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LAZIO

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NUOVI SCENARI CLINICI
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Immuno-terapia del diabete di tipo 1: una lunga storia destinata al successo

Prof. Paolo Pozzilli

Unit of Endocrinology & Diabetes Campus Bio-Medico University Rome, Italy

Centre of Immunobiology, Barts & The London School of Medicine, UK

Editor in Chief, Diabetes Metabolism Research and Reviews

DISCLOSURE STATEMENT

Il ***Prof. Paolo Pozzilli*** dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Dompè

- Altheia

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Emerging Drugs for cure of Type 1 Diabetes

- Recent advancements in immunology and islet biology have unveiled remarkable prospects for the post-ponement of Type 1 diabetes (T1D) through the strategic modulation of the immune system.
- Many investigational new drugs fall under the category of immunomodulators, such as the recently FDA-approved CD3 monoclonal antibody teplizumab.
- Although immunomodulators can aid in protecting beta cells and reversing the immune response, overall, this approach has not been successful in reversing T1D complications.
- An alternative approach that is gaining support is to target the beta cell itself. Several novel drugs fall under the category of non-immunomodulators that may have more direct effect on beta-cells.

Collier J et al., Pharmacological Research 2024

Ajmal N et al., Cells, 2023

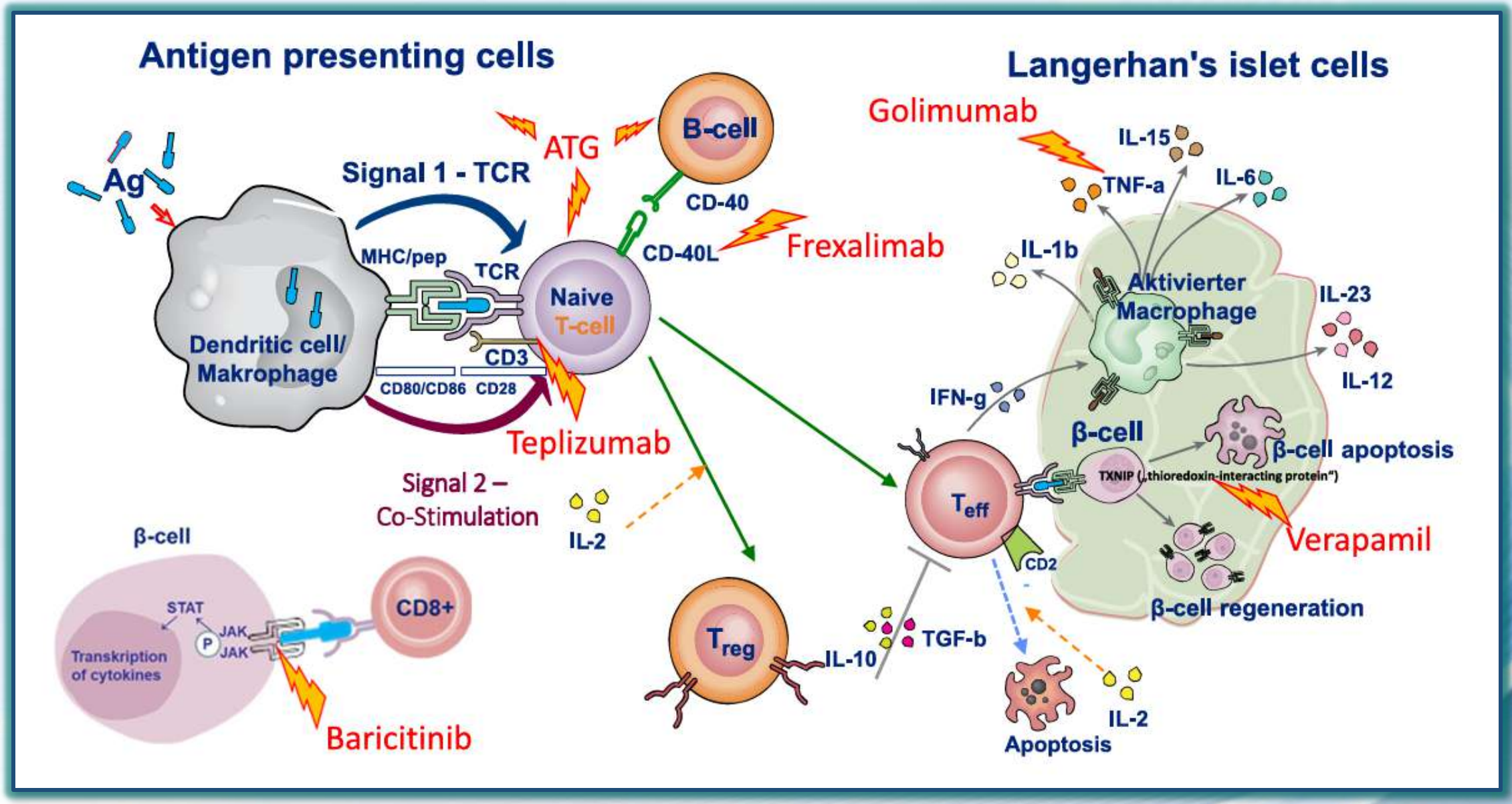
A new vision of type 1 diabetes based on endotypes

Properties (strength of association marked by +)		Endotypes					
		T1DE1	T1DE2	T1DE3	T1DE4	T1DE5	T1DE6
	Age at onset (pre-pubertal, pubertal, young-adult, adult, senior)	+	++	+++	+++	++++	All-ages, COVID induced
	Genetic (HLA)	++++	+++	+++	++	++	+
	Immunological (number and titer of autoantibodies)	++++	+++	+++	++	++	+
	C-peptide levels (< 0.3, 0.3-0.7, > 0.7 nM/L)	+	++	++	+++	++++	+++
	BMI (overweight, obese)	+	+	++	++++	+++	++

LADA

Pozzilli P. et al. Diabetes Metab Res Rev. 2024

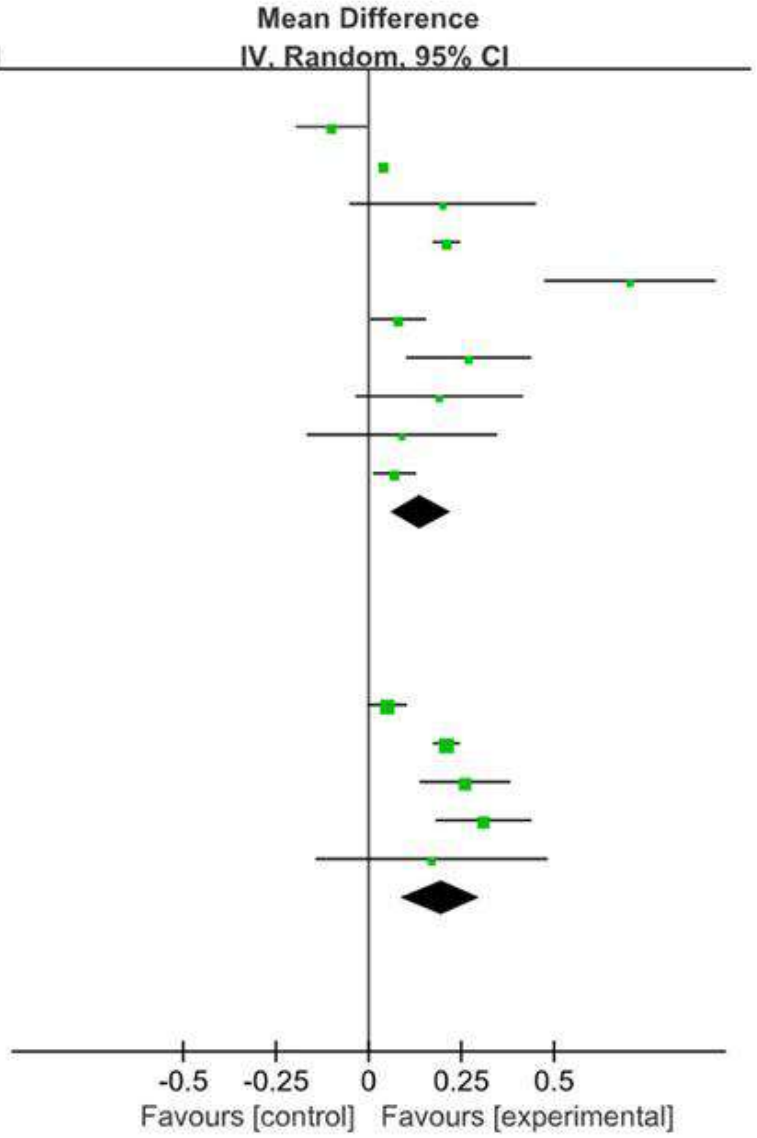
Examples of potential therapeutic approaches modulating the autoimmune disease in T1D



Weiskorn J., Danne T., Horm Res Paediatr 2024

Meta-analyses of anti-CD3 mAbs vs. placebo for change in C-peptide AUC in recent-onset T1D

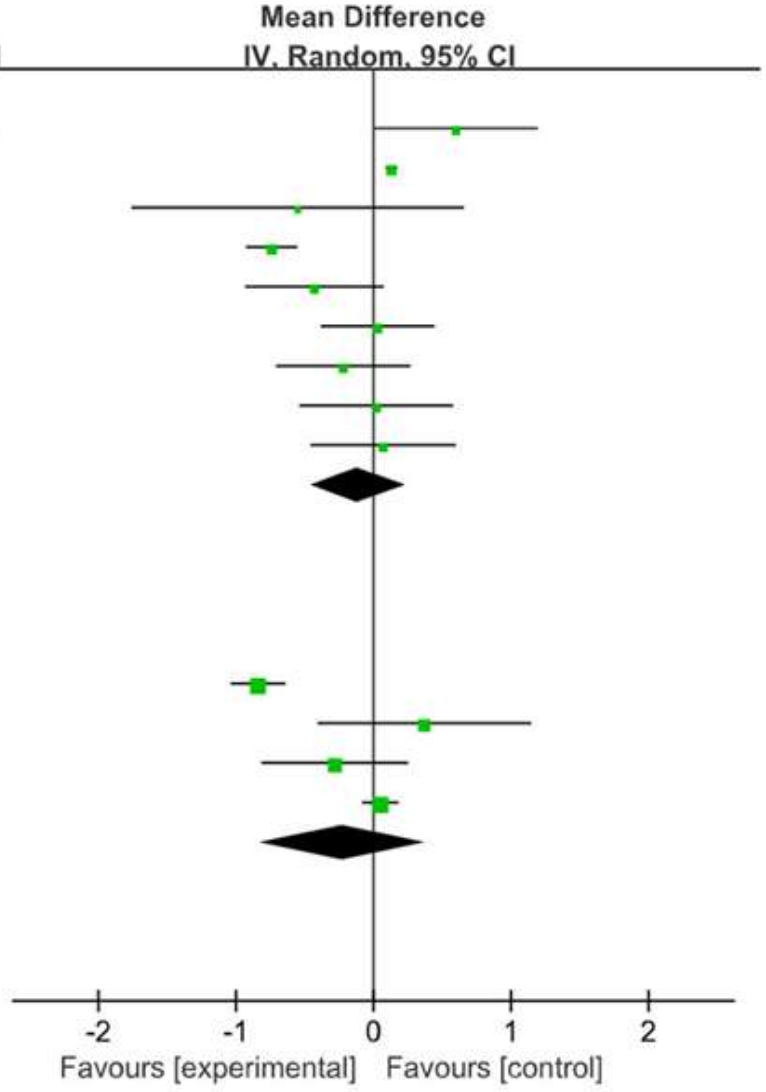
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Duration = 1 year								
Ambery 2014	-0.23	0.31	96	-0.13	0.24	45	11.9%	-0.10 [-0.19, -0.01]
Aronson 2014	0.54	0.03	181	0.5	0.04	91	14.2%	0.04 [0.03, 0.05]
Herold 2002	0.48	0.38	12	0.28	0.22	12	6.0%	0.20 [-0.05, 0.45]
Herold 2005	0.48	0.07	21	0.27	0.04	21	13.9%	0.21 [0.18, 0.24]
Herold 2009	0.894	0.245	6	0.189	0.119	4	6.6%	0.71 [0.48, 0.93]
Herold 2013(1)	0.45	0.15	31	0.37	0.13	27	12.8%	0.08 [0.01, 0.15]
Herold 2013(2)	0.61	0.38	52	0.34	0.33	25	8.8%	0.27 [0.10, 0.44]
Keymeulen 2005	0.89	0.41	40	0.7	0.59	40	6.7%	0.19 [-0.03, 0.41]
Keymeulen 2021	-0.06	0.28	24	-0.15	0.26	5	5.8%	0.09 [-0.16, 0.34]
sherry 2011	-0.07	0.29	415	-0.14	0.24	98	13.3%	0.07 [0.01, 0.13]
Subtotal (95% CI)			**878**			**368**	**100.0%**	**0.14 [0.06, 0.22]**
Heterogeneity: Tau² = 0.01; Chi² = 139.16, df = 9 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.51 (P = 0.0005)								
Duration = 2 years								
Hagopian 2013	-0.14	0.16	131	-0.19	0.17	64	25.7%	0.05 [0.00, 0.10]
Herold 2005	0.35	0.06	21	0.14	0.05	21	26.6%	0.21 [0.18, 0.24]
Herold 2013(2)	0.44	0.32	52	0.18	0.21	25	20.1%	0.26 [0.14, 0.38]
Keymeulen 2010	0.87	0.15	21	0.56	0.2	13	19.5%	0.31 [0.18, 0.44]
Keymeulen 2021	-0.18	0.33	24	-0.35	0.32	5	8.0%	0.17 [-0.14, 0.48]
Subtotal (95% CI)			**249**			**128**	**100.0%**	**0.20 [0.09, 0.30]**
Heterogeneity: Tau² = 0.01; Chi² = 34.64, df = 4 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 3.66 (P = 0.0003)								



Liu Y et al., Endocrine 2023

Meta-analyses of anti-CD3 mAbs vs. placebo for change in HbA1c in recent-onset T1D

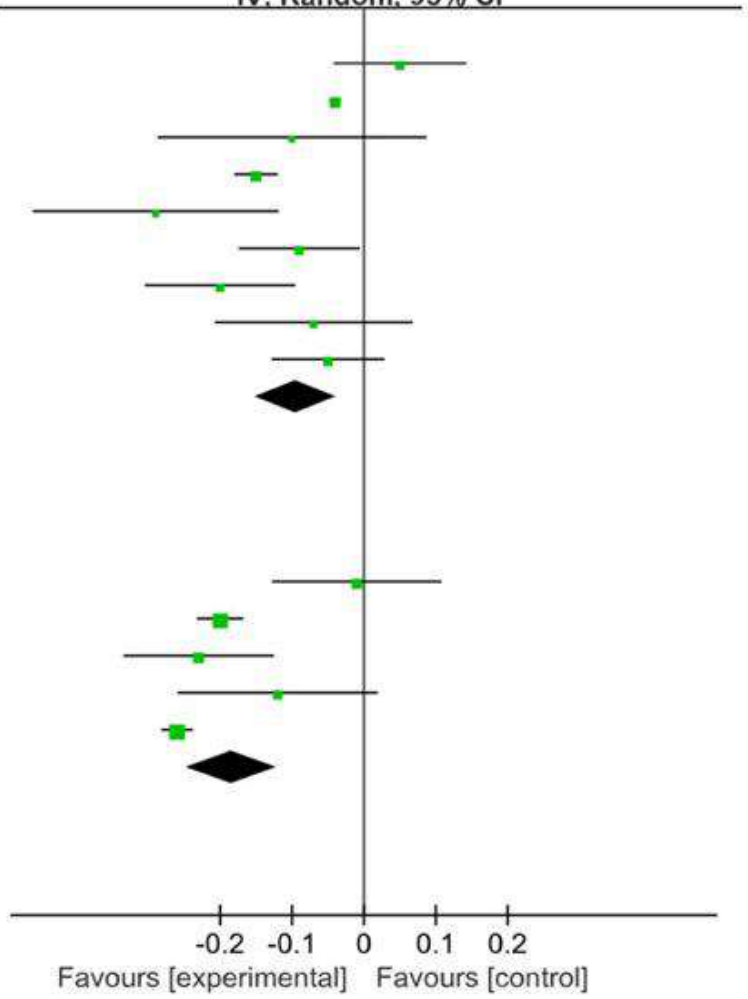
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Duration = 1 year								
Ambery 2014	-0.3	1.8	97	-0.9	1.6	45	10.2%	0.60 [0.01, 1.19]
Aronson 2014	7.04	0.116	181	6.91	0.147	91	14.5%	0.13 [0.10, 0.16]
Herold 2002	6.98	1.7	12	7.53	1.27	12	5.3%	-0.55 [-1.75, 0.65]
Herold 2005	6.73	0.35	21	7.47	0.23	21	13.9%	-0.74 [-0.92, -0.56]
Herold 2009	6.78	0.48	6	7.21	0.32	4	11.2%	-0.43 [-0.93, 0.07]
Herold 2013(1)	7.11	0.81	31	7.08	0.76	27	12.1%	0.03 [-0.37, 0.43]
Herold 2013(2)	7.12	1	52	7.34	1.01	25	11.3%	-0.22 [-0.70, 0.26]
Keymeulen 2005	6.78	1.47	40	6.76	1	40	10.6%	0.02 [-0.53, 0.57]
sherry 2011	7.87	2.18	415	7.8	2.4	98	10.9%	0.07 [-0.45, 0.59]
Subtotal (95% CI)			**855**			**363**	**100.0%**	**-0.11 [-0.46, 0.23]**
Heterogeneity: Tau² = 0.22; Chi² = 97.48, df = 8 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 0.63 (P = 0.53)								
Duration = 2 years								
Herold 2005	7.22	0.29	21	8.06	0.34	21	28.1%	-0.84 [-1.03, -0.65]
Herold 2009	8.42	0.76	6	8.05	0.48	4	19.6%	0.37 [-0.40, 1.14]
Herold 2013(2)	7.57	1.1	52	7.85	1.1	25	23.7%	-0.28 [-0.80, 0.24]
Keymeulen 2010	7.03	0.27	30	6.98	0.21	27	28.6%	0.05 [-0.07, 0.17]
Subtotal (95% CI)			**109**			**77**	**100.0%**	**-0.22 [-0.82, 0.38]**
Heterogeneity: Tau² = 0.32; Chi² = 60.63, df = 3 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 0.71 (P = 0.48)								



Liu Y et al., Endocrine 2023

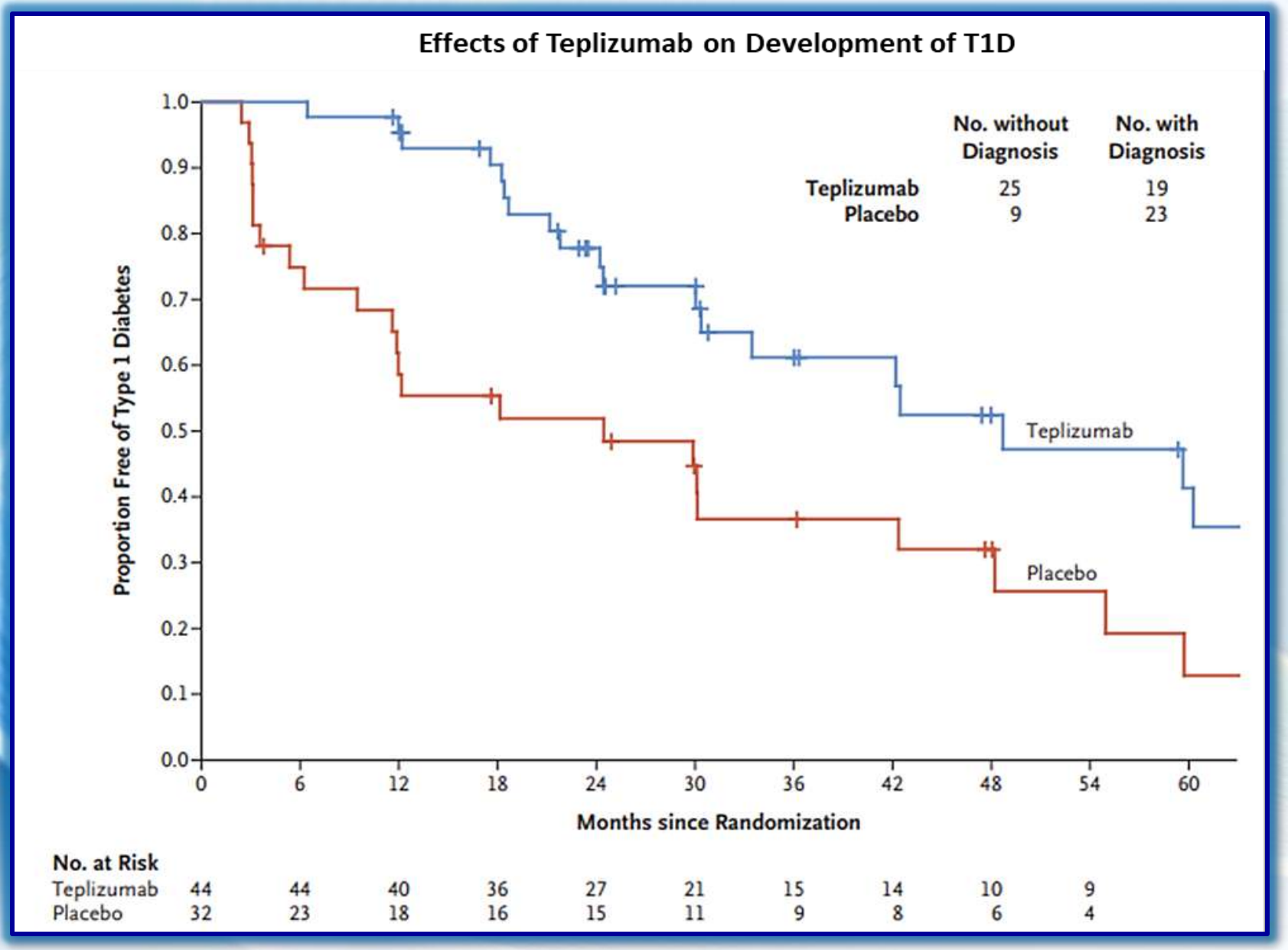
Meta-analyses of anti-CD3 mAbs vs. placebo for change in insulin dose in recent-onset T1D

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Duration = 1 year								
Ambery 2014	0.05	0.25	45	0	0.14	26	11.5%	0.05 [-0.04, 0.14]
Aronson 2014	0.39	0.017	181	0.43	0.026	91	16.4%	-0.04 [-0.05, -0.03]
Herold 2002	0.49	0.28	12	0.59	0.17	12	5.9%	-0.10 [-0.29, 0.09]
Herold 2005	0.43	0.06	21	0.58	0.03	21	15.8%	-0.15 [-0.18, -0.12]
Herold 2009	0.33	0.08	6	0.62	0.16	4	6.6%	-0.29 [-0.46, -0.12]
Herold 2013(1)	0.5	0.16	31	0.59	0.16	27	12.2%	-0.09 [-0.17, -0.01]
Herold 2013(2)	0.46	0.33	52	0.66	0.13	25	10.6%	-0.20 [-0.30, -0.10]
Keymeulen 2005	0.4	0.3	40	0.47	0.32	40	8.4%	-0.07 [-0.21, 0.07]
sherry 2011	-0.04	0.48	415	0.01	0.31	98	12.6%	-0.05 [-0.13, 0.03]
Subtotal (95% CI)			**803**			**344**	**100.0%**	**-0.09 [-0.15, -0.04]**
Heterogeneity: Tau² = 0.01; Chi² = 76.77, df = 8 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 3.27 (P = 0.001)								
Duration = 2 years								
Hagopian 2013	0.06	0.43	171	0.07	0.46	87	14.7%	-0.01 [-0.13, 0.11]
Herold 2005	0.51	0.04	21	0.71	0.06	21	27.7%	-0.20 [-0.23, -0.17]
Herold 2009	0.45	0.11	6	0.68	0.055	4	16.5%	-0.23 [-0.33, -0.13]
Herold 2013(2)	0.62	0.34	52	0.74	0.26	25	12.2%	-0.12 [-0.26, 0.02]
Keymeulen 2010	0.38	0.04	30	0.64	0.04	29	28.8%	-0.26 [-0.28, -0.24]
Subtotal (95% CI)			**280**			**166**	**100.0%**	**-0.18 [-0.25, -0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 27.81, df = 4 (P < 0.0001); I² = 86%								
Test for overall effect: Z = 5.76 (P < 0.00001)								



Liu Y et al., Endocrine 2023

Teplizumab, Anti-CD3 MoAb, in 1st degree relatives at risk for T1D



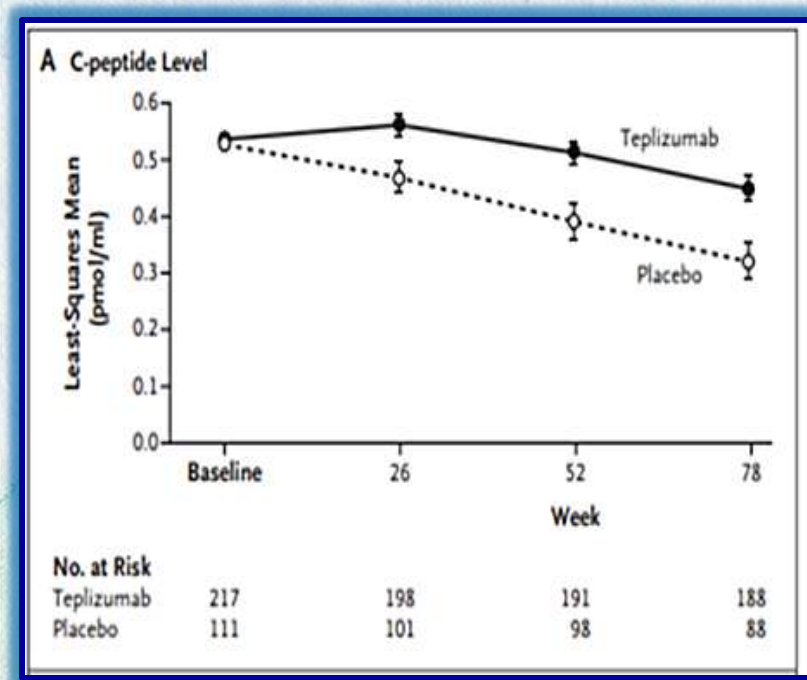
Teplizumab delayed progression to clinical T1D in high-risk participants. The median time to diagnosis of T1D was 48.4 months in the Teplizumab group and 24.4 months in the placebo group.

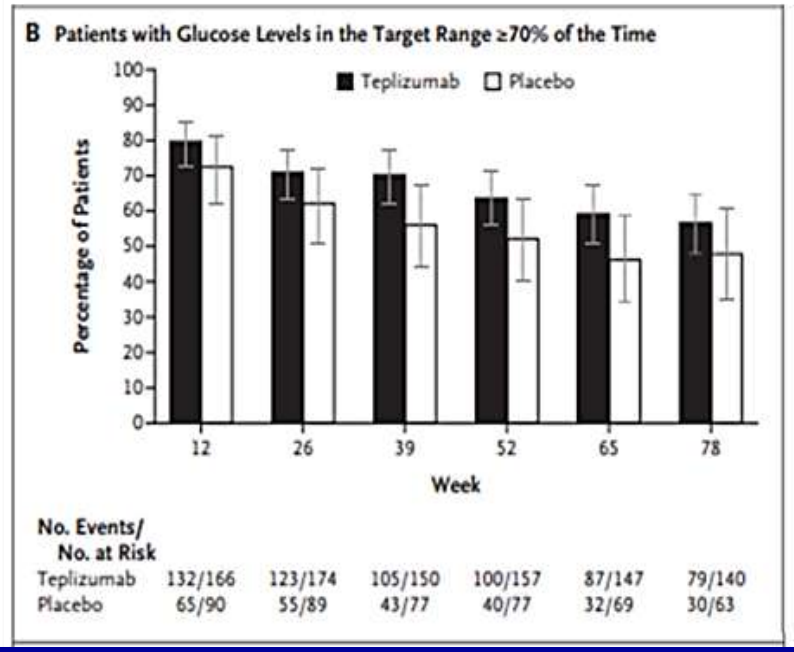
Herold KC et al., NEJM 2019

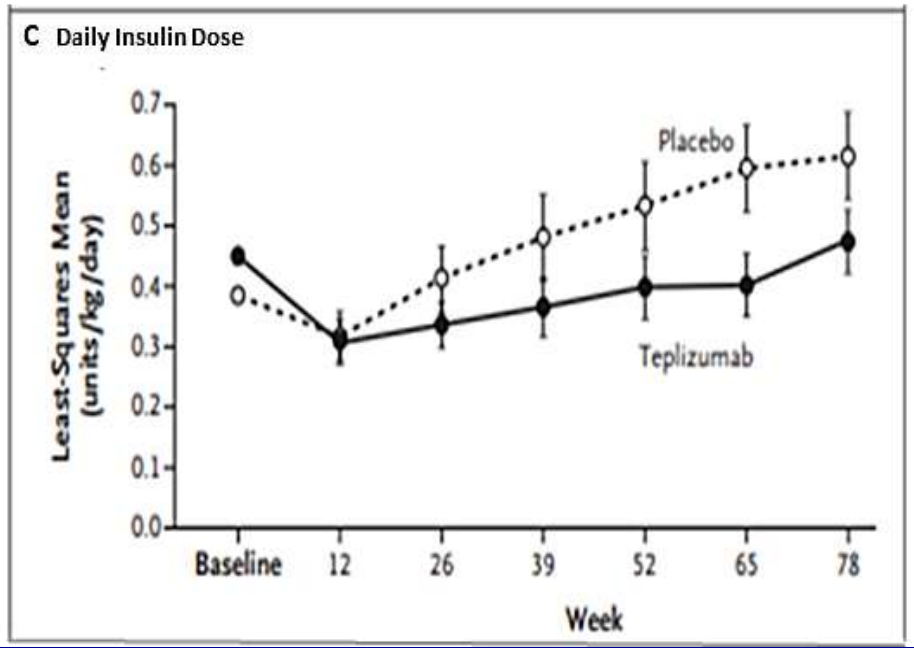
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Teplizumab and β-Cell Function in Newly Diagnosed Type 1 Diabetes



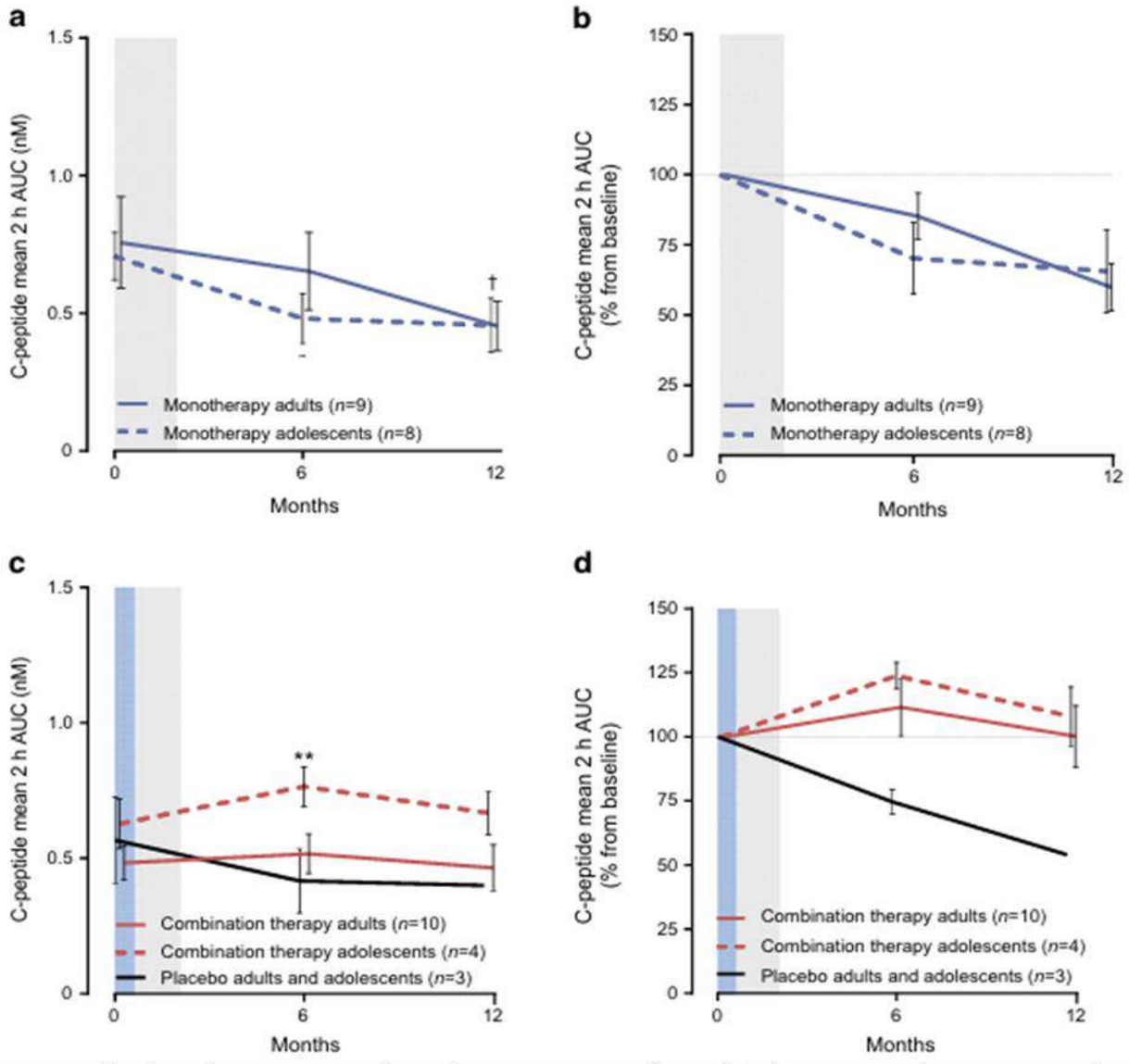




Two 12-day courses of teplizumab in children and adolescents with newly diagnosed T1D showed benefit with respect to the primary end point of preservation of β-cell function, but no significant differences between the groups were observed with respect to the secondary end points.

Ramos EL et al., NEJM 2023

A first-in-human, open-label Phase 1b clinical trial in recent-onset T1D with teplizumab in combination with AG019 (capsule of Lactococcus lactis genetically modified to express human proinsulin and human IL-10) as monotherapy



AG019= food-grade Lactococcus lactis bacteria genetically modified to express human proinsulin and human IL-10.

Monotherapy

In the adult monotherapy cohort, the mean 2 h C-peptide AUC at 12 months (60% of baseline, p=0.03).

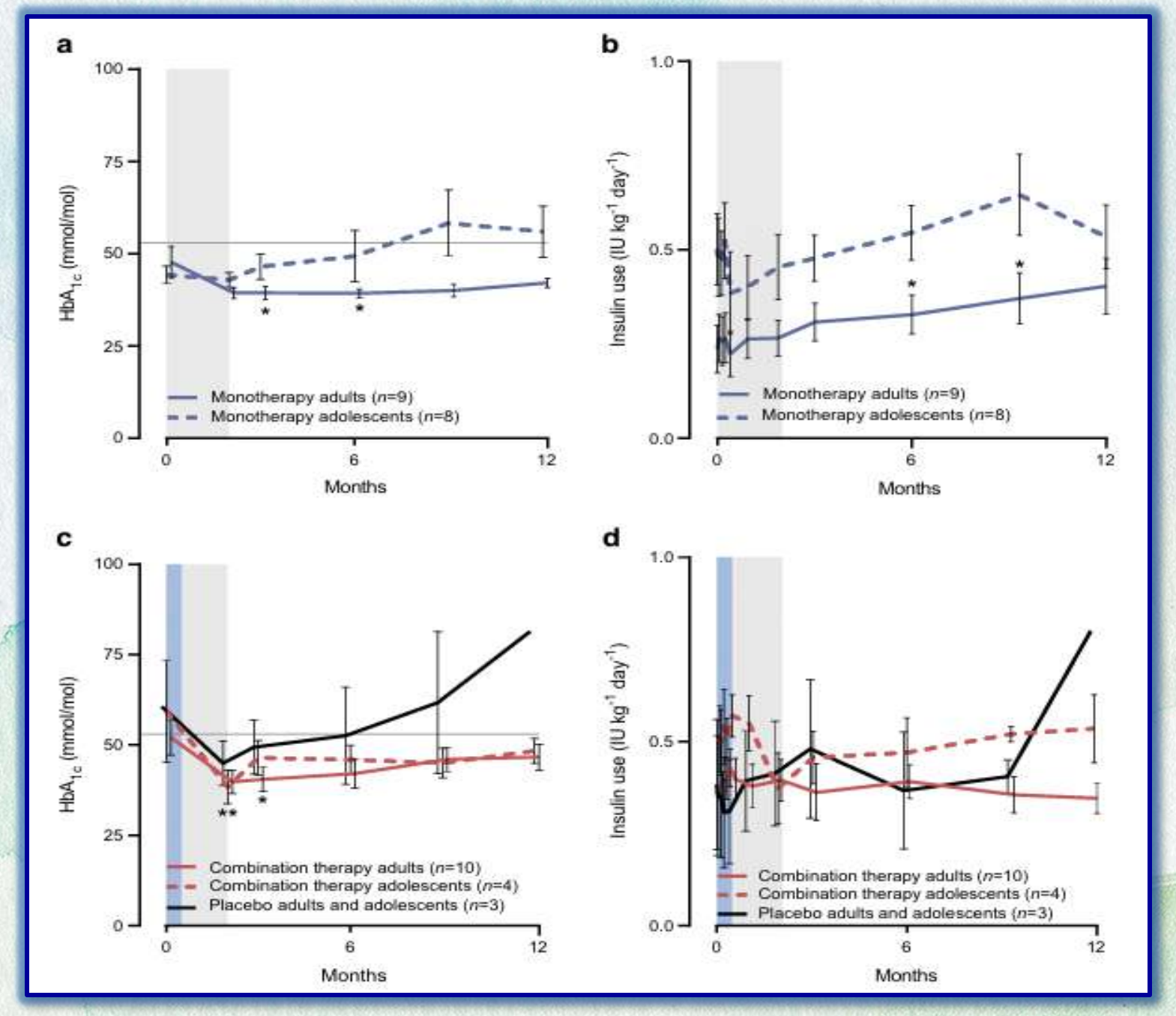
Among adolescents, the mean 2 h C-peptide AUC declined at 6 months (70% of baseline, p=0.044) and 12 months (66% of baseline, p=0.07).

Combination therapy

In the adult cohort, the C-peptide response increased (112%) at 6 months and was unchanged (100%) at 12 months compared with declines in the placebo-treated group (73% and 54% of baseline).

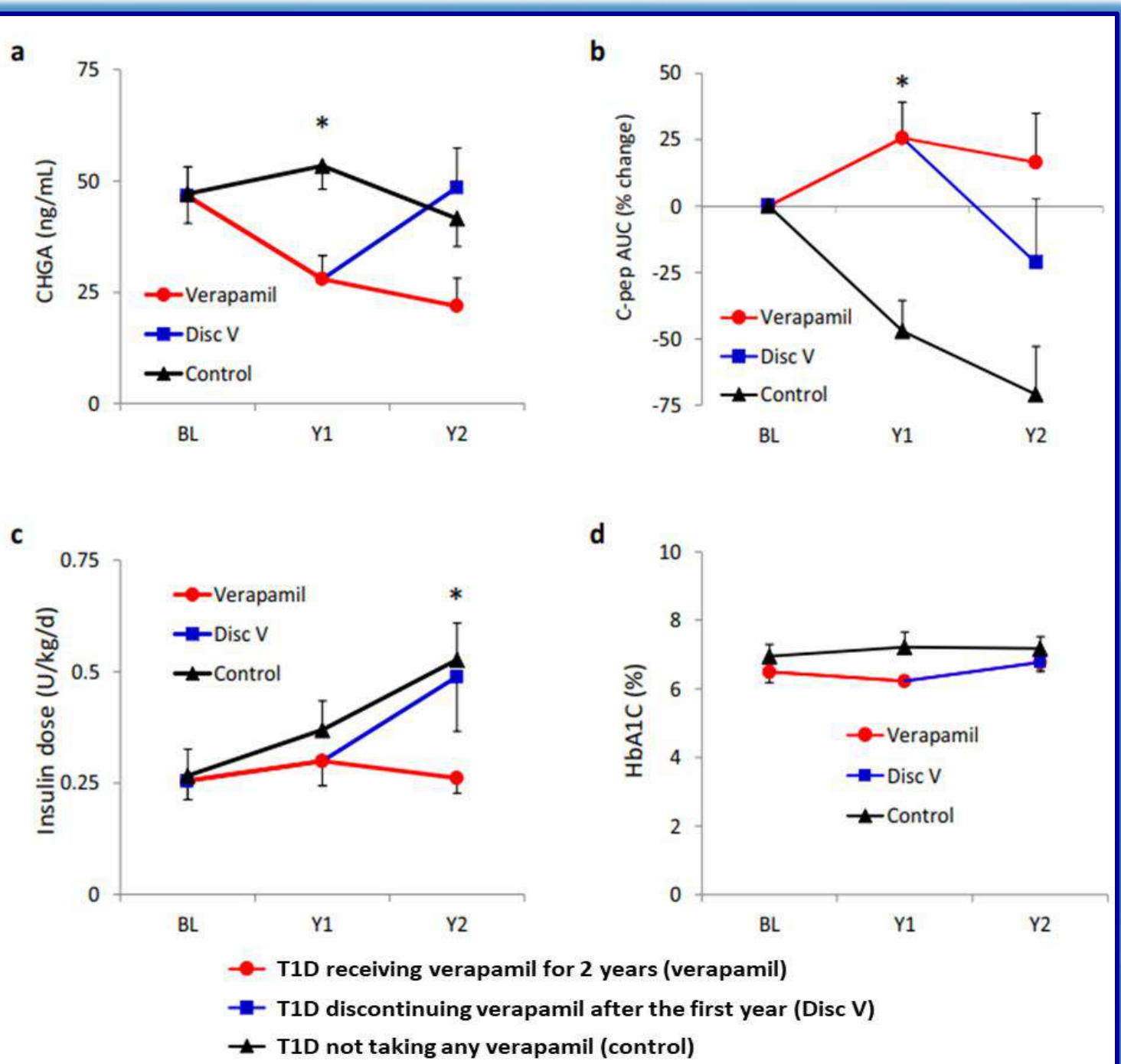
In adolescents, the C-peptide increased to 124% of baseline levels at 6 months (p=0.007) and 108% at 12 months vs 77% in the placebo-treated adolescent at 6 months.

Mathieu C et al., Diabetologia 2023



AG019 as monotherapy and in combination with teplizumab: HbA1c and insulin dose

Mathieu C et al., Diabetologia 2023



Exploratory study reveals far reaching systemic and cellular effects of VERAPAMIL treatment in recent-onset T1D

Verapamil regulates the thioredoxin system and promotes an anti-oxidative, anti-apoptotic and immunomodulatory gene expression profile in human islets.

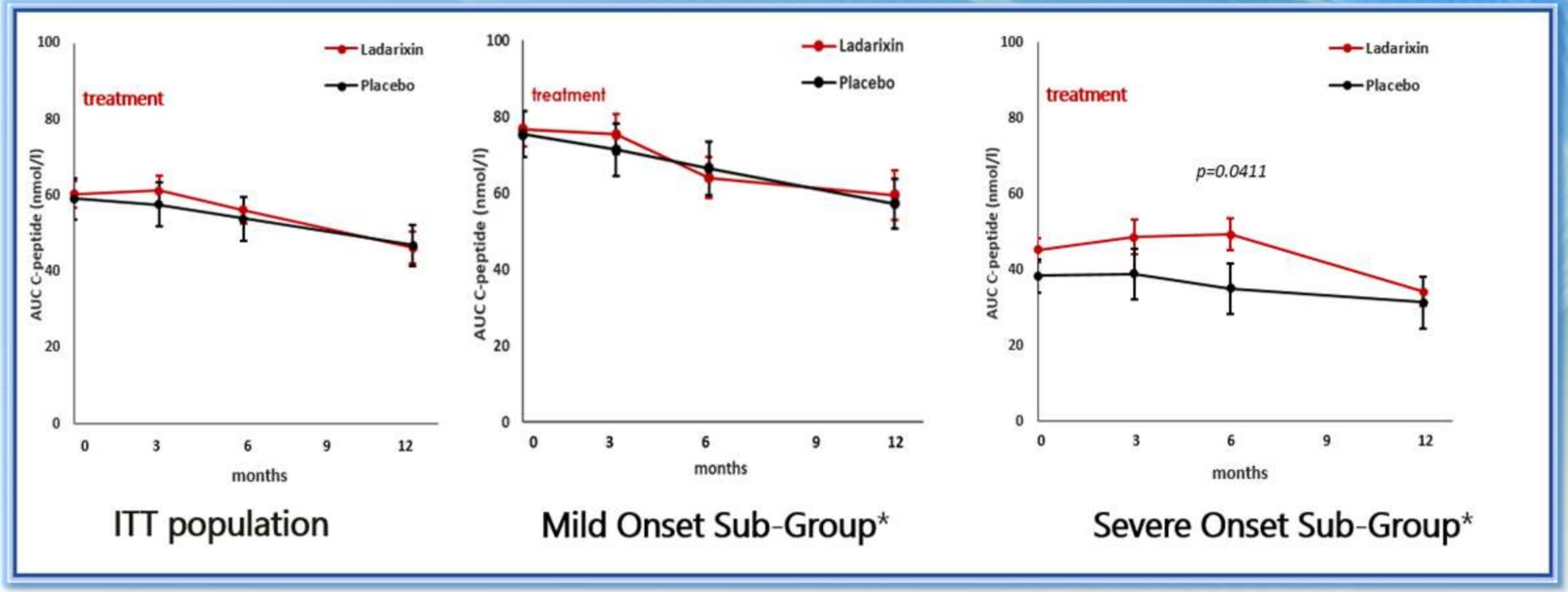
Continuous use of oral verapamil (360 mg sustained-release daily) in individuals with T1D may delay disease progression and lower insulin requirements for at least 2 years post-diagnosis and is associated with normalization of serum chromogranin A (CHGA) levels as well as of proinflammatory IL-21 levels.

These benefits are lost upon discontinuation

Xu G et al., Nature Communications 2022

A Randomized, Double-Blind Phase 2 Trial of the CXCR1/2 Inhibitor Ladarixin in Adult Patients with New-Onset Type 1 Diabetes

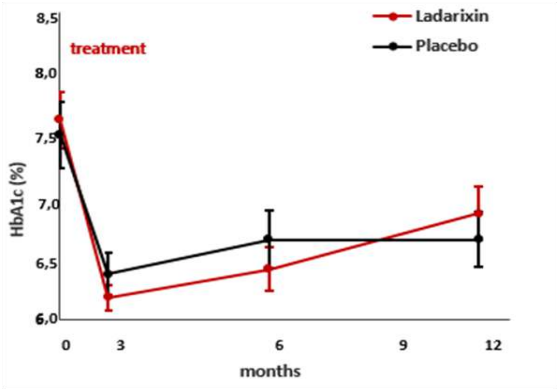
Primary Endpoint - AUC of C-peptide



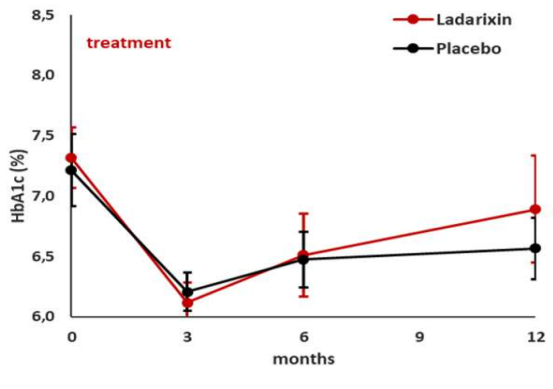
*Subsets were pre-specified in SAP

Piemonti L.,..., Pozzilli P., et al. DOM 2022

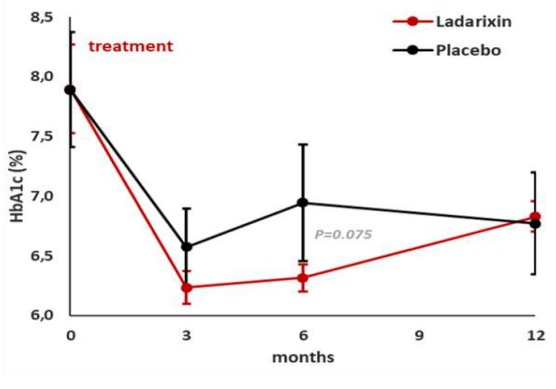
Secondary Endpoint - HbA1c (%)



ITT population



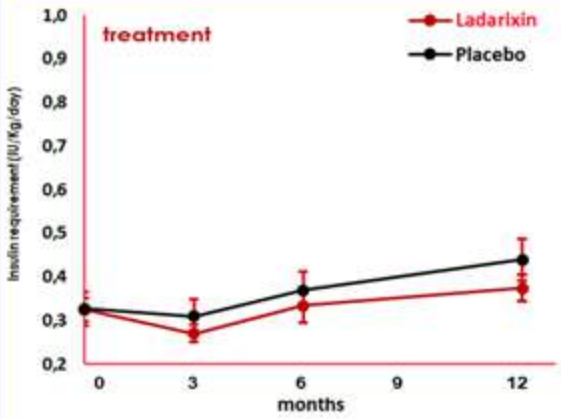
Mild Onset Sub-Group*



Severe Onset Sub-Group*

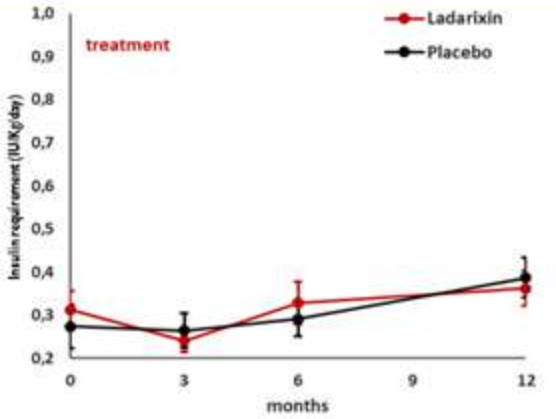
*Subsets were pre-specified in SAP

Secondary Endpoint: Daily Insulin Requirement (IU/Kg/day)

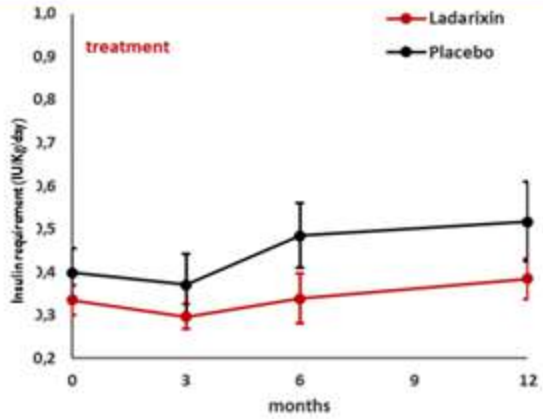


ITT population

p=NS



Mild Onset Sub-Group*



Severe Onset Sub-Group*

*Subsets were pre-specified in SAP

Significant results in HbA1c and insulin requirement in T1DE1 patients

Piemonti L.,..., Pozzilli P., et al. DOM 2022

Conclusions (I)

The time for immunotherapy in T1D began in 1986 with cyclosporine. Since then, hundreds of trials have been carried out with a variety of compounds but without significant results.

However, we have learnt considerably about the natural history of this disease especially in the pre-pubertal and adolescent subjects of families with one affected member. Data in the general population are scarce.

Conclusions (II)

Novel and old drugs tackling different mechanisms of the disease process are currently being tested in several trials in patients with recent-onset T1D patients and in subjects at risk.

It is important in this context to select carefully the population of T1D patients to include in clinical trials by characterizing the different disease endotypes and the most promising approach accordingly.