# The future of type 1 diabetes therapy

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*Lancet* 2025; 406 : 1520–34
Published Online September 19, 2025
https://doi.org/10.1016/S0140-6736(25)01438-2

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See Online for appendix

**The treatment of type 1 diabetes is entering a transformative era. Teplizumab, the first immunotherapy treatment to delay the onset of clinical type 1 diabetes, has been approved by the US Food and Drug Administration. Other immune-based therapies show promise in preserving β-cell function. Public health screening using islet autoantibodies is expanding, enabling earlier diagnosis, reducing diabetic ketoacidosis, and allowing timely introduction of disease-modifying treatments before the need for insulin therapy. β-cell replacement is shifting from traditional transplantation of organ donor islets and the pancreas to stem cell-derived β cells. Bioengineering methods, such as encapsulation, and gene editing to create hypoimmune cells could reduce the need for immunosuppression that has hampered β-cell replacement, and patient-derived stem cells open doors to personalised therapies. Although these innovations have been made available to a small number of patients, scaling them to widespread use remains a challenge. Meanwhile, glucose regulation is improving through the use of automated insulin delivery systems that combine glucose monitoring with insulin pumps. New-generation insulins (those that are ultrarapid, ultralong, and glucose-responsive) improve outcomes by minimising blood sugar fluctuations. Together, these breakthroughs offer renewed hope for improving long-term management and quality of life for people living with type 1 diabetes.**

## Introduction: a century of progress and a new era in type 1 diabetes treatment

The discovery of insulin more than a century ago revolutionised medicine by enabling individuals with type 1 diabetes to survive and lead full lives. Since then, insulin therapy has undergone remarkable advancements, including the development of human insulin, insulin analogues, insulin pumps, and automated insulin delivery (AID) systems (also referred to as closed-loop systems). Innovations in blood glucose monitoring, such as continuous glucose monitoring, have substantially improved metabolic control. Despite these strides, however, life expectancy remains reduced for individuals diagnosed with type 1 diabetes before age 10 years compared with both people diagnosed after 10 years and people without type 1 diabetes.[1,2] The risk of diabetes-related complications also remains notably high for all people with type 1 diabetes.[1,2]

50 years after the discovery of islet cell antibodies corroborated the autoimmune nature of type 1 diabetes in 1974, the US Food and Drug Administration (FDA) approved the first disease-modifying therapy designed to delay the clinical onset of type 1 diabetes. Targeting the disease in its early, presymptomatic phase has heralded a new era in type 1 diabetes treatment: one defined by treating type 1 diabetes as an immune-mediated disease. By intervening in the disease process, immunotherapy has the potential to reshape the future of type 1 diabetes care by complementing and preceding traditional insulin therapy.

Another important breakthrough was the successful proof of concept for stem cell therapy as an alternative to islet transplantation for replacing insulin-producing cells. This approach offers renewed hope for an eventual cure of type 1 diabetes: endogenous β cells to control blood glucose without the need for exogenous insulin and potentially without the need for much ongoing medication.

The third major development was the creation of AID systems and new-generation insulins. AID systems have led to substantial improvements in clinical outcomes and quality of life for individuals with diabetes.[3] New-generation insulin formulations with enhanced properties compared with previous generations play a crucial role in advancing diabetes treatment. These insulins aim to mimic physiological insulin action and support individualised diabetes management. Innovations such as ultrarapid-acting insulins, ultralong-acting (weekly) insulins, and novel glucose-responsive insulins promise improved safety, efficacy, and simplicity.

### Search strategy and selection criteria

We searched PubMed between Jan 1, 2000, and June 21, 2025 using both MeSH and free-text terms to identify relevant articles. The search focused on terms such as "type 1 diabetes AND", "disease-modifying therapy", "immunotherapy", "adjunct therapies", "anti-CD3", "JAK-inhibitor", "baricitinib", "ATG", "rituximab", "anti-TNF", "IL-2", "DCCT", "C-peptide preservation", "verapamil", "Diamyd", "IL-23", "antigen-based therapy", "CTLA-4", "vaccination", "islet transplantation", "stem cell therapy", "embryonic stem cells", "Vertex-880 cells", "pluripotent stem cells", "insulin", "AID", "diabetes technology", "adjunctive treatment AND insulin", "smart insulin", and "glucose responsive insulin" (appendix pp 1–2). We reviewed guidelines for staging and diagnosing type 1 diabetes published by the American Diabetes Association, the European Association for the Study of Diabetes, and International Society for Pediatric and Adolescent Diabetes. To identify additional eligible studies and trial information, we also searched ClinicalTrials.gov and EudraCT. Additional articles were identified via previous familiarity of the authors. Publications were selected on the basis of their level of evidence, clinical relevance, contribution to the field, originality, and recency of publication. Preference was given to articles published in journals with robust policies on conflict of interest and stringent peer-review standards. Only publications in English were considered.

This Review explores these three paradigm-shifting developments in depth, as each is poised to transform type 1 diabetes treatment.

## Part 1: Preventing and delaying the loss of β-cell function

The onset of clinical type 1 diabetes is characterised by a progressive decline in islet β-cell function. This deterioration continues after commencement of insulin therapy and is primarily driven by active immune-mediated destruction of the β cells. In individuals at early, presymptomatic stages, immune-modulating therapies can delay or even prevent clinical onset. For those with newly established clinical disease, combining immunotherapy with insulin can help preserve residual β-cell function, slow disease progression, and improve metabolic outcomes (panel 1).

### Diagnosing autoimmunity in type 1 diabetes

A crucial prerequisite for the development of disease-modifying therapies in type 1 diabetes is the ability to diagnose the disease at an early, presymptomatic stage through the detection of islet autoantibodies.[7,8] Two early stages of type 1 diabetes are defined, and each is associated with distinct rates of progression to clinical diabetes (figure 1).[9–11] Stage 1 is defined by the presence of at least two islet autoantibodies and normoglycaemia, and accounts for 80–90% of individuals with presymptomatic disease.[8,12] Stage 2 is defined by positive islet autoantibodies accompanied by dysglycaemia.[8,12] Stage 3 is defined by the onset of hyperglycaemia and clinical diabetes. Additional stratification with refined disease progression rates is possible using scores that combine glycaemic variables, IA-2 autoantibody titres, BMI, or C-peptide.

Early detection of type 1 diabetes by islet autoantibodies has been widely practised in relatives of individuals with type 1 diabetes and is now recommended by American Diabetes Association guidelines.[10] In the past 10 years, global screening efforts have expanded to include children from the general public.[9] Although early detection offers clinical benefits, such as statistically significant reductions in diabetic ketoacidosis and a milder onset (ie, fewer symptoms and a lower degree of hyperglycaemia) of clinical diabetes,[13] its most impactful benefit lies in enabling treatment. Screening for early-stage type 1 diabetes is largely research funded. To ensure appropriate, equitable, and regulated implementation of therapy, structured screening must be integrated into standard practice and supported by international guidelines[11] and master screening protocols.[14]

### Treating autoimmunity in type 1 diabetes

*Teplizumab to delay clinical type 1 diabetes*

Teplizumab, a humanised anti-CD3 monoclonal antibody administered as a single 14-day course of daily intravenous infusions,[15] is approved in Israel, Saudi Arabia, the UK, and the USA for delaying the onset of clinical type 1 diabetes in individuals aged 8 years and older with stage 2 type 1 diabetes. Teplizumab is also available for compassionate use in France, Germany, Italy, Spain, and the UK for the same indication.

Teplizumab targets CD3, a component of the T-cell receptor complex crucial for activating $CD4^+$ and $CD8^+$ T cells, which play a key role in the destruction of pancreatic β cells. Treatment induces transient lymphopenia, which begins during the 14-day infusion

***Panel 1:* Key considerations for prescribers**

**Overview**

In the past 5 years, substantial advancements have been made in the treatment of type 1 diabetes, including breakthroughs in screening and diagnosis, disease-modifying therapies, β-cell replacement via stem cells, new insulin formulations and delivery, and adjunctive treatments. Health equity and new treatments intersect at the crucial goal of ensuring all individuals with diabetes have access to these innovative treatments for diabetes regardless of race, income or insurance status.

Screening for islet autoantibodies is recommended for healthy individuals at increased disease risk, such as relatives of people with type 1 diabetes. Certified tests for islet autoantibodies, international consensus guidelines, and master protocols on screening and monitoring early-stage type 1 diabetes are available, with screening increasingly applied to children in the general population.

**Disease-modifying therapies**

Teplizumab is approved by the US Food and Drug Admistration (FDA) for delaying the clinical onset of type 1 diabetes in individuals aged 8 years and older with advanced (stage 2) early-stage type 1 diabetes in the USA, and is available through compassionate use programmes in Germany, France, Belgium, Spain, and the UK.

Few β-cell replacement options that include allogeneic transplantation for defined indications and stem cell-based cell therapy are available within clinical trials at selected sites.

**New-generation insulins**

In the past 20 years, innovations have focused on faster absorption and action, prolonged duration, and glucose-responsive properties. Ultrarapid-acting insulins offer improved post-meal control and improved performance in automated insulin delivery (AID) systems. Longer-acting, once-weekly basal insulins reduce daily injection burdens and improve treatment adherence.[4]

**Adjunctive treatments**

Adjunctive treatments can help improve metabolic control and prevent complications, but important questions about their risk-to-benefit profile limit regulatory approval. The amylin analogue pramlintide is the only US FDA-approved adjunctive therapy for type 1 diabetes. Although pramlintide offers weight loss and glucagon inhibition, it is not widely used for treatment of type 1 diabetes given the burden of injections and the risk of hypoglycaemia. SGLT2 inhibitors are associated with a statistically significant increased risk of ketoacidosis.[5]

**AID systems**

AID systems reduce glycated haemoglobin concentrations and improve time in range in people with type 1 diabetes. These systems have proven to be safe and effective when used from the point of diagnosis and during pregnancy together with adequate training and clinical support.[6] Next-generation AID systems that offer smaller devices, longer wear times, better connectivity, and increased precision are expected to reduce the burden faced by people with type 1 diabetes.

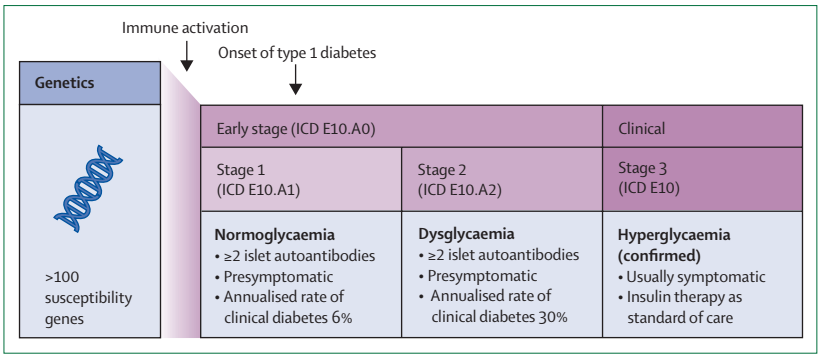


***Figure 1:*** **Stages of type 1 diabetes**
Stage 1 and stage 2 are presymptomatic periods of islet autoimmunity and distinguished by glycaemic criteria. Stage 3 diabetes is the onset of clinical disease. Individuals with stage 3 diabetes usually have diabetes-related symptoms and require insulin. Of individuals identified with presymptomatic diabetes, approximately 85% have stage 1 and 15% stage 2.[4] Normoglycaemia and hyperglycaemia are defined by standard glycaemic criteria.[4,5] Hyperglycaemia is characterised by a fasting plasma glucose of ≥126 mg/dL (7·0 mmol/L), 2-hour oral glucose tolerance test score of ≥200 mg/dL (11·1 mmol/L), $HbA_1c$ measurement ≥6·5% (≥48 mmol/mol), or, in patients with symptoms of hyperglycaemia, a random glucose concentration of ≥200 mg/dL (11·1 mmol/L). Dysglycaemia is defined by impaired fasting plasma glucose of 100–125 mg/dL (5·6–6·9 mmol/L), impaired 2-hour glucose of 140–199 mg/dL (7·8–11·0 mmol/L), high glucose concentrations at intermediate time points on the oral glucose tolerance test (30 min, 60 min, and 90 min measurements of ≥200 mg/dL [11·1 mmol/L]), $HbA_1c$ concentration of 5·7–6·4% (39–47 mmol/mol), or ≥10% increase in $HbA_1c$ concentration.

course, partly resolves during treatment, and typically normalises within 6 weeks. In people who respond to teplizumab therapy, increases in the frequency of exhausted $CD8^+$ T cells ($PD\text{-}1^+KLRG1^+CD57^-$) and anergic $CD8^+$ and $CD4^+$ T cells are observed.[16,17] Additionally, teplizumab downregulates IL-7 receptor expression on $CD8^+$ T cells, which inhibits their growth and expansion. Despite its short course of administration, the prolonged immunomodulatory effects of teplizumab suggest it might promote operational tolerance to type 1 diabetes autoantigens.

Teplizumab delays the onset of clinical type 1 diabetes by a median of 24 months.[18] In one 2019 study with a 2-year delay, annualised rates of clinical diabetes were 15% in the teplizumab group and 36% in the placebo group (table 1).[18] Follow-up after completion of the trial showed an extension of the delay to a median of 32 months.[43]

Side-effects of teplizumab include transient lymphopenia, rash, headache, gastrointestinal symptoms, transient liver transaminase elevation, nausea, and mild cytokine release syndrome. A safety systematic review of five studies involving 561 participants identified increased risks for adverse events related to gastrointestinal systems (odds ratio [OR] 1·6), dermatological systems (OR 6·3), and haematological systems (OR 19·0).[44]

### *Teplizumab to preserve β-cell function after onset of clinical type 1 diabetes*

Although currently being considered but not yet approved for stage 3 type 1 diabetes, teplizumab has shown promise in preserving insulin secretion (table 1). The 2023 PROTECT trial[32] treated children aged 8–17 years with two 12-day infusion courses administered at a 12-month interval. After 78 weeks, participants treated with teplizumab showed higher stimulated C-peptide in response to a standard mixed meal than participants treated with placebo. The earlier Protégé trial,[33,34] which included children and adults, did not meet its primary composite endpoint of a significant difference in the insulin dose and glycated haemoglobin ($HbA_{1c}$) concentrations at 1 year; however, teplizumab treatment reduced the loss of C-peptide response to a standard mixed meal, a prespecified secondary endpoint, at 2 years.[34] Post-hoc analyses identified subgroups with higher baseline C-peptide measurement, lower insulin use, lower $HbA_{1C}$, younger age, and shorter time since diagnosis who benefited most from teplizumab treatment, suggesting greater efficacy with early treatment in paediatric populations.[34]

### *Abatacept for disease modification*

Abatacept, a CTLA-4 immunoglobulin that inhibits T-cell costimulatory signalling through the CD80–CD86 pathway, was evaluated in children and adolescents at the presymptomatic stage.[38] Although 1 year of abatacept treatment for children and adolescents with stage 1 type 1 diabetes did not significantly delay progression to stage 2 or 3 (hazard ratio 0·70; 95% CI 0·45–1·09), it preserved insulin secretion and modified immune cell subsets. Abatacept has also been shown to preserve C-peptide when administered soon after the onset of clinical type 1 diabetes,[19] which warrants more investigation into its potential to modify disease progression.

### *Other immunotherapies*

Numerous strategies have been investigated to preserve β-cell function following the clinical diagnosis of type 1 diabetes. These therapies target diverse immune pathways and mechanisms, including B-cell and T-cell depletion (ie, anti-thymocyte globulin [ATG], alefacept, imatinib, and rituximab),[20,21,28,31,45] cytokine modulation (ie, ustekinumab[35] and the anti-TNF therapies etanercept and golimumab[27,46,47]), and inhibition of cytokine signalling (ie, the Janus kinase [JAK] inhibitor baricitinib; table 1).[23] Compared with teplizumab, some of these therapies not only preserve residual β-cell function, but also reduce insulin requirements and improve glycaemic control, without significant adverse events (table 1). The durability of therapeutic effects varies across treatments, as does the mode of administration. JAK inhibitors, for example, offer the advantage of oral administration, whereas others require intravenous, subcutaneous, or intramuscular delivery (table 1).[23] A very recent trial assessing the efficacy and safety of low-dose ATG showed that β-cell function can be preserved with doses lower than previously considered effective and that the therapy is safe in children 5 years or older.[22] Strategic sequencing or combination therapies, including non-immune

| | Treatment | Participants | Age | Primary outcome *vs* placebo (effect size, if applicable) | Other effects (effect size, if applicable) |
|---|---|---|---|---|---|
| **Stage 3** | | | | | |
| Abatacept,[19] CTLA4-Ig (TN09) | IV infusions on days 1, 14, 28, and then monthly over 2 years | 112 | 6–45 years | Higher stimulated C-peptide at 2 years (p=0·0029) | $HbA_{1c}$ over 2 years (p=0·007) |
| ATG–GCSF[20,21] | IV infusions of low-dose ATG or ATG followed by SC GCSF biweekly for 12 weeks | 89 | 12–45 years | Higher stimulated C-peptide at 1 year in ATG (p=0·0003) and in ATG–GCSF (p=0·031) | $HbA_{1c}$ at 1 year in ATG (p=0·002), in ATG–GCSF (p=0·011) |
| ATG[22] | IV infusions on 2 consecutive days | 117 | 5–25 years | Higher stimulated C-peptide at 1 year with 2·5 mg/kg dose (p=0·003) and with 0·5 mg/kg dose (p=0·014) | HbA1c at 1 year with 0·5 mg/kg dose (p=0·024) |
| Baricitinib,[23] JAK inhibitor (BANDIT) | Oral, once daily for 48 weeks | 91 | 10–30 years | Higher stimulated C-peptide at 48 weeks (p=0·001) | NA |
| GAD-alum[24] | SC injections on days 1 and 30 | 70 | 10–18 years | Higher fasting C-peptide at 15 months (no significant effect) | Fasting C-peptide at 30 months (p=0·045), stimulated C-peptide at 15 months (p=0·01) and 30 months (p=0·04) |
| GAD-alum[25] (TN08) | Two or three SC injections at weeks 0, 4, and 12 | 145 | 3–45 years | Higher stimulated C-peptide at 1 year (no significant effect) | NA |
| GAD-alum,[26] vitamin D (DIAGNODE-2) | Three intralymphatic injections on days 30, 60, and 90, plus oral vitamin D (2000 IE) for 4 months daily from day 1 | 109 | 12–24 years | Higher stimulated C-peptide at 15 months (no significant effect; p=0·50) | Stimulated C-peptide sub-analysis in HLA DR3-DQ2 subgroup (p=0·0078), insulin dose-adjusted $HbA_{1c}$ (p=0·031) |
| Golimumab,[27] TNF inhibitor (T1GER) | SC injections fortnightly for 52 weeks | 84 | 6–21 years | Higher stimulated C-peptide at week 52 (p<0·001) | Less increase in insulin dose over 52 weeks (p=0·001) |
| Imatinib,[28] tyrosine kinase inhibitor | Oral, once daily for 26 weeks | 64 | 18–45 years | Higher stimulated C-peptide at 12 months (90% CI −0·003 to 0·191, p=0·048) | NA |
| Pleconaril and ribavirin,[29,30] antiviral (DiViDInt) | Oral pleconaril and ribavirin, twice daily for 6 months | 96 | 6–15 years | Higher stimulated C-peptide at 12 months (p=0·037; no effect after 2 years) | $HbA_{1c}$ at 3 and 6 months (p<0·0001), no effect after 2 years |
| Rituximab,[31] anti-CD20 (TN05) | IV infusions at weeks 0, 1, 2, and 3 | 87 | 8–40 years | Higher stimulated C-peptide at 12 months (p=0·03); C-peptide over all time points (p<0·001) | $HbA_{1c}$ over the 12 months (p<0·001), insulin dose (p<0·001) |
| Teplizumab,[32] anti-CD3 (PROTECT) | IV infusions (12 days) at weeks 1 and 26* | 328 | 8–17 years | Higher stimulated C-peptide at week 78 (p<0·001) | NA |
| Teplizumab,[33,34] anti-CD3 (Protégé) | IV infusions (6 full dose, or 14 days low dose or high dose) | 516 | 8–35 years | Lower composite of insulin use <0·5 units per kg/day and $HbA_{1c}$ <6·5% at year 1 (no significant effect) | Stimulated C-peptide at 2 years in full-dose 14-day course (p=0·027) |
| Ustekinumab,[35] IL-12 and IL-23 inhibitor (USTEK1D) | SC injections at weeks 0, 4, 12, 20, 28, 36 and 44 | 72 | 12–18 years | Higher stimulated C-peptide at 12 months (p=0·02) | NA |
| Verapamil,[36] calcium channel blocker | Oral, once daily for 12 months | 24 | 18–44 years | Higher stimulated C-peptide at 3 months (p=0·033) and 12 months (p=0·038) | Total daily dose of insulin at 12 months (p=0·031) |
| Verapamil,[37] calcium channel blocker (CLVer) | Oral, once daily for 12 months (60 mg/day or 120 mg/day with dose escalation) | 88 | 7–17 years | Higher stimulated C-peptide at 52 weeks (p=0·04) | NA |
| **Stage 2** | | | | | |
| Teplizumab,[18] anti-CD3 (TN10) | IV infusions on 14 consecutive days | 76 | 8–45 years | Lower rates of stage 3 type 1 diabetes (p=0·006), average delay of 24 months | NA |
| **Stage 1** | | | | | |
| Abatacept,[38] CTLA4-Ig (TN18) | IV infusions at 0, 2, 4 and weeks, and then monthly for 12 months | 212 | 6–45 years | Lower rates of AGT or stage 3 type 1 diabetes (p=0·11) | Stimulated C-peptide at 12 months (p=0·03) |
| Intranasal insulin (DIPP)[39] | Intranasal, daily for median 1·8 years (IQR 0–9·7) | 264 | 1–15 years | Lower rates of stage 3 type 1 diabetes (HR 0·98, 95% CI 0·67–1·43, p=0·91) | NA |
| Oral insulin[40] (DPT-1) | Oral (7·5 mg), daily for median 4·3 years (IQR 2·5–5·5) | 372 | 3–45 years | Lower rates of stage 3 type 1 diabetes (HR 0·764, 95% CI 0·51–1·14, p=0·189) | Subgroup with IAA ≥80 nU/mL (HR 0·57, 95% CI 0·36–0·89, p=0·015) |
| Oral insulin[41] (TN07) | Oral (7·5 mg), daily for median 2·7 years (IQR 1·5–4·6) | 389 | 3–45 years | Lower rates of stage 3 type 1 diabetes (HR 0·87, 95% CI 0–1·2, p=0·21) | Secondary stratum with low first-phase insulin secretion (HR 0·45, 95% CI 0–0·82, p=0·006) |

(Table 1 continues on next page)

| | Treatment | Participants | Age | Primary outcome *vs* placebo (effect size, if applicable) | Other effects (effect size, if applicable) |
|---|---|---|---|---|---|
| (Continued from previous page) | | | | | |
| **Before islet autoimmunity** | | | | | |
| Oral insulin[42] (POInT) | Oral (7·5 mg for 2 months, then 22·5 mg for 2 months, then 67·5 mg until third birthday), daily for a median of 2·5 years (IQR 2·45–2·55) | 1050 | 4–7 months | Data soon to be reported | Data soon to be reported |

Trial names are listed in the first column in parentheses if available. AGT=abnormal glucose tolerance. ATG=anti-thymocyte globulin. GAD-alum=GAD formulated with aluminium hydroxide. GCSF=granulocyte colony-stimulating factor. $HbA_{1c}$=glycated haemoglobin. HR=hazard ratio. IAA=insulin autoantibody. IE=international unit. IV=intravenous. JAK=Janus kinase. NA=not applicable. SC=subcutaneous. *Participants who were unable to receive the second 12-day course due to COVID-19 pandemic restrictions were given the second course at the week 52 visit.

***Table 1:*** **Summary of major randomised placebo-controlled clinical trials for drugs aiming to prevent or delay islet autoantibodies, the loss of β-cell function, or clinical type 1 diabetes**

modulators, could enhance both the magnitude and durability of therapeutic effects and should be considered. Although approved for other indications, these therapies have not yet received regulatory approval for type 1 diabetes, as in most cases, pivotal regulatory approval studies are still outstanding.

*Antigen-based therapies*

Insulin, glutamic acid decarboxylase ($GAD_{65}$), insulinoma antigen 2 (IA-2), and zinc transporter 8 are key autoantigens targeted by T cells and B cells in type 1 diabetes. Insulin, its precursors, and related peptides have been trialled as antigen-based immunotherapies. Subcutaneously or intranasally delivered insulin was found to have no preventive effects.[39,48] Two phase 2 trials evaluated daily oral administration of 7·5 mg insulin in children with multiple autoantibodies.[40,41] Neither trial showed a significant effect in delaying the onset of clinical diabetes; however, subgroup analyses showed a delay in disease progression in individuals with impaired insulin secretion, with the HLA DR4-DQ8 haplotype, or with high concentrations of insulin or IA-2 autoantibodies.[49]

$GAD_{65}$-based therapies delivered via subcutaneous or intralymphatic administration have been tested in multiple clinical trials.[24–26] Overall efficacy in preserving insulin secretion was not shown. Post-hoc subgroup analyses suggested benefits in participants with the HLA DR3-DQ2 haplotype, which is being addressed in ongoing trials (table 2).

## Non-immune modulators

Several approaches aimed at directly protecting β cells or addressing environmental factors have shown encouraging results.

*Verapamil*

Verapamil, a calcium channel blocker commonly used for hypertension and tachycardia, reduces the expression of thioredoxin-interacting protein, which is toxic to islet β cells. In two trials—one in adults and the other in children, both with stage 3 type 1 diabetes—verapamil slowed the decline in C-peptide responses to a mixed meal, more than placebo.[36,37]

*Adjunctive therapies*

Several trials have investigated adjunct therapies, such as metformin or GLP-1 receptor agonists, for newly diagnosed stage 3 type 1 diabetes.[50] The combination of anti-IL-21 and liraglutide preserved C-peptide after 1 year of treatment but led to greater insulin secretion loss after treatment cessation compared with placebo.[51] The combination of saxagliptin and vitamin D preserved pancreatic β-cell function in people with adult-onset type 1 diabetes.[52] Similarly, liraglutide improved residual β-cell function and reduced insulin requirements in people with adult-onset type 1 diabetes during the first year post-diagnosis.[50]

*Antiviral therapies*

Viral infections are associated with islet autoimmunity,[53] and viral traces persist in the islets of people with type 1 diabetes. Treatment with the viral clearing agent pleconaril, together with the broad-spectrum antiviral drug ribavirin, temporarily preserves β-cell function more effectively than placebo (table 1);[29] however, the benefit was not found to be present after 2 years and after 3 years.[30]

## Current trials

A range of novel therapeutic approaches is currently being evaluated in clinical trials (table 2). These approaches include plasmid therapies encoding human pre-proinsulin coupled to TGF-β1 and IL-10, sequential therapies with rituximab and abatacept, and combination therapies involving verapamil, golimumab, ATG, abatacept, and intranasal insulin. Additionally, treatments with new JAK inhibitors, such as abrocitinib and ritlecitinib; a new anti-CD40L antibody that blocks the CD40–CD40L costimulatory pathway (frexalimab); a dual anti-TNF and anti-OX40L nanobody; recombinant $GAD_{65}$; nanoparticles; liraglutide; and DFMO (polyamine biosynthesis) are being investigated. Another trial is underway to investigate extending the indication for teplizumab to children aged 1–8 years.

## Preventing autoimmunity and type 1 diabetes

Understanding the cause of type 1 diabetes could allow primary prevention of islet autoimmunity, which often

| | Trial name, if available (registration number) | Treatment administration | Participants | Inclusion criteria | Primary outcome |
|---|---|---|---|---|---|
| **Stage 3** | | | | | |
| Abatacept (CTLA4-Ig), nasal insulin *vs* placebo | IAA (NCT05742243) | SC weekly or nasal 10 days daily and twice weekly | 62 | Age 6–21 years, random C-peptide >0·3 pmol/mL, stage 3 ≤100 days, and weight ≥20 kg | Stimulated C-peptide at week 48 |
| Abrocitinib (JAK inhibitor) and ritlecitinib (JAK inhibitor) *vs* placebo | JAKPOT T1D (TN31) (NCT05743244) | Oral daily | 78 | Age 12–35 years, stimulated C-peptide >0·2 pmol/mL, and stage 3 ≤100 days | Stimulated C-peptide AUC at week 52 |
| ATG and verapamil *vs* placebo | (NCT06455319) | IV days 1 and 2, or oral daily | 60 | Age 6–35 years, stimulated C-peptide >0·2 pmol/mL, and stage 3 ≤100 days | Stimulated C-peptide AUC at week 26 and 52 |
| ATG, verapamil, or golimumab (anti-TNF) *vs* placebo | T1D-PLUS (IRAS ID 1006723) | Oral daily, IV 2 days, oral, or SC | Adaptive | Age 18–44 years and stage 3 <90 days | Stimulated C-peptide AUC at week 52 |
| CNP-103 (autoantigen nanoparticles) *vs* placebo | (NCT06783309) | IV on days 1, 8, and 90 | 36 | Age 12–35 years, stimulated C-peptide ≥0·2 pmol/mL, and stage 3 <180 days | Safety |
| DFMO (polyamine biosynthesis inhibitor) *vs* placebo | TADPOL (NCT05594563) | Oral twice daily | 70 | Age 4–40 years, non-fasting C-peptide >0·2 pmol/mL, and stage 3 <100 days | Stimulated C-peptide AUC at week 26 |
| Diamyd ($rhGAD_{65}$), colecalciferol *vs* placebo | DIAGNODE-3 (NCT05018585) | Intralymphatic on days 0, 30, and 60, and oral daily | 330 | Age 12–28 years, fasting C-peptide ≥0·12 pmol/mL, stage 3 ≤6 months, and HLA DR3-DQ2 | Stimulated C-peptide AUC at week 104 |
| Frexalimab (anti-CD40L) *vs* placebo | FABULINUS (NCT06111586) | IV day 1, SC bi-weekly | 192 | Age 12–35 years, random C-peptide ≥0·2 pmol/mL, and stage 3 <90 days | Stimulated C-peptide AUC at week 52 |
| NNC0361–0041 (rh pre-proinsulin, TGF-β1, IL-10, and IL-2 plasmid) *vs* placebo | TOPPLE T1D (TN27) (NCT04279613) | SC once weekly | 48 | Age 18–45 years, stimulated C-peptide >0·2 pmol/mL, and stage 3 <48 months | Safety |
| Rituximab-pvvr (anti-CD20), abatacept (CTLA-4 Ig) *vs* placebo | T1D RELAY (TN25) (NCT03929601) | IV 4 weekly doses, SC weekly | 74 | Age 8–45 years, stimulated C-peptide of >0·2 pmol/mL, and stage 3 ≤100 days | Stimulated C-peptide response at week 104 |
| SAR442970 (dual anti-TNF and anti-OX40L nanobody) *vs* placebo | T1D OBTAIN (NCT06812988) | SC | 84 | Age 12–35 years, random C-peptide ≥0·2 pmol/mL, and stage 3 ≤90 days | Stimulated C-peptide AUC at week 26 |
| Verapamil *vs* placebo | Ver-A-T1D (NCT04545151) | Oral daily | 138 | Age 18–44 years, fasting C-peptide ≥0·1 pmol/mL, and stage 3 ≤6 weeks | Stimulated C-peptide AUC at week 52 |
| **Stage 2** | | | | | |
| ATG *vs* placebo | ATG (TN28) (NCT04291703) | IV days 1 and 2 | 101 | Age 6–34 years, multiple islet autoantibodies, and dysglycaemia | Stage 3 |
| Liraglutide (GLP-1 receptor agonist) *vs* placebo | INVESTDIA (NCT02898506) | SC daily | 10 | Age 10–30 years, multiple islet autoantibodies, and dysglycaemia | β-cell function (first-phase insulin response during 10 min IVGTT at week 52) |
| **Stage 1** | | | | | |
| Liraglutide (GLP-1 receptor agonist) *vs* placebo | INVESTDIA (NCT02611232) | SC daily | 10 | Age 18–30 years, multiple islet autoantibodies, and normoglycaemia | β-cell function (first-phase insulin response during 10 min IVGTT at weeks 26 and 104) |
| Oral insulin (67·5 mg) *vs* placebo | Fr1da (NCT02620072) | Oral daily | 220 | Age 2–12 years, multiple islet autoantibodies, and normoglycaemia | Dysglycaemia or diabetes, composite of $CD4^+$ T cell or antibody response to insulin |
| **Before islet autoimmunity** | | | | | |
| *Bifidobacteria infantis* EVC001 *vs* placebo | GPPAD-SINT1A (NCT04769037) | Oral daily | 1149 | Age 7 days to 6 weeks and >10% genetic risk for islet autoantibodies by age 6 years | Multiple islet autoantibodies or diabetes |
| COVID-19 vaccine *vs* placebo | GPPAD-AVAnT1A (NCT06452654) | IM, 3 single doses | 2252 | Age 3–4 months and >10% genetic risk for islet autoantibodies by age 6 years | Multiple islet autoantibodies or diabetes |

ATG=anti-thymocyte globulin. AUC=area under the curve. IV=intravenous. IL=intralymphatic. IM=intramuscular. IV=intravenous. IVGTT=intravenous glucose tolerance test. JAK=Janus kinase. rh=recombinant human. SC=subcutaneous.

***Table 2:*** **Ongoing clinical trials for preventing and delaying the loss of β-cell function**

initiates as early as 1 year of age.[53] Islet autoimmunity has a strong genetic component that enables the identification of infants who have markedly increased risk of more than 10% using polygenic risk scores[54] and thus facilitates prevention trials. Infrastructure for such trials is in place in Europe through the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD). Families of children with a genetic predisposition are counselled and invited to

participate in clinical trials. The first GPPAD clinical trial investigating whether oral insulin therapy can reduce the incidence of islet autoantibodies and type 1 diabetes was recently completed.[42] The GPPAD-SINT1A trial (NCT04769037) is exploring whether probiotic supplementation with *Bifidobacterium infantis* can reduce the incidence of islet autoantibodies by mitigating inflammation and dysbiosis. Recruitment for the ongoing GPPAD-AVAnT1A trial (NCT06452654) is underway (table 2).

### Regulatory challenges

Regulatory approval for drugs treating type 1 diabetes by agencies such as the US FDA requires evidence of treatment efficacy that delays clinical disease onset or reduces insulin requirements or $HbA_{1c}$; however, natural history studies, intervention trials, and transplantation studies consistently show that higher C-peptide responses to a mixed meal are associated with improved glycaemic control, fewer hypoglycaemic episodes, and reduced long-term complications.[55–57] These findings underscore the importance of preserving β-cell function, even if no direct reduction of insulin requirement is found. Regulatory acceptance of C-peptide as a validated surrogate endpoint could substantially expedite the development and approval of disease-modifying therapies for type 1 diabetes.

Another challenge lies in showing that therapies that preserve β-cell function and insulin secretion after the clinical onset of type 1 diabetes can also prevent or delay insulin dependence during earlier stages of the disease. A major bottleneck is the identification and recruitment of individuals in stage 2. Long recruitment periods lead to inflated costs, which deter pharmaceutical companies from pursuing these studies. Improvements are likely to be seen through work done by initiatives such as the European Pre-T1D registry, which monitors individuals in the early stages of type 1 diabetes. A tempting alternative is to consider whether findings from trials involving individuals with stage 3 type 1 diabetes (ie, clinical disease) can be directly applied to individuals with stage 2, without the need for new validation trials. Such an option would be conceivable if stage 2 type 1 diabetes represents a shift to an earlier phase of disease, characterised by progression from dysglycaemia to hyperglycaemia. Following this notion, concurrently including both individuals with stage 2 and those with stage 3 type 1 diabetes into trials could be valuable. Simultaneous approval of therapies for both stages could considerably advance the development of sequential and combinatorial therapies aimed at the prevention of insulin dependency.

For more on the **European Pre-T1D registry** see https://www.pre-t1d-registry.eu/

### Limitations and crucial considerations of immunological interventions

A limitation of clinical trials conducted to date is that most were done in small participant populations. Many of the observed effects have yet to be replicated by independent outcome trials in larger cohorts. Moreover, the observed differences are sometimes marginal and not sustained beyond the treatment period, which suggests that medications might need to be administered continuously to maintain their effects. Thus, drawing robust conclusions about the long-term efficacy and safety of these interventions is difficult.

Going forward, defining the efficacy required for an immunomodulatory therapy to be considered clinically meaningful and advantageous over insulin replacement alone will be essential. Furthermore, whether preventive interventions (initiated before the clinical manifestation of the disease) should be prioritised, particularly if they can significantly delay the need for insulin therapy, should be reconsidered.

## Part 2: Curing diabetes with β-cell replacement therapies

The field of β-cell replacement for type 1 diabetes is going through an exciting period due to scientific advances in developmental biology, stem cell biology, genome editing building on years of experience in delivering deceased-donor islets, and pancreas transplants. Perhaps the greatest challenge for stem cell-derived islets, once technological challenges are overcome, is for them to be seen by clinical endocrinologists as a future mainstream rather than niche treatment for type 1 diabetes (panel 1).

Pancreas transplantation simultaneous with kidney transplantation (SPK) is the standard of care for chronic kidney disease due to type 1 diabetes. This procedure is highly effective despite the initial risk of perioperative morbidity (eg, pancreatic vascular thrombosis), with insulin independence and patient survival at high rates according to registry data.[58] SPK continues to be the standard of care with kidney transplantation due to it frequently resulting in insulin independence when the whole pancreas is transplanted, the fact that the recipients already need to take immunosuppression, and the improved survival compared with kidney transplant alone.

25 years ago, islet transplantation made a major advance when seven consecutive islet transplant recipients in Edmonton, Alberta, Canada had insulin independence.[59] These findings were supported in a subsequent international multicentre study, which showed some unevenness of results between centres that indicated a need for high-quality islet isolation.[60] Islet transplantation is remarkably successful for treatment of severe hypoglycaemia with hypoglycaemia unawareness that has not responded to other measures. This success rate for treating hypoglycaemia shows the importance of endogenous glucose sensing and insulin secretion to avoid hypoglycaemia.[61] Controlled trials[62,63] and follow-up of recipients[64,65] in major centres showed that high rates of insulin independence can be reached, and long duration of graft function is also seen; however, over time, multiple shortcomings of islet transplant have become apparent. These limitations include the

marginal nature of the β-cell replacement with vulnerability to loss of graft function from alloimmunity, autoimmunity, or drug toxicity resulting in loss of insulin independence over time; the side-effects of immunosuppression, including the nephrotoxicity of calcineurin inhibitors; and the shortage of donor organs. In addition, regulatory hurdles from the US FDA, despite pivotal trials done by the Collaborative Islet Transplant group,[62] have been a major stumbling block for the development of islet transplantation technology in the USA. A biological licence was issued by US FDA to CellTrans in June, 2023, but is yet to have a major effect on islet transplant numbers. Nevertheless, islet transplantation continues to be offered, with good outcomes, in many centres because of its effectiveness for treating hypoglycaemia and its usefulness in conjunction with kidney transplantation in people unsuitable for SPK.[62] Recently, islet transplantation after kidney transplantation was associated with superior long-term outcomes to kidney transplantation alone, and islet transplantation reduced mortality compared with kidney transplants and composite negative outcomes including mortality in individuals without kidney transplants.[66,67]

Methods have been developed (figure 2) by which pluripotent stem cells can be differentiated into β-like cells by a series of steps in which differentiation factors are added.[68,69] The stem cells can either be derived from embryonic stem cell lines or induced pluripotent stem cells made from de-differentiation of mature cells. These stem cells begin as proliferative undifferentiated cells that are exposed to a series of cycles of growth and differentiation factors that lead to seven defined stages. The first four stages produce proliferative cells. As the cells differentiate, they become less proliferative.

## Clinical trials

Embryonic stem cell-derived β-cell precursors in macroencapsulation devices implanted subcutaneously did not allow graft survival and function in the Viacyte VC-01 trial because the device biomaterial developed a foreign body reaction and nutrient diffusion was insufficient for cell survival.[70] When the device was modified to allow vessel entry, the cells survived, and C-peptide was measurable with an effect on glucose control and insulin requirement. Vertex-880 (Vertex Pharmaceuticals, Boston, MA, USA) cells were successful in a 2025 phase 1/2 trial.[71] This off-the-shelf embryonic stem cell-derived product consists of differentiated post-mitotic β cells delivered into the portal vein and protected from alloimmune and autoimmune attack by conventional immunosuppression. The transplants take 90–180 days to reach full C-peptide production after transplantation. 10 (83%) of 12 participants who received the full dose were insulin independent at 365 days. Two deaths occurred, neither of which were related to the procedure or the cells. A phase 3 trial has now begun (NCT04786262).

Another landmark event in type 1 diabetes treatment was the reversal of diabetes with β cells derived from autologous induced pluripotent stem cells in a recipient with previous liver transplantation and therefore on immunosuppression.[72] Another two people with type 1 diabetes have received a transplant at the time of writing. These induced pluripotent stem cells were generated by chemical reprogramming of the cells using small molecules to de-differentiate the cells rather than genetic methods. In this study, the cells were transplanted into the rectus sheath in the anterior abdominal wall (table 3).[72]

These studies indicate that current technology can produce stem-cell derived β cells capable of reversing type 1 diabetes (figure 2). Some of the challenges to the introduction of stem-cell derived islets into clinical practice have been recently reviewed.[73]

## Safety

Concerns remain about less differentiated mitotic cells with the potential to form tumours in the transplant recipient.[74] This risk is mitigated by reducing the time in culture to reduce karyotype abnormalities and monitoring for these, and by separating cells into populations associated with later stages of differentiation. So-called suicide switches, such as thymidine kinase, that can be activated, if necessary, after transplantation are also possible. Another approach is encapsulation to contain transplanted cells. In the Vertex 264 phase 1 clinical trial, cells were transplanted within a proprietary encapsulation device; however, this trial did not meet its primary endpoint.[70]

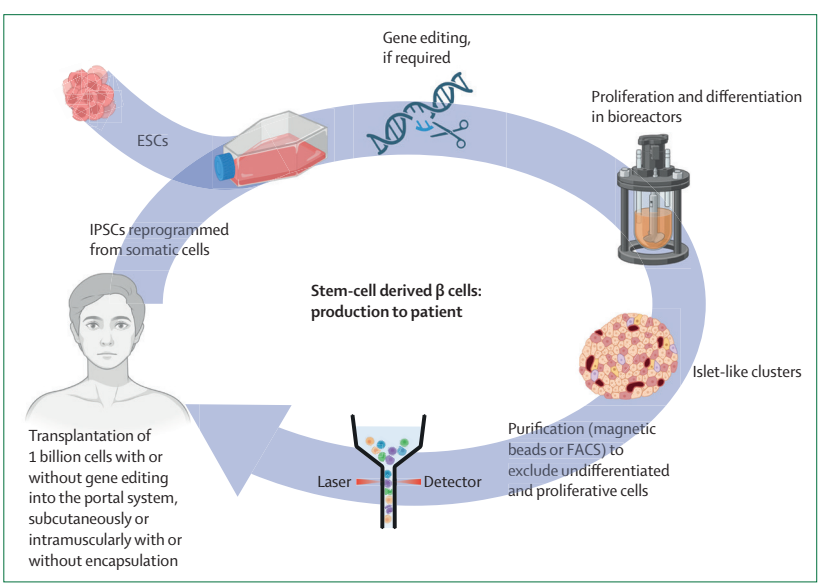


***Figure 2:*** **Production and transplantation of β cells derived from embryonic or induced pluripotent stem cells**
ESCs=embryonic stem cells. FACS=fluorescence-activated cell sorter. IPSCs=induced pluripotent stem cells.

| | Affiliated company | Trial registration number | Immunosuppression | Indication | Site | Origin |
|---|---|---|---|---|---|---|
| Vertex-880 | Vertex (Boston, MA, USA) | NCT04786262 | Full | Hypoglycaemia | Portal vein | Embryonic stem cells |
| Vertex-264 | Vertex (Boston, MA, USA) | NCT05791201 | Encapsulation | Type 1 diabetes | Sub-cut | Embryonic stem cells |
| Hypoimmune islets | Sana (Seattle, WA, USA) | NCT06239636 | Nil | Type 1 diabetes | Muscle | Primary islets |
| Pancreatic endocrine clusters | Seraxis (Germantown, MD, USA) | NCT06651515 | Full | Hypoglycaemia | Omentum | Induced pluripotent stem cells |
| Autologous stem cell-derived β-cells | HangZhou Reprogenix (Hangzhou, China) | ChiCTR2300072200 | Full | Hypoglycaemia | Anterior abdominal wall | Chemically induced pluripotent cells |

*Table 3:* **Trials in β-cell replacement**

### Need for immunosuppression

Cells derived from an individual embryonic stem cell line require protection from alloimmunity and autoimmunity, whereas β cells derived from a recipient's own induced pluripotent stem cells need protection from autoimmunity. Embryonic stem cell-derived transplants used with immunosuppression are likely to have application limited to recipients with severe hypoglycaemia or hyperglycaemia or to recipients in whom immunosuppression is used for another reason, such as kidney transplantation.

Two main approaches are being used to reduce immunosuppression. One approach is to use encapsulation within devices that exclude immune cells from direct interaction with transplanted cells,[73] which is a bioengineering challenge for which high oxygen tension is required. The second approach is to generate hypoimmune cells by using genome editing tools, such as CRISPR, to delete genes within the transplanted cells that the immune system uses to recognise foreign cells or to overexpress genes that can reduce immune attack.[75] Genes targeted include the HLA class I genes either directly or by editing β-2-microglobulin, the light chain of the HLA class I dimer. Additional steps can also be applied, including reduction in major histocompatibility complex class II expression, protection from natural killer cells, and protection from cytokines.

A challenge in reducing immunosuppression is the absence of models to test protection from pre-existing memory autoimmune responses, whereas protection from alloimmunity can be tested in primate studies. Sana Biotechnology (Seattle, WA, USA) reported the 1-month data on the first person treated with donor-derived islets that have been made deficient in β-2-microglobulin and the class II transactivator molecule to reduce major histocompatibility complex class II and overexpression of CD47 to decrease attack by natural killer cells, using a protocol previously reported in primates.[76] The 6-month results of the first patient were reported as showing a small amount of ongoing C-peptide production without any immunosuppression.[77]

### Production scale-up

Treating many people with type 1 diabetes will require substantial scale-up of cell manufacturing and other changes, such as potentially shortening the duration of in-vitro steps to reduce cost and increase efficiency.[78,79] Approximately 1 billion pancreatic progenitor cells are estimated to be required per person, although this number could be less if more mature cells are used.

Problems in growing the very large number of cells that will be required remain unsolved. Until approximately 5 years ago, cells were grown in conventional 2D cultures that required large numbers of culture flasks. Now, cells are grown in suspension cultures that produce more cells with better potential for transplantation.

The cost of production is estimated to be in the hundreds of thousands of US dollars per person, but this cost could decrease, as the cost of goods is less for an off-the-shelf embryonic stem cell-derived product rather than a personalised product from induced pluripotent stem cells.

## Part 3: Improving metabolic control with innovative therapies

### New-generation insulins

#### *Ultrafast or rapid-acting insulins*

Insulins with a faster onset and offset, which replicates physiological insulin action, are highly desired to improve glycaemia by speeding up post-meal glucose clearance and recovery from missed meal insulin boluses, to minimise hypoglycaemia, and to reduce weight gain. Faster-acting insulin aspart has a quicker onset and offset than regular insulin aspart and offers better control of post-meal glucose spikes and less hypoglycaemia 2–5 h after a meal.[80] In children and adolescents with type 1 diabetes, mealtime and post-meal faster-acting insulin aspart combined with insulin degludec provided effective glycaemic control compared with insulin aspart in a 26-week clinical trial, with no safety concerns.

Ultrarapid-acting insulin lispro has been shown to be safe and non-inferior to insulin lispro in children, without any significant $HbA_{1c}$ differences between the ultrarapid-acting insulin lispro group and the insulin lispro group.[81] This finding aligns with those of previous clinical trials that showed faster-acting insulins improve postprandial glucose without compromising overall glycaemic management or safety.[80,81] Other investigational ultrarapid insulin analogues, such as BioChaperone Lispro (Adocia, Lyon, France) and AT247 (Arecor, Cambridge, UK), are being tested in adults with diabetes,[82] and additional novel formulations are being investigated in animal studies.[83]

*Inhaled insulin*

Afrezza (MannKind, Danbury, CT, USA), a human insulin inhaled powder, is the fastest-acting exogenous insulin due to rapid absorption from the lungs, and eliminates the delays seen with subcutaneous injection.[84] US FDA-approved for adults with diabetes, Afrezza has been shown to improve postprandial glycaemia.[85] Preliminary studies in children have shown promising results,[86] and a clinical trial for US FDA approval in this population is ongoing.

*Once-weekly basal insulin analogues*

Insulin icodec, an ultralong-acting, weekly basal insulin with a half-life of approximately 8 days, offers a flat, stable pharmacokinetic profile, low peak-to-trough variation, and consistent glucose-lowering efficacy. A randomised open-label study of 582 adults with type 1 diabetes showed non-inferiority of insulin icodec to daily insulin degludec at 26 weeks of treatment, with better outcomes at 52 weeks of treatment, although more clinically significant hypoglycaemic events occurred with insulin icodec.[87] Similarly, basal insulin Fc (also referred to as insulin efsitora alfa) showed non-inferiority in terms of glycaemic control and hypoglycaemia risk compared with degludec in a study of 266 adults with type 1 diabetes.[88]

*Glucose-responsive insulins*

Glucose-responsive insulins (GRIs), or so-called smart insulins, are designed to automatically adjust their activity on the basis of blood glucose concentrations. Different investigational methods are used to deliver GRIs. The main concept is for the insulin to be released from an in-vivo GRI reservoir during hyperglycaemia and for cessation of insulin release when normoglycaemia is reached. Future GRIs might offer both fast-acting and long-acting formulations for improved postprandial and fasting glycaemic control.[89,90] Research is ongoing regarding various GRI formulations, and GRIs are not clinically available for treatment of diabetes.

## Adjunctive treatments

Adjunctive treatments are available to reduce $HbA_{1c}$ and counter adverse outcomes linked to obesity, insulin resistance, and impaired glucagon suppression. Adjunctive therapies include the amylin analogue pramlintide, metformin, GLP-1 receptor antagonists, and SGLT2 and dual SGLT1 and SGLT2 inhibitors.

Pramlintide, the only US FDA-approved adjunctive therapy for type 1 diabetes, reduces glucagon secretion, slows gastric emptying, and promotes satiety. The efficacy of pramlintide is modest, with an average $HbA_{1c}$ reduction of 0·2–0·4% and average weight loss of approximately 0·5–1 kg. Use of pramlintide is limited by the risk of severe hypoglycaemia and injection burden. Metformin improves insulin sensitivity and cardiovascular outcomes in people with type 1 diabetes.[91,92] GLP-1 receptor agonists reduce bodyweight and insulin dose, with modest improvements in glycaemic control.[93–96] SGLT inhibitors have shown significant reductions in $HbA_{1c}$ of 0·4–0·5%, insulin dose, and bodyweight, without increasing hypoglycaemia risk, although they raise the risk of diabetic ketoacidosis.[5] Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, is the only approved adjunctive therapy in Europe for adults with type 1 diabetes and a BMI of 27 kg/m² or higher. In adults aged 18–30 years with suboptimal glycaemic control, sotagliflozin plus insulin for 12 weeks improved $HbA_{1c}$, postprandial blood sugar, goal attainment, and bodyweight.[97]

## AID systems

Technology has substantially transformed diabetes management and has fostered advancements that have enhanced treatment of the disease. Glucose monitoring and nutrition management are foundational pillars of type 1 diabetes care and are essential for glycaemic control and preventing complications.[98,99] Continuous glucose monitors provide trend data that inform insulin treatment and reflect the effects of lifestyle decisions, including dietary choices, activity, stress, and many other factors, on glycaemia. AID systems automate insulin administration by continuously adjusting insulin doses on the basis of real-time glucose concentrations. This innovation is designed to improve glycaemia, alleviate the burden of manual management, and maintain glucose concentrations within clinically recommended ranges (figure 3A). Next-generation AID systems consist of smart insulin pumps equipped with insulin delivery algorithms and continuous glucose monitoring interfaces.

Clinical trials and real-world data have shown that AID systems effectively reduce $HbA_{1c}$, time above range, and time below range, and increase time in range by an average of 10–15 percentage points when compared with standard care. Time in tight range (TITR; defined as blood glucose concentration of 3·9–7·8 mmol/L) is an emerging glycaemic metric for optimal glycaemic control. Although no TITR goal has been universally established, a TITR of higher than 50% is considered a reasonable target (figure 3B).[100] This improvement in time in range and the reduction in $HbA_{1c}$ were found with no increase (and in

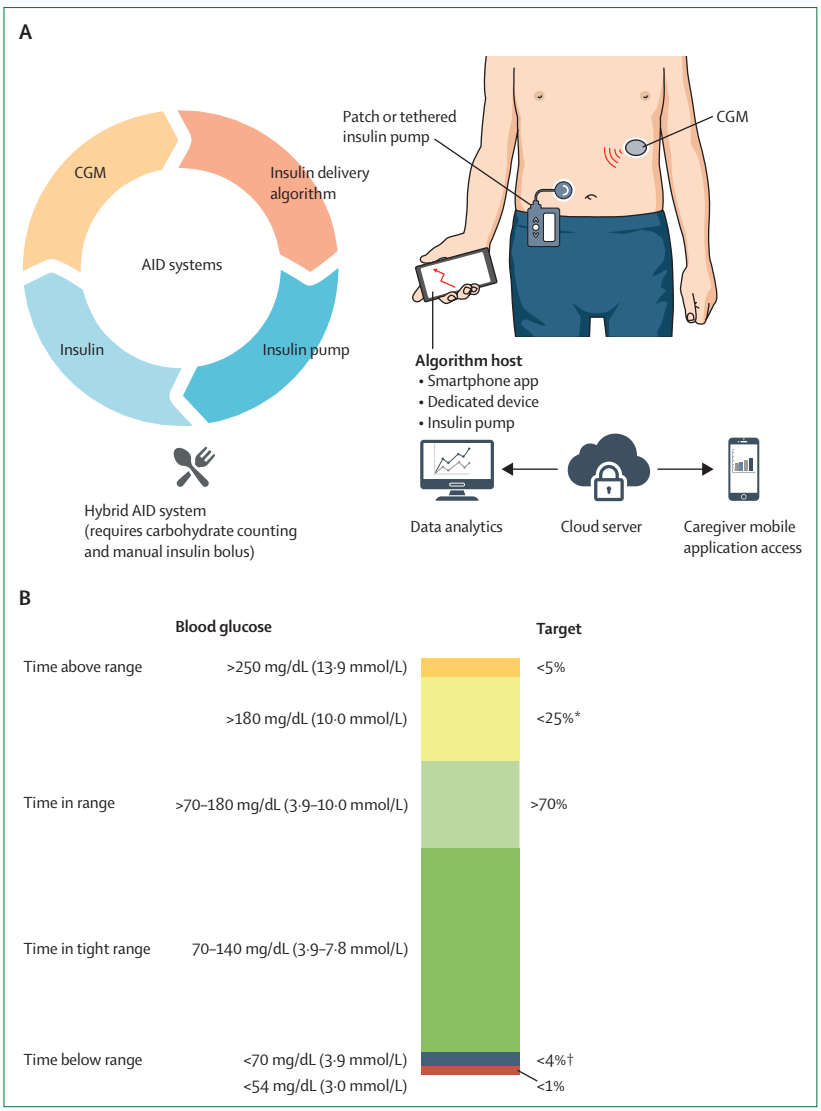


***Figure 3:*** **AID systems and CGM-based glycaemia targets**
(A) AID system with its connected components. Insulin dose is calculated on the basis of CGM values using an insulin delivery algorithm, and insulin is infused by the insulin infusion pump (tethered or patch pump). Dual-hormone systems (investigational and not depicted in the figure) infuse other hormones such as glucagon in addition to insulin. Hybrid AID requires meal-time carbohydrate counting and meal bolus input. CGM and insulin delivery data are uploaded to the cloud server for data analytics and can be accessed by parents, caregivers, and clinicians of people with diabetes. (B) Percentage of readings and time per day within target glucose range, time below target glucose range, time above target glucose range, and time in tight range. AID=automated insulin delivery. CGM=continuous glucose monitor. *Includes percentage of values <250 mg/dL (13·9 mmol/L). †Includes percentage of values <54 mg/dL (3·0 mmol/L).

some cases, a reduction) in hypoglycaemia across all age groups.[100] Real-world data also aligned with clinical trial outcomes showing $HbA_{1c}$ reductions of 0·3–0·7% across diverse age groups.[95,101,102] Improvements have been especially notable in vulnerable populations, such as young children[103] and pregnant women with type 1 diabetes.[104] Only one AID system is approved for use during pregnancy, and it has been shown to improve time in the target glucose range of 3·5–7·8 mmol/L without increasing the risk of hypoglycaemia.[104]

### *Challenges of AID systems*

Despite the considerable advantages of AID systems, several challenges can affect their effectiveness and widespread adoption. A key physiological challenge is the ability of the system to adapt to rapidly changing insulin requirements within an individual. AID systems do not distinguish between variations in insulin needs caused by stress, illness, or physical activity; however, integrating signals from other wearable devices could help the system make more informed decisions about insulin delivery.

Additionally, events such as AID insulin delivery failure could be detected through continuous ketone sensors and could improve safety by providing early alerts. Insulin action can be delayed and vary between individuals and with different insulin analogues, which limits the ability of the AID system to respond promptly to rising glucose concentrations.[105] As a result, glucose concentrations can increase before insulin takes effect, even when meal announcements are made, and AID systems often struggle to maintain postprandial glucose concentrations within the desired range. Studies involving ultrarapid insulins used in conjunction with hybrid AID systems have not consistently shown significant improvements in time in range, which highlights the need for the development of novel ultrarapid-acting insulins.

### *New AID system developments*

Alternative routes of insulin delivery, such as intraperitoneal insulin and the addition of pre-meal inhaled insulin (Afrezza) to AID systems, are being investigated.[106] Research is exploring multihormone AID systems, which involve the combined use of insulin with glucagon or pramlintide, either through separate infusions or as a coformulation. Additionally, adjunctive treatments that pair AID with GLP-1 receptor agonists and SGLT2 inhibitors are being studied with the aim of improving postprandial hyperglycaemia.

Fully automated AID systems are highly anticipated. Unlike hybrid AID systems, fully automated versions do not require meal announcements or boluses to cover meals and snacks. A fully automated AID system equipped with a meal detection algorithm is considered the ultimate solution to addressing the missed meal insulin boluses, and investigational systems have already shown substantial progress in this field.[107] Some data suggest that providing the system with information about the macronutrient amount of meals can have a favourable effect on postprandial glycaemia. Understanding this relationship is crucial and highly relevant for the development of personalised insulin dosing algorithms.

## Accessibility to screening, disease-modifying therapies, and diabetes technologies

People in underserved or low-income communities are most likely to face challenges accessing screening for

islet autoantibodies, disease-modifying therapies, and diabetes technology due to poor health-care infrastructure, awareness, and insurance coverage. In Europe, access to health care might be generally more equitable due to universal health-care systems.

Access to teplizumab and similar disease-modifying therapies will largely depend on their cost and whether these therapies are covered by public or private health insurance. If payment falls on individuals, affordability will become a major obstacle for people in low-income settings, especially in countries without comprehensive health-care coverage. People with language barriers will also face challenges in accessing and choosing whether to participate in screening and accept therapy.

Actions needed include ensuring broad insurance coverage for both diagnostic testing and interventions, and addressing social determinants of health, such as language barriers and trust in health-care systems, which often affect migrant and low-income populations disproportionately. Both screening and therapy are an individual or family choice.

## Future aspects

Future efforts in type 1 diabetes care should shift towards more personalised immunotherapies with durable efficacy and towards combination therapies that target complementary pathways. Subanalyses of trials in individuals with early-stage type 1 diabetes or with stage 3 type 1 diabetes suggest greater efficacy in distinct genetic and phenotypic subgroups. An important step in this direction will be personalised response analyses across trials that lead to robust conclusions and the identification of biomarkers predictive of therapy response. Although stem-cell therapy has shown remarkable results in a few people,[71,72] its promise as a therapy for broad application is dependent on the safe engineering of cells that avoid both alloimmunity and autoimmunity, and on production methods that meet the global demand for cell-based therapy at affordable costs. Insulin therapy will be an integral part of treatment for most people. Advances will be driven by AID systems, and by bihormonal or trihormonal therapies and the development and testing of new glucose-responsive insulins, all of which will optimise and enhance AID systems.

### Contributors

A-GZ contributed to conceptualisation, supervision of the writing process, and final verification of the manuscript. A-GZ drafted the abstract, introduction, part 1, future aspects section, and the panel. TWHK drafted part 2. EC drafted part 3. A-GZ and TWHK created the tables. All authors contributed to the literature search, created the figures, and reviewed, edited, and approved the final version of the manuscript.

### Declaration of interests

A-GZ has received consulting fees from The Leona M and Harry B Helmsley Charitable Trust and from Sanofi France; honoraria from Georg Thieme Verlag, Novo Nordisk Norway, and Deutsche Diabetes Gesellschaft; and support for attending meetings from Sanofi France. She is member of the data monitoring committee for Provention Bio, Sanofi, Sanofi US Services, and ITB-Med, and is advising the advisory board for Sanofi France and Sanofi-Aventis US. EC has received honoraria for presentations from the Medical Learning Institute, Children with Diabetes, and Advanced Technologies and Treatments for Diabetes. She is a member of the scientific advisory boards of Novo Nordisk, Eli Lilly, MannKind, PortalInsulin, Tandem, and Arecor, and had a leadership or fiduciary role at the International Society for Pediatric and Adolescent Diabetes and the American Diabetes Association. TWHK has received institutional research grants from Breakthrough T1D, the National Health and Medical Research Council, and the Medical Research Future Fund; provisions from Eli Lilly, Pfizer, and AbbVie; consulting fees from SAB Biotherapeutics; and an honorarium from Sanofi for a talk and travelling. He holds a Patent Cooperation Treaty (application number PCT/IB2023/055258) and a provisional patent (application number 63/503,588), is a member of the Scientific Advisory Board of Biotherapeutics, and was president of the International Pancreas and Islet Transplant Association.

### Acknowledgments

We thank Ramona Lickert for assistance with tables, figures, and the literature search, and Sandra Steinebrunner for assistance with references.

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