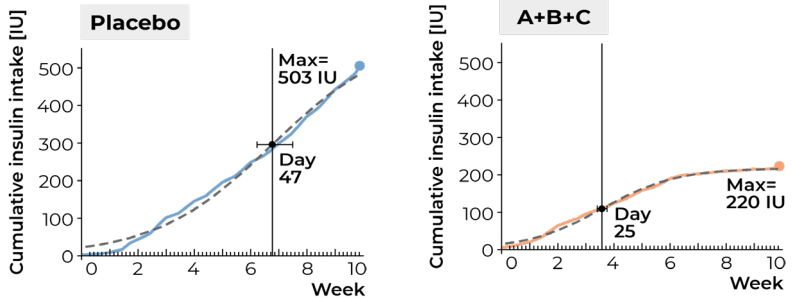
Dynamic changes of C-peptide levels (nmol/l)



Dosing and administration of insulin

Blood glucose range	Dose of insulin glargine
30.0- 33.3 mM/L	1.5 units/day
> 33.3 mM/L in a single measurement	1.5 units - morning 1 unit - evening
> 33.3 mM/L in two consecutive measurements	1.5 units - morning 1.5 units in the evening

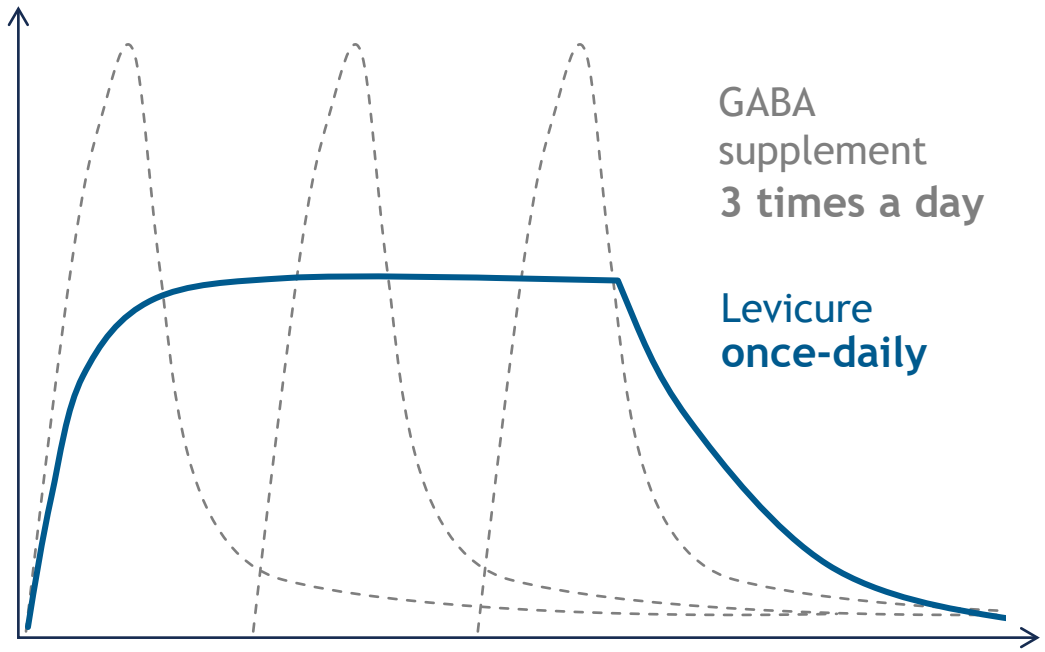
Cumulative exogenous insulin intake (IU)



Superior Pharmaceutical Offering: proprietary extended-release and gastro-retentive GABA formulation

Suitable GABA dosage forms with appropriate release profiles are not commercially available

Schematic pharmacokinetic plasma concentration/time curve

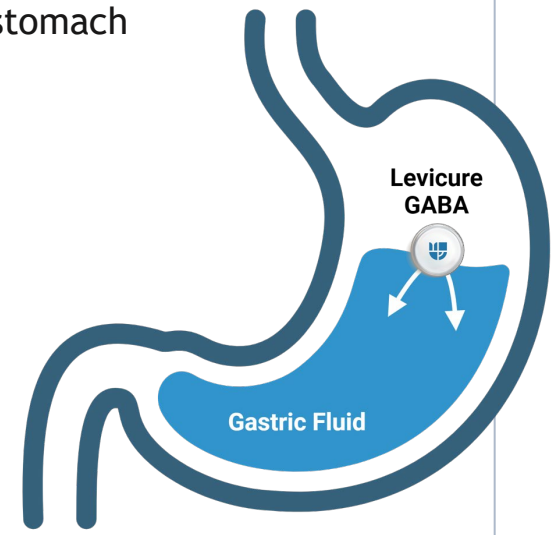


Our own-developed patented proprietary GABA is formulated for optimal therapeutic effect

GABA

Extended-release (ER) GABA in **gastro-retentive (GR)** form retained in the stomach with a combination of swelling and floating mechanisms:

- Maintain more **consistent plasma concentration** for optimal therapeutic effect
- Provide **once-daily** dosing
- Maximize **GABA bioavailability** at a lower dose
- Minimize potential side effects



Phase 2 trial with focus on regeneration of ß-cell mass and rate of T1D remission

LEVICURE aims to conduct a prospective, randomized, multi-center, placebo-controlled, double-blind Phase 2 trial for oral combination drug therapy

Successful Pre-IND meeting with FDA

- **505(b)(2)** (3 safe and well-established drugs) - decreased regulatory risk, development time and cost
- **Phase 2 ready** (No safety required)
- **Potential accelerated approval** and flexibility on factorial design is suggested based on Phase 2 results

Trial design

Patients diagnosed with T1D in the last 6 months confirmed by the presence of at least 1 diabetes-related autoantibody (either GAD65, IA-2, or ZnT8) and c-peptide > 100 pmol/l

Duration of treatment	**36 weeks**
Ages	**16 - 45 years**
Number of subjects (ratio of 2:1)	**56 active** **28 placebo**

Primary endpoint

- **0-4 hr area under the curve (AUC) for the C-peptide response to mixed-meal tolerance test (MMTT)**

Secondary endpoints

- **Rate of diabetes remission (No Insulin administration, HbA1c equal or less than 6.5%)**
- Insulin/weight ratio (units/kg/day)
- HbA1c
- IDA-A1c
- Time to remission
- 0-2hr AUC for the insulin response, glucagon and fasting blood glucose to MMTT
- Mean daily glucose, time-in-range, time below and time above target range via continuous glucose monitoring (CGM)
- Other parameters (Plasma cytokines, GLP-1, Gastrin, Identification of HLA)

Levicure's industry experts are dedicated to transform the lives of patients living with T1D

DANIIL KOSHELEV

CEO & co-Founder

- 12 years executive and business development
- Former CEO in biotech

MIKE TEILER

Chief Pharmaceutical Officer

- 35 years pharma experience
- Former VP Generic R&D, Teva International

SHMUEL LEVIT, MD, PhD

Founder & CMO

- Over 38 years of clinical practice
- Head of Endocrinology, Diabetes & Metabolism Institute

YAFIT STARK, PhD

Head of Clinical Development

- 34 years clinical development experience
- Former VP Head of Global Clinical Development and CCO, Teva

School of Medicine
Faculty of Medical & Health Sciences
Tel Aviv University

LUCY KOSHELEVA

R&D & co-Founder

- Former VP Investor relationship
- Uppsala researcher (molecular signaling in T1D)

OLGA KARPINCHYK

Accounts & Operations

- Former executive at a private medical centre
- Accounts and operational

VALENTINE SUKHOVEEVA

CFO & COO

- Former investment director at a private equity fund
- 10+ years of project management roles

Levicure's advisors are uniquely equipped to guide Levicure in launching disease-modifying treatment in T1D

ALEX RABINOVITCH, MD, FRCP(C)
Senior Scientific Advisor

DANIEL KAUFMAN, PhD
Senior Scientific Advisor

ALEXANDER FLEMING, MD, PhD
Regulatory Advisor

WALKER HAGAN, PhD
Scientific Advisor

MARGERY FISCHBEIN, MBA
Financial Advisor

CHRIS HOWARD, MBA
Business Advisor

ERIC DUTCHER, MBA
Fundraising Advisor

AMOS ANATOT
Strategic & Executive Advisor

LEVICURE REVERSE THE IRREVERSIBLE

NOW IS THE TIME

Join us on our way to T1D remission!

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