Workshop: 21st Century Clinical Trials in New-Onset Type 1 Diabetes

Briefing Document: C-Peptide as a Surrogate Endpoint in T1D Clinical Trials

This document is prepared as an informal briefing book for all attendees in advance of a virtual workshop "21st Century Trials in New-Onset Type 1 Diabetes" to be conducted June 17-18, 2025. This workshop will bring together regulators, individuals with lived experience of Type 1 Diabetes (T1D), patient advocates, physicians, academic investigators, and drug developers for the purpose of seeking to clarify current thinking on and advance the acceptance of C-peptide as a surrogate endpoint for evaluating disease-modifying therapies in T1D to preserve beta-cell (β-cell) function.

This document is presented by the Type 1 Diabetes Consortium (T1DC), [1]Critical Path Institute (C-Path) and has been reviewed by a cross section of consortium representatives from Breakthrough T1D, Diamyd Medical, Novo Nordisk and Sanofi.

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[1]C-Path is a nonprofit, public-private partnership with the Food and Drug Administration (FDA) and created under the auspices of the FDA's Critical Path Initiative program in 2005. C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of solutions that aid in the scientific development and evaluation of new therapies

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3. Executive Summary

The purpose of this briefing document is to present the rationale for and evidence supporting the use of C-peptide as a surrogate endpoint for the traditional approval of disease-modifying therapies (DMTs) in new-onset type 1 diabetes (T1D). Core elements of this document will be presented and discussed in a virtual public meeting to be held June 17-18th, 2025.

T1D is a chronic autoimmune condition characterized by the destruction of pancreatic β-cells, leading to absolute insulin deficiency and subsequent hyperglycemia. In the last decade, evidence for the role of the β-cell itself in the disease process has also emerged, adding complexity to the picture of disease progression. T1D necessitates lifelong insulin replacement therapy, which has a high burden of management and is itself associated with significant and potentially life-threatening complications.

The use of C-peptide, a short peptide resulting from proinsulin processing and released in equimolar concentrations with insulin from β-cells, as a primary endpoint in clinical trials for new-onset T1D has been a topic of discussion for over two decades (See appendix B), driven by its role as a direct measure of β-cell function and therefore serving as a marker of the underlying disease activity. To date the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) view C-peptide as a relevant biomarker in T1D but have held evolving positions on its status as an endpoint for clinical trials. EMA considers the change from baseline in C-peptide (e.g. C-peptide area under the curve [AUC]) or, if appropriately justified, the percentage of patients with C-peptide increases above a clinically meaningful threshold following a physiological and glycated hemoglobin (HbA1c), frequency of hypoglycemic episodes, particularly severe events, as co-primary endpoints. Similarly, the FDA has considered C-peptide as a reasonably likely surrogate endpoint (RLSE) in the past but has sought additional clinical endpoints such as HbA1c for traditional approvals. FDA recently issued a draft guidance discussing metabolic endpoints for diabetes, however no current draft or final guidance references how C-peptide may be used in the evaluation of clinical trials of T1D.

The development of DMTs, that aim to preserve residual β-cell function by targeting the autoimmune attack and/or by restoring or maintaining β-cell health, is essential for improving both short-term and long-term outcomes. However, the conduct of clinical trials for new-onset T1D presents significant operational challenges across trial design, recruitment, conduct, retention, and study length. These challenges are particularly pronounced when evaluating DMTs aimed at preserving β-cell function in pediatric populations (40% of new stage 3 T1D diagnoses). Currently accepted endpoints that can support traditional product approval, including HbA1c and rates of hypoglycemic events, are challenging to assess in clinical trials in new-onset stage 3 T1D.

In summary, most people living with T1D remain unable to reach glycemic targets, and available data reveal that individuals live with elevated levels of distress, cognitive and emotional burden, and burnout. The unmet needs in T1D and its rising incidence (1–3% annually) necessitate rapid development of appropriate therapeutics. The adoption of C-peptide as a validated surrogate endpoint, which unlike HbA1c, measures the actual underlying disease process, could accelerate the development of DMTs by enabling parallel, smaller, faster, and more efficient trials leading to the increased availability of treatment options for patients.

4.0 Background and Rationale

4.1 Type 1 Diabetes Overview

T1D necessitates lifelong insulin replacement therapy, which has a high burden of management and is itself associated with significant and potentially life-threatening complications. T1D is a has long been thought of as a chronic autoimmune condition characterized by the destruction of pancreatic β-cells, leading to absolute insulin deficiency and subsequent hyperglycemia, however research over the past decade has also implicated the β-cell as playing an important role and DMTs are emerging that directly target β-cell survival and function.

T1D is staged based on the presence of autoantibodies and metabolic status, as outlined by the American Diabetes Association (ADA) (Phillip et al., 2024), European Association for the Study of Diabetes (EASD) (Phillip et al., 2024), International Society for Pediatric and Adolescent Diabetes (ISPAD) (Haller et al., 2024), and Breakthrough T1D (Insel et al., 2015):

- Stage 1: Presence of two or more diabetes-related autoantibodies with normal glucose tolerance, indicating early autoimmune activity without symptoms
- Stage 2: Presence of autoantibodies with dysglycemia, such as impaired fasting glucose or impaired glucose tolerance, still asymptomatic but at high risk of progression
- Stage 3: Clinical diabetes with symptomatic hyperglycemia, significant β-cell loss, and the need for insulin therapy, marked by symptoms like polyuria, polydipsia, and weight loss

This staging system facilitates early identification and intervention, particularly in at-risk individuals, and is crucial for designing clinical trials for DMTs.

4.2 C-peptide: Definition and Its Role as a Biomarker in Type 1 Diabetes

C-peptide is a 31-amino acid polypeptide that is an inactive byproduct of insulin synthesis, produced in equimolar amounts to insulin by pancreatic β-cells. It is cleaved from proinsulin in the β-cell secretory granules during insulin maturation, with insulin and C-peptide subsequently released into the bloodstream in a 1:1 molar ratio (Steiner et al., 1967), (Weiss et al., 2000). Unlike insulin, which is rapidly cleared by the liver (first-pass metabolism), C-peptide has a longer half-life (approximately 30 minutes) and is primarily excreted by the kidneys, making it a reliable marker of endogenous insulin production (Horwitz et al., 1975). Its measurement is unaffected by exogenous insulin administration, which is a significant advantage in clinical settings where patients are receiving insulin therapy (Maddaloni et al., 2022).

C-peptide levels are typically measured in serum or plasma using immunometric assays, such as enzyme-linked immunosorbent assays (ELISA) or electrochemiluminescence immunoassays (ECLIA), with high sensitivity and specificity (Leighton et al., 2017). Common tests include fasting C-peptide, postprandial C-peptide, or stimulated C-peptide (e.g., after a mixed meal tolerance test [MMTT] or glucagon stimulation), with the MMTT being more reflective of β-cell secretory capacity (Greenbaum et al., 2008). Normal fasting C-peptide levels in healthy individuals range from approximately 0.3 to 0.9 nmol/L, though reference ranges vary by assay and laboratory standards (Leighton et al., 2017).

Role of C-peptide as a Biomarker in Type 1 Diabetes

In T1D, C-peptide levels are typically low or undetectable due to the loss of endogenous insulin production (Atkinson et al., 2014). In new-onset T1D, particularly within the first year of diagnosis, some residual β-cell function may persist, as evidenced by detectable C-peptide

levels (e.g., ≥0.2 nmol/L during stimulation tests) (Greenbaum et al., 2012). This residual function is clinically significant because it is associated with improved glycemic control (lower HbA1c), reduced risk of severe hypoglycemia, and lower incidence of diabetic ketoacidosis (DKA). For example, the Diabetes Control and Complications Trial (DCCT) demonstrated that T1D patients with stimulated C-peptide levels ≥0.2 pmol/mL had a 0.5–1.0% lower HbA1c and a 50% reduction in severe hypoglycemic events (SHEs) compared to those with undetectable levels ("Effects of Age, Duration and Treatment of Insulin-Dependent Diabetes Mellitus on Residual Beta-Cell Function," 1987).

C-peptide is a vital biomarker of endogenous insulin production, offering insights into β-cell function in T1D. In T1D, C-peptide is used as a key marker to assess residual β-cell function, differentiate diabetes types, monitor disease progression, and evaluate therapeutic interventions. However, challenges remain with its use, including assay variability and the need for harmonized standards (discussed in Appendix C) to ensure comparability across studies (Dekker et al., 2022).

4.3 Type 1 Diabetes Therapy and Unmet Need

The cornerstone of stage 3 T1D management is insulin replacement therapy, administered via multiple daily injections or continuous subcutaneous insulin infusion using insulin pumps. Insulin analogs, such as rapid-acting (e.g., insulin lispro) and long-acting (e.g., insulin glargine), provide more physiological insulin profiles, and improved glycemic control (Jacobsen et al., 2023). Adjunctive approaches include technologies such as continuous glucose monitor (CGM) systems, which offer real-time glucose data, and emerging automated insulin delivery systems that deliver insulin based on glucose levels (Akturk et al., 2024). Education on carbohydrate counting, hypoglycemia awareness, and sick-day management is essential for effective self-management.

Recent advances include the FDA approval of Lantidra, a cellular therapy involving islet cell transplantation that reduces insulin needs for adults with established T1D who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia, with some patients insulin-free for over 5 years. Stem cell therapy, such as VX-880 by Vertex Pharmaceuticals, aims to replace destroyed β-cells in an advanced disease state. Immunotherapy, like teplizumab, delays disease onset in at-risk individuals by modulating the autoimmune response.

T1D is associated with both acute and chronic complications. Acute complications include hypoglycemia, DKA, and hyperglycemic hyperosmolar state, which can be life-threatening if not managed promptly. Chronic complications include microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as macrovascular complications encompass cardiovascular disease, all resulting from prolonged hyperglycemia.

Quality of life (QOL) in T1D is significantly impacted by the burden of daily management, including frequent insulin injections, blood glucose monitoring, and fear of hypoglycemia (Starr et al., 2025). Studies indicate that T1D reduces QOL, with patients reporting lower scores on health-related QOL scales due to the chronic nature of the disease and its management demands (Cho & Kim, 2021) (Alvarado-Martel et al., 2015).

Quality-Adjusted Life Years (QALY) measures account for both the quantity and quality of life, Research on QALY loss for T1D is often embedded within broader diabetes studies, but specific estimates can be inferred from age-specific data. The Center for Disease Control's Diabetes State Burden Toolkit (*Home Page - Burden Toolkit*, n.d.), based on 2013-2017 National Health

Interview Survey and 2021 Behavioral Risk Factor Surveillance System data (*Behavioral Risk Factor Surveillance System*, 2025), reports average QALYs lost due to diabetes by age group (Table 1). For individuals aged 18-44, the average QALY loss is 9.7, with the following breakdown:

Table 1: Average QALYs Lost Due to Diabetes by Age Group

Category	Age Group	Average QALYs Lost	Number of Persons with Diabetes (thousands)	Total QALYs Lost (thousands)
Overall	18-44	9.7	3,963	38,408
Overall	45-64	5.5	12,438	68,004
Overall	65-74	2.7	7,581	20,522
Overall	75+	1.4	5,486	7,924
Overall	Total	4.6	29,470	134,858

Given that T1D is more prevalent in younger populations, the 9.7 QALY loss for the 18-44 age group is a reasonable proxy for T1D patients in this demographic. Young adults with T1D, in particular, may suffer from excess mortality and cardiovascular risk (Rawshani et al., 2018) and women may be particularly vulnerable (Huxley et al., 2015). Overall reductions in lifespan for people with T1D have been estimated at approximately 10-20 years, supporting the 9.7 QALY loss estimation (Arffman et al., 2023; Huo et al., 2016, 2016; Livingstone et al., 2015; Ou et al., 2016; Petrie et al., 2016; Stene, 2016; Tran-Duy et al., 2021).

In conclusion, T1D is a complex, lifelong condition requiring comprehensive management to mitigate both immediate and long-term risks. Advances in technology and ongoing research continue to improve outcomes, but challenges remain in treating the disease and preventing its complications, with significant impacts on QOL, QALY, and expected lifespan.

4.4 Rationale for Disease-Modifying Therapies in New-Onset Type 1 Diabetes

New-onset T1D, typically within the first year of diagnosis, presents a critical window where some residual β-cell function may still exist, as evidenced by detectable C-peptide levels. Despite advancements in insulin therapy, CGMs, and insulin pumps, these approaches primarily manage symptoms rather than addressing the underlying disease process. DMTs, which aim to preserve residual β-cell function (or even restore it to at least some degree) by targeting the autoimmune attack and/or β-cell survival or function directly, are essential for improving both short-term and long-term outcomes.

Benefit:Risk Considerations for Disease-Modifying Therapies in Type 1 Diabetes: Benefits of Disease-Modifying Therapies in Type 1 Diabetes

- Preservation of β-cell Function: DMTs aim to slow or stop β-cell destruction. Several DMTs have shown the ability to slow the rate of C-peptide decline in clinical trials in new-onset T1D (summarized in Appendix D).

- Improved Short-Term Outcomes: Preserving β-cell function reduces insulin requirements, improves glycemic stability, and lowers hypoglycemia risk (Greenbaum et al., 2012; Gubitosi-Klug et al., 2021; Rickels et al., 2020).
- Potential for Long-Term Benefits: By delaying β-cell loss, DMTs may reduce long-term complications like retinopathy and nephropathy.
- Reduce Psychological Burden: The lifelong requirement for insulin therapy and constant glucose monitoring imposes significant psychological stress, especially in children and adolescents, who must also manage the challenges of diabetes education and self-care (Mazzotta et al., 2024). DMTs have the potential to reduce these burdens by providing more predictable glucose control due to preservation of endogenous insulin secretin.

Risks of Disease-Modifying Therapies in Type 1 Diabetes:

- Immunosuppression: Many DMTs involve immunosuppressive agents, which may increase infection risk. Other DMTs that target the β-cell directly are less likely to have this risk but may have other risks associated with their use.
- Long-Term Safety: The long-term effects of immune-based DMTs on children's developing immune systems are not fully understood. DMTs directly targeting the β-cell may similarly lack long-term pediatric safety data. Pediatric trials should carefully monitor for growth issues, developmental delays, or future immune dysfunction, as noted in consensus reports (Wherrett et al., 2015).
- Uncertain Long-Term Effects: While some DMTs show promise in clinical trials, most of the studies that have been conducted are two years or less in duration, and their long-term efficacy in preserving β-cell function as well as potential long-term risks in the context of T1D remain under investigation.

Pediatric Benefit:Risk Considerations

For pediatric patients with T1D, the aggressive nature of the disease makes early intervention with DMTs particularly appealing. Children often experience more rapid β-cell loss than adults (Greenbaum et al., 2012; Hao et al., 2016), so preserving even partial β-cell function could have significant benefits. Furthermore, early intervention with DMTs could preserve more β-cell mass than in adults (Leete et al., 2018; Steck et al., 2020). This could simplify disease management and improve QOL, as seen in several clinical trials that have shown reduced insulin needs in pediatric trial participants (Appendix D). Children face decades of living with T1D, making early preservation of β-cell function particularly valuable for delaying complications. Reducing reliance on exogenous insulin could simplify management for children and their families, reducing the psychological burden (Mazzotta et al., 2024). Pediatric trials must prioritize long-term safety due to children's developing immune systems. However, experience with DMTs in other pediatric autoimmune diseases suggests manageable risks when carefully monitored, as seen in juvenile idiopathic arthritis and pediatric multiple sclerosis (Chitnis et al., 2012; Ringold et al., 2019). These examples show that DMTs can used effectively in pediatric autoimmune diseases when benefits are deemed to outweigh risks. For T1D, where early intervention is critical due to rapid β-cell loss in children, DMTs could offer similar advantages. DMTs in development that seek to affect β-cell dependent mechanisms of disease directly may not have safety information from other clinical settings and their application in pediatric settings will require careful consideration.

Conclusion

DMTs are essential for new-onset T1D because they address the underlying destruction and/or dysfunction of β-cells, offering the potential to preserve residual β-cell function as evidenced by

C-peptide levels. Current treatments and technologies manage symptoms effectively but do not halt disease progression or prevent long-term complications.

While many DMTs carry risks such as immunosuppression and may have long-term safety concerns, their benefits may outweigh these risks in carefully selected patients. In addition, DMTs with less robust benefit, but with limited safety concerns may also achieve favorable benefit:risk. Parallels from other autoimmune diseases like multiple sclerosis and juvenile idiopathic arthritis demonstrate that DMTs targeting the autoimmune side of the equation can achieve a favorable benefit:risk when used in pediatric populations when benefits are clear. Continued research into all types of DMTs for T1D is crucial to develop safe and effective therapies that can be administered early in the disease course to preserve β-cell function and improve patient outcomes.

5.0 Scientific Evidence Supporting C-Peptide as a Surrogate Endpoint in New-Onset Type 1 Diabetes

C-peptide, a byproduct of insulin synthesis, is a biomarker of residual β-cell function in T1D. Its preservation in new-onset T1D is hypothesized to reduce the risk of long-term secondary complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease, by improving glycemic control. The evidence in the literature linking preservation of C-peptide to short and long-term clinical benefits is extensive. This section highlights some of the key evidence linking C-peptide levels to these complications, assessing the strengths and weaknesses of existing studies, areas of consensus and discrepancy, and the suitability of C-peptide as a surrogate endpoint for confirmatory pivotal clinical trials in new-onset T1D.

5.1 Review of Evidence Linking C-Peptide to Long-Term Secondary Complications in Type 1 Diabetes

Multiple studies, including prospective cohort studies and randomized controlled trials (RCTs), have investigated the association between C-peptide levels and T1D complications. The DCCT and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, provide foundational evidence. In the DCCT, participants with stimulated C-peptide levels ≥0.2 pmol/mL at baseline (indicating preserved β-cell function) exhibited lower rates of retinopathy, nephropathy, and hypoglycemia compared to those with undetectable C-peptide. The EDIC study extended these findings, showing that higher baseline C-peptide was associated with reduced microvascular complications over 30 years (Lachin et al., 2014). Similarly, a 2016 study (Kuhtreiber et al., 2015) found that patients with sustained C-peptide (>0.1 nmol/L) had a 50% lower incidence of nephropathy and retinopathy compared to those with negligible levels.

Cross-sectional and longitudinal studies further support these findings. Steffes et al. (Steffes et al., 2003) analyzed DCCT data and reported that detectable C-peptide was associated with a 30% reduction in severe hypoglycemia and improved HbA1c, indirectly reducing complication risks levels.

Adding to this body of evidence, a large prospective cohort study examined 6,076 individuals with T1D from the Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO) who were followed for an average of 5.2 years (Jeyam et al., 2021). The aim was to assess how residual C-peptide secretion (a marker of remaining endogenous insulin production) relates to glycemic control and microvascular complications. Several key observations further strengthen the relationship between preserved C-peptide and clinical benefits. First even minimal residual C-peptide was found to be associated with clinical benefits including a significantly lower risk of serious hypoglycemic episodes in individuals with C-peptide between 30 and 200 pmol/L having about half the risk of experiencing at least one serious hypoglycemic episode in the previous year compared to those with C-peptide <5 pmol/L (odds ratio 0.56, $P = 6 \times 10^{-8}$). Second, higher C-peptide levels (≥200 pmol/L) were associated with a 9% lower insulin dose at baseline ($P = 2 \times 10^{-17}$) and a 4.9 mmol/mol lower HbA1c during follow-up ($P = 3 \times 10^{-13}$). However, these effects were mainly observed at higher residual C-peptide levels; at lower levels, the impact on insulin dose and HbA1c was less pronounced.

In terms of microvascular complications, the SDRNT1BIO study showed there was a strong, continuous inverse relationship between C-peptide levels and incident diabetic retinopathy even at low C-peptide concentrations (odds ratio 0.51 for ≥200 vs. <5 pmol/L, P = 0.0003) (Jeyam et al., 2021). A reduced risk of DKA was only apparent at C-peptide levels ≥200 pmol/L (hazard ratio 0.44, P = 0.0001)] and no significant association was found between residual C-peptide and incident diabetic kidney disease, possibly due to confounding by reduced renal clearance of C-peptide in kidney disease. Similarly, while C-peptide correlated with reduced microvascular

complications such as retinopathy (as discussed above), the effect size diminished after adjusting for HbA1c and diabetes duration (Jeyam et al., 2021). Regression models showed that the inverse relationship between C-peptide and incident retinopathy was strong, but the association with glycemic outcomes like HbA1c was complicated by confounding from glycemic control itself, and the effect was attenuated after adjustment for these factors (Jeyam et al., 2021).

A more recent analysis presented SDRNT1BIO at the Immunology of Diabetes Society meeting in 2024 that examined the longer-term association (11-year follow-up) between baseline C-peptide and clinical outcomes (Mellor, Joseph H et al., 2024). Higher C-peptide at baseline was associated with reduced risk of DKA, transition to any retinopathy or maculopathy, progression of retinopathy by ≥1 grade or incident maculopathy, and a predefined composite endpoint comprising first of any of the above or incident cardiovascular disease or transition to Stage 3 chronic kidney disease. The incidence rate ratio for the first of these events in those with C-peptide ≥200 pmol/L at baseline versus those with undetectable C-peptide at baseline was DKA, retinopathy, composite event. Higher C-peptide was associated with lower HbA1c. No significant effect of C-peptide on cardiovascular disease or death was found. The results confirm the assumption that minimal C-peptide secretion in autoimmune T1D could have a clinical benefit.

A cross-sectional analysis that included 3984 participants from Finnish Diabetic Nephropathy Study (FinnDiane) (Jansson Sigfrids et al., 2025) found 19.4% of 3984 FinnDiane participants had residual random serum C-peptide secretion (>0.02 nmol/L) and that C-peptide was inversely associated with hypertension, HbA1c, and cholesterol, but also independently with microvascular complications (adjusted OR 0.61 [95% CI 0.38–0.96], p=0.033, for nephropathy; 0.55 [0.34–0.89], p=0·014, for retinopathy (Harsunen et al., 2023).

These results highlight the potential clinical value of therapies that preserve or restore even minimal endogenous insulin secretion in T1D. Several studies have concluded that while higher fasting C-peptide values in T1D are associated with a lower prevalence of microvascular complications, the relationship between C-peptide levels and macrovascular risk in T1D remains unclear, with some studies reporting that no significant association (Lopes et al., 2024) (Panero et al., 2009) (Alan et al., 2025) is observed. Nevertheless, the evidence base is considered robust, leveraging large, well-designed studies like the DCCT/EDIC, which included over 1,400 participants and long-term follow-up (>30 years). These studies used standardized C-peptide assays (e.g., radioimmunoassay, later ECLIA) and validated clinical endpoints, enhancing reliability. The consistency of findings across diverse cohorts (U.S., Europe) strengthens generalizability. Mechanistically, C-peptide's role in improving glycemic stability and reducing glucotoxicity is supported by physiological studies, providing a plausible biological basis for its protective effects (Hills & Brunskill, 2009).

While the evidence supporting long-term benefit of preserved C-peptide is strong, some limitations exist. Many studies rely on observational data, introducing confounding factors like glycemic control, diabetes duration, and lifestyle, which may obscure C-peptide's independent effect. Assay variability is a significant concern; older studies used less sensitive radioimmunoassays, while newer studies employ ECLIA, leading to inconsistent C-peptide thresholds (e.g., 0.1 vs. 0.2 nmol/L) for "preserved" function (Dekker et al., 2022). Lack of C-peptide assay standardization complicates some cross-study comparisons (see Appendix C). Additionally, the evidence is stronger for microvascular complications than macrovascular ones, with conflicting findings on cardiovascular outcomes. Few studies focus specifically on new-onset T1D, limiting direct applicability to this population. Finally, the magnitude of C-peptide's effect varies, with some studies reporting modest reductions in complication risk (10–20%) after

adjustments and disagreement arises regarding whether preserved C-peptide is associated with a reduction in macrovascular complications. These discrepancies may stem from differences in study populations, follow-up duration, or adjustment for confounders like HbA1c.

In conclusion, the evidence strongly supports an association between preserved C-peptide and reduced microvascular complications in T1D, with consistent findings from high-quality studies like DCCT/EDIC. The evidence for macrovascular outcomes may need to be further substantiated in real life, and the challenge of variability in assay methods can be addressed through assay standardization as proposed by the C-peptide Standardization Committee organized by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (Little et al., 2017) and similar to National Glycohemoglobin Standardization Program certification for HbA1c (Little et al., 2011).

5.2 Review of Evidence Linking C-Peptide to Short-Term Benefits in Type 1 Diabetes

Short-term clinical outcomes include lower HbA1c, reduced hypoglycemic events, enhanced time in range (TIR), and lower incidence of DKA. In new-onset T1D, preserving C-peptide through DMTs may enhance these outcomes, supporting its potential as a surrogate endpoint in clinical trials. As is the case with long-term complications, the literature linking preserved C-peptide to short-term benefits is extensive. This section evaluates some of the key evidence linking C-peptide to short-term benefits, incorporating findings from the Trial Outcome Markers Initiative in Type 1 Diabetes (TOMI-T1D) database (Taylor et al., 2023) and reports the results of additonal analyses (Section 5.3).

The DCCT established that participants with stimulated C-peptide ≥0.2 pmol/mL at baseline had lower HbA1c (7.8% vs. 8.5%) and a 50% reduction in severe hypoglycemic events compared to those with undetectable C-peptide (“Effect of Intensive Therapy on Residual Beta-Cell Function in Patients with Type 1 Diabetes in the Diabetes Control and Complications Trial. A Randomized, Controlled Trial. The Diabetes Control and Complications Trial Research Group,” 1998). confirmed these findings, reporting a 0.5–1.0% HbA1c reduction and 40% lower hypoglycemia risk in patients with C-peptide >0.1 nmol/L over 2 years. A 2023 meta-analysis evaluated 21 clinical trials of DMTs (the TOMI-T1D database) in new-onset T1D, finding that a 55% improvement in C-peptide preservation (measured as AUC or stimulated C-peptide) was associated with 0·64% lower HbA1C (p<0·0001) (Taylor et al., 2023). Additional analyses of this relationship using the TOMI-T1D database have been conducted in advance of this workshop and are presented and discussed in section 5.3.

A more recent study linked C-peptide ≥0.1 nmol/L to a 60% lower DKA incidence in children over 1 year (Marren et al., 2019), corroborated by an analysis of DCCT/EDIC data presented at the 2024 ADA meeting that reported those with detectable C-peptide level had a 93% reduction in the hazard for recurrent DKA [hazard ratio (HR) 0.07, 95% CI 0.01 to 0.48, p=0.007] (Abuabat et al., 2024).

C-Peptide and Time in Range as Assessed by Continuous Glucose Monitoring

While HbA1c has been considered the gold standard for monitoring glycemic status and for assessment of long-term risk of diabetes complications, it does not provide information about either hypoglycemia or hyperglycemia, short term glucose trends or glycemic variability. It is also affected by age, pregnancy, chronic kidney disease hemoglobinopathies and ethnic and racial differences in glycation rates. In short, HbA1c “may not be an optimal indicator of an individual’s glycemic control because of the wide range of mean glucose concentrations that can be associated with a given HbA1c level” (Beck et al., 2017). The advent of CGMs is rapidly changing the practice of diabetes management and compared to HbA1c these devices can

provide high resolution, real-time data of a person's glycemic control. TIR, typically defined as the percentage of time glucose levels remain between 3.9-10 mmol/L (70-180 mg/dL), has emerged as a critical metric in diabetes management, although additional CGM-based parameters are likely important to consider as well (Battelino et al., 2019).

Multiple studies have consistently demonstrated a strong inverse correlation between greater TIR (percent of time blood glucose is 70–180 mg/dL) and lower HbA1c in people with diabetes. This is summarized in Table 2 adapted from Jee Hee Yoo and Jae Hyeon Kim (Yoo & Kim, 2020).

Table 2. Estimation of HbA1c for Given CGM-Derived Time in Range

TIR (70–180 mg/dL)	Vigersky et al.[a] (*n*=1,137 participants with T1D or T2D)	Beck et al.[b] at baseline (*n*=455 participants with T1D)	Beck et al.[b] in month 6 (*n*=545 participants with T1D)	Fabris et al.[c] (*n*=168 participants with T1D)
20%	10.6	9.4	8.8	9.3
30%	9.8	8.9	8.4	8.9
40%	9.0	8.4	8.0	8.5
50%	8.3	7.9	7.6	8.1
60%	7.5	7.4	7.2	7.7
70%	6.7	7.0	6.8	7.3
80%	5.9	6.5	6.4	6.9
90%	5.1	6.0	6.0	6.5
Baseline HbA1c, %	NA	7.5±1.0	7.2±0.8	NA
Equation	HbA1c=12.32–0.081×TIR	HbA1c=10.31–0.048×TIR	HbA1c=9.65–0.041×TIR	HbA1c=10.12–0.04×TIR
Every 10% increase in TIR	~0.8% HbA1c reduction	~0.5% HbA1c reduction	~0.4% HbA1c reduction	~0.4% HbA1c reduction

HbA1c, glycosylated hemoglobin; CGM, continuous glucose monitoring; TIR, time in range; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; NA, not applicable.

[a]Data sets were from 18 clinical trials using CGM for a minimum of 3 days,
[b]Data used in analyses were from four randomized trials using CGM for a minimum of 10 days for baseline and 14 days in month 6,
[c]Linear regression analysis was used to analyze 3-month full CGM data for this equation.

References in table: (Vigersky & McMahon, 2019) (Beck et al., 2019) (Fabris et al., 2020)

(Table adapted from Diabetes Metab J. 2020 Dec 23;44(6):828–839. doi: 10.4093/dmj.2020.0257)

Several studies have consistently demonstrated a correlation between residual C-peptide secretion and improved TIR. In a retrospective study of 112 patients with T1D, those with

detectable C-peptide levels (defined as ≥ 0.05 ng/mL) had significantly higher TIR compared to those with undetectable levels (Lopes et al., 2024). This association remained significant both before (β = 7.13, p = 0.044) and after (aβ = 11.42, p = 0.001) adjustment for covariates including sex, disease duration, body mass index (BMI), and insulin delivery method. Similarly, a Chinese study reported that preserved C-peptide (fasting C-peptide > 10 pmol/L) was associated with higher TIR after adjustment for diabetes duration (62.4% vs. 50.3%, adjusted p = 0.003) (Liu et al., 2024). Finally a 2022 TrialNet study reported that teplizumab preserved C-peptide and while the frequency of diabetic oral glucose tolerance tests (OGTT) increased in both groups after 3 months, they did so at a slower rate in the teplizumab treated participants, who mostly maintained dysglycemic OGTT status. (Sims et al., 2021).

Higher C-peptide is also associated with less time above range (TAR) (typically >180 mg/dL), reflecting better hyperglycemia control (Buckingham et al., 2015; Rickels et al., 2020) (Fuhri Snethlage et al., 2024). The relationship between C-peptide and time below range (TBR)(typically <70 mg/dL) is less consistent with several studies report that higher C-peptide is not significantly associated with reduced TBR or hypoglycemia risk, especially in the early years after diagnosis (Liu et al., 2024), however other studies do report an association between C-peptide and reduced risk of hypoglycemia (Amendolara et al., 2025) (Sherr et al., 2012) (Gibb et al., 2020)

In conclusion, even minimal residual β-cell function appears beneficial for glycemic control and stability, with higher levels of C-peptide correlating with better outcomes across multiple measures underscoring the potential value of therapeutic approaches aimed at preserving or restoring β-cell function in T1D.

C-Peptide Preservation and Glucagon

In patients with T1D, β-cells are destroyed and/or dysfunctional, leading to deficiency of endogenous insulin secretion. This might cause secondary abnormalities in the function of other pancreatic islet cells, like abnormal glucagon release by *α*-cells**.** Diminished glucagon response to hypoglycemia and insufficient stimulation of glycogenolysis and gluconeogenesis are major reasons for SHEs (Bolli et al., 1983; Cryer, 2010; Gerich et al., 1973). In a study examining the impact of C-peptide status on glucagon response and endogenous glucose production (EGP) during hypoglycemia in T1D patients with C-peptide (≥0.05 nmol/L; 0.16 ± 0.1 (0.05–0.36)) had higher glucagon levels and higher EGP values compared to negative controls (no detectable C-peptide) suggesting preserved β-cell function may contribute to counter regulation during hypoglycemia in patients with T1D.

A more recent study (Wang X and Zhang M (2024) found that the abnormal late postprandial glucagon response in T1D is a function of differences in stimulated C-peptide concentrations (Zhang et al., 2024). This study divided T1D patients into C-peptide-low (CPL) (<200 pmol/L) and C-peptide-high (CPH) (≥200 pmol/L) groups during a steamed bread meal tolerance test. Higher glucagon levels were observed in CPL vs. CPH at 60, 120, and 180 minutes post-meal, with peak glucagon elevated in CPL (11.01 vs. 8.24 pmol/L, P = 0.018) and an inverse correlation existed between peak C-peptide and late glucagon response (iAUC 30–180 glucagon; r = -0.581, P < 0.001), suggesting preserved β-cell function suppresses excessive glucagon secretion during hyperglycemia.

The reports of improved glucagon responses in individuals with higher levels of C-peptide provides additional mechanistic rationale, in addition to retaining at least some physiological insulin response, to account for some aspects of short-term clinical benefits associated with C-peptide.

Evidence from Transplant Studies

Islet transplantation is a therapeutic approach for T1D aimed at restoring endogenous insulin production, with stimulated C-peptide levels serving as a key biomarker of graft function. Stimulated C-peptide, typically measured during a MMTT or glucose challenge, reflects β-cell activity and is associated with clinical benefits such as improved glycemic control, reduced insulin requirements, and decreased hypoglycemic events. Below is a summary of evidence from islet transplantation studies demonstrating the relationship between stimulated C-peptide levels and clinical outcomes, with a critical perspective on the findings.

Improved Glycemic Control and Insulin Independence:

- **Ryan et al. (2005)**: In a pivotal study of 65 T1D patients undergoing islet transplantation under the Edmonton Protocol, stimulated C-peptide levels (post-MMTT) were strongly correlated with glycemic control. Patients achieving insulin independence had median peak C-peptide levels of >0.6 nmol/L, with higher levels associated with lower HbA1c (mean 5.8% vs. 7.2% in partial function, $p<0.01$). Sustained C-peptide production (≥0.2 nmol/L) was linked to reduced glycemic variability and stable fasting glucose levels, even in those with partial graft function (Ryan et al., 2005).
- **Hering et al. (2016)**: A phase 3 trial of 48 T1D patients receiving purified human pancreatic islets reported that 87.5% achieved HbA1c ≤7.0% at 1 year, with 71% insulin independent. Stimulated C-peptide levels ≥0.3 nmol/L (90-minute MMTT) were associated with a primary endpoint of HbA1c <7.0% and no SHEs. Higher C-peptide levels (e.g., >0.5 nmol/L) correlated with sustained insulin independence and lower glucose variability on CGM (Hering et al., 2016).
- **Shapiro et al. (2017)**: A long-term follow-up of 255 islet transplant recipients showed that sustained C-peptide production (stimulated levels >0.2 nmol/L) was associated with HbA1c <7.0% in 80% of patients at 5 years, even in those requiring supplemental insulin. The study highlighted that C-peptide levels above 0.3 nmol/L were predictive of prolonged graft survival and reduced insulin doses (median 0.15 U/kg/day vs. 0.45 U/kg/day in low C-peptide patients, $p<0.05$) (Shapiro et al., 2017).

Reduction in Severe Hypoglycemic Events:

- **Baidal et al. (2018)**: Fasting C-peptide was highly predictive for acute SHEs (ROC-AUC 0.906; optimal cut point 0.070 nmol/L) and the optimal outcome (ROC-AUC 0.845; optimal cut point 0.33 nmol/L). MMTT–stimulated C-peptide-to-glucose ratio (CPGR) outperformed both fasting and stimulated C-peptide for all outcomes except acute SHEs. The optimal cut point for the optimal outcome was 0.12 nmol/mmol for MMTT-stimulated CPGR and 0.97 nmol/L for MMTT-stimulated C-peptide. (Baidal et al., 2023).
- **Lablanche et al. (2018)**: The median number of SHEs per year was zero in the immediate transplantation group with two in the insulin group ($p<0.0001$). The median number of non-SHEs was zero in the immediate transplantation group versus five in the insulin group ($p=0.0003$). 23 (92% [95% CI 74–99]) patients in the immediate transplantation group were free from severe hypoglycemia versus eight (36% [17–59]) in the insulin group (Lablanche et al., 2018).

Enhanced Quality of Life and Reduced Complications:

- **Foster et al. (2018)**: A QOL analysis in 25 islet transplant recipients showed that stimulated C-peptide levels ≥0.3 nmol/L were associated with improved diabetes-specific QOL

(Diabetes Distress Scale score reduced by 1.5 points, p=0.03) and lower fear of hypoglycemia (Hypoglycemia Fear Survey score reduced by 20%, p=0.01). These benefits were attributed to reduced glycemic excursions and insulin requirements (Foster et al., 2018).

- **Brennan et al. (2016)**: A longitudinal study of 44 islet transplant patients reported that sustained C-peptide production (>0.3 nmol/L) was associated with a lower incidence of microvascular complications (e.g., retinopathy progression reduced by 40%, p=0.04) at 5 years. Patients with higher C-peptide levels also had lower insulin doses and better cardiovascular risk profiles (e.g., LDL cholesterol reduced by 15%, p=0.03) (Brennan et al., 2016)).

Threshold Effects and Partial Graft Function:

- **Verhoeff et al (2023):** A cross-sectional retrospective cohort study evaluating patients undergoing islet transplantation at a single center from 1999 to 2018 evaluating 192 transplant recipients. Patients with insulin independence had a median (interquartile range) fasting C-peptide level of 0.66 nmol/L (0.34 nmol/L), compared with 0.49 nmol/L (0.25 nmol/L) for those being insulin dependent without hypoglycemia and 0.07 nmol/L (0.05 nmol/L) for patients experiencing hypoglycemia ($P < 0.001$). Optimal fasting C-peptide cutoffs for insulin independence and hypoglycemia were ≥0.50 nmol/L and ≥0.12 nmol/L, respectively. Cutoffs for insulin independence and freedom of hypoglycemia using stimulated C-peptide were ≥1.2 nmol/L and ≥0.68 nmol/L, respectively, whereas optimal cutoff BETA-2 scores were ≥16.4 and ≥5.2 (Verhoeff et al., 2023).

Stimulated C-peptide reflects functional β-cell mass, which stabilizes glucose homeostasis by reducing exogenous insulin needs and improving counter-regulatory responses (e.g., glucagon secretion during hypoglycemia). This aligns with findings from non-transplant T1D studies showing C-peptide's role in glycemic stability. While >0.3 nmol/L is a common threshold for significant benefits, even lower levels (0.1–0.2 nmol/L) provide measurable improvements, suggesting a continuum of benefit. However, insulin independence typically requires higher levels (>0.5 nmol/L) (Baidal et al., 2023). Some limitations include the fact that most studies are observational or small-scale, with potential selection bias (e.g., healthier patients selected for transplantation). Long-term graft function declines in 50–70% of patients by 5 years, reducing C-peptide and associated benefits (Brennan et al., 2016; Catarinella et al., 2025). Immunosuppression risks (e.g., infection, nephrotoxicity) may offset benefits, a factor rarely quantified in these analyses.

Conclusion

Evidence from islet transplantation studies consistently demonstrates that higher stimulated C-peptide levels (≥0.3 nmol/L) are associated with significant clinical benefits, including improved HbA1c, increased TIR, reduced SHEs, enhanced QOL, and lower complication rates. Even low C-peptide levels (0.1–0.3 nmol/L) confer benefits, particularly in reducing hypoglycemia and glycemic variability. These findings underscore the importance of preserving β-cell function and highlight C-peptide as a critical endpoint in evaluating transplant success.

5.3 Extended Analysis of the Trial Outcome Markers Initiative in Type 1 Diabetes Dataset; Relationship of C-peptide to HbA1c

The T1DC has conducted additional analyses of the TOMI-T1D database to provide extended insight into the relationship between C-peptide and HbA1c. The results of the TOMI-T1D analysis reported in 2023 (Taylor et al., 2023) are reproduced (Figure 1 and Figure 2) for

convenience. The conclusion of the previous analyses was that as early as six months after treatment, a 24.8% greater C-peptide preservation in positive studies (where positive or negative is based on the individual study-defined criteria) was associated with a 0.55% lower HbA_{1c} ($p<0{\cdot}0001$), with differences being detectable as early as 3 months. Cross-sectional analysis, combining positive and negative studies, was consistent with this proportionality: a 55% improvement in C-peptide preservation was associated with 0·64% lower HbA1C ($p<0{\cdot}0001$).

The additional analyses presented here add individual patient-level data from the clinical studies in the TOMI-T1D database. An analysis of all participant level data at all time points for HbA1c and C-peptide AUC (Figure 3) suggests that modeling the relationship between C-Peptide AUC and HbA1c using linear assumptions is not fully adequate. A locally estimated scatterplot smoothing (LOESS) plot applied to the data shows that the linear relationship breaks down at low C-peptide AUCs (below approximately 0.2-0.3 nmol/L) and at high C-peptide AUCs (above approximately 1.5 nmol/L). Within this range a 1.0 nmol/L increase in C-peptide AUC is associated with a 1.45% reduction in HbA1c. For the linear model the correlation is significant ($P<0.001$, $R = -0.41$).

Stratifying the data by age and comparing pediatric (0-17 years of age) vs adult (>18 years of age (Figure 4) we observe comparable results with modeling using linear assumptions showing a shallower slope equation compared to linear modeling of all data and pediatric data showing a steeper slope compared to the modeling of all data. The LOESS plots for both populations again show linear assumptions are inadequate at low and high C-peptide AUCs, although the effect is less pronounced at low C-peptide AUCs in the pediatric population.

Examining the effect of baseline C-peptide on the correlation between C-peptide and HbA1c we observe a significant ($p<0.001$), inverse correlations at all quartiles (as defined in Taylor et al) examined (Figure 5). LOESS plots are shown (overlaid) and again confirm that at low and high C-peptide AUCs the linear model breaks down. This is most noticeable in the analysis of the highest baseline C-peptide AUC quartile (>0.92 nmol/L), however the other quartiles show overlap between the linear and LOESS plots except at the levels of C-peptide AUC above approximately 1 nmol/L.

A weighted meta-analysis, using an inverse variance method with trial size as a proxy for precision, was performed across the interventional clinical trials included in the TOMI-T1D database (Figure 6, Panel A). Assuming minimal/no measurement error in the independent variable (weighted absolute difference in C-peptide AUC between treatment arms from baseline to one year)) and comparing the weighted difference in HbA1c between treatment from baseline to one year, a linear regression shows a significant inverse correlation ($p=0.04$; R -0.48). A Deming regression assuming a variance in HbA1c of 4% and a variance in C-peptide AUC of 10% estimates a stronger negative relationship, however a LOESS plot more closely conforms to the standard linear regression. Plotting the data as weighted difference in HbA1c between treatment from baseline to one year vs weighted difference in C-peptide preservation change (percentage) from baseline to one year the standard linear regression and Deming regression are overlapping while the LOESS plot loosely tracks with the two regressions (wider 95% CIs are observed at high levels of C-peptide preservation where only two studies exceeded 20%) . However, significance is lost ($P = 0.1$) in the standard linear regression when the data is plotted in this manner)

An internal FDA analysis of the new-onset tepliuzmab studies examining the relationship between HbA1c and C-peptide AUC was conducted as part of the clinical review of teplizumab (U.S. Food and Drug Administration. Division of Diabetes, Lipid Disorders and Obesity (DDLO)/Office of New Drugs (OND), 2022). This analysis (Figure 7) includes two teplizumab

new-onset T1D studies (Encore and Study 1) that are not in the TOMI-T1D dataset and serves, to some extent, as independent confirmation showing that across all four studies and inverse linear relationship between C-peptide AUC and percentage of HbA1c as observed. Slope equations and statistical analysis was not specifically reported in the clinical review however the FDA reviewer commented “These exploratory analyses strongly support a conclusion that the meta-analysis results of C-peptide change from baseline are predictive of a clinically meaningful effect and provide robust support for the use of C-peptide AUC change from baseline as confirmatory evidence of effectiveness”.

Conclusions

A consistent inverse correlation is observed in all the analyses of individual level data with higher levels of C-peptide AUC associated with lower percentage of HbA1c. The observations are also consistent with what has been previously reported in Taylor et al and with internal FDA analysis of teplizumab new-onset studies. Using linear modeling assumptions, C-peptide AUC accounts for a minority of the variance observed in percentage of HbA1c (generally about 20%), similar to what has been reported in an independent analysis of data from the Diabetes Prevention Trial–Type 1 study (Ismail et al., 2019). This is most likely because all patients will have been using exogenous insulin, expected to be a main driver of HbA1c in any study of new-onset T1D. The LOESS plots of the individual level data suggest that a full exploration of the relationship will require the development of a multi-variate model examining the relationship between insulin, C-peptide AUC and percentage of HbA1c. Multivariate modeling along with further surrogacy analyses (e.g., refinement of the weighted meta-regression, impact of missing data, subgroup analyses) are planned to be developed in future.

Several previous clinical trials in new-onset T1D have achieved significant preservation of C-peptide AUC (as defined by the study criteria) in active vs placebo arms (Appendix D) but have not shown magnitude of change in HbA1c predicted in Taylor et al. and from the models discussed here. This may be explained by several factors, the most likely being that the clinical trials in new-onset T1D conducted to date are generally underpowered to detect a significant difference in the HbA1c endpoint, differences in patient populations (e.g. age, baseline C-peptide), differences in study drugs and insulin regimes across trials.

Nevertheless, some studies have been able to show a significant reduction in HbA1c including the etanercept study (not included in TOMI-T1) (Mastrandrea et al., 2009) that showed an increase C-peptide AUC from baseline to week 24 of 39% with a 20% decrease in the placebo group ($P < 0.05$) and significantly lower HbA1c at 24 weeks in the etanercept group (5.91 +/- 0.5%) compared with that in the placebo group (6.98 +/- 1.2%; $P < 0.05$). This is broadly in line with the magnitude of effect predicted in the models presented here and in Taylor et al. However, this was a small study (17 participants aged 3–18 years) and all participants were enrolled within 30 days of diagnosis. Baseline HbA1c (etanercept: 12.8% ± 3.2; placebo: 12.4% ± 2.5) and C-peptide AUC (etanercept 0.9 ng/ml ± 0.4; placebo 1.1 ng/ml ± 0.8) were both high relative to other studies (likely due to enrolling study participant very near to their diagnosis). A subsequent study examining the effect of anti-tumor necrosis factor (TNF)-α inhibition using a different molecule (golimumab) was able to largely reproduce the C-peptide differential and did observe a non-significant difference in HbA1c at one year (0.3% lower HbA1c in treatment vs placebo), However there were differences in study design, most notably the inclusion of patients within 100 days (vs 30 days in the etanercept study) of diagnosis and baseline HbA1c and C-peptide AUC (lower in the golimumab study vs etanercept) (Quattrin et al., 2020).

Two additional studies demonstrating a significant effect on HbA1c are the TN05 study (Pescovitz et al., 2009) using anti-CD20 (rituximab) and the TN19 study using low-dose ATG+GCSF (Haller et al., 2018). These two studies are included in the TOMI-T1D dataset. The

TN05 study showed a significant (P = 0.03) C-peptide AUC difference of 0.09 nmol/L at 12 months, (rituximab mean 2-hour C-peptide AUC = 0.565 nmol/L [95% CI, 0.50 to 0.63] vs. placebo AUC= 0.475 nmol/L [95% CI, 0.39 to 0.55]) with an HbA1c difference of 0.24% at 12 months (rituximab mean HbA1c = 6.76% ± 1.24% vs. 7.00% ± 1.30% placebo [p<0.001]). The TN19 study showed the 1-year mean AUC C-peptide was significantly higher in subjects treated with ATG (0.646 nmol/L) versus placebo (0.406 nmol/L; *P* = 0.0003). The difference in HbA1c for ATG vs placebo was not explicitly reported (estimated at approximately 1.0% at 12-months based on the published data), but was stated as significant with P = 0.002 (Haller et al., 2018). In this study, the ATG+GCSF arm did not show a significant difference in C-peptide AUC compared to placebo, but a significant difference in HbA1c (P = 0.011) was observed (estimated at approximately 0.8% at 12-months based on the published data).

REFERENCE FIGURE 1 from:

Taylor PN, Collins KS, Lam A, Karpen SR, Greeno B, Walker F, Lozano A, Atabakhsh E, Ahmed ST, Marinac M, Latres E, Senior PA, Rigby M, Gottlieb PA, Dayan CM; Trial Outcome Markers Initiative collaboration. C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. Lancet Diabetes Endocrinol. 2023 Dec;11(12):915-925. doi: 10.1016/S2213-8587(23)00267-X. Epub 2023 Nov 3. Erratum in: Lancet Diabetes Endocrinol. 2024 Feb;12(2):e12. doi: 10.1016/S2213-8587(23)00381-9. PMID: 37931637.

Figure 1. Time normalized C-peptide AUC, change in C-peptide from baseline and HbA1c means across 12 months, and change in C-peptide from baseline, HbA1c, insulin dose, and insulin dose adjusted A1c across 24 months.

Mean value of time-normalized C-peptide AUC across 12 months (A), percent change in C-peptide AUC from baseline across 12months (B), HbA1c across 12 months (C), change in C-peptide AUC from baseline across 24 months (D), HbA1c across 24 months (E), total daily insulin across 24 months (F), and insulin-dose adjusted A1c across 24 months (G). Error bars represent 95% CIs. Active groups are in red and control groups are in blue. AUC=area under the curve. p values are reported above each timepoint. Only studies with two years or more of follow-up were included in panels D–G.

C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. Taylor, Peter N, Greenbaum, Carla et al. The Lancet Diabetes & Endocrinology, Volume 11, Issue 12, 915 - 925

REFERENCE FIGURE 2 from:

Taylor PN, Collins KS, Lam A, Karpen SR, Greeno B, Walker F, Lozano A, Atabakhsh E, Ahmed ST, Marinac M, Latres E, Senior PA, Rigby M, Gottlieb PA, Dayan CM; Trial Outcome Markers Initiative collaboration. C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. Lancet Diabetes Endocrinol. 2023 Dec;11(12):915-925. doi: 10.1016/S2213-8587(23)00267-X. Epub 2023 Nov 3. Erratum in: Lancet Diabetes Endocrinol. 2024 Feb;12(2):e12. doi: 10.1016/S2213-8587(23)00381-9. PMID: 37931637.

Figure 2. C-peptide preservation and change in HbA1c across time.

Mean change in HbA1c (%) stratified by quartiles of percentage C-peptide preservation at 6 months (A), 1 year (B), and 2 years (C) from baseline, and at 6 months (D), 1 year (E), and 2 years (F) from 3 months. Error bars in panels A–F represent 95% CIs as do the shaded regions in panel G. Loess HbA1c trajectories stratified by quantiles of baseline C-peptide and preservation at 2 years (G). Each panel represents a baseline C-peptide quartile >0·92, 0·64–0·92, 0·44–0·63, and <0·44 nmol/L. Loess curves within each panel are stratified by preservation of C-peptide from baseline at 2-year quartiles: >76%, 48-76%, 22-47%, and <22%. N represents the total number of individuals in each panel. Only individuals with 2-year C-peptide had data included.

C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. Taylor, Peter N, Greenbaum, Carla et al. The Lancet Diabetes & Endocrinology, Volume 11, Issue 12, 915 – 925

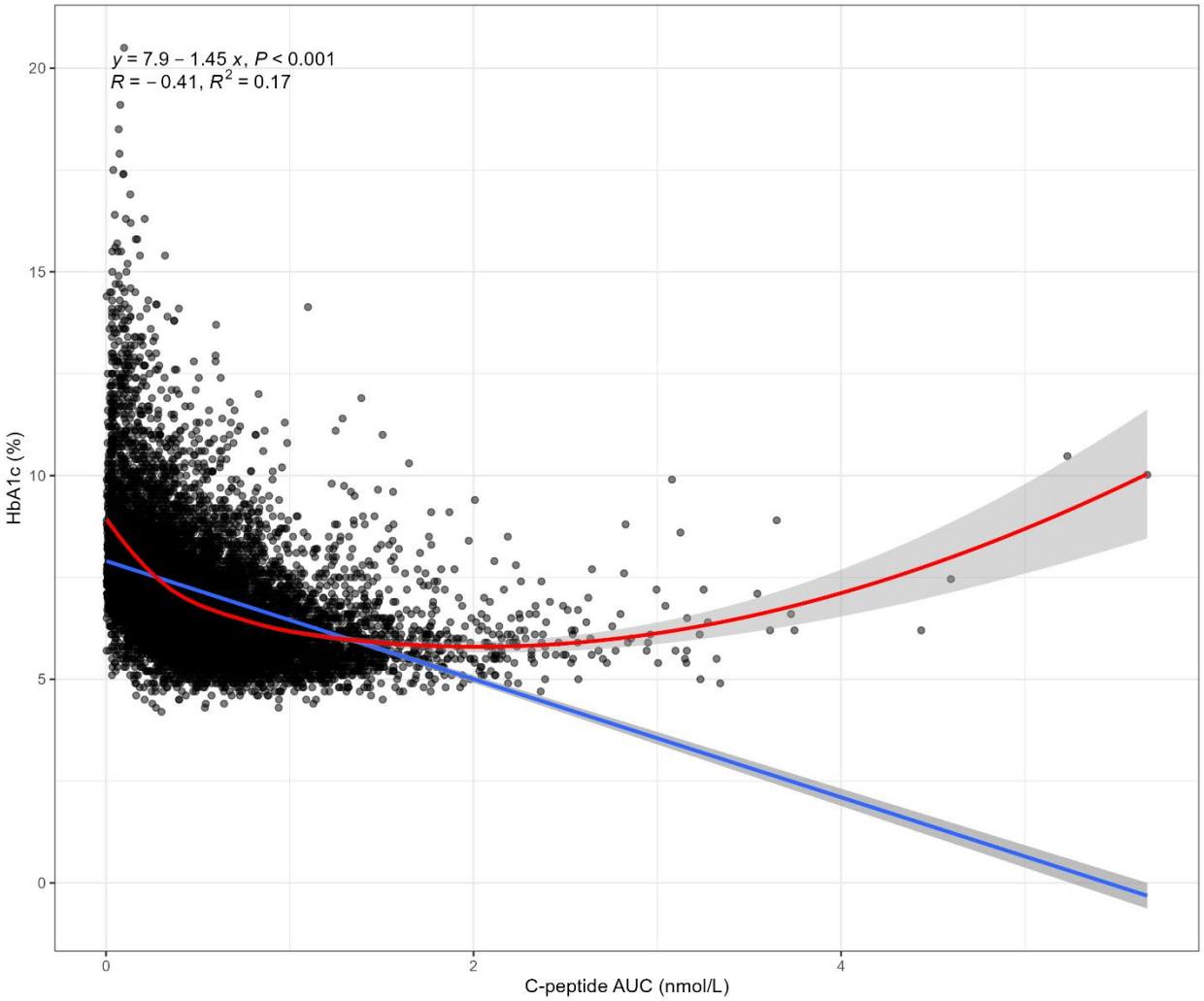


Figure 3. Correlation between HbA1c and C-peptide AUC for individuals at all available timepoints.

Correlation between HbA1c and C-peptide AUC in 2414 individuals represented in the TOMI-T1D database across all available timepoints. Blue line represents the linear regression, and red line represents the LOESS curve. The 95% confidence intervals are shown by shading. The slope equation, significance, R value (Pearson's correlation coefficient) and R^2 for the linear regression are shown at upper left of the plot.

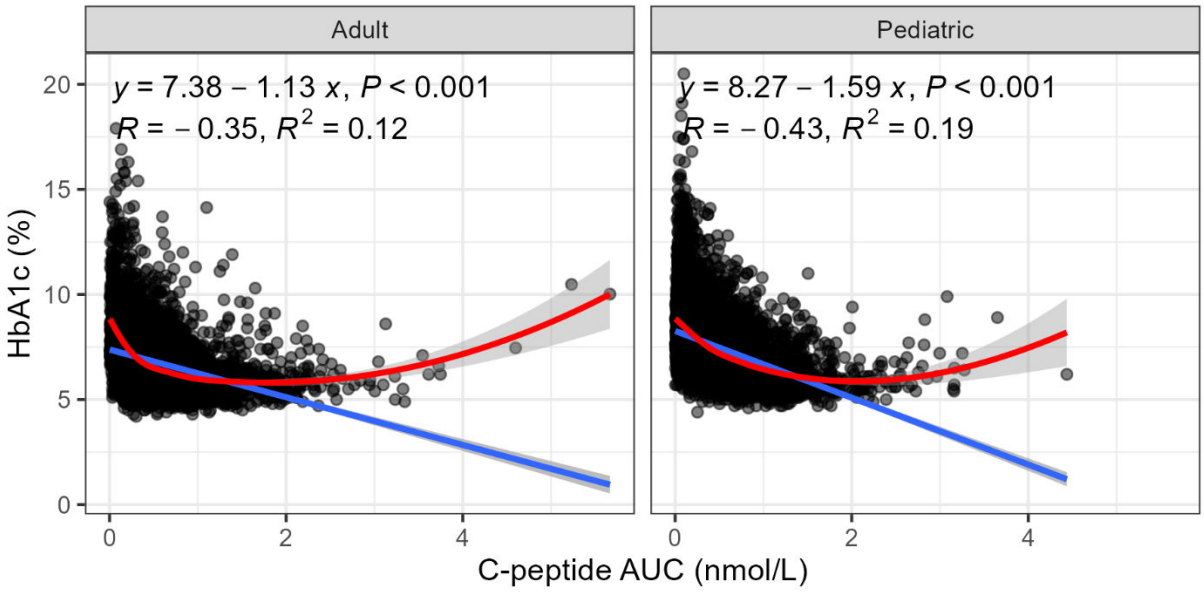


Figure 4. Correlation between HbA1c and C-peptide stratified by age.

Correlation between HbA1c and C-peptide AUC in individuals across all available timepoints stratified by age. Blue line represents the linear regression, and red lines represent LOESS curves 95% confidence intervals for each indicated by shading. The slope equation, significance, R value (Pearson's correlation coefficient) and R^2 for the linear regression are shown at upper left of each panel.

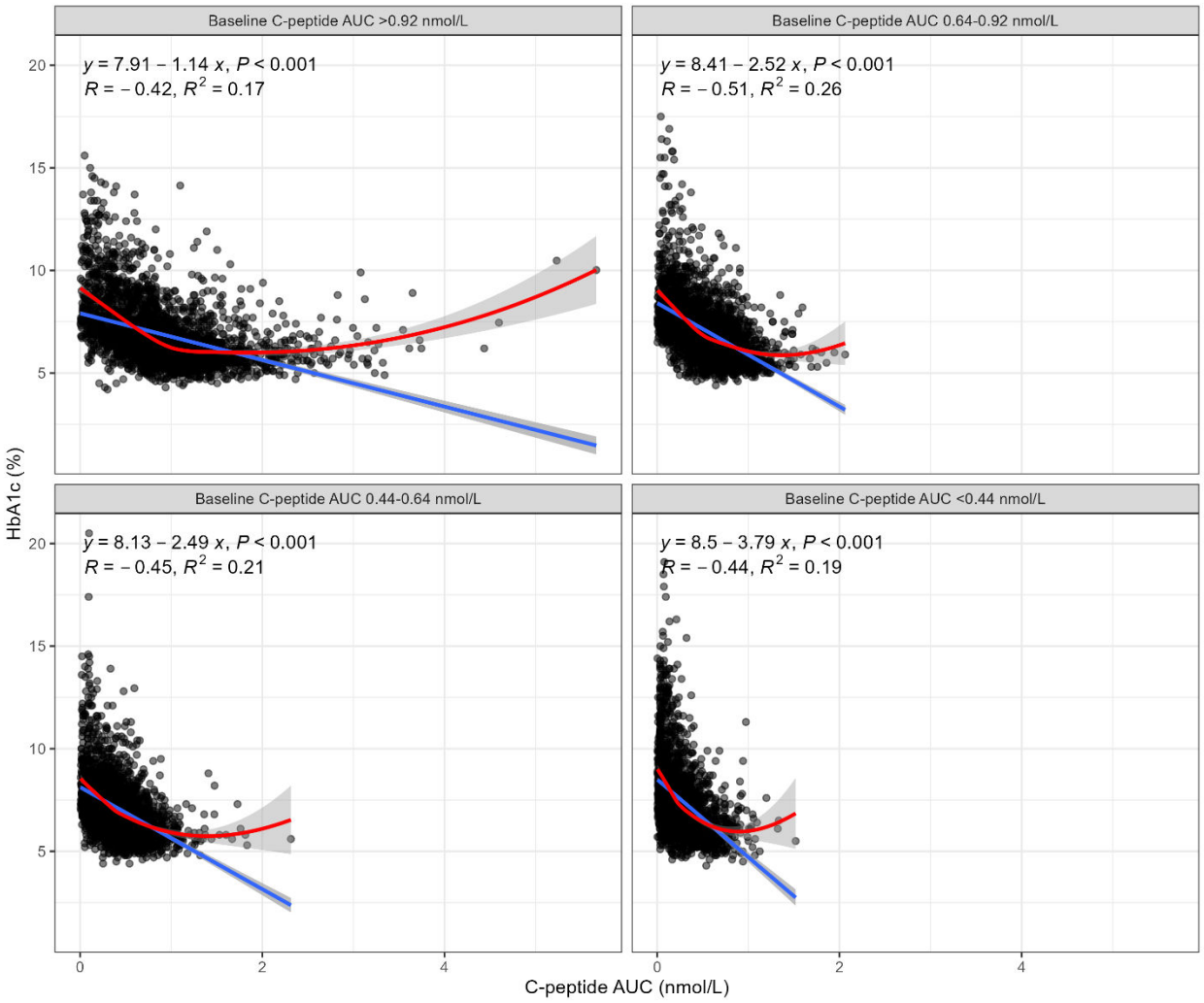


Figure 5. Correlation between HbA1c and C-peptide stratified by baseline C-peptide.

Correlation between HbA1c and C-peptide AUC in individuals across all available timepoints stratified by quartiles of C-peptide at baseline. Blue lines represent the linear regression, and red lines represent LOESS curves with 95% confidence intervals for each indicated by shading. The slope equation, significance, R value (Pearson's correlation coefficient) and R^2 for the linear regression are shown at upper left of each panel.

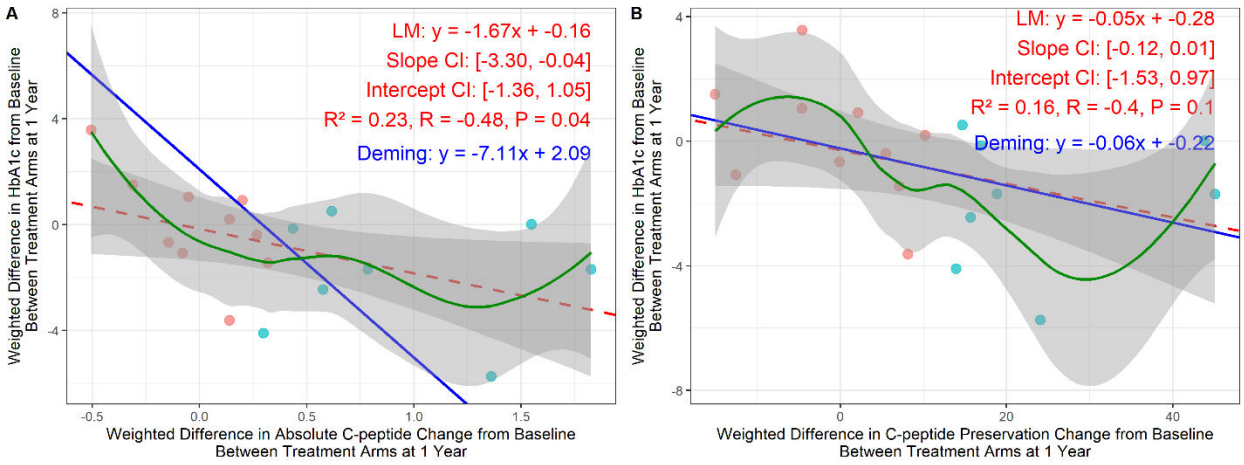


Figure 6. Correlation between change in HbA1c and C-peptide in a weighted meta-analysis of Eighteen Interventional Clinical Trials from the TOMI-T1D Database.

Correlations between change in HbA1c and change in C-peptide AUC (A) and C-peptide preservation (B) at one year. Each dot is an individual study with red dots indicating a study with a self-defined negative outcome and blue dots indicating those with a study-defined positive outcome. Measures are using weighted values from an inverse variance weighted meta-analysis. Red dotted lines represent the linear regression, the green lines represent the LOESS curves, and the blue solid line represents the Deming regression, Deming assumes a variance ratio of 6.25 (based on an estimated 4% CV in measures of HbA1c (Heinemann & Freckmann, 2015); College of American Pathologists (CAP) GH5 Survey Data: 2019 (updated 6/19) https://ngsp.org/CAP/CAP19a.pdf and 10% CV in measures of C-peptide (Little et al., 2008). 95% confidence intervals for standard linear regression and LOESS plots are indicated by shading.

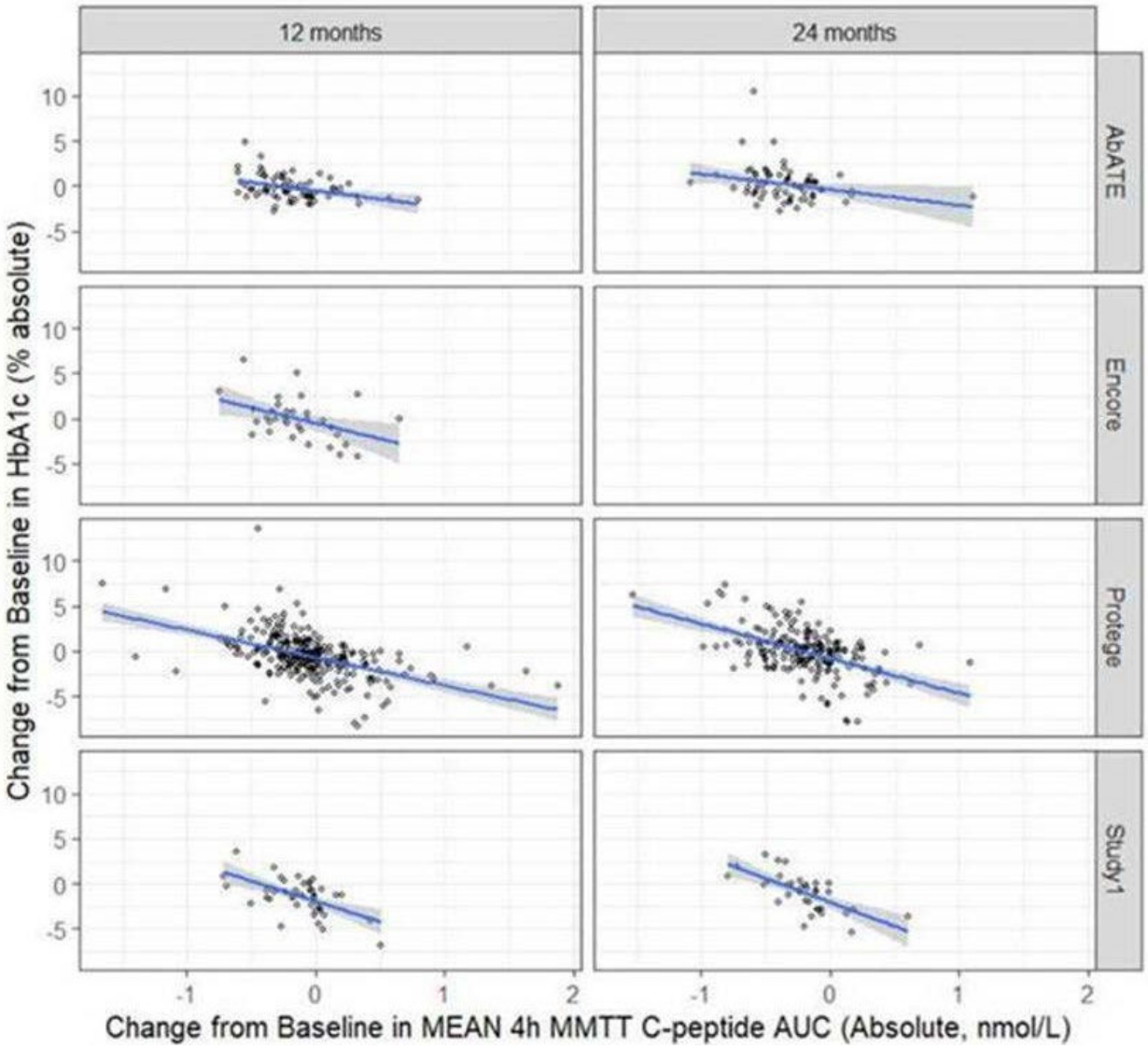


Figure 7. FDA Exploratory Analysis of effect of change from baseline mean C-peptide AUC on HbA1c change from baseline (%) at 12 months and 24 months by study for pooled teplizumab and comparator treatment arms.

Figure Source: (FDA. (2021/2022). BLA 761183 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761183Orig1s000MedR.pdf)

6.0 Impact of Using C-peptide as a Surrogate Endpoint on Clinical Trial Design and Conduct of Studies of Disease-Modifying Therapies in New-Onset Type 1 Diabetes

Conducting clinical trials for new-onset T1D presents significant operational challenges across trial design, recruitment, conduct, retention, and study length. This section addresses these challenges, argues why C-peptide is the optimal endpoint compared to HbA1c for T1D trials, especially for DMTs, and discusses how differences between pediatric and adult populations impact trial considerations. The adoption of C-peptide as a surrogate endpoint could accelerate the development of DMTs by enabling more efficient trials.

6.1 Operational Challenges in Conducting Trials for New-Onset Type 1 Diabetes

Trial Design: Designing trials for new-onset T1D requires selecting endpoints that directly reflect the preservation of β-cell function, the primary goal of DMTs. Traditional endpoints like HbA1c, which measures long-term glycemic control, do not capture the immediate effects of DMTs on β-cell function. Trials must incorporate standardized methods for measuring C-peptide, such as MMTT or glucagon stimulation tests, to ensure consistency and reliability (Leighton et al., 2017). The rapid decline in β-cell function post-diagnosis necessitates short trial windows to capture meaningful changes, complicating the balance between statistical power and feasibility. This emphasizes the need for endpoints like C-peptide that align with the mechanism of DMTs, alongside ethical considerations for pediatric populations (Wherrett et al., 2015).

Recruitment for trials: New-onset T1D is a relatively rare condition, with estimates of new diagnoses/year ranging from roughly 20,000 - 64,000/year (Pettitt et al., 2014; Rogers et al., 2017). The window for intervention is relatively narrow, depending on the presence of residual β-cell function and trials typically try to recruit participants within 100 days of a stage 3 T1D diagnosis. Patients and families are often overwhelmed by the new diagnosis (Whittemore et al., 2012), making recruitment challenging. Identifying eligible participants requires collaboration with pediatric endocrinologists, diabetes clinics, and registries that can facilitate rapid enrollment. Nonetheless enrolling studies of even modest size (80-120 participants, 7-10 consented per month across 15-20 centers) requires considerable time and running multiple concurrent trials in new-onset T1D (necessary if we hope to develop new drugs at a reasonable pace) will extend these recruitment times even further. Large multicenter or international trials will likely be necessary to achieve adequate sample sizes for even modestly powered phase 3 studies using HbA1c as an endpoint, increasing logistical complexity and further restricting the ability to conduct concurrent studies with different candidate drugs. Recruitment strategies must prioritize rapid identification through healthcare networks and leverage registries to target newly diagnosed patients, with sensitivity to the emotional and logistical burdens faced by families.

Conduct of trials: Conducting trials in new-onset T1D involves managing participants who are still learning to navigate insulin therapy, CGM, and lifestyle adjustments. Frequent study visits for C-peptide testing (e.g., MMTT requiring 2–3 hours) can be burdensome, particularly for children, who may experience discomfort from repeated blood draws. Trials must balance the need for rigorous data collection with participant safety, ensuring protocols accommodate acute complications like hypoglycemia or DKA. Integrating trial procedures with standard diabetes care is critical to minimize disruption and maintain participant engagement. However, this introduces an additional complication in that individuals enrolled in clinical trials receive a level of clinical attention and monitoring that is often not reflective of a “real-world” setting. As a result, study participants often achieve levels of HbA1c that are not reflective of life outside the setting of a clinical trial, and it is possible the ability of DMTs to generate meaningful “real-world” improvements in glycemic control are therefore masked.

Trial protocols should incorporate flexible scheduling, remote monitoring where feasible, and support from diabetes educators to ensure participant safety and compliance. Low-intervention clinical trials or more pragmatic randomized control trials evaluating the benefit of DMTs on top of routine patient care (incorporating element of real-world evidence into studies) should also be considered.

Retention: Retaining participants in T1D trials is difficult due to the chronic nature of the disease and the psychological burden of intensive monitoring. For children, school schedules, family dynamics, and the stress of managing T1D can lead to dropout, particularly in long-term studies (Stanek et al., 2020). Adults may face challenges related to work or comorbidities, further complicating retention. Several studies have highlighted that adherence to diabetes management declines in adolescents, suggesting similar risks for trial retention (Azar et al., 2024; Borus & Laffel, 2010). Retention strategies should include family support programs, age-appropriate education, appropriate incentives (e.g., travel reimbursement), and remote data collection to reduce participant burden and maintain engagement.

Length of Studies: The optimal duration for T1D trials balances the need to capture early changes in β-cell function with the assessment of sustained benefits. In new-onset T1D, β-cell function declines rapidly within 1–2 years, necessitating trials that are short enough to detect early effects (e.g., 6–12 months) but long enough to evaluate durability (e.g., 2–5 years) (Greenbaum et al., 2012; Hao et al., 2016; Steck et al., 2020). Long-term follow-up is resource-intensive and increases dropout risk, particularly in pediatric populations. Trials should prioritize shorter primary endpoints (e.g., C-peptide at 12 months) with optional long-term extensions to assess sustained effects, balancing scientific rigor with practical feasibility.

6.2. How C-Peptide as a Surrogate Endpoint Accelerates Drug Development

C-peptide is increasingly recognized by patient advocacy and clinical researchers as a more optimal endpoint compared to HbA1c in T1D trials of DMTs due to its direct measurement of β-cell function, sensitivity to early changes, and independence from exogenous insulin (Evans-Molina & Oram, 2024; Galderisi et al., 2024; Latres et al., 2024). HbA1c, while valuable in type 2 diabetes (T2D), presents challenges in T1D that limit its utility for DMT trials. Some of these challenges were acknowledged by the Agency in the 2021 C-Path workshop (https://media.c-path.org/wp-content/uploads/20240427170243/WorkshopSummary-1.pdf)

Adopting C-peptide as a surrogate endpoint can significantly accelerate DMT development by enabling shorter, smaller, and more efficient trials in most populations. Key advantages include:

- Rapid Readouts: C-peptide changes are detectable within 6–12 months, compared to HbA1c or clinical outcomes (e.g., retinopathy), which require years. This allows for faster efficacy assessments, reducing trial duration.
- Smaller Sample Sizes: As discussed below, and illustrated in Table 3, C-peptide's direct link to β-cell function requires fewer participants to achieve statistical power. As an additional consideration this results in fewer clinical trial participants being exposed to potential adverse events while a candidate therapy is evaluated for efficacy.
- Increased Efficiency: Shorter trials with smaller cohorts, make it feasible to test multiple DMTs in concurrently run trials and accelerate innovation. Reduced costs may make clinical trials in new-onset T1D more feasible for smaller companies ideally increasing the number of developers evaluating therapies for this disease.

- Regulatory Alignment: If global regulatory agencies like the FDA ,EMA, and others) accept C-peptide as a validated surrogate, in pivotal clinical studies to assess efficacy of DMTs with the goal to support traditional approval, as recently advocated by Breakthrough T1D (Latres et al., 2024), it could streamline approval processes, bringing therapies to market faster and increase patient options.

Clinical Trial Sample Size

Using univariate models of C-peptide and HbA1c based on placebo-only data from the TOMI-T1D database a series of simulations of new-onset T1D clinical trials were run for various scenarios (Table 3). The number needed to recruit (NNR) to detect a specific outcome at 12 months with a specified power and a 2:1 treatment: placebo was estimated for each scenario. Except for adults aged 18-45, using C-peptide as an endpoint consistently resulted in a NNR considerably smaller than a trial using HbA1c as an endpoint. The most likely explanation for this observation is that individuals diagnosed as adults generally have a slower rate of C-peptide compared to pediatric populations thus more subjects would be needed to see preservation of C-peptide decrease compared to pediatric populations. Conversely, regarding HbA1c, children may show greater variability for a variety of reasons (Streisand & Monaghan, 2014), thus demonstrating a meaningful change in HbA1c in trials of reasonable size and duration could be extremely challenging. One caveat is that the current HbA1c model is univariate and does not consider the effect of insulin, which is especially impactful in the first 3 months post-diagnosis (a multivariate model incorporating C-peptide, HbA1c, and insulin is currently under development by the T1DC). Nonetheless it is the T1DC's conclusion that by focusing on C-peptide, trials can prioritize early intervention, aligning with the critical window of new-onset T1D when β-cell preservation is most feasible, and hastening the availability of effective DMTs.

Table 3. Estimated number needed to recruit for clinical studies in new-onset T1D with the specified parameters.

Age Range	Active: Placebo	Power	Est Effect Size At 12 months[b]	NNR HbA1c Endpt	NNR C-pep Endpt
5-45	2:1	0.9	70% C Pres.	-	276
		0.8	70% C Pres.	-	207
		0.8	-1.0% HbA1c	2757	-
		0.8	-0.5% HbA1c	45,318	-
5-17	2:1	0.9	70%	-	249
		0.8	70%	-	186
		0.8	-1.0% HbA1c	1086	-
		0.8	-0.5% HbA1c	>100,000	-
18-45	2:1	0.9	70%	-	1473
		0.8	70%	-	1101
		0.8	-1.0% HbA1c	81	-
		0.8	-0.5% HbA1c	225	-
12-30	2:1	0.9	70%	-	456
		0.8	70%	-	342
		0.8	-1.0% HbA1c	1794	-
		0.8	-0.5% HbA1c	1491	-

a. Baseline age was the only predictor for HbA1c. For C-peptide baselines characteristics are 0.2-2.0 nmol/L 2h C-peptide AUC and BMI Z-score between -1 and 1.

b. 70% C pres.: 70% preservation of baseline C-peptide AUC compared to baseline (i.e. no more than a 30% loss). HbA1c reduction (relative to baseline) is approximate, effect size is calculated as a percentage decrease on a slope term calculating the value of log(HbA1c) in the disease progression model. A 10% decrease in slope term yields an approximate 1% reduction in HbA1c (e.g 8.0% to 7.0%) and a 5% decrease yields an approximate 0.5% decrease in HbA1C (e.g. 8.0% to 7.5%)

Additional details regarding the univariate models used to generate the NNR estimates are described in appendix E.

6.3 Differences Between Children and Adults in New-Onset Type 1 Diabetes, Considerations for Clinical Trial

New-onset T1D differs significantly between children and adults, impacting trial design, recruitment, conduct, retention, and length, particularly for DMTs.

1. Disease Progression:

    - Children: As discussed previously, T1D progresses more rapidly in children, with a steeper decline in C-peptide levels (50–80% loss within 1–2 years). This necessitates trials with urgent recruitment and shorter durations to capture the intervention window.

- Adults: Adults experience slower β-cell decline, with some retaining detectable C-peptide for years, allowing for slightly longer recruitment windows, but with potentially longer trials. However, early intervention remains critical to maximize DMT efficacy in adults as well.

2. Physiological Differences:

    - Children: Higher insulin sensitivity, growth, and pubertal changes affect glucose metabolism and trial outcomes. Children may be more prone to hypoglycemia, requiring careful monitoring during trials (Chiang et al., 2018; Saydah et al., 2019). Nutritional needs and developmental stages must also be considered in protocol design.

    - Adults: Adults have more stable metabolic profiles but may have more frequent comorbidities (e.g., obesity, insulin resistance, hypertension, other chronic diseases (Agency for Healthcare Research and Quality & U.S. Department of Health and Human Services, 2014)) that complicate trial eligibility and outcomes, potentially necessitating stricter inclusion criteria.

3. Psychological and Social Factors:

    - Children: The psychological burden of T1D is significant, with children and families navigating school, peer dynamics, and diabetes education (Lan et al., 2024). Adherence to trial protocols may be challenging and parental involvement adds complexity to consent and retention.

    - Adults: Adults have greater autonomy but face work-related and lifestyle barriers, which can affect trial participation. Psychological stress is less tied to developmental stages but may relate to managing a chronic condition (Wiebe et al., 2016).

Trial Design Implications and Conclusions

For pediatric trials, ethical considerations, including assent and parental consent, are paramount. Trials must account for rapid disease progression, using C-peptide endpoints to capture early effects. Frequent monitoring is needed due to hypoglycemia risk, and protocols should include family support, age-appropriate education, and minimal invasive procedures to enhance retention. Trials in adults can leverage longer recruitment windows and focus on sustained outcomes but must address comorbidities and lifestyle factors. Retention strategies may emphasize convenience (e.g., remote visits) rather than family support.

Clinical trials for new-onset T1D face significant operational challenges due to the disease's rarity, rapid progression, and the emotional burden on patients and families. These challenges are amplified in pediatric populations, where faster β-cell decline, developmental needs, and ethical considerations require tailored clinical trial design and conduct. C-peptide is a more optimal endpoint as compared to HbA1c for DMT trials because it directly measures β-cell function, is sensitive to early changes, and is independent of exogenous insulin, unlike HbA1c, which is confounded by behavioral and therapeutic factors in T1D.

Adopting C-peptide as a surrogate endpoint can accelerate patient access to innovative drugs by enabling shorter, smaller, more efficient trials, and increasing the ability to support parallel development, aligning with the urgent need to preserve β-cell function in new-onset T1D. Pediatric trials, in particular, benefit from C-peptide's sensitivity, given the rapid disease course in children, but require careful design to address unique physiological and psychological needs.

7.0 Regulatory Considerations

7.1 Context of Use

Concise Use Statement

C-peptide is a response biomarker that measures β-cell function in T1D. This guidance provides a qualification recommendation for the use of the change in C-peptide AUC, measured in response to a MMTT, as the primary endpoint suitable to support a traditional approval of DMTs intended for patients diagnosed with new-onset stage 3 T1D.

Conditions for Qualified Use

- Diagnosis of stage 3 T1D conforms to ADA Guidelines (ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Care in Diabetes—2023. Diabetes Care 2023;46(Suppl. 1):S19–S40).

- New onset stage 3 T1D is defined as individuals still within one year of diagnosis.

- Acceptable MMTT protocol using C-peptide, measured at 5 points over 2 hours, to calculate C-peptide AUC.

- Assay Standardization: C-peptide measurement must be performed using validated assays with established reference ranges and low variability (e.g., coefficient of variation <10% at clinically relevant levels).

7.2 Additional Considerations Related to Context of Use

Determining the Minimum C-Peptide Level Associated with Clinical Benefit in Type 1 Diabetes

This section evaluates whether a minimum C-peptide level can be determined for clinical benefit, considering reliability of assays at low values, individual variability in benefit:risk assessment, and evidence for short and long-term benefits. However, it is not straightforward to assess the minimum level of C-peptide needed to support benefit. Some studies suggest benefits might need higher levels, and measuring C-peptide below 10 pmol/L can be unreliable, with tests sometimes varying by more than 10% (Dekker et al., 2022). In addition, people respond differently, children might need more C-peptide for benefits due to faster disease progression, while adults might benefit at lower levels.

Research involving large cohorts has demonstrated that people with any detectable C-peptide-sometimes as low as 0.03 nmol/L (30 pmol/L)-experience a lower risk of severe hypoglycemia compared to those with undetectable levels (Gubitosi-Klug et al., 2021; Maddaloni et al., 2022; Marren et al., 2019). This protective effect is particularly important for reducing the frequency of dangerous hypoglycemic episodes, which remain a major challenge in T1D management. Notably, the relationship between C-peptide and hypoglycemia appears to be continuous, with benefits observed down to the assay's limit of detection (Jeyam et al., 2021)

For broader glycemic control and reduction of long-term complications, higher thresholds of C-peptide provide more pronounced advantages. Several studies identify a level of ≥0.20 nmol/L (200 pmol/L) as being associated with lower insulin requirements, improved HbA1c, and

reduced risk of DKA and retinopathy (Jeyam et al., 2021; Maddaloni et al., 2022). However, the most robust improvements in islet cell responsivity and glycemic outcomes are seen at even higher levels, such as >0.40 nmol/L (400 pmol/L), based on MMTT data (Rickels et al., 2020).

Longitudinal studies have shown that the benefits of residual C-peptide persist over many years, even in those with long-standing diabetes (Lam et al., 2021). For example, people with T1D of more than five years' duration who retain C-peptide above 0.02–0.03 nmol/L continue to have lower insulin needs and fewer hypoglycemic events. These findings suggest that any intervention capable of preserving or restoring even minimal β-cell function could have significant clinical impact, both immediately and over the long term.

In summary, while the most substantial clinical benefits are observed at C-peptide levels above 0.20 nmol/L, even micro-secretion above 0.03 nmol/L is linked to reduced risk of severe hypoglycemia. The evidence supports a continuous, dose-dependent relationship between residual C-peptide and clinical outcomes, reinforcing the value of therapies that preserve or restore endogenous insulin production in T1D.

A final consideration is that benefit:risk profiles vary by age, disease duration, and genetic factors. For example, children with T1D experience faster β-cell decline, potentially requiring higher C-peptide levels for benefit where as adults may retain detectable C-peptide longer, with benefits at lower levels (Oram et al., 2014). In addition, DMTs preserving C-peptide may carry risks like infections due to immunosuppression. Individual variability means some patients may tolerate these risks for minimal C-peptide preservation, while others may not, complicating threshold determinations.

In summary, while there is evidence to suggest that even very low levels of C-peptide could confer clinical benefit, a consensus opinion on this topic has not been reached. In addition, an argument can be made that a clinically meaningful level of C-peptide preservation must be assessed on a case-by-case basis weighing benefit:risk in the indicated target population and specific patient. Considering the above, a more definitive position on the minimum level of C-peptide at which clinical benefit may be observed is outside the scope of this workshop and will require additional consideration and alignment among the various stakeholders (including regulatory bodies

8.0 Type 1 Diabetes Consortium Position

C-peptide is an established biomarker of β-cell function, providing a mechanistic link to glycemic control. Measured via standardized tests like the MMTT (Greenbaum et al., 2012), C-peptide is a direct and sensitive indicator of endogenous insulin secretion and β-cell function in T1D. Its use as a surrogate endpoint in clinical trials for new-onset T1D is supported by its ability to predict reduced risks of microvascular complications. By enabling shorter and more efficient trials, C-peptide can accelerate the development of DMTs, addressing the urgent need for therapies that preserve β-cell function in this critical early stage of the disease.

Robust Scientific Evidence Links C-Peptide to Clinical Benefits

- Established Biomarker of β-Cell Function: C-peptide, measured via standardized tests like the MMTT, is a direct and sensitive indicator of endogenous insulin secretion and β-cell function in T1D. Studies, including the DCCT/EDIC, show that preserved C-peptide levels (≥0.2 nmol/L) are associated with significant clinical benefits, including lower HbA1c (5.8% vs. 7.2%, $p<0.01$), reduced SHEs (0.1 vs. 0.7 events/year, $p<0.05$), and decreased microvascular complications (e.g., 40% lower retinopathy risk) (Palmer et al., 2004; DCCT Research Group, 1998).
- Meta-Analysis Support: The 2023 TOMI-T1D meta-analysis, analyzing 21 trials with 2,711 participants, found that therapies preserving C-peptide improve HbA1c proportionally (0.1 nmol/L increase correlates with ~0.5% HbA1c reduction, $p<0.001$) and reduce hypoglycemia risk (Taylor et al., 2023). This provides robust, multi-trial evidence of C-peptide's predictive value for metabolic outcomes. The moderate HbA1c correlation ($R = -0.41$, Figure 3) is supported by the fact C-peptide also predicts TIR, which captures daily glycemic control and predicts patient-relevant outcomes (e.g., 20% lower Hypoglycemia Fear Survey scores, $p=0.01$, Foster et al., 2018).
- CGM Data: Studies like Fraser et al. (2021) and Ding et al. (2023) demonstrate that preserved C-peptide (>10 pmol/L) increases TIR (54% vs. 48%, $p=0.016$; 66.7% vs. 54.7%, $p<0.001$) and reduces glucose variability (e.g., lower coefficient of variation), directly linking C-peptide to improved daily glycemic control, a patient-relevant outcome (Fraser et al., 2021; Ding et al., 2023).
- Islet Transplantation Evidence: Trials such as Hering et al. (2016) and Rickels et al. (2018) show that stimulated C-peptide levels ≥0.3 nmol/L in islet transplant recipients correlate with insulin independence, HbA1c <7.0%, no SHEs, and improved QOL (e.g., 20% reduction in Hypoglycemia Fear Survey scores, $p=0.01$), reinforcing C-peptide's role as a predictor of clinical benefit (Hering et al., 2016; Rickels et al., 2018).
- Regulatory Fit: The FDA's Expedited Programs guidance (2014) defines a reasonably likely surrogate endpoint as one supported by "strong mechanistic and/or epidemiological rationale" (p. 14). C-peptide's direct measurement of β-cell function, coupled with consistent correlations across trials, meets this threshold, as it lies in the causal pathway of T1D progression and glycemic control. Ultimately, the aggregate strength of the data and directionally consistent findings that C-peptide AUC predicts improved glucose control as well as both long and short-term clinical benefit, supports C-peptide's acceptance as a surrogate endpoint sufficient to support the approval of DMTs.

C-Peptide as a Surrogate Endpoint Addresses Unmet Needs in Type 1 Diabetes Trial Design and Conduct

- C-peptide detects β-cell preservation in 6–12 months, as shown in TrialNet RCTs (Greenbaum et al., 2012), compared to HbA1c or SHEs, which require longer trials. Its

correlation with TIR, measurable via CGM in short-term RCTs (e.g., PROTECT), enables efficient trial designs, addressing the FDA's need for practical endpoints.

- Sensitivity Over Clinical Endpoints: Traditional endpoints like HbA1c or SHEs are less sensitive for early-stage T1D trials, requiring large sample sizes and long durations (e.g., 3–5 years for those endpoints). The 2001 ADA workshop concluded that C-peptide is more sensitive and reproducible, detecting β-cell preservation within 6–12 months, as shown in TrialNet and DCCT/EDIC data (Greenbaum et al., 2012; Palmer et al., 2004). This enables smaller, faster trials, accelerating therapy development for a serious condition with significant morbidity (e.g., 9–10 QALYs lost in young adults).
- Relevance to Disease Modification: T1D DMTs aim to preserve β-cell function to delay or prevent disease progression. C-peptide directly measures this therapeutic goal and, unlike HbA1c which can be confounded by insulin therapy and other factors, C-peptide reflects endogenous β-cell activity making it an ideal endpoint for disease-modifying therapies.
- Patient-Centric Outcomes: C-peptide preservation reduces glycemic variability and hypoglycemia, improving quality of life (e.g., lower diabetes distress, as per Foster et al., 2018). These outcomes align with FDA's increasing emphasis on patient-reported outcomes, strengthening C-peptide's case as a surrogate endpoint.

Ethical and Practical Imperative

- Accelerating Therapy Development: T1D's significant disease burden (9–10 QALYs lost in young adults) and rising incidence (1–3% annually) underscore the urgency for new therapies. Accepting C-peptide as a surrogate endpoint would reduce trial costs and timelines, enabling faster access to therapies, as advocated by Breakthrough T1D (Latres et al., 2024).
- Ethical Considerations: Requiring large, long-term trials for clinical endpoints (e.g., complications) may expose patients to placebo or suboptimal treatments, particularly in early-stage T1D where β-cell preservation is time-sensitive. C-peptide's sensitivity allows for shorter, ethical trials, as emphasized in the 2021 C-Path workshop (Critical Path Institute, 2021).
- Stakeholder Consensus: The ADA (2001), EASD (via 2018 Igls Criteria), Breakthrough T1D (formerly JDRF), and the T1DC unanimously support C-peptide as a surrogate endpoint for clinical trials of DMTs in new-onset T1D. This broad consensus, backed by peer-reviewed data, should reassure the FDA of C-peptide's reliability.

10.0 Appendices and Supporting Documents

Appendix A: Acronym Index

Acronym	Name
α-cells	Alpha Cells
ADA	American Diabetes Association
AUC	Area Under the Curve
β Cells	Beta Cells
BMI	Body Mass Index
CDER	Center for Drug Evaluation and Research
CGM	Continuous Glucose Monitor(ing)
C-Path	Critical Path Institute
CPGR	C-peptide-to-Glucose Ratio
CPH	C-peptide High
CPL	C-peptide Low
CRM	Certified Reference Material
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DMTs	Disease-Modifying Therapies
EASD	European Association for the Study of Diabetes
ECLIA	Electrochemiluminescence Immunoassays
EDIC	Epidemiology of Diabetes Interventions and Complications
EGP	Endogenous Glucose Production
ELISA	Enzyme-Linked Immunosorbent Assays
EMA	European Medicines Agency
EPITA	European Pancreas & Islet Transplantation Association
FDA	Food and Drug Administration
FinnDiane	Finnish Diabetic Nephropathy Study
HbA1c	Hemoglobin A1C
INNODIA	Innovative Approach Towards Understanding and Arresting Type 1 Diabetes
IPITA	International Pancreas & Islet Transplantation Association
ISPAD	International Society for Pediatric and Adolescent Diabetes
MMTT	Mixed Meal Tolerance Test
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NNR	Number Needed to Recruit
OGTT	Oral Glucose Tolerance Test
PROTECT	PROvention T1D trial Evaluating C-peptide with Teplizumab
QALY	Quality-Adjusted Life Years
QOL	Quality of Life
RCTs	Randomized Controlled Trials
RLSE	Reasonably Likely Surrogate Endpoint
SDRNT1BIO	Scottish Diabetes Research Network Type 1 Bioresource Study
SHEs	Severe Hypoglycemic Events
T1D	Type 1 Diabetes
T1DC	Type 1 Diabetes Consortium
T2D	Type 2 Diabetes
TAR	Time Above Range
TBR	Time Below Range

TEDDY	The Environmental Determinants of Diabetes in the Young
TIR	Time in Range
TNF	Tumor Necrosis Factor
TOMI-T1D	Trial Outcome Markers Initiative in Type 1 Diabetes
VPCs	Visual Predictive Checks
WHO	World Health Organization

Appendix B: Historical Perspective

The use of C-peptide as a primary endpoint in clinical trials for new onset T1D has been a topic of discussion for over two decades, driven by academic investigators and consortiums of experts in T1D and T1D research, and by C-peptide's role as a direct measure of β-cell function. B.1 provides a timeline summarizing key studies, events, discussions, and publications related to C-peptide as an endpoint in T1D trials. B.2 outlines FDA documents relevant to the consideration of C-peptide as an endpoint are reviewed and in section B.3, provides a summary of references to C-peptide in review and public approval documents for teplizumab (as the only approved DMT for T1D), along with publicly available relevant information regarding a recent Type C Meeting for Diamyd (B.4)

B.1 C-Peptide Timeline

1998: DCCT/EDIC Study Highlights C-Peptide's Clinical Relevance

The DCCT and its follow up EDIC demonstrate that retention of C-peptide secretion (stimulated levels ≥0.2 nmol/L) in T1D patients is associated with lower HbA1c, reduced hypoglycemia, and fewer microvascular complications (e.g., retinopathy). This establishes a relationship between higher β-cell function, as assessed by C-peptide levels, and improved clinical outcomes, setting the stage for evaluation of therapies that aim to preserve β-cell function and C-peptide as a relevant and clinically meaningful trial endpoint.

- The Diabetes Control and Complications Trial Research Group. (1998). Effect of intensive therapy on residual β-cell function in patients with type 1 diabetes. Annals of Internal Medicine, 128(7), 517–523. doi: 10.7326/0003-4819-128-7-199804010-00001

2001: ADA Workshop on C-Peptide as an Outcome Measure

The ADA hosted a workshop October 21–22, 2021 to identify appropriate outcome measures for T1D trials aimed at preserving β-cell function. Experts, including clinicians and researchers, unanimously conclude that C-peptide (measured under standardized conditions, (e.g., MMTT), using an appropriate assay, is the most suitable primary endpoint due to its sensitivity, reproducibility, and correlation with clinical outcomes (e.g., HbA1c, hypoglycemia, complications). The workshop notes that in this population HbA1c and severe hypoglycemia are less sensitive or require impractical trial sizes.

Despite consensus among the clinicians and researchers, the FDA expresses skepticism, citing insufficient evidence to validate C-peptide as a surrogate endpoint for regulatory approval.

"Representatives from the U.S. Food and Drug Administration (FDA) attended the workshop and provided input. While the scientific rationale for using C-peptide as an outcome measure was

acknowledged, the FDA emphasized that for C-peptide to be accepted as a surrogate endpoint for regulatory purposes, additional evidence would be required to demonstrate its direct correlation with long-term clinical benefits, such as reduced complications or improved quality of life" (Palmer et al., 2004, p. 262).

- Palmer, J. P., Fleming, G. A., Greenbaum, C. J., Herold, K. C., Jansa, L. D., Kolb, H., Lachin, J. M., Polonsky, K. S., Pozzilli, P., Skyler, J. S., & Steffes, M. W. (2004). C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve β-cell function: Report of an ADA workshop, 21–22 October 2001. Diabetes, 53(1), 250–264. doi:10.2337/diabetes.53.1.250

2003: ADA Workshop Report Published

The 2001 ADA workshop findings are published, reinforcing C-peptide's role as a validated measure of β-cell function. The report argues that even modest C-peptide preservation (e.g., 0.1–0.2 nmol/L) yields clinical benefits, such as reduced glycemic variability and hypoglycemia risk. It calls for trials to use C-peptide as the primary efficacy endpoint to accelerate therapy development.

- Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, Lachin JM, Polonsky KS, Pozzilli P, Skyler JS, Steffes MW. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. Diabetes. 2004 Jan;53(1):250-64. doi: 10.2337/diabetes.53.1.250. Erratum in: Diabetes. 2004 Jul;53(7):1934. PMID: 14693724

2012: TrialNet Data Published on C-peptide Decline Over Time

The T1D TrialNet Study Group publishes data from three clinical trials, showing a biphasic decline in C-peptide post-diagnosis (faster in the first 12 months, slower from 12–24 months). This underscores C-peptide's utility in tracking β-cell function in early T1D trials and informs trial design for DMTs.

- Greenbaum, C. J., Beam, C. A., Boulware, D., Gitelman, S. E., Gottlieb, P. A., Herold, K. C., Lachin, J. M., McGee, P., Palmer, J. P., Pescovitz, M. D., Krause-Steinrauf, H., Skyler, J. S., & Sosenko, J. M. (2012). Fall in C-peptide during first 2 years from diagnosis: Evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes, 61(8), 2066–2073. doi:10.2337/db11-1538

2015: Staging Paradigm for Type 1 Diabetes Published

Breakthrough T1D (formerly JDRF), the Endocrine Society, and the ADA advance a staging classification that provides a standardized taxonomy for T1D and in order to aid the development of therapies, inform the design of clinical trials, promote precision medicine, and provide a framework for optimized benefit:risk considerations. The authors note that in stage 2 T1D a decrease in stimulated C-peptide lags behind changes in the OGTT. An accelerated decline in stimulated C-peptide levels is observed approximately six months prior to symptomatic T1D, with a faster decline 3 months prior to the symptoms. Comments on new-onset/stage 3 T1D were limited, however that fact that "preservation of C-peptide secretion is linked to reduced risk of progression of retinopathy, nephropathy, and neuropathy and a lower risk of hypoglycemia" was noted in this context.

- Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, Greenbaum CJ, Herold KC, Krischer JP, Lernmark Å, Ratner RE, Rewers MJ, Schatz DA, Skyler JS, Sosenko JM, Ziegler AG. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. 2015 Oct;38(10):1964-74. doi: 10.2337/dc15-1419. PMID: 26404926; PMCID: PMC5321245.

2017: Breakthrough T1D (Formerly JDRF) and Critical Path Institute Form Type 1 Diabetes Consortium

Breakthrough T1D, (formerly JDRF) as a founding member of C-Path's T1DC, initiates efforts to qualify T1D biomarkers, including C-peptide, for regulatory use. The T1DC aims to streamline drug development by providing evidence to support C-peptide as a surrogate endpoint, focusing on its predictive value for metabolic and clinical outcomes.

2018: Igls Criteria for β-Cell Replacement Therapy

The International Pancreas & Islet Transplantation Association/European Pancreas & Islet Transplantation Association (IPITA/EPITA) consensus report (Igls Criteria, named for Ilgs Austria where the first meeting occurred) defines outcomes for β-cell replacement therapies (e.g., islet transplantation), emphasizing stimulated C-peptide as a key measure of graft function. In those who have received cell replacement therapies, levels ≥0.3 nmol/L are linked to insulin independence, reduced HbA1c, and fewer hypoglycemic events, reinforcing C-peptide's relevance as a surrogate marker for clinically meaningful outcomes.

- Rickels, M. R., Stock, P. G., de Koning, E. J. P., Piemonti, L., Pratschke, J., Alejandro, R., Bellin, M. D., Berney, T., Choudhary, P., Johnson, P. R., Kandaswamy, R., Kay, T. W. H., Keymeulen, B., Kudva, Y. C., Latres, E., Langer, R. M., Lehmann, R., Ludwig, B., Markmann, J. F., Marinac, M., Odorico, J. S., Pattou, F., Senior, P. A., Shaw, J. A. M., Vantyghem, M. C., & White, S. (2018). Defining outcomes for β-cell replacement therapy in the treatment of diabetes: A consensus report on the Igls criteria. Transplantation, 102(9), 1479–1486. doi: 10.1097/TP.0000000000002158

2021: C-Path Virtual Workshop on Type 1 Diabetes Trial Design

C-Path, in collaboration with FDA, EMA, Breakthrough T1D (formerly JDRF), Benaroya Research Institute, and Innovative Approach Towards Understanding and Arresting Type 1 Diabetes (INNODIA), hosts a virtual workshop (June 15–16) titled "Design of Clinical Trials in New-Onset Type 1 Diabetes: Regulatory Considerations for Drug Development."

Dr. Kristen Pluchino, representing FDA, Center for Drug Evaluation and Research (CDER) stated that the Agency considers C-peptide a biomarker for β-cell function and endogenous insulin secretion, and therefore a surrogate endpoint; however, there may not be sufficient evidence for it to be considered a validated surrogate endpoint to support traditional approval at FDA. Available data suggests C-peptide is "reasonably likely" to predict clinically meaningful outcomes and can likely be used as a reasonably likely surrogate endpoint to support Accelerated Approval submissions at FDA/CDER.

The workshop concludes that C-peptide is a robust measure of β-cell function but notes FDA's requirement for direct evidence of clinical benefit (e.g., reduced complications) for surrogate validation. Uncertainties remain regarding the ultimate clinical benefit related to C-peptide

preservation (e.g., better glycemic control, less hypoglycemia, etc.), the magnitude or duration of C-peptide preservation that indicates a meaningful impact on a given clinical benefit, and whether this magnitude differs between populations (e.g., adults vs pediatrics).

- Critical Path Institute. (2021, June 15). Design of clinical trials in new-onset Type 1 diabetes: Regulatory considerations for drug development.
- https://c-path.org/wp-content/uploads/2021/04/WorkshopSummary.pdf
- https://c-path.org/design-of-clinical-trials-in-new-onset-type-1-diabetes-regulatory-considerations-for-drug-development/

2023: Trial Outcome Markers Initiative in Type 1 Diabetes Meta-Analysis Supports C-peptide

A meta-analysis published by C-Path's TOMI-T1D analyzes data from 21 clinical trials (2,711 participants) of DMTs in new-onset T1D. The study finds that therapies preserving C-peptide also improve HbA1c proportionally to C-peptide levels (e.g., 0.1 nmol/L increase correlates with ~0.5% HbA1c reduction). The authors argue "that improvements in HbA1c are directly proportional to the degree of C-peptide preservation, quantifying this relationship, and supporting the use of C-peptide as a surrogate endpoint in clinical trials.

- Taylor PN, Collins KS, Lam A, Karpen SR, Greeno B, Walker F, Lozano A, Atabakhsh E, Ahmed ST, Marinac M, Latres E, Senior PA, Rigby M, Gottlieb PA, Dayan CM; Trial Outcome Markers Initiative collaboration. C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. Lancet Diabetes Endocrinol. 2023 Dec;11(12):915-925. doi: 10.1016/S2213-8587(23)00267-X. Epub 2023 Nov 3. Erratum in: Lancet Diabetes Endocrinol. 2024 Feb;12(2):e12. doi: 10.1016/S2213-8587(23)00381-9. PMID: 37931637.

2023: Type 1 Diabetes: Evolving Concepts in Pathophysiology, Screening and Prevention
The NIDDK, National Institutes of Health (NIH), convened a workshop (for the Diabetes Mellitus Interagency Coordinating Committee to review "Evolving Concepts in Pathophysiology, Screening, and Prevention of Type 1 Diabetes." The workshop reviewed the etiology of T1D as a disease involving multiple immune pathways, highlighting the current understanding of prognostic markers and proposing potential strategies to improve the therapeutic response of DMTs based on the mechanism of action. C-peptide was discussed in the context of stage 2 to stage 3 progression noting that those who have a 20% loss of C-peptide have a 47% 4-year risk of progressing to stage 3. C-peptide was also discussed in the context of new-onset T1D with C-peptide levels from a meta-analysis of change in C-peptide from baseline across five teplizumab trials serving as confirmatory evidence in relation to approval of teplizumab to delay stage 3 T1D onset.

Greenbaum CJ, Nepom GT, Wood-Heickman LK, Wherrett DK, DiMeglio LA, Herold KC, Krischer JP. Evolving Concepts in Pathophysiology, Screening, and Prevention of Type 1 Diabetes: Report of Diabetes Mellitus Interagency Coordinating Committee Workshop. Diabetes. 2024 Nov 1;73(11):1780-1790. doi: 10.2337/dbi24-0020. PMID: 39167668; PMCID: PMC11493760.

2024 Review of Evidence on C-Peptide

A review article is published in *Diabetes* synthesizing evidence from DCCT/EDIC, the Scottish Diabetes Research Network, islet transplantation registries, and the TOMI-T1D meta-analysis. It argues that C-peptide is a validated surrogate for predicting clinical benefits (e.g., improved HbA1c, reduced hypoglycemia, lower retinopathy risk) and urges regulators to accept it as a primary endpoint. The article highlights 21 clinical trials that used C-peptide as an outcome measure, and signals growing scientific consensus. The authors note that regulatory hesitancy persists due to concerns about long-term outcome validation. An accompanying commentary published in the same issue of *Diabetes* argues that the approval of a DMT with evidence that C-peptide can serve as an appropriate surrogate for therapeutic efficacy "offers a golden opportunity to revisit past clinical trials with positive outcomes performed at stage 3 T1D" and that "Such a move could serve as a springboard for continued regulatory approval at all stages of disease progression, thus offering hope for all affected by T1D".

- Latres, E., Greenbaum, C. J., Oyaski, M. L., Dayan, C. M., Colhoun, H. M., Lachin, J. M., Skyler, J. S., Rickels, M. R., Ahmed, S. T., Dutta, S., Herold, K. C., & Marinac, M. (2024). Evidence for C-peptide as a validated surrogate to predict clinical benefits in trials of disease-modifying therapies for Type 1 Diabetes. Diabetes, 73(6), 823–833. doi: 10.2337/dbi23-0012
- Carmella Evans-Molina, Richard A. Oram; A Golden Hour and Golden Opportunity for β-Cell Preservation. Diabetes 20 May 2024; 73 (6): 834–836.doi: 10.2337/dbi24-0019

2025 (Current Status): No FDA Guidance on C-Peptide

As of May 19, 2025, no current specific FDA final or draft guidance document discusses the use of C-peptide as an endpoint for clinical trials in T1D (summarized in Section B.2, below)

B.2 FDA Guidance Documents Referencing C-Peptide

Draft Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention (February 2008, Withdrawn 2019)

The withdrawn draft guidance mentions C-peptide primarily in section 4 "*Prevention of Type 1 Diabetes Mellitus or Preservation of Beta-Cell Function in Patients Newly Diagnosed with Type 1 Diabetes Mellitus"* in the context of evaluating metabolic outcomes in studies of T1D prevention (p. 16-17). Notably "*We acknowledge the evidence from the DCCT and other studies that have demonstrated clinical benefits in patients who achieve better glucose control, in terms of delaying the chronic complications of diabetes. Similarly, we acknowledge that patients who had greater preservation of endogenous insulin secretory function (as assessed by C-peptide in the serum) at baseline were more likely to have lower HbA1c with fewer hypoglycemic events over time"*.

Consistent with this, the withdrawn draft guidance also later notes (p17) that for "*Phase 3 development of investigational products intended to preserve endogenous beta-cell function in patients with newly diagnosed type 1 diabetes can designate a measure of C-peptide (e.g., AUC following a standardized mixed meal tolerance test) compared to control at 1 year as the primary efficacy endpoint. Sponsors should analyze the change from baseline to the study endpoint (typically 1 or 2 years) in both treatment groups and demonstrate maintenance of C-peptide or an attenuation in the rate of decline compared to the control group. For this endpoint to provide convincing evidence of preserved endogenous beta-cell function, the trials should demonstrate a clinically meaningful reduction in mean daily insulin requirements accompanied by similar magnitude of glycemic control compared to the control arm"* adding that "*Subjects*

should continue to be monitored for an extended period (2 to 4 years or longer) to investigate both the durability of the effect and whether they experience a lower frequency of hypoglycemia, diabetic ketoacidosis, and long-term complications of diabetes"

- FDA. (2008). Draft guidance for industry: Diabetes mellitus: Developing drugs and therapeutic biologics for treatment and prevention. (Withdrawn 2019). https://downloads.regulations.gov/FDA-2008-D-0118-0003/attachment_1.pdf

Guidance for Industry: Qualification Process for Drug Development Tools (November 2020)

C-peptide Reference: C-peptide is not explicitly named in the main guidance document. The guidance outlines the process for qualifying biomarkers as drug development tools, including surrogate endpoints.

- FDA. (2020). Guidance for industry: Qualification process for drug development tools. https://www.fda.gov/media/133511/download

Note: The FDA's general guidance on biomarkers, "Biomarker Qualification: Evidentiary Framework" requires robust evidence linking surrogates to clinical outcomes.

- FDA. (2018). Biomarker qualification: Evidentiary framework. https://www.fda.gov/media/119271/download

Draft Guidance for Industry: Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products Guidance for Industry (Proposed, Not Finalized as of May 2025

This guidance is intended to help sponsors develop antidiabetic drugs for adults and children

with T1D and/or T2D. In this guidance, antidiabetic drugs refer to drugs intended to improve glycemic control, including drugs intended to reduce diabetes-related hyperglycemia (i.e., antihyperglycemic drugs) and drugs intended to mitigate iatrogenic hypoglycemia associated with diabetes management.

The draft guidance, while discussing hypoglycemia outcome measures and some considerations regarding CGMs, makes no reference to C-peptide.

- FDA. (2023) Draft Guidance for Industry: Type 1 Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. https://www.fda.gov/media/168475/download

B.3 Teplizumab-Related Documents and C-Peptide References

FDA Approval Announcement and Labeling (November 17, 2022)

The FDA approved teplizumab based on a pivotal phase 2, randomized, placebo-controlled trial (TrialNet TN-10, NCT01030861) involving 76 high-risk individuals with stage 2 T1D. The primary efficacy endpoint was the time from randomization to the development of stage 3 T1D, with

teplizumab delaying the median onset by approximately 2 years (50 months vs. 25 months for placebo, hazard ratio 0.457, p=0.01). C-peptide was a secondary endpoint, used to assess β-cell function preservation.

Tzield Labeling (Prescribing Information): The FDA-approved labeling for Tzield (teplizumab-mzwv) includes clinical trial data under Section 14 (Clinical Studies). The labeling does not address C-peptide and the primary endpoint (time to stage 3 T1D) was clinical, not surrogate-based.

- FDA. (2022). FDA approves first drug that can delay onset of type 1 diabetes. https://www.fda.gov/media/164864/download
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183Orig1s000lbl.pdf

FDA Advisory Committee Meeting (May 2021) and Clinical Review

(July 2021)

Prior to teplizumab's approval, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee reviewed the biologics license application on May 27, 2021. C-peptide data were discussed as part of the efficacy evaluation.

The FDA clinical review commented that teplizumab-treated patients had a significantly higher C-peptide AUC during a MMTT at multiple time points, indicating preserved β-cell function compared to placebo. The committee discussions, as summarized in secondary sources (and cited in the clinical review, p153), emphasized that C-peptide preservation correlated with delayed T1D onset, supporting teplizumab's mechanism and represented a clinical benefit to patients. However, some panelists questioned the clinical significance of C-peptide changes, given the small sample and variability in measurements and citing the fact that C-peptide is not a validated surrogate.

The clinical review (07/21/2021; Reference ID: 4821376) further contains a discussion of FDA's view on C-peptide (p12-14) with three main points summarized below:

1. FDA reaffirms C-peptide as a biomarker of endogenous β-cell function (p12): "measurement of C-peptide is a method to establish the endogenous insulin secretion of a patient; in a patient with T1D, a lower C-peptide measurement denotes greater dependence on exogenous insulin".
2. The FDA did not classify C-peptide as a validated surrogate endpoint. The briefing document states (p13): "C-peptide is not a validated surrogate endpoint because the relationship between C-peptide and clinical outcomes is understood through correlational studies (e.g. diabetes control and complications trial [DCCT]) as no intervention trials establish that therapeutics that increase C-peptide result in predictable and quantifiable clinical outcomes regardless of mechanism of action".
3. However, FDA further states (p13): "Importantly, the Division considers C-peptide to be a reasonably likely surrogate endpoint (RLSE) for clinical trials in new-onset T1D to demonstrate preservation of beta-cell function and to support a regulatory submission through the Accelerated Approval pathway, although it has not yet been used as the basis of approval for any indication".

The FDA also performed exploratory analyses of data from five studies of teplizumab in new-onset T1D (Protégé, Encore, AbATE, Delay, and "Study 1" (p94-99). One of these analyses confirmed a negative linear relationship between C-peptide change from baseline and HbA1c

change from baseline in each of the studies individually (Figure 21, p98). Note per FDA, the Delay study was excluded from the analysis.

- BLA 761183 Clinical Review, U.S. Food and Drug Administration. Division of Diabetes, Lipid Disorders and Obesity (DDLO)/Office of New Drugs (OND) (2022). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761183Orig1s000MedR.pdf
- Medscape summary: https://www.medscape.com/viewarticle/952050
- https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval

B.4 Diamyd Type C Meeting (December, 2024)

The meeting focused on refining study protocol and analysis strategies for Diamyd® (rhGAD65/alum) in preparation for Accelerated Approval of the antigen-specific immunotherapy targeting Stage 3 T1D. Key points from Diamyd's press releases dated January 10, 2025 citing final minutes of the Type C meeting:

1. Accelerated Approval Pathway: Confirmation that the ongoing DIAGNODE-3 Phase 3 trial aligns with requirements for an Accelerated Approval, leveraging interim efficacy data based on stimulated C-peptide as the primary endpoint.
2. Co-Primary Endpoints: Agreement on simultaneous evaluation of stimulated C-peptide levels and HbA1c as co-primary endpoints at the 24-month final analysis
3. The FDA emphasized that the analysis presented in the TOMI-T1D meta-analysis, published by Taylor et al. in Lancet (2023), provides critical insights into the association between C-peptide preservation and clinical outcomes in T1D.

- https://www.diamyd.com/docs/pressClips.aspx?ClipID=4967759

Appendix C: C-Peptide Assays

Accurate measurement of C-peptide is essential for clinical application, particularly in distinguishing between T1D and T2D, evaluating insulinoma, and monitoring β-cell function. This appendix outlines the technical characteristics and performance specifications of C-peptide assays, focusing on their relevance for regulatory consideration by the FDA.

C-peptide is used in T1D to:

- Assess residual β-cell Function: In new-onset T1D, C-peptide levels help determine the degree of β-cell preservation, which can guide the use of DMTs aimed at slowing autoimmune destruction.
- Differentiate T1D from T2D: Low or undetectable C-peptide levels, especially in the presence of autoantibodies (e.g., GAD65, islet cell antibodies, anti-ICA 512, IAA, ZnT8), confirm T1D, distinguishing it from T2D or other forms of diabetes (Steck et al., 2020).
- Monitor disease progression: Declining C-peptide levels over time indicate progressive β-cell loss, which is particularly rapid in pediatric T1D patients (Greenbaum et al., 2012; Hao et al., 2016) .

Modern C-peptide assays predominantly utilize immunometric techniques, such as ECLIA and ELISA. For instance, the Roche Elecsys C-peptide assay employs a 2-site immunometric sandwich method with electrochemiluminescence detection. This assay involves a patient specimen reacting with biotinylated and ruthenium-labeled monoclonal antibodies specific to C-peptide, forming a complex bound to streptavidin-coated microparticles. A voltage-induced chemiluminescent emission is measured against a calibration curve to quantify C-peptide levels in serum, plasma, or urine. Similarly, the IBL-America C-Peptide ELISA uses a solid-phase competitive format, leveraging monoclonal antibodies to detect C-peptide in biological samples. These assays are designed for in vitro diagnostic use on automated platforms like the Roche Cobas® e analyzers.

Assays are calibrated against the World Health Organization (WHO) International Reference Reagent (NIBSC code: 84/510) (*C-Peptide of Human Insulin, International Reference Reagent*, n.d.), ensuring traceability. More recently, as the 84/510 WHO C-peptide certified reference material (CRM) is no longer available, companies are now using the newer 13/146 CRM. Currently, only two manufacturers have adopted the newer CRM, while others are at various stages of migration (Rohlfing et al., 2025). Cross-reactivity with proinsulin (<10%) and potential interference from heterophile antibodies or high-dose biotin must also be mitigated to ensure accuracy. The assays' ability to measure C-peptide in multiple matrices (serum, plasma, urine) enhances their clinical utility.

Technical Performance Specifications

Performance specifications for C-peptide assays include sensitivity, specificity, precision, detection limits, and measurement range. However, studies indicate variability in assay performance, particularly at low concentrations, with only 12% of publications reporting detection limits and 11% detailing precision (Dekker et al., 2022; Jones & Hattersley, 2013).

Standardization remains a challenge. To address this, the C-peptide Standardization Committee, organized by the NIDDK in 2002, advocates for metrologically traceable reference measurement procedures, such as isotope dilution-mass spectrometry, to harmonize results across platforms (Little et al., 2017). However, as recently reported, current assays consistently tend to overestimate C-peptide levels across the entire range, though the degree of overestimation varies (Rohlfing et al., 2025). As mentioned above, the recent establishment of a new WHO International Standard (13/146) (WHO Expert Committee on Biological Standardizatio, 2015) aims to improve calibration and comparability.

Conclusion

C-peptide assays are vital diagnostic tools with advanced technical characteristics, but variability in performance and standardization poses some challenges, making the standardization of the assay a mandatory prerequisite for use of C-peptide as a surrogate endpoint in registrational clinical studies. Ongoing efforts to harmonize assays through CRM and standardized protocols are critical for ensuring reliable clinical outcomes. Manufacturers should provide comprehensive validation data to support assay accuracy and reproducibility.

- C-peptide Standardization Home Page; https://cpeptide.org/
- NIDDK C-peptide Standardization Committee: Randie Little (Chair, University of Missouri), Kuanysh Kabytaev (Co-chair, University of Missouri), William Hagopian (University of Washington), Andy Hoofnagle (University of Washington), Paulo Pozzilli (Campus Bio-Medico University of Rome, Italy), Robert Wielgosz (Bureau International des Poids et Mesures, , Sèvres Cedex, France), Beena Alkokar (NIH/NIDDK Liaison), Salvatore Sechi (NIH/NIDDK Liaison)

Appendix D. Summary Table of Clinical Trials in New-Onset T1D

Note, not all studies are included in the TOMI-T1D dataset. TOMI status is noted as Y (included) or N (not included)

Trial Name	Age Range	C-peptide Result	HbA1c Result	Insulin Use	References
T1DAL Study (Alefacept) Anti-CD2 NCT00965458 TOMI: Y	12–35 years	Alefacept group had a mean increase of 0.015 nmol/l (95% CI -0.080 to 0.110) in the 2-hr C-peptide AUC at 12 months whereas the placebo group had a mean decrease of 0.115 nmol/l (95% CI -0.278 to 0.047	At 12 months, alefacept group had a mean HbA1c of 6.9% vs. 7.2% placebo (p=0.75; not significant).	Insulin use at 12 months was lower in the alefacept vs. placebo group (0.36 vs. 0.48 units/kg/day, respectively, p=0.02)	Lancet Diabetes Endocrinol. 2013 Dec;1(4):284-94. doi: 10.1016/S2213-8587(13)70111-6.
T1GER Study (Golimumab) Anti-TNFα NCT02846545 TOMI: Y	6–21 years	At week 52, the 4-hourC-peptide AUC was 0.64±0.42 nmol/L in the golimumab group and 0.43±0.39 nmol/L in the placebo group (P<0.001)	At 52 weeks HbA1c in the golimumab group was 7.3±1.5% and the placebo group vs. 7.6±1.2% in placebo (p=0.80)	Insulin use at week 52, was lower in the golimumab group (0.51 U/kg/day per day) than in the placebo group (0.69 U/kg/day; p=0.001)	N Engl J Med. 2020 Nov 19;383(21):2007-17. doi: 10.1056/NEJMoa2006136.
TN09 (Abatacept) CTL4-Ig NCT00505375 TOMI: Y	6–45 years	At 24 months, abatacept group had geometric mean 2-hour C-peptide AUC of 0.375 nmol/L (95% CI, 0.290–0.465) vs. placebo of 0.266nmol/L (95% CI, 0.172–0.368), p=0.0022.	The abatacept group had a lower adjusted mean HbA1c than the placebo group (for all time points, including baseline, in the aggregate, p=0·002)	Insulin doses in the two groups at 24 months were similar (p=NS)	Lancet. 2011 Aug 6;378(9790):412-9. doi: 10.1016/S0140-6736(11)60886-6.
AbATE (Teplizumab) Anti-CD3 NCT00129259 TOMI: Y	8–30 years	At 24 months, teplizumab group had mean 2-hour C-peptide AUC decline of -0.28 nmol/L (95% CI, -0.36 to -0.20) vs. -0.46 nmol/L control (95% CI, -0.57 to -0.35), p=0.002. Absolute C-peptide AUC at 24 months was 0.39nmol/L in the teplizumab group and 0.19 nmol/L in the control	There was not a significant difference in the HbA1c levels in the drug and control groups (P = 0.093) over the 24-month study,	The drug-treated group used significantly less insulin to achieve this level of glycemic control (P = 0.036. Exact values were not stated.	Diabetes. 2013 Nov;62(11):3766-74. doi: 10.2337/db13-0345.

PROTÉGÉ (Teplizumab) Anti-CD3 NCT00385697 TOMI: Y	8-35	Median change in AUC of C-peptide from baseline (nmol/L per min; IQR). Full dose:−0·06 (−0·25 to 0·12); low dose:−0·13 (−0·33 to 0·01); 6-d full dose:−0·08 (−0·31 to 0·11); Placebo: −0·14 (−0·30 to 0·02); P= 0·046	There was not a significant difference in the HbA1c levels in the drug and control groups	There was not a significant difference in daily insulin use between the drug and control groups	Lancet. 2011 Aug 6;378(9790):487-97. doi: 10.1016/S0140-6736(11)60931-8.
START Antithymocyte globulin NCT00515099 TOMI: Y	12–35 years	At 12 months, no significant difference in 2-hour C-peptide AUC between ATG and placebo (p=0.896).	At 12 months, no significant difference in HbA1c between ATG and placebo (p=0.157); exact values not explicitly reported.	There was no difference in exogenous insulin use between the ATG and placebo groups ($p = 0.136$	Diabetologia. 2016 Jun;59(6):1153-61. doi: 10.1007/s00125-016-3917-4.
Buffalo Study (Etanercept) TNF inhibitor: p75 TNF receptors fused to hu Fc-IgG NCT00730392 TOMI: N	7–18 years	At 24 weeks, etanercept group had mean 2-hour C-peptide AUC increase of 39% (3.9 ng/mL·h vs. 3.1 ng/mL·h baseline, p<0.05); placebo decreased 20% (3.6 ng/mL·h vs. 4.7 ng/mL·h baseline, P<0.05).	At 24 weeks, HbA1c was lower in the etanercept group (5.91 +/- 0.5%) compared with that in the placebo group (6.98 +/- 1.2%; P < 0.05)	Change in insulin does at week 24 showed a mean decrease of 18% in the etanercept group compared with a mean increase of 23% in the placebo group ($P <$ 0.05). Exact values were not stated.	Diabetes Care. 2009 Jul;32(7):1244-9. doi: 10.2337/dc09-0054.
CLVer (Verapamil) calcium channel blocker NCT04233034 TOMI: N	8–17 years	In the verapamil group, the mean C-peptide area under the curve was 0.66 nmol/L at baseline and 0.65 nmol/L at 52 weeks compared with 0.60 nmol/L at baseline and 0.44 nmol/L at 52 weeks in the placebo group (adjusted between-group difference, 0.14 nmol/L [95% CI, 0.01 to 0.27 nmol/L]; P = .04	At 12 months, verapamil group had mean HbA1c of 6.6% vs. 6.9% placebo adjusted (between-group difference, −0.3% [95% CI, −1.0% to 0.4%])	In the verapamil group, the total insulin dose was 0.74 units/kg/d at baseline and 0.65 units/kg/d at 52 weeks compared with 0.64 units/kg/d and 0.74 units/kg/d, respectively, in the placebo group (mean between-group difference at 52 weeks, −0.12 units/kg/d [95%	JAMA. 2023 Mar 28;329(12):990-9. doi: 10.1001/jama.2023.2064.

				CI −0.30 to 0.05 units/kg/d]).	
Anti-NNC0114-0006 (anti-IL21)/Liraglutide Trial NCT02443155 TOMI: Y	18–46 years	At 54 weeks, the decrease in MMTT-stimulated C-peptide concentration from baseline to week 54 was significantly smaller with combination treatment (0·90, 10% decrease; estimated treatment ratio 1·48, 95% CI 1·16–1·89; p=0·0017), compared with placebo (ratio to baseline 0·61, 39% decrease), but not with anti-IL-21 alone (1·23, 0·97–1·57; p=0·093) or liraglutide alone (1·12, 0·87–1·42; p=0·38)	At 54 weeks, all active treatments (anti-IL21/liraglutide, anti-IL21, liraglutide) had -0.50% decrease in HbA1c vs. -0.10 placebo, not significant; exact values not explicitly reported.	In the combination arm, total daily insulin dose decreased from baseline to week 54 by 12% (0·04 U/kg; compared with placebo (dose increase of 28%; 0·09 U/kg; p=0·0006)	Lancet Diabetes Endocrinol. 2021 Apr;9(4):212-24. doi: 10.1016/S2213-8587(21)00019-0.
TN05 Rituximab Trial (anti-CD20) NCT00279305 TOMI: Y	8–40 years	At 12 months, rituximab group had mean 2-hour C-peptide AUC of 0.565 nmol/L (95% confidence interval [CI], 0.50 to 0.63) vs. 0.475 nmol/L (95% CI, 0.39 to 0.55) placebo (p=0.03).	At 12 months, rituximab group had mean HbA1c of 6.76% ± 1.24% vs. 7.00% ± 1.30% placebo (p<0.001).	At 12 months, rituximab group required lower doses of insulin; 0.39±0.22 U/kg of body weight vs. 0.48±0.23 U/kg in placebo (P<0.001)	N Engl J Med. 2009 Nov 26;361(22):2143-52. doi: 10.1056/NEJMoa0904452.
TN19 Low-Dose ATG/GCSF Trial NCT02215200 TOMI: Y	12–45 years	At 12 months mean AUC C-peptide was significantly higher in subjects treated with ATG (0.646 nmol/L) versus placebo (0.406 nmol/L) (*P* = 0.0003) but not in those treated with ATG/GCSF (0.528 nmol/L) versus placebo (*P* = 0.031)	HbA1c was significantly reduced at 1 year in subjects treated with ATG and ATG/GCSF, *P* = 0.002 and 0.011, respectively. Exact values were not stated.	There were no statistically significant differences in insulin use between either experimental treatment group or the placebo group. Exact values were not stated.	Diabetes Care. 2018 Sep;41(9):1917-1925. doi: 10.2337/dc18-0494.
GAD-Alum Trial (Diamyd Phase 3) NCT00723411 TOMI: N	10–20 years	The stimulated C-peptide level at 15 months did not differ significantly between the combined active-drug groups and the placebo group (P=0.10)	At 15 months, no significant difference in HbA1c between GAD-alum and placebo (p=0.64); exact values not explicitly reported.	At 15 months, no significant difference in daily insulin dose between GAD-alum and placebo (p=0.64); exact values not	N Engl J Med. 2012 Feb 2;366(5):433-42. doi: 10.1056/NEJMoa1107096.

				explicitly reported.	
TN08 GAD-Alum Trial NCT00529399 TOMI: Y	3-45 years	At 1 year, the 2-h AUC of C-peptide, adjusted for age, sex, and baseline C-peptide value, was 0·412 nmol/L (95% CI 0·349–0·478) in the GAD-alum group, 0·382 nmol/L (0·322–0·446) in the GAD-alum plus alum group, and 0·413 nmol/L (0·351–0·477) in the alum group.	HbA1c did not differ between groups	Insulin dose did not differ between groups	The Lancet, Volume 378, Issue 9788, 319 – 327. doi: 10.1016/S0140-6736(11)60895-7
PROTECT Study (Teplizumab) Anti-CD3 NCT03875729 TOMI: N	8–17 years	Patients treated with teplizumab had significantly higher stimulated C-peptide levels than patients receiving placebo (111 patients) at week 78 (least-squares mean difference, 0.13 nmol/L; 95% confidence interval [CI], 0.09 to 0.17; P<0.001)	At 78 weeks, teplizumab group had mean HbA1c of 6.97% vs. 7.07% placebo (difference -0.10%, not significant).	At week 78, the estimated mean daily insulin dose was 0.46U/kg in patients treated with teplizumab and 0.59 U/kg in those receiving placebo (difference, 0.13 units per kilogram per day [95% CI, –0.28 to 0.02],	N Engl J Med. 2023 Nov 2;389(18):1672-84. doi: 10.1056/NEJMoa2308743.
BANDIT Study (Baricitinib) Janus kinase (JAK) inhibitor ACTRN12620000239965 TOMI:N	10–30 years	The median of the mixed-meal–stimulated mean C-peptide level at week 48 was 0.65 nmol per liter per minute (interquartile range, 0.31 to 0.82) in the baricitinib group and 0.43 nmol per liter per minute (interquartile range, 0.13 to 0.63) in the placebo group (P=0.001)	At week 48, the mean HbA1c level was 7.0% (95% CI, 6.6 to 7.4), in the baricitinib group and 7.5% (95% CI, 51.9 to 63.9), in the placebo group, similar to baseline.	At week 48, the mean daily insulin dose was 0.41 U/kg/day (95% CI, 0.35 to 0.48) in the baricitinib group and 0.52 U/kg/day (95% CI, 0.44 to 0.60	N Engl J Med. 2023 Dec 7;389(23):2140-50. doi: 10.1056/NEJMoa2306691.
Ustekinumab Trial Anti-IL12/23 ISRCTN 14274380 TOMI:N	12–18 years	At 12 months, (ustekinumab 0.45 nmol per liter per minute versus placebo 0.30 nmol per liter per minute, geometric ratio of ustekinumab:placebo 1.49 (95% confidence interval (CI) 1.08, 2.06); P = 0.02)	No difference was seen in HbA1c between the groups (mean difference between Ustekinumab and placebo at week 52 = −0.83, 95% CI of the	No difference between the groups after adjustment for baseline factors (mean difference between groups at week 52 = 0.04, 95% CI of the difference = −0.	Nat Med **30**, 2657–2666 (2024). doi.org/10.1038/s41591-024-03115-2

			difference = −7.2, 5.55, P = 0.15	13, 0.21, P = 0.38)	
Imatinib Trial tyrosine kinase inhibitor NCT01781975 TOMI:Y	18–45 years	The adjusted mean difference between the imatinib and placebo-treated groups in 2-hour C-peptide AUC in response to an MMTT at 12 months was 0·0946 (90% CI: −0·00279, 0·191) (p=0·048, 1-tailed test)	HbA1c trended lower in the imatinib than placebo group during the active treatment phase, with the greatest difference in groups at 3 months (mean difference −0·422%, [95% CI: −0·772, −0·0676]	Insulin use trended lower in the imatinib group compared to placebo at the initial assessment at 3 months and persisted through the 6-mo treatment period (at 6 months, mean difference −0·137 units/kg, [95% CI: −0·260, −0·0458]), with no statistically significant difference thereafter	The Lancet Diabetes & Endocrinology. 2021, 9(8), 502-514. doi:10.1016/S2213-8587(21)00139-X
Tocilizumab Trial (EXTEND) Anti-IL6 NCT02293837 TOMI: Y	6–17 years	At 12 months, no significant difference in 2-hour C-peptide AUC between tocilizumab and placebo	At 12 months, no significant difference in HbA1c between tocilizumab and placebo	No significant differences were seen between treatment arms with respect to average total daily insulin usage	Diabetes Care. 2020 Jul;43(7):1480-8. doi: 10.2337/dc19-2516.
TN14/AIDA Canakinumab/ Anakinra Trials Anti-IL-1β/IL-1Ra NCT00947427 NCT00711503 TOMI: N, N	6–45 years	The difference in C peptide area under curve between the canakinumab and placebo groups at 12 months was 0·01 nmol/L (95% CI −0·11 to 0·14; p=0·86), and between the anakinra and the placebo groups at 9 months was 0·02 nmol/L (−0·09 to 0·15; p=0·71).	Percentages of HbA1C were similar between canakinumab-treated and placebo-treated participants at 1 year (p=0·76)	At 12 months, no significant difference in insulin dose at 1 year between groups (p=0·53)	Lancet. 2013 Jun 1;381(9881):1905-15. doi: 10.1016/S0140-6736(13)60023-9
TN02 MMF/DZB Trial NCT001001178 TOMI: Y	8–45 years	The geometric mean stimulated C-peptide AUC at 24 months was 0.28 nmol/L (95% CI 0.19–0.37) in those treated with MMF plus DZB, compared with 0.27	All groups achieved A1C of 7.2–7.3% throughout the study	Daily insulin use at 24 months 0.57 units/kg with MMF plus DZB versus 0.61 units/kg among control	Diabetes Care. 2010 Apr;33(4):826-32. doi: 10.2337/dc09-1349

		(0.18–0.37) for their control subjects, *P* = 0.47; and 0.25 (0.14–0.37) in MMF alone treated subjects, compared with 0.23 (0.12–0.35) for their control subjects, *P* = 0.41		subjects (*P* = 0.17); and to 0.65 units/kg with MMF alone versus 0.62 units/kg among control subjects (*P* = 0.68)	
ExTOD Exercise to Preserve β-cell function ISRCTN91388505 TOMI: Y	16-60	Estimated mean C-peptide AUC from fully adjusted model showed no difference between the intervention and control group	No difference in mean HbA1c between groups at 6 or 12 months	No significant difference in insulin use between groups at 6 or 12 months	Diabet Med. 2017 Nov;34(11):1521-1531. doi: 10.1111/dme.13439. Epub 2017 Sep 14. PMID: 28905421. doi: 10.1111/dme.13439
GSK-ALB Albiglutide NCT02284009 TOMI: Y	18-30	mean (s.d.) change from baseline to week 52 in MMTT-stimulated 2-h C-peptide AUC was -0.16 nmol/L (0.366) with placebo and -0.13 nmol/L (0.244) with albiglutide. For the primary Bayesian analysis (including prior study data) the posterior treatment difference (95% credible interval) was estimated at 0.12 nmol/L (0-0.24); P=0.097	No significant difference in mean HbA1c	No significant difference in mean daily insulin use	J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa149. doi: 10.1210/clinem/dgaa149.
RETAIN Alpha-1-antitrypsin NCT01183468 TOMI:Y	8-35	At week 52, adult cohort the mean (SD) for the C-peptide 2-h mAUC of the MMTT was 0.73 (0.60) pmol/mL [2.20 (1.82) ng/mL] which represented a mean (SD) rise from baseline of +0.013 (0.43) pmol/mL [+0.04 (1.30) ng/mL]. In the pediatric cohort at week 52, the actual C-peptide two-hour mAUC was 0.53 (0.49) pmol/mL [1.60 (1.48) ng/mL], which was a mean (SD) change from baseline of −0.19 (0.41) pmol/mL [−0.58 (1.23) ng/mL]. Study was open label	During the first 52 weeks, mean HbA1c levels generally remained in the range 6.5–7.5% (48–58 mmol/mol),	Mean daily insulin use generally remained in the range 0.2–0.4 U/kg/day for both cohorts during the first 12 months, although the pediatric cohort tended to have a higher mean insulin use than the adult cohort	Pediatr Diabetes. 2018 Aug;19(5):945-954. doi: 10.1111/pedi.12660.

JAEB Effect of metabolic control on T1D progression NCT00891995 TOMI-Y	6-45	No difference in preserving β-cell function compared with current standards of care	N/A	N/A	Krischer, Jeffrey (2015). Effect of Metabolic Control at Onset of Diabetes on Progression of Type 1 Diabetes (TN12) (Version 1) [Dataset] NIDDK Central Repository. https://doi.org/10.58020/hqfv-a985

Appendix E: Summary points describing Univariate Models of C-Peptide and HbA1c Used to Generate "Number Needed to Recruit" for Table 3

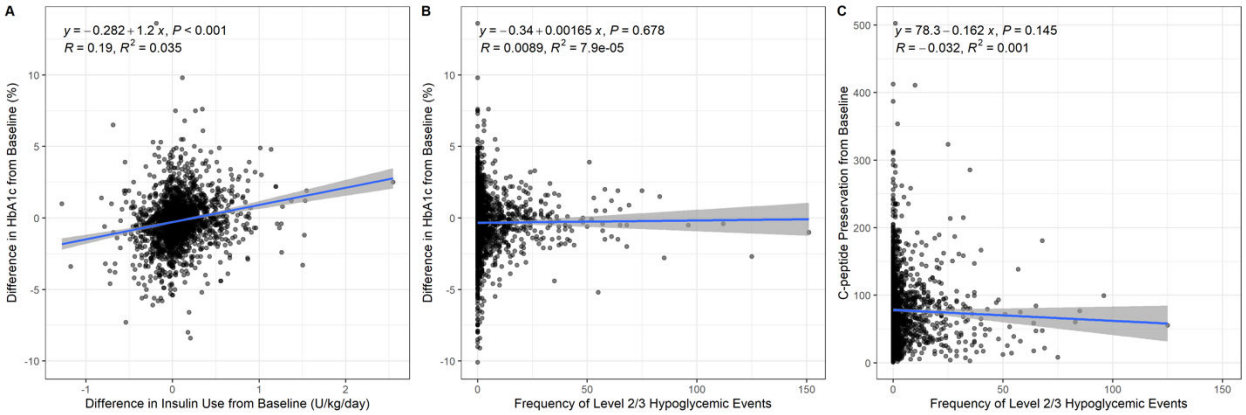
C Peptide Placebo Univariate Model Summary Points:

C-peptide model was developed using the 2-hour C-peptide AUC from the MMTT. Data was log-transformed to prevent negative predictions. A sigmoidal Emax model best described the trajectory of C-peptide progression. Significant covariates that are reflected in the clinical trial simulation tool include baseline BMI Z-score, age and C-peptide. Visual predictive checks (VPCs), with a training dataset utilizing 80% of the data and a validation dataset using the other 20% of the data, demonstrate good fit with predicted and observed data falling well within the 95% confidence intervals.

HbA1c Placebo Univariate Model Summary Points:

HbA1c data was log-transformed. The model was trained and validated using an 80/20 data split. Stepwise covariate model building was used to test the following covariates: baseline (HbA1c, age, BMI, disease duration), sex, race, ethnicity, and HLA genotypes. HbA1c was best described by a sigmoidal Emax equation with an exponential function to describe the honeymoon phase dip in HbA1c. Baseline age was the only predictor of HbA1c. Model performance was guided by standard goodness-of-fit measures and VPCs. VPCs on the training and validation dataset showed good performance.

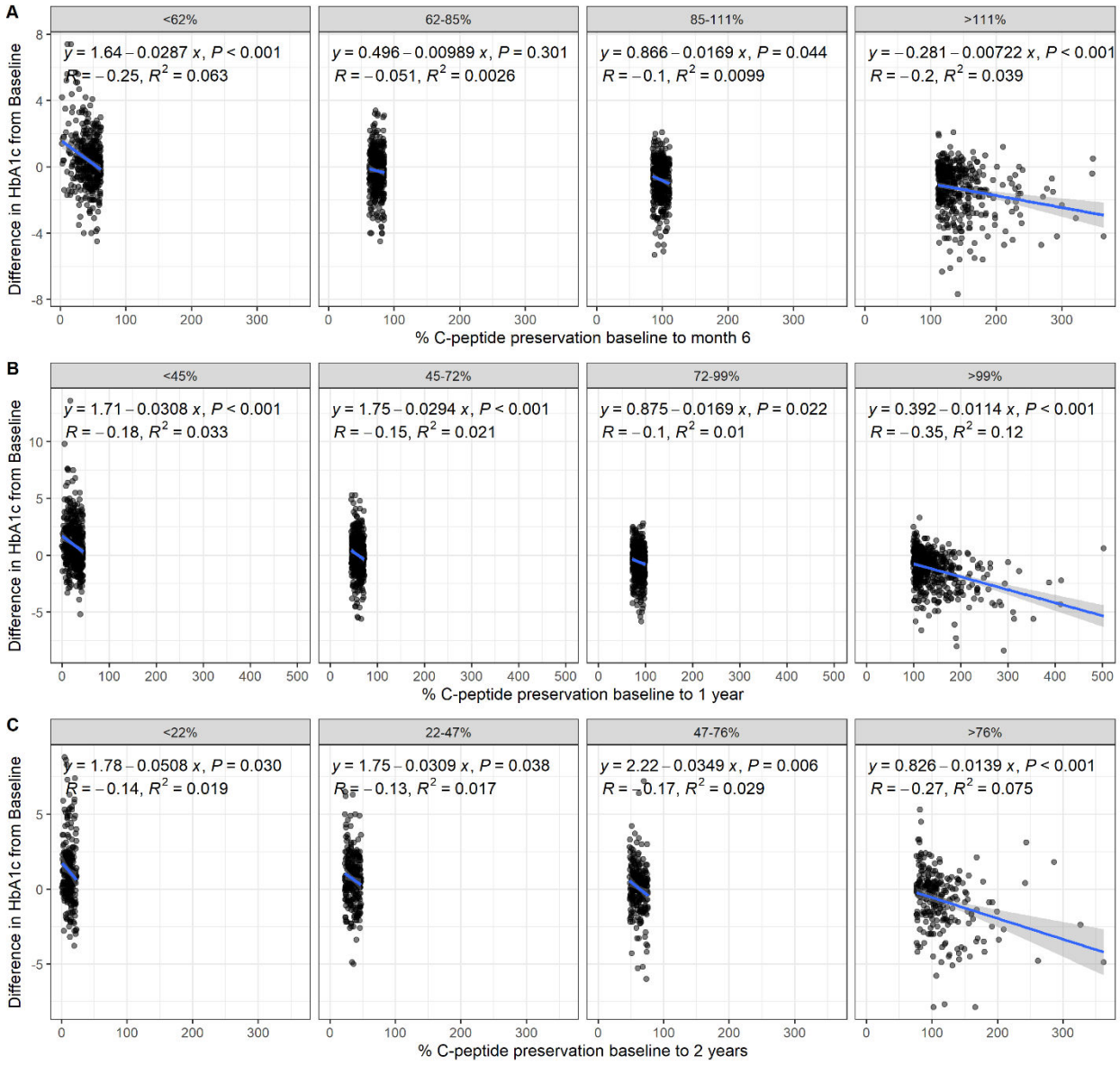
Appendix F: Supplementary Figures



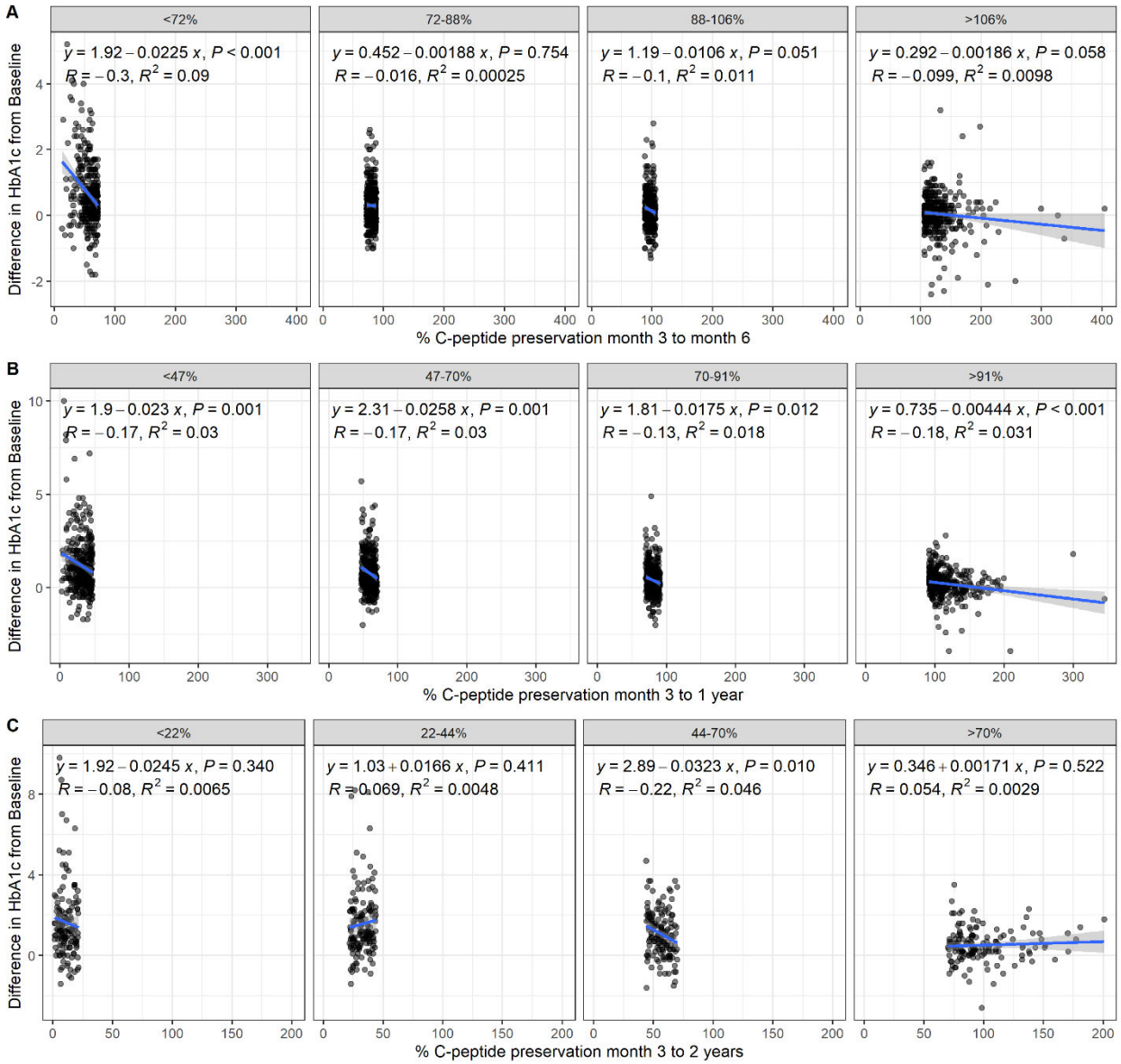
Supplementary Figure 1. Correlations with insulin use and frequency of hypoglycemia.

Correlation between (A) change in HbA1c and change in insulin, (B) change in HbA1c and cumulative frequency of hypoglycemic events and (C) C-peptide preservation and cumulative frequency of hypoglycemic events at 1 year. Blue line represents the linear regression with 95% confidence interval. R value represents Pearson's correlation coefficient.

Note: while hypoglycemia data is plotted for the sake of completeness, caution is urged in interpretation. There was substantial variation between studies in how hypoglycemia was recorded. The hypoglycemic data were non-standardized with some trials capturing home capillary blood glucose readings in diaries, while others used participants recall of hypoglycemic events. Because of this, the number of hypoglycemic events ranged per participant ranged between 0 and 253 and many events were most likely missed given the scarcity of continuous glucose monitoring data. Overall, there were few hypoglycemic events and a wide variation in numbers of recorded events among studies.

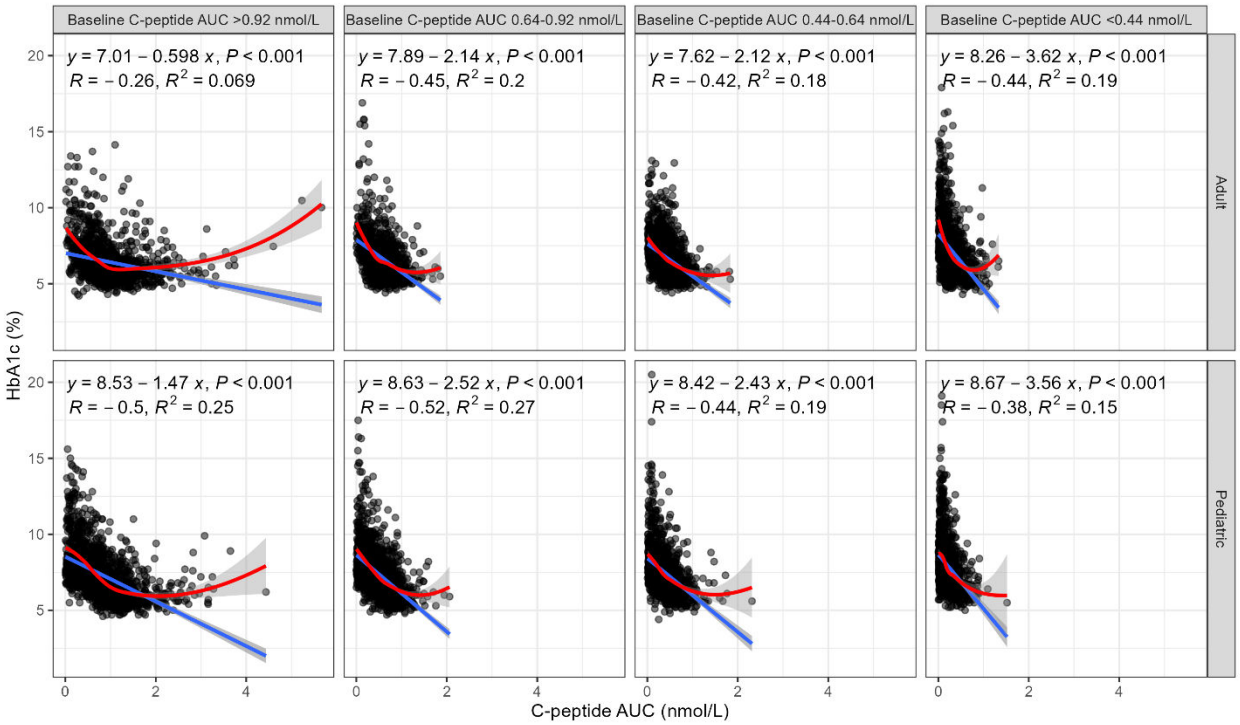


Supplementary Figure 2. Individual level correlations between changes in HbA1c and percent of C-peptide preservation stratified by C-peptide preservation quartiles.
Individual correlations from baseline to month 6 (A), 1 year (B), 2 years (C) stratified by C-peptide preservation quartiles as previously determined (Taylor et al., 2023). Black dots represent an individual represented in the TOMI-T1D database. Blue lines represent the linear regression with 95% confidence intervals. R values represent the Pearson correlation coefficient



Supplementary Figure 3. Individual correlations between changes in HbA1c and percent of C-peptide preservation from study month 3 to month 6, year 1 and year 2 stratified by C-peptide preservation quartiles.

Individual correlations from month 3 to month 6 (A), 1 year (B), 2 years (C) stratified by C-peptide preservation quartiles as previously determined (Taylor et al., 2023). Black dots represent an individual represented in the TOMI-T1D database. Blue lines represent the linear regression with 95% confidence



Supplementary Figure 4. Correlation between HbA1c and C-peptide stratified by baseline C-peptide and age.

Correlation between HbA1c and C-peptide AUC in individuals across all available timepoints stratified by quartiles of C-peptide at baseline and age. Blue line represents the linear regression, and red lines represent LOESS curves 95% confidence intervals for each indicated by shading. The slope equation, significance, R value (Pearson's correlation coefficient) and R^2 for the linear regression are shown at upper left of each panel

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