STATISTICAL ANALYSIS PLAN

Study title	An Open-Label Study to Evaluate the Safety of Teplizumab (PRV-031) in At-Risk Relatives Who Develop Type 1 Diabetes
Study No/Code	PRV-031-002
Phase	II
Sponsor	Provention Bio, Inc.
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This study was conducted in accordance with GCP.

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the time-versus-concentration curve
BMI	Body Mass Index
BSA	Body Surface Area
CMV	Cytomegalovirus
CTCAE	NCI Common Terminology Criteria for Adverse Events
EBV	Epstein-Barr Virus
GADA	Glutamic Acid Decarboxylase (GAD65)
HbA1c	Hemoglobin A1c
IA-2	Islet Antigen 2
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IV	Intravenous(ly)
MedDRA	Medical dictionary for regulatory activities
mIAA	Major Islet Autoantibodies against Insulin
MMTT	Mixed meal tolerance test
PK	Pharmacokinetics
qPCR	Quantitative Polymerase Chain Reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System
SD	Standard deviation
T1D	Type 1 diabetes
TEAE	Treatment emergent adverse event
TN-10	Anti-CD3 Monoclonal Antibody (Teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus Trial
WHODrug	World health organization drug dictionary
ZnT8	Zinc Transporter 8

1 INTRODUCTION

This is a statistical analysis plan (SAP) for study PRV-031-002 which is based on the final study protocol version 1.0 (dated 02DEC2019). This SAP describes the statistical analyses which will be presented in the clinical study report.

The SAP is a supplement to the study protocol, which should be referred to for additional details on study objectives, endpoints, study design, study conduct, and other operational aspects of the study.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of teplizumab treatment, administered intravenously (IV) to participants in the TN-10 trial who have developed T1D.	• Incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
Secondary	
• To evaluate the pharmacokinetics (PK) and immunogenicity of teplizumab	• Levels of teplizumab in the serum and anti-drug antibodies
• To evaluate whether teplizumab treatment reduces the loss of β cells, over 78 weeks (18 months), in individuals with recent diagnosis of T1D.	• The area under the time-versus-concentration curve (AUC) of C-peptide after a 4-hour (4h) mixed-meal tolerance test (MMTT), a measure of endogenous insulin production and β cell function, over 78 weeks
• To evaluate key clinical parameters of diabetes management, including insulin use, hemoglobin A1c (HbA1c), and clinically important hypoglycemic episodes over 78 weeks	• HbA1c levels; insulin use, defined as a daily average dose in units per kilogram per day (U/kg/day); and frequency of clinically important hypoglycemic episodes over 78 weeks
• To evaluate whether treatment with teplizumab increases the frequency of exhausted T cells	• Frequency of CD8+ TIGIT+ KLRG1+ T cells

3 STUDY TYPE AND DESIGN

This is a single-arm, multi-center, open-label clinical trial. Teplizumab-treated and placebo participants from the TN-10 trial who develop clinical type 1 diabetes after the conclusion of that trial, are eligible to enroll and receive teplizumab treatment in this open-label study within one year of Stage 3 clinical T1D diagnosis.

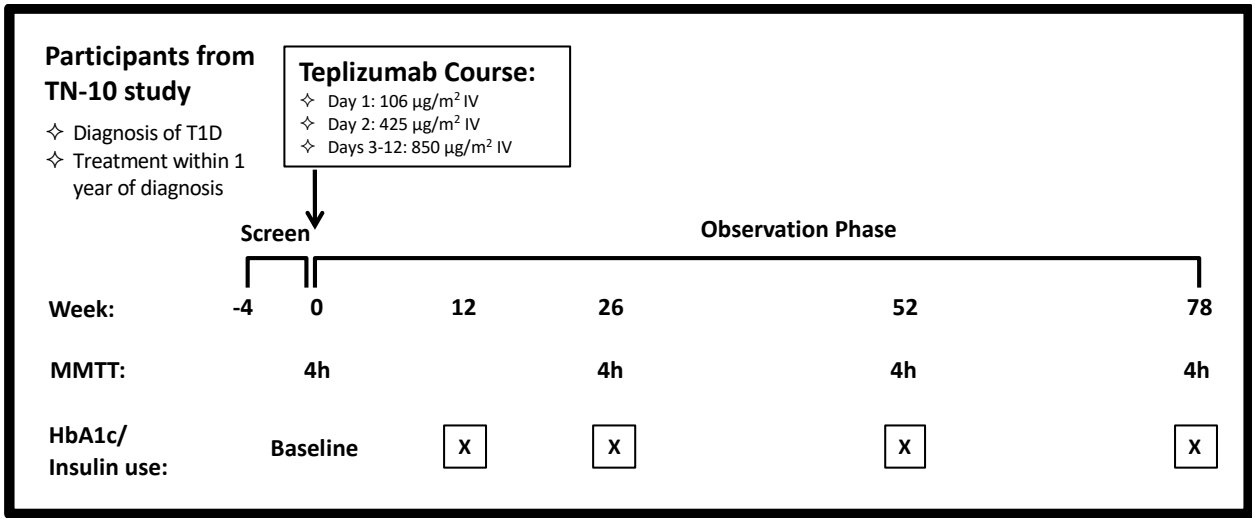
Up to 30 participants may be enrolled in this study.

All participants will receive a 12-day course of teplizumab given through a daily IV infusion. The participant's dosing course will be based on the body surface area (BSA), in m^2, calculated on Study Day 1. The drug dosing is as follows:

- Day 1: 106 µg/m^2
- Day 2: 425 µg/m^2
- Days 3-12: 850 µg/m^2

Participants will have a screening period of up to 4 weeks, a treatment period of 12 days, and a follow-up period of up to 78 weeks (18 months) from the first dose of treatment. The study schema is shown in Figure 1.

Figure 1 Study Schema



4 RANDOMIZATION

Randomization is not applicable for this open-label study.

5 STATISTICAL HYPOTHESES

There is no formal statistical hypothesis to be tested in this study. The primary objective is to evaluate the safety of teplizumab administration in participants of the TN-10 trial who have developed clinical T1D. For the secondary endpoints, it is proposed that teplizumab treatment will reduce the loss of beta cell function (as measured by C-peptide) and will increase the frequency of exhausted T cells, TIGIT + KLRg1 + CD8 + T cells, compared to baseline (at the start of study drug administration).

6 ESTIMATION OF SAMPLE SIZE

Sample size calculation was not based upon any formal statistical considerations. The sample size will include a maximum of 30 participants who develop clinical T1D after the conclusion of the TN-10 trial.

7 STATISTICAL METHODS

7.1 Analysis sets

The Enrolled analysis set will be comprised of all participants who sign the informed consent and/or assent.

The Safety analysis set will be comprised of all participants who receive at least one dose of the study drug.

The PK analysis set will be comprised of participants from the Safety analysis set who have at least one evaluable sample for PK analysis.

The Immunogenicity analysis set will be comprised of participants from the Safety analysis set who have at least one evaluable sample for Immunogenicity analysis.

7.2 General statistical considerations

No inferential statistical analysis will be performed. Only descriptive statistics will be presented. Data listings will provide both the participant identification number and treatment arm from the TN-10 trial as well as the participant identifier in the TN-10 Extension study. Summary tables will, in general, have a Total column only; however, where noted, tables will be presented by prior treatment (teplizumab or placebo) in the parent TN-10 trial.

Continuous variables and the respective changes from baseline (if applicable) will be summarized by assessment time using the number of observations (n), mean, standard deviation (SD), median and minimum and maximum. Unless otherwise specified, categorical variables will be presented by the number of participants and percentages based on the respective analysis set.

Decimal places for summary statistics are given in Table 2. For derived variables such as BMI, value should be rounded to 1 decimal place and the same rules should be applied as in Table 1.

Table 1 Decimal places for summary statistics of continuous variables

Statistic	Number of digits
Minimum, maximum	Same as original data
Mean, median	1 more than in original data
SD	2 more than in original data
Frequencies (%)	1 decimal place

7.2.1 Definition of derived variables

Definition of Baseline
Unless otherwise specified, the baseline value will be taken as the last non-missing value available prior to the start of dosing with teplizumab.

Definition of Study Day
In data listings, the day of the first dose of teplizumab administration will be designated Study Day 1. The day before the day of the first dose of teplizumab administration will be designated Study Day -1.

Body Mass Index
Body mass index (BMI) is calculated using the formula:

$$BMI\left(\frac{kg}{m^2}\right) = \frac{weight(kg)}{[height(m) \cdot height(m)]}$$

Body Surface Area

Body Surface Area (m^2) is calculated using the Mosteller formula:

$$BSA(m^2) = \sqrt{\frac{[Height(cm)x\ Weight(kg)]}{3600}}$$

7.2.2 Imputing missing values

In general, missing values will not have any imputation, with some exceptions noted below:

Adverse Events, Prior Medications and Concomitant Medications
Partial dates for adverse event start/stop or concomitant medication start/stop will not be imputed in data listings. However, information from partial adverse event start dates may be used to determine whether an adverse event is treatment emergent. Information from partial start dates may be used to determine between prior medications and concomitant medications.

7.3 Disposition of participants

The number of participants enrolled will be tabulated as well as the number and percentage of enrolled participants who are in the Safety, PK, and Immunogenicity analysis sets.

The number and percentage of participants in the Safety analysis set who discontinue study drug early and reason for early discontinuation of study drug [adverse event, Investigator decision, participant decision, other] will be tabulated.

The number and percentage of participants in the Safety analysis set who discontinue the study early and complete the study will be tabulated along with reasons for early study discontinuation [lost to follow-up, withdrawal of consent/assent, death, Investigator or Sponsor judgement, pregnancy, other].

Disposition of participants will be provided in a separate data listing which will include information about informed consent/assent. Additional data listings will detail inclusion/exclusion criteria not met and protocol deviations in the Safety analysis set.

7.4 Demographic and baseline characteristics and medical history

The following demographic and baseline characteristics (including disease characteristics) will be summarized on the Safety analysis set:

- Age at screening (years)
- Sex
- Ethnicity
- Race
- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m^2)
- Body Surface Area (m^2)
- Type of positive T1D-related autoantibody (GADA, IA-2, mIAA, ZnT8)
- Number of positive autoantibodies (1,2,3,4)
- Time from T1D diagnosis to first dose of teplizumab in TN-10 Extension (weeks)

Time from T1D diagnosis to first dose of teplizumab in TN-10 Extension will be calculated as (Date of first dose of teplizumab in TN-10 Extension – Date of T1D diagnosis)/7.

Demographic and baseline characteristics will also be provided in data listings for the Safety analysis set. This listing will include a calculation of Time from TN-10 trial treatment start to T1D diagnosis (months), calculated as (Date of T1D diagnosis – Date of first dose of teplizumab in TN-10 trial + 1)/30.4375.

Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Authorities (MedDRA) applicable at the time of database lock. A data listing of medical history by participant will be provided for the Safety analysis set.

7.5 Prior and concomitant medications

Prior and concomitant medications will be coded using the latest version of the WHODrug dictionary applicable at the time of database lock. Prior medications are those which start and stop before the first dose of study treatment. Concomitant medications are those which start before study treatment and continue into the study treatment period as well as medications which start after the first dose of study treatment is administered.

A data listing of medications will be provided for the Safety analysis set with a designation of whether a medication is prior or concomitant. If there is not enough available data to make this designation, a medication will be assumed to be both prior and concomitant.

7.6 Extent of exposure and compliance

Extent of exposure will be summarized for the Safety analysis set showing:

- Number of participants dosed with teplizumab at each visit
- Number of doses received per participant
- Descriptive statistics of follow up time (years) and total follow up time (person-years)
- Cumulative total teplizumab dose (µg) in TN-10 Extension study
- Received prior teplizumab treatment in TN-10 trial (Yes, No)
    - Time between last teplizumab exposure in TN-10 trial and first teplizumab dose in TN-10 Extension study (months) [in subjects receiving teplizumab in TN-10 trial]
- Cumulative total teplizumab dose (µg) in TN-10 and TN-10 Extension study

Follow up time (years) per participant will be calculated as (Date of end of study participation – date of first dose of teplizumab in TN-10 Extension + 1)/365.25.

Time between last teplizumab exposure in TN-10 trial and first teplizumab dose in TN-10 Extension study (months) will be calculated as (Date of first teplizumab dose in TN-10 Extension study – date of last dose of teplizumab in TN-10 trial)/30.4375.

Extent of exposure will also be provided in a data listing. The listing will include any relevant information about dose slowing, interruptions, or discontinued dosing administrations. A separate listing will also provide an exposure summary from TN-10 and the TN-10 Extension study for each TN-10 Extension participant.

7.7 Analysis of safety and tolerability

All safety analyses will be performed based on the Safety analysis set.

7.7.1 Adverse events

Adverse events will be coded using the latest version of MedDRA applicable at the time of database lock.

A treatment emergent adverse event (TEAE) is defined as an adverse event which starts during or after the first dose of teplizumab. If an adverse event occurring the same day as the first dose of teplizumab cannot be determined to occur before or after the dosing begins, it will be assumed to be treatment emergent.

Adverse event severity is assigned according to the National Cancer Institute CTCAE v5.0. In the case of summaries by CTCAE grade, the highest grade experienced by the participant will be used for the reporting category.

Relationship of an adverse event to study treatment will be considered as "Related" in tabular summaries if the options of "Possible", "Probable", or "Definite" are selected for the adverse event in the eCRF. Options of "Unrelated" or "Unlikely" will be considered as "Not Related".

An adverse event is defined as an Adverse Event of Special Interest (AESI) if it meets any of the following criteria:

- All ≥ Grade 3 infections (includes all opportunistic infections): viral, fungal, bacterial
- Acute mononucleosis-like illness (e.g., fever, pharyngitis, lymphadenopathy, clinical EBV and CMV infections and reactivations)
- Malignancies including lymphomas
- Severe hypoglycemic episodes
- ≥ Grade 3 liver function abnormalities (AST, ALT, bilirubin), i.e., an AST or ALT value >5.0x ULN or a bilirubin value >3.0x ULN
- ≥ Grade 3 thrombocytopenia (platelet counts less than 50,000/μL)
- ≥ Grade 3 neutropenia (<1000 PMN/μL on 2 consecutive evaluations performed on different days)
- ≥ Grade 4 allergic/hypersensitivity reaction (anaphylaxis)
- ≥ Grade 3 Rash
- ≥ Grade 4 cytokine-release syndrome
- Lymphocyte count <500/mm^3 for 7 days or longer

Table 2 The Search Criteria for AESI

AESI	**Search Criteria**
≥ Grade 3 infections (will include all opportunistic infections)	SOC – 'Infections and Infestations'; ≥ Grade 3
Acute mononucleosis-like illness (e.g., fever, pharyngitis, lymphadenopathy)	PT – 'Mononucleosis syndrome', 'Epstein-Barr virus antibody positive', 'Epstein-Barr virus test positive', 'Epstein-Barr viremia', 'Cytomegalovirus antibody positive', 'Cytomegalovirus test positive', 'Infectious mononucleosis', 'Lymphadenopathy','Epstein-Barr virus infection', and 'Cytomegalovirus infection'
Lymphomas or other malignancies	SOC – 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' and HLT – includes 'malignant' or 'lymphomas' or 'benign'

Severe hypoglycemic episodes	PT – 'Hypoglycaemic seizure', 'Hypoglycaemic coma', 'Hypoglycaemic unconsciousness' of any grade; PT – 'Hypoglycaemia' of ≥ Grade 3
≥ Grade 3 liver function abnormalities (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin) i.e., an AST or ALT value >5.0x upper limit of normal (ULN) or a bilirubin value >3.0x ULN	PT – 'Alanine aminotransferase increased', 'Aspartate aminotransferase increased', 'Blood bilirubin increased', 'Liver function tests increased', 'Hypertransaminasemia', 'Transaminase elevation', 'Hyperbilirubinemia'; ≥ Grade 3
≥ Grade 3 thrombocytopenia (platelet counts less than 50,000/µL)	PT – 'Thrombocytopenia'; ≥ Grade 3
≥ Grade 3 neutropenia (<1000 polymorphonuclear leukocytes [PMN]/µL) on 2 consecutive evaluations performed on different days	PT – 'Neutropenia'; ≥ Grade 3
≥ Grade 4 allergic/hypersensitivity reaction, i.e., anaphylaxis	PT – 'Dermatitis allergic', 'Drug hypersensitivity', 'Anaphylactic reaction', 'Immune reaction', 'Anaphylaxis', 'Hypersensitivity', 'Infusion related reaction', 'Serum sickness'; ≥ Grade 4
≥ Grade 3 rash	SOC – 'Skin and subcutaneous tissue disorders'; ≥ Grade 3
≥ Grade 4 cytokine-release syndrome, i.e., life-threatening; pressor or ventilatory support indicated	PT – 'Cytokine release syndrome'; ≥ Grade 4
Lymphocyte count <500 mm^3 for 7 days or longer	PT – 'Lymphopenia'; ≥Grade 3; at least 7 days

SOC = system organ class; PT = preferred term; HLT = high level term
Note: Nasopharyngitis, Pharyngitis, pharyngitis streptococcal should not be included in search criteria.

Summary Tables

An overall summary table of treatment emergent adverse events will display the number and percentage of participants with at least one

- TEAE
- TEAE related to study treatment
- TEAE leading to study treatment discontinuation
- TEAE leading to study discontinuation
- TEAE leading to death
- TEAE by CTCAE grade
- TEAE of special interest (AESI)
- Serious TEAE
- Serious TEAE related to study treatment

Summary tables will be produced which display the number and percentage of participants having at least one of the following categories by MedDRA System Organ Class (SOC) and Preferred Term (PT):

- TEAE
- TEAE related to study treatment
- TEAE leading to study treatment discontinuation
- TEAE leading to study discontinuation
- Serious TEAE
- Serious TEAE related to study treatment

Summary tables will be produced by descending frequency of MedDRA Preferred Term (PT) for the following categories:

- TEAE

A summary table will be produced by AESI category (defined in Table 2) and MedDRA Preferred Term for the following category:

- TEAE of special interest (AESI)

Participants with more than one TEAE in each SOC or PT will only be represented once per row in these summary tables by SOC and/or PT.

Data Listings

The following data listings for adverse events will be produced:

- TEAE
- Adverse events which are not treatment emergent
- TEAE leading to study treatment discontinuation
- TEAE leading to study discontinuation
- TEAE leading to death
- TEAE of special interest (AESI)
- Serious TEAE

7.7.2 Laboratory safety variables

Local laboratory results for serum chemistry and hematology parameters will be converted to the units below and provided in a data listing. The parameters for inclusion in listings are as follows:

Serum Chemistry	Sodium (mmol/L) Potassium (mmol/L) Chloride (mmol/L) CO2 (mmol/L) Glucose (mmol/L) Blood Urea Nitrogen (mmol/L) Creatinine (µmol/L) Alanine Aminotransferase (U/L) Aspartate Aminotransferase (U/L) Lactate Dehydrogenase (U/L) Alkaline Phosphatase (U/L) Total Protein (g/L) Albumin (g/L) Total Bilirubin (µmol/L) Direct Bilirubin (µmol/L)
Hematology	Red Blood Cells (10^{12}/L) White Blood Cells (10^9/L) Platelet Count (10^9/L) Hemoglobin (g/L) Hematocrit (fraction of 1) Neutrophils (10^9/L) Lymphocytes (10^9/L) Monocytes (10^9/L) Eosinophils (10^9/L) Basophils (10^9/L)

The listing will also include additional details as to whether the laboratory value was considered abnormal or whether it was clinically significant (Yes/No).

7.7.3 Vital signs and anthropomorphic measurements

Vital sign measurements including temperature (degrees Celsius), heart rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and respiratory rate (breaths/min) will be provided in a data listing. Details will include the assessment (normal/abnormal) and clinical significance (Yes/No).

A data listing will also be provided for all measurements of Height (cm), Weight (kg), and BSA (m^2) collected for a participant.

7.7.4 Physical examination

A data listing will be provided detailing the results of physical examinations. The listing will include the body system examined, the result (normal/abnormal), clinical significance (Yes/No), and any additional details.

7.7.5 Pregnancy

A data listing will be provided which contains the results of pregnancy tests conducted. The listing will contain information about whether the test was done (if N/A due to non-childbearing potential, the reason for non-childbearing potential) and the pregnancy test result.

7.7.6 Epstein-Barr virus (EBV) antibodies and cytomegalovirus (CMV) antibodies

A data listing will contain local results for EBV IgG (negative/positive), EBV IgM (negative/positive), EBNA (negative/positive), CMV IgG (negative/positive), and CMV IgM (negative/positive).

A separate data listing will contain central lab results for EBV qPCR (IU/mL) as well as CMV qPCR (IU/mL).

7.8 Other analyses

7.8.1 Mixed Meal Tolerance Test (MMTT)

The area under the time-versus-concentration curve (AUC) of C-peptide after a 4-hour MMTT will be calculated using the trapezoidal rule. To adjust the potential different durations of the MMTT test, C-peptide AUC will first be standardized by the duration of the MMTT test for the analysis. If the C-peptide values at time -10 minutes and time 0 minutes are missing, the AUC will be set to missing for the MMTT. If fewer than two measurements are available to calculate the AUC for a MMTT, the AUC will be set to missing.

A summary table will provide descriptive statistics of the C-peptide ln(AUC+1) by visit and by prior treatment in the TN-10 trial. As historical data have shown the C-peptide AUC is right skewed, the ln(AUC+1) transformation will be applied before summarization.

The values of the MMTT results, including both untransformed and transformed AUC, will be presented in a data listing.

Graphical presentation of the ln(AUC+1) over time may be explored.

7.8.2 HbA1c (%)

A summary table will provide descriptive statistics of HbA1c (%) by visit and by prior treatment in the TN-10 trial.

A data listing will be provided displaying results of local HbA1c (%) testing.

7.8.3 Exogenous Insulin

Exogenous average daily insulin use (unit/kg/day) in the TN-10 Extension study will be presented by visit and prior treatment in the TN-10 trial.

The average daily insulin use for a particular visit will be derived based on the 3 days of insulin recorded in the case report form prior to a visit. The body weight (kg) at the visit, if available, will be used in the calculation; otherwise, the average of the closest prior and post-visit weights will be used.

Information on exogenous insulin will be presented in a data listing. The listing will include the nominal day reported (3 days prior to visit, 2 days prior to visit, 1 day prior to visit) as well as the insulin name and dosing.

7.8.4 Insulin Discontinuation Criteria

TN-10 Extension participants meeting insulin discontinuation criteria (defined as HbA1c ≤6.5% and average daily insulin use ≤0.25 unit/kg/day) at each visit will be summarized, by prior TN-10 trial

treatment and overall. Only participants who have available HbA1c and insulin data at the relevant visit will be included in the summary.

7.8.5 Severe Hypoglycemic Episodes

Severe hypoglycemic episodes following the AESI definition in Table 2 will be provided in a data listing.

7.8.6 Pharmacokinetics and Immunogenicity

Blood samples will be obtained on Days 1, 4, 9, 12 (before study drug infusion) and on Days 28, 182, and 364 to measure teplizumab trough levels, anti-drug antibodies, and neutralizing antibodies.

Teplizumab concentrations will be provided in a data listing on the PK analysis set.

The titers of anti-drug antibodies and presence of neutralizing antibodies will be measured in samples collected. Information including antibody titer will be provided in a data listing on the Immunogenicity analysis set.

7.8.7 Mechanistic Assessments

Details of the mechanistic assessments, including the secondary endpoint of assessing frequency of CD8+ TIGIT+ KLRG1+ T cells, will be provided in a separate mechanistic analysis plan.

7.9 Interim analysis

An interim analysis is not planned.

7.10 Changes in the statistical plans from those presented in the study protocol (if applicable)

- The protocol specifies the use of both an ITT and Safety analysis set. The SAP defines only the Safety analysis set as those participants who receive at least one dose of study drug.
- The frequency of CD8+ TIGIT+ KLRG1+ T cells will be part of a separate mechanistic analysis plan.
- The protocol specifies that comparisons will be made in C-peptide with historical controls. Due to the small number of patients enrolled in the TN-10 Extension study, these comparisons will not be performed as part of this SAP.
- The definition of adverse event of special interest (AESI) in the SAP is different from the study protocol and aligns with the AESI definition as agreed upon with FDA for the Integrated Summary of Safety (ISS) for the at-risk BLA approved in November 2022.

7.11 Execution of statistical analyses

Statistical analysis will be performed by IQVIA Biotech under the supervision of Provention Bio, Inc. and Sanofi.

8 HARDWARE AND SOFTWARE

Statistical analysis, tables, figures, and participant data listings will be performed with SAS® for Windows version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

9 REFERENCES

1) SAS, Institute Inc., Cary, NC, USA.

10 APPENDICES

None

11 DOCUMENT HISTORY

Version number	Version date	Author	Comments
0.1	17MAR2021	[redacted]	N/A – First version

0.2	24MAY2023	[redacted]	Updated to clarify most presentations would be data listings due to expected enrolment.
1.0	25OCT2023	[redacted]	Updated per PRVB team review
1.0	18JAN2024	[redacted]	Finalization of SAP text per 2nd team review
1.0	21FEB2024	[redacted]	Minor editorial changes prior to signature of V1.0.