Introduction:

On June 15 and 16, 2021, the Critical Path Institute (C-Path) hosted a two-day public workshop titled “Design of Clinical Trials in New-Onset Type 1 Diabetes: Regulatory Considerations for Drug Development”. C-Path is a not-for-profit 501(c)3 organization that operates as a trusted and neutral third-party that convenes pre-competitive public-private partnerships. These collaborations include patient advocates, industry, academicians, clinicians, regulators, and others to accelerate and enhance medical product development. C-Path leverages its expertise in regulatory science, data science, quantitative methodologies and modeling, biomarkers, and clinical outcome assessments to put forth novel solutions that meet pressing unmet drug development needs.

This workshop was held in collaboration with the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and had two primary objectives:

1. Provide a virtual workshop environment for type 1 diabetes drug developers, researchers, clinicians, patient organizations, and regulators to examine clinical trial design and regulatory considerations of drug development for new-onset T1D
2. Discuss amongst the T1D community the use of C-peptide as a primary endpoint in registration studies of therapeutic agents in new-onset T1D

A workshop planning committee was convened consisting of subject matter experts from FDA (CDER and CBER), EMA, INNODIA, TrialNet, and JDRF. The full workshop agenda is seen below.

In total, the workshop included 27 speakers or panelists from more than 15 organizations, and featured patient and caregiver perspectives during a roundtable discussion on clinically meaningful measures. The workshop was well attended with approximately 200 people attending virtually each day.

Recordings of the meeting’s proceedings are publicly available, and a summary recap of the meeting’s proceedings is provided here.

The presentations given by FDA employees (including their participation in panel sessions) reflect the views of the presenter and should not be construed to represent FDA’s views or policies.

Design of Clinical Trials in New-Onset Type 1 Diabetes: Regulatory considerations for drug development Day 1			
Time (EST)	**Title**	**Presenter**	**Time (minutes)**
10:00	**Welcoming Remarks and Housekeeping**	Inish O'Doherty, C-Path	5
10:05	**FDA Introductory Remarks**	Ilan Irony, FDA	5-10
10:15	**Patient Perspective Opening Remarks: Unmet Need**	Aaron Kowalski, JDRF	10
10:25	**Session I: Regulatory Framework for Clinical Investigations in New/Recent Onset T1D**		
10:25	FDA perspective	Kristen Pluchino, FDA	20
10:45	EMA perspective	Peter Mol, EMA	20
11:05	**Break: 20 minutes**		
11:25	**Session II: Scientific Framework: The rationale for C-peptide preservation and use as a clinical trial endpoint**		
11:30	C-Peptide as Primary Endpoint & Natural History	Kevan Herold, Yale University	30
12:00	Islet Transplantation: Relationship of C-peptide and clinically meaningful outcomes	Michael Rickels, University of Pennsylvania	20
12:20	Differential Rates of C-Peptide Decline	Carla Greenbaum, Benaroya Research Institute	20
12:40	C-Peptide as a Primary Endpoint	Stephen Gough, Novo Nordisk	20
13:00	Panel Discussion	**Moderators:** Session II co-chairs **Panelists:** Session II speakers + Mark Peakman, Lisa Yanoff, Peter Mol	40
13:40	**Day 1 Closing Remarks**	Inish O'Doherty, C-Path	5

Design of Clinical Trials in New-Onset Type 1 Diabetes: Regulatory considerations for drug development Day 2			
Time (EST)	**Title**	**Presenter**	**Time (minutes)**
10:00	**Day 2 Opening Remarks**	Inish O'Doherty, C-Path	10
10:10	**Session III: Establishing/Confirming Clinical Benefit**		
10:15	Perspective from people living with T1D: Clinically meaningful measures	Chantal Mathieu, INNODIA, Marjana Marinac, JDRF, Kyle Jacques Rose, INNODIA PAC, Melissa Schwaber, Caregiver	30
10:45	FDA Perspective: Clinical endpoints and validated surrogates	Lauren Wood Heickman, FDA	10
10:55	EMA Perspective: Clinical endpoints and validated surrogates	Carine de Beaufort, EMA	10
11:05	General considerations for trial design for confirmatory endpoints	Allison Goldfine, Novartis Institutes of Biomedical Research	15
11:20	Additional Clinical Outcomes: Considerations and current limitations	Joe Hedrick, Janssen	15
11:35	Panel Discussion	**Moderators:** Session III co-chairs **Panelists:** Session III speakers	40
12:15	**Break: 20 Minutes**		
12:35	**Session IV: Overall Issues of Study Design**		
12:40	Ethical Considerations of Trial Design	Donna Snyder, FDA	20
13:00	Statistical Considerations for Trial Design and Feasibility	Tee Bahnson, Benaroya Research Institute	15
13:15	Considerations for Trial Design and Feasibility	Regine Bergholdt, Novo Nordisk	15
13:30	Final Panel Discussion/Open Comment	**Moderators:** Session IV co-chairs **Panelists:** Session IV speakers + Francisco Leon, Peter Mol, Carine de Beaufort, Lisa Yanoff, Jackson Burton	60
14:30	**Workshop Closing Remarks**	Lisa Yanoff, FDA	5

Opening Remarks:

After brief introductory remarks by C-Path, the workshop was opened with FDA (Dr. Ilan Irony) and JDRF emphasizing the unmet needs of people living with T1D. As a chronic auto-immune disorder, T1D is characterized by a progressive auto-immune destruction of insulin producing beta cells. Insulin replacement therapy, the mainstay of T1D treatment, is associated with significant adverse effects, including risk of hypoglycemia, a high burden of day-to-day care, and fails to help most patients achieve treatment goals. Disease modifying therapies (DMTs) that change disease progression are not yet available and are greatly needed.

There are several challenges in the development of DMTs, including significant heterogeneity in the rate of T1D progression and a lack of validated endpoints for pivotal trials. Broad collaborations between regulators, drug sponsors, patients, funders, and researchers are needed to bring DMTs to patients.

Session I: Regulatory framework for clinical investigations in new/recent onset T1D

The goal of Session I was to provide a general overview of the regulatory considerations when seeking medical product approval and to discuss important considerations for trial design in the context of new or recent onset T1D. Session I consisted of two speakers, one from FDA/CDER (Dr. Pluchino) and one from EMA (Dr. Mol), who both presented their perspective on their respective Agency's regulatory frameworks. Both Agencies recognized that no DMTs have been approved for use in new-onset T1D, so there is currently no clear direct regulatory precedent established.

In Dr. Pluchino's presentation, surrogate endpoints were defined as a substitute for how a patient feels, functions, or survives, and are not a direct measure of, but instead predict clinical benefit (as opposed to clinical endpoints which directly measure clinical benefit). Surrogate endpoints may be considered "candidate," "reasonably likely," or "validated" surrogate endpoints, depending on the level of evidence available to support their use. Reasonably likely surrogate endpoints (RLSEs) are expected to have a meaningful clinical benefit but have not yet been fully validated. As such, gaps exist when considering their use to support drug approval, as benefits may not be fully quantifiable while risks must still be adequately measured. FDA's Accelerated Approval program exists to allow for drug approval on the basis of a RLSE and is only available for serious or life-threatening conditions. The program provides faster patient access to promising therapies; however, confirmatory post-marketing studies are required to ensure the clinical benefits outweigh the risks. Validated surrogate endpoints, such as HbA1c, can be assessed in lieu of directly measuring the clinical outcome of interest, such as microvascular complications, and can form the basis of full/traditional approval, where no confirmatory studies are required post-approval.

Dr. Pluchino stated that, C-peptide is a biomarker for beta cell function and endogenous insulin secretion, and is 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 RLSE to support Accelerated Approval submissions at FDA/CDER. 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). Analytical assay considerations were also discussed.

Existing EMA guidelines on the treatment or prevention of diabetes mellitus were cited and discussed [1]. As presented at the workshop regarding the preservation of β-cell function, the current draft guideline states the use of C-peptide (likely change from baseline or, if justified, percentage of patients with C-peptide increase above a clinically meaningful threshold) as an endpoint should be accompanied by an established clinically meaningful co-primary endpoint, such as HbA1c, frequency of hypoglycemia, especially severe hypoglycemia, and/or the percentage of patients not requiring insulin or with a relevant reduction in insulin dose. Secondary endpoints should include any of the above if not assessed as co-primary endpoints, plus fasting and post-prandial blood glucose, 24-hour glucose profile, total daily insulin use, and occurrence of diabetic ketoacidosis. The effect on a primary endpoint should be evaluated at one year and sustained for a minimum of two years. Finally, adult populations should be studied first, followed by a step-down approach into younger populations

The EMA presentation also provided further perspective on general trial design considerations, including the use of surrogate endpoints, where the major concern is that an unvalidated surrogate marker does not actually have an anticipated effect on the clinical outcome of interest. Various mechanisms in which EMA serves as enablers of innovation, rather than gatekeepers, were also discussed. EMA's PRIME designation helps to facilitate earlier patient access to life-saving medications by facilitating more dedicated support from regulators including accelerated assessment for promising medications in areas of high unmet needs. Finally, conditional marketing authorization (CMA) can provide a one-year renewable MA, subject to specific obligations, for seriously debilitating diseases or in other scenarios, and requires demonstration of a positive benefit-risk balance, based on preliminary clinical data with the ability to generate comprehensive data post approval, and that "the benefit to public health of the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required". In T1D, as insulin therapy is considered by EMA to be a very good option with a well characterized adverse event profile, it would be difficult to utilize the CMA pathway.

Key takeaways:

- Drs. Pluchino, Irony, and Mol discussed the unmet need for DMTs in T1D, and the use of C-peptide as an endpoint in new-onset T1D trials that may provide meaningful information when considering new product approvals. Additionally, Drs. Pluchino and Moldiscussed that C-peptide as the sole primary endpoint for registration trials is not yet sufficiently validated to support full marketing authorization.
- Dr. Pluchino discussed that CDER supports the use of C-peptide as RLSE in submissions to the Accelerated Approval pathway, wherein a product's effects on a clinically meaningful measure to patients is demonstrated in a required post-marketing trial.
- EMA indicated full marketing authorization rather than conditional marketing authorization, may be more appropriate for new-onset T1D, given the availability of insulin therapy. EMA encouraged the use of the PRIME designation for new-onset T1D therapies and submissions to the qualification of novel methodologies pathway to qualify the use of C-peptide as a surrogate endpoint.

Session II: Scientific Framework: The rationale for C-peptide preservation and use as a clinical trial endpoint

The goals of Session II were to discuss the current use of C-peptide in new-onset T1D clinical studies, the quantitative relationship between β-cell preservation and clinically meaningfully outcomes, and C-peptide's potential use as a surrogate endpoint for the basis of medical

product approval decisions. Session II included a series of three talks from researchers presenting a) the biology of islet function and insulin secretion in the context of T1D, b) the relationship between C-peptide and clinically meaningfully outcomes by examining the biomarker's use in islet transplantation, and c) the heterogeneity that underpins differential rates of C-peptide decline in various populations and methods to address this heterogeneity in clinical studies. A fourth presentation provided an industry perspective and experiences designing studies that use C-peptide as a primary endpoint. Following these presentations, a panel discussion with each speaker, as well as additional industry and regulator representatives was held.

Data were presented to demonstrate endogenous insulin secretion from β-cells in the islets of Langerhans is not well replicated by exogenously delivered insulin. Preservation of insulin secretory capacity (as measured by C-peptide) is associated with reduced rates of T1D complications, and data from the DCCT and EDIC studies demonstrate that individuals who retain C-peptide (at least 0.2 pmol/mL) have a reduced risk of secondary end organ complications and reduced rates of severe hypoglycemia [2]. Further work in these populations found that C-peptide levels below 0.2 pmol/ml are associated with a reduction in severe hypoglycemia, with relatively higher levels of C-peptide being required for maintenance of glycemic control [3]. C-peptide levels associated with a reduction in hypoglycemia and other complications in the DCCT trial (≥0.2 pmol/mL) are present in more than 90% and 60% of individuals at one- and two-years following diagnosis, respectively [4]. Thus, the benefits of C-peptide preservation on a reduction in hypoglycemia and other complications is unlikely to be demonstrable in short-term clinical studies (i.e., less than four to five years). HbA1c is also unlikely to be useful in new-onset clinical studies because of ethical requirements to maintain HbA1c in all trial subjects according to standards of care. Data were presented indicating that while more C-peptide is associated with better physiologic response to hypoglycemia (as measured by glucagon secretion) and more glucose time-in-range, there is no clear threshold at which these effects are seen [5].

T1D is associated with insulin resistance (an independent risk factor for cardiovascular disease), and data were discussed suggesting iatrogenic hyperinsulinemia, and not hyperglycemia, drives this insulin resistance [6]. Intensive insulin therapy is associated with weight gain, itself a risk factor for cardiovascular outcomes. Reduction in insulin dose should be considered an additional clinically relevant endpoint for clinical studies in T1D, as preservation of endogenous insulin secretion should result in a reduced need for exogenous insulin.

According to presented data, baseline C-peptide levels and rate of change of C-peptide over time show significant variation, with age (higher age is associated with slower rates of decline) and baseline C-peptide level explaining much of the variation in C-peptide decline [1][7]. Cross trial analysis demonstrates consistency in the natural history of C-peptide, and C-peptide at one-year following diagnosis is highly predictable when accounting for age and baseline levels. A quantitative response (QR) metric can be calculated as the difference between predicted and actual C-peptide [8].

Data were presented demonstrating stimulated C-peptide levels following islet transplantation to be associated with reduced glucose variability as measured by continuous glucose monitors (seen as improved percent time in range), and reduction in daily insulin dose [9]. Although this patient population is different than those with new-onset T1D, these data demonstrate the beneficial impact that of reintroduction of functional beta cell mass can have on clinically meaningful outcomes.

Key takeaways:

- Presenters from session II (i.e., researchers, industry representatives) described the existing data correlating C-peptide with clinical outcomes, and agreed that preservation of C-peptide is reasonably likely to result in clinically meaningful benefit to patients. However, further information is required to understand what specific level of C-peptide preservation will yield a quantitative improvement in clinically meaningful outcomes.
- Given the number of patients with residual C-peptide in the first two years following diagnosis, clinical studies that assess hypoglycemia, HbA1C, and various other clinically meaningful outcomes may require large patient populations, challenging the feasibility of studies using classical submission pathways.
- Dr. Yanoff agreed that C-peptide's use as a reasonably likely surrogate endpoint, which can be used as the basis of product approvals through FDA's Accelerated Approval Pathway, is likely to be justified. Accelerated Approval pathway provides a means to demonstrate benefit in the post-marketing setting. Given the natural history of C-peptide is well understood and well characterized, FDA indicated it may be possible to leverage historical controls to streamline clinical trials, however further work needs to be done to assess the acceptability of this approach.
- EMA encouraged the submission of additional evidence in support of C-peptide's use as a surrogate endpoint to the scientific advice working party through the qualification of novel methodologies pathway. Currently, EMA does not consider C-peptide related endpoints alone to be appropriate as primary endpoints of efficacy [1].

Session III: Establishing/confirming clinical benefit

Session III goals were to further discuss means to establish clinical benefit to patients during clinical trials, strengths and limitations of currently acceptable endpoints, and considerations for the use of C-peptide and other potential measures of clinical benefit. Further, Session III highlighted the patient perspective by including a patient and caregiver roundtable discussion on clinically meaningful measures. In addition to the roundtable, Session III included four talks, with speakers from FDA/CDER (Dr. Wood Heickman), EMA, and industry, and a panel discussion with each speaker and patient or caregiver.

The burden for patients living with T1D is extremely high and there are no endorsed means to measure this burden in the context of a clinical trial. Despite access to improved technologies, such as continuous glucose monitors (CGMs) and insulin pumps, and better overall standards of care, the frequency of severe hypoglycemia has not meaningfully changed in decades [10]. Patients and care givers discussed the immense impact and burden glycemic excursion have on day-to-day life. For patients on the panel, insulin management became increasingly burdensome as the disease progressed and insulin requirements increased. While the gold standard for patient impact would be complete insulin independence, modifying the disease process so that endogenous insulin production is maintained for as long as possible provides substantial benefit to patients. Further, reducing the variability and facilitating more consistency in day-to-day insulin requirements would be meaningful.

Dr. Wood Heickman, Dr. De Beaufort, and industry colleagues discussed the regulatory realties of using validated measures of glycemic control. It was acknowledged that measures such a HbA1c and severe hypoglycemia do not adequately describe the glycemic variability described by patients, and there is no patient-reported outcome (PRO) measure validated for regulatory use that adequately captures the burden of diabetes management in new-onset T1D. Thus, currently no PROs are capable of being used as a primary endpoint to inform regulatory

decision making. There was interest in the development of new clinical endpoints and validated surrogate endpoints derived from CGM devices and instruments to capture patient voice.

Dr. Wood Heickman provided commentary on the trial endpoints that are currently acceptable by CDER, namely HbA1c, severe hypoglycemia (Level 3), and potentially <54 mg/dL from finger stick glucometer (Level 2) [11]. The inability of HbA1c to fully describe glycemic variability and the infrequency of severe hypoglycemic events in the new-onset T1D population were acknowledged. To date, reduction of insulin dose on its own has not been considered clinically meaningful by FDA/CDER.

EMA discussed the value of C-peptide as a primary endpoint and emphasized that, on its own, C-peptide is not currently acceptable as the only primary endpoint for approval of new therapies. It was indicated that co-primary endpoints should be assessed at one year following treatment initiation, and the effect should persist for at least two years. Endpoints include insulin independence, improved HbA1c, reduced insulin dose (<0.5 U/kg/day) with adequately controlled HbA1c (<7.5/7.0/6.5%), and potentially others. A comprehensive analysis of all these endpoints would provide an understanding of the extent to which disease progression is meaningfully halted, and may potentially support a DMT's claims in new-onset T1D.

Key takeaways:

- Although C-peptide is a relevant biomarker capable of informing regulatory decisions, it is not yet accepted as a sole primary endpoint in registration studies and currently must be used with established measures of glycemic control, including HbA1c, or hypoglycemia.
- Dr. Wood Heickman discussed that FDA/CDER currently supports the use of C-peptide as a reasonably likely surrogate endpoint as part of the Accelerated Approval program, with confirmation of clinical benefit occurring in the post-marketing setting. EMA indicated C-peptide should be used as a co-primary endpoint with validated measures of glycemic control, as discussed above.
- Frequently, outcomes that are clinically meaningful to patients are not validated for regulatory decisions making. However, there is a strong desire for collaboration amongst the drug development community to translate those measures to the drug development process.

Session IV: Overall issues of study design

Session IV goals were to consider overall issues of study design in new-onset T1D, including ethical considerations for inclusion of pediatric populations and for confirmatory trials, statistical considerations given variability in rates of C-peptide decline, and trial feasibility when using C-peptide or validated endpoints. Session IV included three presentations from FDA/CDER (Dr. Snyder), industry, and academic research perspectives and concluded with a panel discussion including session speakers and others from the regulatory agencies, industry, and research institutes.

Dr. Snyder discussed the basic ethical framework for including pediatric populations in trials and presented an overview of federal guidelines for the inclusion of pediatric subjects in clinical trials [12]. In order for pediatric patients to be included in a clinical trial, for interventions that exceed the minor increase over minimal risk threshold, the child must be offered a prospect of direct benefit. The benefit from study participation must justify the risk and be at least as favorable as any available alternative treatments. The level of evidence required to demonstrate the prospect of direct benefit is not necessarily as great as the level of evidence required for regulatory

approval of a product. For example, in a phase 2 trial, an anticipated change in a surrogate endpoint could be considered to offer a prospect of direct benefit to the participants. These findings could then be used to support the design of a phase 3 trial that could lead to the approval of a drug. At both regulatory agencies, additional considerations include assuring the dose and duration of exposure to a treatment are adequate to expect a beneficial effect. Further, good information about the potential long-term effects and adverse effects of a therapy on pediatric populations would be required.

Additionally, Dr. Snyder discussed challenges and solutions for the use of the Accelerated Approval program at FDA/CDER at a high-level. Important ethical considerations during phase IV confirmatory trials include the selection of control arms. Initially, equipoise exists as there is genuine uncertainty regarding safety and efficacy of the conditionally approved product. However, maintaining equipoise as the product remains on the market can be challenging if benefit is perceived. Sponsors will benefit from discussing their trials with FDA for timely review and feedback. Seeking concurrent scientific advice from EMA may also streamline global development strategies.

As discussed in Session II, heterogeneity in the rate of decline of C-peptide is largely accounted for by age and baseline C-peptide. Data from five clinical studies were used to develop a "Quantitative Response" (QR) metric that predicts one-year C-peptide based on these sources of variability [8]. During the meeting, data from nine studies were presented discussing the utility of the QR metric. The QR metric can provide significant value in clinical trials as the rate of decline and absolute value of C-peptide may not be indicative of actual treatment benefit. The QR metric was discussed to afford more statistical precision by adjusting for the known sources of variability, age and baseline C-peptide. Given the nature of C-peptide decline over time, adaptive clinical trial designs or the use of historical or synthetic control arms could be feasible. Close discussion with regulators, for example by seeking EMA scientific advice is recommended when considering these approaches.

Industry perspective and past learnings were shared regarding scenarios for pivotal clinical trials in new onset T1D. Three scenarios, using HbA1c, hypoglycemia, or C-peptide as primary endpoints, were presented. In one scenario considering HbA1c as a primary endpoint in a phase three study, an expected treatment difference of 0.34% (based on internal Phase 2 data and expected dropout rates) was assessed. To have a minimum of 90% power to demonstrate a significant effect on both HbA1c and C-peptide, 1332 subjects would be required. While HbA1c is clinically relevant, baseline HbA1c is low and variability is high in new onset trials, making HbA1c difficult to use as a primary endpoint. Improvements in background standard of care or the use of CGMs may also provide challenges for detecting differences in clinical studies, as smaller than expected treatment effect differences in HbA1c (e.g., 0.25% instead of 0.5%) leads to large changes in the number of subjects required.

When considering hypoglycemia as a primary endpoint, to have 90% power to demonstrate a significant reduction in hypoglycemia after 2 years (defined as 25% lower rate in a composite measure of level 2 and level 3), 570 subjects would be required. Dr. Yanoff indicated that this composite (level 2 and level 3 hypoglycemia) may be acceptable in future trials, while EMA welcomed further dialogue on this and other potential endpoints through both Sponsor submissions and the Qualification of novel methodologies process. The increasing use of CGMs in routine clinical care must also be considered when considering clinical trial design because use of certain CGMs may reduce hypoglycemia event rates.

Pursuing new means to include C-peptide as a meaningful measure to facilitate future trials, potentially through the use of historical controls or through additional measures that capture clinical meaningfulness, would be valuable for industry and for patients.

Key takeaways:

- For FDA/CDER, the ethical inclusion of pediatric populations in clinical trials requires several key criteria to be met, including that for interventions that exceed the minor increase over minimal risk threshold, that there be a prospect of direct benefit to justify the risk and that that risk be at least as favorable as available alternatives
- Equipoise initially exists during confirmatory trials of conditionally approved products, as there is genuine uncertainty regarding safety and efficacy of the new product, relative to currently available standards of care. However, as confirmatory trials progress, it may be difficult to maintain equipoise as the effects of investigational products are confirmed.
- The rate of decline of C-peptide is highly variable with significant patient heterogeneity. Accounting for known sources of variability, such as age and baseline C-peptide levels, can enhance C-peptide's utility in clinical trials by facilitating use of predictive metrics, like the QR metric, or facilitating use of historical controls to supplement control arm populations.
- Dr. Yanoff noted that CDER may be open to the use of a composite of Level 2 and Level 3 hypoglycemia, as reliance on Level 3 hypoglycemia alone may require unfeasible trials. Further, FDA/CDER considers Level 2 hypoglycemia (<54mg/dL) likely to be acceptable as a clinically meaningful surrogate endpoint that could be used in clinical trials. However, the ultimate clinical benefit should be defined, and considerations for the method of detection (e.g., glucometer versus CGM), should be addressed.
- Given the frequency of severe hypoglycemic events in the new-onset T1D populations and ethical requirements to maintain standard of care target HbA1c levels, clinical trials that include these measures as primary or co-primary endpoints require large trial populations to see potential treatment effects. The incorporation of C-peptide as an acceptable trial endpoint can improve feasibility of new-onset T1D clinical trials.

Citations:

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