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Generalizability of progression risk in the TN-10 trial to a European population with or without a first-degree relative with type 1 diabetes

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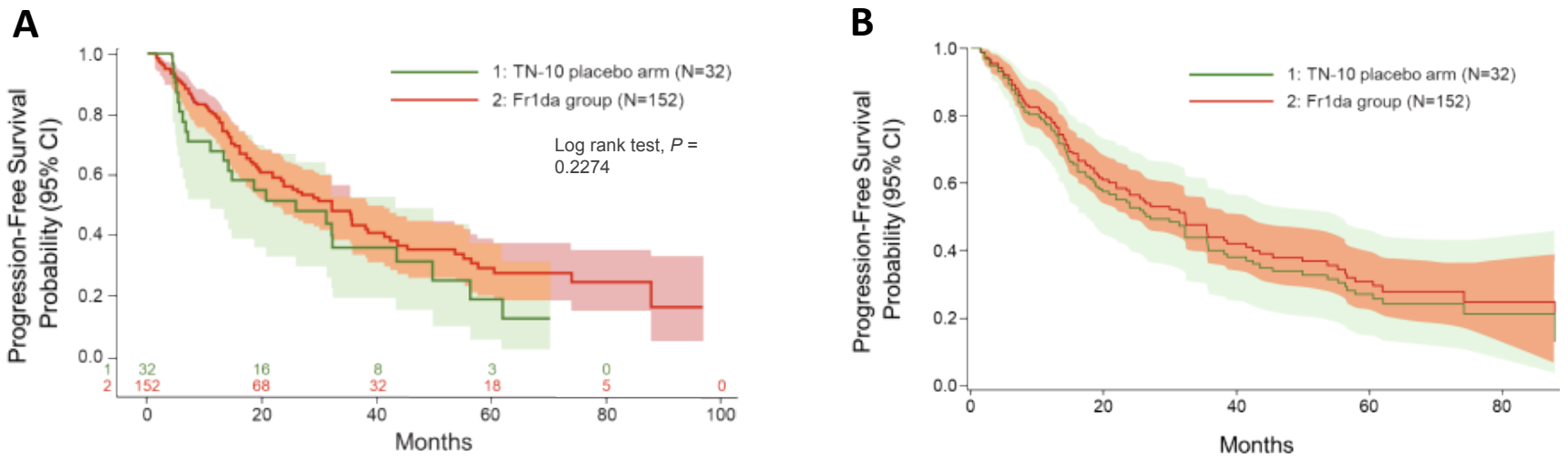
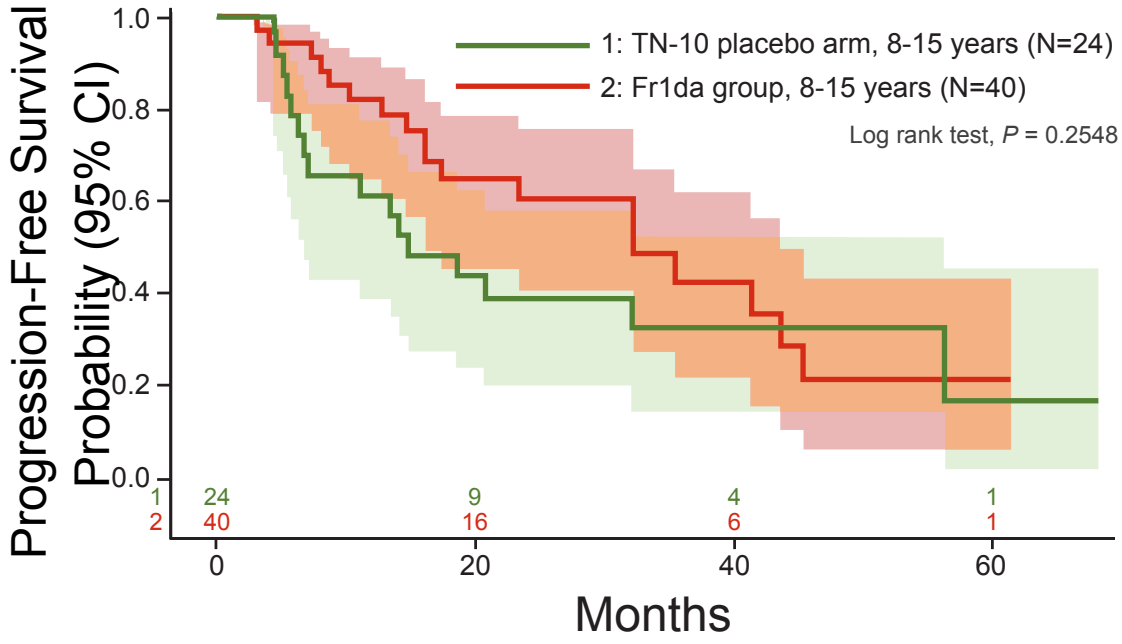

A
Progression-Free Survival Probability (95% CI)
1.0
0.8
0.6
0.4
0.2
0.0
1: TN-10 placebo arm (N=32)
2: Fr1da group (N=152)
Log rank test, P = 0.2274
1 32 16 8 3 0
2 152 68 32 18 5 0
0 20 40 60 80 100
Months
B
Progression-Free Survival Probability (95% CI)
1.0
0.8
0.6
0.4
0.2
0.0
1: TN-10 placebo arm (N=32)
2: Fr1da group (N=152)
0 20 40 60 80
Months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Probability (95% CI)
1.0
0.8
0.6
0.4
0.2
0.0
1: TN-10 placebo arm, 8-15 years (N=24)
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Log rank test, P = 0.2548
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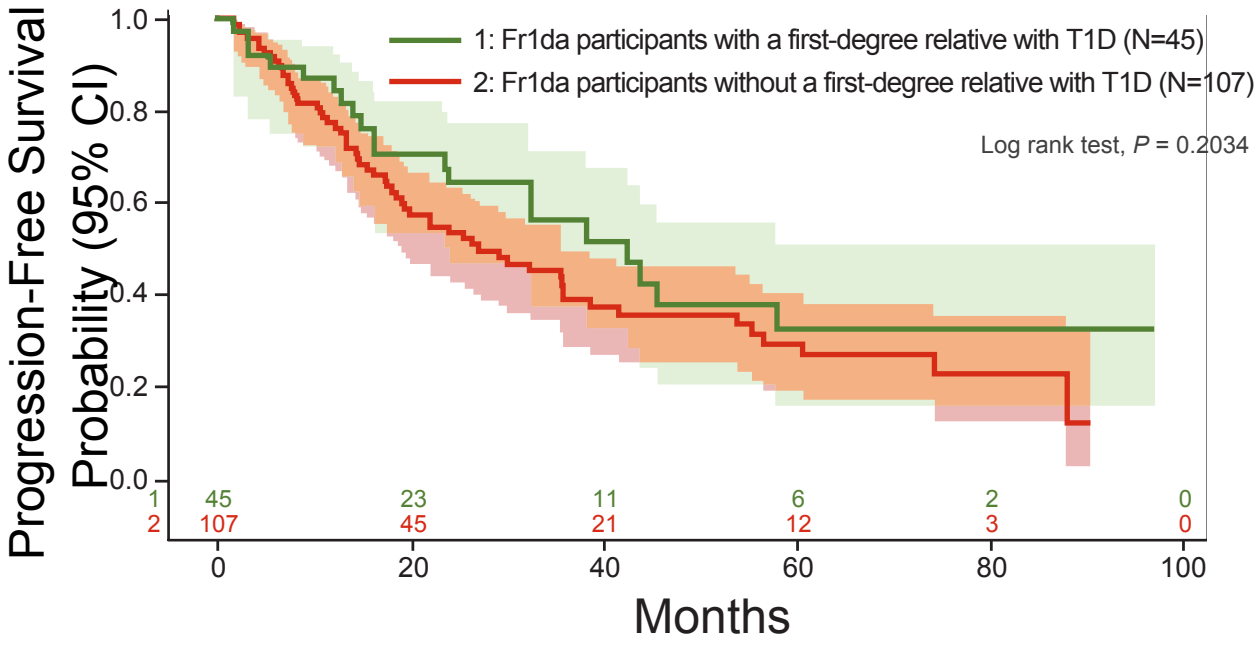
0
20
40
60
Months


Progression-Free Survival Probability (95% CI)
1.0
0.8
0.6
0.4
0.2
0.0
1: Fr1da participants with a first-degree relative with T1D (N=45)
2: Fr1da participants without a first-degree relative with T1D (N=107)
Log rank test, P = 0.2034
1 45 23 11 6 2 0
2 107 45 21 12 3 0
0 20 40 60 80 100
Months

Generalizability of progression risk in the TN-10 trial to a European population with or without a first-degree relative with type 1 diabetes

Short running title: Generalizability of progression risk in TN-10 (45/47 characters including spaces)

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Twitter summary: [200 characters max]

Time to development of symptomatic T1D in the placebo arm of the North American-based TN-10 trial was similar to people in the European-based Fr1da group, with and without relatives with T1D.

Keywords: Type 1 Diabetes, Registries, Progression, North American, European(s), Screening

Word count: (3917/4000 words)

Table count: 1

Figure count: 3

Plain language summary

WHAT IS IT ABOUT?

The TN-10 clinical trial showed that in comparison to treatment with no drug (i.e. placebo), teplizumab can delay the onset of symptomatic type 1 diabetes in a population of individuals with presymptomatic (stage 2) type 1 diabetes mainly from the US and Canada who had a relative with type 1 diabetes. The goal of this study was to learn if the risk of developing symptomatic type 1 diabetes in the TN-10 clinical trial is similar to that in a European population regardless of whether or not they have immediate family members with type 1 diabetes. Researchers assessed and compared the time needed to develop symptomatic type 1 diabetes in individuals treated with placebo in the TN-10 trial with the time needed in a group of individuals from the German population-based screening program, Fr1da. The time to develop symptomatic type 1 diabetes was similar between the TN-10 placebo group and Fr1da group and between individuals in the Fr1da group with and without immediate family with type 1 diabetes.

WHY IS IT IMPORTANT?

The approval of teplizumab by the United States Food and Drug Administration was largely based on findings from the TN-10 trial. The results from this study suggest that population risk of progression from presymptomatic (stage 2) to symptomatic type 1 diabetes is similar between patients in the United States and those in Europe, and between patients in Europe with or without immediate family members with type 1 diabetes.

Abstract

Objective

In the TrialNet 10 (TN-10) trial, teplizumab delayed onset of stage 3 type 1 diabetes in US and Canadian individuals with stage 2 disease who had a relative with type 1 diabetes. Here, the generalizability of the population risk in TN-10 to a European population with or without first-degree relatives (FDRs) with type 1 diabetes was investigated.

Research Design and Methods

This retrospective study used data from participants with stage 2 type 1 diabetes from the TN-10 placebo arm and the Fr1da population-based screening program in Germany (Fr1da group) to investigate time to progression from stage 2 to 3 type 1 diabetes. The study only had sufficient power to detect large differences.

Results

Risk of progression to stage 3 type 1 diabetes was comparable between the TN-10 placebo arm (n=32) and the Fr1da group (n=152; HR=1.3 [95% CI: 0.8-2.1]). Once prognostic factors significantly associated with progression in this study (anti-IA-2 antibodies, HbA1c >5.7%, and 120-minute OGTT) were included in the model, the adjusted HR was 1.1 (95% CI: 0.6-2.1). Fr1da group participants with (n=45) and without (n=107) FDRs with type 1 diabetes had similar time to progression to stage 3. Age-based subanalysis demonstrated minimal impact of age on progression time.

Conclusions

Time to progression to stage 3 appeared similar between the TN-10 placebo arm and the Fr1da group and between participants with and without FDRs with disease. Results suggest progression risk from the TN-10 trial may be generalizable to European populations with or without FDRs with type 1 diabetes.

Article Highlights

- **Why did we undertake this study?**

  Whether risk of progression to type 1 diabetes in the TN-10 trial is generalizable to individuals from Europe with or without relatives with disease was unknown.

- **What is the specific question(s) we wanted to answer?**

  Is time to symptomatic type 1 diabetes development in the North American-based TN-10 placebo group similar to European-based Fr1da group and between individuals with and without relatives with disease?

- **What did we find?**

  Time to symptomatic type 1 diabetes development in the TN-10 placebo group was similar to the Fr1da group and between Fr1da participants with and without first-degree relatives with the disease.

- **What are the implications of our findings?**

  Progression risk from the TN-10 trial may be generalizable to European populations without relatives with type 1 diabetes.

Type 1 diabetes is a significant global health burden that can have detrimental effects on individuals, their caregivers, and health care systems.(1; 2) It is a chronic, progressive disease driven by the autoimmune-mediated destruction of insulin-producing beta cells in the pancreas. Immune mediators that have been shown to contribute to this disease process include autoreactive T cells and B cells and pro-inflammatory cytokines.(3-6) This autoimmune process can begin years prior to the development of the sustained hyperglycemia that is characteristic of clinical type 1 diabetes.(7) Accordingly, the disease process of type 1 diabetes can be stratified into 3 stages. Stage 1 is defined by the presence of two or more islet autoantibodies with normal blood glucose levels (normoglycemia).(8; 9) In stage 2, two or more islet autoantibodies and impaired glucose tolerance (dysglycemia) are present.(8; 9) Stage 3 is defined by clinical symptoms typically associated with diabetes and the presence of sustained hyperglycemia.(8; 9)

Delaying the onset of stage 3 and therefore shortening the lifetime duration of clinical type 1 diabetes may reduce the likelihood of long-term complications and reduce the duration of disease burden.(10-14) Teplizumab, a humanized anti-CD3 monoclonal antibody, is the first and, to date, only drug approved to delay onset of stage 3 type 1 diabetes.(11) The United States Food and Drug Administration (FDA) approval was based on results from the TrialNet Anti-CD3 Prevention (TN-10) trial.(15) The TN-10 trial was a randomized phase 2 trial of teplizumab in individuals from the US and Canada aged 8 to 45 years with stage 2 type 1 diabetes who were identified by screening individuals with relatives with type 1 diabetes and followed from the time of randomization to assess disease progression to stage 3 type 1 diabetes.(16) This study demonstrated that teplizumab treatment delayed the progression from stage 2 to stage 3 type 1 diabetes by a median of 24 months compared with placebo.(16)

To investigate the generalizability of the progression risk in the TN-10 trial placebo cohort to a European population, the Germany-based Fr1da study was selected as the data source for a comparison group because it is one of the largest population-based screening programs for early diagnosis of type 1 diabetes in children.(17; 18) To date, almost 200,000 individuals aged 1 to 21 years have participated in screening through the Fr1da study.(19) In addition to its large cohort size, the Fr1da study was selected because autoantibody testing and other data similar to those collected in the TN-10 trial were available, and dysglycemia could be defined using the same criteria as in the TN-10 trial.

The Fr1da study is also an appropriate dataset to investigate potential differences in individuals with and without a documented first-degree relative (FDR) with type 1 diabetes because all participants were enrolled using the same population-based process, and there was a relatively even distribution of participants who did and did not have FDRs with type 1 diabetes.

In summary, our study aimed to evaluate the generalizability of the risk of progression in the TN-10 population to a European population and to individuals without an FDR with type 1 diabetes. The primary objectives were to assess the similarity of time to progression from stage 2 to stage 3 type 1 diabetes between the TN-10 placebo arm and participants from the Fr1da study with stage 2 type 1 diabetes. The analysis was conducted in all individuals from each group (aged 8 to 49 years in TN-10 and 1 to 21 years in Fr1da) and in individuals aged 8 to 15 years only, as this was the age group with the most overlap between the groups. A second analysis was conducted between Fr1da study subgroups based on whether participants had an FDR with type 1 diabetes or not. The secondary objective was to assess the similarity of the demographic and clinical characteristics between the TN-10 trial participants and a cohort from the Fr1da study with stage 2 type 1 diabetes.

Research Design and Methods

Study Design

This study was a retrospective study that used pre-existing data from participants with stage 2 type 1 diabetes from the TN-10 trial and the Fr1da study. The participant selection periods were the enrollment periods for the respective studies, which were August 2010 to November 2018 for the TN-10 trial and February 2015 to February 2024 for the Fr1da study. During the participant selection periods, eligible patients with stage 2 type 1 diabetes were identified with the index date defined as the date of the first stage 2 diagnosis for TN-10 trial participants and the age (in days) at stage 2 diagnosis for the Fr1da group. The baseline period was the period up to and including the index date for both the TN-10 trial participants and the Fr1da group. The follow-up period began the day after the index date and ended at the date of whichever of the following came first: diagnosis of stage 3 type 1 diabetes or the last study visit before the end of the study period **(Supplementary Figure 1).**

Participants

Participants in this study were individuals diagnosed with stage 2 type 1 diabetes, with no prior diagnosis of stage 3 type 1 diabetes.

TN-10 Participants

Key inclusion criteria for the TN-10 interventional trial included having stage 2 type 1 diabetes, having a family history of type 1 diabetes, being 8 years of age or older, having a body weight ≥26 kg, and demonstrating abnormal glucose tolerance defined as fasting plasma glucose

≥110 mg/dL and <126 mg/dL, or 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL, or 30-, 60-, or 90-minute value on the oral glucose tolerance test (OGTT) ≥200 mg/dL within 7 weeks of the baseline visit. Exclusion criteria characteristic of interventional studies such as being pregnant or lactating were also applied. Participants in both the placebo and treatment arms of the TN-10 trial were included for the description of demographic and clinical characteristics. For the main analysis, only participants in the TN-10 placebo arm were included.

Fr1da Participants

The Fr1da study was a population-based study, so individuals were screened for islet autoantibodies by primary care pediatricians during routine visits.(19) For the present study, individuals with stage 2 type 1 diabetes with evidence of dysglycemia assessed using the same methods and criteria used in TN-10 were selected from this cohort and are referred to here as the Fr1da group. In the Fr1da study, screening was offered to individuals aged 1.75 to 10.99 years regardless of whether they had a relative with stage 3 type 1 diabetes, and to individuals aged 1 to 21 years who had a relative with type 1 diabetes.(19; 20) Because individuals with multiple islet autoantibodies were prospectively followed and monitored, stage 2 diagnosis could happen during the follow-up, beyond the age range for screening offered by Fr1da.(20) To be included in the present study, Fr1da participants needed to have 2 or more confirmed type 1 diabetes autoantibodies present (anti-glutamic acid decarboxylase 65 [GAD65], micro-insulin autoantibody [mIAA], zinc transporter 8 [ZnT8], and insulinoma-associated antigen 2 [IA-2] autoantibodies) on 2 occasions within 6 months of index or at index. They also needed to have dysglycemia diagnosed by OGTT or any relevant alternative test at index.

Outcome Measures

The primary outcome measure was a diagnosis of stage 3 type 1 diabetes, defined by the presence of unequivocal hyperglycemia or based on glucose testing using the American Diabetes Association (ADA) plasma glucose criteria.(21) Unequivocal hyperglycemia was defined by the presence of symptoms of hyperglycemia (i.e., polyuria, polydipsia, and unexplained weight loss) with a random plasma glucose level of ≥200 mg/dL. In the absence of unequivocal hyperglycemia, the individual had to have either a fasting plasma glucose level ≥126 mg/dL or a 2-hour plasma glucose level of ≥200 mg/dL based on OGTT on 2 samples obtained on different days at least 1 day apart. OGTT was performed. In children, adjustments to the glucose load based on body weight were made. Criteria used here for the diagnosis of stage 3 type 1 diabetes differ from the current ADA criteria.(22)

Statistical Analyses

The primary objective analysis consisted of an assessment of the time from diagnosis of stage 2 to diagnosis of stage 3 type 1 diabetes in individuals in the TN-10 placebo arm and the Fr1da group. For the TN-10 placebo arm, this time was the difference in days between the dates of diagnosis of stage 2 and stage 3 type 1 diabetes, whereas for the Fr1da group, this time was the difference in days between the age at diagnosis of stage 2 and stage 3 type 1 diabetes.

The ratio of the number of people with new onset of stage 3 type 1 diabetes to total person-years at risk of stage 3 onset was used to estimate the incidence rates of stage 3 onset for the TN-10 placebo arm and the Fr1da group. Cumulative incidence rates of stage 3 onset were calculated by using the cumulative incidence function derived from the Kaplan–Meier (KM) estimator. The 95% confidence intervals (CIs) for the incidence and cumulative incidence rates were estimated based on the exact CI approach.

Time-to-event analyses were used to describe progression to stage 3, including estimating KM curves and fitting Cox proportional hazards (PH) regression models. KM curves stratified by data source (i.e., the TN-10 placebo arm and Fr1da group) were estimated, and the median time to progression to stage 3 type 1 diabetes as well as the proportions of individuals who progressed were determined for these 2 groups. The unadjusted hazard ratios (HRs) with 95% CI for progression to stage 3 for the TN-10 and Fr1da group were tabulated and interpreted. Univariate Cox PH models were applied to the TN-10 placebo arm and Fr1da group to investigate the association of potential prognostic factors with progression from stage 2 to stage 3, including age, sex, body mass index, existence of an FDR with stage 3 type 1 diabetes, islet autoantibody positivity, presence of human leukocyte antigen (HLA) risk alleles, glycated hemoglobin (HbA_{1c}) levels, and OGTT results. Prognostic factors significantly associated with progression to stage 3 were subsequently included in a multivariate Cox PH model, with study group (TN-10 placebo arm or Fr1da group) included as the primary predictor, that provided an adjusted HR. Because the age ranges of individuals included in the TN-10 study and the Fr1da group differed, an unadjusted time-to-event analysis was also performed in a subgroup of TN-10 placebo arm and Fr1da group participants aged 8 to 15 years at index date. Additionally, to investigate whether TN-10 results could be generalized to individuals without an FDR with type 1 diabetes, an unadjusted time-to-event analysis was performed in Fr1da group participants with and without an FDR with stage 3 type 1 diabetes.

For the secondary objective analysis, demographic and clinical characteristics were described at index date for the overall TN-10 trial population, the TN-10 trial treatment arm, the TN-10 trial placebo arm, the TN-10 trial placebo arm aged 8 to 15 years, the Fr1da group, the Fr1da group with FDR with type 1 diabetes, the Fr1da group without FDR with type 1 diabetes

and the Fr1da group aged 8 to 15 years. The characteristics described aligned with baseline characteristics described in the TN-10 trial. Standardized mean differences (SMDs) and standardized proportion differences were used to assess the similarity of quantitative and categorical characteristics, respectively, between the TN-10 placebo arm and the Fr1da group, the subgroups of the TN-10 placebo arm and Fr1da group aged 8 to 15 years, and Fr1da group participants with an FDR with type 1 diabetes and without an FDR with type 1 diabetes.

Sensitivity Analysis

TN-10 trial participants were diagnosed with stage 2 type 1 diabetes up to 7 weeks prior to trial randomization. Therefore, there was a period in which individuals could not be diagnosed with stage 3 type 1 diabetes, introducing an immortal time bias. This may have led to an overestimate of the time to progression to stage 3 in the TN-10 placebo arm. To determine whether this bias was minimal, the KM curve comparing the TN-10 placebo arm with the Fr1da group was rerun using the randomization date as the index date, instead of the stage 2 diagnosis date.

Data and Resource Availability

Qualified researchers may request access to more detailed results. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/. TN-10 data can be accessed at: https://repository.niddk.nih.gov/studies/trialnet/. Access to more detailed Fr1da data can be requested from the corresponding author by providing a methodologically sound proposal and completing a Data Use Agreement with Helmoltz Munich. This study was conducted under the guidelines for good pharmacovigilance and pharmacoepidemiology practices issued by the

International Society for Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws and regulations including General Data Protection Regulation.

Results

Participants and Baseline Characteristics

A total of 76 participants from the TN-10 trial (44 in the teplizumab arm; 32 in the placebo arm) and 152 participants from the Fr1da group were included in this study **(Supplementary Figure 2).** The demographic and clinical characteristics of study participants at stage 2 diagnosis are reported in **Table 1** and **Supplementary Tables 1, 2, and 3.** The TN-10 group was older than the Fr1da group, with a median (interquartile range [IQR]) age of 13.0 years (10.5–15.5) for the TN-10 placebo arm and 5.0 years (3.0–8.0) for the Fr1da group (SMD = 1.4). Additionally, the proportion of participants in the TN-10 placebo arm with an FDR with type 1 diabetes was higher than the proportion in the Fr1da group (87.5% vs. 29.6%; SMD 1.5) **(Table 1).** Differences in clinical characteristics between the TN-10 placebo arm and the Fr1da group were observed in the percentages of participants with positivity for specific autoantibodies, proportions of participants with particular HLA risk alleles, mean HbA_{1c} levels, and OGTT results **(Supplementary Table 1).** The median (IQR) follow-up time was 1.2 years (0.5–2.7) for the TN-10 placebo arm and 1.3 years (0.7–2.6) for the Fr1da group.

Progression From Stage 2 to Stage 3 Type 1 Diabetes

A total of 71.9% (*n* = 23) of individuals in the TN-10 placebo arm and 52.6% (*n* = 80) of those in the Fr1da group progressed to stage 3. The incidence rates and cumulative incidence of

stage 3 onset per 1000 person-years in each group are reported in **Supplementary Tables 4 and 5,** respectively. Specifically, the unadjusted HR (95% CI) for the comparison of the rate of progression between the 2 groups was 1.3 (0.8–2.1). Application of univariate Cox models to the TN-10 placebo arm and Fr1da group demonstrated that anti-IA-2 antibodies (HR 2.0; 95% CI, 1.1–3.5), HbA_{1c} >5.7% (HR 4.5; 95% CI, 2.7–7.5), and 120-minute OGTT results (HR 1.0; 95% CI, 1.0–1.0) were significantly associated with disease progression to stage 3. These prognostic factors were thus included in a multivariate Cox PH model. The resulting adjusted HR (95% CI) for the comparison of the rate of progression between the 2 groups was 1.1 (0.6–2.1). However, the wide confidence interval suggests a degree of uncertainty for this value. The type II error for the unadjusted and adjusted Cox PH models is provided in **Supplementary Table 6**. The KM curves for progression to stage 3 in the TN-10 placebo arm (n = 32) and the Fr1da group (n = 152) are shown in **Figure 1.** The median (95% CI) time to progression from stage 2 to stage 3 was 26.0 months (11.1–43.5) in the TN-10 placebo arm and 32.3 months (22.0–41.4) in the Fr1da group.

For individuals aged 8 to 15 years at index date in the TN-10 placebo arm (n = 24) and the Fr1da group (n = 40), the KM curves for progression from stage 2 to stage 3 are shown in **Figure 2.** Median (95% CI) time to progression to stage 3 for these groups was 14.9 months (6.7–56.4) in the TN-10 placebo arm and 32.3 months (16.2–43.7) in the Fr1da group.

Additionally, the KM curves for progression to stage 3 in Fr1da group participants with (n = 45) and without (n = 107) FDRs with type 1 diabetes are shown in **Figure 3.** The median (95% CI) time to progression from stage 2 to stage 3 was 42.4 months (23.4–not estimable) for Fr1da group participants with FDRs with type 1 diabetes and 27.1 months (18.5–35.7) for those without.

Sensitivity Analysis: TN-10 Placebo Arm and Fr1da Group Comparison

Lastly, the KM curves for progression to stage 3 for the TN-10 placebo arm using the randomization date as the index date and for the Fr1da group are shown in **Supplementary Figure 3.**

Conclusions

The goal of this study was to investigate whether the risk of the population included in the TN-10 trial, which demonstrated the efficacy of teplizumab in delaying stage 3 onset, could be generalized to a European population with or without an FDR with type 1 diabetes. This was investigated by comparing time to progression from stage 2 to stage 3 between the TN-10 placebo arm and the Fr1da group and between Fr1da group participants with and without an FDR with stage 3 type 1 diabetes.

Although the study only had sufficient power to detect large differences, the findings suggest that the time to progression to stage 3 was similar for the TN-10 placebo arm and the Fr1da group, with comparable KM curves for each study group. Time to progression to stage 3 was also not significantly different in a subgroup of the TN-10 placebo arm and the Fr1da group aged 8 to 15 years as well as for Fr1da group participants with and without FDR with type 1 diabetes. These similarities suggest that the TN-10 population risk is likely generalizable to European populations with or without an FDR with type 1 diabetes.

Progression rates to stage 3 did not differ between groups, despite some differences in characteristics. In particular, the Fr1da group had a lower median age. Although limited by statistical power, no differences were observed when comparisons were restricted to the

subgroup aged 8 to 15 years, suggesting that age may have had a minimal impact on the comparison of time to progression in this analysis. While age at seroconversion has been shown to be associated with a higher risk of progression to stage 3, the age assessed in this study was not age at seroconversion but instead was age at stage 2 diagnosis. Additionally, although the TN-10 placebo arm and the Fr1da group had similar HbA_{1c} levels, a higher proportion of Fr1da participants had increased HbA_{1c} values. While rising HbA_{1c} levels have been associated with increased risk of progression, it is possible that increases in HbA_{1c} in this study were not large enough to impact time to progression.(23) HLA genotypes in the populations also differed slightly.(24; 25) Interpreting differences in HLA status between these 2 groups should be done with caution because there was a high prevalence of missing data on HLA status in the Fr1da group, and the sample size was insufficient for detecting statistically significant differences in participant characteristics **(Supplementary Table 1);** however, the 2 groups had similar proportions of participants with HLA DR3. Other genetic factors such as non-HLA alleles may have also influenced study findings as they have been associated with type 1 diabetes risk but were not assessed in these studies.(9; 26)

Several of the differences observed between the TN-10 and Fr1da groups were primarily due to the differences in study designs for selecting patients into each group. Differences in median age between the TN-10 placebo arm and Fr1da group, for example, were driven by differences in the eligibility criteria between the 2 studies; the TN-10 trial excluded individuals aged younger than 8 years, whereas the Fr1da study enrolled participants aged 1 to 21 years, leading to the younger median age in the Fr1da group. Additionally, a higher proportion of participants in the TN-10 placebo arm had an FDR with type 1 diabetes because having a relative with type 1 diabetes was a requirement for trial entry. The difference in the most frequent FDR

type in the TN-10 group and the Fr1da group (sibling and parent, respectively) also most likely reflects the younger age of the Fr1da group participants.

Fasting plasma glucose levels were also slightly higher in the TN-10 placebo arm than in the Fr1da group **(Supplementary Table 1)**. As higher body mass index has been previously associated with higher fasting glucose levels, it is possible that this difference could be due to a higher proportion of individuals in the TN-10 group being overweight compared to the Fr1da group **(Supplementary Table 2)**.(27)

The presence of anti-IA-2 antibodies, HbA_{1c} >5.7%, and 120-minute OGTT results were identified in univariate Cox models to be associated with progression from stage 2 to stage 3. Adjusting for these factors resulted in an HR that was closer to 1 than the unadjusted analysis. Anti-IA-2 antibodies have been associated with increased progression risk across all stages of disease, with a recent study demonstrating that individuals with anti-IA-2 antibodies alone had a greater progression risk than anti-IA2 negative individuals at stage 1.(17; 28-31) Therefore, these factors may be considered in future investigations of risk factors for progression to stage 3 in addition to previously identified risk factors.(24; 25; 32; 33)

The Fr1da group's relatively large stage 2 type 1 diabetes cohort size and the fact that it includes individuals from a population-based screening program is a strength. Many studies assessing rate of progression to clinical type 1 diabetes have not investigated cohorts of individuals that have stage 2 type 1 diabetes exclusively or are limited to individuals who are screened because of a high genetic risk of developing clinical type 1 diabetes either due to their family history or genotype.(23; 24; 33) The findings of this study are particularly important given the observation that approximately 90% of individuals who will be diagnosed with clinical

type 1 diabetes have no family history of the disease, and most of the population are unaware of their genetic risk for development of type 1 diabetes.(34-36)

A limitation of this study is the presence of an immortal time bias in the TN-10 trial participants, resulting from the fact that the stage 2 diagnosis occurred prior to randomization. However, bias introduced through immortal time was believed to be minimal based on the sensitivity analysis that showed similar time to stage 3 diagnosis using the randomization date as the index date (and not diagnosis of stage 2). There was also variation in data availability. Race/ethnicity, islet antigen test results, and C-peptide levels were not recorded for the Fr1da group and therefore were not included as variables in this study. Unmeasured differences in these variables between the study groups may confound the findings. Additionally, as mentioned previously, this study only had sufficient power to detect relatively large differences in the progression rates between groups, or patient characteristics between the study groups or subgroups.

In this study, time to stage 3 type 1 diabetes onset did not differ significantly between the TN-10 placebo arm and the Fr1da group in unadjusted and adjusted analyses. Furthermore, progression rates did not differ when analyses were restricted to those aged 8 to 15 years, and when Fr1da group participants were stratified by presence of an FDR with type 1 diabetes. Together, these results suggest that despite differences in demographics and the methodological limitations highlighted, the risk of type 1 diabetes progression from the TN-10 trial appears to be generalizable to European populations with and without FDRs with type 1 diabetes.

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Conflict of Interest

A.G.Z. is a member of the data monitoring committee for 2 clinical trials for Sanofi and serves on an advisory board for Sanofi. T.K. and M.Y. are employees of Evidera. M.B., O.G., and J.Z. are employees of Sanofi and may hold shares and/or stock options in the company. M.K., C.W., S.H., and A.W. have no relevant disclosures.

Author Contributions and Guarantor Statement

M.K. was involved in data collection, conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

C.W. was involved in data collection, conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

S.H. was involved in conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

A.W. was involved in conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

T.K. was involved in analysis and interpretation of data for the study and edited, reviewed, and approved the final version of the manuscript.

M.Y. was involved in analysis and interpretation of data for the study and edited, reviewed, and approved the final version of the manuscript.

M.B. was involved in conception, design, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

O.G. was involved in conception, design, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

J.Z. was involved in conception, design, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

A.G.Z. was involved in conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript. She is the principal investigator of Fr1da.

A.G.Z. is also the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation

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Table 1—Baseline demographic characteristics of study participants at or near stage 2 diagnosis

Characteristic	**TN-10 trial: Overall (*n* = 76)**	**TN-10 trial: Teplizumab arm (*n* = 44)**	**TN-10 trial: Placebo arm (*n* = 32)**	**Fr1da group (*N* = 152)**	**SMD (placebo arm of the TN-10 trial vs Fr1da group)**
Age in years					1.35
N	76	44	32	152	
Mean (SD)	17.9 (11.5)	18.7 (11.9)	16.8 (11.0)	5.9 (3.1)	
Median (IQR)	13.0 (11.0–19.0)	14.0 (11.0–22.0)	13.0 (10.5–15.5)	5.0 (3.0–8.0)	
Minimum, maximum	8.0, 49.0	8.0, 49.0	8.0, 44.0	2.0, 15.0	
Missing, *n*	0	0	0	0	
Age categories, *n* (%)					2.61
<8 years	0 (0.0)	0 (0.0)	0 (0.0)	112 (73.7)	
≥8 and <15 years	45 (59.2)	24 (54.5)	21 (65.6)	39 (25.7)	
≥15 and <18 years	10 (13.2)	5 (11.4)	5 (15.6)	1 (0.7)	
≥18 years	21 (27.6)	15 (34.1)	6 (18.8)	0 (0.0)	
Sex, *n* (%)					-0.12
Male	42 (55.3)	25 (56.8)	17 (53.1)	90 (59.2)	
Female	34 (44.7)	19 (43.2)	15 (46.9)	62 (40.8)	
Z-score BMI for participants aged 24–228 months*					0.41
N	35	20	15	129	
Mean (SD)	0.34 (1.129)	0.07 (1.331)	0.70 (0.668)	0.32 (1.117)	
Median (IQR)	0.50 (-0.30–1.10)	0.05 (-0.70–1.05)	0.70 (0.20–1.10)	0.20 (-0.50–0.90)	

Characteristic	**TN-10 trial: Overall (*n* = 76)**	**TN-10 trial: Teplizumab arm (*n* = 44)**	**TN-10 trial: Placebo arm (*n* = 32)**	**Fr1da group (*N* = 152)**	**SMD (placebo arm of the TN-10 trial vs Fr1da group)**
Minimum, maximum	-2.8, 2.4	-2.8, 2.4	-0.4, 1.9	-1.6, 3.5	
Missing, *n*	20	9	11	23	
BMI (kg/m^2) for participants ≥229 months old[*]					NA
N	19	13	6	0	
Mean (SD)	27.63 (6.231)	27.50 (7.183)	27.90 (3.976)	NA (NA)	
Median (IQR)	26.40 (23.20–31.40)	24.30 (21.80–31.40)	27.30 (24.80–30.90)	NA	
Minimum, maximum	19.3, 42.4	19.3, 42.4	23.2, 33.9	NA	
Missing, *n*	2	2	0	NA	
FDR with diagnosed stage 3 T1D, *n* (%)[†]					1.45
Yes	70 (92.1)	42 (95.5)	28 (87.5)	45 (29.6)	
No	6 (7.9)	2 (4.5)	4 (12.5)	107 (70.4)	
Second-degree relative with diagnosed stage 3 T1D, *n* (%)[†]					NA
Yes	12 (15.8)	5 (11.4)	7 (21.9)	NA	
No	64 (84.2)	39 (88.6)	25 (78.1)	NA	
Third- or higher-degree relative with diagnosed stage 3 T1D, *n* (%)[†]					NA
Yes	3 (3.9)	1 (2.3)	2 (6.3)	NA	
No	73 (96.1)	43 (97.7)	30 (93.8)	NA	
Relationship to FDR with diagnosed stage 3 T1D, *n* (%)					

Characteristic	TN-10 trial: Overall (*n* = 76)	TN-10 trial: Teplizumab arm (*n* = 44)	TN-10 trial: Placebo arm (*n* = 32)	Fr1da group (*N* = 152)	SMD (placebo arm of the TN-10 trial vs Fr1da group)
Sibling	49 (64.5)	30 (68.2)	19 (59.4)	13 (8.6)	1.27
Offspring	13 (17.1)	7 (15.9)	6 (18.8)	0 (0.0)	0.68
Parent	13 (17.1)	7 (15.9)	6 (18.8)	33 (21.7)	-0.07
Sibling and another FDR	6 (7.9)	3 (6.8)	3 (9.4)	1 (0.7)	0.41

*Values closest to the index date (i.e., date of stage 2 confirmation) during baseline period (which starts at earliest available data and ends at index date, inclusive) were considered for all baseline characteristics. However, not all patients have a measurement for these specific variables during this period, hence the missing values at baseline for these variables.

†FDR is defined as having at least 50% of shared genes (i.e., full siblings, parents, and offspring) with the subject; second-degree relative is defined as having 25% of shared genes (i.e., grandparents, grandchildren, half-siblings, aunts, and uncles); third-degree relative is defined as having 12.5% of shared genes (i.e., first cousins, great-grandparents, and great-grandchildren). A subject can have multiple relationships to persons with T1D; in such cases, all relevant relationship groups are included in the relevant analysis.

BMI = body mass index; FDR = first-degree relative; IQR = interquartile range; NA = not available; SD = standard deviation; SMD = standardized mean difference; T1D, type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention

Figure Legends

Figure 1. Stage 3 T1D progression-free survival probability in TN-10 placebo arm and Fr1da group

A) Analyses were unadjusted. Unadjusted HR was 1.3 (95% CI: 0.8-2.1). B) Analyses were adjusted for anti-IA-2 antibodies, HbA1c >5.7%, and 120-minute OGTT results. Adjusted HR was 1.1 (95% CI: 0.6-2.1).

CI = confidence interval; HbA1c = glycated hemoglobin; HR = hazard ratio; IA-2 = islet antigen-2; OGTT = oral glucose tolerance test; T1D = type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention

Figure 2. Stage 3 T1D progression-free survival probability in the TN-10 placebo arm and Fr1da group aged 8 to 15 years

Analyses were unadjusted.

CI = confidence interval; T1D = type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention

Figure 3. Stage 3 T1D progression-free survival probability in Fr1da participants with and without first-degree relatives diagnosed with T1D

Analyses were unadjusted.

CI = confidence interval; T1D = type 1 diabetes

Generalizability of progression risk in the TN-10 trial to a European population with or without a first-degree relative with type 1 diabetes

Short running title: Generalizability of progression risk in ~~Generalizability of the~~ TN-10 ~~trial to Fr1da~~ (45/47 characters including spaces)

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Twitter summary: [200 characters max]

Time to development of symptomatic T1D in the placebo arm of the North American-based TN-10 trial was similar to people in the European-based Fr1da group, with and without relatives with T1D.

Keywords: Type 1 Diabetes, Registries, Progression, North American, European(s), Screening

Word count: (391798/4000 words)

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Plain language summary

WHAT IS IT ABOUT?

The TN-10 clinical trial showed that in comparison to treatment with no drug (i.e. placebo), teplizumab can delay the onset of symptomatic type 1 diabetes in a population of individuals with presymptomatic (stage 2) type 1 diabetes mainly from the US and Canada who had a relative with type 1 diabetes. The goal of this study was to learn if~~, based on~~ the risk of ~~the populations, findings from~~developing symptomatic type 1 diabetes in the TN-10 clinical trial is similar~~can be generalized or applicable~~ to that in a European population regardless of whether or not they have immediate family members with type 1 diabetes. Researchers assessed and compared the time needed to develop symptomatic type 1 diabetes in individuals treated with placebo in the TN-10 trial with the time needed in a group of individuals from the German population-based screening program, Fr1da. The time to develop symptomatic type 1 diabetes was similar between the TN-10 placebo group and Fr1da group and between individuals in the Fr1da group with and without immediate family with type 1 diabetes.

WHY IS IT IMPORTANT?

The approval of teplizumab by the United States Food and Drug Administration was largely based on findings from the TN-10 trial. The results from this study suggest that population risk of progression from presymptomatic (stage 2) to symptomatic type 1 diabetes is similar between patients in the United States and those in Europe, and between patients in Europe with or without immediate family members with type 1 diabetes.

Abstract

Objective

In the TrialNet 10 (TN-10) trial, teplizumab delayed onset of stage 3 type 1 diabetes in US and Canadian individuals with stage 2 disease who had a relative with type 1 diabetes. Here, the generalizability of the population risk in TN-10 to a European population with or without first-degree relatives (FDRs) with type 1 diabetes was investigated.

Research Design and Methods

This retrospective study used data from participants with stage 2 type 1 diabetes from the TN-10 placebo arm and the Fr1da population-based screening program in Germany (Fr1da group) to investigate time to progression from stage 2 to ~~stage~~ 3 type 1 diabetes. The study only had sufficient power to detect large differences.

Results

Risk of progression to stage 3 type 1 diabetes was comparable~~similar~~ between the TN-10 placebo arm (n=32) and the Fr1da group (n=152; HR=1.3 [95% CI: 0.8-2.1]). Once prognostic factors significantly associated with progression in this study (anti-IA-2 antibodies, HbA1c >5.7%, and 120-minute OGTT) were included in the model, the adjusted HR was 1.1 (95% CI: 0.6-2.1). Fr1da group participants with (n=45) and without (n=107) FDRs with type 1 diabetes had similar time to progression to stage 3 ~~disease~~. Age-based subanalysis demonstrated minimal impact of age on progression time.

Conclusions

Time to progression to stage 3 ~~type 1 diabetes~~ appeared~~was~~ similar between the TN-10 placebo arm and the Fr1da group and between ~~Fr1da group~~ participants with and without FDRs with disease~~type 1 diabetes~~. Results suggest progression risk from the TN-10 trial may be generalizable to European populations with or without FDRs with type 1 diabetes.

Article Highlights

- **Why did we undertake this study?**

  Whether risk of progression to type 1 diabetes in the TN-10 trial ~~findings in a population with relatives with type 1 diabetes~~ is~~are~~ generalizable to individuals from Europe with or without relatives with disease was unknown.

- **What is the specific question(s) we wanted to answer?**

  Is time to symptomatic type 1 diabetes development in the North American-based TN-10 placebo group similar to European-based Fr1da group and between individuals with and without relatives with disease?

- **What did we find?**

  Time to symptomatic type 1 diabetes development in the TN-10 placebo group was similar to the Fr1da group and between Fr1da participants with and without first-degree relatives with the disease.

- **What are the implications of our findings?**

  Progression risk from the TN-10 trial may be generalizable to European populations without relatives with type 1 diabetes.

Type 1 diabetes is a significant global health burden that can have detrimental effects on individuals, their caregivers, and health care systems.(1; 2) It is a chronic, progressive disease driven by the autoimmune-mediated destruction of insulin-producing beta cells in the pancreas. Immune mediators that have been shown to contribute to this disease process include autoreactive T cells and B cells and pro-inflammatory cytokines.(3-6) This autoimmune process can begin years prior to the development of the sustained hyperglycemia that is characteristic of clinical type 1 diabetes.(7) Accordingly, the disease process of type 1 diabetes can be stratified into 3 stages. Stage 1 is defined by the presence of two or more islet autoantibodies with normal blood glucose levels (normoglycemia).(8; 9) In stage 2, two or more islet autoantibodies and impaired glucose tolerance (dysglycemia) are present.(8; 9) Stage 3 is defined by clinical symptoms typically associated with diabetes and the presence of sustained hyperglycemia.(8; 9)

Delaying the onset of stage 3 and therefore shortening the lifetime duration of clinical type 1 diabetes may reduce the likelihood of long-term complications and reduce the duration of disease burden.(10-14) Teplizumab, a humanized anti-CD3 monoclonal antibody, is the first and, to date, only drug approved to delay onset of stage 3 type 1 diabetes.(11) The United States Food and Drug Administration (FDA) approval was based on results from the TrialNet Anti-CD3 Prevention (TN-10) trial.(15) The TN-10 trial was a randomized phase 2 trial of teplizumab in individuals from the US and Canada aged 8 to 45 years with stage 2 type 1 diabetes who were identified by screening individuals with relatives with type 1 diabetes and followed from the time of randomization to assess disease progression to stage 3 type 1 diabetes.(16) This study demonstrated that teplizumab treatment delayed the progression from stage 2 to stage 3 type 1 diabetes by a median of 24 months compared with placebo.(16)

To investigate the generalizability of the progression risk in the TN-10 trial placebo cohort to a European population, the Germany-based Fr1da study was selected as the data source for a comparison group because it is one of the largest population-based screening programs for early diagnosis of type 1 diabetes in children.(17; 18) To date, almost 200,000 individuals aged 1 to 21 years have participated in screening through the Fr1da study.(19) In addition to its large cohort size, the Fr1da study was selected because autoantibody testing and other data similar to those collected in the TN-10 trial were available, and dysglycemia could be defined using the same criteria as in the TN-10 trial.

The Fr1da study is also an appropriate dataset to investigate potential differences in individuals with and without a documented first-degree relative (FDR) with type 1 diabetes because all participants were enrolled using the same population-based process, and there was a relatively even distribution of participants who did and did not have FDRs with type 1 diabetes.

In summary, our study aimed to evaluate the generalizability of the risk of progression in the TN-10 population to a European population and to individuals without an FDR with type 1 diabetes. The primary objectives were to assess the similarity of time to progression from stage 2 to stage 3 type 1 diabetes between the TN-10 placebo arm and participants from the Fr1da study with stage 2 type 1 diabetes. The analysis was conducted in all individuals from each group (aged 8 to 49 years in TN-10 and 1 to 21 years in Fr1da) and in individuals aged 8 to 15 years only, as this was the age group with the most overlap between the groups. A second analysis was conducted between Fr1da study subgroups based on whether participants had an FDR with type 1 diabetes or not. The secondary objective was to assess the similarity of the demographic and clinical characteristics between the TN-10 trial participants and a cohort from the Fr1da study with stage 2 type 1 diabetes.

Research Design and Methods

Study Design

This study was a retrospective study that used pre-existing data from participants with stage 2 type 1 diabetes from the TN-10 trial and the Fr1da study. The participant selection periods were the enrollment periods for the respective studies, which were August 2010 to November 2018 for the TN-10 trial and February 2015 to February 2024 for the Fr1da study. During the participant selection periods, eligible patients with stage 2 type 1 diabetes were identified with the index date defined as the date of the first stage 2 diagnosis for TN-10 trial participants and the age (in days) at stage 2 diagnosis for the Fr1da group. The baseline period was the period up to and including the index date for both the TN-10 trial participants and the Fr1da group. The follow-up period began the day after the index date and ended at the date of whichever of the following came first: diagnosis of stage 3 type 1 diabetes or the last study visit before the end of the study period **(Supplementary Figure 1).**

Participants

Participants in this study were individuals diagnosed with stage 2 type 1 diabetes, with no prior diagnosis of stage 3 type 1 diabetes.

TN-10 Participants

Key inclusion criteria for the TN-10 interventional trial included having stage 2 type 1 diabetes, having a family history of type 1 diabetes, being 8 years of age or older, having a body weight ≥26 kg, and demonstrating abnormal glucose tolerance defined as fasting plasma glucose

≥110 mg/dL and <126 mg/dL, or 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL, or 30-, 60-, or 90-minute value on the oral glucose tolerance test (OGTT) ≥200 mg/dL within 7 weeks of the baseline visit. Exclusion criteria characteristic of interventional studies such as being pregnant or lactating were also applied. Participants in both the placebo and treatment arms of the TN-10 trial were included for the description of demographic and clinical characteristics. For the main analysis, only participants in the TN-10 placebo arm were included.

Fr1da Participants

The Fr1da study was a population-based study, so individuals were screened for islet autoantibodies by primary care pediatricians during routine visits.(19) For the present study, individuals with stage 2 type 1 diabetes with evidence of dysglycemia assessed using the same methods and criteria used in TN-10 were selected from this cohort and are referred to here as the Fr1da group. In the Fr1da study, screening was offered to individuals aged 1.75 to 10.99 years regardless of whether they had a relative with stage 3 type 1 diabetes, and to individuals aged 1 to 21 years who had a relative with type 1 diabetes.(19; 20) Because individuals with multiple islet autoantibodies were prospectively followed and monitored, stage 2 diagnosis could happen during the follow-up, beyond the age range for screening offered by Fr1da.(20) To be included in the present study, Fr1da participants needed to have 2 or more confirmed type 1 diabetes autoantibodies present (anti-glutamic acid decarboxylase 65 [GAD65], micro-insulin autoantibody [mIAA], zinc transporter 8 [ZnT8], and insulinoma-associated antigen 2 [IA-2] autoantibodies) on 2 occasions within 6 months of index or at index. They also needed to have dysglycemia diagnosed by OGTT or any relevant alternative test at index.

Outcome Measures

The primary outcome measure was a diagnosis of stage 3 type 1 diabetes, defined by the presence of unequivocal hyperglycemia or based on glucose testing using the American Diabetes Association (ADA) plasma glucose criteria.(21) Unequivocal hyperglycemia was defined by the presence of symptoms of hyperglycemia (i.e., polyuria, polydipsia, and unexplained weight loss) with a random plasma glucose level of ≥200 mg/dL. In the absence of unequivocal hyperglycemia, the individual had to have either a fasting plasma glucose level ≥126 mg/dL or a 2-hour plasma glucose level of ≥200 mg/dL based on OGTT on 2 samples obtained on different days at least 1 day apart. OGTT was performed. In children, adjustments to the glucose load based on body weight were made. Criteria used here for the diagnosis of stage 3 type 1 diabetes differ from the current ADA criteria.(22)

Statistical Analyses

The primary objective analysis consisted of an assessment of the time from diagnosis of stage 2 to diagnosis of stage 3 type 1 diabetes in individuals in the TN-10 placebo arm and the Fr1da group. For the TN-10 placebo arm, this time was the difference in days between the dates of diagnosis of stage 2 and stage 3 type 1 diabetes, whereas for the Fr1da group, this time was the difference in days between the age at diagnosis of stage 2 and stage 3 type 1 diabetes.

The ratio of the number of people with new onset of stage 3 type 1 diabetes to total person-years at risk of stage 3 onset was used to estimate the incidence rates of stage 3 onset for the TN-10 placebo arm and the Fr1da group. Cumulative incidence rates of stage 3 onset were calculated by using the cumulative incidence function derived from the Kaplan–Meier (KM) estimator. The 95% confidence intervals (CIs) for the incidence and cumulative incidence rates were estimated based on the exact CI approach.

Time-to-event analyses were used to describe progression to stage 3, including estimating KM curves and fitting Cox proportional hazards (PH) regression models. KM curves stratified by data source (i.e., the TN-10 placebo arm and Fr1da group) were estimated, and the median time to progression to stage 3 type 1 diabetes as well as the proportions of individuals who progressed were determined for these 2 groups. The unadjusted hazard ratios (HRs) with 95% CI for progression to stage 3 for the TN-10 and Fr1da group were tabulated and interpreted. Univariate Cox PH models were applied to the TN-10 placebo arm and Fr1da group to investigate the association of potential prognostic factors with progression from stage 2 to stage 3, including age, sex, body mass index, existence of an FDR with stage 3 type 1 diabetes, islet autoantibody positivity, presence of human leukocyte antigen (HLA) risk alleles, glycated hemoglobin (HbA_{1c}) levels, and OGTT results. Prognostic factors significantly associated with progression to stage 3 were subsequently included in a multivariate Cox PH model, with study group (TN-10 placebo arm or Fr1da group) included as the primary predictor, that provided an adjusted HR. Because the age ranges of individuals included in the TN-10 study and the Fr1da group differed, an unadjusted time-to-event analysis was also performed in a subgroup of TN-10 placebo arm and Fr1da group participants aged 8 to 15 years at index date. Additionally, to investigate whether TN-10 results could be generalized to individuals without an FDR with type 1 diabetes, an unadjusted time-to-event analysis was performed in Fr1da group participants with and without an FDR with stage 3 type 1 diabetes.

For the secondary objective analysis, demographic and clinical characteristics were described at index date for the overall TN-10 trial population, the TN-10 trial treatment arm, the TN-10 trial placebo arm, the TN-10 trial placebo arm aged 8 to 15 years, the Fr1da group, the Fr1da group with FDR with type 1 diabetes, the Fr1da group without FDR with type 1 diabetes

and the Fr1da group aged 8 to 15 years. The characteristics described aligned with baseline characteristics described in the TN-10 trial. Standardized mean differences (SMDs) and standardized proportion differences were used to assess the similarity of quantitative and categorical characteristics, respectively, between the TN-10 placebo arm and the Fr1da group, the subgroups of the TN-10 placebo arm and Fr1da group aged 8 to 15 years, and Fr1da group participants with an FDR with type 1 diabetes and without an FDR with type 1 diabetes.

Sensitivity Analysis

TN-10 trial participants were diagnosed with stage 2 type 1 diabetes up to 7 weeks prior to trial randomization. Therefore, there was a period in which individuals could not be diagnosed with stage 3 type 1 diabetes, introducing an immortal time bias. This may have led to an overestimate of the time to progression to stage 3 in the TN-10 placebo arm. To determine whether this bias was minimal, the KM curve comparing the TN-10 placebo arm with the Fr1da group was rerun using the randomization date as the index date, instead of the stage 2 diagnosis date.

Data and Resource Availability

Qualified researchers may request access to more detailed results. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/. TN-10 data can be accessed at: https://repository.niddk.nih.gov/studies/trialnet/. Access to more detailed Fr1da data can be requested from the corresponding author by providing a methodologically sound proposal and completing a Data Use Agreement with Helmoltz Munich. This study was conducted under the guidelines for good pharmacovigilance and pharmacoepidemiology practices issued by the

International Society for Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws and regulations including General Data Protection Regulation.

Results

Participants and Baseline Characteristics

A total of 76 participants from the TN-10 trial (44 in the teplizumab arm; 32 in the placebo arm) and 152 participants from the Fr1da group were included in this study **(Supplementary Figure 2).** The demographic and clinical characteristics of study participants at stage 2 diagnosis are reported in **Table 1** and **Supplementary Tables 1, 2, and 3.** The TN-10 group was older than the Fr1da group, with a median (interquartile range [IQR]) age of 13.0 years (10.5–15.5) for the TN-10 placebo arm and 5.0 years (3.0–8.0) for the Fr1da group (SMD = 1.4). Additionally, the proportion of participants in the TN-10 placebo arm with an FDR with type 1 diabetes was higher than the proportion in the Fr1da group (87.5% vs. 29.6%; SMD 1.5) **(Table 1).** Differences in clinical characteristics between the TN-10 placebo arm and the Fr1da group were observed in the percentages of participants with positivity for specific autoantibodies, proportions of participants with particular HLA risk alleles, mean HbA_{1c} levels, and OGTT results **(Supplementary Table 1).** The median (IQR) follow-up time was 1.2 years (0.5–2.7) for the TN-10 placebo arm and 1.3 years (0.7–2.6) for the Fr1da group.

Progression From Stage 2 to Stage 3 Type 1 Diabetes

A total of 71.9% (*n* = 23) of individuals in the TN-10 placebo arm and 52.6% (*n* = 80) of those in the Fr1da group progressed to stage 3. The incidence rates and cumulative incidence of

stage 3 onset per 1000 person-years in each group are reported in **Supplementary Tables 4 and 5,** respectively. ~~The risk of progression from stage 2 to stage 3 was similar in participants in the TN-10 placebo arm and in the Fr1da group.~~ Specifically, the unadjusted HR (95% CI) for the comparison of the rate of progression between the 2 groups was 1.3 (0.8–2.1). Application of univariate Cox models to the TN-10 placebo arm and Fr1da group demonstrated that anti-IA-2 antibodies (HR 2.0; 95% CI, 1.1–3.5), HbA_{1c} >5.7% (HR 4.5; 95% CI, 2.7–7.5), and 120-minute OGTT results (HR 1.0; 95% CI, 1.0–1.0) were significantly associated with disease progression to stage 3. These prognostic factors were thus included in a multivariate Cox PH model. The resulting adjusted HR (95% CI) for the comparison of the rate of progression between the 2 groups was 1.1 (0.6–2.1). However, the wide confidence interval suggests a degree of uncertainty for this value. The type II error for the unadjusted and adjusted Cox PH models is provided in **Supplementary Table 6**. T~~Additionally, t~~he KM curves for progression to stage 3 in ~~were similar between~~ the TN-10 placebo arm (n = 32) and the Fr1da group (n = 152)~~, with overlapping 95% CIs throughout~~ are shown in ~~(~~**Figure 1**~~)~~**.** The median (95% CI) time to progression from stage 2 to stage 3 was 26.0 months (11.1–43.5) in the TN-10 placebo arm and 32.3 months (22.0–41.4) in the Fr1da group.

For individuals aged 8 to 15 years at index date in the TN-10 placebo arm (n = 24) and the Fr1da group (n = 40), the KM curves for progression from stage 2 to stage 3 ~~were also similar and had overlapping 95% CIs throughout~~ are shown in ~~(~~**Figure 2**~~)~~**.** Median (95% CI) time to progression to stage 3 for these groups was 14.9 months (6.7–56.4) in the TN-10 placebo arm and 32.3 months (16.2–43.7) in the Fr1da group.

Additionally, the KM curves for progression to stage 3 in ~~were similar between~~ Fr1da group participants with (n = 45) and without (n = 107) FDRs with type 1 diabetes~~, with~~

~~overlapping 95% CIs throughout~~ are shown in ~~(~~**Figure 3**~~)~~**.** The median (95% CI) time to progression from stage 2 to stage 3 was 42.4 months (23.4–not estimable) for Fr1da group participants with FDRs with type 1 diabetes and 27.1 months (18.5–35.7) for those without.

Sensitivity Analysis: TN-10 Placebo Arm and Fr1da Group Comparison

Lastly, the KM curves for progression to stage 3 for the TN-10 placebo arm using the randomization date as the index date and for the Fr1da group are shown in ~~were also similar, with overlapping 95% CIs throughout~~ ~~(~~**Supplementary Figure 3**~~)~~**.**

Conclusions

The goal of this study was to investigate whether the risk of the population included in the TN-10 trial, which demonstrated the efficacy of teplizumab in delaying stage 3 onset, could be generalized to a European population with or without an FDR with type 1 diabetes. This was investigated by comparing time to progression from stage 2 to stage 3 between the TN-10 placebo arm and the Fr1da group and between Fr1da group participants with and without an FDR with stage 3 type 1 diabetes.

Although the study only had sufficient power to detect large differences, the findings suggest that the t~~T~~ime to progression to stage 3 was similar for the TN-10 placebo arm and the Fr1da group, with comparable ~~with the 95% CI of the~~ KM curves for each study group~~overlapping~~. Time to progression to stage 3 was also not significantly different~~similar~~ in a subgroup of the TN-10 placebo arm and the Fr1da group aged 8 to 15 years as well as for Fr1da group participants with and without FDR with type 1 diabetes. These similarities suggest that the

TN-10 population risk is likely generalizable to European populations with or without an FDR with type 1 diabetes.

Progression rates~~Time to progression~~ to stage 3 did not differ~~was similar~~ between groups, despite some~~there being slight~~ differences in characteristics. In particular, ~~Although the median age of~~ the Fr1da group had a lower median age. Although limited by statistical power, no differences were observed when comparisons were restricted to ~~was younger, the time to progression to stage 3 was similar to the TN-10 placebo group for both the overall group and~~ the subgroup aged 8 to 15 years, suggesting that age may have had a minimal impact on the comparison of time to progression in this analysis. While age at seroconversion has been shown to be associated with a higher risk of progression to stage 3, the age assessed in this study was not age at seroconversion but instead was age at stage 2 diagnosis. ~~Recent studies suggest that age may not be a predictor of progression once early type 1 diabetes has been detected, with a study showing that once a person is in stage 2, progression appears to be independent of age.(23)~~ Additionally, although the TN-10 placebo arm and the Fr1da group had similar HbA_{1c} levels, a higher proportion of Fr1da participants had increased HbA_{1c} values. While rising HbA_{1c} levels have been associated with increased risk of progression, it is possible that increases in HbA_{1c} in this study were not large enough to impact time to progression.(24) HLA genotypes in the populations also differed slightly.(25; 26) Interpreting differences in HLA status between these 2 groups should be done with caution because there was a high prevalence of missing data on HLA status in the Fr1da group, and the sample size was insufficient for detecting statistically significant differences in participant characteristics **(Supplementary Table 1);** however, the 2 groups had similar proportions of participants with HLA DR3. Other genetic factors such as non-

HLA alleles may have also influenced study findings as they have been associated with type 1 diabetes risk but were not assessed in these studies.(9; 27)

Several of the differences observed between the TN-10 and Fr1da groups were primarily due to the differences in study designs for selecting patients into each group. Differences in median age between the TN-10 placebo arm and Fr1da group, for example, were driven by differences in the eligibility criteria between the 2 studies; the TN-10 trial excluded individuals aged younger than 8 years, whereas the Fr1da study enrolled participants aged 1 to 21 years, leading to the younger median age in the Fr1da group. Additionally, a higher proportion of participants in the TN-10 placebo arm had an FDR with type 1 diabetes because having a relative with type 1 diabetes was a requirement for trial entry. The difference in the most frequent FDR type in the TN-10 group and the Fr1da group (sibling and parent, respectively) also most likely reflects the younger age of the Fr1da group participants.

Fasting plasma glucose levels were also slightly higher in the TN-10 placebo arm than in the Fr1da group **(Supplementary Table 1)**. As higher body mass index has been previously associated with higher fasting glucose levels, it is possible that this difference could be due to a higher proportion of individuals in the TN-10 group being overweight compared to the Fr1da group **(Supplementary Table 2)**.(28)

The presence of anti-IA-2 antibodies, HbA_{1c} >5.7%, and 120-minute OGTT results were identified in univariate Cox models to be associated with progression from stage 2 to stage 3. Adjusting for these factors resulted in an HR that was closer to 1 than the unadjusted analysis~~, suggesting that any difference in risk observed in the unadjusted analysis may have been driven by differences in these baseline characteristics between the TN-10 and Fr1da groups~~. Anti-IA-2 antibodies have been associated with increased progression risk across all stages of disease, with

a recent study demonstrating that individuals with anti-IA-2 antibodies alone had a greater progression risk than anti-IA2 negative individuals at stage 1.(17; 29-32) Therefore, these factors may be considered in future investigations of risk factors for progression to stage 3 in addition to previously identified risk factors.(25; 26; 33; 34)

The Fr1da group's relatively large stage 2 type 1 diabetes cohort size and the fact that it includes individuals from a population-based screening program is a strength. Many studies assessing rate of progression to clinical type 1 diabetes have not investigated cohorts of individuals that have stage 2 type 1 diabetes exclusively or are limited to individuals who are screened because of a~~at~~ high genetic risk of developing clinical type 1 diabetes either ~~determined by~~ due to their family history or genotype.(24; 25; 34) The findings of this study are particularly important given the observation that approximately 90% of individuals who will be diagnosed with clinical type 1 diabetes have no family history of the disease, and most of the population are unaware of their genetic risk for development of type 1 diabetes.(35-37)

A limitation of this study is the presence of an immortal time bias in the TN-10 trial participants, resulting from the fact that the stage 2 diagnosis occurred prior to randomization. However, bias introduced through immortal time was believed to be minimal based on the sensitivity analysis that showed similar time to stage 3 diagnosis using the randomization date as the index date (and not diagnosis of stage 2). There was also ~~a~~ variation in data availability. Race/ethnicity, islet antigen test results, and C-peptide levels were not recorded for the Fr1da group and therefore were not included as variables in this study. Unmeasured differences in these variables between the study groups may confound the findings. Additionally, as mentioned previously, ~~while sufficiently powered to detect a HR of 1 for progression from stage 2 to stage 3 disease in the primary analysis Cox model~~this study only had sufficient power to detect relatively

large differences in the progression rates between groups~~was not designed to detect statistically significant differences in the survival curves presented, the median time to progression~~, or patient characteristics between the study groups or subgroups.

In t~~T~~his study~~, demonstrated that~~ time to stage 3 type 1 diabetes onset did not differ significantly ~~was similar~~ between the TN-10 placebo arm and the Fr1da group in unadjusted and adjusted analyses. Furthermore, progression rates did not differ~~was similar~~ when analyses were restricted to those aged 8 to 15 years, and when Fr1da group participants were stratified by presence of an FDR with type 1 diabetes. Together, these results suggest~~indicate~~ that despite differences in demographics and the methodological limitations highlighted, the risk of type 1 diabetes progression from the TN-10 trial appears to be generalizable to European populations with and without FDRs with type 1 diabetes.

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Conflict of Interest

A.G.Z. is a member of the data monitoring committee for 2 clinical trials for Sanofi and serves on an advisory board for Sanofi. T.K. and M.Y. are employees of Evidera. M.B., O.G., and J.Z. are employees of Sanofi and may hold shares and/or stock options in the company. M.K., C.W., S.H., and A.W. have no relevant disclosures.

Author Contributions and Guarantor Statement

M.K. was involved in data collection, conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

C.W. was involved in data collection, conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

S.H. was involved in conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

A.W. was involved in conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

T.K. was involved in analysis and interpretation of data for the study and edited, reviewed, and approved the final version of the manuscript.

M.Y. was involved in analysis and interpretation of data for the study and edited, reviewed, and approved the final version of the manuscript.

M.B. was involved in conception, design, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

O.G. was involved in conception, design, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

J.Z. was involved in conception, design, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript.

A.G.Z. was involved in conception, design, conduct, and interpretation of the study and edited, reviewed, and approved the final version of the manuscript. She is the principal investigator of Fr1da.

A.G.Z. is also the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1—Baseline demographic characteristics of study participants at or near stage 2 diagnosis

Characteristic	TN-10 trial: Overall (*n* = 76)	TN-10 trial: Teplizumab arm (*n* = 44)	TN-10 trial: Placebo arm (*n* = 32)	Fr1da group (*N* = 152)	SMD (placebo arm of the TN-10 trial vs Fr1da group)
Age in years					1.35
N	76	44	32	152	
Mean (SD)	17.9 (11.5)	18.7 (11.9)	16.8 (11.0)	5.9 (3.1)	
Median (IQR)	13.0 (11.0–19.0)	14.0 (11.0–22.0)	13.0 (10.5–15.5)	5.0 (3.0–8.0)	
Minimum, maximum	8.0, 49.0	8.0, 49.0	8.0, 44.0	2.0, 15.0	
Missing, *n*	0	0	0	0	
Age categories, *n* (%)					2.61
<8 years	0 (0.0)	0 (0.0)	0 (0.0)	112 (73.7)	
≥8 and <15 years	45 (59.2)	24 (54.5)	21 (65.6)	39 (25.7)	
≥15 and <18 years	10 (13.2)	5 (11.4)	5 (15.6)	1 (0.7)	
≥18 years	21 (27.6)	15 (34.1)	6 (18.8)	0 (0.0)	
Sex, *n* (%)					-0.12
Male	42 (55.3)	25 (56.8)	17 (53.1)	90 (59.2)	
Female	34 (44.7)	19 (43.2)	15 (46.9)	62 (40.8)	
Z-score BMI for participants aged 24–228 months*					0.41
N	35	20	15	129	
Mean (SD)	0.34 (1.129)	0.07 (1.331)	0.70 (0.668)	0.32 (1.117)	
Median (IQR)	0.50 (-0.30–1.10)	0.05 (-0.70–1.05)	0.70 (0.20–1.10)	0.20 (-0.50–0.90)	

Characteristic	**TN-10 trial: Overall (*n* = 76)**	**TN-10 trial: Teplizumab arm (*n* = 44)**	**TN-10 trial: Placebo arm (*n* = 32)**	**Fr1da group (*N* = 152)**	**SMD (placebo arm of the TN-10 trial vs Fr1da group)**
Minimum, maximum	-2.8, 2.4	-2.8, 2.4	-0.4, 1.9	-1.6, 3.5	
Missing, *n*	20	9	11	23	
BMI (kg/m^2) for participants ≥229 months old*					NA
N	19	13	6	0	
Mean (SD)	27.63 (6.231)	27.50 (7.183)	27.90 (3.976)	NA (NA)	
Median (IQR)	26.40 (23.20–31.40)	24.30 (21.80–31.40)	27.30 (24.80–30.90)	NA	
Minimum, maximum	19.3, 42.4	19.3, 42.4	23.2, 33.9	NA	
Missing, *n*	2	2	0	NA	
FDR with diagnosed stage 3 T1D, *n* (%)†					1.45
Yes	70 (92.1)	42 (95.5)	28 (87.5)	45 (29.6)	
No	6 (7.9)	2 (4.5)	4 (12.5)	107 (70.4)	
Second-degree relative with diagnosed stage 3 T1D, *n* (%)†					NA
Yes	12 (15.8)	5 (11.4)	7 (21.9)	NA	
No	64 (84.2)	39 (88.6)	25 (78.1)	NA	
Third- or higher-degree relative with diagnosed stage 3 T1D, *n* (%)†					NA
Yes	3 (3.9)	1 (2.3)	2 (6.3)	NA	
No	73 (96.1)	43 (97.7)	30 (93.8)	NA	
Relationship to FDR with diagnosed stage 3 T1D, *n* (%)					

Characteristic	TN-10 trial: Overall (*n* = 76)	TN-10 trial: Teplizumab arm (*n* = 44)	TN-10 trial: Placebo arm (*n* = 32)	Fr1da group (*N* = 152)	SMD (placebo arm of the TN-10 trial vs Fr1da group)
Sibling	49 (64.5)	30 (68.2)	19 (59.4)	13 (8.6)	1.27
Offspring	13 (17.1)	7 (15.9)	6 (18.8)	0 (0.0)	0.68
Parent	13 (17.1)	7 (15.9)	6 (18.8)	33 (21.7)	-0.07
Sibling and another FDR	6 (7.9)	3 (6.8)	3 (9.4)	1 (0.7)	0.41

*Values closest to the index date (i.e., date of stage 2 confirmation) during baseline period (which starts at earliest available data and ends at index date, inclusive) were considered for all baseline characteristics. However, not all patients have a measurement for these specific variables during this period, hence the missing values at baseline for these variables.

†FDR is defined as having at least 50% of shared genes (i.e., full siblings, parents, and offspring) with the subject; second-degree relative is defined as having 25% of shared genes (i.e., grandparents, grandchildren, half-siblings, aunts, and uncles); third-degree relative is defined as having 12.5% of shared genes (i.e., first cousins, great-grandparents, and great-grandchildren). A subject can have multiple relationships to persons with T1D; in such cases, all relevant relationship groups are included in the relevant analysis.

BMI = body mass index; FDR = first-degree relative; IQR = interquartile range; NA = not available; SD = standard deviation; SMD = standardized mean difference; T1D, type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention

Figure Legends

Figure 1. Stage 3 T1D progression-free survival probability in TN-10 placebo arm and Fr1da group

A) Analyses were unadjusted. Unadjusted HR was 1.3 (95% CI: 0.8-2.1). B) Analyses were adjusted for anti-IA-2 antibodies, HbA1c >5.7%, and 120-minute OGTT results. Adjusted HR was 1.1 (95% CI: 0.6-2.1).

CI = confidence interval; HbA1c = glycated hemoglobin; HR = hazard ratio; IA-2 = islet antigen-2; OGTT = oral glucose tolerance test; T1D = type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention

Figure 2. Stage 3 T1D progression-free survival probability in the TN-10 placebo arm and Fr1da group aged 8 to 15 years

Analyses were unadjusted.

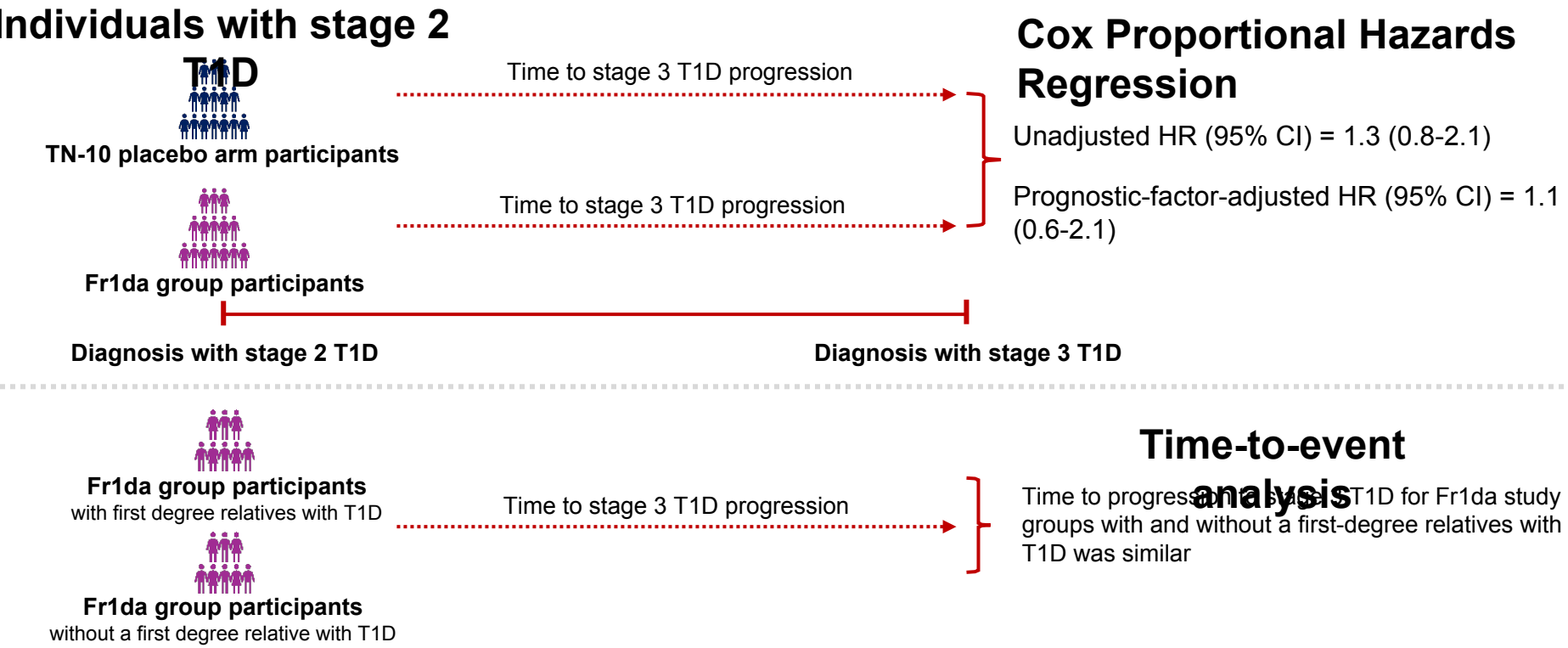
CI = confidence interval; T1D = type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention

Figure 3. Stage 3 T1D progression-free survival probability in Fr1da participants with and without first-degree relatives diagnosed with T1D

Analyses were unadjusted.

CI = confidence interval; T1D = type 1 diabetes

Time to progression to stage 3 T1D for TN-10 trial and Fr1da study groups and for Fr1da study groups with and without a first-degree relative with T1D was similar



Population risk from TN-10 is generalizable to European populations, with and without relatives with T1D

Melanie Koeger, Christiane Winkler, Sandra Hummel, Andreas Weiss, Thibaut Koutangni, Mark Yates, Mireille Bonnemaire, Oliver Guenther, Julia Zaccai, Anette-Gabriele Ziegler – Generalizability of the TN-10 trial to a European population with or without a first-degree relative with type 1 diabetes, 2025

~~Teplizumab to delay stage 3 type 1 diabetes:~~ Generalizability of progression risk in the TN-10 trial to a European population with or without a first-degree relative with type 1 diabetes

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SUPPLEMENTARY METHODS

Study Design

Eligibility Criteria

Key differences in eligibility criteria in TN-10 trial and Fr1da study include:

- Age
    - TN-10 trial – ≥8 years
    - Fr1da study – 1-21 years
- Body weight
    - TN-10 trial – ≥26 kg
    - Fr1da study – no requirement
- Family history
    - TN-10 trial – 1st-, 2nd-, or 3rd-degree relative with type 1 diabetes required
    - Fr1da study – no requirement

Assessment of Prognostic Factors for Progression from stage 2 to stage 3 type 1 diabetes

Univariate Cox PH models were applied to the TN-10 placebo arm and Fr1da group to investigate the association of the following prognostic factors with progression to stage 3 type 1 diabetes:

- Age at index date
- Sex
- BMI category
    - *Z*-score BMI for participants aged 24–228 months
    - BMI (kg/m^2) for participants ≥229 months old
- Existence of an FDR with diagnosed stage 3 type 1 diabetes
- Positivity of each anti-islet autoantibody (anti-GAD65, anti-mIAA, anti-IA-2, anti-ZnT8)

- Number of positive autoantibodies
- Presence of DR3 allele
- Presence of DR4 allele
- HbA_{1c} level
- HbA_{1c} categories (normal: <5.7%, prediabetes: 5.7%–6.4%)
- OGTT results at 0, 30, 60, 90, and 120 minutes (mg/dL)

Supplementary Table 1—Baseline clinical characteristics of study participants at or near stage 2 diagnosis

Characteristics	**TN-10 trial: Overall (*N* = 76)**	**TN-10 trial: Teplizumab arm (*N* = 44)**	**TN-10 trial: Placebo arm (*N* = 32)**	**Fr1da group (*N* = 152)**	**SMD (TN-10 placebo arm vs Fr1da group)**
Age in years					1.35
n	76	44	32	152	
Mean (SD)	17.9 (11.5)	18.7 (11.9)	16.8 (11.0)	5.9 (3.1)	
Median (IQR)	13.0 (11.0–19.0)	14.0 (11.0–22.0)	13.0 (10.5–15.5)	5.0 (3.0–8.0)	
Minimum, maximum	8.0, 49.0	8.0, 49.0	8.0, 44.0	2.0, 15.0	
Missing, *n*	0	0	0	0	
Islet autoantibody test positivity					
Anti-GAD65, *n* (%)					0.23
Positive	68 (89.5)	40 (90.9)	28 (87.5)	120 (78.9)	
Negative	8 (10.5)	4 (9.1)	4 (12.5)	32 (21.1)	
mIAA, *n* (%)					-0.97
Positive	30 (39.5)	19 (43.2)	11 (34.4)	118 (77.6)	
Negative	46 (60.5)	25 (56.8)	21 (65.6)	34 (22.4)	
Anti-IA-2, *n* (%)					-0.16
Positive	50 (65.8)	26 (59.1)	24 (75.0)	124 (81.6)	
Negative	26 (34.2)	18 (40.9)	8 (25.0)	28 (18.4)	
ICA, *n* (%)					NA
Positive	57 (75.0)	29 (65.9)	28 (87.5)	NA	

Characteristics	**TN-10 trial: Overall (*N* = 76)**	**TN-10 trial: Teplizumab arm (*N* = 44)**	**TN-10 trial: Placebo arm (*N* = 32)**	**Fr1da group (*N* = 152)**	**SMD (TN-10 placebo arm vs Fr1da group)**
Negative	19 (25.0)	15 (34.1)	4 (12.5)	NA	
Anti-ZnT8, *n* (%)					-0.09
Positive	56 (73.7)	32 (72.7)	24 (75.0)	120 (78.9)	
Negative	20 (26.3)	12 (27.3)	8 (25.0)	32 (21.1)	
Number of positive autoantibodies, * *n* (%)					NA
1	1 (1.3)	1 (2.3)	0 (0.0)	0 (0.0)	
2	19 (25.0)	12 (27.3)	7 (21.9)	37 (24.3)	
3	16 (21.1)	11 (25.0)	5 (15.6)	52 (34.2)	
4	26 (34.2)	12 (27.3)	14 (43.8)	63 (41.4)	
5	14 (18.4)	8 (18.2)	6 (18.8)	NA	
HLA risk alleles					
DR3 present, *n* (%)					0.97
Yes	35 (46.1)	20 (45.5)	15 (46.9)	52 (34.2)	
No	38 (50.0)	21 (47.7)	17 (53.1)	52 (34.2)	
Missing	3 (3.9)	3 (6.8)	0 (0.0)	48 (31.6)	
DR4 present, *n* (%)					1.01
Yes	47 (61.8)	26 (59.1)	21 (65.6)	83 (54.6)	
No	26 (34.2)	15 (34.1)	11 (34.4)	21 (13.8)	
Missing	3 (3.9)	3 (6.8)	0 (0.0)	48 (31.6)	

Characteristics	**TN-10 trial: Overall (*N* = 76)**	**TN-10 trial: Teplizumab arm (*N* = 44)**	**TN-10 trial: Placebo arm (*N* = 32)**	**Fr1da group (*N* = 152)**	**SMD (TN-10 placebo arm vs Fr1da group)**
HLA risk allele categories, *n* (%)					1.03
Neither DR3 nor DR4	8 (10.5)	5 (11.4)	3 (9.4)	5 (3.3)	
DR3 only	18 (23.7)	10 (22.7)	8 (25.0)	16 (10.5)	
DR4 only	30 (39.5)	16 (36.4)	14 (43.8)	47 (30.9)	
Both DR3 and DR4	17 (22.4)	10 (22.7)	7 (21.9)	36 (23.7)	
Missing	3 (3.9)	3 (6.8)	0 (0.0)	48 (31.6)	
HbA_{1c} and glucose levels					
HbA_{1c} (%)†					-0.53
n	55	33	22	146	
Mean (SD)	5.18 (0.321)	5.15 (0.341)	5.23 (0.288)	5.40 (0.360)	
Median (IQR)	5.20 (4.90–5.40)	5.20 (4.90–5.30)	5.30 (5.20–5.40)	5.40 (5.20–5.60)	
Minimum, maximum	4.3, 6.1	4.6, 6.1	4.3, 5.6	4.0, 6.4	
Missing, *n*	21	11	10	6	
HbA_{1c} (%), *n* (%)†					1.00
Normal: <5.7%	52 (68.4)	30 (68.2)	22 (68.8)	117 (77.0)	
Prediabetes: 5.7%–6.4%	3 (3.9)	3 (6.8)	0 (0.0)	29 (19.1)	
Diabetes: ≥6.5%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Missing	21 (27.6)	11 (25.0)	10 (31.3)	6 (3.9)	
Glucose tolerance test results					

Characteristics	**TN-10 trial: Overall (*N* = 76)**	**TN-10 trial: Teplizumab arm (*N* = 44)**	**TN-10 trial: Placebo arm (*N* = 32)**	**Fr1da group (*N* = 152)**	**SMD (TN-10 placebo arm vs Fr1da group)**
At 0 minutes (mg/dL)					0.84
n	76	44	32	152	
Mean (SD)	96.20 (9.085)	96.25 (8.278)	96.13 (10.229)	85.14 (15.374)	
Median (IQR)	94.50 (89.50–103.00)	95.50 (90.00–103.00)	94.00 (88.50–103.00)	84.00 (73.50–95.00)	
Minimum, maximum	79.0, 118.0	82.0, 113.0	79.0, 118.0	43.0, 121.0	
Missing, *n*	0	0	0	0	
At 30 minutes (mg/dL)					-0.20
n	76	44	32	151	
Mean (SD)	168.12 (28.937)	167.34 (30.336)	169.19 (27.337)	175.46 (36.118)	
Median (IQR)	171.50 (148.00–186.50)	169.00 (148.00–187.50)	173.00 (148.00–186.50)	178.00 (148.00–202.00)	
Minimum, maximum	99.0, 237.0	99.0, 237.0	112.0, 219.0	88.0, 260.0	
Missing, *n*	0	0	0	1	
At 60 minutes (mg/dL)					0.34
n	76	44	32	151	
Mean (SD)	187.57 (30.674)	189.32 (33.130)	185.16 (27.267)	174.36 (36.064)	
Median (IQR)	187.00 (168.50–210.00)	187.00 (167.00–216.00)	187.50 (168.50–205.00)	171.00 (149.00–202.00)	
Minimum, maximum	97.0, 257.0	97.0, 254.0	124.0, 257.0	74.0, 263.0	
Missing, *n*	0	0	0	1	

Characteristics	TN-10 trial: Overall (*N* = 76)	TN-10 trial: Teplizumab arm (*N* = 44)	TN-10 trial: Placebo arm (*N* = 32)	Fr1da group (*N* = 152)	SMD (TN-10 placebo arm vs Fr1da group)
At 90 minutes (mg/dL)					0.50
n	76	44	32	149	
Mean (SD)	174.00 (32.338)	176.61 (31.660)	170.41 (33.415)	153.33 (35.198)	
Median (IQR)	175.00 (150.00–198.00)	177.50 (156.50–200.50)	172.00 (145.00–189.50)	154.00 (128.00–178.00)	
Minimum, maximum	101.0, 244.0	113.0, 236.0	101.0, 244.0	70.0, 235.0	
Missing, *n*	0	0	0	3	
At 120 minutes (mg/dL)					0.49
n	76	44	32	152	
Mean (SD)	155.72 (28.715)	158.11 (28.056)	152.44 (29.730)	138.02 (29.592)	
Median (IQR)	150.00 (140.50–175.00)	155.00 (140.00–175.00)	147.50 (141.50–176.50)	142.50 (115.00–157.50)	
Minimum, maximum	81.0, 242.0	87.0, 242.0	81.0, 198.0	51.0, 197.0	
Missing, *n*	0	0	0	0	

*ICA was not measured in the Fr1da group. Therefore, it was not expected that participants in the Fr1da group would have up to 5 autoantibodies as among the TN-10 trial participants.
†Values closest to the index date (i.e., date of stage 2 confirmation) during baseline period (which starts at earliest available data and ends at index date, inclusive) were considered for all baseline characteristics. However, not all patients have a measurement for these specific variables during this period, hence the missing values at baseline for these variables.

GAD65 = glutamic acid decarboxylase 65-kDA form; HbA_{1c} = glycated hemoglobin; HLA = human leukocyte antigen; IA-2 = insulinoma-associated antigen 2; ICA = islet cell autoantibody; IQR = interquartile range; mIAA = micro-insulin autoantibody; NA = not available; SD = standard deviation; SMD = standardized mean difference; TN-10 = TrialNet Anti-CD3 Prevention; ZnT8 = zinc transporter 8

Supplementary Table 2—Baseline characteristics of study participants at or near stage 2 diagnosis in the TN-10 placebo arm and Fr1da group aged 8 to 15 years

Variable	Descriptive Data	Bivariate Comparison	
	TN-10 placebo arm aged 8-15 years	Fr1da group aged 8-15 years	TN-10 placebo arm aged 8-15 years vs Fr1da group aged 8-15 years
	N=24	N=40	SMD
Demographic data			
Age, years			0.5276
n	24	40	
Mean (SD)	11.5 (2.4)	10.3 (1.8)	
Median (IQR)	11.5 (9.0–13.5)	10.0 (9.0–11.0)	
Minimum, maximum	8.0, 15.0	8.0, 15.0	
Missing, n	0	0	
Age categories, n (%)			0.3867
<8 years	0 (0.0%)	0 (0.0%)	
≥8 and <15 years	21 (87.5%)	39 (97.5%)	
≥15 and <18 years	3 (12.5%)	1 (2.5%)	
≥18 years	0 (0.0%)	0 (0.0%)	
Sex, n (%)			-0.0167
Male	13 (54.2%)	22 (55.0%)	
Female	11 (45.8%)	18 (45.0%)	
Z-score BMI*			-0.0604
n	13	34	
Mean (SD)	0.70 (0.711)	0.76 (1.259)	
Median (IQR)	0.70 (0.20–1.10)	0.60 (-0.40–1.90)	
Minimum, maximum	-0.4, 1.9	-1.3, 3.5	

Variable	Descriptive Data	Bivariate Comparison	
	TN-10 placebo arm aged 8-15 years	**Fr1da group aged 8-15 years**	**TN-10 placebo arm aged 8-15 years vs Fr1da group aged 8-15 years**
	N=24	N=40	SMD
Missing, n	11	6	
Z-score BMI categories, n (%)*			1.0037
Normal weight	8 (33.3%)	20 (50.0%)	
Overweight	5 (20.8%)	6 (15.0%)	
Obese	0 (0.0%)	8 (20.0%)	
Missing	11 (45.8%)	6 (15.0%)	
Existence of a first-degree relative† with diagnosed stage 3 T1D, n (%)			0.8133
Yes	20 (83.3%)	19 (47.5%)	
No	4 (16.7%)	21 (52.5%)	
Existence of a second-degree relative† with diagnosed stage 3 T1D, n (%)			NA
Yes	6 (25.0%)	NA	
No	18 (75.0%)	NA	
Existence of a third- or higher-degree relative† with diagnosed stage 3 T1D, n (%)			NA
Yes	2 (8.3%)	NA	
No	22 (91.7%)	NA	
Relationship to first-degree relative with diagnosed stage 3 T1D, n (%)			
Sibling	18 (75.0%)	6 (15.0%)	1.5119
Offspring	0 (0.0%)	0 (0.0%)	0
Parent	5 (20.8%)	13 (32.5%)	-0.2661

Variable	Descriptive Data	Bivariate Comparison	
	TN-10 placebo arm aged 8-15 years	**Fr1da group aged 8-15 years**	**TN-10 placebo arm aged 8-15 years vs Fr1da group aged 8-15 years**
	N=24	N=40	SMD
Sibling and another first-degree relative	3 (12.5%)	0 (0.0%)	0.5345
Islet autoantibody test positivity			
Anti-GAD65, n (%)			0.3244
Positive	21 (87.5%)	30 (75.0%)	
Negative	3 (12.5%)	10 (25.0%)	
mIAA, n (%)			-0.3730
Positive	10 (41.7%)	24 (60.0%)	
Negative	14 (58.3%)	16 (40.0%)	
Anti-IA-2, n (%)			-0.1526
Positive	19 (79.2%)	34 (85.0%)	
Negative	5 (20.8%)	6 (15.0%)	
ICA, n (%)			NA
Positive	22 (91.7%)	NA	
Negative	2 (8.3%)	NA	
Anti-ZnT8, n (%)			-0.1841
Positive	18 (75.0%)	33 (82.5%)	
Negative	6 (25.0%)	7 (17.5%)	
Number of positive autoantibodies, n (%)			0.9979
1	0 (0.0%)	0 (0.0%)	
2	4 (16.7%)	12 (30.0%)	
3	4 (16.7%)	15 (37.5%)	
4	10 (41.7%)	13 (32.5%)	
5	6 (25.0%)	NA	

Variable	Descriptive Data	Bivariate Comparison	
	TN-10 placebo arm aged 8-15 years	**Fr1da group aged 8-15 years**	**TN-10 placebo arm aged 8-15 years vs Fr1da group aged 8-15 years**
	N=24	N=40	SMD
HLA risk alleles*			
DR3 present, n (%)			0.8666
Yes	13 (54.2%)	17 (42.5%)	
No	11 (45.8%)	12 (30.0%)	
Missing	0 (0.0%)	11 (27.5%)	
DR4 present, n (%)			1.0053
Yes	15 (62.5%)	23 (57.5%)	
No	9 (37.5%)	6 (15.0%)	
Missing	0 (0.0%)	11 (27.5%)	
HLA risk allele categories, n (%)			1.0088
Neither DR3 nor DR4	2 (8.3%)	0 (0.0%)	
DR3 only	7 (29.2%)	6 (15.0%)	
DR4 only	9 (37.5%)	12 (30.0%)	
Both DR3 and DR4	6 (25.0%)	11 (27.5%)	
Missing	0 (0.0%)	11 (27.5%)	
HbA_{1c} and glucose levels			
HbA_{1c} (%)*			-0.9673
n	14	38	
Mean (SD)	5.23 (0.209)	5.47 (0.291)	
Median (IQR)	5.25 (5.20:5.40)	5.40 (5.30:5.60)	
Minimum, maximum	4.8, 5.5	5.1, 6.4	
Missing, n	10	2	

Variable	Descriptive Data	Bivariate Comparison	
	TN-10 placebo arm aged 8-15 years	**Fr1da group aged 8-15 years**	**TN-10 placebo arm aged 8-15 years vs Fr1da group aged 8-15 years**
	N=24	N=40	SMD
HbA_{1c} (%), n (%)*			1.1366
Normal: <5.7%	14 (58.3%)	33 (82.5%)	
Prediabetes: 5.7%–6.4%	0 (0.0%)	5 (12.5%)	
Diabetes: ≥6.5%	0 (0.0%)	0 (0.0%)	
Missing	10 (41.7%)	2 (5.0%)	
Glucose tolerance test results			
At 0 minutes (mg/dL)			0.1480
n	24	40	
Mean (SD)	93.71 (8.483)	91.93 (14.774)	
Median (IQR)	93.50 (86.50:102.50)	94.50 (79.00:102.50)	
Minimum, maximum	79.0, 107.0	61.0, 121.0	
Missing, n	0	0	
At 30 minutes (mg/dL)			-0.2214
n	24	40	
Mean (SD)	168.92 (29.095)	175.53 (30.579)	
Median (IQR)	173.00 (145.00:185.50)	178.00 (148.00:199.00)	
Minimum, maximum	112.0, 219.0	121.0, 257.0	
Missing, n	0	0	
At 60 minutes (mg/dL)			0.6132
n	24	40	
Mean (SD)	189.46 (28.719)	168.60 (38.594)	
Median (IQR)	198.50 (171.50:207.50)	169.50 (146.50:197.50)	
Minimum, maximum	124.0, 257.0	74.0, 247.0	

Variable	Descriptive Data	Bivariate Comparison	
	TN-10 placebo arm aged 8-15 years	Fr1da group aged 8-15 years	TN-10 placebo arm aged 8-15 years vs Fr1da group aged 8-15 years
	N=24	N=40	SMD
Missing, n	0	0	
At 90 minutes (mg/dL)			0.6154
n	24	40	
Mean (SD)	173.33 (29.517)	152.15 (38.710)	
Median (IQR)	175.00 (148.00:194.50)	161.00 (125.00:176.50)	
Minimum, maximum	124.0, 234.0	76.0, 235.0	
Missing, n	0	0	
At 120 minutes (mg/dL)			0.5582
n	24	40	
Mean (SD)	158.17 (24.043)	143.08 (29.727)	
Median (IQR)	154.00 (142.00:176.50)	146.00 (129.50:165.50)	
Minimum, maximum	115.0, 198.0	76.0, 194.0	
Missing, n	0	0	

*Values closest to the index date (i.e., date of stage 2 confirmation) during baseline period (which starts at earliest available data and ends at index date, inclusive) were considered for all baseline characteristics. However, not all patients have a measurement for these specific variables during this period, hence the missing values at baseline for these variables.

†First-degree relative is defined as having at least 50% of shared genes (i.e., full siblings, parents, and offspring) with the subject; second-degree relative is defined as having 25% of shared genes (i.e., grandparents, grandchildren, half-siblings, aunts, and uncles); third-degree relative is defined as having 12.5% of shared genes (i.e., first cousins, great-grandparents, and great-grandchildren). A subject can have multiple relationships to persons with T1D; in such cases, all relevant relationship groups are included in the relevant analysis.

BMI = body mass index; GAD65 = glutamic acid decarboxylase 65-kDA form; HbA_{1c} = glycated hemoglobin; HLA = human leukocyte antigen; IA-2 = insulinoma-associated antigen 2; ICA = islet cell autoantibody; IQR = interquartile range; mIAA = micro-insulin autoantibody; NA = not available; SD = standard deviation; SMD = standardized mean difference; T1D = type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention; ZnT8 = zinc transporter 8

Supplementary Table 3—Baseline characteristics of study participants at or near stage 2 diagnosis in the Fr1da group with and without first-degree relatives diagnosed with T1D

Variable	Descriptive Data	Bivariate Comparison	
	Fr1da group (with FDRs diagnosed with stage 3 T1D)	Fr1da group (without FDRs diagnosed with stage 3 T1D)	Participants in the Fr1da group with FDRs diagnosed with stage 3 T1D vs without
	n=45	n=107	SMD
Demographic data			
Age in years			0.5218
n	45	107	
Mean (SD)	7.1 (3.5)	5.5 (2.8)	
Median (IQR)	7.0 (4.0:10.0)	5.0 (3.0:7.0)	
Minimum, maximum	2.0, 15.0	2.0, 14.0	
Missing, n	0	0	
Age categories, n (%)			0.5092
<8 years	26 (57.8%)	86 (80.4%)	
≥8 and <15 years	18 (40.0%)	21 (19.6%)	
≥15 and <18 years	1 (2.2%)	0 (0.0%)	
≥18 years	0 (0.0%)	0 (0.0%)	
Sex, n (%)			-0.1054
Male	25 (55.6%)	65 (60.7%)	
Female	20 (44.4%)	42 (39.3%)	
Z-score BMI*			0.3906
n	35	94	
Mean (SD)	0.63 (0.974)	0.21 (1.150)	
Median (IQR)	0.60 (0.00:1.20)	0.00 (-0.60:0.70)	
Minimum, maximum	-1.3, 2.6	-1.6, 3.5	

Variable	Descriptive Data	Bivariate Comparison	
	Fr1da group (with FDRs diagnosed with stage 3 T1D)	Fr1da group (without FDRs diagnosed with stage 3 T1D)	Participants in the Fr1da group with FDRs diagnosed with stage 3 T1D vs without
	n=45	n=107	SMD
Missing, n	10	13	
Z-score BMI categories, n (%)*			0.3909
Normal weight	23 (51.1%)	74 (69.2%)	
Overweight	8 (17.8%)	11 (10.3%)	
Obese	4 (8.9%)	9 (8.4%)	
Missing	10 (22.2%)	13 (12.1%)	
Existence of an FDR† with diagnosed stage 3 T1D, n (%)			NA
Yes	45 (100.0%)	0 (0.0%)	
No	0 (0.0%)	107 (100.0%)	
Relationship to FDR with diagnosed stage 3 T1D, n (%)			
Sibling	13 (28.9%)	0 (0.0%)	NA
Offspring	0 (0.0%)	0 (0.0%)	NA
Parent	33 (73.3%)	0 (0.0%)	NA
Sibling and another FDR	1 (2.2%)	0 (0.0%)	NA
Islet autoantibody test positivity			
Anti-GAD65, n (%)			0.3725
Positive	40 (88.9%)	80 (74.8%)	
Negative	5 (11.1%)	27 (25.2%)	
mIAA, n (%)			0.1605
Positive	37 (82.2%)	81 (75.7%)	
Negative	8 (17.8%)	26 (24.3%)	

Variable	Descriptive Data	Bivariate Comparison	
	Fr1da group (with FDRs diagnosed with stage 3 T1D)	Fr1da group (without FDRs diagnosed with stage 3 T1D)	Participants in the Fr1da group with FDRs diagnosed with stage 3 T1D vs without
	n=45	n=107	SMD
Anti-IA-2, n (%)			-0.1365
Positive	35 (77.8%)	89 (83.2%)	
Negative	10 (22.2%)	18 (16.8%)	
ICA, n (%)			NA
Positive	NA	NA	
Negative	NA	NA	
Anti-ZnT8, n (%)			-0.0405
Positive	35 (77.8%)	85 (79.4%)	
Negative	10 (22.2%)	22 (20.6%)	
Number of positive autoantibodies, n (%)			0.3312
1	0 (0.0%)	0 (0.0%)	
2	11 (24.4%)	26 (24.3%)	
3	11 (24.4%)	41 (38.3%)	
4	23 (51.1%)	40 (37.4%)	
5	NA	NA	
HLA risk alleles*			
DR3 present, n (%)			0.3067
Yes	18 (40.0%)	34 (31.8%)	
No	11 (24.4%)	41 (38.3%)	
Missing	16 (35.6%)	32 (29.9%)	

Variable	Descriptive Data	Bivariate Comparison	
	Fr1da group (with FDRs diagnosed with stage 3 T1D)	**Fr1da group (without FDRs diagnosed with stage 3 T1D)**	**Participants in the Fr1da group with FDRs diagnosed with stage 3 T1D vs without**
	n=45	n=107	SMD
DR4 present, n (%)			0.1280
Yes	23 (51.1%)	60 (56.1%)	
No	6 (13.3%)	15 (14.0%)	
Missing	16 (35.6%)	32 (29.9%)	
HLA risk allele categories, n (%)			0.4215
Neither DR3 nor DR4	0 (0.0%)	5 (4.7%)	
DR3 only	6 (13.3%)	10 (9.3%)	
DR4 only	11 (24.4%)	36 (33.6%)	
Both DR3 and DR4	12 (26.7%)	24 (22.4%)	
Missing	16 (35.6%)	32 (29.9%)	
HbA_{1c} and glucose levels			
HbA_{1c} (%)*			-0.1431
n	43	103	
Mean (SD)	5.37 (0.258)	5.42 (0.395)	
Median (IQR)	5.30 (5.20:5.50)	5.40 (5.20:5.60)	
Minimum, maximum	4.8, 6.0	4.0, 6.4	
Missing, n	2	4	
HbA_{1c} (%), n (%)*			0.2160
Normal: <5.7%	37 (82.2%)	80 (74.8%)	
Prediabetes: 5.7%–6.4%	6 (13.3%)	23 (21.5%)	
Diabetes: ≥6.5%	0 (0.0%)	0 (0.0%)	
Missing	2 (4.4%)	4 (3.7%)	

Variable	Descriptive Data	Bivariate Comparison	
	Fr1da group (with FDRs diagnosed with stage 3 T1D)	Fr1da group (without FDRs diagnosed with stage 3 T1D)	Participants in the Fr1da group with FDRs diagnosed with stage 3 T1D vs without
	n=45	n=107	SMD
Glucose tolerance test results			
At 0 minutes (mg/dL)			0.3457
n	45	107	
Mean (SD)	88.98 (16.971)	83.53 (14.432)	
Median (IQR)	89.00 (77.00:99.00)	83.00 (73.00:95.00)	
Minimum, maximum	43.0, 121.0	45.0, 118.0	
Missing, n	0	0	
At 30 minutes (mg/dL)			-0.0210
n	45	106	
Mean (SD)	174.93 (35.594)	175.69 (36.504)	
Median (IQR)	180.00 (150.00:200.00)	176.00 (148.00:203.00)	
Minimum, maximum	100.0, 257.0	88.0, 260.0	
Missing, n	0	1	
At 60 minutes (mg/dL)			-0.3625
n	44	107	
Mean (SD)	165.09 (36.963)	178.17 (35.156)	
Median (IQR)	165.50 (143.50:198.00)	175.00 (153.00:204.00)	
Minimum, maximum	93.0, 243.0	74.0, 263.0	
Missing, n	1	0	
At 90 minutes (mg/dL)			-0.4210
n	45	104	
Mean (SD)	143.02 (36.096)	157.79 (34.017)	

Variable	Descriptive Data	Bivariate Comparison	
	Fr1da group (with FDRs diagnosed with stage 3 T1D)	Fr1da group (without FDRs diagnosed with stage 3 T1D)	Participants in the Fr1da group with FDRs diagnosed with stage 3 T1D vs without
	n=45	n=107	SMD
Median (IQR)	142.00 (113.00:169.00)	157.00 (130.00:184.00)	
Minimum, maximum	70.0, 220.0	78.0, 235.0	
Missing, n	0	3	
At 120 minutes (mg/dL)			-0.0903
n	45	107	
Mean (SD)	136.16 (28.490)	138.80 (30.141)	
Median (IQR)	145.00 (111.00:157.00)	142.00 (117.00:158.00)	
Minimum, maximum	76.0, 183.0	51.0, 197.0	
Missing, n	0	0	

*Values closest to the index date (i.e., date of stage 2 confirmation) during baseline period (which starts at earliest available data and ends at index date, inclusive) were considered for all baseline characteristics. However, not all patients have a measurement for these specific variables during this period, hence the missing values at baseline for these variables.

†Fr1da group includes participants with first-degree relatives with T1D and those with no known relationship with a relative diagnosed with T1D. First-degree relative is defined as having at least 50% of shared genes (i.e., full siblings, parents, and offspring) with the subject. A subject can have multiple relationships to persons with T1D; in such cases, all relevant relationship groups are included in the relevant analysis.

BMI = body mass index; FDR = first-degree relative; GAD65 = glutamic acid decarboxylase 65-kDA form; HbA_{1c} = glycated hemoglobin; HLA = human leukocyte antigen; IA-2 = insulinoma-associated antigen 2; ICA = islet cell autoantibody; IQR = interquartile range; mIAA = micro-insulin autoantibody; NA = not available; SD = standard deviation; SMD = standardized mean difference; T1D = type 1 diabetes; ZnT8 = zinc transporter 8

Supplementary Table 4—Incidence rates of stage 3 T1D onset per 1,000 person-years in the TN-10 placebo arm and the Fr1da group

	Main Analysis		Subgroup Analyses			
	TN-10 placebo arm N=32	Fr1da group N=152	Aged 8-15 years		Fr1da group by FDR status	
			TN-10 placebo arm n=24	Fr1da group n=40	With FDRs diagnosed with stage 3 T1D n=45	Without FDRs diagnosed with stage 3 T1D n=107
Number of people with new onset of stage 3 T1D	23 (71.9%)	80 (52.6%)	16 (66.7%)	18 (45.0%)	20 (44.4%)	60 (56.1%)
Total person-years at risk	69.6	323.1	42.8	67.6	102.5	220.6
Incidence rate of stage 3 T1D onset (per 1,000 person-years)	330.7	247.6	373.4	266.4	195.2	271.9
95% CI	209.6, 496.2	196.3, 308.1	213.4, 606.4	157.9, 421.1	119.2, 301.4	207.5, 350.0

CI = confidence interval; FDR = first-degree relative; T1D = type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention
Note: Participants with FDRs excluded those with only second- or third-degree relatives in the Fr1da study and the TN-10 trial.

Supplementary Table 5—Cumulative incidence of stage 3 T1D diagnosis for the TN-10 placebo arm and Fr1da group

Time From Index	Cumulative Incidence (95% CI)	
	TN-10 placebo arm (N=32)	Fr1da group (N=152)
6 months	19.2 (9.1–37.8)	9.4 (5.6–15.6)
9 months	28.9 (16.2–48.2)	16.7 (11.5–24.1)
12 months	32.1 (18.7–51.5)	20.6 (14.7–28.4)
18 months	41.8 (26.8–60.9)	35.6 (28.0–44.6)
24 months	48.5 (32.7–67.1)	43.7 (35.4–53.0)
36 months	63.9 (46.7–80.9)	56.7 (47.6–66.2)
48 months	68.4 (50.9–84.6)	64.6 (55.1–74.1)
70 months (end of follow-up)	87.4 (68.4–97.6)	72.4 (62.5–81.5)

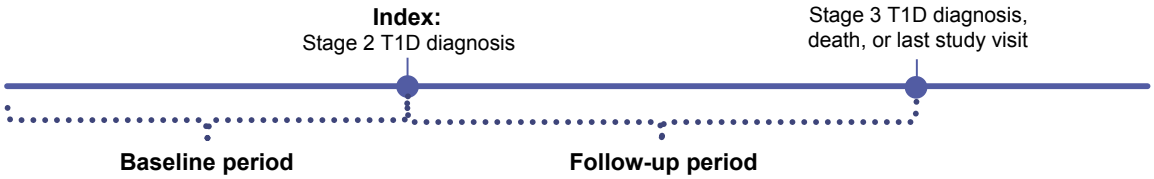
CI = confidence interval; T1D = type 1 diabetes; TN-10 = TrialNet Anti-CD3 Prevention

Supplementary Table 6—Type II error for the unadjusted and adjusted Cox proportional hazards model with a one-tailed alpha of 0.05*

HR	**1.5**	**2**	**2.5**	**3**
Type II error (beta) for the unadjusted analysis†	53.4%	15.4%	3%	0.5%
Type II error (beta) for the adjusted analysis‡	63.0%	27.5%	9.3%	2.8%

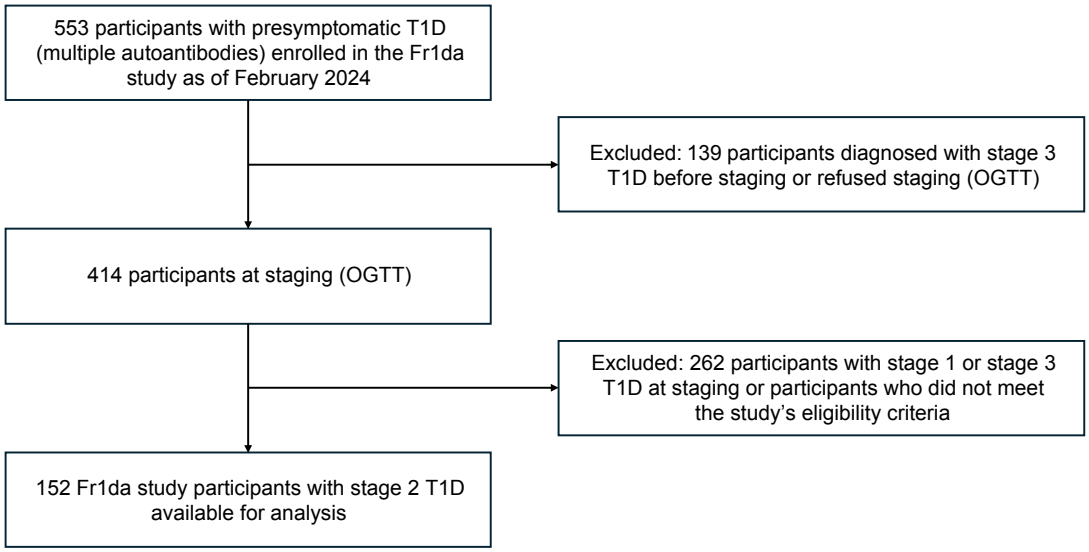
*A one-tailed alpha of 0.05 was used as inferiority was being assessed.
†Sample size = 184; proportion exposed = 152/184; proportion with outcome = 103/184.
‡Sample size = 168; proportion exposed = 146/168; proportion with outcome = 92/168.
HR = hazard ratio.

Supplementary Figure 1—Study design schematic

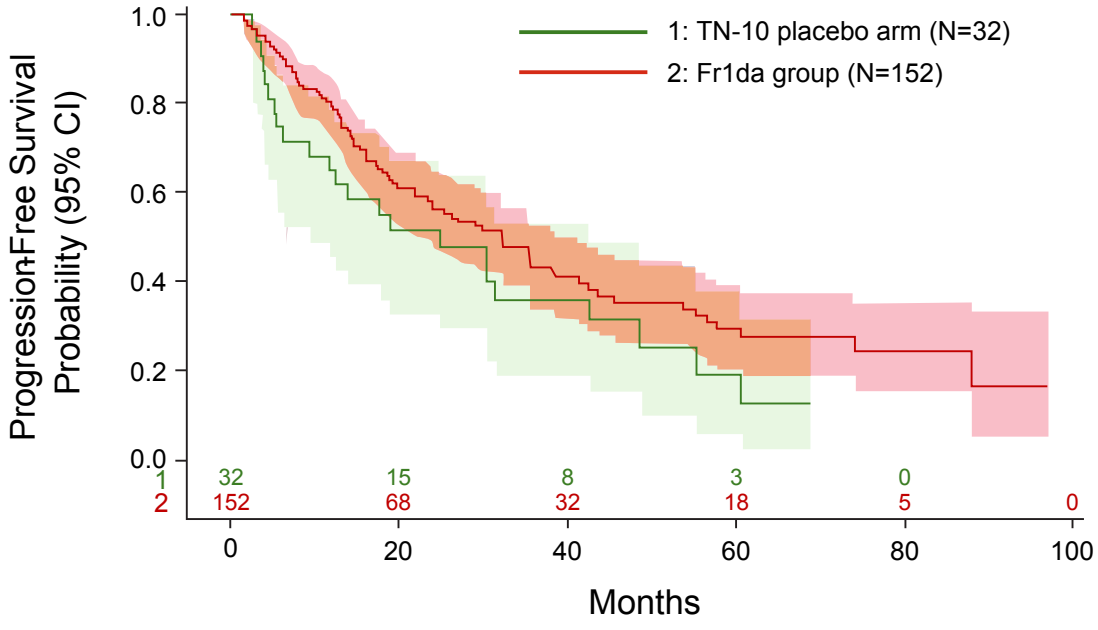


T1D = type 1 diabetes

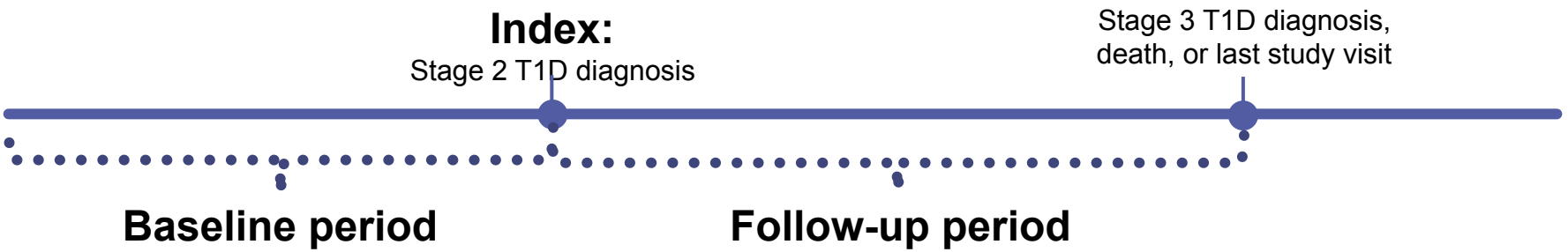
Supplementary Figure 2—Fr1da group selection attrition

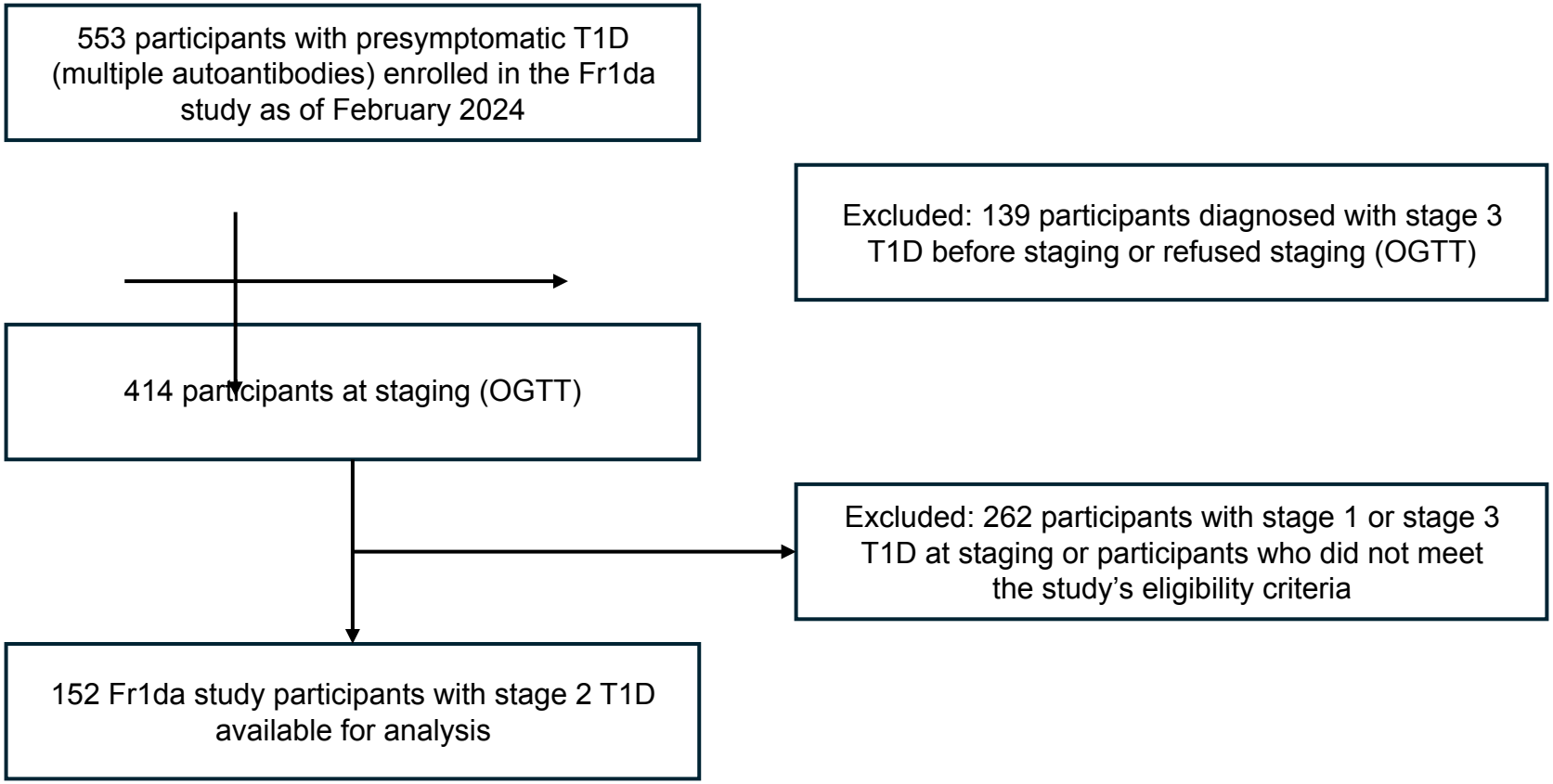


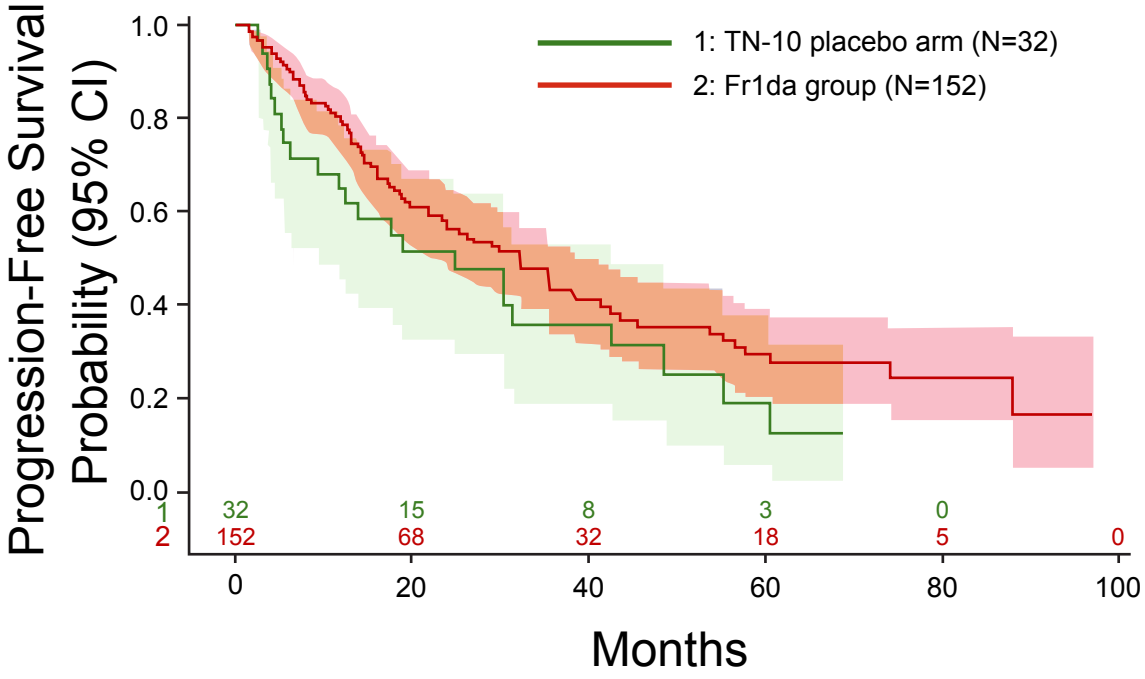
OGTT = oral glucose tolerance test; T1D = type 1 diabetes**Supplementary Figure 3—Stage 3 T1D progression-free survival probability in the TN-10 placebo arm and the Fr1da group using randomization date as index date for TN-10 placebo arm instead of stage 2 confirmation date – sensitivity analysis**



T1D = type 1 diabetes


Index:
Stage 2 T1D diagnosis
Stage 3 T1D diagnosis, death, or last study visit
Baseline period
Follow-up period


553 participants with presymptomatic T1D (multiple autoantibodies) enrolled in the Fr1da study as of February 2024
Excluded: 139 participants diagnosed with stage 3 T1D before staging or refused staging (OGTT)
414 participants at staging (OGTT)
Excluded: 262 participants with stage 1 or stage 3 T1D at staging or participants who did not meet the study's eligibility criteria
152 Fr1da study participants with stage 2 T1D available for analysis


Progression-Free Survival
Probability (95% CI)
1.0
0.8
0.6
0.4
0.2
0.0
1: TN-10 placebo arm (N=32)
2: Fr1da group (N=152)
1 32 15 8 3 0
2 152 68 32 18 5 0
0
20
40
60
80
100
Months