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Supplementary information

Type 1 diabetes mellitus prevention: present and future

In the format provided by the authors and unedited

Supplementary Table 1. Previous and Current Clinical Trials for Delay and/or Prevention of T1DM. New onset clinical trial at Stage 3 are also included here as these are common pathways to prevention trials for regulatory authorities such as the FDA.

Therapy	Mechanisms	Clinical trial	Primary Endpoints	Outcomes	Stage	Status	Clinical Trial Registration
T cell-based							
Teplizumab (Anti CD3)	Partial TCR agonist, leading to the increase in exhaustion status of CD8+ T cells evidenced by increase in KLRG1 and TIGIT expression.	PROTECT - Phase 3 Randomized Double-Blind Multinational Placebo-Controlled Study to Evaluate Efficacy and Safety of teplizumab, a Humanized Fc Receptor (FcR) Non-Binding Anti-cluster of Differentiation 3 (CD3) Monoclonal Antibody, in Children and Adolescents With Newly Diagnosed Type 1 Diabetes	Change in C-peptide ln(AUC+1) Standardized by Duration of the Mixed Meal Tolerance Test (MMTT) at week 78 of therapy vs Placebo.	Patients treated with teplizumab (217 patients) had significantly higher stimulated C-peptide levels than patients receiving placebo (111 patients) at week 78. The groups did not differ significantly with regard to the key secondary end points. Adverse events occurred primarily in association with administration of teplizumab or placebo and included headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome.	Phase III	Completed	NCT03875729 [1]
Anti-thymocyte globulin (ATG)	T cell depletion via antibody mediated augmentation of classic complement mediated lysis of T lymphocytes, masking of T cell antigens and expansion of negative regulatory cells.	Low dose Anti-thymocyte Globulin (ATG) and Pegylated Granulocyte Colony Stimulating Factor (GCSF) in New Onset Type 1 Diabetes	Mean area under the curve (AUC) for C-peptide during a 2 hour MMTT after 12 months of therapy initiation. Test low dose ATG alone and in combination with GCSF on primary end point	Low-dose ATG preserved beta cell function by slowing C-peptide decline and maintaining HbA_{1c} levels that were significantly lower than placebo (indicative of better long-term blood	Phase II	Active	NCT02215200 [2, 3]

				glucose control). Addition of GCSF did not augment this.			
		The Study of Thymoglobulin to ARrest T1D [START] trial	Changes in stimulated C-peptide response over the first 2 hours of a mixed meal tolerance test at 12 months	A brief course of ATG substantially depleted T cell subsets, including regulatory cells, but did not preserve islet function 24 months later in the majority of patients with new-onset type 1 diabetes.	Phase II	Completed	NCT00515099 [4]
		STOP-T1D Low Dose Anti-thymocyte Globulin (ATG) to Delay or Prevent Progression to Stage 3 T1DM	Delay or prevention of progression to Stage 3 T1DM in people aged 6-34 who have a 50% risk of clinical diagnosis within 2 years after therapy initiation	Ongoing	Phase II	Currently enrolling Expected completion - Dec 2029	NCT04291703
		MELD-ATG Minimum effective low dose: anti-human thymocyte globulin (MELD-ATG): phase II, dose ranging, efficacy study of anti-thymocyte globulin (ATG) within 6 weeks of diagnosis of type 1 diabetes	Changes in stimulated C-peptide response over the first 2 hours of a mixed meal tolerance test at 12 months for 2.5 mg/kg ATG arm vs the placebo.	Ongoing	Phase II	Active. Expected completion - Dec 2024	NCT03936634
Abatacept (CTLA4 antibody)	A CTLA-4 fusion protein that blocks CD80 and CD86 pathways on APCs, preventing their interaction with CD28, a T cell costimulatory molecule. Prevents T-cell activation	Effects of CTLA-4 Ig (Abatacept) on the Progression of Type 1 Diabetes in New Onset Subjects – TN09	Area under the stimulated C-peptide curve over the first 2 hours of a mixed meal tolerance test conducted at the 2 year visit. Ages 6-36	Abatacept slowed reduction in β-cell function at 2 years, with delayed C-peptide reduction (59%). HbA_{1c} also decreased but no change in insulin requirements. However, no additional benefit after	Phase II	Completed	NCT00505375 [5]

				6 months of treatment with abatacept with β-cell function parallel to the placebo from 6-24 months.			
		CTLA4-Ig (Abatacept)for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At -Risk for Type 1 Diabetes)	Time from randomisation to confirmed abnormal Glucose Tolerance test, defined by: (i) Fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L) and < 126 mg/dL (7 mmol/L); (ii) 2 hour plasma glucose ≥ 140 mg/dL (7.8 mmol/L) and < 200 (11.1 mmol/L); or (iii) 30, 60, 90 minute plasma glucose during OGTT ≥ 200 mg/dL (11.1 mmol/L)	Abatacept treatment did not significantly delay the time of progression to glucose intolerance in at-risk individuals	Phase II clinical trial	Completed	NCT01773707 [6]
Low dose IL-2 (Aldesleukin)	Low doses of rhIL-2 induce and activate regulatory T cells (Tregs), a population of immune cells controlling the immune Teffector responses.	Dose Finding Study of IL-2 at Ultra-low Dose in Children With Recently Diagnosed Type 1 Diabetes (DF-IL2-Child)	The primary outcome was change in Tregs, expressed as a percentage of $CD4^+$ T cells at day 5. It pre-specified that a ≥60% increase in Tregs from baseline would identify Treg high responders	The safety profile at all doses, the dose-dependent effects on Tregs and the observed variability of the Treg response to ld-IL2 in children with newly diagnosed type 1 diabetes call for use of the highest dose in future studies. However, there was no significant change in glycaemic control	Phase I/II	Completed	NCT01862120 [7]

		Interleukin-2 Therapy of Autoimmunity in Diabetes (ITAD)	The primary objective is to assess the effects of ultra-low dose Aldesleukin administration on endogenous β-cell function as measured by frequent home dried blood spot (DBS) fasting and post-prandial C-peptide in children and adolescents with newly diagnosed T1DM. Differences in slopes of DBS C-peptide over the 6 month-treatment period between the active and placebo groups.	Ongoing	Phase II	Active	EudraCT 2017-002126-20 [8]
Ustekinumab STELARA®	Inhibition of the IL-17A and IFN-γ axes through p40 blockade	Phase II/III Study of Ustekinumab in Patients with New-onset Type 1 Diabetes (UST1D2)	(i) Baseline change in 2-hour mixed meal-stimulated C-peptide AUC at week 52. (ii) Rate, frequency and severity of all adverse events including hypoglycemic episodes; injection reactions; hypersensitivity reactions; evidence of infection and posterior leukoencephalopathy syndrome.	Ongoing	Phase II/III	Active; Expected Completion Nov 2026	NCT03941132
		Phase 2, multicenter, double-blind, randomized placebo-controlled trial of ustekinumab in children and adolescents within 100 days of diagnosis of T1DM (the USTEKID study)	(i) Baseline change in 2-hour mixed meal-stimulated C-peptide AUC at week 52.	At 12 months, β-cell function, measured by stimulated C-peptide, was 49% higher in the	Phase II	Completed	ISRCTN 14274380 [9]

				intervention group (P = 0.02), meeting the prespecified primary outcome.			
Alefacept (Amevive)	Blocks the interaction between the leukocyte-function-associated antigen (LFA)-3 and CD2 and thereby impedes the activation and proliferation of T cells.	Inducing remission in Type 1 diabetes with Alefacept (T1DAL)	2-Hour-C-peptide Area under the curve result in response to standardized Mixed Meal Tolerance Test.			Terminated Early (Amevive Licence sold)	NCT00964658
IMCY-0098 (Imotope)	Synthetic peptide encompassing a proinsulin C20-A1 epitope and a thioredox motif, which has been shown to induce a cytolytic phenotype in a human CD4 T cell line and is able to eliminate antigen-presenting cells (APCs) that present the proinsulin epitope.	IMCY-0098 Proof of ACtion in Type 1 Diabetes - IMPACT Study. A Phase Ib/IIa, randomized, double-blind placebo-controlled, multicenter adaptive design clinical trial to evaluate the immune signature of the treatment with the Imotope™ IMCY-0098 and its effect on the preservation of beta-cell function in young adult and adolescent patients with a recent onset Type 1 diabetes	Change in stimulated C-peptide response during the first two hours of a mixed meal tolerance test (MMTT) from baseline to 48 weeks between IMCY-0098 and placebo groups	No efficacy at primary analysis after 1 year. Long term follow-up stopped.	Phase II	Terminated Early. May 2024.	NCT04524949
Siplizumab (Anti-CD2)	Blockade of CD2/LFA-3 engagement limits cell adhesion to antigen-presenting cell (APC), antigen recognition and subsequent T-cell activation. Siplizumab-based tolerance induction regimens deplete T cells globally while enriching regulatory T cells (Tregs)	A 12-month, randomized, single-blind, placebo-controlled exposure-response study of TCD601 (siplizumab) in new onset type 1 diabetes patients (STRIDE)	Area Under the Stimulated C-peptide Curve Over the First 2 Hours of a 4-hour Mixed Meal Tolerance Test (MMTT) Administered at 1 Year	Ongoing	Phase1 b/II	Active; Expected Completion Jan 2027	EudraCT 2022-001713-39
B cell-based							
Rituximab (Anti-CD20)	A monoclonal antibody that binds to the CD20 surface marker expressed on B cells. Leads to B cell depletion by several mechanisms including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis	Effects of Rituximab on the Progression of Type 1 Diabetes in New Onset Subjects (TN05)	Area Under the Stimulated C-peptide Curve Over the First 2 Hours of a 4-hour Mixed Meal Tolerance Test (MMTT) Administered at 1 Year	At 1 year, the mean AUC for the level of C peptide was significantly higher in the rituximab group than in the placebo group. The rituximab group also had significantly lower levels of glycated hemoglobin and required less insulin.	Phase II	Completed	NCT00279305 [10, 11]

Iscalimab (Anti-CD40; CFZ533)	Receptor expressed on APCs. Targets CD40-CD154 co-stimulatory pathway, attenuating B cell activation signal (T cell-dependent B cell proliferation)	Investigator- and Subject-blinded, Randomized, Placebo-controlled Study to Evaluate Safety, Tolerability, Pharmacokinetics and Efficacy Trial of CFZ533 in Paediatric and Young Adult Subjects With New Onset Type 1 Diabetes (T 1DM)	(i) Proportion of subjects with adverse events (AE)/serious adverse events (SAE) in treatment groups. (ii) Stimulated C-peptide AUC by mixed meal tolerance test (MMTT) at 12 months.	Number of participants with treatment emergent AEs (any AE regardless of seriousness), AEs led to study treatment discontinuation, and SAEs. No efficacy to preserve c-peptide.	Phase II	Active; Completed Jan 2025 and results posted clinical trials.gov.	NCT04129528
Janus Kinase Inhibitors							
Baricitinib	Acts as an inhibitor of JAK activity, blocking the subtypes JAK1 and JAK2 and STAT signalling	A Phase 2, Randomised, Placebo Controlled Study Investigating the Efficacy of Baricitinib in New Onset Type 1 Diabetes Mellitus	Change from baseline of plasma C-peptide area under the curve (AUC) over 2 hours following a mixed meal at 48 weeks post-therapy commencement.	In patients with type 1 diabetes of recent onset, daily treatment with baricitinib over 48 weeks appeared to preserve β-cell function as estimated by the mixed-meal–stimulated mean C-peptide level.	Phase II	Completed	NCT04774224 [12]
Abrocitinib and Ritlecitinib		JAKPOT T1D A Phase 2 Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subtype-Selective JAK Inhibitors for Preservation of Pancreatic B Cell Function in Newly Diagnosed Type 1 Diabetes Mellitus	Stimulated C-peptide curve over the 2-hour mixed meal glucose tolerance test conducted at the 12-month visit (Y_AUC) over the 2-hour mixed meal glucose tolerance test conducted at the 12-month visit	Ongoing	Phase II	Active, Expected Completion - June 2027	NCT05743244
Tyrosine kinase inhibitor							
Imatinib	Binds to BCR-ABL kinase domain, inhibiting directly the constitutive tyrosine kinase activity	Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-Onset Type 1 Diabetes Mellitus	The primary endpoint was the difference in the AUC mean for C-peptide response in the first 2h of an mixed meal tolerance test (MMTT) at 12 months in the imatinib	Improvement of 2-hour C-peptide AUC in response to a MMTT at 12 months; However, this effect was not sustained out to 24 months. 71% experienced a grade 2 or	Phase II	Completed	NCT01781975 [13]

			group versus the placebo group	higher adverse event, compared to 59% of placebo-treated subjects			
Channel-based therapy							
Verapamil (calcium channel blocker)	Decreases the expression of thioredoxin-interacting protein, which induces β-cell apoptosis	Repurposing of Verapamil as a β-cell Survival Therapy in Type 1 Diabetes	Functional Beta Cell Mass as determined by the area under the curve (AUC) from a 2-hour Mixed Meal-Stimulated C-peptide after daily verapamil for 12 months.	Verapamil added to standard insulin therapy promotes endogenous β-cell function and lowers exogenous insulin requirements and hypoglycemic episodes in recent-onset adult T1DM patients	Phase II	Completed	NCT02372253
		A randomised, double-blind, placebo controlled, parallel group, multi-centre trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of Verapamil SR on preservation of beta-cell function (Ver-A- T1D)	The preservation of beta-cell function measured as stimulated C-peptide after 12 months compared to placebo.	Ongoing	Phase II	Active. Expected completion May 2026.	NCT04545151
		Hybrid Closed Loop Therapy and Verapamil for Beta Cell Preservation in New Onset Type 1 Diabetes (C LVer)	The primary outcome is the C-peptide in response to a 2-hour MMTT at 52 weeks.	In children and adolescents with newly diagnosed type 1 diabetes, verapamil partially preserved stimulated C-peptide secretion at 52 weeks from diagnosis compared with placebo.	Phase II	Completed	NCT04233034 [14]
Combination Therapy							
Liraglutide + anti-interleukin-21	Anti-interleukin (IL)-21 antibody induces low-grade and transient immunomodulation; liraglutide improves β-cell function	A Randomised, Double-blind, Double-dummy, Placebo-controlled, Parallel-group Multi-centre Clinical Proof-of-principle Trial in Adult Subjects With Newly	Change in MMTT-stimulated C-peptide concentration at week 54 (end of	The decrease in MMTT-stimulated C-peptide concentration was significantly	Phase II clinical trial	Completed	NCT02443155 [15]

		Diagnosed Type 1 Diabetes Mellitus Investigating the Effect of NNC0114-0006 and Liraglutide on Preservation of Beta-cell Function	treatment) relative to baseline, measured via the area under the concentration -time curve (AUC) over a 4 h period	smaller with combination treatment, but not with anti-IL-21 or liraglutide alone			
Antigen-specific Immunotherapy							
Insulin	Down-regulation of islet β-cell antigens as a consequence of metabolic effects of insulin; induction of regulatory T cells or tolerance to insulin antigenic determinants by daily exposure to insulin and alteration of lymphocyte function as a direct consequence of insulin binding to insulin receptors on lymphocytes.	The Diabetes Prevention Trial of Type 1 Diabetes (DPT-1)	Rate of T1DM per year. Glucose tolerance was measured every 6 months for up to 6 years.	The annualized rate of progression to DM was 15.1% in the intervention group and 14.6% in the observation group. The cumulative incidence of T1DM was similar in both groups.	Phase III	Completed	NCT00004984 [16]
		Pilot Study Using Oral Insulin at Early Age for Immune Efficacy in Primary Prevention of Type 1 Diabetes	The primary outcome for immune efficacy is the activation of an immune response (antibody or CD4+ T cell) against insulin.	Immune responses to insulin were observed in children who received both insulin (54.5%) and placebo (66.7%), and the trial did not demonstrate an effect on its primary outcome.	Phase II	Completed	NCT02547519 [17]
		Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus	Rate of T1DM per year among individuals in the primary stratum when treated with oral inulin versus placebo.	During a median follow-up of 2.7 years in the main study group, T1DM was diagnosed in 28.5% of participants in the oral insulin group and 33% of the placebo group. Time to T1DM was not significantly different.	Phase III	Completed	NCT00419562 [18]
		Intranasal Insulin for Prevention of Type 1 Diabetes in Children Carrying Increased HLA-Conferred Genetic Risk	Development of clinical T1DM.	Administration of nasal insulin soon after autoantibodi	Phase III	Completed	NCT00223613 [19]

				es did not prevent or delay T1DM.			
		A Randomised, Double-blind, Placebo-controlled Trial of Intranasal Insulin (440 IU) in Children and Young Adults at Risk of Type 1 Diabetes: Intranasal Insulin Trial II	Diagnosis of DM at 5 years according to ADA/WHO criteria.	T1DM developed in 12 participants with negligible ß-cell function at entry after a median of 1.1 year. Of the remaining 26, the majority the ß-cell function remained stable over a median follow-up of 3.0 years. There was an increase in antibody and a decrease in T-cell responses to insulin.	Phase II	Completed	NCT00336674 [20]
GAD65	Enzyme that catalyses the decarboxylation of glutamate to gamma-aminobutyric acid (GABA) and carbon dioxide (CO_2). Leads to an upregulation of type 2 helper T cells (Th2), with a stepwise increase in Th2 markers (such as interleukin-13 and interleukin-5), while type 1 helper T cell (Th1) markers decrease.	Open Label Pilot Trial in Adults With Recent-onset T1D to Evaluate the Safety, Diabetes Status and Immune Response of GAD-antigen (Diamyd®) Therapy Administered Into Lymph Nodes in Combination With an Oral Vitamin D Regimen	Evaluate safety after a fourth injection with 4 µg GAD-Alum direct into an inguinal lymph gland in 3 adult patients from the main study and evaluate the influence of the treatment in the immune system and endogenous insulin secretion. ((Mean Change in Fasting C-peptide Value; mixed-meal tolerance tests).	There were no apparent treatment-related adverse events except for mild transient injection-site reactions. There was preservation of residual ß-cell function in six patients (fasting and maximum stimulated C-peptide levels from baseline to 6 months did not decrease); After 15 months, the average of C-peptide AUC levels remained stable in 4 patients, accompanied by a 34% increase in fasting C-peptide	Phase I	Completed	NCT02352974 [21]

				levels. Additionally, HbA1c levels and insulin requirements decreased in all patients.			
		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	The primary outcome was the change in stimulated serum C-peptide (AUC after a MMTT) between baseline and 15 months.	The primary endpoint was not met in the full analysis. However, GAD-alum–treated patients with HLA DR3-DQ2 showed significantly better C-peptide preservation after 15 months compared to placebo recipients with the same genotype.	Phase II	Completed	NCT03345004 [22]
		A Phase I/II Open Label Pilot Study to Evaluate the Safety and Feasibility of an Additional Intralymphatic Booster Administration of GAD-alum (Diamyd®) in Individuals With Type 1 Di abetes	Evaluate safety and adverse effects. Secondary outcome measures included change in stimulated C-peptide during a MMTT, change in HbA1c, change in daily exogenous insulin dose, change in insulin-dose-adjusted HbA1c, change in time in glycaemic target and in time in hyperglycemic range.	No adverse events were documented. After 30-month treatment, efficacy was still seen in 8/12 patients. HbA1c, insulin requirement and insulin dose-adjusted A1c remained stable.	Phase I/II	Completed	NCT05351879 [23]
		Open Label Trial to Evaluate the Tolerability of a Combination Therapy Consisting of GAD-alum (Diamyd®), Etanercept and Vitamin D in Children and Adolescents Newly	Primary outcomes included safety and tolerability. Secondary outcomes	There were no reported treatment-related serious adverse events. After	Phase II	Completed	NCT02464033 [24]

		Diagnosed With Type 1 Diabetes	included C-peptide AUC during an MMTT change from baseline, HbA1c change from baseline, exogenous insulin dose change from baseline, among others.	6 months, C-peptide improved in some patients, but later declined, while HbA1c and insulin needs remained stable.			

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