Amsterdam, 13 November 2025
EMA/39938/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TEIZEILD

International non-proprietary name: Teplizumab

Procedure No. EMEA/H/C/005496/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under curve
BG	blood glucose
BMI	body mass index
BSA	body surface area
CGM	continuous glucose monitoring
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CMA	Conditional marketing authorisation
CMC	Chemistry, manufacturing and controls
COMP	Committee for Orphan Medicinal Products
COVID-19	coronavirus disease 2019
CPRD	clinical practice research datalink
CRF	case report form
CSP	clinical study protocol
CSR	clinical study report
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DP	drug product
DPT-1	Diabetes Prevention Trial- of Type 1
DS	drug substance
DTSQ	diabetes treatment satisfaction questionnaire
ECG	electrocardiogram
eCTD	Electronic common technical document
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of trial
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GAD	glutamic acid decarboxylase
GCP	good clinical practice
GLP	good laboratory practice
GMP	good Manufacturing Practice
HbA1c	glycated hemoglobin
HFS	hypoglycaemia fear scale
HLT	high-level term
HLA	human leukocyte antigen
HR	hazard ratio
IAA	insulin autoantibodies

ICA	islet cell antibodies
ICE	intercurrent event
IgG-1	immunoglobulin G1
INN	International Nonproprietary Name
INR	international normalised ratio
IQR	interquartile range
IRR	incidence rate ratio
IRR	infusion-related reaction
ISE	integrated summary of efficacy
ITT	intent-to-treat
IV	intravenous
LS	least squares
MAA	marketing authorisation application
mAb	monoclonal antibody
MAH	Marketing authorisation holder
MDS	modified dosing schedule
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MMTT	mixed meal tolerance test
MNAR	missing not at random
nAb	neutralizing antibody
NOD	non-obese diabetic
OGTT	oral glucose tolerance test
OL	open-label
PD	pharmacodynamics
PH	proportional hazard
PIP	Paediatric investigation plan
PK	pharmacokinetics
PP	per protocol
PPQ	Process performance qualification
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient repoted outcome
PT	preferred term
RMP	Risk management plan
RNA	ribonucleic acid
RWE	real world evidence
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SC	subcutanous
SCE	summary of clinical efficacy
SD	standard deviation
SmPC	Summary of product characteristics
SOC	System Organ Class
T1D	Type 1 diabetes
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIR	time in range
U	unit

UAE	United Arab Emirates
UK	United Kingdom
ULN	upper limit of normal
US	United States
ZnT8	zinc transporter 8

1. Executive Summary

On 13 November 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Teizeild (teplizumab), indicated to delay the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D. Teizeild is a PRIME medicine.

Teplizumab is a humanised immunoglobulin G1 monoclonal antibody that binds to the CD3ε chain of the T cell receptor (TCR)-complex on human T lymphocytes. The mechanism of action of teplizumab is not fully understood, but it is thought to involve partial agonistic signalling and deactivation of pancreatic beta-cell autoreactive T lymphocytes.

Teizeild is available as a 1 mg/ml concentrate for solution for infusion and should be administered by intravenous infusion (over a minimum of 30 minutes), using a body surface area (BSA)-based dosing, once daily for 14 consecutive days.

Teizeild preserves beta cell function and delays the onset of stage 3 T1D. The main evidence for the efficacy of Teizeild was based on a multicentre, double-blind, randomised, placebo-controlled study (TN-10) in people high risk for T1D. The study showed that the median time to progression to stage 3 T1D was 49.5 months in the Teizeild group, compared with 24.9 months in the placebo group.

The most frequently reported adverse reactions were lymphopenia, leukopenia, neutropenia, rash, and decreased blood bicarbonate. The most frequent serious adverse reaction was the cytokine release syndrome.

This report summarizes the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).

2. Administrative/regulatory information and recommendations on the procedure

2.1. Scientific advice

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
28 February 2019	clinical	EMEA/H/SA/1107/2/2018/SME/II	Please see below
17 September 2020	Non-clinical	EMEA/H/SA/1107/3/2020/SME/PR/I	Please see below
10 December 2020	Clinical And Quality	EMEA/H/SA/1107/4/2020/SME/II And EMEA/H/SA/1107/5/2020/SME/PR/I	Please see below

The applicant received Scientific Advice on the development of teplizumab for prevention of T1D. The Scientific Advice pertained to the following aspects:

- Comparability testing for drug substance and drug product after change in manufacturing process; release specifications; stability testing.
- Choice of species for animal testing, general non-clinical evidence generation strategy, need for carcinogenicity testing
- Design and evidentiary contribution of phase 2 TN-10 study: clinical relevance of effect size on primary endpoint (delayed T1D diagnosis), role of supportive evidence regarding C-peptide preservation, extrapolation of evidence generated in individuals with a first degree relative with T1D to high-risk patients in general population
- Design of the phase 3 PROTECT study: general design, study population definition, primary and secondary efficacy endpoints, dosing regimen
- Overall evidence base to support MA
- Safety database
- Planned supportive studies: Phase 3 study in children 8-17 years of age with stage 3 T1DM and two planned studies in stage 2 individuals (safety/PK in children 0-7 years of age).

2.2. PRIME

Teizeild (teplizumab) was granted eligibility to PRIME on 17 October 2019 in the following indication: Treatment to delay or prevent clinical Type 1 diabetes mellitus in "at-risk" individuals

Eligibility to PRIME was granted at the time in view of the following: There is an unmet medical need for a treatment to delay or prevent clinical T1D in 'at-risk' individuals given there are no available established treatment options.

2.3. Eligibility to the centralised procedure

The applicant Sanofi Winthrop Industrie submitted on 19 December 2024 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Teizeild (teplizumab), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 October 2019.

The applicant initially applied for the following indication:

Teizeild is a disease modifying agent that preserves beta cell function indicated:

• to delay the onset of Stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with Stage 2 T1D.

• to delay the progression of Stage 3 T1D in adult and paediatric patients 8 years of age and older recently diagnosed with Stage 3 T1D.

2.4. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/ supporting certain test(s) or study(ies).

2.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0386/2024 and EMA/PE/0000243095 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0386/2024 and EMA/PE/0000243095 were not yet completed as some measures were deferred.

2.6. Information on orphan market exclusivity

Not applicable

2.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.7. Applicant's request(s) for consideration

2.7.1. Accelerated assessment request

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. However, this request was withdrawn by the Applicant.

2.7.2. New active substance status

The applicant requested the active substance teplizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that teplizumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

2.8. Patient experience data

Patient experience data submitted with this application				***Section where discussed (if applicable)***
☒	Patient experience data submitted by the applicant:			
	☒	Clinical outcome assessments (COAs) such as		
		☒	Patient-reported outcomes (PRO)	6.3.7.
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☒	Other patient experience data not submitted by the applicant but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		

Patient experience data submitted with this application			Section where discussed (if applicable)
	☒	CHMP early dialogue with patient organisations	6.3.7.
	☐	Third party interventions from patients and patient groups	
	☐	Other (such as medical literature, summaries/analysis from patient engagement activities - please specify)	

2.9. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Kristina Dunder
Co-Rapporteur:	Karin Janssen van Doorn

The application was received by the EMA on	19 December 2024
The procedure started on	23 January 2025
The CHMP Rapporteur's first Assessment Report was received on	14 April 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	16 April 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	28 April 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 May 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 July 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	27 August 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	18 September 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 October 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 October 2025
A SAG was convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	9 September 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to TEIZEILD on	13 November 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	13 November 2025

2.10. Final CHMP outcome

2.10.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 2.6 of this report.

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0386/2024 and EMA/PE/0000243095 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet. Relevant paediatric statement in Section 5.1 of the SmPC if the EMA has deferred a paediatric development have also been included.

2.10.2. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Teizeild is favourable in the following indication:

Teizeild is indicated to delay the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

Divergent position(s)

Divergent position to the majority recommendation on Benefit/risk – Full CHMP opinion is appended to this report.

2.10.3. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

2.10.4. Other conditions and requirements of the marketing authorisation

Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

2.10.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Healthcare professional (HCP) guide

The objective is to ensure (at prescription and initiation of the treatment with teplizumab) a conversation between the prescribing/treating HCPs and the patient/legal representative around specific information and important recommendation related to the treatment with teplizumab.

These are pertaining to the following safety concerns:

- Cytokine Release Syndrome,
- Lymphopenia,
- Severe infections

The HCP guide includes the following key elements:

- Information related to the requirement to premedicate patients, to monitor total blood count, liver enzymes prior to, during or after the treatment,
- Guidance for vaccination prior to or after the treatment,

Patient Guide

The objective of this guide is for patients treated with teplizumab and their legal representative to know the risks related to the use of teplizumab and to be able to recognize the signs and symptoms indicative of those risks.

At the time of treatment initiation, the patient guide will be given by the HCPs to the patient/legal representative (which the patient should keep and be able to share with other HCPs involved with their treatment). HCPs can download this patient guide in countries, where available.

The patient guide helps the patient identify the following safety concerns:

- Cytokine Release Syndrome,
- Lymphopenia,
- Severe infections

The patient guide includes the following key elements:

- Information to educate patient about signs/symptoms which could be indicative of these risks and to tell their doctor or nurse immediately if these occur,
- Guidance for vaccinations prior to or after the treatment,
- Recommendation for the patients/legal representative to read the package leaflet (PL) thoroughly.

2.10.6. Proposed list of recommendations

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends several points for investigation.

3. Introduction

3.1. Therapeutic Context

Type 1 diabetes (T1D) is a chronic autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells by a T-cell-dependent autoimmune attack, resulting in life-long dependence on exogenous insulin. T1D occurs in both children and adults. T1D is commonly initially diagnosed in children, with more than half of T1D patients diagnosed before the age of 14 years. The aim of treatment with exogenous insulin is to keep the blood sugar within an acceptable range, where the patient has no symptoms of high blood sugar, nor symptoms of low blood sugar (hypoglycemia). The aim is also to prevent long-term complications of T1D, such as retinopathy, impaired kidney function, peripheral neuropathies, and cardio-vascular diseases.

Symptoms which lead to the diagnosis of T1D typically include thirst, polydipsia, polyuria, fatigue, weakness, and weight-loss. Not seldom, both for children and adults, the acute symptoms of abdominal pain, thirst and weakness lead to the diagnosis of high blood sugar, ketoacidosis and T1D.

The clinical progression of T1D is relatively well understood and predictable as it is a continuum marked by clinically relevant biomarkers that identify stages of the disease (1). The process of beta-cell destruction generally begins years before the onset of clinical disease (2). The autoimmune destruction of beta cells may be clinically silent, but it can be identified by the detection of autoantibodies such as islet cell antibodies (ICA), anti-glutamic acid decarboxylase (GAD) 65 antibody, anti-ICA512 (also termed islet antigen 2 [IA-2]) antibodies, insulin autoantibodies (IAA) (3) and antibodies to zinc transporter 8 (ZnT8) (4) as well as abnormal glucose metabolism such as dysglycemia. Immune-mediated beta cell destruction continues and physiologic insulin demand cannot be met by the remaining beta cells, resulting in hyperglycemia and clinical diagnosis of T1D (5, 6).

In an individual with normoglycemia with genetic risk (which may be influenced for instance by human leukocyte antigen [HLA] haplotypes), the natural history of T1D has been described in 3 stages (1):

- Stage 1: emergence of 2 or more T1D-related autoantibodies, which reflects the initiation of the autoimmune process; this stage is associated with normoglycemia.
- Stage 2: persistence of T1D-related autoantibodies with further loss of beta cell function and development of dysglycemia. This represents a more advanced but still pre-symptomatic stage of the disease.

- Stage 3: symptomatic or clinical T1D, when remaining beta cell capacity is insufficient to maintain glucose metabolism and exogenous insulin replacement is needed.

The progression to clinical T1D (Stage 3) is not a matter of "if" but "when" as >95% of patients in Stage 1 and virtually all of patients in Stage 2 will progress to Stage 3 and become insulin dependent. For Stage 2 T1D, the diagnosis of this early stage is highly depending on the implementation of screening programs and thus may vary across countries and even regions.

The recommended standard treatment for Stage 3 T1D according to scientific guidelines is replacement with exogenous insulin. Despite advances in insulin products, delivery systems and glucose monitoring technologies, in clinical practice, the majority of patients fail to reach the target HbA1c level <7%.

In 2022, there were 8.75 million individuals worldwide with T1D. In Europe 31 000 new cases of T1D in children and adolescents (0-19 years) are diagnosed each year (7). The burdens placed on patients and their families/caregivers when clinical T1D is diagnosed is multifaceted, including social and emotional aspects, and also for patients in some countries an economic burden.

T1D screening programs, identifying individuals at risk of or with early-stage T1D, significantly reduce the rate of diabetes ketoacidosis (DKA) and reduce hospitalisation when coupled with long-term monitoring (8). Screening for early-stage T1D is advancing in Europe. Started in 2015, the Fr1da study is a large population-based screening registry for children aged 2 to 10 years (screening was later expanded to include older siblings) living in Germany, with the aim of diagnosing T1D at a pre-symptomatic stage (9). In Italy, it was decided in 2023, to implement a national screening program for T1D and celiac disease among children aged 1 to 17 years, as endorsed by the European Diabetes Forum 2023 (10).

There are currently no treatments approved for Stage 2 T1D in the EU. Allogenic pancreas islet cell transplantation or islet cellular therapy used in conjunction with concomitant immunosuppression has been recently introduced and exists as non-standard treatment for clinically overt T1D which represents a more advanced population than early-T1D and may be considered when patients experience severe hypoglycemia despite intensive diabetes management and education.

3.2. Aspects of development

Ten randomized, controlled clinical studies with teplizumab (9 in participants with T1D and 1 in healthy participants) have been conducted to evaluate the efficacy of teplizumab for the indication of delaying the onset of Stage 3 T1D, and for the indication of delaying the progression of Stage 3 T1D:

- 1 study in participants with Stage 2 T1D: the pivotal study TN-10.
- 6 studies in participants recently diagnosed with Stage 3 T1D including the pivotal study, PROTECT (PRV-031-001), and the 5 supportive studies: Protégé (CP-MGA031-01), Encore (CP-MGA-031-03), Study 1 (ISCT-MGA031-001), AbATE (ITN027, Study 4), and Delay (Study 5).
- 2 extension studies: TN-10 Extension (PRV-031-002) and Protégé Extension (CP-MGA031-02)
- 1 study in healthy participants: a single dose biocomparability study (PRV-031-004).

At the time of submission of the application, teplizumab was approved for the indication to delay the

onset of Stage 3 T1D in adult and peadiatric patients 8 years of age and older with Stage 2 T1D by the Food and Drug Administration (FDA) in the United States (US) in November 2022 and in the United Arab Emirates (UAE) and Israel in 2024.

3.2.1. Scientific advice/Protocol assistance

Teplizumab was granted PRIME designation by the EMA in October 2019 and received scientific advice (See section 2.2 and section 2.3 above).

3.3. Description of the product

Teplizumab (hOKT3γ1 [Ala,Ala]), also referred to as SAR446681, PRV-031, MGA031, or CNTO311, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to the CD3ε chain of the T cell receptor (TCR)-complex on human T lymphocytes.

Initially, the proposed indications and administration schemes were the following:
Indication:

- to delay the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D (Indication 1)
- to delay the progression of stage 3 T1D in adult and paediatric patients 8 years of age and older recently diagnosed with stage 3 T1D (Indication 2).

Teplizumab should be administered by intravenous infusion, using a body surface area (BSA)-based dosing, once daily for:

- 14 consecutive days (Indication 1)
- 12 consecutive days for each of 2 treatment courses. The treatment courses should be given 6-12 months apart (Indication 2).

3.4. Inspection issues

3.4.1. GMP inspection(s)

No inspection required.

3.4.2. GLP inspection(s)

No inspection required.

3.4.3. GCP inspection(s)

No inspection required.

4. Quality aspects

4. 1. Introduction

Teplizumab, the active substance in Teizeild, is a monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. It binds with high specificity to CD3, a cell surface antigen present on T lymphocytes.

Teplizumab is formulated with dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 80, sodium chloride and water for injections.

The finished product is presented as a concentrate for solution for infusion in single use glass vial. Each vial contains 2 mg of teplizumab in 2 mL of concentrate, corresponding to a strength of 1 mg/mL.

4.2. Active substance

4.2.1. General information

Teplizumab (INN) is a recombinant humanised monoclonal antibody (IgG1 kappa subclass) that binds with high specificity to the CD3ε chain of the T cell receptor (TCR)-complex on human T lymphocytes.

This antibody molecule contains 16 disulfide bonds and an unpaired cysteine residue at position 105 in the heavy chain (HC). Each HC polypeptide contains a single site for N-linked glycosylation site at Asn299. Teplizumab exhibits a high degree of C-terminal lysine cleavage. The total molecular weight is 145,6 kDa. The Fc region of teplizumab has been modified to minimise Fc effector functions.

4.2.2. Manufacture, characterisation, and process controls

Manufacturing Process and Process Controls:

The active substance is manufactured at AGC Biologics, 21511 23rd Drive SE, Bothell, WA 98021, USA. All sites involved in manufacture and controls of the active substance operate in accordance with EU GMP.

The manufacturing process for teplizumab active substance begins with the thaw of a single working cell bank (WCB) vial followed by upstream manufacturing and downstream manufacturing. Upstream manufacturing consists of cell expansion, production, harvest, and harvest clarification. Downstream manufacturing consists of affinity chromatography, viral inactivation, anion exchange chromatography, viral filtration, formulation by ultrafiltration/diafiltration (UF/DF) and filling.

The manufacturing process and in-process controls (IPCs) are satisfactorily summarised in flow charts and tables. The purpose of each step is clearly stated and a brief description of each step is provided. Process parameters are acceptably listed, including criticality assignment and acceptable ranges.

and each bioreactor produces one single active substance batch. The batch definition and the batch numbering system are acceptably described.

Control of Materials

Raw materials

The Applicant's system of raw material acceptance is described and endorsed. Compendial and non-compendial raw materials are listed. For non-compendial materials both critical and non-critical materials are acceptably described, with material, supplier, test specification/acceptance criteria and use in manufacture.

The containers used for every in-process storage (hold time) of intermediate solutions are indicated in the manufacturing process description.

The chromatographic resins, the filters and the membranes used in the active substance manufacturing process are listed, along with information on the quality and control of these materials.

Plasmid and cell construct

The construction and preparation of the expression vector have been described in sufficient detail. Furthermore, the cell line construction with host cell line and the plasmid, and the transfection and screening with finally selected subclone, are acceptably described.

The selection process and the adaption to serum-free medium, the nucleotide and amino acid sequences of the light and heavy chains are provided, as well as a flow diagram describing the process.

The information on the plasmid and cell construct provided is found in line with ICH Q5B and ICH Q5D and considered as acceptable.

Generation and testing of cell banks

The preparation and testing of the master cell bank (MCB), WCB and limit of *in vitro* cell age (LIVCA) cells (process performance qualification (PPQ) are described at an adequate level. Long-term storage is split between two locations (described in S.2.1) in case of catastrophic events.

The testing for adventitious viral agents in the cell banks is found to be in compliance with ICH Q5A. The MCB was tested for cell growth characteristics, identity, adventitious virus, retrovirus, species specific viruses and sterility and mycoplasma. For the testing, the original reports are provided.

The methods used for the characterisation and testing of the cell banks are sufficiently described. The virus testing methods are presented with principles, summaries of methods and acceptance criteria included.

Storage stability testing of the MCB is tested minimally every, the cells are monitored for viability and productivity. This is accepted. Genetic stability was tested by gene copy number, the structural organisation of the integrated expression cassette and phenotypic characteristics. It is found that ICH Q5D has been adhered to.

LIVCA was, however, defined at based on the verification of the product quality attributes for PPQ. Section 3.2.R includes a post-approval change management protocol (PACMP, see below) to further extend this LIVCA up to, which is found acceptable.

It is noted that the Applicant did not include a protocol for the manufacture and testing of future new WCBs. This is acceptable and the Applicant is reminded that in this case introduction of a new WCB should be done via a post-approval variation application.

This information provided on generation and testing of cell banks is considered acceptable.

Control of Critical Steps and Intermediates:

Process inputs, or process parameters, are designated as critical process parameter (CPP), key operational parameter (KOP), and non-key operational parameter (nKOP). Process outputs are controlled with IPCs and are designated as either in-process limits (IPL) or in-process specifications (IPS), having action limits or acceptance criteria, respectively. Definitions of these concepts have been acceptably provided.

The deviation handling system is adequately described. In the event that a process parameter value falls outside the normal operating range, or if an IPL or an IPS is breached, an investigation is triggered. The investigation will evaluate the product quality impact and the disposition of the lot will depend on the outcome of the investigation.

CPPs and KOPs, along with the rationale for each designation, are provided. In addition, proven acceptable ranges (PAR) are provided for each parameter.

The microbial control strategy during the upstream and downstream manufacturing process of teplizumab is acceptably described.

Normal operating ranges (NORs) and PARs hold times for in-process intermediates have been established based on at-scale samples (for microbial) and down-scaled aliquots active substance samples from the PPQ lots (for chemical stability), respectively. Hold time studies conducted on the process steps are listed. Validation of in-process hold times and details on microbial and chemical testing, is acceptably discussed.

For end-of-production cells (EOP), the acceptance criteria are acceptably described (bioburden, mycoplasma, minute virus of mice (MMV) and *in vitro* adventitious viral agents).

The analytical procedures for in-process testing are listed.

For safety-related critical IPCs (mycoplasma, MMV and other adventitious agents) for end of production cells (Unprocessed Bulk), the Applicant confirmed that deviation from acceptance criteria would lead to batch rejection.

The information provided in this section is acceptable.

Process Validation and/or Evaluation:

Process Performance Qualification

The teplizumab active substance commercial manufacturing process was validated with a prospective validation approach, through the successful purification of three consecutive full-scale) bioreactor harvest batches, at AGC Biologics. The genealogy of the PPQ batches is acceptably described. PPQ results for the CPPs, KOPs and IPCs, identified at the time of PPQ, are provided. It is described that all results met the acceptance criteria. A corresponding summary for the nKOPs has also been provided.

The description of the PPQ outcome is in general acceptable; it can be assessed that the consistency and robustness of the process have been demonstrated by the PPQ campaign.

Hold Time Validation for Process Intermediates

The in-process product stability (hold time) validation was conducted using a combination of at-scale samples (for microbial) and down-scaled aliquots of in-process pools (for chemical stability), from the three PPQ lots.

Resin Lifetime and column performance

Studies have been made regarding reusable chromatography resins in order to establish satisfactory performance throughout the entire lifetime of usage (i.e. maximum number of cycles and total length of time in use). It is currently planned to reuse one chromatography resin).

To date, scale-down data has been generated, to allow to define the maximum allowable number of cycles. The results of this small-scale lifetime study will be confirmed with an at-scale validation study (ongoing) following a concurrent validation approach. Small-scale resin lifetime data has been generated on a small-scale model), which is bracketed with the qualified small-scale model (step consisting of a) and the at-scale conditions.

Column integrity tests (asymmetry & plate count) performed along with regularly interspersed blank runs showed consistent results across. Silver stain SDS-PAGE was performed to confirm that no detectable carryover was present in, up to, and confirms column cleaning procedure is adequate. No trend of these product quality attributes with cycle number was observed. Hence, it is acknowledged that the scale-down data generated to date indicate that this resin, when re-used for up to, does not show any adverse impact on product quality. However, considering that the asymmetry values is close to the high limit after, and given the conclusions made in the used resin viral clearance report, it is accepted that the lifetime for currently is set at.

The at-scale resin lifetime study will demonstrate that the chromatography resin performs within the established operating parameters, over multiple uses, at commercial scale. The study protocol has been put in place for collection and analysis of samples from execution runs including product runs and blank runs to demonstrate consistent performance and absence of protein carryover between runs. The procedure is assessed to be acceptable.

The resin used for lots executed to support the at-scale resin lifetime study has been used for, with. Column integrity tests, as well as step yield, showed consistent results; all results met acceptance criteria. The results indicate that, up to ten cycles: a) the resin performance does not deteriorate, and b) no impact is observed on the product quality.

Hold time validation for media, buffers and solutions

A process solution stability risk assessment was conducted to evaluate the hold conditions of the media, buffers, and solutions used during the production of the active substance. Each solution was evaluated for key variables impacting hold stability (chemical stability, or microbial stability). For each solution, a score of to respective conditions influencing the hold stability. The risk prioritisation number (RPN) for chemical hold and microbial hold was calculated for each solution by multiplying the individual scores under each category.

Results from the risk assessment are presented. Process solutions (one medium and one buffer) with the highest RPNs for chemical stability, microbial stability, and combined scores are discussed with justification for the selection of the hold validations that were performed. For media the Cell Production Media was chosen as the tested solution. The study performed is described and the results are presented. For buffers the, was chosen. The study performed is described and the results are presented.

Mixing validation

A risk assessment was conducted to evaluate the mixing conditions of the process solutions used during the production of the active substance. Each process solution was evaluated by the criteria mixing criticality, viscosity, solute concentration, solubility/miscibility and process criticality, yielding a total RPN. Results from the risk assessment are presented.

The Feed medium, and the, scored high RPNs, and were subject to mixing validations, which were conducted over three runs executed during the PPQ campaign.

The mixing validations demonstrated: a) Homogeneity of the solutions, b) Complete dissolution of all added raw materials, and c) Adequacy of the specified mixing time and speed, to achieve homogeneity and dissolution.

Extractables and leachables

An extractable and leachable (E&L) risk assessment was conducted to evaluate the potential of materials (components), to release leachable compounds that may impact product quality and/or safety. The output of this assessment was a list of product-contact equipment and materials, ranked from the highest to lowest relative risk, based on a comprehensive set of relevant risk factors. Items that were identified as higher risk were profiled in greater detail. A list of all materials included in the teplizumab manufacturing process was assembled. A RPN was calculated for each item based on the relative potential of that item to contribute extractable/leachable compounds that may impact product quality. The distribution of RPN scores across the components was analysed and a threshold was defined, over which components were identified and further evaluated. Adequate manufacturer's literature was provided for all items, and no items were identified for further studies.

The conclusion is that there are no materials used during the production of active substance that contribute leachable compounds that may impact product quality. It is assessed that the presentation of the procedure and results, and the conclusion from this evaluation, are acceptable.

Shipping validation

The purpose of the active substance shipping validation study was to verify that the cold chain transportation of bulk active substance (BDS) in 1 L bottles at meets the predetermined temperature criteria. Testing was performed using commercial scale PPQ BDS lots as they were shipped to the designated fill/finish or storage site. This study consisted of a minimum of three separate shipments, with at least one shipment occurring during summer to include worst-case conditions.

It is acknowledged that the cold chain transport validation successfully met the pre-established acceptance criteria. The temperature data confirm that the product also was maintained within the standard temperature criteria for active substance storage.

Continued process verification

Continued process verification (CPV) has been initiated to ensure that the commercial manufacturing process remains within the validated state. This purpose is achieved through process monitoring and reporting for each production process step and assessing for statistical trends. The focus of evaluation during CPV is to continuously assess these data for opportunities for continuous process improvement. The description of the CPV program is assessed to be acceptable.

Clearance of process impurities

Clearance through the purification processes operation and/or through the test of active substance, for the PPQ batches, were assessed to be acceptable.

Manufacturing Process Development

Critical Quality Attributes

Active substance critical quality attributes (CQAs) are described as properties or characteristics of the active substance that can potentially impact the safety and/or efficacy of the product. CQAs are

identified based on the knowledge gained during process development and are in general acceptably listed with the potential effect, test used, rationale for criticality and control strategy.

Overall Process Development

After initial development, several manufacturers were involved in the manufacturing of teplizumab active substance as summarised. The process designs are similar; the same process operations are included for all these process variants. The process differences are acceptably described. In general, the process changes are performed to align to new facilities and for improved process control.

Process Comparability

Stage 1

The comparability study covers biochemical and biophysical properties, peptide mapping analysis of primary amino acid sequence and location of disulfide bonds, and functional/biological properties. Lots used in the comparability study are listed.

The description of the process employed is brief; but given that product manufactured is only used in very early development, asking for more details on the manufacturing process description is not further pursued. Given the fact that material was not used in pivotal studies, the information pertaining to analytical comparability is considered sufficient. Overall, materials from the two processes showed comparable results. The teplizumab material was found to be comparable in all biological and functional aspects investigated. The information is limited but considering the early process development phase the conclusions are assessed to be acceptable.

Stage 2

Two lots were produced to supply material to the Phase III clinical trials. During the transfer, improvements and changes were made to manufacturing process, both to upstream and downstream. The changes in the manufacturing process and the rationale for these changes are acceptably described, in detail for each process operation. The batches used for the process change evaluation are summarised. For each process operation it is concluded that the process changes should have no negative impact on the process performance. This is assessed to be correct.

For the analytical comparability exercise the active substance lots chosen are acceptably described.

Regarding the comparability exercise, the actual values were compared and evaluated for each analysis. They are assessed to be acceptably comparable.

Characterisation data also showed comparable profiles in structural integrity and post-translational modifications for active substance from the two processes, which is acknowledged.

A separate comparability assessment was undertaken to evaluate the pre- and post-change lots using functional assays, which included measures of. The materials were judged to be comparable in these assays, which is acknowledged.

Stability studies under accelerated conditions have been performed on finished product lots. The data indicate that the stability behaviour is similar.

Stage 3

Teplizumab active substance batches were manufactured and used to manufacture finished product lots used in clinical studies. An updated version of the manufacturing process has been developed by to manufacture new batches of teplizumab active substance. The changes in the manufacturing process and the rationale for these changes are acceptably described, in detail for each process operation. The batches used for the process change evaluation are summarized. For each process

operation changes and differences in process performance is discussed, but it is concluded that the process changes should have no negative impact on the process performance. This is assessed to be correct.

Analytical comparability was assessed based on comparison of results from release and additional characterisation testing. The study included data from a reanalysis.

Overall, the conclusion of the Applicant is that active substance material from the two processes showed comparable results with respect to release assays, and that physicochemical characterisation, further confirms comparability. It is also stated that the comparison of biological activity also demonstrates comparability, and that no concerns relating to the safety of teplizumab lots are raised by the functional assay comparison. Data from batches is also provided, to further support the comparability of the pre- and post-change active substance. The actual values are compared and evaluated for each analysis. They are assessed to be acceptably comparable, or at lower levels.

In order to complement the comparability conducted on active substance batches, analyses of finished product lots manufactured from pre-change and post-change active substance lots were compared and found comparable.

Data from historical finished product lots stored at were compared to the stability data from post-change finished product lots manufactured) stored at for evaluation of stability comparability. Similar degradation profiles and rates of degradation were observed, which is acknowledged.

Overall conclusion on comparability

Based on the totality of the comparability data provided, including the different levels of comparison, the number of batches included, and the high degree of consistency between pre- and the post-change batch data, comparability is considered demonstrated.

Commercial process control strategy development

The process control strategy was developed through the following steps:

- Formal risk assessments based on process knowledge derived from detailed process information: Each process parameter (input) was ranked for its impact on each in-process intermediate output attribute i.e. performance or product quality attribute.
- Small-scale model qualification (SMQ) studies were performed to qualify bench scale model that were used for process characterisation studies. Material from at-scale was used for the qualification studies. Selected process performance and/or the quality attributes obtained from each process step at small-scale, were statistically compared with data from at-scale, and considered as qualified when data from small scale model were found to be not statistically different from the at-scale data. Small-scale models were qualified for N-1 Expansion, N Bioreactor, Affinity Capture Chromatography, Depth Filtration Anion Exchange Chromatography and Ultrafiltration/Diafiltration Buffer Exchange. The SMQ procedures and results are described in sufficient details and the conclusions are supported.
- Process characterisation studies were performed for process parameters identified as higher risk on product quality and process performance during risk assessment, using qualified small-scale models. The studies were performed to determine the impact of selected parameters on the process performance and/or product quality relevant to the step beyond their normal operating range. The results of the studies were used to support identification of CPPs and KOPs. PARs were established by models predicting the responses of the CQA and process performance outcomes as a function of the process parameters.

- Data from the PPQ campaign in combination with the finalised data packages from the small-scale qualification and characterisation activities were leveraged post-PPQ to improve process control. A list of all the changes applied to the active substance process parameters post-PPQ have been presented, along with a justification for these changes.

Characterisation

Elucidation of structure and other characteristics

Characterisation of active substance was performed with regards to primary structure, post-translational modifications, glycosylation, higher order structure including disulfide structure, mass and charge heterogeneity and a panel of biological assays to address antigen (CD3) binding, T-cell activation analyses and effector functions. The choice of batches produced using the commercial process for the extended characterisation is endorsed. The analytical methods used are state-of-the-art, and for most parts relevant characteristics have been evaluated and representative data have been provided.

Primary Structure

In order to confirm the primary structure of teplizumab light and heavy chain, peptide mapping using trypsin digest was performed and the results obtained from tandem mass spectrometry (MS/MS) spectra were compared with the theoretical amino acid sequences. A sequence coverage of 100 % is reported. In conclusion, it is agreed that the primary sequence of teplizumab is sufficiently verified.

Post-Translational Modifications by Peptide Mapping

Liquid chromatography tandem mass spectrometry (LC-MS/MS) peptide mapping obtained by trypsin protein cleavage was also used to investigate the presence of post-translational modifications (PTMs) in teplizumab. In addition to glycosylation, the data showed heavy chain N-terminal pyroglutamic acid cyclisation and C-terminal lysine loss in the heavy chain. The approach to use peptide mapping to reveal PTMs is acknowledged and the determined levels of the two major PTMs are found acceptable.

Carbohydrate Structure

Teplizumab is an IgG1-derived antibody predicted with a single N-glycosylation site at Asn299. The N-glycosylation site was indeed confirmed by peptide mapping to be N299 on each heavy chain. Hydrophilic interaction chromatography (HILIC) was further used to establish the N-glycan profile. Summarised tabulated data obtained from platform analysis and by the release method is presented. It is acknowledged that minor modifications to the glycosylation profile of teplizumab are not expected to affect its mechanism of action since Asn299 is located in the Fc-region. In teplizumab the Fc-region has been modified by site directed mutagenesis (L236A, L237A) to minimise Fc receptor and complement binding. This is deemed acceptable.

Mass Heterogenity

Intact mass analysis of teplizumab by LC-MS demonstrated that theoretical molecular weights correspond to the full-length glycoprotein with the C- and N-terminal modifications (loss of C-terminal lysine and conversion glutamines to in the HC N-terminals) seen by the peptide mapping. According to the Applicant, the relative abundance of glycoforms detected by intact mass analysis is in agreement with the abundance obtained by N-glycan analysis. This is supported.

Disulfide Structure & Free Sulfhydyl

Confirmation of teplizumab disulfide structure was performed by non-reduced and reduced peptide mapping. Annotated LC-UV profiles from non-reduced peptide mapping can be found in S.2.6,

comparability study Eli Lilly-Macrogenics, supporting the formation of 16 disulfide bonds (four interchains and twelve intrachains). This is found acceptable.

Free sulfhydryl content, as determined by treating samples with Ellman's reagent followed by spectrophotometric analysis, showed levels of ≤ 2.5 %, consistent with the HCCys105 being unpaired. This conclusion is found acceptable.

Higher Order Structure

Higher-order structures were analysed by a circular dichroism (CD) spectroscopy. Far-UV and near-UV CD spectrum confirmed typical β pleated sheet secondary structures with well-defined tertiary structure as expected for an IgG1 antibody. From the sedimentation velocity analytical ultracentrifugation (SV-AUC) analysis, it is evident that the quaternary structure is represented by a monomeric oligomeric state in solution. This is found acceptable.

Size Heterogeneity

Size heterogeneity was analysed by size exclusion high performance liquid chromatography (SE-HPLC), SV-AUC and capillary electrophoresis sodium dodecyl sulfate (CE-SDS). Teplizumab was shown to be predominantly monomeric in solution with a low propensity for aggregation). The high molecular weight (HMW) species are presented as dimers with a low percentage of trimers.

Charge Heterogeneity

Charge heterogeneity was evaluated using imaged capillary isoelectric focusing (icIEF) for detection of peaks with different isoelectric points (pIs), followed by characterisation of enriched acidic, basic and main peak fractions isolated by Cation exchange chromatography (CEX). icEIF results showed main peaks acidic isoforms and basic isoforms Each of the isolated cation exchange chromatography fractions was analysed using the gene reporter assay to assess potency. All the isolated fractions (acidic, main, and basic) showed comparable results for potency with the exception of a small amount action that showed lower potency. The purity remained consistent across the different isolated fractions as seen by non-reduced CE-SDS.

Extinction Coefficient Verification

The teplizumab extinction coefficient measured from batch by amino acid analysis and absorption at 280 nm was determined to be. Therefore, the use of the theoretical extinction coefficient for total protein concentration of teplizumab active substance and finished product at release by UV spectroscopy is assessed to be acceptable.

Functional Assays

Biological characterisation was performed to address antigen (CD3) binding, T-cell activation analyses and effector functions. The teplizumab potency assay (release assay) relies on a bioassay that utilises a Jurkat T cell line engineered to stably express an NFAT-responsive luciferase reporter gene. Dose-response curves from this assay as well as from a CD3 binding assay by flow cytometry are supportive of the CD3 binding capability of teplizumab. T-cell activation was characterized by cytokine release, mitogenicity and CD69 upregulation assays. Lack of effector functions was demonstrated in binding studies using BLI (biolayer interferometry) to a panel of Fc receptors and C1q. Furthermore, the inability of teplizumab to induce antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity was demonstrated in a set of cell-based assays. In contrast, a control antibody with wild-type Fc region was capable of inducing these effector functions. The biological characterisation of the full-length protein is found sufficient and acceptable.

FcRn binding

In section 3.2.S.2.6, the Applicant declares that "*While differences in FcRn binding could possibly result in differences in teplizumab exposure, PK/PD analyses conducted in the teplizumab clinical program to date have not identified any clinical impact of variations in teplizumab exposure (e.g., anti-drug antibodies impacted exposure but not efficacy or safety in the Protégé study). It is thus unlikely that any potential FcRn binding differences between pre- and post-change lots would impact either the efficacy or the safety of teplizumab.*" The absence of impact of teplizumab exposure on safety/efficacy is not endorsed since the biocomparability study PRV-031-004 has revealed differences in AUCinf between Eli Lilly and AGC batches, which have led to a dose adjustment during the PROTECT study. Consequently, it is considered that FcRn binding should be suitably monitored in order to prevent any FcRn-related change in teplizumab exposure and potential consequences in efficacy/safety. This is acceptable.

Overall, it can be assessed that the results confirm the identity of teplizumab and that it has the covalent structure, post-translational modifications, and other characteristics of a monospecific human IgG1 antibody with engineered Fc-region, derived from CHO cells.

Process-Related Impurities

The potential and actual process-related impurities associated with teplizumab active substance manufacture fall into the following groups: cell culture additives, host cell-derived residuals, and purification process residuals. A risk assessment was conducted using impurity safety factor (ISF) to determine which potential residual materials from cell culture and harvest to consider for further safety assessment and compounds with an ISF score of $\geq$ 1000 were considered to be of minimal risk and were not evaluated further. Clearance of process impurities through purification processes and/or through the test of active substance were also assessed. It is acknowledged that in general no safety risk is anticipated from potential residual process-related impurities.

Product Related Impurities

Product-related impurities may include IgG aggregates, reduced antibody species and non-native cross-linked species. Specification limits for these impurities have been established to ensure that they do not exceed allowances. The characterisation of the product-related impurities is found acceptable.

Aggregates by SE-HPLC and fragments by CE-SDS are controlled at active substance release. The % HMW were also characterised by analytical ultracentrifugation, which are consistent with the SE-HPLC results.

The LC-MS data revealed that the following chemical modifications and degradations can occur: hinge region fragmentation (between His226 and Thr227) in the HC, Asn-Pro clipping (cleavage between Asn93 and Pro94) in the complementarity-determining region (CDR) of the LC, oxidation of His103 and Cys105 residues in the CDR of the HC, generation of half antibody and free LC products, oxidation of Met residues (predominantly in the Fc region), and deamidation of Asn residues (mainly in the Fc region).

LC-MS peptide map analysis indicated that very limited amounts of oxidation in the CDR (HC His103, HC Cys105, HC Met34, HC Met254, and HC Met430) were detected in aged finished product samples but not in active substance lots. Cys105 oxidation in the CDR of the HC is controlled at the release of the teplizumab active substance and finished product.

Limited deamidation was observed in the active substance lots and aged finished product lots, but they are not expected to have any effect on the bioactivity of the molecule since these deamidation sites are in the Fc region.

4.2.3. Specification

Specifications

Specifications for the active substance include control of identity, purity and impurities, quantity, potency and other general tests.

The proposed acceptance criteria for active substance release and stability testing are considered adequately justified.

The active substance acceptance criteria for residual HCP are in line with clinically qualified levels.

Microbial attributes (bioburden and endotoxins) are not tested at shelf-life, with no proper justification for this absence. These attributes were, however, tested in the supporting stability studies conducted on batches, and suitable microbial control was shown.

The specifications were adequately justified.

Analytical methods

The analytical methods are correctly identified by either their Ph. Eur. reference number (for compendial methods), or a unique in-house method identification number (for non-compendial methods).

The non-compendial methods are in general summarised in a structured and adequate way. It is noted that the. This is deemed sufficient and development is not considered necessary. This is acceptable.

The Applicant has clearly summarised the validation and submitted the validation and transfer reports. The section is adequately described.

It is noted that the active substance and finished product are tested for endotoxin using the compendial LAL test based on the Limulus Amoebocyte Lysate (Ph. Eur. 2.6.14). Any post-approval change to the control of the active substance and finished product will require a variation application.

Batch analyses

The Applicant presented batches produced, including 3 PPQ batches, post PPQ batches are also presented. The section is adequately described.

Reference standard

A two-tier reference standard system has been implemented for teplizumab.

Information on the historical reference standard numbers, manufacturing sites, batch number of the parental batches and manufacturing dates are provided. This information is found acceptable and sufficient.

The protocols for qualification of reference standards are acceptably described, including selection and preparation of the material, and requalification procedures. The critical tests (protein concentration and potency) and primary test acceptance criteria are either tighter or the same as the release specifications, while the secondary tests have the same acceptance criteria as active substance release.

Detailed information on the preparation of the has been acceptably provided. Qualification of the PRS was performed using the critical, primary, and secondary tests, as described in the PRS Qualification Protocol, and all provided results met the acceptance criteria. Characterisation of the PRS was also performed according to the protocol, and all acceptance criteria were met. The PRS will be retested annually according to the protocol. The performance of the PRS will also be monitored through

trending and evaluation of data from any use of the PRS in routine batch release and ongoing stability testing.

Detailed information on the preparation of the WRS has been acceptably provided. Qualification of the WRS was performed using the critical, primary, and secondary tests according to the WRS Qualification Protocol. All results met the acceptance criteria. The WRS will be requalified annually according to the protocol. The performance of the WRS will also be monitored through trending and evaluation of data from any use of the WRS in routine batch release and ongoing stability testing.

Provided successful qualification according to the criteria set in Section 3.2.S.5, future reference standards. This, in combination with the WRS proposed acceptance criteria. It is agreed that the information provided is acceptable and that the current PRS and WRS are adequately qualified to be used as reference standards for teplizumab.

Container Closure System

The containers used for storage of active. The components of the container are sufficiently described, and are controlled by adequate specifications, including identity of the material of construction and critical dimensions.

The components are gamma irradiation sterilised.

It is acknowledged that the system components comply with current regulations (FDA 21 CFR and ISO 13485:2016).

The capability of the system to protect active substance from microbial contamination was also demonstrated during the stability studies. These conclusions are assessed as acceptable.

The compatibility of the CCS to the active substance is proven by acceptable long-term and accelerated stability data. Moreover, no risk of extractable and leachables was identified for the CCS that may impact product quality and/or safety. These conclusions are assessed to be acceptable.

4.2.4. Stability

Stability testing of teplizumab active substance has been performed in line with recommendations in relevant ICH guidelines. Information on the stability studies for the active substance, manufactured at the commercial bioreactor scale and stored in a bottle, are acceptably summarised.

The shelf-life conclusions are based upon long-term stability data from primary stability studies on production scale batches, stored in a container closure system assessed to be representative of the commercial one.

All available long-term storage and accelerated stability results met the acceptance criteria for the tested CQAs.

Forced degradation studies were performed on active substance, to characterize and describe the potential degradation pathways under various stressed conditions. Specifically, the effects of the following conditions were studied: photostability, agitation/shear, freeze/thaw, oxidation, elevated/reduced pH, storage at elevated temperature. The methods and results are acceptably described. As a precaution, protection from light is recommended for the long-term storage of teplizumab active substance.

Ongoing stability studies and post-approval stability studies will be performed according to the protocols described in the dossier. The Applicant commits to continue these studies through the proposed shelf-life. An acceptable post-approval stability testing protocol has been provided.

The information in this section is found acceptable. The claimed shelf life for the active substance is acceptable.

4.3. Finished medicinal product

4.3.1. Description of the product and pharmaceutical development

Description and Composition of the Finished product

Teplizumab finished product is supplied as a sterile solution with a concentration of 1.0 mg/mL for intravenous infusion. It contains 1 mg/mL teplizumab in a buffer composed of 10 mM sodium phosphate at pH 6.1 containing 150 mM sodium chloride and 0.05 mg/mL polysorbate 80. The concentration, function, and grade of each component in teplizumab finished product is summarised. The description and composition of the finished product is adequate.

All excipients are pharmacopeial. There are no novel excipients or of human or animal origin.

The finished product is packaged in a USP/Ph. Eur. 2 mL Type I borosilicate glass vial with a 13 mm FluroTec®-coated butyl rubber stopper. The vial is sealed with a 13 mm flip off aluminium closure with a plastic matte-top overseal. Detailed information of the finished product vial configuration is described in. The nominal fill volume is 2 mL.

The description and composition of the finished product is adequate, with concentration and nominal amounts per vial. The excipients are compendial and their functions listed. The CCS components are described, fill volume and overfill stated.

Pharmaceutical Development:

Active substance & excipients

The components of the finished products are adequately described, and further information is referred to other sections. This is found acceptable.

Formulation development, overage, physiochemical and biological properties

A basic formulation selection was made based on heat stress, process simulation, freeze thaw and shipping simulation studies. The formulation has not been changed during clinical development. The basic selection along with the long-term experience and stability data is considered adequate and acceptable for development of the commercial formulation.

There is no overage and physiochemical and biological parameters are adequately described.

Manufacturing process development and Comparability

The Applicant describes the manufacturing process development over three finished product processes. The finished product manufacturing site has been the same throughout the development. The CCS and formulation are unchanged. The Applicant has tabulated clear comparisons between Process 1 & 2, as well as 2 & 3. A major change is the installation and use of a new fill line in conjunction with the introduction of process 3. No formal finished product comparability was made between Process 1 & 2

since the changes on the finished product process were minimal. This is acceptable. A finished product comparability exercise between Process 2 & 3 is included where active substance and finished product comparability was established (finished product through batch release data, accelerated stability and forced degradation).

The analytical comparability of release data between only one pre-change finished product batch manufactured by Process 2 and two post-change finished product batches manufactured by Process 3. Based on these finished product stability results and the overall active substance/finished product comparability data, the results point towards finished product comparability between pre- and post-change finished product batches, which is considered sufficient.

On *control strategy*, the Applicant adequately describes the development. This includes thawing and mixing studies to establish normal operating ranges, as well as bioburden and sterile filter integrity and compatibility testing. The parameters identified were used in PPQ batches. A final criticality evaluation of the parameters was done post-PPQ with some reassessments of criticality. The manufacturing process development and comparability are adequately described and found acceptable.

Container closure system

The Applicant has selected common immediate biologics CCS components, Type I Ph. Eur. borosilicate glass vial and FluroTec-coated butyl rubber stopper, meeting Ph. Eur. requirements. Further description and component drawings are presented. Protection and compatibility are demonstrated through long-term stability studies. Extractable/leachable studies are performed including a real-time leachable study with validated methods. From this study, 24 months of data is available, the protocol is extended. The description of the container closure system is found acceptable.

Microbiological attributes

The Applicant has addressed appropriate measures to maintain sterility, especially container closure integrity testing and the process parameters affecting the closure, i.e. line speed and crimping pressure. A rabbit pyrogen test has also been executed on three finished product lots. The section is adequately described and acceptable.

Compatibility

In-use compatibility studies have been performed. The materials and procedures claimed in the SmPC in section 6.6 are found supported by the presented compatibility studies.

The Applicant describes a two-step in-use dilution procedure to prepare the solution for infusion, and compatibility studies reflects this accordingly. The first step is a 1:10 dilution of teplizumab in 0.9% saline (2 mL teplizumab + 18 mL saline), the second step is a dilution in 25 mL of 0.9 % saline with the amount teplizumab that corresponds to the calculated dose based on body surface area (BSA).

The Applicant has performed compatibility evaluation, microbial hold and confirmation studies (mock infusion). The studies identified both compatible and incompatible materials. The Applicant concludes that the studies support that either glass, polycarbonate (PC) or polypropylene (PP) can be used in the preparation of teplizumab prior its transfer to IV bags and that IV bags made from polyvinylchloride (PVC) with Di(2-ethylhexyl) phthlate (DEHP) should be used for its administration.

It is noted that the product information has been updated with "complete infusion within 6 hours of the start of preparation" instead of previous 4 hours. Therefore, it can be agreed that the in-use shelf-life of 6 hrs can be considered acceptable.

Also, the Applicant has updated the table regarding "Materials Compatible for Teplizumab Administration" in section 3.2.P.2.6. The addition of compatibilities with pump syringes made of different materials are all endorsed. The compatibilities are supported by additional in-use studies with

pump syringes (2nd dilution occurs directly in the pump syringes instead of the use of IV bags). The SmPC section 6.6 is also adequately amended to include the compatibility of the finished product with the PP, PC or glass syringes.

In conclusion, section P.2 is adequately described.

4.3.2. Manufacture of the product and process controls

Manufacturing process and controls

All sites involved in manufacture and controls of the finished product operate in accordance with GMP.

The manufacturing process includes active substance thawing, pooling, finished product formulation, bioburden reduction filtration, sterile filtration, aseptic filling, visual inspection, packaging and storage.

Hold times and maximum time out of refrigeration are defined. No reprocessing is allowed. The Applicant describes the control actions in the event of an CPP or IPC to be out of normal operating range or action limit failure to be an investigation that will determine impact on product quality and lot disposition.

The final formulation bulk finished product process step is sufficiently described.

Process validation and/or evaluation

The section is adequately described. The three PPQ batches data are within the predefined criteria / normal operating ranges defined in the process development as well as fulfilling specifications. It is noted that no deviations are listed for the PPQ batches.

The process has 100 % weight checks and automatically rejects vials out of range. Hold times were challenged and are supported by data. Sterile filter validation included microbial retention, compatibility, leachables and bubble point determination. Product contact components are single use; hence no cleaning validation is needed.

Filter validation and the bracketing approach media fill program are adequately described. The most recent media fills are listed. The process maximum fill duration is covered by the media fill program. This is acceptable.

Transport validation was conducted through vibration studies according to ASTM-D4169-16 standard and a main shipping validation using validated transport containers. The main shipping study was conducted with ground and air transport within the American continent. This is acceptable.

4.3.3. Product specification

Specifications

Specifications for the finished product include control of identity, purity and impurities, quantity, potency and other general tests.

Potency

Furthermore, based on the available active substance and finished product long-term stability results and acknowledging multiple results between during the proposed shelf life of 36 months (most likely due to variability of the analytical method), the proposed lower limit for active substance and finished product stability testing can be agreed.

The Applicant has, as requested, tightened the lower finished product release limit for potency to. Any wider limit was not found clinically justified based on the currently available batch data. The Applicant also aligned the lower active substance release limit to.

Cys105 oxidation

It can be agreed that the Cys105 oxidation limit is maintained, and further tightening will not be pursued.

However, given that the analytical method for measurement of Cys105

Purity

The Applicant has further tightened the finished product stability specifications limits for purity) to, as initially requested. This is found acceptable.

Size variants

The Applicant has tightened the active substance stability and finished product (release and stability) specification limits for % main peak to, as initially requested. This is found acceptable.

Charge variants

Finished product acceptance criteria are different for release and shelf-life specifications, . The Applicant has updated sections 3.2.S.4 and 3.2.P.5 and amended the tightened finished product stability specification limits for charge variants. This is found acceptable.

Extractable volume

The Applicant proposes to maintain the 100% fill weight check and included this test in the finished product specifications, as requested. This is considered acceptable.

Overall, the finished product specifications are adequately described and acceptable.

Analytical procedures

Analytical procedures and validations are clearly listed and referenced to appropriate sections. Container closure integrity test (CCIT) is used in lieu of sterility for stability monitoring, which is acceptable.

Batch analyses

The Applicant presents batch analyses, including 3 PPQ and post-PPQ batches. The section is considered adequately described.

Characterisation of impurities

The section focuses on impurities that might arise during finished product manufacturing and storage. Otherwise, impurities are the same as those for active substance and discussed in S.3.2. Microbial contamination, particulate matter, leachables, elemental impurities and nitrosamines have been addressed by the Applicant in line with relevant guidelines. Risk assessments on nitrosamines for finished product and active substance are presented. The risk assessments adequately address the risks with the different materials and process steps and concluded no hazard. This is acceptable.

Reference Standards or Materials:

The Applicant refers to section S.5. This is acceptable.

4.3.4. Stability of the product

The claimed shelf-life is 36 months at 5°C±3°. Product stability was evaluated using the process and container closure system proposed for commercial marketing.

Storage conditions were evaluated on five production scale finished product batches manufactured at:

An overview of the batches supporting the teplizumab finished product stability assessment was provided. The sensitivity of the active substance to light is endorsed as well as the marketing packaging protects the finished product from light. the claim of light sensitivity for the finished product is endorsed.

The Applicant presents a post-approval stability protocol and commits to place a lot a year on stability (if produced). Any out-of-specification (OOS) or atypical trends will be investigated. The stability data is clearly tabulated.

The claimed shelf-life of 36 months at 5°C±3°C storage condition (unopened vial) is supported by data and acceptable.

After dilution:

- IV infusion bags:

Chemical, physical and microbial in-use stability has been demonstrated for 6 hours at ambient temperature (15°C to 25°C). From a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 6 hours at ambient temperature (15°C to 25°C).

- Syringe-based infusions:

Chemical, physical and microbial in-use stability has been demonstrated for 12 hours under refrigerated conditions (2 °C to 8°C), followed by no more than 6 hours at ambient temperature (15°C to 25°C). From a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 12 hours under refrigerated conditions (2 °C to 8 °C), followed by no more than 6 hours at ambient temperature (15 °C to 25°C).

4.3.5. Adventitious agents

Materials of animal origin

There are no materials of animal origin used in the generation of the MCB, WCB or production. Some materials of animal origin were used for the derivation of the original cell clone. Information with certificates from suppliers and a certificate of suitability from EDQM are provided in 3.2.A.2). The information is found sufficient and the risk of TSE is assessed to be negligible.

Non-viral adventitious agent testing

Microbial controls testing for bioburden and endotoxin is shown with acceptable results for the GMP-1 and three PPQ batches. This is regular testing throughout the downstream process with start at the unprocessed bulk. Mycoplasma is also tested for on the unprocessed bulk harvest. It is acknowledged that microbial agents are sufficiently controlled with this test programme.

Testing of unprocessed bulk

The unprocessed bulk is routinely tested for in vitro adventitious viruses using three indicator cell lines, MRC-5, VERO and CHO, in addition a quantitative PCR (qPCR) assay is performed for MMV. Transmission electronic microscopy (TEM) results are also presented for the GMP-1 batch as well as the three PPQ batches. Approximately 7 log10 retrovirus-like particles (RVLPs) per mL are found which is an expected result for CHO cells.

Virus clearance studies

Model viruses used for the clearance studies were, acceptable rationales have been given. The viruses differ in characteristics, enveloped vs. non-enveloped, sizes, genome and physico-chemical resistance. The selected viruses are endorsed.

Prior the viral clearance studies, the relevant process intermediates were assessed for cytotoxicity and/or interference in the qPCR and infectivity assays so as to find a proper dilution of the samples.

The small-scale models of the Protein A chromatography step and the anion exchange membrane chromatography step have been qualified. Information on these qualifications is found in section S.2.6. For the virus clearance studies, rationales have been provided for the studied steps for selected worst case conditions where applicable. NOR and studied ranges (S.2.6) are shown with settings for the clearance studies. The information provided is found acceptable.

The study design is discussed including if the step has been studied by qPCR or an infectivity assay. Results with chromatograms for the protein A (affinity) and steps (flow through) are shown. The

In the low-pH studies it is known that there is limited effect on non-enveloped viruses. Studies were performed with the enveloped viruses were good effect was seen. Kinetics of inactivation are shown.

For the nanofiltration step, a high membrane loading was chosen and pressure was at set point. In addition, both lower and higher operating pressure was studied at the study. A high volumetric throughput for the flush and a pause in filter flow was evaluated, this is endorsed. A robust clearance of all viruses was demonstrated.

The lowest log reduction factor (LRF) for each step was used for the calculation of minimum total claimed LRF as a conservative approach. For Protein A chromatography, fresh resin results were used as equivalent viral clearance results were demonstrated for aged resin that went through product cycles. This is accepted also considering that aged resin studies are not expected as earlier discussed.

The virus safety factor calculated for RVLPs are per dose. This is an acceptable result. It is concluded that the viral and non-viral safety has been sufficiently demonstrated.

Overall, adventitious agents safety is considered sufficiently assured.

3.6. Post-approval change management protocols

A PACMP is included to extend the LIVCA.

It is found that the PACMP to extend the LIVCA is acceptable.

4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The dossier is appropriately structured. No GMP issues have been found, and no pre-authorisation inspections are deemed necessary.

The active substance manufacturing process is adequately described. Description of origin and control of cell banks and gene constructs is acceptable. Characterisation of teplizumab was performed using an extensive panel of appropriate methods and is considered acceptable. The control of active substance is found acceptable. The provided data to support the shelf-life claim for the active substance is considered acceptable and justified.

The development and manufacture of the finished product have been sufficiently described and justify the chosen formulation as well as the commercial manufacturing process.

The claimed shelf life of 36 months for the finished product when stored at the recommended storage condition at 2°C to 8°C is supported by real-time data.

Adventitious agents safety including TSE have been sufficiently assured.

Overall, the quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Teizeild is considered approvable from the quality point of view.

4.5. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends several points for investigation.

5. Non-clinical aspects

5.1. Introduction

Teizeild consists of the active substance teplizumab, a humanized monoclonal antibody (IgG1 sub-class) that binds to the CD3ε chain of the T-cell receptor (TCR) complex on human T cells, which leads to internalisation of the teplizumab/CD3 complex. The mechanism of action of teplizumab to prevent beta-cell destruction in T1D is not fully understood.

In vitro pharmacology testing included measurement of affinity for target (CD3ε) for teplizumab and a surrogate antibody, specific for mouse CD3ε; evaluation of target engagement through testing of T-cell responses within PBMC cultures (T-cell activation via upregulation of activation marker molecules; T cell proliferative responses; cytokine release) and specificity through examination of human tissue cross-reactivity.

In vivo pharmacology testing included assessment of efficacy, delivery of drug candidate and safety. As teplizumab is a biologic drug (monoclonal antibody), non-clinical safety evaluation was performed according to ICH S6(R1) and other associated ICH guidelines as appropriate. Because of the limited availability of animal models with cross-reactive target antigens, the initial clinical trials with teplizumab for T1D patients were supported by a limited number of non-clinical pharmacology, pharmacokinetic (PK), and toxicology studies.

The studies for teplizumab included:

- single-dose toxicology studies in chimpanzees [Study T-2002-009] and mice,

- a PK study to assess the bioequivalence of two lots of teplizumab and two lots of another produced teplizumab [Study RSS00606],

- and an ex vivo human tissue cross-reactivity study [Study IM187].

- An additional study was conducted to compare the effects of teplizumab on cytokine release using PBMCs purified from psoriatic patients and healthy volunteers [Study MGA031-HL003].

To expand and further investigate the non-clinical safety profile, a hamster/mouse chimeric surrogate mAb that binds to the CD3ε receptor on mouse T cells was developed. Eight non-clinical safety studies were conducted with the surrogate antibody in CD-1 mice, including single-dose, repeat dose and reproductive and developmental toxicity studies. All of the studies included toxicokinetic (TK) evaluation, and seven of the studies included assessment of pharmacologic activity of the surrogate antibody based on immunophenotyping (IPT) of peripheral blood, spleen, or thymus. The innate immune response (release of cytokines) was evaluated in a single-dose study [Study 7608-796] and the humoral immune response (T-cell dependent antibody response) was investigated in F1 progeny in the pre- and postnatal study [Study WIL 353232]. The production of anti-drug antibodies (ADA) against the surrogate antibody was assessed in two pharmacology studies [Study RND-MGA031-10-1001] and [Study RND-MGA-10-1002].

5.2. Analytical methods

Validated ELISA assays were used to support the GLP single-dose toxicology study of teplizumab in chimpanzee (3) and the GLP repeat-dose toxicity studies and reproductive and developmental toxicology studies of the surrogate antibody in mice. Although the validation was not performed in accordance with the guideline on bioanalytical method validation and study sample analysis (ICH M10) that came into effect 2023, the possible impact of uncertainties linked to the quantification of teplizumab in the pivotal chimpanzee toxicity study is low. A non-validated ELISA assay was used for quantification of teplizumab in rat serum in a single-dose PK study to assess the bioequivalence of two lots of teplizumab and two lots of another produced teplizumab.

5.3. Pharmacology

The pharmacology of teplizumab has been evaluated in non-clinical studies in vitro and in vivo. Due to the limited availability of animal models with cross-reactive target antigens to teplizumab, the most relevant assessment of non-clinical pharmacology was obtained from a single-dose toxicity study in chimpanzees [Study T-2002-009]. In addition, a mouse surrogate anti-CD3 antibody, with the same Fc-modification as teplizumab was evaluated in mice.

5.3.1. Pharmacodynamics

Primary pharmacodynamics

Teplizumab is a humanized monoclonal antibody (IgG1 sub-class) that binds to the CD3ε chain of the T-cell receptor (TCR) complex on human T cells, which leads to internalisation of the teplizumab/CD3 complex. The mechanism of action of teplizumab to prevent beta-cell destruction in T1D is not fully understood but proposed to involve partial agonistic signalling and deactivation of pancreatic beta-cell autoreactive T lymphocytes. Teplizumab is a humanised version of Muromonab/OKT3, which was the first mAb to be approved for clinical use in humans, that has been engineered in the Fc region (234-Ala, 235-Ala, 'LALA mutation') to reduce Fc effector functions.

In silico analysis of the contact residues of the CD3ε epitope recognized by the parent mAb of teplizumab, OKT®3, confirmed previously demonstrated lack of cross-reactivity with other species than human, gorilla, chimpanzee and gibbon (Study 031-2101-09).

The pharmacologic effect of teplizumab was evaluated in a single-dose toxicity study in chimpanzee (T-2002-009), where almost complete depletion of T-cells from circulation was observed one day after treatment. The effect persisted up to D7 or D14 with recovery by D42. Whilst the magnitude of depletion was not dose related, the recovery was quicker at low doses. Levels of $CD4^+$ and $CD8^+$ T cells were reduced to a similar extent, but no further T-cell phenotyping was performed. Reductions were also seen in number of circulating B cells ($CD19^+$) and NK cells ($CD56^+$). The magnitude of the observed changes was similar to those observed in human studies. Annexin-V-positive staining of $CD4^+$ and $CD8^+$ cells suggested that the decreased number of T cells after teplizumab treatment was caused by the induction of T cell apoptosis.

A mouse surrogate antibody was developed and demonstrated to have similar affinity to its target as teplizumab (Study 031-2102-09). The surrogate contains the same Fc modifications as teplizumab and is of isotype IgG2a, which is the mouse isotype most similar to human IgG1 in terms of FcR binding and effector function. However, the surrogate antibody differed in kinetic parameters from teplizumab in that it had a slower on-rate and a slower off-rate.

The mouse surrogate CD3 antibody was evaluated in a T1D disease model, the NOD mouse, and demonstrated to delay diabetes onset in this model (Study RND-MGA031-10-1001). No immunophenotyping was performed in order to evaluate the mechanism behind the observed effect in NOD mice. Of note, all NOD mice treated with a second course of antibody (teplizumab surrogate or isotype control) died within 1.5 h due to severe anaphylactic reactions. Similar severe IgG1-mediated reactions, resulting in lethal shock, have been reported earlier in the NOD mouse after injection of human peptides (Pedotti et al. 2003, BMC Immunol. doi: 10.1186/1471-2172-4-2, and Liu et al. 2002, JCI 2002. doi: 10.1172/JCI15488).

The surrogate antibody was more immunogenic in NOD mice and in female CD-1 mice than in BALB/c, C57BL/6J, or male CD-1 mice, as indicated by a 10 to 20-fold higher median level of ADA (Study RND-MGA031-10-1002).

Immunophenotyping was performed in CD-1 mice treated with the surrogate antibody in a series of toxicology studies, all showing a transient T-cell reduction, in line with the effects observed both in chimpanzees and humans. In lymphoid organs (spleen and thymus) a decrease in overall T cells and T lymphocyte sub-populations also occurred. $CD4^+$ and $CD8^+$ T-cell subtypes were reduced to a similar extent. No further immune-cell analyses were performed in the non-clinical studies but published data from patients treated with teplizumab suggest an increase in regulatory T cells and expression of genes associated with a partially exhausted phenotype.

Secondary pharmacodynamics

Compared to OKT®3, teplizumab carries an ALA-ALA modification of the Fc region that reduces CDC and ADCC effector functions. A PBMC cytokine release assay *ex vivo* demonstrated no difference in cytokine induction between cells from psoriatic and healthy donors when treated with teplizumab (Study MGA031-HL003). Teplizumab treatment induced TNF-α and IFN-γ release, but overall, the cytokine levels were lower than those induced by the parent mAb, OCT3, in line with the ALA-ALA modification of the Fc region. No additional dedicated studies of secondary pharmacology were submitted, but secondary pharmacology endpoints were included in the toxicology studies. A tissue cross-reactivity assay demonstrating specific staining in the expected lymphoid tissues (Study IM187) is described and assessed in the toxicology section.

Cytokine release was observed after teplizumab treatment in the chimpanzee (Study T-2002-009), where dose-dependent increases in circulating TNF-α, IL-6, IL-10 and IFN-γ were observed, in line with findings in human studies. With the surrogate antibody in mice (Study 7608-796), secretion of IL-6 and IL-12 was observed, but no treatment-related induction of IL-5, IL-5, IL-10, or IL-17 in contrast to a reference CD3 mAb without the Fc modification, indicating a reduced but not abolished cytokine release.

In vitro, no ADCC activity was mediated by either the teplizumab reference standard or the muromonab positive control when Jurkat cells were employed as target cells. The underlying cause of the lack of activity of the positive control remains unknown. As an alternative strategy, HPB-ALL cells were used as target cells and the ADCC assay was performed with an E:T ratio of 20:1. Under those conditions, the muromonab positive control produced dose-dependent ADCC activity whereas the teplizumab reference standard and negative control produced similar responses. Overall, those data are indicative of low potential of teplizumab to mediate ADCC.

A recent in vitro CDC assay was conducted by the applicant with several batches of teplizumab. However, the CD3 mab positive control (muromonab/OKT3) failed to show cytotoxicity towards CD3+ cells (Jurkat cells, HPB-ALL cells) under the experimental conditions, thus raising question about the validity of the assay. This is in contrast with the results of Xu et al., 2000 showing complement-dependent HPB-ALL cell lysis by mOKT3 whereas huOKT3g1(A234, A23s) was inactive.

Safety pharmacology

No dedicated safety pharmacology studies were conducted with teplizumab, but, in line with ICH S6, safety pharmacology parameters were evaluated in the single-dose study in chimpanzees following SC doses at 0.1, 1.0, and 10.0 mg/kg (Study T-2002-009). No treatment-related effects on safety pharmacology endpoints, including body temperature, ECGs, heart rate, blood pressure, or respiratory rate were seen. Cardiovascular parameters were monitored 1h post dose despite the Tmax for the SC route of administration being achieved 1-2 days post-dose. Nevertheless, the systemic exposure remained comparable to that observed in human for the proposed therapeutic dose/regimen.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted with teplizumab. No interactions are expected based on the mode of action. This is considered acceptable.

5.3.2. Pharmacokinetics

Due to the limited availability of other animal models than the chimpanzee with cross-reactive target antigens, non-clinical pharmacokinetic (PK) studies have been limited, although some additional studies have been conducted using a hamster/mouse chimeric monoclonal antibody (mAb) that binds to the CD3ε receptor on mouse T cells. The applicant did not submit studies on distribution, metabolism and excretion. No radiolabelled tissue distribution/mass balance or metabolism studies with teplizumab were submitted and no serum protein binding assay was submitted.

Validated ELISA assays were used to support the GLP single-dose toxicology study of teplizumab in chimpanzee (T-2002-009) and the GLP repeat-dose toxicity studies and reproductive and developmental toxicology studies of the surrogate antibody in mice. A non-validated ELISA assay was used for quantification of teplizumab in rat serum in a single-dose PK study to assess the bioequivalence of two lots of produced teplizumab and two lots of another produced teplizumab.

Absorption

Only one pivotal study with assessment of teplizumab TK was conducted, a single dose toxicity study in chimpanzee (Study T-2002-009). This demonstrated exposure to teplizumab for >7 days after SC administration of 0.1, 1.0 or 10 mg/kg. The half-life changed with dose and appeared to be shorter at lower doses (5.2 days at 10.0 mg/kg, 3.68 days at 1.0 mg/kg, and 1.94 days at 0.1 mg/kg). No estimation of volume distribution is presented. Teplizumab was quantified in serum with an ELISA assay with a LLOQ at 19.79 ng/mL.

Although no other pharmacologically relevant species than the chimpanzee are available, PK for teplizumab was also assessed in rats where bioequivalence was demonstrated of manufactured teplizumab and another manufactured teplizumab after single-dose administration IV (Study RSS00606).

For assessment of the Toxicokinetic (TK) properties of the mouse surrogate antibody, see section 5.4.6.

5.4. Toxicology

A limited toxicology program with teplizumab and its surrogate antibody has been evaluated in non-clinical studies in agreement with relevant guidelines (ICH M3, ICH S6).

The toxicity profile of teplizumab has been characterized via an acute single toxicity study in chimpanzees. As there are no relevant species for teplizumab than chimpanzees, which is ban and not a suitable species for these purposes, evaluation continued in mice with a surrogate antibody in a GLP 6 days repeat dose toxicology (RDT) study, male/female fertility and early embryonic (FEED) studies, embryonic development (EFD) and a pre-postnatal development (PPND) study. The surrogate antibody binds to mouse CD3ε chain with similar target affinity and distribution, and MoA as teplizumab has to CD3ε chain in humans.

No genotoxicity studies have been performed in the programme since teplizumab is an IgG sub-class antibody and is therefore unlikely to directly interact with DNA or other chromosomal components. Further, no standard carcinogenicity studies have been performed, as standard carcinogenicity assays are considered inappropriate for mAb products. However, the Applicant has submitted a product-specific Carcinogenicity Assessment Document (CAD) performed in accordance with the ICH S6 (R1) guideline, addressing the potential carcinogenic risk associated with teplizumab treatment.

5.4.1. Single-dose toxicity

Acute toxicity was tested in a GLP DRF study in chimpanzees with teplizumab and a non-GLP DRF study in mice with the surrogate antibody. In the chimpanzee study an older teplizumab batch was used however its characteristics appear similar to clinically relevant batches. Besides the standard parameters, blood immunophenotyping (see section 5.3.1.1), cytokine measurement (section 5.3.1.2) and safety pharmacology assessment (5.3.1.3) have also been evaluated. Those results are discussed under the Pharmacology section of this report. In addition, a non-GLP exploratory study in C57BL/6 mice given teplizumab IP was provided. However, this study was considered not relevant as teplizumab does not cross binds to CD3 cells in mice.

In the single toxicology study in chimpanzees dosed at 0.1, 1.0 and 10 mg/kg SC treatment related mortality occurred on study day 31/33 in all 3 high dose animals. Just prior to death it was recorded

that these animals had very marked elevated levels of white blood cells and significant changes of clinical chemistry and blood parameters. Following histopathological review this was attributed to lymphoproliferative disease present in all 3 animals identified as post-transplant lymphoproliferative disorder. In situ hybridization studies showed the presence of a lymphocryptoviral (Epstein-Barr virus [EBV]-like) in proliferating lymphocytes, possibly explaining the flu-like symptoms observed. Investigators theorized reactivation of the EBV-like virus due to the initial T-cell depletion observed with teplizumab. Clonal expansion of EBV could however not be confirmed due to the assay using a probe only recognising a small fraction of monkey EBV DNA. EBV reactivation has not frequently been observed in clinical trials so far and the low number of cases were not severe. Nevertheless, serious infections and lymphopenia are recognised as potential adverse events with recommendation for interruption/ management are specified in the SmPC of the product.

In non-GLP DRF study in mice using the surrogate antibody no changes were observed at doses up to 60 mg/kg SC and 30 mg/kg IV.

5.4.2. Repeat-dose toxicity

Repeat toxicity has only been performed with the surrogate antibody targeting CD3ε receptor on mouse T cells since there was a lack of an appropriate species for teplizumab. One GLP repeated dose toxicology study of 6 days duration with 6 weeks of recovery have been performed in CD-1 mice (study 7608-797). This study utilized the surrogate antibody which was administrated both subcutaneously and intravenously to assess toxicity and toxicokinetic. No chronic studies with the surrogate were conducted in accordance with the ICH S6 (R1) guideline. The interrupted study 8233170 would have covered this requirement. The applicant's position that a further chronic study is not required is based on the short-term administration of two 14 days cycles, the 100% bioequivalence between SC and IV administration and the fact that the pharmacological effect and the toxicological profile observed with a single dose of teplizumab in chimpanzee and with 6 SC daily doses of surrogate in mice are similar. Considering the absence of target organ for toxicity in both species and the comparable PD effect of teplizumab and the mouse surrogate on the immune cell populations, the absence of longer duration studies can be accepted. The main identified risk is related to the modulation of the immune system and to the depletion of the lymphocytes populations leading to increased risk of infection. The longer-term evaluation of this risk has been superseded by clinical data.

The certificate of analysis for the pivotal mouse studies (6 days RDT, all reproduction toxicity studies) is neither GLP nor GMP and it only mentioned the concentration of the test item. For each study, the protein content analysis and test article formulations were performed under GLP principles. Although further characterisation should have been performed this is not considered an issue, and therefore not further pursued, knowing that the pharmacology response on the immune cell population was confirmed in vivo.

In the GLP repeated dose study, no measurable Cmax and AUC values was recorded on study day 1 at 0.03 and 0.3 mg/kg although IPT recorded a decrease of T cells indicating pharmacologic activity. On study day 6 the Cmax and AUC_{0-t} increased with SC repeated dosing with values higher in males than females while the serum concentrations were decreased in a multi-exponential manner following the IV dose. The Tmax ranged from 4 to 24 hours indicating slow absorption after SC administration. The exposure (AUC) was comparable in the SC and IV 0.3mg/kg dose groups and complete bioavailability was indicated as males and females showed 132% and 87.5% bioavailability. There were no treatment related deaths in the study and in food consumption was noted but was not considered adverse as no

bodyweight changes was recorded and the decrease of food intake was resolved during the 6-week recovery period.

Histopathological findings at the end of dosing and recovery period showed a reduction of the cellularity of the medulla in the thymus, which correlated with the decrease in T lymphocyte populations.

Other compound-related changes that could not be directly attributed to the reduction of T cells were observed in the spleen, mandibular lymph node and bone marrow at >0.03 mg/kg by SC injection and included: minimal to moderate hematopoiesis in the spleen characterized by an increase in the number of megakaryocytes and scattered erythroid element, a finding more comment in rodent than in human; minimal to slight neutrophil infiltrates within medullary cords of the mandibular lymph node that were not present in the mesenteric lymph node; and minimal to marked myeloid hyperplasia within the bone marrow. The relationship with the test item remains unknown and those changes were not accompanied by any evidence of inflammation in other tissues. At the end of the 6-week recovery phase, the changes in the thymus, spleen, and lymph node generally persisted but at lower levels of incidence and severity. The myeloid hyperplasia in the bone marrow was not present at the end of the recovery phase.

Overall, as expected with monoclonal antibodies, toxicity may arrive from exaggerated pharmacological activity.

Study 8233170 which was interrupted at week 9 of the 3-month recovery, included Q3D SC dosing of the surrogate in CRl:CDI(ICR) mice at 0.3; 3 and 20 mg/kg for 1 month. Although no report was written, the in-life phase of this study was GLP compliant. Notably, starting from the 4th dose onwards, 19 animals (3M/1F at low dose and 2M/13F at mid dose) died due to clinical signs consistent with anaphylaxis reaction. This finding was not addressed due to the study interruption. However, such a finding was not observed in the male fertility study at the same dosage. As part of the primary pharmacology (see section 5.3.1.1) the ADA occurrence and the anaphylactic response upon rechallenge was investigated and revealed higher sensitivity in the NOD mice. Although it is recognised that a mice surrogate is of limited relevance to predict the immunogenicity potential of teplizumab in human, a risk for ADA formation, anaphylactic reaction, or reduced exposure cannot be excluded in human. Cytokine release syndrome and hypersensitivity reactions are both recognised as potential risks based on clinical data and reflected in the SmPC of the product.

5.4.3. Genotoxicity

The genotoxicity studies routinely conducted for pharmaceuticals are not applicable to antibody pharmaceuticals and therefore are not needed. It is not expected that teplizumab would interact directly with DNA or other chromosomal material.

5.4.4. Carcinogenicity

The absence of carcinogenicity studies is justified by the weight of evidence approach in line with the ICH S1B (R1) and ICH S6 (R1) guidelines. Due to the absence of toxicologically relevant species and the use of a surrogate leading to immunogenicity, a carcinogenicity study in mice would not be feasible. The weight of evidence approach considered the target biology, the secondary pharmacology, the histopathology finding and the immune modulation. The genotoxicity and hormonal effects discussion was omitted, which is agreed. The conclusion that further non-clinical studies to assess the carcinogenicity potential of teplizumab will not provide additional meaningful information and are

unnecessary is accepted. However, teplizumab exhibits an immunosuppressive activity, as evidenced by EBV reactivation and lymphoproliferative effects at a dosage of 10 mg/kg in chimpanzees. A low carcinogenicity risk in human due to the mode of action cannot be fully excluded especially considering the claim for a long-term immunomodulatory effect. This is reflected in the SmPC section 5.3.

5.4.5. Developmental and reproductive toxicity

GLP-compliant reproductive studies were conducted with the surrogate antibody in mice and included separate fertility and early embryonic (FEED) studies in males and females, an embryo-fetal development (EFD) study and a prenatal and postnatal development (PPND) study.

In the male and female fertility studies the purposes was to assess toxicity, reproductive performance and toxicokinetic of the surrogate antibody. In these studies the vehicle control was included for the TK phases. In borth studies, no or low exposure was detected for animals at 0.03 and 0.3 mg/kg. No changes in male and female reproductive performance was observed. The mortalities that occurred at 0.3 and 20 mg/kg were not related to treatment. Therefore, NOAEL was set to 20 mg/kg in both studies, which is agreed.

In the EFD study, no or low exposure of surrogate antibody serum concentrations was detected. The only measurable exposure was recorded at 0.3 and 20 mg/kg at GD6 and at 20 mg/kg at GD 14. In females treated with 20 mg/kg of the surrogate antibody a decrease of body weights and food consumption was noted. In the same dose group an increase in post-implantation loss occurred in 6/ 26 pregnant dams and a lower mean number of viable fetuses and litter proportion of viable fetuses. In fetuses, external and skeletal malformation occurred in the 0.03 and 0.3 mg/kg dose groups but this was also seen in control animals. As a result, the NOAEL was established at 0.3 mg/kg for both maternal and embryofoetal toxicity.

In the PPND study, the exposure of the dams increased almost proportional to dose at 3.0 and 20 mg/kg on GD6 and LD10. In pups at PND10 exposure was higher at 3.0 mg/kg than at 20 mg/kg. No exposure was detectable in dams and pups at 0.3 mg/kg on LD10 or PND10, respectively. The study identified immune related changes in the F1 generation consisting of increased thymus weight (high dose) associated with increased cellularity of the medulla and expansion of lymphocytes populations (high and mid dose). In addition, a decrease fertility performance was observed in both F1 male and females (high dose), a trend of decreased sperm motility at the high dose was further noted. Serum exposure to the surrogate was noted in the pups on PND 11-13 for the maternal dose of 20 mg/kg thus indicating placental transfer and/or transfer via maternal milk.

Overall, the surrogate administered at doses tolerated in the dams was found to negatively affect embryofoetal development, fertility of both sexes and sperm motility in the F1 generation. Due to the lack of sustained exposure at lower doses, the EFD and PPND NOAELs should be interpreted with caution. Through placental transfer and/or breast milk, modulation in both T and B lymphocytes populations was transmissible to the F1 generation and sustained after weaning. Immunotoxicity is discussed in the other toxicity studies section (see section 5.4.8).

Contraception recommendations and breastfeeding restrictions are specified in the SmPC.

No juvenile toxicity study was conducted. The applicant justifies the absence of an animal juvenile study based on that there is no relevant animals' species for teplizumab for this type of study and that a rodent juvenile toxicity study with the surrogate antibody would not add any value, which is agreed.

Further, the clinical safety profile for teplizumab is known and has been shown to be consistent and predictable across age groups and T1D stages and the cumulative clinical safety data are consistent with mechanism of action and safety data in older children and adolescents.

5.4.6. Toxicokinetics and exposure margins

Repeated-dose TK for the surrogate antibody was determined in the 6-days repeated dose toxicology study and in the DART studies (FEED, EFD and PPND studies).

In the 6-days repeat toxicology study no measurable Cmax and AUC values was recorded on study day 1 at 0.03 and 0.3 mg/kg although IPT recorded a decrease of T cells indicating pharmacologic activity. On study day 6 the C_{max} and AUC_{0-t} increased with SC repeated dosing with values higher in males than females while the serum concentrations were decreased in a multi-exponential manner following the IV dose. The Tmax ranged from 4 to 24 hours indicating slow absorption after SC administration. The exposure (AUC) was comparable in the SC and IV 0.3mg/kg dose groups and complete bioavailability was indicated as males and females showed 132% and 87.5% bioavailability.

In male and female studies, no or low exposure was detected for animals at 0.03 and 0.3 mg/kg although IPT showed pharmacological activity of the surrogate antibody in these dose groups. Further, it is noted that the decrease of T-cells is slightly lower in the high dose group compared to low and intermediate dose groups.

In the EFD study, no or low exposure of surrogate antibody serum concentrations was detected. The only measurable exposure was recorded at 0.3 and 20 mg/kg at GD6 and at 20 mg/kg at GD 14. Although, pharmacological activity in terms of decreased number of T cell was observed in 0.03 and 0.3 mg/kg dose groups. Consistent what was observed in the fertility studies, a slightly lower decrease of T-cells was seen in the high dose group compared to low and intermediate dose groups.

In the PPND study, the exposure of the dams increased almost proportional to dose at 3.0 and 20 mg/kg on GD6 and LD10. In pups at PND10 exposure was higher at 3.0 mg/kg than at 20 mg/kg. No exposure was detectable in dams and pups at 0.3 mg/kg on LD10 or PND10, respectively. The exposure did not match the decreases of T-cells observed. Consistent what was observed in other DART studies, the IPT showed a lower pharmacologic activity at 20mg/kg than at 0.3 and 3.0 mg/kg.

Teplizumab is indicated for the treatment to delay the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D. According to the applicant the clinical dose is 0.24 mg/kg or 14.6 mg 60 kg adult resulting in an exposure of AUC 5945 ng/ml*h and Cmax 938 ng/ml (data from TN-10 Phase-2 study). Safety margins are only considered for the single dose chimpanzee toxicity study with teplizumab. Margins of exposure based on a mice surrogate are not considered informative. However, the clinical safety margins cannot be decided as there is no NCA data regarding the Cmax and AUC exposures are available from the target population and there are issues are raised concerning the pop-PK model (see clinical section of this AR).

5.4.7. Local tolerance

No standalone local tolerance studies were conducted instead the local tolerance was assessed as part of the SD toxicity study in chimpanzee via SC dosing and with the mice surrogate in the 6 days RDT study. No adverse findings were noted following a single injection of teplizumab or repeated administration of the surrogate. As SC dosing is not the clinical route of administration, the batch of teplizumab and the surrogate formulation are of limited clinical relevance, the local tolerance assessment is considered to be superseded by clinical data related to the IV dosing.

5.4.8. Other toxicity studies

The applicant conducted an in vivo cytokine release assay in CD1 mice using the surrogate antibody and a cross-reactivity study on human tissue with teplizumab. A mild increase in IL-6 and IL-12 at

0.65 and 19.5 mg/kg that lasted until 24h post dose was noted. Additional IL-2, IL-4, IL 5, IL-17, INF-γ, and TNF-α increase were sporadically observed. Cytokine release is a recognised risk as discussed in section 5.3.1.2. In the tissue cross reactivity study, no unexpected staining was observed.

However, these studies are not GLP compliant and of unknown reliability. As the cytokine release potential is recognized clinically and due to the broad expression of CD3, further studies would not provide additional information.

Immunotoxicity assessment was limited to the in vitro T cell proliferation response incorporated in the SD chimpanzee study conducted with teplizumab and in a TDAR assessment the F1 generation of the PPND study conducted with the mouse surrogate.

Upon stimulation ex-vivo following a single dose of teplizumab, the lymphocytes appear competent for cytokine secretion as compared to the control. The TDAR however indicated a decrease in primary (IgM and IgG) and secondary (IgG) humoral response in this short-term study. These results have not been elaborated upon and no in-depth evaluation of the immunotoxicity potential of teplizumab was conducted.

5.4.9. Environmental risk assessment

No ERA studies have been conducted. The applicant has submitted a justification for the absence of studies as this concerns a recombinant monoclonal antibody and as such does not pose a risk to the environment. This justification is accepted since monoclonal antibodies such as teplizumab are catabolized to individual amino acids and/or small peptides by endogenous proteases and high molecular weight prevents intact urinary excretion. As such, excretion of active drug is not expected.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, teplizumab is not expected to pose a risk to the environment.

5.5. Overall discussion and conclusions on non-clinical aspects

5.5.1. Discussion

Pharmacology

Teplizumab is a humanized monoclonal antibody (IgG1 subclass) that binds to the CD3ε chain of the T-cell receptor (TCR) complex on human T cells, which leads to internalisation of the teplizumab/CD3 complex. The mechanism of action of teplizumab to prevent beta-cell destruction in T1D is not fully understood but proposed to involve partial agonistic signalling and deactivation of pancreatic beta-cell autoreactive T lymphocytes.

Due to the limited availability of animal models with cross-reactive target antigens to teplizumab, the most relevant assessment of non-clinical pharmacology was obtained from the single-dose toxicity study in chimpanzees. Lack of cross-reactivity with other species than human, gorilla, chimpanzee and gibbon was confirmed in silico, and it is therefore agreed that, in addition to chimpanzee, no relevant species for further non-clinical testing of teplizumab are available. The use of great apes in research was banned in the EU 2010, but this study was performed already in 2002 and use of the data generated is acceptable. In addition, a mouse surrogate anti-CD3 antibody, with the same Fc-modification as teplizumab was evaluated in mice. The surrogate antibody was demonstrated to have

similar affinity to its target as teplizumab, and it contains the same Fc modifications as teplizumab. However, the surrogate antibody differed in kinetic parameters from teplizumab in that it had a slower on-rate and a slower off-rate. It is agreed that this observed difference does not compromise overall comparison, but it may be important for interpretation of results from studies with the mouse surrogate.

The reduction in number of circulating T cells by teplizumab in humans is suggested by the applicant to be due to margination of T cells to the vasculature rather than depletion, since apoptosis is not observed in human T cells after teplizumab treatment, but direct supportive data for such mechanism are missing. Some degree of apoptosis was seen in chimpanzee $CD8^+$ and $CD4^+$ T cells, suggesting a T-cell depleting effect of teplizumab in this model, but, considering the limited effector functions expected due to the Fc modification, the underlying mechanism remains to be elucidated.

The mouse surrogate CD3 antibody was evaluated in a T1D disease model, the NOD mouse, and demonstrated to delay diabetes onset. However, the NOD mouse model has little resemblance with human T1D, and more than 200 interventions have demonstrated efficacy in preventing disease in this model (but not in humans), questioning its translation to the clinic (Roep & Atkinson, Diabetologia 2004). No additional animal models (e.g. the BB rat) were used to demonstrate proof-of-concept, no immunophenotyping was performed in order to evaluate the mechanism behind the observed effect, and the ability of teplizumab to delay progression after disease onset (stage 3) was not evaluated. This is considered acceptable as available non-clinical disease models have limited value for understanding how teplizumab would lead to reduced beta-cell destruction in human T1D.

Immunophenotyping was performed in CD-1 mice treated with the surrogate antibody in a series of toxicology studies, all showing a transient T-cell reduction, in line with the effects observed both in chimpanzees and humans. $CD4^+$ and $CD8^+$ T-cell subtypes were reduced to a similar extent. No further immune-cell analyses were performed in the non-clinical studies but published data from patients treated with teplizumab suggest an increase in T cells expressing genes associated with a partially exhausted phenotype.

Overall, the mechanism of action of teplizumab is not fully elucidated. Published data do show an increase in markers of exhaustion and anergy in the T-cell pool, particularly in treated subjects that remain diabetes-free, suggesting deactivation of activated T cells, but there is little support that teplizumab preferentially acts on auto-reactive cells. Rather, data from patients treated with teplizumab suggest that deactivation affects all activated T cells independently of target. The observed lymphopenia induced by teplizumab is transient and seems to be attributed to a reduced number of circulating T cells, both in animal studies and in patients treated with teplizumab. The Applicant speculates that "rebalancing of immune activation and immune regulation" is part of the mechanism behind the delay in beta-cell loss. However, the mechanism behind the beta-cell destruction in T1D is not fully understood, and it is not known which changes are needed to stop the destruction.

It is noted that the applicant's view of T1D pathogenesis is "T-cell-centric", which is in line with the proposed MoA and CD3 being the target of teplizumab. However, although strong links to HLA class I and II genes may suggest a role for T cells in the disease process, numerous other cellular and molecular mechanisms have been implicated and there is no full understanding of the aetiology and pathogenesis of T1D.

In addition to teplizumab, several other therapeutic strategies in clinical trials to prevent or treat T1D have focused on modulating the immune system. However, the vast majority of studies that have followed these strategies have shown a small initial benefit or no benefit at all. In cases where clinical benefit was observed, after an initial improvement in insulin production, the decline matched that observed in untreated patients with some delay. Teplizumab, administered for 14 consecutive days (for stage 2 indication) is suggested by the applicant to 're-establish beta cell self-tolerance' and to have a

long-term beta-cell protective effect over years following treatment. Yet, the effect on PD endpoints in the non-clinical and clinical studies (reduced T-cell count and total lymphocyte count) was transient and restored to baseline within weeks. Academic publications suggest some alterations in immune cell phenotypes that remain for months to years in treated subjects, including markers of T cell exhaustion, but it is not known which changes are essential to slow down the beta-cell destruction. In the end, clinically relevant endpoints must inform on the duration of treatment effect, and it is not clear from a mechanistic point of view how teplizumab would preserve beta-cell function over time.

Analysis of the secondary pharmacodynamics of teplizumab showed a cytokine induction in line with earlier publications of IgG1 antibodies (including teplizumab) containing the 234-Ala, 235-Ala (LALA) modification in the Fc-region, demonstrating at least 100-fold reduced binding to FcgRI and FcgRII compared to non-engineered teplizumab analogue. The LALA modification has been used in already approved therapeutic antibodies (risankizumab 2019 and spesolimab 2022), where binding and activation of Fc receptors is undesirable, but does not completely eliminate binding to Fc receptors. Induction of cytokine secretion may also be partly attributed to the CD3 agonistic activity of teplizumab. The potential for cytokine secretion is clinically relevant and may explain the cases of cytokine release syndrome observed in clinical studies as reflected in the SmPC. A tissue cross-reactivity assay demonstrating specific staining in the expected lymphoid tissues is described and assessed in the toxicology section.

Safety pharmacology endpoints included in the SD chimpanzee study did not demonstrate notable changes in cardiovascular parameters, behaviour or respiratory rate. Although parameters were not assessed at T_{max}, exposure was comparable to that observed at clinical doses. In addition, the cardiovascular assessment has been superseded by the clinical data which did not identify significant effect on the ECG parameters.

Pharmacokinetics

The applicant did not submit studies on distribution, metabolism and excretion. No radiolabelled tissue distribution/mass balance or metabolism studies with teplizumab were submitted and no serum protein binding assay was submitted. This is acceptable as this is in accordance with regulatory guidelines for biotechnology-derived pharmaceuticals (ICH S6). Tissue distribution studies with radiolabelled compound are considered difficult to interpret due to confounding factors (e.g. in vivo degradation, release of label from the protein following degradation, and potential reincorporation of radiolabelled amino acids into the endogenous protein pools), and metabolism studies or mass balance are not considered necessary. The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids. Estimation of Vd in the studies performed had been valuable to support the assumption of limited distribution from the blood, but the issue is not further pursued.

Validated ELISA assays were used to support the GLP single-dose toxicology study of teplizumab in chimpanzee (T-2002-009) and the GLP repeat-dose toxicity studies and reproductive and developmental toxicology studies of the surrogate antibody in mice. Although the validation was not performed in accordance with the guideline on bioanalytical method validation and study sample analysis (ICH M10) that came into effect 2023, the possible impact of uncertainties linked to the quantification of teplizumab in the pivotal chimpanzee toxicity study is low. This is considered acceptable.

Only one pivotal study with assessment of teplizumab TK was conducted, a single dose toxicity study in chimpanzee. This demonstrated exposure to teplizumab for >7 days after SC administration of 0.1, 1.0 or 10 mg/kg. The half-life changed with dose and appeared to be shorter at lower doses (5.2 days

at 10.0 mg/kg, 3.68 days at 1.0 mg/kg, and 1.94 days at 0.1 mg/kg). Possibly, the non-linear increase in $AUC_{0\text{-}inf}$ and increase in elimination half-life is due to target-mediated elimination and saturation of binding to the target.

Toxicology

The toxicological program has been conducted in pivotal studies with SC injection (just one IV dose group with the surrogate antibody was included in the RPT study). However, the intended clinical IV route is considered to be covered in clinical studies.

The toxicology profile of teplizumab was only evaluated in a single dose toxicology study in chimpanzees as this is considered the only relevant animal species (based on target sequence similarity between chimpanzee CD3 ε and human CD3ε). The study was finalized in 2005 and at that time, there was no restrictions in EU to use this species for research purposes. The ban in EU to use great apes (including chimpanzees) for research purposes has been in place since January 2013.

In the study, the animals were dosed by SC single dose at 0.1, 1.0 and 10 mg/kg SC. The major finding was mortality in all 3 animals given 10.0 mg/kg teplizumab. Following histopathological review, those findings were attributed to polymorphic lymphoproliferative disease. In situ hybridization studies showed the presence of a lymphocryptoviral (Epstein-Barr virus [EBV]-like) in proliferating lymphocytes, possibly explaining the flu-like symptoms observed. Investigators theorized reactivation of the EBV like virus due to the initial T-cell depletion observed with teplizumab. Clonal expansion of EBV could however not be confirmed due to the assay using a probe only recognizing a small fraction of monkey EBV DNA. EBV reactivation has not frequently been observed in clinical trials so far and the low number of cases were not severe. Nevertheless, serious infections and lymphopenia are recognized as a potential adverse event with recommendation for interruption/ management included in the SmPC of the product. No adverse findings were observed in the other dose groups at 0.1 and 1.0 mg/kg although robust decrease of CD3 lymphocytes, indicating pharmacologic activity of teplizumab, occurred in these dose groups.

As chimpanzees is not a suitable species, the development continued with RPT and DART studies in mice using a surrogate antibody. This is in line with ICH 6 that states that if no proper relevant species exists studies could be performed with a homologous monoclonal antibody, in this case the surrogate antibody, in suitable species to identify potential hazards associated with target pathway inhibition but due to their inherent limitations are not useful for quantitative risk assessment.

In the 6-days RPT study (including a 6-week recovery phase) and DART studies the surrogate antibody was generally well tolerated. However, in RPT study decreased organ weight of a number of lymphoid organs was observed and which the changes of thymus and spleen partially persisted until the end of recovery phase. Similar changes of the thymus were observed in the PPND study in F1 progeny. These findings are considered to be related to the pharmacologic activity of T-cell suppression of the surrogate antibody and thus, not considered adverse.

Exposure was not maintained throughout the reproduction toxicity studies with Q3D SC dosing with the surrogate at low and/or mid doses. This has been partly attributed to ADA occurrence however the presence of ADA was not investigated in any pivotal study. The surrogate administered at doses tolerated in dams negatively affects embryofoetal development, fertility of both sexes and sperm motility in the F1 generation. Due to the lack of sustained exposure at lower doses in the EFD and PPND studies, the NOAELs should be interpreted with caution. The modulation in both T and B lymphocytes populations is transmissible to the F1 generation through placental transfer and/or breast

milk and such finding was sustained after weaning. Contraception recommendations and breastfeeding restrictions are specified in section 4.6 of the SmPC with a cross reference to section 5.3.

The absence of carcinogenicity studies is justified by weight of evidence approach in line with ICH S1B (R1) and ICH S6 (R1) guidelines. Due to the absence of toxicologically relevant species and because of the immunogenicity properties of the surrogate, a mice study would not be considered feasible. Immunotoxicity assessment was limited to the in vitro T cell proliferation response as part of the SD chimpanzee study conducted with teplizumab and in a TDAR assessment in the F1 generation of the PPND study conducted with the mouse surrogate. Upon stimulation ex-vivo following a single dose of teplizumab the lymphocytes appear competent for cytokine secretion as compared to the control. The TDAR however indicated a decrease in primary (IgM and IgG) and secondary (IgG) humoral response.

It is acknowledged that the initial reduction of T cell populations is due to margination instead of depletion and will not lead to long-term immunosuppression. However, uncertainties remain with regards to the effect of the long-term immune modulation. Based on the weight-of-evidence from literature and teplizumab data from animal toxicology studies and clinical trials, and considering the short-term clinical treatment schedule, the theoretical risk of carcinogenicity is considered extremely low under the conditions of the labelled dosing. This is reflected in section 5.3 of the SmPC.

5.5.2. Conclusions

The non-clinical package is limited by that fact that teplizumab being only pharmacologically active in the chimpanzee (in addition to humans) and therefore most knowledge comes from studies with a mouse surrogate CD3 monoclonal antibody.

The surrogate antibody was shown to delay disease onset in the non-obese diabetic (NOD) mouse and treatment with teplizumab in chimpanzee and humans, as well as the surrogate antibody in mice, leads to transient lymphopenia and reduction in circulating T-cell counts. No further mechanistic support for long-term immunomodulatory effect is presented, and uncertainties remain on how teplizumab reduces beta-cell destruction in human T1D.

Except for a single dose toxicology study in chimpanzees with teplizumab, RDT and DART studies were conducted in mice with the surrogate antibody to identify hazards related to CD3 binding. These studies identified limited toxicities while findings noted effects on reproduction parameters.

From a non-clinical perspective, there are no issues precluding a recommendation for a marketing authorisation for teplizumab.

6. Clinical aspects

6.1. Introduction

6.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Regarding the clinical trial TN-10, the applicant stated that the trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline. GCP inspections of four study sites in the US were performed. No serious GCP non-compliance nor confirmed scientific misconduct was reported to or detected by the sponsor for the study.

The clinical trial PROTECT was conducted in compliance with Good Clinical Practices, including the archiving of essential documents, according to the statement of the applicant. A GCP inspection was performed at a site in Namur (BELGIUM). The outcome of this inspection was: no critical finding, 1 major finding and 5 minor findings. The major finding was related to exclusion criteria not properly verified for one patient (patient was included without the result of serology tests). Serology was performed later (after randomization) to confirm the eligibility. The conclusion for this site is that the trial was conducted in compliance with GCP and the findings (including the major finding) are not expected to impact the safety of the patients or the quality of data.

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier.

6.1.2. Tabular overview of clinical trials

Table 1 Tabular overview of clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
TN-10 Pivotal study Indication 1	Study start: August 2010. Follow-up duration: defined by time to protocol-specified number of T1D events observed; median duration ~24.5 months for all participants. Last subject completed November 2018	Randomised, double-blind, placebo-controlled, 2arm, multicenter study	Teplizumab versus placebo; daily IV infusion Day 0: 51 µg/m^2 Day 1: 103 µg/m^2 Day 2: 207 µg/m^2 Day 3: 413 µg/m^2 Days 4-13: 826 µg/m^2 Total dose: 9034 µg/m^2 Single 14-day course	Participants with at least 2 T1Dassociated autoantibodies and dysglycemia N= teplizumab 44, placebo 32
PROTECT Pivotal study indication 2	Study start April 2019. Follow-up duration 18 months: completed May 2023	Randomized, double-blind, placebo-controlled, multinational study	Teplizumab versus placebo; daily IV infusion **2 courses. Per course**: Day 1: 106 µg/m^2 Day 2: 425 µg/m^2 Day 3-12: 850 µg/m^2	Participants with Stage 3 T1D diagnosis ≤6 weeks before randomization N=teplizumab 217, placebo 111

			Total per course: 9031 µg/m^2 Teplizumab administered in addition to the standard of care (insulin treatment) Two 12-day courses, at Week 1 and Week 26 (or Week 52 modified dosing schedule due to COVID-19 pandemic)	
Protégé	Follow-up duration: 24 months	**Segment 1**: Open-label **Segment 2**: Randomized, double-blind, placebo-controlled, multicenter, multinational, 4arm, dose-ranging	Teplizumab versus placebo; daily IV infusion **Segment 1 (open-label):** As TN-10, see above **Segment 2 (randomized):** **Arm 1**: Full 14-day regimen As TN-10, see above **Arm 2**: 1/3 14-day regimen As TN-10 divided by three. Total dose: 2985 µg/m^2 **Arm 3**: Full 6-day regimen As TN-10 days 0-5. Total dose: 2426 µg/m^2 **Arm 4**: Placebo 14-day course Teplizumab was administered in addition to the standard of care (insulin treatment) **Segment 1**: Two 14-day courses, 26 weeks apart **Segment 2**: Two identical courses, 26 weeks apart	Participants with Stage 3 T1D diagnosis ≤12 weeks before randomization. N=98 placebo 453 teplizumab (includes 38 in open-label segment)

Protégé Extension Early terminated by the Sponsor	Follow-up duration: 3 years	Double-blind, multicenter, multinational, placebo-controlled study.	No study drug administered Duration: not applicable	Participants with newly diagnosed T1D (treatment within 12 weeks of diagnosis) who completed Day 728 (about 2 years) evaluations of Protégé, regardless of how many doses of study drug received. N=219 Total (90 followed through 6 months) Teplizumab: - Open-label Segment: 32 - Double-blind Segment: 149 Placebo: 38
Encore Early terminated by the Sponsor	Follow-up duration: planned for 24 months; study modified when Protégé primary endpoint not met; 89.8% completed 12 months and 29.1% completed 24 months	Randomized, double-blind, placebo-controlled, multinational, 4-arm, dose ranging study	Teplizumab versus placebo; daily IV infusion **Arm 1:** Full 14-day regimen; total dose: 9034 µg/m^2 **Arm 2**: 1/3 14-day regimen; total dose: 2985 µg/m^2 **Arm 3**: Full 6-day regimen; total dose: 2426 µg/m^2 **Arm 4:** Placebo 14-day course Teplizumab administered in addition to the standard of care (insulin treatment) Two identical courses, 26 weeks apart 14-day (full or 1/3 regimen) or 6-day (curtailed regimen) course of teplizumab or placebo	Participants with Stage 3 T1D diagnosis ≤12 weeks before randomization. N=62 placebo 192 teplizumab

Study 1	Follow-up duration: 24 months	Randomized, controlled, open-label, multicenter study	Teplizumab versus no intervention; daily IV infusion **Group A** (n=12) 14-day regimen Day 1: 1.42 µg/kg Day 2: 5.67 µg/kg Day 3: 11.3 µg/kg Day 4: 22.6 µg/kg Days 5-14: 45.4 µg/kg Total dose: 495 µg/kg **Group B** (n = 9) 12-day regimen Day 1: 455 µg/m^2 Day 2: 919 µg/m^2 Days 3-12: 1818 µg/m^2 Total dose: 19.5 mg/m^2 Teplizumab administered in addition to the standard of care (insulin treatment)	Participants with Stage 3 T1D diagnosis ≤6 weeks before randomization N=21 control 21 teplizumab

AbATE (Study 4)	Follow-up duration: 24 months	Randomized, open-label, controlled, 2arm, multicenter study Control subjects received standard of care only	Teplizumab versus no intervention daily IV infusion Day 0: 51 µg/m^2 Day 1: 103 µg/m^2 Day 2: 207 µg/m^2 Day 3: 413 µg/m^2 Days 4-13: 826 µg/m^2 Total dose: 9034 µg/m^2 Two 14-day courses of teplizumab, 12 months apart Teplizumab administered in addition to the standard of care (insulin treatment)	Participants with Stage 3 T1D diagnosis ≤8 weeks before randomization N= 25 control 52 teplizumab
Delay (Study 5)	Follow-up duration: 12 months	Randomized, double-blind, placebo-controlled, multicenter study	Teplizumab versus placebo; daily IV infusion Day 0: 51 µg/m^2 Day 1: 103 µg/m^2 Day 2: 207 µg/m^2 Day 3: 413 µg/m^2 Days 4-13: 826 µg/m^2 Total dose: 9034 µg/m^2 Teplizumab administered in addition to the standard of care (insulin treatment) Single 14-day course of teplizumab or placebo infusion	Participants with Stage 3 T1D diagnosis at least 4 months, but not more than 12 months before randomization. N= 28 placebo 32 teplizumab
TN-10-Extension		Single-arm open-label, multicenter study Follow-up period of up to 78 weeks (18 months) from the first dose of treatment	Teplizumab; daily IV infusion Day 1: 106 µg/m^2 Day 2: 425 µg/m^2 Days 3-12: 850 µg/m^2 daily Total per course: 9031 µg/m^2 Single 12-day course	Teplizumab-treated and placebo participants in the TN-10 study who had developed Stage 3 T1D (within 1 year of clinical diagnosis) after the conclusion of TN-10 study) N=6

RD = randomised; DB = double blind; PC = placebo controlled; SA = single arm; OL =open label; yrs = years;

6.2. Clinical pharmacology

6.2.1. Methods

Pharmacokinetics

In the Protégé and Encore studies, the bioanalytical method for the measurement of teplizumab concentrations in serum was a quantitative sandwich enzyme immunoassay technique. The validation report is dated to august 2007 and the Applicant states that it is validated in accordance with the at that time available Guidelines. The final bioanalytical report from the Protégé (CP-MGA031-01) study samples cannot be found. The bioanalytical report from Encore show acceptable QC-performance but do not include ISR or statements on sample analysis within the demonstrated stability-period.

In the TN-10, PRV-031-004, and PROTECT (PRV-031-001) studies, teplizumab concentrations in serum were determined using a Meso Scale Discovery Electrochemiluminescence (MSD-ECL) method. The method is validated and applicable to the quantitation of teplizumab within a nominal range of 2.50 to 125 ng/mL. Long-term stability in frozen matrix for up to 734 days at -25 °C and up to 1178 days at -80 °C has been demonstrated. Bioanalytical reports from the studies are available showing acceptable performance of QC-samples and ISR. In study TN-10 Samples were stored for a maximum of 2880 days between sample collection and analysis. Additional stability will be evaluated to cover the age of the samples.

PD biomarkers

A number of biologic markers have been identified that relate to the PD effects of teplizumab. The initial PD effect is occupancy (coating) of the CD3 receptor and subsequent modulation (clearance) of the CD3 receptor. Downstream PD effects include transient and reversible lymphopenia, ascribed to margination of T cells, and changes in T cell phenotype and subsets resulting from CD3 partial agonism.

The following is the sequence of events foreseen, and the PD assays used to assess each step of the process:

• Upon IV infusion, teplizumab circulates in the body and binds to the CD3 molecules co-located in the T cell receptor complex present on the surface of T cells, followed by the internalization of the CD3/teplizumab complex (“CD3 modulation”), which triggers an intracellular activation signal (teplizumab binding affinity to CD3 is measured by the association and dissociation rate, or Kd; CD3 occupancy is measured by competition assay with labelled OKT3; internalization is measured by assessment of surface vs intracellular CD3).

• The activation signal leads to a number of downstream events, which includes the expression of a family of signal transduction molecules called Nuclear Factor of Activated T-cells (NFAT)) (assessed with NFAT assay in vitro). After signalling, the CD3/teplizumab complex is degraded inside the T cells (8, 9).

• In the nucleus, NFAT triggers a T cell activation cascade, leading to the expression of activation molecules such as CD69 on the cell surface (T cell activation assessed by flow cytometric detection of

CD69 expression). Expression of CD69 is transient, consistent with the partial agonistic effect of teplizumab.

• The T cell activation leads to its transient sequestration of lymphocytes from the circulation to the blood vessel walls and the lymphoid tissues, a process termed "margination" (assessed by change in circulating lymphocyte levels).

• Partial or incomplete activation signal results in deactivation of highly activated T cells (but not quiescent or regulatory T cells), a process called "anergy" (unresponsiveness); this subsequently leads to T cell "exhaustion" and eventual removal or deletion of the formerly autoreactive T cells. The entire process is reported to be rapid at the molecular level, resulting in detectable exhausted T cells in a matter of days or weeks (10). The end result of a 12- or 14-day course of teplizumab is the cessation of the autoimmune attack of beta cells and the preservation of endogenous insulin production for months or years in responders (measured by circulating C-peptide levels, a marker for endogenous insulin production).

Immunogenicity

Immunogenicity evaluations of teplizumab have been conducted using several ADA assays that were developed and validated according to industry and regulatory recommendations available at the time. For certain studies sample analysis in the ADA assays used a tiered approach that consisted of screening, confirmatory and titering steps with confirmed positive samples moved forward to testing in the NAb assay.

The Protégé and Encore studies was modified after it was determined that the 1-year primary endpoint was not met. One modification was the elimination of immunogenicity assessments and limited samples are available. Linear regression analysis was used to calculate the concentration of antibody in a participant sample, using a polyclonal goat anti-teplizumab (Fv-specific) as a surrogate reference material to prepare assay standards and controls ranging from 3.125 to 1600.000 ng/mL.

In PRV-031-004, TN-10 and Protect studies a (MSD-ECL) bridging assay was applied. Acid-dissociated test samples are neutralized and then incubated with a master mix of biotin-labeled teplizumab and sulfo-tag-labeled teplizumab. ADAs present in samples form a bridge between the two labeled teplizumab molecules, and the complex is then captured on blocked MSD-Streptavidin (MSD-SA) plates and detected by an ECL signal. A polyclonal goat anti-teplizumab (Fv-specific) antibody was used as the positive control to characterize assay performance. A tiered approach was used with cut-points determined in accordance with current guidance (using 50 individual serum from healthy subjects) and the method validated in accordance with regulatory requirements. The method is capable of detecting low levels antibodies at 3.5 ng/ml with a drug tolerance where 10 ng/ml antibody can be detected in the presence of 12,5 μg/ml teplizumab. During sample analysis it was determined to use an in study cut point for the Protect study.

A cell-based NAb assay was developed using Jurkat cells. Anti-teplizumab antibody that is present in the test sample, if neutralizing, will inhibit teplizumab-induced Jurkat cell activation, which is determined by the level of induction of CD69, an early T cell activation marker. Cells are stained with phycoerythrin (PE)-conjugated mouse anti-human CD69 antibody and analysed by FACS Calibur and the mean fluorescence intensity (MFI) was recorded for each sample. A goat anti-PRV-031 (Fv-specific) antibody was used as the positive control to characterize assay performance. The relative sensitivity was determined to be 665 ng/mL.

6.2.2. Pharmacokinetics

Introduction

A limited clinical pharmacology package is included in this application. Considering the proposed 12 or 14-day long one, or possibly two, course dosing regimen where steady state is never achieved, and with a monoclonal antibody as active substance a limited study package is considered acceptable. However, different products have been used throughout the clinical program which cannot be concluded comparable, different not fully validated bioanalytical methods have been applied which have not been cross-validated, limited PK-sampling in the studies and deficiencies in the reporting of the data renders the PK-data uncertain. The popPK model is used to simulate the recommended dosing regimen for the commercial product in indication 1 and for this purpose adequate PK-data is of importance. However, the model is not acceptable for this use and the slightly higher dose proposed for indication 1 relies on the post-marketing safety data in 414 individuals from US and the fact that these slight adjustments of a dose for a Mab generally are not clinically relevant.

Evaluation and qualification of models

Population Pharmacokinetics

The applicant provided several popPK analyses, of which Study POH21902 is considered the final analysis.

Study POH21902 (model 454)

The population PK Model 454 was based on data from studies TN-10, PRV-031-004, and PROTECT (Courses 1 and 2). The data set consisted of data from 337 participants contributing a total of 2770 quantifiable PK samples. From the PROTECT study Course 1, there were data from 147 participants who received the Eli Lilly product and 65 participants who received the AGC Biologics product; from Course 2, there were data from 66 participants who received the Eli Lilly product and 122 participants who received the AGC product. The number of subjects and samples from each study and on each product, respectively, are presented in Table 12.

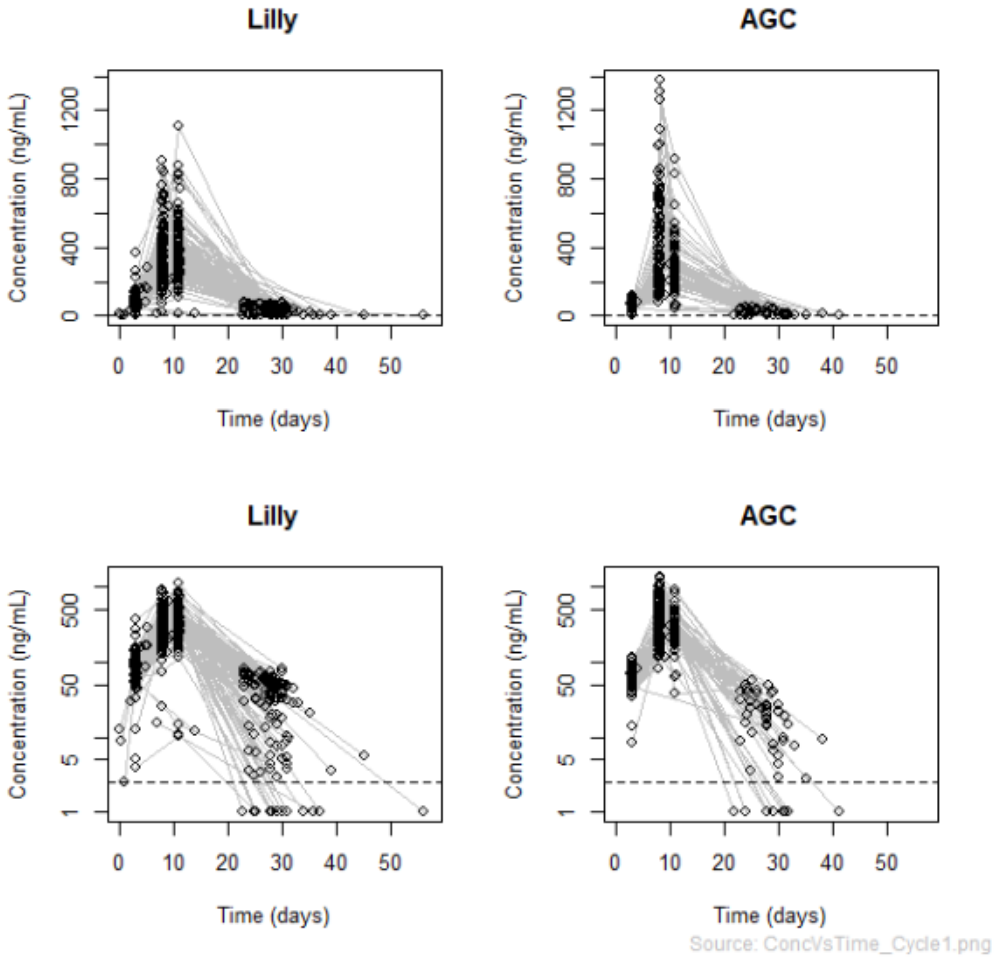
Observed teplizumab serum concentrations from the PROTECT study are shown in Figure 2 and Figure 3, separately for each product and course of treatment.

Table 2 Number of subjects and samples from TN-10, PRV-031-004, and PROTECT studies in the analysis data set.

Study	Product	Number of Subjects	Number of Quantifiable Concentrations	Number of Post-Dose BQL samples
TN-10	MacroGenics	16	66	1
TN-10	Eli Lilly	9	32	2
PRV-031-004	Eli Lilly	49	618	59
PRV-031-004	AGC	51	587	123
PROTECT, Course 1	Eli Lilly	147	561	16
PROTECT, Course 1	AGC	65	282	11
PROTECT, Course 2	Eli Lilly	66[a]	221	39
PROTECT, Course 2	AGC	122[a]	403	80
Total		**337**	**2770**	**331**

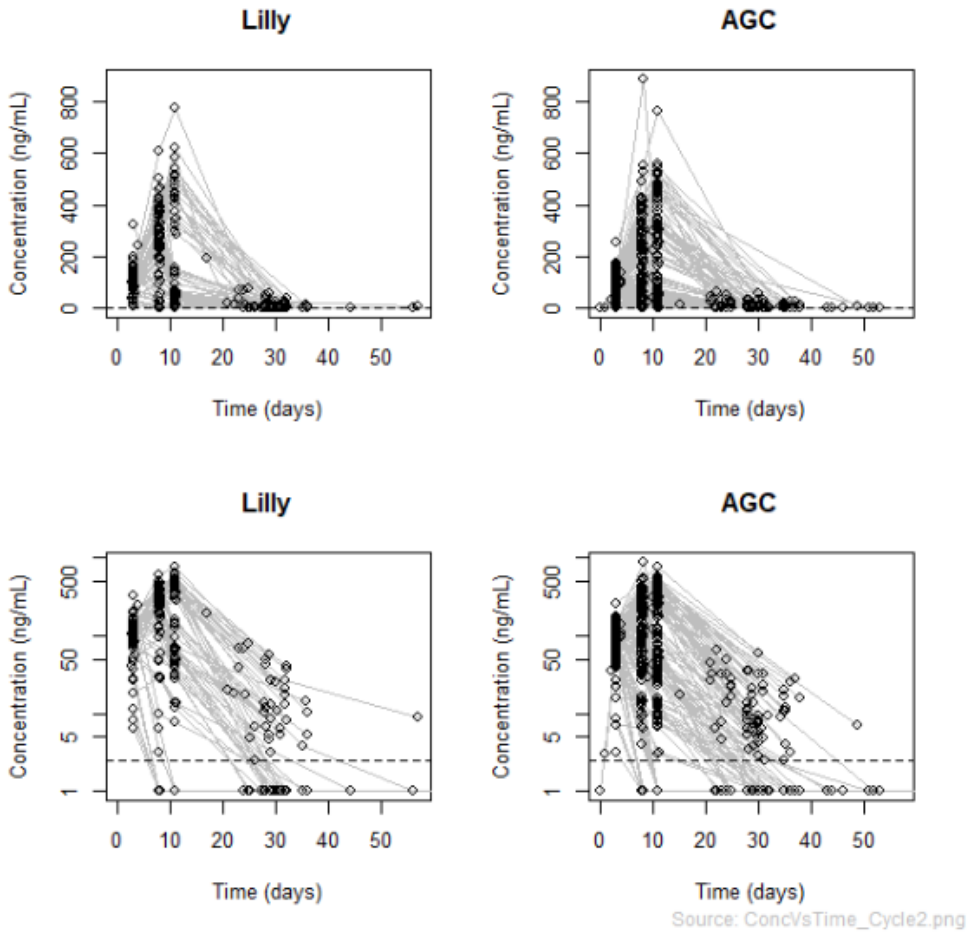
a. These subjects were also in Course 1 of PROTECT

Figure 1 Observed Teplizumab Serum Concentrations for Lilly and AGC Products in Course 1 of PROTECT study.



Top: concentrations on arithmetic scale, **Bottom**: concentrations on semi-log scale. Points are observed concentrations. BQL concentrations were assigned the value of 1 to be seen on the plots. Grey lines connect points of a subject. Dashed line represents the LLOQ level.

Figure 2 Observed Teplizumab Serum Concentrations for Lilly and AGC Products in Course 2 of PROTECT study.



Top: concentrations on arithmetic scale, **Bottom**: concentrations on semi-log scale. Points are observed concentrations. BQL concentrations were assigned the value of 1 to be seen on the plots. Grey lines connect points of a subject. Dashed line represents the LLOQ level.

The PK of teplizumab was described by a three-compartment (central, peripheral, and an additional very fast peripheral compartment) quasi-steady-state target-mediated drug disposition (TMDD) model. The model was parameterized in terms of clearance (CL), central and 2 peripheral volumes of distribution (Vc, Vp, Vp2), inter-compartmental clearances (Q and Qp2), concentration of target at baseline (BASE), the quasi-steady-state constant (Kss), an internalization rate constant (Kint), and a target degradation rate constant (Kdeg). The model included target-mediated binding in all compartments and a linear non-specific elimination from the central compartment.

The following covariate effects were included in the final model:

Clearance and volumes of central and peripheral compartments of teplizumab were higher in subjects with higher body weight. Clearance was also influenced by ADA titres. For PROTECT study, clearance increased linearly with time-dependent value of log(titer) above the estimated threshold. In Course 2 of the PROTECT study, there was also an additional effect of ADAs implemented as a decrease of bioavailability as a Hill function of maximum log(titer) at an estimated time of onset of this effect. For the TN-10 study, where there was only one post-dose ADA measurement 3 months post treatment start, clearance did not depend on the ADA value. The effects of AGC product included lower Kss and

higher clearance. The effect of the AGC product on clearance was higher following the single low dose in study PRV-031-004 compared to multiple therapeutic doses in PROTECT study.

Parameter estimates of the final model are presented in Table 13 and Table 14, for fixed-effect and variability parameters, respectively. Visual predictive checks (VPCs) for the final model on PROTECT study data are presented in Figure 4 and Figure 5, for the Eli Lilly and AGC products, respectively.

Table 3. Parameter estimates of the final population PK model (model 454), fixed-effect parameters.

Parameter		Estimate	RSE (%)	95%CI
CL (L/day)	θ1	1.62	6.55	1.42 ; 1.83
V_c (L)	θ2	2.55	4.22	2.34 ; 2.76
Q (L/day)	θ3	6.34	4.51	5.78 ; 6.9
V_p (L)	θ4	5.51	7.16	4.74 ; 6.28
BASE (ng/mL)	θ6	123	7.67	105 ; 142
K_{SS} (ng/mL)	θ7	22.4	8.44	18.7 ; 26.1
Vc_{WT}, Vp_{WT}	θ8	0.632	8.78	0.524 ; 0.741
CL_{WT}	θ9	0.321	26.9	0.152 ; 0.49
Kint (1/day)	θ11	0.0353	12.3	0.0268 ; 0.0439
Kdeg (1/day)	θ12	0.423	9.55	0.344 ; 0.502
Qp_2 (L/day)	θ13	49.2	7.63	41.8 ; 56.6
Vp_2 (L)	θ14	0.963	5.58	0.858 ; 1.07
Kss_{AGC}	θ15	0.594	6.95	0.513 ; 0.674
CL_{AGCLow}	θ16	3.07	8.34	2.57 ; 3.57
$CL_{AGC\ PROTECT}$	θ17	1.23	5.46	1.1 ; 1.37
Thresh	θ18	6.05	1.72	5.85 ; 6.26
$CL_{LTITRV\ PROTECT}$	θ19	0.659	8.02	0.556 ; 0.763
$Base_2$	θ20	0.571	5.21	0.513 ; 0.629
F_{MTITR2}	θ21	1.40	12.9	1.05 ; 1.75
T_{50} (day)	θ22	10.4	21.9	5.96 ; 14.9
γ	θ23	6.05	14.2	4.37 ; 7.73

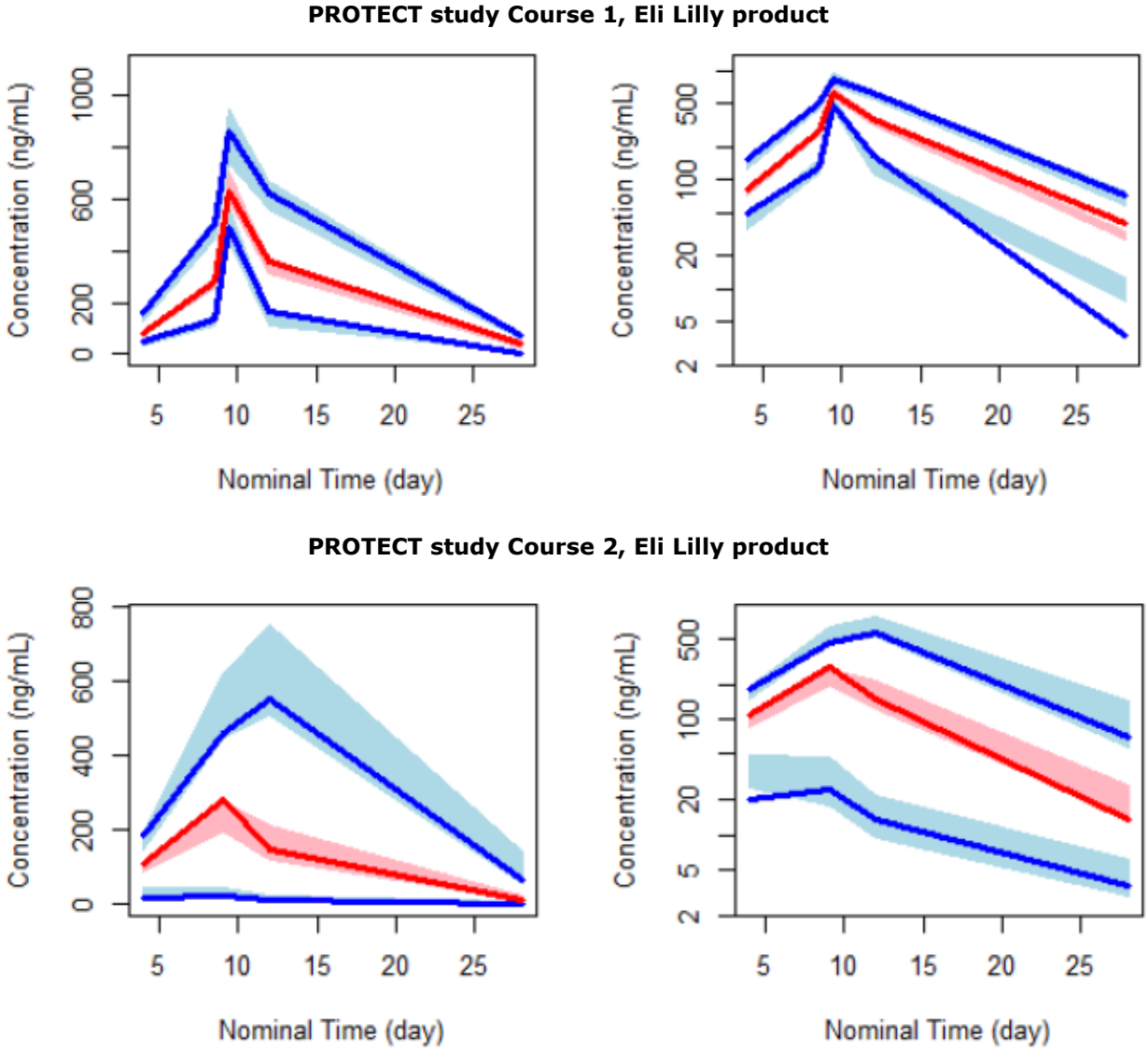
SE: Standard Error: RSE: Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate; 95% CI: 95% confidence interval. CL: clearance; Vc, Vp, and Vp2: volumes of central and 2 peripheral compartments; Q and Qp_2: inter-compartmental clearance of the peripheral compartments; BASE: concentration of target (in drug units) at baseline; K_{SS}: quasi-steady-state constant; Kint: internalization rate constant; K_{deg}: target degradation rate constant; CL_{WT}, Vc_{WT}, Vp_{WT}: power exponent for dependence of CL, Vc, and Vp on body weight; Thresh: ADA titer threshold; Kss_{AGC}: multiplicative effect of AGC product on Kss; $CL_{AGC\ Low}$: multiplicative effect of AGC on CL in Study PRV-031-004; $CL_{AGC\ PROTECT}$: multiplicative effect of AGC on CL in PROTECT study; $CL_{LTITRV\ PROTECT}$: slope of fractional increase of CL with LTITRV in PROTECT; $Base_2$: fraction of BASE at the start of Course 2; FMTITR2, T50 and γ: parameters that describe time-dependent bioavailability in Course 2 as follows
$EFFmax = [FMTITR2*DMTITR2]^{\gamma}$, $F = 1/(1+ EFFmax * TIME^5/(T50^5+ TIME^5))$, and DMTITR2 = (MLTITR2 - Thresh)/3.8 or 0, whatever is greater.

Table 4. Parameter estimates of the final population PK model (model 454), variability parameters.

Parameter		Estimate	RSE (%)	95%CI	CV (%)	Shrinkage (%)
ω^2_{CL}	Ω(1,1)	0.132	14.1	0.0953 ; 0.168	36.3	21.8
$\omega_{CL,CL2}$	Ω(2,1)	0.0896	25.1	0.0456 ; 0.134	R=0.461	-
ω^2_{CL2}	Ω(2,2)	0.212	13.6	0.155 ; 0.269	53.6	29.9
ω^2_{Q}	Ω(3,3)	0.0346	42.2	0.00596 ; 0.0631	18.6	67.9
ω^2_{Vp}	Ω(4,4)	0.168	15.2	0.118 ; 0.218	41.0	25.2
ω^2_{Qp2}	Ω(5,5)	0.193	30	0.0794 ; 0.307	44.0	26.1
ω^2_{Vc}	Ω(6,6)	0.0239	11.9	0.0183 ; 0.0295	15.5	9.5
ω^2_{KSS}	Ω(7,7)	0.16	16	0.11 ; 0.21	40.0	30.9
ω^2_{T50}	Ω(8,8)	0.142	20.7	0.0844 ; 0.2	37.7	34.6
σ_{prop}	θ5	0.276	14.1	0.0953 ; 0.168	27.6	16.5
EPS_{ST4}	θ10	0.315	25.1	0.0456 ; 0.134	-	-

SE: Standard Error, RSE: Relative Standard Error, %RSE=100·SE/PE, where PE is a parameter estimate; 95% CI: 95% confidence interval, CV: coefficient of variation; ω2CL, ω2CL2:: variances of inter-individual random effects for CL in courses 1 and 2 respectively; RCL,CL2: correlation between CL and CL2; ω2Kss, ω2Vp, ω2Q, ω2T50: variances of inter-individual random effects for Kss, Vp, Q, and ω2T50; ω2Qp2, ω2Vc: variances of inter-individual random effects for Qp2 and Vc for subjects with dense sampling; EPSST4: fraction of standard deviation for the residual error in study PRV-031-004.

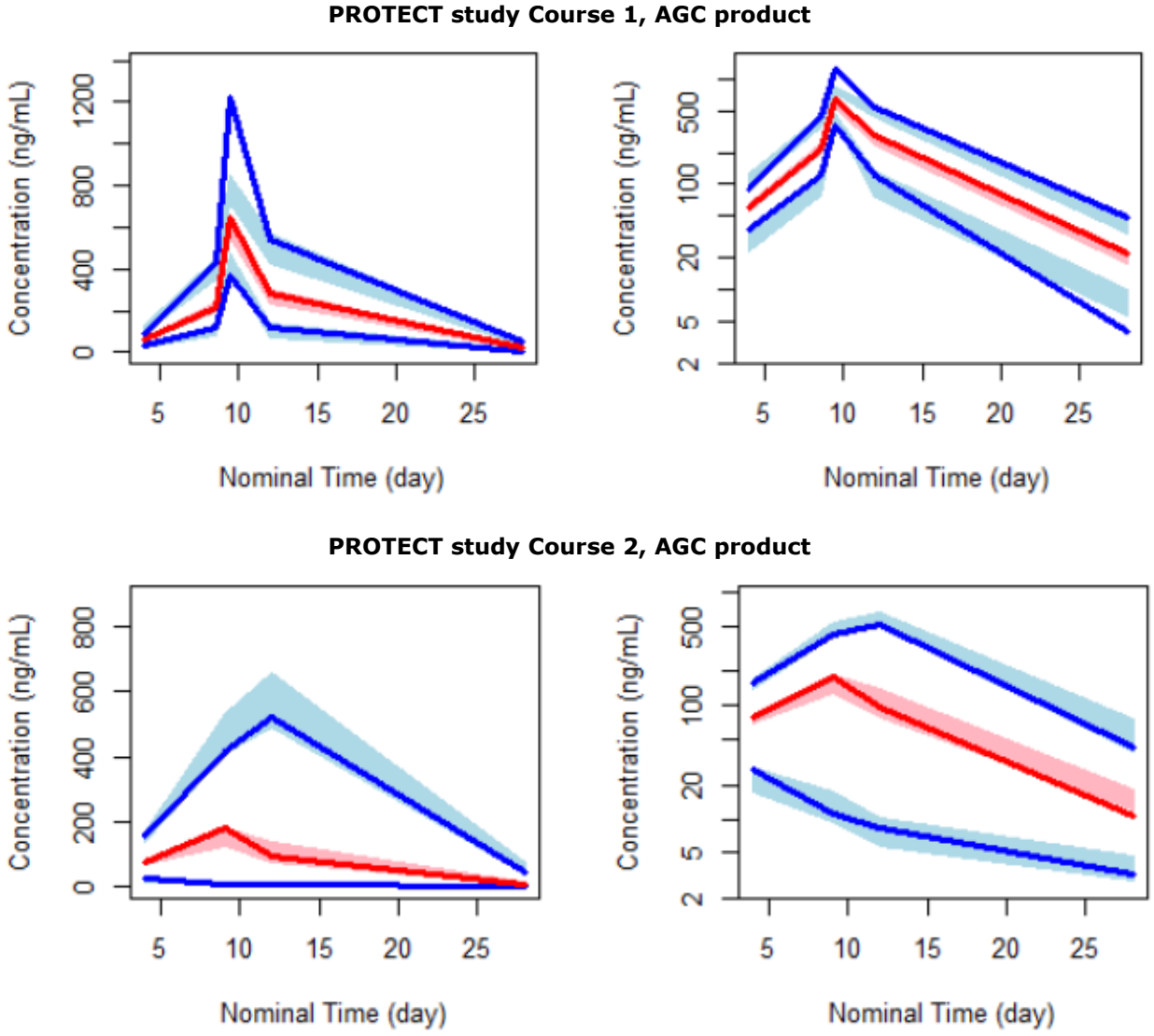
Figure 3. Visual predictive check for the final population PK model (model 454), PROTECT study, Eli Lilly product.



The solid lines are median (red), and 5th and 95th percentiles (blue) of observed concentrations. The shaded regions show the 90% confidence intervals on these quantities obtained by simulations from the model.

The simulated values were computed from 500 simulated trials with dosing, sampling, and covariate values in the data set. Nominal Time for data on Day 9 Course 1 was slightly modified to separate troughs and peaks on the plots.

Figure 4. Visual predictive check for the final population PK model (model 454), PROTECT study, AGC product.



The solid lines are median (red), and 5th and 95th percentiles (blue) of observed concentrations. The shaded regions show the 90% confidence intervals on these quantities obtained by simulations from the model.

The simulated values were computed from 500 simulated trials with dosing, sampling, and covariate values in the data set. Nominal Time for data on Day 9 Course 1 was slightly modified to separate troughs and peaks on the plots.

Absorption, Distribution, metabolism and Elimination

Teplizumab is administered as an intravenous (IV) infusion of at least a 30-minute duration. Bioavailability is per definition 100% and food is not expected to have an effect.

Based on popPK modelling, a central volume of distribution of 2.55 L was estimated for a participant of 60 kg. Protein binding has not been determined.

Teplizumab is a monoclonal antibody with a MW of approximately 140 kDa thus renal elimination is not expected. Based on popPK modelling, target-mediated drug disposition (TMDD) is present for teplizumab, a linear clearance of 1.62 L/day was estimated for a participant of 60 kg. Teplizumab is expected to be metabolized into small peptides by catabolic pathways.

Biosimilarity

During the clinical development there have been changes in the manufacturing process/manufacturer for the drug substance. The drug product used in the Protégé study was manufactured by MacroGenics (MGNX). The TN-10 study used both MGNX and Eli Lilly products. In preparation for the commercial launch of teplizumab, Provention Bio implemented a new and improved manufacturing process for the drug substance at AGC Biologics which was introduced in the ongoing Protect study.

Analytical comparability is discussed in the quality section. Importantly, differences in galactosylation profiles between the AGC and Eli Lilly product were noted by the Applicant. Although these quality differences were considered unlikely to cause clinically relevant changes (i.e. in PK, efficacy or safety) a clinical PK-study was initiated to support comparability (study PRV-031-004).

PRV-031-004

Is a Phase 1, randomized, double-blind, parallel group, single-dose study including 100 subjects. 51 subjects assigned to the test product (AGC Biologics) group and 49 assigned to the reference product (Eli Lilly) group. A single dose of 207 μg/m^2 body surface area was administered IV. This dose was selected as it was expected to provide measurable PK and PD parameters based on PK modelling with minimal risk for AEs. However, the majority of subjects did not have measurable teplizumab concentrations beyond Day 3 (28 of 51) for the test product and beyond Day 8 (46 of 48) for the reference product. The %AUC extrapolated for the majority of the calculated AUC 0-∞ values were >20%, rendering this exposure metrics unreliable.

Figure 5 Mean (SD) Teplizumab Serum Concentration-Time Profile

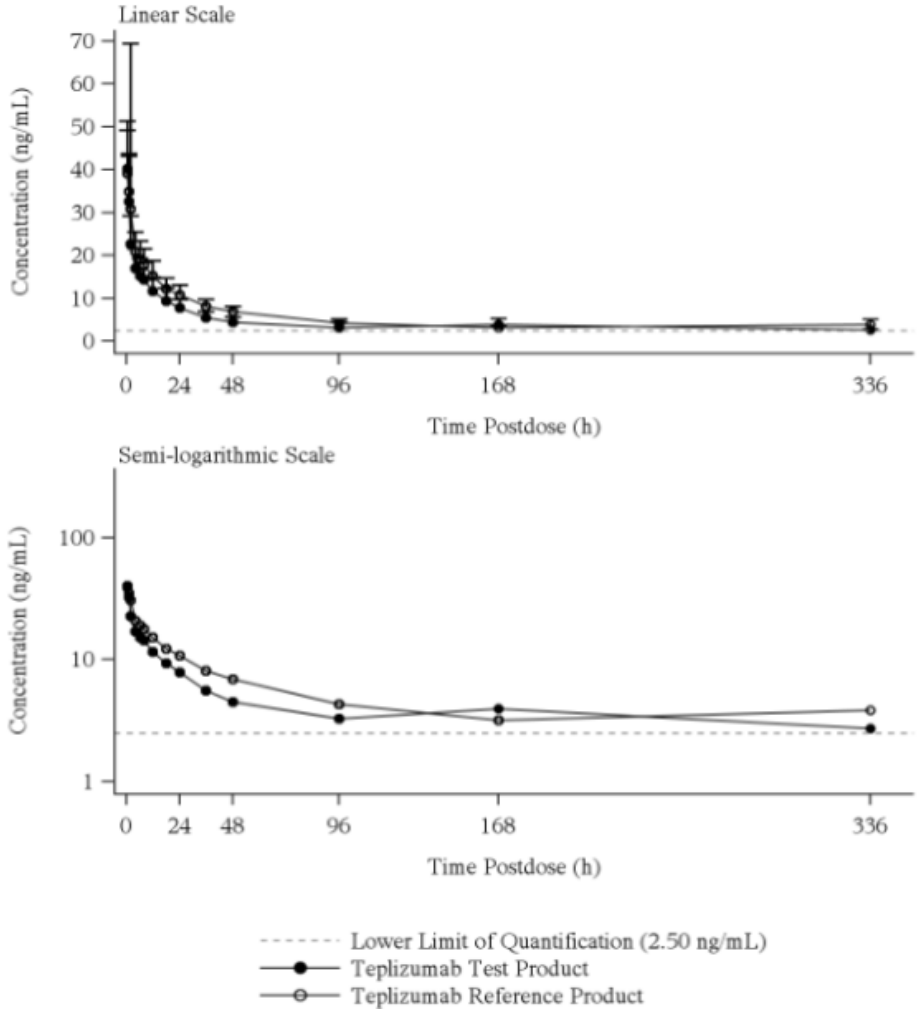


Table 5 Statistical analysis of Cmax and AUCs in study PRV-031-004

	Teplizumab Product (AGC Biologics)		Teplizumab Product (Eli Lilly)		AGC Biologics versus Eli Lilly
Parameter (units)	**n**	**GLSM**	**n**	**GLSM**	**Ratio of GLSMs, % (90% CI)**
C_{max} (ng/mL)	51	38.9	49	41.2	94.5 (84.5, 106)
AUC_{0-12} (h*ng/mL)	51	202	49	246	82.2 (75.6, 89.5)
AUC_{0-18} (h*ng/mL)	51	263	49	327	80.5 (74.2, 87.3)
AUC_{0-24} (h*ng/mL)	51	314	49	396	79.2 (73.2, 85.7)
AUC_{0-48} (h*ng/mL)	51	452	49	598	75.5 (70.3, 81.2)
AUC_{0-last} (h*ng/mL)	51	540	49	1050	51.5 (45.6, 58.2)
AUC_{0-inf} (h*ng/mL)	37	706	37	1450	48.5 (43.6, 54.1)

Biocomparability could be concluded based on Cmax. Comparisons of the AUC estimates however showed a lower exposure to teplizumab following administration of the test product when compared to the reference product.

The incidence of anti-drug antibodies (ADA) and ADA titers were generally comparable between the two products, see Table 16 below. By Day 15, 29.41% and 26.53% subjects in the test and reference product groups had NAb, respectively.

Table 6 Incidence of ADAs in study PRV-031-004

Timepoint	Teplizumab Test Product (N=51)	Teplizumab Reference Product (N=49)
Day 1, Predose	1 (1.96%)[a]	1 (2.04%)[a]
Day 2	1 (1.96%)[a]	1 (2.04%)[a]
Day 3	1 (1.96%)[a]	0
Day 5	3 (5.88%)	1 (2.04%)
Day 8	14 (27.45%)	7 (14.29%)
Day 15	32 (62.75%)	31 (63.27%)

[a]The subjects with positive anti-drug antibodies (ADA) at multiple time points were the same subjects (#1140 in the test group and #1021 in the reference group).

Study PRV-031-001 (PROTECT) PK/PD sub-study

The Eli Lilly product was initially used in this phase-3 study and gradually replaced by the AGC Biologics. For any individual participant, the same product was administered for a full treatment course. Participants who received the Eli Lilly product in Course 1 may have been subsequently switched to AGC Biologics in Course 2. Each course was administered over 12 days: Day 1: 106 μg/m^2, Day 2: 425 μg/ m^2, and Days 3-12: 850 μg/ m^2 /day.

Pre-dose PK samples were collected on day 1, 4, 9 and 12. On Day 9 of Treatment Course 1, an additional PK sample was to be obtained within 45 ± 15 minutes after infusion was completed. Additional PK samples after the 12-day treatment course were collected at day 28.

The PK population included all 217 participants randomized to the teplizumab group. The overall mean serum concentrations of teplizumab were somewhat lower in Course 2 compared with Course 1 at each time point. The mean serum concentrations of teplizumab were higher in participants who received the Eli Lilly product than those who received the AGC Biologics product at each time point.

Figure 6 Box plot of teplizumab serum concentrations over time

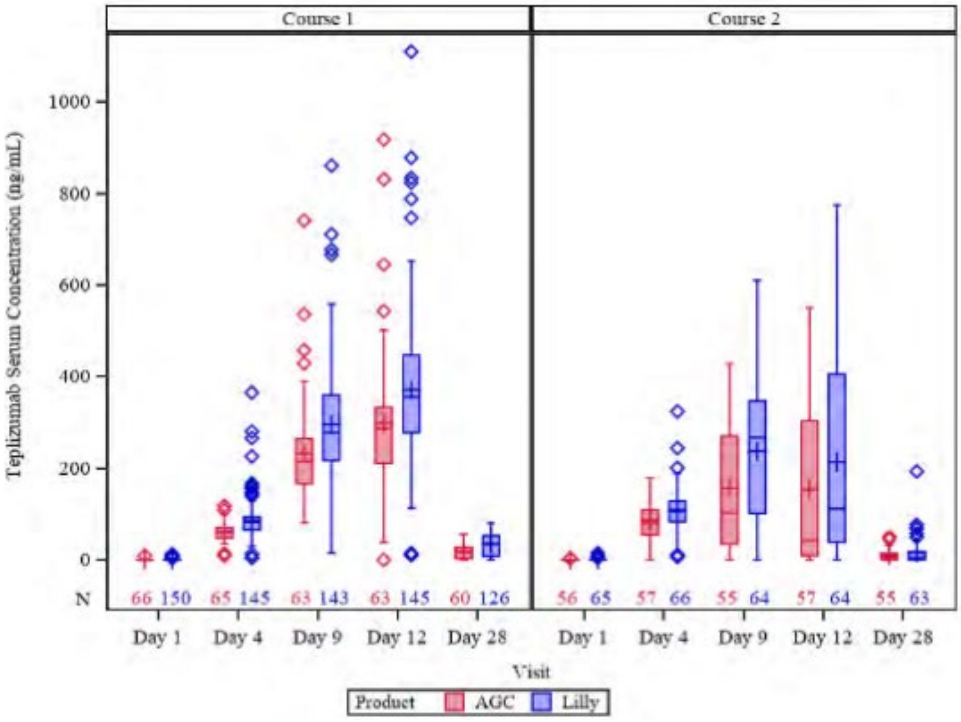


Table 7 ADA incidence by treatment in the Protect study

Statistic	Teplizumab Lilly/Lilly N=57 n (%)	Teplizumab AGC/AGC N=54 n (%)	Teplizumab Lilly/AGC N=64 n (%)	Teplizumab All N=201 n (%)
Course 1				
n	57	54	64	201
Positive	56 (98.2)	50 (92.6)	62 (96.9)	189 (94.0)
Negative	1 (1.8)	4 (7.4)	2 (3.1)	12 (6.0)
Course 2				
n	57	54	64	175
Positive	56 (98.2)	53 (98.1)	63 (98.4)	172 (98.3)
Negative	1 (1.8)	1 (1.9)	1 (1.6)	3 (1.7)

Dose proportionality and time dependency

Teplizumab is intended for a single treatment course (indication 1). Steady state is not reached within a treatment course. No analysis of dose-proportionality is presented.

Immunogenicity

Teplizumab is immunogenic with the overall ADA incidence varying between 50-94% as observed during the first course across the studies. ADA incidence increased, when a second course of treatment was administered. More than 46% of ADAs were positive in the NAb assay.

The presence of ADAs/Nabs caused a decrease in the measured teplizumab concentration in Course 2. If by increased drug clearance due to ADAs or by an interfering effect of the neutralizing antibodies with the teplizumab PK assay is unknown.

Pharmacokinetics in the target population

TN-10

TN-10 was a multicenter, double-masked, randomized, placebo-controlled study to determine whether treatment with teplizumab in subjects at high risk for diabetes resulted in delay or prevention of clinical T1D. Of the 76 randomized subjects, 44 were assigned to the teplizumab treatment group. A 14-day course of teplizumab was administered IV. Teplizumab pre-dose serum concentration samples were collected at baseline [Day 0], Day 10, Day 11, Day 12 and Day 13 visits. Of the 25 individuals with PK-samples 16 subjects received the MGNX-product and 9 subjects received the Eli Lilly-product. Anti-teplizumab antibody samples were collected at screening and 3-month visits.

At day 10 the geometric mean pre-dose teplizumab concentration was 434 ng/ml (51% CV) and at day 13 the geometric mean pre-dose teplizumab concentration was 528 ng/ml (50% CV).

Study PRV-031-001 (PROTECT)

Also described in section on biosimilarity above where data is presented by product.

In Course 1, the mean (SD) trough concentration prior to the last dose of teplizumab administered on Day 12 was 349 (164) ng/mL, compared with 185 (200) ng/mL in Course 2. In Course 1 the mean (SD) day 9 pre-dose concentration was 277 (124) ng/ml and the post-dose concentration (within 45 ± 15 minutes after infusion) was 668 (221) ng/ml. At day 28 in Course 1 the mean serum concentrations of teplizumab was 29 ng/ml (23). In Course 2 it was 13 ng/ml (23).

Special populations

No dedicated studies have been performed. Demographics are evaluated by popPK-modelling.

The majority of participants in the patient-studies were <18 years of age (72.1%, range 8-50 years), male (62.0%) and white (76.2%). 20.6% were asian. In the clinical studies patients with total bilirubin >1.5 x upper limit of normal (ULN) or Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 x ULN were excluded. In the PROTECT study also participants with significant renal deficiency were excluded.

Pharmacokinetic interaction studies

Due to the mode of action as a partial agonist of CD3 receptor, no interactions with other drugs are expected. Therefore, no interaction studies have been conducted.

6.2.3. Pharmacodynamics

Mechanism of action

Teplizumab (hOKT3γ1 [Ala-Ala]), also referred to as SAR446681, PRV-031, MGA031, or CNTO311, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to the CD3ε chain of the T cell receptor (TCR)-complex on human T lymphocytes.

Binding of teplizumab to the TCR-CD3 complex have shown a number of effects on specific sub-populations of T cells that are integral to the initiation and propagation of the autoimmune process causing beta cell destruction. Teplizumab reduces the effector function of T cells, presumably including that of autoreactive T cells, given the observed increased beta cell survival. In addition, teplizumab appears to increase the number and function of regulatory T cells as a result of CD3 partial agonism (13,14,15,16). More recent studies indicate that teplizumab also induces partial "exhaustion" in a subset of effector CD8+ T cells believed to be previously autoreactive (15,17). Importantly, the increase in exhausted CD8+ T cells has been associated with delayed progression to clinical T1D in the natural course of the disease (18) and correlates with clinical response to teplizumab (15, 19).

Mechanistic data results of studies, suggest that the immunomodulatory effect of teplizumab involves not only the inhibition of the immune process leading to beta cell destruction but also facilitates the rebalancing of effector and regulatory arms involved in T1D autoimmunity.

Primary and secondary pharmacology

Pharmacodynamic data included total lymphocytes, CD4+ and CD8+ T cell subset, FOXP3+ regulatory T cells, and CD69+ T cells in the Protégé and Encore studies, while the TN-10 and PRV-031-004 studies only included total lymphocyte counts. The PROTECT study included %CD3 occupancy and T cell activation data.

Choice of dose and dosing regimen

The early development of teplizumab focused on replacing OKT3 (approved in 1986) for the treatment of acute renal transplant rejection. OKT3, a mouse monoclonal antibody, was associated with significant cytokine release syndrome and immunogenicity. Teplizumab was derived from grafting of the OKT3 complementarity-determining region (CDR) onto a human IgG1 antibody background to minimize immunogenicity and mutating the Fc region to decrease the FcR-binding activity. The dosing regimen of teplizumab in the acute renal transplant study was modelled after the approved OKT3 regimen of daily IV administration for 10 to 14 days.

A study in participants with psoriatic arthritis tested 4 dosing regimens of teplizumab. Observed toxicity led to the adoption of a ramp-up dosing period.

Another study in psoriatic arthritis was designed to test 4 monthly courses of teplizumab, with each cycle consisting of 5 days dosing. One study patient developed cytokine release syndrome and elevated liver function test after the first dose (1 mg), and study drug was discontinued.

Based on pre-clinical data on the effect of teplizumab in preventing or reversing diabetes in non-obese diabetic (NOD) mice, clinical studies in recent-onset T1D participants were initiated in the late 1990s.

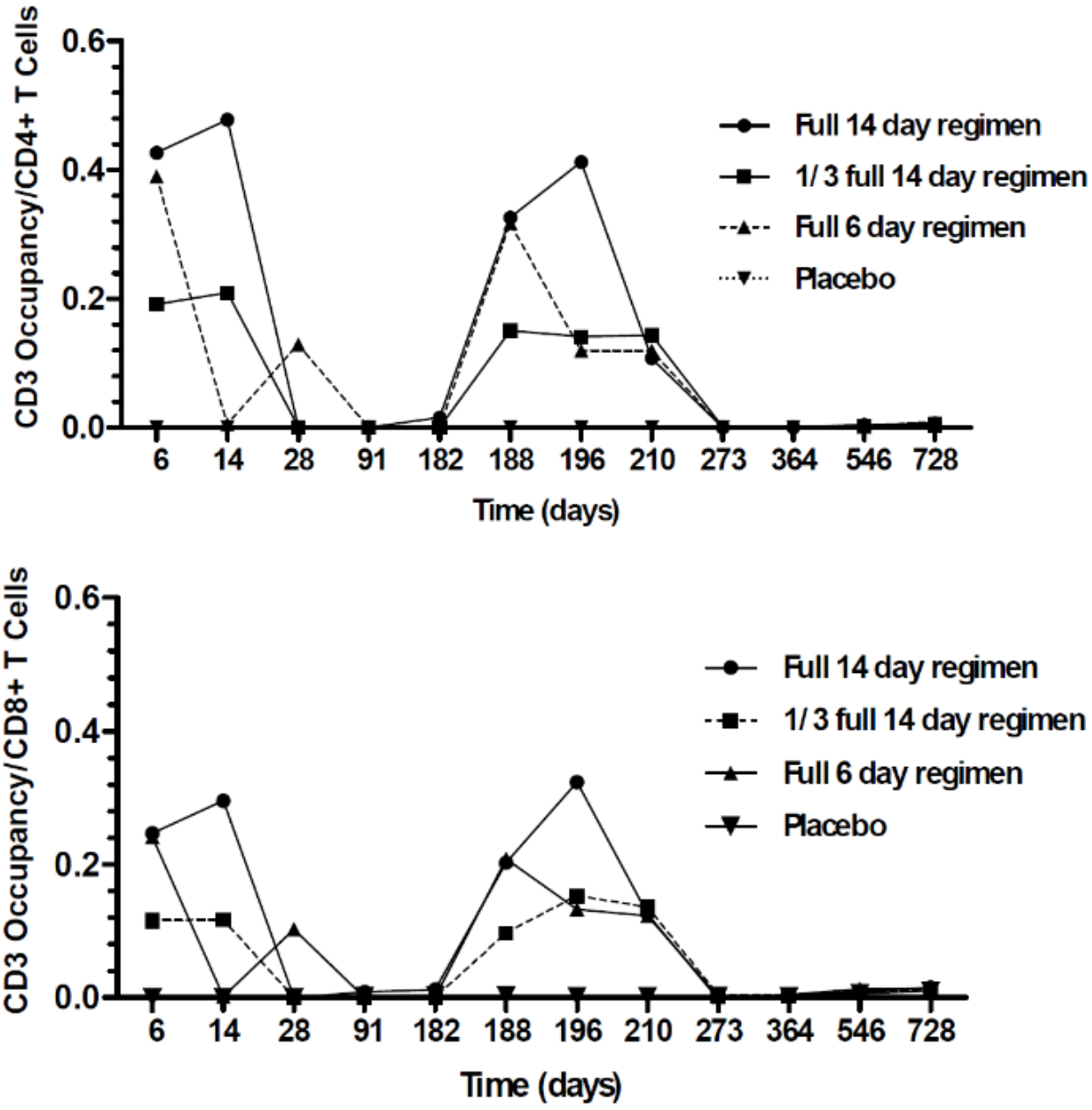
Pharmacodynamic studies

In four studies, PD properties of teplizumab were investigated. These studies and main results are presented below.

Protégé study (CP-MGA031-01)

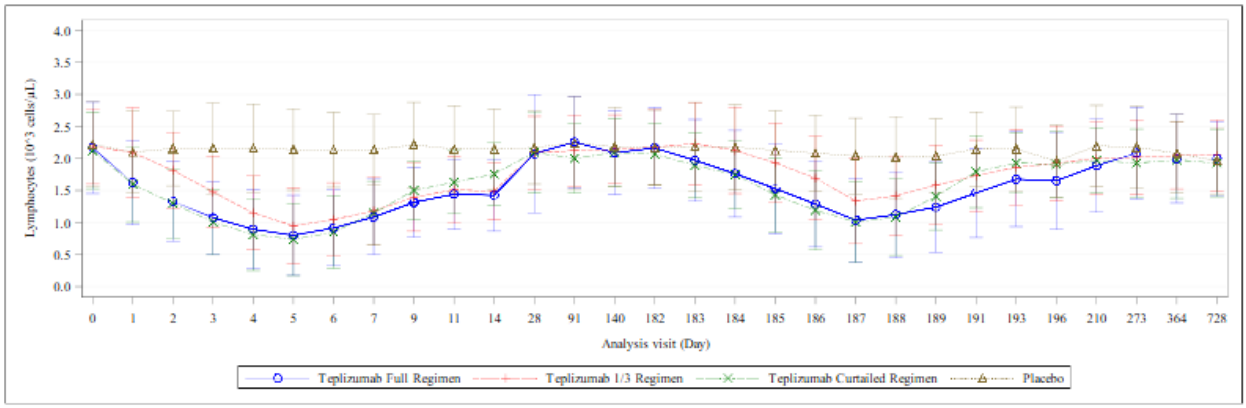
Data from the Protégé study (5.3.5.1 Study CP-MGA-031-01 [Section 11.4.1.3]) showed that in all treatment groups, teplizumab was transiently bound to CD3 molecules on the surface of both CD4+ and CD8+ T cells during treatment (Figure 8). However, the full 14-day treatment regimen resulted in longer duration and highest intensity of receptor occupancy (more teplizumab binding per cell) supporting the suitability of this dosing regimen.

Figure 7 Relative CD3 occupancy on CD4+ and CD8+ T cells over 2 years



A decline in the total lymphocyte count is generally observed with a nadir on the fifth day of dosing, during a 14-day course of teplizumab treatment. The lymphocyte counts start to recover on the sixth day of the treatment course while dosing is continued and is fully recovered by 6 weeks. Thus, the lymphocyte profile during dosing is considered a predictable PD marker for teplizumab effect. In the Protégé study, total lymphocytes decreased on Day 1, with the nadir observed on Day 5 (Figure 9).

Figure 8 Total lymphocyte counts by treatment regimen: Protégé Segment 2



Source: 5.3.5.3 ISI Figures 08SEP2020, Figure 3.1.1.

The levels of both T cell subsets CD4+ and CD8+ showed transient reductions with similar patterns as the total lymphocyte counts. Immunophenotyping of lymphocyte subsets, including FOXP3+ regulatory T cells, was evaluated in all participants in the open-label segment (Segment 1) and a subset of participants in the double-blind segment (Segment 2). Increased percentage of total FOXP3+ regulatory T cells, compared to placebo, were observed during both courses of treatment, with the peak at Day 6 for both courses.

Encore study

Circulating total lymphocyte levels, CD4+, and CD8+ T cell subsets decreased transiently from baseline after initiation of dosing. Nadir at Day 5 (total lymphocytes) or Day 6 (the first available time point for T cell subsets) and a return to near baseline levels at Day 28.

TN-10 study

In the TN-10 study, total lymphocytes were measured. A similar pattern of decline and recovery in total lymphocyte counts during the treatment course was observed.

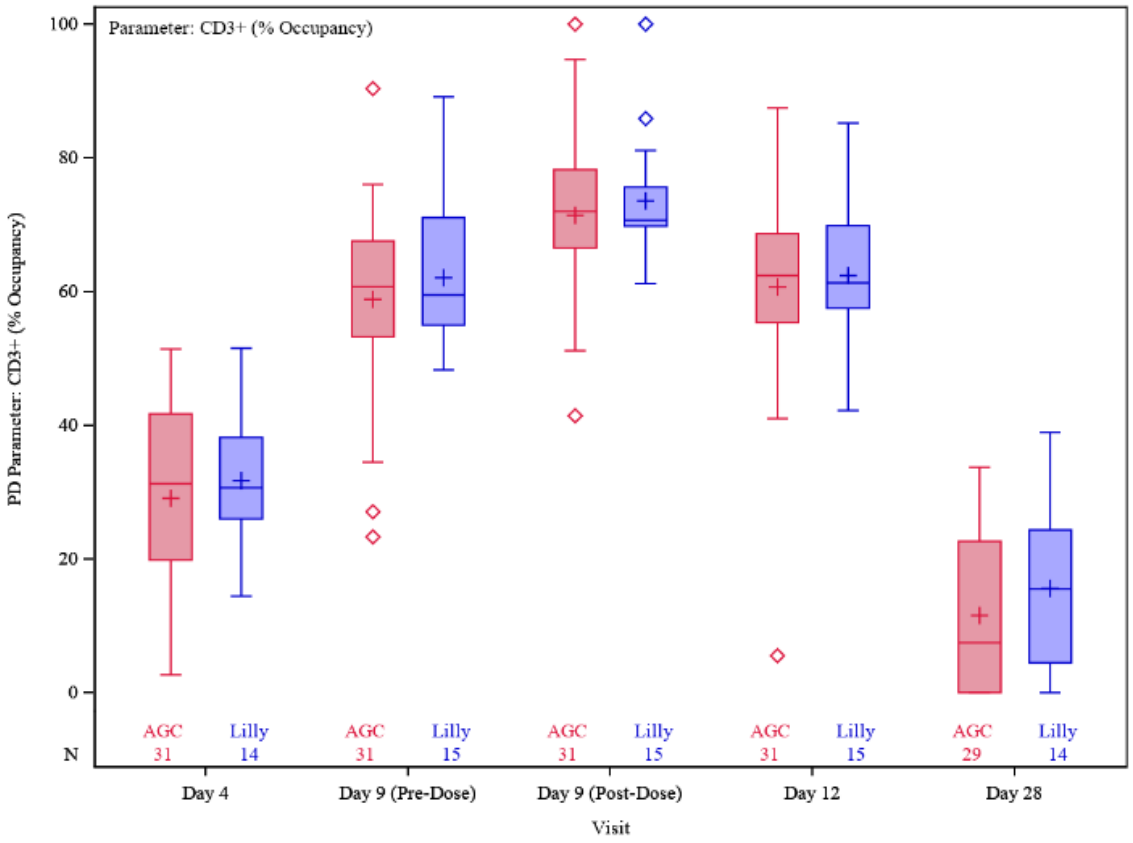
PROTECT (PRV-031-001) PK/PD sub-study

In order to compare the PK and PD effects of teplizumab between the Eli Lilly and AGC Biologics products, a sub-study was conducted during the main study. In the PK/PD sub-study, an additional PK sample was drawn at 45 minutes after the end of infusion on Day 9 of the first course to better characterize the PK profile of teplizumab. Additional blood samples were collected for PD analysis at all North American sites. The following PD markers were evaluated: circulating lymphocyte counts (all participants), CD3 receptor occupancy (participants at all North American sites), and T-cell activation (participants at all North American sites). The analyses in the PK/PD sub-study included all data from participants who had completed the first course of treatment. The PK/PD sub-study included 49 participants who received Course 1 teplizumab treatment and provided post-treatment samples for analysis, including 15 participants who received the Eli Lilly product and 34 participants who received the AGC Biologics product. The full results are presented in the clinical study report (see 5.3.5.1 Study PRV-031-001 [Section 11.5]).

CD3+ occupancy

The teplizumab occupancy on CD3+ cells by visit is shown in Figure 10. The % occupancy of teplizumab on CD3+ cells increased from Day 4 to Day 9 but was similar between Day 9 and Day 12 (pre-dose levels). Despite a 2.5-fold increase in mean teplizumab concentrations from pre-dose to post-dose on Day 9, the % occupancy increased by only approximately 12 percentage points. This suggests that CD3+ receptor occupancy plateaued by Day 9. The occupancy on CD3+ cells at all visits were similar between the Eli Lilly product and the AGC Biologics product.

Figure 9 Box plot of teplizumab % occupancy CD3+ cells by visit (PROTECT PK/PD substudy)

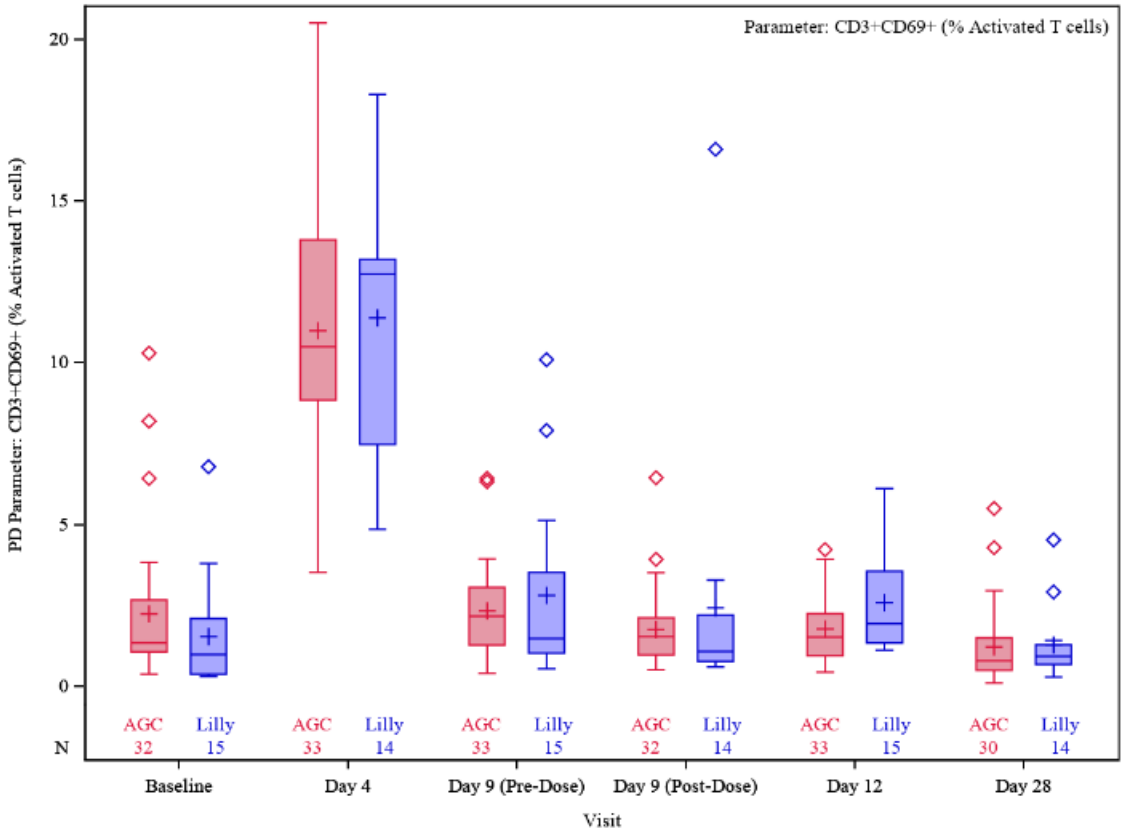


Abbreviation: PD=pharmacodynamics.
Note: PD samples were collected prior to dosing except for Day 9. An additional PD sample was collected 45 minutes after infusion on Day 9.
Source: 5.3.5.1 Study PRV-031-001 Figures, Figure 14.4.1.1.

Activation of T cells and subsets

As shown in Figure 11, the percentage of activated CD3+ cells (ie, CD3+CD69+ cells) over time showed a transient increase on Day 4 and returned to baseline at subsequent visits. The trend of CD3+ cell activation is consistent with the mechanism of action of teplizumab as a partial agonist. The levels of CD3+ cell activation at all visits were comparable between the Eli Lilly product and AGC Biologics product.

Figure 10 Box plot of activated CD3+ cells by visit and teplizumab product (PROTECT PK/PD substudy)



Abbreviation: PD=pharmacodynamics.
Note: PD samples were collected prior to dosing except for Day 9. An additional PD sample was collected 45 minutes after infusion on Day 9.
Source: 5.3.5.1 Study PRV-031-001 Figures, Figure 14.4.1.2.

Lymphocyte counts

A similar pattern of decline and recovery in total lymphocyte counts during the treatment course was observed in the PROTECT PK/PD sub-study. The circulating lymphocyte counts in the 28 days after the start of each treatment course show similar pattern with the Eli Lilly as the AGC Biologics products.

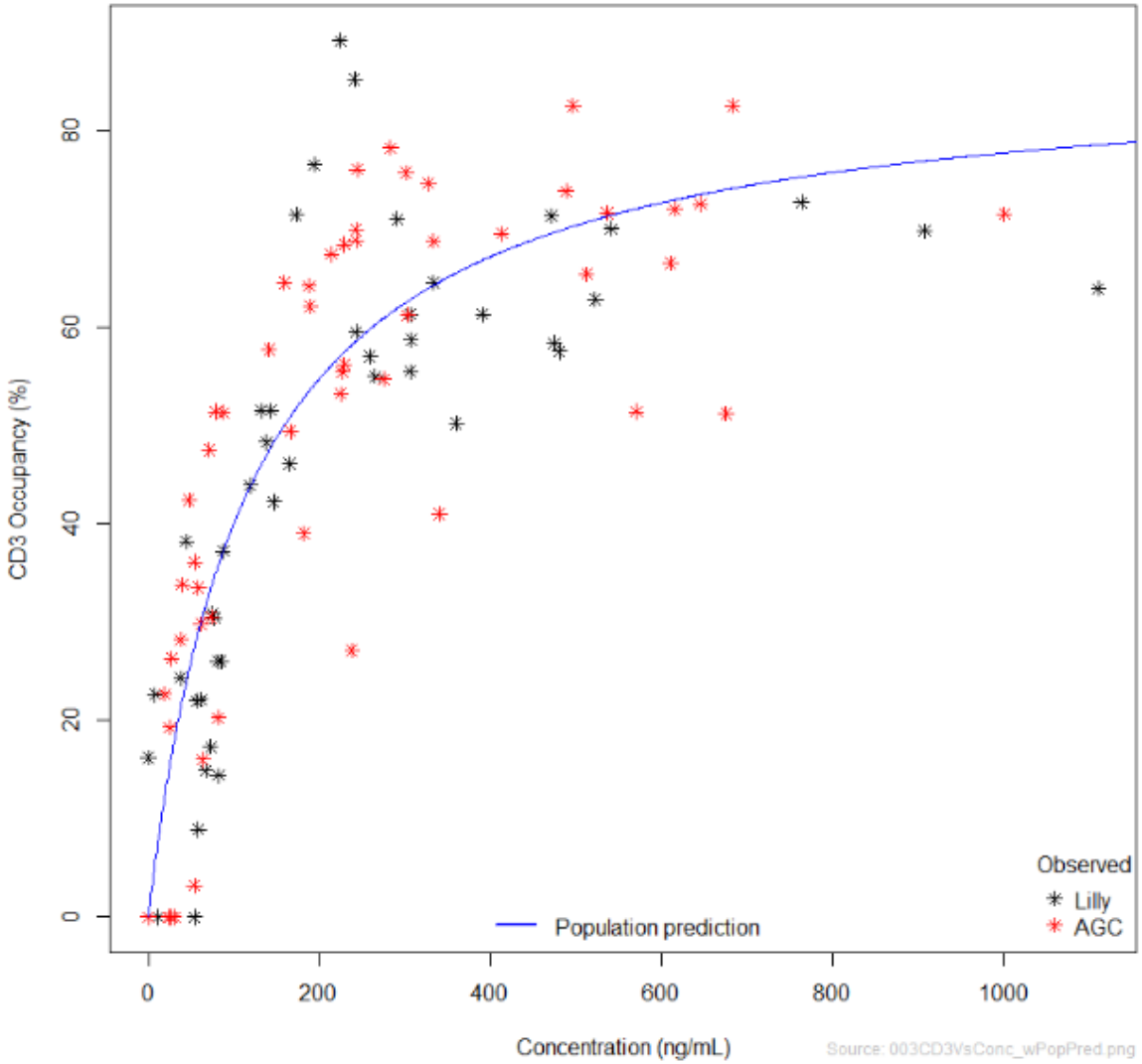
Concentration-effect relationships

Relationship of teplizumab concentrations with %CD3 receptor occupancy

An analysis was conducted to evaluate the relationship of teplizumab concentrations in serum with % CD3 receptor occupancy based on the data from the PROTECT (PRV-031-001) PK/PD substudy and to assess whether this relationship differs between the Eli Lilly and AGC Biologics products.

The population predictions from the final model and the observed data are presented in Figure 12.

Figure 11 % CD3 receptor occupancy: population predictions from the final model versus observed data



Source: 5.3.3.5 Study 20220205, Figure 2.

The CD3 occupancy increased with increasing teplizumab concentrations. The relationship was described by an Emax model of teplizumab concentrations, where the maximum attainable CD3 occupancy (Emax) was estimated as 86.8% (95% confidence interval [CI]: 80.8 to 92.8%) and teplizumab concentration at half the maximum occupancy (EC50) was estimated to be 117 ng/mL (95% CI: 79.3 to 154 ng/mL). Concentrations achieved in the substudy appeared to be close to the Emax (Figure 12). The estimated EC50 value was the same for the 2 products. In summary, there was no significant difference in the relationship of % CD3 receptor occupancy with teplizumab concentration between the Eli Lilly and AGC Biologics products.

Relationship of teplizumab exposure and C-peptide

The relationship of teplizumab exposure to efficacy, as measured by C-peptide preservation in Stage 3 (recently diagnosed) T1D, was examined utilizing the Protégé study data. Model-predicted teplizumab total AUC values versus change from baseline in C-peptide were plotted and an Emax analysis was performed. Data demonstrate that at teplizumab total AUC levels greater than ~1500 ng*day/mL, no additional improvement in C-peptide with increased teplizumab exposure was

observed.

Secondary pharmacology

Effect of teplizumab concentrations on QTc prolongation

In the Encore study, single electrocardiograms (ECGs) were collected at screening for all participants. A sub-group of 46 participants in the US received additional triplicate ECG assessments on Day 0 (pre-dose), Day 5 (pre-dose and 60 minutes post-dose), and Day 28 (2 weeks after last dose of study medication). ECG results were available from 11, 12, 12, and 11 participants in the Herold Regimen (full 14-day regimen), 1/3 Herold regimen (one-third regimen), Curtailed Herold Regimen (full 6-day regimen), and placebo group, respectively. An evaluation of the effect of teplizumab on the QTc interval corrected for heart rate (HR) using the Fridericia method (QTcF) was conducted; HR, PR, QRS, interval and morphologic ECG changes were also evaluated. A by-time point analysis of the mean placebo-corrected ΔQTcF (ΔΔQTcF) across post-dose time points during treatment ranged between –11.6 ms on Day 5, pre-dose in the 1/3 Herold Regimen and -4.0 ms on Day 5, 1-hour post-dose in the Herold Regimen (Table 18). The mean placebo-adjusted ΔQTcF (ΔΔQTcF) at Day 28 ranged between –3.8 and –2.7 ms across treatment groups.

Table 8 Placebo-corrected change-from-baseline QTcF (ΔΔQTcF) at each time point with statistical modeling (Encore study)

Parameter: ΔΔQTcF			Teplizumab		
Day	**Time point**	**Statistics**	**Full 14-day Regimen**	**One-third Regimen**	**Full 6-day Regimen**
Day 5	Pre-dose	n	9	12	12
		LS Mean	-8.3	-11.6	-6.7
		SE	4.48	4.15	4.15
		90% CI	(−15.82, −0.71)	(−18.58, −4.60)	(−13.74, 0.26)
	1 h Post-dose	n	8	12	12
		LS Mean	-4.0	-4.8	-5.1
		SE	5.27	4.80	4.80
		90% CI	(−12.90, 4.86)	(−12.91, 3.27)	(−13.20, 2.98)
Day 28		n	9	12	12
		LS Mean	-2.7	-2.9	-3.8
		SE	4.68	4.34	4.34
		90% CI	(−10.63, 5.14)	(−10.21, 4.42)	(−11.15, 3.50)

Abbreviations: CI=confidence interval; LS=least square; n=count (number of participants); ΔΔQTcF=placebo-corrected change from baseline in QT interval corrected for heart rate using Fridericia correction method; SE=standard error.
Based on a linear mixed-effects model: ΔQTcF = Time + Treatment + Time×Treatment + Baseline QTcF. An unstructured covariance structure was used to specify the repeated measures (time within subject).
Source: 5.3.5.1 Study CP-MGA031-03 Cardiac safety report, Table 14.1.6.1.

The relationship between estimated ΔΔQTcF and the individually observed teplizumab serum concentrations demonstrates that QTc does not increase with increased teplizumab serum concentrations. The predicted ΔΔQTcF at the geometric mean peak teplizumab concentration was investigated. The 90% 2-sided upper confidence bound for ΔΔQTcF was below 10 ms at all time points. It must be noted that the appropriate ECG and PK sampling were not conducted during the maximum exposure (ie, Day 14). However, the relationship between teplizumab concentration and placebo-adjusted ΔQTcF was effectively flat through the exposures evaluated in this trial (up to approximately

400 ng/mL). Teplizumab had no clinically significant effect on HR, PR interval, or QRS duration. No clinically significant ECG morphologic changes were observed. In summary, no clinically relevant effects of teplizumab on cardiac parameters were detected in this study.

Relationships of teplizumab exposure and treatment-emergent adverse events in study PROTECT

For the analysis of relationships of teplizumab exposure and treatment-emergent adverse events (TEAEs) in study PROTECT, individual teplizumab Cmax and AUC0-inf values were divided in respective quartiles. The observation periods covered the respective treatment course and through 28 days after the last dose. No evidence for a trend indicating a relationship between teplizumab exposure and TEAEs was observed.

Pharmacodynamic interactions with other medicinal products or substances

No studies to evaluate effects of extrinsic factors or to evaluate effects of Teplizumab on other drugs have been conducted as no interactions are expected based on the mode of action. There are no suggested precautions or warnings in the SmPC regarding interaction with other medicinal products or substances.

Immunological events

During clinical development of teplizumab, the Protégé, Encore, TN-10 and PROTECT studies evaluated the immunogenicity of teplizumab in T1D participants through the detection and characterization of ADAs and neutralizing antibodies (NAbs). ADAs and NAbs were evaluated for their impact on PK, PD, efficacy, and safety.

Based on this evaluation, teplizumab is immunogenic with the overall ADA incidence varying between 50-94% as observed during the first course across the various treatment regimens and across the 4 studies. ADA incidence increased to almost 100%, when a second course of treatment was administered. The median ADA titers were low (between 0.88 log10 and 4.49 log10). Most ADAs were positive in the NAb assay, and thus have neutralizing potential. Furthermore, the following conclusions can be made regarding the impact of teplizumab immunogenicity on PK, PD, efficacy, and safety data.

• Pharmacodynamics: ADAs (binding/NAbs) did not appear to impact teplizumab's effect on the transient decline in total lymphocytes and the T cell subsets, of CD4+ or CD8+ T cells or regulatory T cells or CD3 receptor occupancy. In PROTECT, an effect of ADA on pharmacodynamics was not seen by assessing maximum ADA quartile or visit-specific ADA titer quartile. The limited number of ADA negative participants prevent a definitive conclusion.

• Efficacy: ADAs (Binding/NAbs) did not appear to have an impact on efficacy as measured by change from baseline in C peptide levels (Protégé, Encore, TN-10, PROTECT) and HbA1c (PROTECT). The limited number of ADA negative participants prevent a definitive conclusion. In PROTECT, an effect of ADA on C peptide and HbA1c was not seen by assessing maximum ADA quartile or visit-specific ADA titer quartile. While the median time to diagnosis (TN-10) appears to be shorter for ADA positive patients, the mean times of diagnosis were similar. However, due to the small number of participants evaluated, it is not possible to make a definitive conclusion regarding any impact of ADA status on time of clinical T1D diagnosis.

• Safety: ADAs were not associated with immune system-related treatment emergent adverse events. There was no evidence for ADA-mediated hypersensitivity reactions. 50%-94% of clinical trial

participants who received a single treatment course developed ADA, many of which appear to be neutralizing based on the limited data. Safety risks from immunogenicity are low as most of the adverse events (which are transient and manageable) appear to be related to drug treatment and not related to immunogenicity.

6.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Model-predicted teplizumab total AUC values versus change from baseline in C-peptide were plotted and an Emax analysis was performed. No clear conclusions can be drawn from this analysis.

6.2.5. Dose selection and therapeutic window

The dosing schemes for the two pivotal studies TN-10 and PROTECT, with daily iv administration 14 days and 2 times 12 days, respectively, including a ramp-up dosing period, and dosing according to body surface area, are the results of several early studies in which different doses were tested, see section dose response study below.

6.2.6. Overall discussion and conclusions on clinical pharmacology

Discussion

Except for one BA study in healthy participants, no dedicated PK studies were conducted. The PK of teplizumab in patients was assessed by means of a population PK approach.

Methods

The bioanalytical method (method 8-14-01) to determine teplizumab plasma concentrations applied in studies Protégé and Encore is not considered adequately validated. Accuracy and precision have been adequately addressed but other validation parameters have been omitted or not analysed according to current standards during the validation process. No bioanalytical report is available from the Protégé study and thus information on method performance, study sample storage, reanalyses and ISR is not available. There are several deficiencies both in the validation and during study sample analysis that would normally have to be addressed. However, the studies are old, and it is not sure samples are available and as a new method has been developed and been used in the other pivotal clinical studies it is unlikely that this method will be started again. It is proposed to accept that the PK-data generated with these two methods are uncertain, and as no cross-validation has been performed it is also uncertain how the data relate to the data generated with the more recent method. The data from the Protégé study were initially included in the popPK model but has been excluded as requested in the updated model.

The method used in the TN-10, PRV-031-004, and PROTECT (PRV-031-001) studies (method ICD 788) is more appropriately validated. The analytical performance of the method, based on intra- and inter-assay precision and accuracy, is considered acceptable. The Applicant has not demonstrated that the specificity of the method is adequate as required in the guideline. There are some data available to indicate that this may not be a relevant issue, but uncertainties remain. Due to the limited use of PK in this application this issue is not further pursued.

Selectivity has been adequately evaluated in normal, haemolytic and lipemic plasma however the presence of ADAs/Nabs are likely to influence the measurements and this has not been investigated. The method does not contain any dissociation steps and likely only measures free (unbound) fraction

of teplizumab. Concentration measurements from samples containing ADAs are not reliable as it will not be possible to conclude if there is an effect on clearance, on the analytical method by ADAs or a combination of both.

Long-term stability has been demonstrated for up to 1178 days. In the TN-10 study it is stated that samples were stored for up to 2880 days. Upon request the Applicant has clarified that all samples were analysed outside validated stability and that further stability data will be provided to cover storage times. Until then the data from TN-10 must be interpreted with caution.

There are uncertainties associated with the ADA assay used in the Protégé study. No cut-points have been determined; drug tolerance is not established and there seem to be a substantial number of subjects with pre-existing ADAs in segment 1 of the study. The data should therefore be interpreted with caution but seem similar to results from other studies. As there are also uncertainties with the PK-assay for this study the data from this study relating to ADAs effect on the pharmacokinetics of teplizumab must be considered very uncertain. In the SmPC immunogenicity data from Protégé is not reported which is endorsed, methodological issues are therefore not further pursued.

A standard multi-tiered approach was developed including screening, confirmatory and titer and characterization assays (bridging ELISA format) to evaluate anti-drug antibodies in TN-10, PRV-031-004 and PROTECT. The assay is acceptably selective and sensitive, capable of detecting low levels antibodies at 3.5 ng/ml. Drug tolerance is considered acceptable where 10 ng/ml antibody can be detected in the presence of 12,5 μg/ml teplizumab. Mean trough concentrations in the patient studies were below 0,7 μg/ml. The methodology to establish cut-points were acceptable and based on a sufficient number (50) of individual drug naïve human serum sample lots. An in study cut point was established in PROTECT using acceptable methods. Although the rational for (data leading up to) the decision to use an in study cut-point in PROTECT (and not in TN-10) is not summarized, in general the use of an in study cut-point is acceptable as cut-points should be established in the target disease state serum. The observed false-positive rate of 4.8% for the screening samples supports the use of the validation cut points in study TN-10. In PROTECT, pre-existing antibodies to teplizumab were observed in 7.0% of the participants. 3932 original samples were received but only 2575 samples analysed. Placebo samples were also considered in the number of original samples and were excluded from ADA sample analysis.

Regarding the Nab assay, the use of a cell-based format is supported as teplizumab is a partial agonist of the complex TCR-CD3. The set-up of the Nab assay is deemed acceptable. The sensitivity and drug tolerance of the NAb-assay is not optimal, the method is adequate enough to detect high titers of NAbs at least on non-dosing days. This is considered sufficient for the product at hand.

Evaluation and qualification of models

The population PK model is complex, with target-mediated binding in all three distribution compartments. Given that the quasi steady-state approximation (applied in the model) assumes measurement of total concentration, whereas the bioanalysis method appears to only measure free fraction, the model appears to rely on an erroneous assumption. Estimated parameters should therefore not be given a physiological interpretation. Differences in exposure between the Eli Lilly product and the AGC product are, in the model, described by a lower quasi-steady-state constant (Kss) and a higher linear clearance for the AGC product. In addition, the effect of the AGC product on clearance was considerably higher following the single low dose in study PRV-031-004 (by 307%) compared to multiple therapeutic doses in the PROTECT study (by 23%). It is agreed with the applicant that this indicates that teplizumab PK has a higher complexity between low and high doses than depicted by the model. Furthermore, effects of ADAs are included on clearance (Course 1 and 2)

and bioavailability (Course 2), although it is highly uncertain whether ADAs do affect teplizumab PK or only the bioanalysis of teplizumab concentrations. Hence, the effects of ADAs on tepelizumab PK are not considered adequately characterized.

Although the final model provides an adequate description of the observed data, the possibly erroneous assumption regarding measured concentrations renders parameter estimates uninterpretable. No parameter estimates should therefore be included in section 5.2 of the SmPC and the model cannot support any claims regarding e.g. elimination pathways. Furthermore, given indications of dose-/exposure dependencies not properly described by the model, simulations and predictions outside the data range on which the model was developed, especially simulations of new dosing regimens, are not supported.

ADME

No dedicated ADME-studies have been conducted. The general ADME-properties of teplizumab are based on the common properties for monoclonal antibodies which is acceptable. More specific PK-properties are analysed by popPK, indicating a for a MAb somewhat atypical PK described by a three-compartment TMDD model. There are issues raised regarding the model, see discussion above.

Biosimilarity/Comparability

During development of teplizumab, products manufactured by Macrogenics, Eli Lilly and AGC Biologics (to-be-marketed product, corresponding to the product currently marketed in the US) were used in patients. Changes in the manufacturing process/manufacturer for the drug substance triggered comparability exercises. In study TN-10, where both the MGNX and Eli Lily product was used, the limited PK-results (only 25 subjects of 44 randomized to teplizumab had PK samples) were similar to the ones from study Protégé, though the comparison does not present data for the different products in the TN-10 study separately. Of the 25 individuals with PK-samples 16 subjects received the MGNX-product and 9 subjects received the Eli Lilly-product. Available PK-data by product from study TN-10 (as Protégé-data are not considered reliable) has been presented and while limited do not indicate a relevant difference between the two products.

The low dose used in study PRV-031-004 for safety reasons resulted in difficulties measuring AUCinf and half-life as many samples from later time-points were BLQ. Based on the less reliably determined AUClast and AUCinf the exposure of the test product (AGC) appears to be approximately half of that for the reference product (Eli Lily). Based on partial AUCs the exposure of the test product is in the range of 75-80% of the reference product and biocomparability cannot be concluded. Data from the PK/PD sub-study in PROTECT is mainly analysed with popPK, observed mean troughs are lower for the AGC-product compared to the Eli Lily product. The reliability of the popPK model is questioned however the difference between the two products seem smaller after clinical dosing compared to the single low dose study. Uncertainties remain on the reasons for the difference in clearance/PK between the drug products from Lilly and AGC. Based on this difference the Applicant propose that the recommended dose for indication 1 only should be adjusted and popPK has been used to simulate the higher dose included in the SmPC. Considering the relatively small difference in total exposure (~20%) but similarity in PD-data and the issues related to the models (used both to analyse the difference and to simulate the new dose) this dose adjustment for the commercial product is questionable. The adjusted dose has been approved by the FDA and post marketing safety data from approximately 414 individuals have been submitted and do not raise any concerns.

Overall, PK-data are limited and affected by uncertainties regarding bioanalytical issues (analysis

outside stability and validation of method) as well as modelling limitations. There are no compelling data (PK, PD or efficacy) indicating a need for adjusting the dose in indication for stage 2 T1D. Furthermore, the available post-marketing safety data with this dose are reassuring and the proposed posology is considered acceptable to address potential uncertainties regarding efficacy.

Pharmacokinetics in the target population

The pivotal study TN-10 is the only study in participants with Stage 2 T1D. There are 3 studies in participants recently diagnosed with Stage 3 T1D including PK-sampling; the pivotal study, PROTECT (PRV-031 001), and the supportive studies: Protégé (CP MGA031 01), Encore (CP MGA 031 03). PK-data from Protégé and Encore studies are not considered fully reliable, due to analytical issues and Protégé failed to meet its primary endpoint and Encore was terminated by the Sponsor.

Observed data from the patient studies show a relatively high intersubject variability with %CV around 50%.

Two patient populations with different immunologic stages of the beta cell deterioration are included in this application. The total dose of teplizumab (~9 mg/m^2 per course) is similar for both populations (stage 2 and stage 3 T1D) but the dose ramp-up and the length of the treatment course differs. The Applicant does not anticipate any differences in PK between the two populations.

Impact of ADAs

ADAs are a statistically significant covariate on the PK of teplizumab, but ADAs may also interfere with the bioanalytical method. There is insufficient data to allow a meaningful comparison of teplizumab PK between ADA positive and negative subjects as there are very few individuals thar are ADA negative. This is also reflected in the SmPC considering the relatively low sensitivity in the NAb assay and potential misclassification of occasional samples due to limited drug tolerance the numbers of NAb-positives are less exact, but in this case where such a large proportion of samples are positive the risk will be obvious in clinical praxis anyway and issues not further pursued.

Special populations

Given that teplizumab is a monoclonal antibody with a high molecular weight of 146 kDa, it is not expected to undergo significant renal nor hepatic elimination and its pharmacokinetics is therefore not expected to be impacted by renal nor by hepatic impairment. The absence of dedicated studies is acceptable. Moreover, given the young target population renal and hepatic impairment is not expected to be common.

No subjects above 50 years were included in the studies, and in the studies involving patients, the oldest person was 35 years. This is considered acceptable as early stages of T1D are generally occurring in children and younger adults.

Drug-drug interactions

Modulation of the release of cytokines by teplizumab as anti-CD3 monoclonal antibody has been further discussed in humans, cytokine release syndrome accompanied by a slight and transient increase in IL-6 concentrations may occur with Teizeild, which is not expected to have any relevant cytochrome P450 mediated drug-drug interactions.

Pharmacodynamics

The mechanism of action described by the applicant is considered plausible. But, as stated in a cited article (15): The immunological mechanism(s) of action whereby teplizumab preserves C-peptide levels in the progression of patients with recent onset type 1 diabetes (T1D) is still not well understood. Following binding of teplizumab to the CD3 receptor, downstream PD effects have been identified with transient and reversible decrease in a number of biological markers.

The choice of PD endpoints was described, and the endpoints are considered relevant. The applicant has described the development of doses and dosing regimens. This development was primarily driven by observed toxicity and other adverse events, motivating a ramp-up dosing regimen. Problems with doses actually delivered due to filtration step, did also influence the development of dosing, and the doses chosen. This introduction overview is considered adequate.

The pharmacodynamic properties of teplizumab were studied in the four clinical studies Protégé, Encore, TN-10 and PROTECT.

In the Protégé study, a decline in lymphocytes was detected with the lowest concentration at infusion day 5 (of 14). Due to the quick recovery in T cell counts while dosing continued, the applicant suggests that the lymphopenia is not due to depletion but rather to mild cytokine release which results in margination of lymphocytes to the blood vessel wall.

Total lymphocyte counts and levels of subsets of T-cells show transient reduction. These data are considered reliable and fits with the theoretical mechanism of action of teplizumab. However, they do not support any long-term effect in the T cells or induction of immune tolerance (see non-clinical discussion on PD). The Encore and TN-10 studies gave similar results on the T-cell levels over time.

The results from a CD3 receptor occupancy study are provided. According to the applicant, there was no significant difference in the relationship of % CD3 receptor occupancy with teplizumab concentration between the Eli Lilly and AGC Biologics products. It is agreed that the data indicate no clinically relevant difference in receptor occupancy between the products.

No relevant effect of teplizumab on cardiac parameters has been detected. Relationship of teplizumab exposure and QTc-time was investigated. The applicant concludes that no effect was seen on QTc. This is agreed. For effects on other cardiac parameters such as ECG morphologic changes, HR and others (see Clinical Safety section).

At teplizumab total AUC levels greater than ~1500 ng*day/mL, no additional improvement in C-peptide with increased teplizumab exposure was observed. No evidence for a correlation between HbA1c and quartiles of AUC0-inf of teplizumab was observed. No evidence for a trend indicating a relationship between teplizumab exposure and TEAEs was observed.

Since clinical studies have been made, including children and adolescents, a comparison of PD response in children pre vs post puberty could have been interesting to evaluate. But a major shift in PD response is not foreseen with this monoclonal antibody directed towards T-cells. Efficacy and safety data are provided in some studies per age group. Results from these studies can in part indicate that no important PD differences are suspected. No need for questions on this issue.

Immunogenicity was examined in many studies. Majority of the study subjects (50-94%) developed ADAs, many of which appear to be neutralizing, and the presence of ADAs seems to cause a decrease in the teplizumab concentration. Important effects of ADAs on pharmacodynamics, efficacy and safety were not seen in the studies where ADAs were measured. The applicant indicates that conclusions cannot be made regarding ADA effects on PK, PD, efficacy and safety, since the number of ADA

negative participants was limited, and in some cases (e.g. study TN-10), the number of study participants was small. This is agreed.

Conclusions

A limited clinical pharmacology package has been submitted. Few studies have been performed, with one exception using sparse sampling and popPK analyses. Although there are remaining uncertainties regarding the concentration measurements, these do not affect the assessment as PK-data only have a limited role in the overall clinical evaluation for teplizumab.

Although the final popPK-model provides an adequate description of the observed data, the model appears to rely on an erroneous assumption regarding measured concentrations, which renders parameter estimates uninterpretable. No parameter estimates should therefore be included in the SmPC, and the model cannot support any claims regarding e.g. elimination pathways.

Overall, PK-data are limited and affected by uncertainties regarding bioanalytical issues (analysis outside stability and validation of method) as well as modelling limitations.

There are no compelling data (PK, PD or efficacy) indicating a need for adjusting the dose in the indication for stage 2 T1D. Furthermore, the available post-marketing safety data with this dose are reassuring and the proposed posology is considered acceptable to address potential uncertainties regarding efficacy.

6.3. Clinical efficacy

6.3.1. Dose response studies

In early studies of teplizumab for the treatment of acute renal transplant rejection and psoriatic arthritis, daily iv administration for 10-14 days was used, and a ramp-up dosing period was adopted due to toxicity including nausea, vomiting and fever, observed for a patient the highest initial dose in a psoriatic arthritis study.

In Study 1, a single 14-day course of teplizumab was tested: 1.42, 5.7, 11.3, and 22.6 µg/kg were administered IV on Days 1, 2, 3, and 4, respectively, followed by 45.4 µg/kg once daily from Days 5 through 14 (20). However, because of anti-idiotypic antibody development and the participants being predominantly paediatric, this regimen was modified to BSA-based dosing: 455 and 919 µg/m^2 IV on Days 1 and 2, respectively, and 1818 µg/m^2 IV once daily on Days 3 through 12.

Study 2 was initially designed to test 3 dosing regimens to be administered once every 6 months to recently diagnosed participants with T1D (21). However, due to the frequency of adverse events in the first regimen tested, only 6 participants were dosed with a single 12-day course of teplizumab with 460 and 919 µg/m^2 on Days 1 and 2, respectively, and 1818 µg/m^2 once daily from Days 3 through 12. Further investigation showed that a filtration procedure used before study drug preparation for Study 1 but not for Study 2, affected the amount of drug delivered to participant. The amount of teplizumab actually given to participants in Study 1 was closer to 60% of the planned dose, and the actual amount of teplizumab administered in Study 2 was approximately 2-fold greater compared to that in Study 1.

Study 3 was designed to identify a dosing regimen that would result in predictable steady-state drug levels and a safety profile similar to Study 1. As a result, a dosing regimen approximately 50% of amount administered in the earlier studies was chosen. Since this 12-day dosing regimen was tolerated in the first 5 participants tested, the dose was increased by 25% for the sixth participant. However, Grade 4 hyperbilirubinemia, possibly cytokine release-related, was observed in this participant, and no further doses were administered.

The mean serum teplizumab concentrations on Days 10 to 12 was approximately 99 ng/mL, which replicated the steady-state concentrations in Study 1. As a result, the dosing regimen used in the first 5 participants was adopted in subsequent studies, with an additional 2 days to the ramp-up period, resulting in a 14-day regimen.

In the Protégé and Encore studies, 3 teplizumab dosing regimens were evaluated. The administration of a second course of therapy at 6 months was predicated on the observation that the beneficial effects of teplizumab appear to be maximal 6 months after the initial course and then begin to decline slowly (22).

The 3 teplizumab dosing regimens were as follows:

- Full 14-day regimen: cumulative dose of ~9 mg/m^2 per course ("Herold Regimen")
- 1/3 14-day regimen: cumulative dose of ~3 mg/m^2 per course ("1/3 Herold Regimen")
- Full 6-day regimen: cumulative dose of ~2.4 mg/m^2 per course (Curtailed Herold Regimen)

The total dose chosen for the pivotal study TN-10 was the same as applied per dosing round in the pivotal study PROTECT although differences in number of infusion days.

6.3.2. Main studies

6.3.2.1. TN-10 (ISCT-MGA031-005)

6.3.2.1.1. Study title

TN-10 Anti-CD3 mAb (Teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus

6.3.2.1.2. Study design

TN-10 was a multicenter, double-blind, randomized (1:1), placebo-controlled study to determine whether a single 14-day course of teplizumab treatment compared to placebo (saline solution) in participants at high risk for T1D (in Stage 2) resulted in delaying the diagnosis of clinical Stage 3 T1D.

Study Treatment

Active group: a 14-day course of teplizumab consisting of daily IV doses of 51 µg/m^2, 103 µg/m^2, 207 µg/m^2, and 413 µg/m^2 on Study Days 0 to 3, respectively, and 1 dose of 826 µg/m^2 on each of

Study Days 4 to 13. The total dose for the 14-day course was approximately 9.0 mg/m^2. For participants weighing 70 kg and having a body surface area (BSA) of 1.92 m^2, this dosing schedule delivered approximately 18 mg of teplizumab.

Placebo group: saline infusion for 14 days.

After the treatment course, visits occurred at Day 20, Week 6, Month 3, Month 6, and every 6 months thereafter until study termination or until clinical Stage 3 T1D was diagnosed.

Figure 12: Study design and schedule of assessments

Week of Trial															2		6												
Month of Trial																		3	6	12	18	24	30	36	42	48	54	60	66	72[10]
Day of Trial	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	20													
Visit number	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Study drug[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X															
Chemistries[2,3]	X	X	X	X	X	X	X	X					X		X		X		X	X		X		X		X		X	X	X
INR[2]	X	X	X	X	X	X	X						X		X															
CBC with diff[2]	X	X	X	X	X	X	X	X		X			X		X	X	X	X	X	X	X	X		X		X		X	X	X
Liver Function[2,3]	X	X	X	X	X	X	X	X					X		X		X		X	X		X		X		X		X	X	X
mAb levels[4]		X										X	X	X	X															
Anti-teplizumab response	X																	X												
EBV and CMV viral loads[5]	X															X	X	X		X		X		X		X				
EBV/CMV serology	X																			X		X		X		X				
History/Physical exam[6]	X	X					X					X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral Glucose Tolerance[7]	X	X																X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, HepB and C serology	X																													
PPD test	X																													
Urine pregnancy test	X	X																X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X																	X	X	X	X	X	X	X	X	X	X	X	X	X
Mechanistic assessments[8]		X														X		X	X	X	X	X	X	X	X	X	X	X	X	X
glycemic status[9]	X																													
EKG		X																		X										

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CBC=complete blood count, CMV=cytomegalovirus, EBV=Epstein-Barr virus, EBNA=Epstein-Barr nuclear antigen, EKG=electrocardiogram, HbA1c=hemoglobin A1c, HIV=human immunodeficiency virus, INR=international normalized ratio, LDH=lactate dehydrogenase, mAb=monoclonal antibody, OGTT=oral glucose tolerance test, PPD=tuberculin purified protein derivative, VCA=viral capsid antigen.

Footnotes:

1. Drug dosing: Day 0: 51 mcg/m^2, Day 1: 103 µg/m^2, Day 2: 207 µg/m^2, Day 3: 413 µg/m^2, Days 4 - 13: 826 µg/m^2.
2. These test results had to be reviewed prior to drug administration. INR and CBC with differential were done locally at all specified visits.
3. Liver Function tests (ALT, AST, LDH, alkaline phosphatase, total protein, albumin, total and direct bilirubin) and chemistries (sodium, potassium, chloride, CO_2, glucose, BUN, creatine) were done locally at specified visits 0-13. Tests were done centrally at all other specified visits.
4. These PK samples were done on the first 12 subjects in each of the age strata: ≥16, 12-15, and 8-11 years.
5. At Screen, EBV viral load were measured on all subjects except those VCA IgG+, VCA IgM-, EBNA+ by serology. After study drug treatment, EBV and CMV viral load samples were collected from all subjects. Viral loads were measured in symptomatic subjects.
6. Directed/limited physical exam for visits at month 3, 6, 18, 30, 42, 54, 66, and then q 6 months.
7. Screening OGTT only applicable for subjects ≥18 years, unless abnormal glucose tolerance had been previously confirmed by a test in TrialNet within 7 weeks (52 days) of randomization. If OGTT was consistent with diabetes, it was repeat within 1 month. Glucose, insulin, and C-peptide were collected at each OGTT. Subjects <18 years underwent an OGTT at or prior to the baseline visit (visit 0). The results of this study were not used to determine eligibility for the study.
8. Included samples for RNA, plasma, serum, DNA, measures of B and T cell number and function to understand the effect of therapy on the immune system and infectious disease. The schedule for these assessments could vary as appropriate. At no time would the blood draw volume exceed what was allowable according to the subject's age and body weight. (For subjects <18, 5 mL/kg per visit, 9.5 mg/kg in an 8-week period.)
9. Screening random glucose only applicable for subjects <18 years of age not undergoing an OGTT on the same day. All subjects had interim contact with study personnel for formal inquiry about adverse events, presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss. In addition, random glucose samples were obtained at 3-month intervals in which there was no OGTT scheduled. Those with symptoms or glucose >200 mg/dL underwent fasting glucose or OGTT evaluation. Additional samples will be drawn in the case of drug withholding (see protocol: drug withholding Section 4.5.2 of the protocol in Appendix 16.1.1).
10. The assessments at month 72 were repeated every 6 months.

Randomisation

The participants were to be randomised 1:1 to receive either teplizumab or placebo. Treatment assignment was to be determined by randomisation lists created using two stratification parameters:

1) TrialNet (the protocol) study site and

2) age (<18 and >=18 years of age). The block size used for each substratum to create the randomisation lists was 4. Randomisation lists were created using the SAS procedure PLAN. A detailed description of the randomisation method was to be stored by TrialNet Coordinating Center (TNCC).

Blinding

Both participants and investigators were to be masked to the treatment assignment. The intervention protocol was to be conducted at approved TrialNet clinical sites. All blood and serum samples for the primary and secondary outcome determinations were sent to the TrialNet Core Laboratories for analysis. Clinical laboratory tests for determining eligibility for study drug infusion were to be performed at the local sites.

Emergency unmasking was to occur upon notification of the TrialNet Central Pharmacy and TNCC via the 24-hour emergency number and approval by TrialNet Chair, NIDDK TrialNet program officer, or TrialNet Medical Monitor. Non-emergent unmasking was to occur upon notification of the TNCC and approval TrialNet Chair or NIDDK TrialNet program officer. If unmasking was approved, the study sponsor and appropriate TrialNet committees were not to be unmasked.

As per the study's Pharmacy Manual, all kits (e.g, treatment kits and bulk supply kits), either active study drug or placebo, had unique kit numbers. The kits were identified by a 6-digit kit number on the label and each vial within the kit had the same 6-digit number as the kit. The site and the TrialNet Coordinating Center (TNCC) were blinded as to which kits were placebo and which kits were active drug as placebo and teplizumab vials were visually identical and indistinguishable regarding which kits contained active drug versus placebo.

The formulation buffer for the teplizumab solution was 10 mM sodium phosphate, 150 mM sodium chloride, and 0.05 mg/mL Tween 80. The solution had a pH of 6.1 and was colourless. The formulation buffer solution was also used for the placebo.

Participants, study personnel, and laboratory personnel were blinded to treatment.

Patient population

Enrolled participants (in US, Canada, and Germany) were aged 8 to 45 years and were identified through the TrialNet TN-01 Pathway to Prevention Trial. The participants were at high risk of developing T1D on the basis of indicators including:

Having a relative who had been diagnosed with T1D,

Abnormal glucose tolerance at baseline, 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 oral glucose tolerance test (OGTT) ≥200 mg/dL,

- Presence of 2 or more T1D-related autoantibodies on 2 occasions. The second occasion must occur within the 6 months prior to study drug administration but did not need to involve the same 2 autoantibodies as found on the first occasion. The T1D-related autoantibodies tested for their presence were: anti-GAD65, anti-ICA512, micro-insulin autoantibody (mIAA), ZnT8, ICA.

A selection of criteria for exclusion from the trial included:

- Diagnosis of diabetes, Current use of non-insulin pharmaceuticals that affect glycemic control.
- Lymphopenia, or Neutropenia or Thrombocytopenia or Anemia,
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or Total bilirubin >1.5 x upper limit of normal (ULN). International normalization ratio (INR) >0.1 above ULN at the study center's laboratory.
- Chronic active infection, or vaccination with a live virus or killed virus within 8 weeks or 4 weeks of randomization, respectively.
- A history of infectious mononucleosis within the 3 months prior to enrolment, acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV) or serological evidence of current or past HIV, hepatitis B or hepatitis C infection.
- Pregnancy or anticipated getting pregnant, or lactating.
- Chronic use of steroids or other immunosuppressive agents, Prior OKT®3 or other anti-CD3 treatment or administration of an mAb within the year before randomization.

a. Objectives and estimands

Primary objective

The primary objective of the study was to determine whether intervention with teplizumab will delay the development of T1DM in high-risk autoantibody positive non-diabetic relatives of patients with T1DM.

The primary endpoint was defined as the difference in hazard ratio of diabetes onset between the Teplizumab treatment group and placebo group. The primary endpoint was tested as follows: H0: HRTeplizumab ≥ HRplacebo against the alternative H1: HRTeplizumab < HRplacebo where HRTeplizumab, HRplacebo denote hazard rates of diabetes onset in the Teplizumab treatment group and placebo group respectively. The hypotheses were tested using a one-sided, 0.025 level of significance.

Estimand for the primary objective

The estimand framework was not used for the primary objective in the study TN-10.

Statistical methods for estimation and sensitivity analysis on primary estimand

The estimand framework was not applied.

Analysis set

The intention-to-treat (ITT) population was used for primary analyses on efficacy and consisted of all randomised subjects.

Multiplicity control

The primary efficacy endpoint was tested at one-sided 0.025 level. No multiple testing procedure (MTP) was defined.

Main analysis methods for primary efficacy endpoint

According to the CSP amendment (dated 25 June 2014), the final analysis was to be conducted after at least n=40 T1D events had occurred, and the last subject had had at least 1 post-baseline visit. The data cutoff date for the final analysis was late 2018.

The time to T1D was analysed using the Cox Proportional Hazards (PH) model with discrete time intervals at 3 months, 6 months, and subsequent 6-months OGTT intervals. The test of treatment effect was adjusted for the design strata as well age at enrolment. Subjects who were lost to follow-up before developing T1D or were being followed at the study closure were censored at the last OGTT measurement or physical examination, whichever was later.

The cumulative incidence of T1D onset over time since randomisation was also to be estimated for each treatment group using the Kaplan-Meier method.

Sensitivity analyses on the primary efficacy endpoint

Prespecified sensitivity analyses included a tipping point analysis. To deal with the potential loss of drug effect, the treatment arms were also to be compared at 5 years, as if the study did follow the original plan (i.e., had the study progressed according to the original plan with the minimum accrual, 50% of the subjects would have been followed for 4 years and 50% for 5 years).

Performed sensitivity analyses included a worst-case imputation (i.e., imputation of T1D event) for subjects who withdrew consent or were lost to follow-up and imputation of a follow-up time of 12 months for subjects with <12 months of follow-up, respectively. These were not prespecified.

Subgroup analyses

Subgroup analyses on the primary efficacy endpoint were specified in the SAP addendum. The results were to be presented by means of forest plots and Kaplan-Meier graphs.

Handling of missing data

The methodology employed in analysing the primary efficacy endpoint was to utilise whatever follow-up that had been recorded for each subject (i.e., maximum utilisation of follow-up time).

Sample size determination

The sample size was based on the primary efficacy endpoint. The hazard and accrual rates for the control group were estimated from the TrialNet Natural History (TN-01). Based on TN-01, 55% of the subjects enrolled were to constitute the age group <18 years, and the weighted average hazard rate and median time to T1D for the control group was projected to be 0.209 per year and 3.31 years, respectively.

To achieve statistical power of 80% for a one-sided Wald test at the 0.025 significance level and with an assumed effect size of 50% reduction of T1D, an estimated enrolment and follow-up of enough participants to observe n=69 T1D events were anticipated.

In a CSP amendment (dated 25 June 2014), the assumed effect size of reduction of T1D was changed to 60%. The sample size calculation according to this amendment also involved changes in the definitions of age strata and the related assumptions. To achieve statistical power of 80% for a one-sided Wald test at the 0.025 significance level and with an assumed effect size of 60% reduction of T1D, an estimated enrolment and follow-up of enough participants to observe n=40 T1D events were anticipated.

Interim analysis

According to the CSP issued 22 June 2010, interim analyses on the primary efficacy endpoint were to be conducted periodically for assessment of effectiveness and safety. If a group sequential stopping boundary was crossed, the Data and Safety Monitoring Board (DSMB) could have decided to terminate the trial early. The Lan and DeMets spending function with an O'Brien-Fleming boundary was used to protect the type 1 error probability for the primary outcome analyses, and to assess the significance of the interim results periodically during the trial.

The boundaries were based on a method described by Lachin (Lachin, 2009). The study was to be stopped if the futility of rejecting the null hypothesis was observed.

According to the CSP amendment dated 25 June 2014, an interim analysis was to be conducted when 50% of the expected number of cases of T1D had been observed. The interim analysis outcome was reviewed by the DSMB for assessment of effectiveness and safety.

Secondary objective

To determine whether treatment with teplizumab was superior to placebo with respect to changes in C-peptide responses as indicator of beta cell function.

Estimand for the secondary objective

The estimand framework was not used for the secondary objective in the study TN-10.

In T1D, a reduction of endogenous insulin production occurs as beta cell function is declining. C-peptide is co-secreted in a 1:1 molar ratio with endogenous insulin. Therefore, C-peptide can be used to assess the endogenous insulin secretion and beta cell function. To determine whether treatment with teplizumab was superior to placebo in delaying beta cell deterioration, C-peptide responses to oral glucose, were obtained from timed collections during longitudinal tests.

Statistical methods for estimation and sensitivity analysis on the secondary estimand

The estimand framework was not applied and no MTP was defined.

The secondary efficacy endpoint: change in the mean 2-hour C-peptide AUC from baseline to month 3, month 6, month 12, and consecutive 6-month windows, adjusted for the baseline C-peptide response, was to be analysed by means of a linear mixed effects repeated measures (MMRM) model.

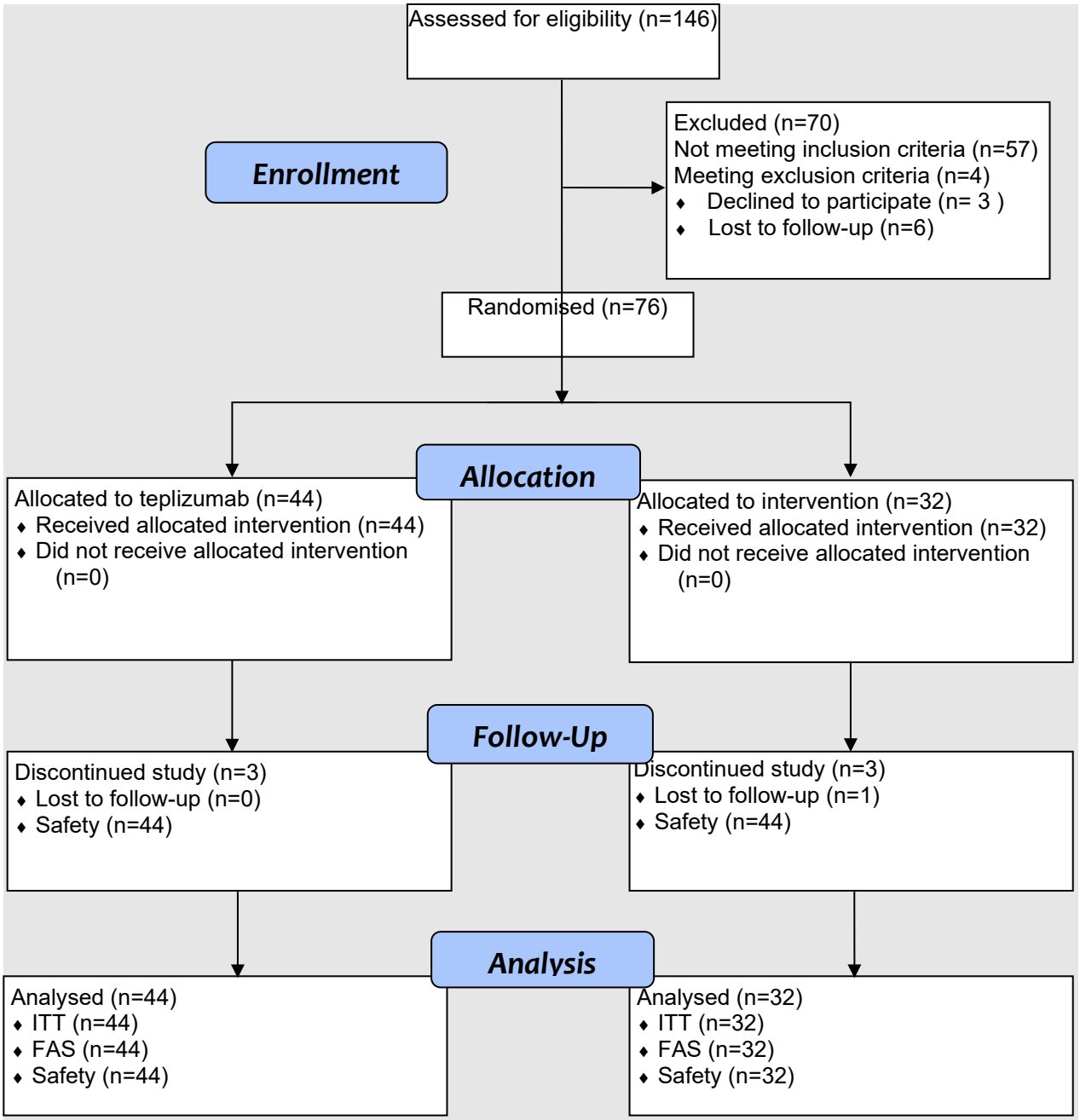
Missing values on C-peptide AUC were to be handled by means of a compete case approach and by multiple imputation (MI).

6.3.2.1.3. Results

Participant flow and numbers analysed

The study initiation date is 18 July 2011, which is the date for the enrolment of the first participant. The last subject completed the 30 November 2018, which is the primary completion date.

Figure 13: Participant flow



Abbreviations: ITT=intent to treat, FAS=full analysis set, Safety=safety population

Seventy subjects were screen failures. A listing 1.1.1. includes subject IDs for "screen failures". 30 screen failure subjects are described in the list 1.1.3. Of these subjects, 27 subjects did not meet

inclusion criteria, 1 had diabetes and 2 were excluded for unknown reasons (subject to committee decision).

Deviations from study plan

Protocol amendments

There were amendments to the protocol initial study protocol (dated 13 November 2009). The amendments are mentioned in the CSR body, and all versions of the protocol are included in an appendix to the study protocol. Due to slower enrolment rate, the original protocol (n= 144 subjects) with an estimated minimum of T1D events (n=69), was revised in June 2014 to reduce the estimated minimum number of events to n=40 (sample size to 71). OGTT-related inclusion criteria were modified, along with other inclusion and exclusion criteria in that revision. Other amendments to the study protocol were updates on study results from other studies, and changes of wording for clarification purposes.

Protocol deviations

Details on all protocol deviations are provided in an EOT listing. The applicant stated that there were no significant protocol deviations that could potentially have affected the study results or interpretation.

Baseline data

Table 9 Demographic and baseline characteristics (ITT population)

Characteristic	Teplizumab N=44	Placebo N=32	Total N=76
Age, year			
mean (SD)	19 (11.9)	18 (11.1)	19 (11.5)
median (min, max)	14 (8.5, 49.5)	13 (8.6, 45.0)	14 (8.5, 49.5)
Age group, n (%)			
<18 years	29 (65.9)	26 (81.3)	55 (72.4)
≥18 years	15 (34.1)	6 (18.8)	21 (27.6)
Sex, n (%)			
Female	19 (43.2)	15 (46.9)	34 (44.7)
Male	25 (56.8)	17 (53.1)	42 (55.3)
Covariate strata			
<18 years and confirmed OGTT	24 (54.5)	23 (71.9)	47 (61.8)
<18 years and unconfirmed OGTT	5 (11.4)	3 (9.4)	8 (10.5)
≥18 years and confirmed OGTT	15 (34.1)	6 (18.8)	21 (27.6)

Ethnicity, n (%)			
Hispanic or Latino	1 (2.3)	1 (3.1)	2 (2.6)
Not Hispanic or Latino	43 (97.7)	29 (90.6)	72 (94.7)
Unknown	0	2 (6.3)	2 (2.6)
Race			
White	44 (100)	30 (93.8)	74 (97.4)
Asian	0	1 (3.1)	1 (1.3)
Multiple	0	1 (3.1)	1 (1.3)
Weight, kg			
mean (SD)	58 (24.7)	57 (19.5)	57 (22.5)
median (min, max)	52 (26.6, 143.5)	61 (27.2, 117.1)	55 (26.6, 143.5)
BMI, kg/m^2			
mean (SD)	22.0 (6.38)	22.1 (4.39)	22.0 (5.59)
median (min, max)	20.0 (14.7, 43.7)	21.6 (16.0, 34.6)	21.0 (14.7, 43.7)
BMI subgroup			
< median	26 (59.1)	12 (37.5)	38 (50.0)
≥ median	18 (40.9)	20 (62.5)	38 (50.0)
Relationship with person with T1D,[a] n (%)			
Sibling	30 (68.2)	19 (59.4)	49 (64.5)
Offspring	7 (15.9)	6 (18.8)	13 (17.1)
Parent	7 (15.9)	6 (18.8)	13 (17.1)
Sibling and another first-degree relative	3 (6.8)	3 (9.4)	6 (7.9)
Second-degree relative	5 (11.4)	7 (21.9)	12 (15.8)
Third-degree relative or further removed	1 (2.3)	2 (6.3)	3 (3.9)

Abbreviations: BMI=body mass index, ITT=intent to treat, OGTT=oral glucose tolerance test, SD=standard deviation, T1D=type 1 diabetes.
[a]First-degree relative is defined as having at least 50% of shared genes (e.g., full siblings, parents, offspring) with the subject; second-degree relative is defined as having 25% of shared genes (e.g., grandparents, grandchildren, half-siblings, aunts and uncles); third-degree relatives is defined as having 12.5% of shared genes (e.g., first cousins, great grandparents and great grandchildren). A subject can have multiple relationships to persons with T1D; in such case, all relevant relationship groups are included in the calculation.
Source: EOT Table 1.2

The age range among all randomised subjects was from 8.5 to 49.5 years. The median age was 14 years in the teplizumab group and 13 years in the placebo group. The males were 55.3% of the population, and almost all participants were white (97.4%). The teplizumab group had a lower proportion of participants less than 18 years of age compared with the placebo group (65.9% versus 81.3%, respectively) and a higher proportion of participants with BMI below median (59.1% versus 37.5%, respectively). Mean (SD) BMI at baseline was 19.10 (3.72) kg/m^2 and 20.74 (3.27) kg/m^2 in the teplizumab and control groups, respectively, (see Table 20).

In participants ≥18 years of age, the mean (SD) body weight at baseline was 81.0 (24.5) kg in the teplizumab group and 80.7 (19.0) kg in the control group. Mean (SD) BMI at baseline was 27.45 (6.94) kg/m^2 and 27.85 (4.12) kg/m^2 in the teplizumab and control groups, respectively.

Table 10. TN-10 study: Body weight and BMI at baseline by age group - ITT Population

	Teplizumab (N=44)	Placebo (N=32)	Total (N=76)
Subjects with age < 18	29	26	55
Body Weight at baseline (kg)			
Number	29	26	55
Mean (SD)	45.9 (14.2)	51.5 (15.3)	48.6 (14.9)
Median	43.5	50.8	45.9
Min ; Max	27 ; 84	27 ; 74	27 ; 84
Baseline Weight by category (kg) [n (%)]			
Number	29	26	55
< 50	20 (69.0)	13 (50.0)	33 (60.0)
50 to <100	9 (31.0)	13 (50.0)	22 (40.0)
≥100	0	0	0
BMI at baseline (kg/m2)			
Number	29	26	55
Mean (SD)	19.10 (3.72)	20.74 (3.27)	19.88 (3.58)
Median	18.00	21.10	18.90
Min ; Max	14.7 ; 27.6	16.0 ; 28.2	14.7 ; 28.2
BMI at baseline by category (kg/m2) [n (%)]			
Number	29	26	55
< 18.5	16 (55.2)	8 (30.8)	24 (43.6)
18.5 to <25	9 (31.0)	16 (61.5)	25 (45.5)
25 to <30	4 (13.8)	2 (7.7)	6 (10.9)
≥30	0	0	0
BMI Z-score at baseline (kg/m2)			
Number	29	26	55
Mean (SD)	0.04 (1.23)	0.69 (0.57)	0.35 (1.02)
Median	0.06	0.61	0.52
Min ; Max	-2.9 ; 2.0	-0.4 ; 1.9	-2.9 ; 2.0
Subjects with age ≥ 18	15	6	21
Body Weight at baseline (kg)			
Number	15	6	21
Mean (SD)	81.0 (24.5)	80.7 (19.0)	80.9 (22.6)
Median	74.0	75.7	74.5
Min ; Max	52 ; 144	65 ; 117	52 ; 144

The study subjects were identified by having at least one first-degree or second-degree relative with T1D. The amount of study subjects with siblings is 68,2% for the teplizumab group vs 59% for the placebo group.

The types and frequencies of T1D autoantibodies as well as HLA DR3 and DR4 genotypes are presented in Table 21, eCTD 5.3.5.1 CSR Body. Approximately half of the subjects had 4 (34.2%) or 5 (18.4%) positive autoantibodies at baseline. A small proportion (10.5%) of subjects had neither the DR3 nor DR4 allele.

Table 11 Type and frequency of autoantibodies at baseline and presence of HLA risk alleles (ITT population)

	Teplizumab N=44	**Placebo** N=32	**Total** N=76
	n (%)	n (%)	n (%)
Autoantibodies			
Anti-GAD65			
Negative	4 (9.1)	4 (12.5)	8 (10.5)
Positive	40 (90.9)	28 (87.5)	68 (89.5)
mIAA			
Negative	25 (56.8)	21 (65.6)	46 (60.5)
Positive	19 (43.2)	11 (34.4)	30 (39.5)
Anti-IA-2			
Negative	18 (40.9)	8 (25.0)	26 (34.2)
Positive	26 (59.1)	24 (75.0)	50 (65.8)
ICA			
Negative	15 (34.1)	4 (12.5)	19 (25.0)
Positive	29 (65.9)	28 (87.5)	57 (75.0)
Anti-ZnT8			
Negative	12 (27.3)	8 (25.0)	20 (26.3)
Positive	32 (72.7)	24 (75.0)	56 (73.7)
Number of positive autoantibodies			
1	1 (2.3)[a]	0	1 (1.3)[a]
2	12 (27.3)	7 (21.9)	19 (25.0)
3	11 (25.0)	5 (15.6)	16 (21.1)
4	12 (27.3)	14 (43.8)	26 (34.2)
5	8 (18.2)	6 (18.8)	14 (18.4)
HLA risk alleles			
Neither DR3 nor DR4	5 (11.4)	3 (9.4)	8 (10.5)
	n (%)	n (%)	n (%)
DR3 only	10 (22.7)	8 (25.0)	18 (23.7)
DR4 only	16 (36.4)	14 (43.8)	30 (39.5)
Both DR3 and DR4	11 (25.0)	7 (21.9)	18 (23.7)
Missing	2 (4.5)	0	2 (2.6)
DR3 absent	21 (50.0)	17 (53.1)	38 (51.4)
DR3 present	21 (50.0)	15 (46.9)	36 (48.6)
DR absent	15 (35.7)	11 (34.4)	26 (35.1)
DR4 present	27 (64.3)	21 (65.6)	48 (64.9)

Abbreviations: Anti-GAD65=anti-glutamic acid decarboxylase antibody, anti-IA-2=anti-islet antigen 2 antibody, anti-ZnT8=anti-zinc transporter 8 antibody, HLA=human leukocyte antigen, ICA=islet cell antibody, ITT=intent to treat, mIAA=micro-insulin autoantibody.
[a]Subject 558054 had 1 definite autoantibody detected, but the titer for the second autoantibody was borderline between positive and negative. This subject was permitted to enroll in the study at the Investigator's discretion.
Note: First-degree relative: at least 50% of shared genes (e.g., full siblings, parents, offspring); second-degree relative: 25% of shared genes (e.g., grandparents, grandchildren, half-siblings, aunts and uncles); third-degree relatives: 12.5% of shared genes (e.g., first cousins, great grandparents and great grandchildren). Subjects can have multiple relationship to persons with T1D; in such case, subjects are presented for all relevant relationship groups.
Note: Autoantibody is counted positive by the following cutoff values: anti-GAD65 >20 units/mL, anti-IA-2 >5 units/mL, mIAA >0.010, ICA ≥10 JDF units, anti-ZnT8 >0.020.
Source: EOT Table 1.2

Metabolic parameters (changes in glucose and C-peptide levels, glucose and C-peptide AUC, peak C-peptide) are presented in Table 22, eCTD 2.7.3.

Table 12 Baseline metabolic characteristics

	All N=76	Placebo N=32	Teplizumab N=44
Sex			
Female	34 (44.74%)	15 (46.88%)	19 (43.18%)
Male	42 (55.26%)	17 (53.13%)	25 (56.82%)
Race			
Asian	2 (2.63%)	2 (6.25%)	0 (0.00%)
Hispanic	2 (2.63%)	1 (3.13%)	1 (2.27%)
White	72 (94.74%)	29 (90.63%)	43 (97.73%)
Age, mean (SD)	18.52 (11.51)	17.53 (11.10)	19.24 (11.87)
BMI at baseline, mean (SD)	22.01 (5.60)	22.08 (4.39)	21.95 (6.39)
Log BMI at baseline, mean (SD)	3.06 (0.23)	3.08 (0.19)	3.05 (0.26)
BMI-for-age z-score, mean (SD)	0.74 (1.23)	0.98 (0.75)	0.55 (1.47)
Mean Glucose AUC, mean (SD)	159.46 (22.69)	155.31 (22.94)	162.47 (22.28)
Mean C-peptide AUC, mean (SD)	1.94 (0.79)	1.89 (0.72)	1.97 (0.84)
Peak C-peptide, mean (SD)	2.68 (1.09)	2.58 (0.99)	2.75 (1.16)
Index60, mean (SD)	1.95 (0.58)	1.85 (0.64)	2.02 (0.53)
DPTRS, mean (SD)	8.17 (1.02)	8.10 (1.06)	8.22 (1.01)
C-peptide AUC/Glucose AUC (x1000)	12.14 (4.71)	12.08 (4.34)	12.18 (5.01)
log(C-peptide AUC/Glucose AUC)	-4.48 (0.36)	-4.47 (0.34)	-4.48 (0.38)
30 - 0 min C-peptide	1.07 (0.61)	1.11 (0.61)	1.04 (0.62)
60 - 0 min C-peptide	1.56 (0.80)	1.50 (0.69)	1.60 (0.87)
120 - 60 min C-peptide	0.29 (0.69)	0.18 (0.84)	0.37 (0.56)
30 - 0 min glucose	70.07 (27.63)	69.88 (22.47)	70.20 (31.10)
60 - 0 min glucose	83.92 (35.75)	77.53 (37.21)	88.57 (34.33)
120 - 60 min glucose	-26.66 (36.51)	-25.81 (38.26)	-27.27 (35.62)
Glucose, mean (SD)			
0 minutes	95.32 (10.71)	94.94 (13.69)	95.59 (8.05)
30 minutes	165.38 (28.55)	164.81 (24.17)	165.80 (31.62)
60 minutes	179.24 (35.86)	172.47 (38.50)	184.16 (33.40)
90 minutes	169.26 (38.96)	163.16 (44.27)	173.70 (34.44)
120 minutes	152.58 (32.12)	146.66 (34.89)	156.89 (29.62)
C-peptide, mean (SD)			
0 minutes	0.61 (0.29)	0.61 (0.31)	0.61 (0.27)
30 minutes	1.67 (0.76)	1.71 (0.79)	1.65 (0.75)
60 minutes	2.16 (0.97)	2.11 (0.89)	2.21 (1.02)
90 minutes	2.38 (1.10)	2.28 (0.98)	2.45 (1.19)
120 minutes	2.46 (1.06)	2.29 (0.97)	2.58 (1.11)

Extracted from Sims et al. Diabetes 2021 (57).
DPTRS = Diabetes Prevention Trial Type 1 Risk Score is a composite of glucose and C-peptide measurements and logBMI and age; Index 60 = a composite measure of fasting and 60-minute C-peptide and 60-minute glucose.

Fasting plasma glucose and 2-hour plasma glucose after OGTT at baseline are provided by treatment group in Table 23, including Mean (SD) (also present in Table 22 above) and also Median and Min:Max values. In Table 24, the placebo group is separated by time to T1D diagnosis.

Table 13. TN-10: Fasting plasma glucose and 2 hour OGTT plasma glucose at baseline - ITT population

Laboratory parameter (unit)	Teplizumab (N=44)	Placebo (N=32)
Baseline Glucose (mg/dL)		
Fasting		
Number	44	32
Mean (SD)	95.7 (8.3)	95.7 (11.5)
Median	94.5	96.5
Min ; Max	79 ; 115	64 ; 119
OGTT 30 minutes		
Number	44	32
Mean (SD)	165.8 (31.6)	164.8 (24.2)
Median	160.5	165.0
Min ; Max	99 ; 237	121 ; 223
OGTT 60 minutes		
Number	44	32
Mean (SD)	184.3 (33.5)	172.5 (38.5)
Median	185.5	172.5
Min ; Max	97 ; 244	77 ; 233
OGTT 90 minutes		
Number	44	32
Mean (SD)	173.7 (34.4)	163.2 (44.3)
Median	174.5	158.5
Min ; Max	98 ; 242	82 ; 244
OGTT 120 minutes		
Number	44	32
Mean (SD)	156.9 (29.6)	146.7 (34.9)
Median	151.5	144.0
Min ; Max	87 ; 240	81 ; 217

PGM=PRODOPS/SAR446681/MGA031_005/QREG/REPORT/PGM/lab_gluc_i_t.sas
OUT=REPORT/OUTPUT/lab_gluc_base_i_t_i.rtf (13JUN2025 11:30)

Table 14. TN-10: Fasting plasma glucose and 2 hour OGTT plasma glucose at baseline by time to T1D diagnosis in placebo group - ITT population

Laboratory parameter (unit)	Teplizumab (N=44)	Patients without T1D diagnosis before 6 months (N=24)	Placebo with T1D diagnosis before 6 months (N=8)	Total (N=76)
Baseline Glucose (mg/dL)				
Fasting				
Number	44	24	8	76
Mean (SD)	95.7 (8.3)	94.4 (11.4)	99.4 (11.6)	95.7 (9.7)
Median	94.5	92.5	100.5	94.8
Min ; Max	79 ; 115	64 ; 113	80 ; 119	64 ; 119

Laboratory parameter (unit)	Teplizumab (N=44)	Patients without T1D diagnosis before 6 months (N=24)	Placebo with T1D diagnosis before 6 months (N=8)	Total (N=76)
OGTT 30 minutes				
Number	44	24	8	76
Mean (SD)	165.8 (31.6)	164.1 (26.0)	166.9 (18.8)	165.4 (28.5)
Median	160.5	165.0	167.5	162.0
Min ; Max	99 ; 237	121 ; 223	132 ; 189	99 ; 237
OGTT 60 minutes				
Number	44	24	8	76
Mean (SD)	184.3 (33.5)	167.3 (33.4)	188.1 (50.4)	179.3 (35.9)
Median	185.5	170.0	200.0	182.0
Min ; Max	97 ; 244	92 ; 223	77 ; 233	77 ; 244
OGTT 90 minutes				
Number	44	24	8	76
Mean (SD)	173.7 (34.4)	158.0 (39.6)	178.8 (56.2)	169.3 (39.0)
Median	174.5	153.0	189.5	168.0
Min ; Max	98 ; 242	82 ; 244	91 ; 239	82 ; 244
OGTT 120 minutes				
Number	44	24	8	76
Mean (SD)	156.9 (29.6)	143.0 (32.3)	157.6 (42.3)	152.6 (32.1)
Median	151.5	142.0	171.5	147.0
Min ; Max	87 ; 240	81 ; 217	91 ; 197	81 ; 240

PGM=PRODOPS/SAR446681/MGA031_005/QREG/REPORT/PGM/lab_gluc_i_t.sas
OUT=REPORT/OUTPUT/lab_gluc_base_t1d_6m_i_t_i.rtf (13JUN2025 11:30)

The most common medical history was allergies, EOT Table 1.5 in eCTD 5.3.5.1. A history of autoimmune diseases was rare. Concomitant medications taken by the subjects were listed in an EOT listing (eCTD 5.3.5.1).

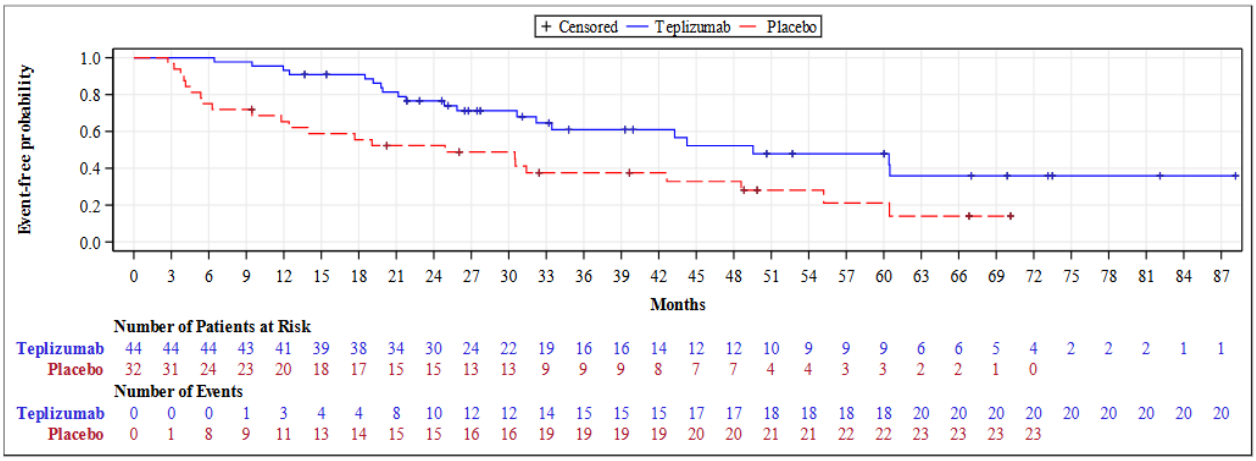
Concerning treatment compliance, study drugs were administered via IV infusion at each site by qualified personnel. The date and time of each study drug administration for each subject are detailed in EOT Listing 1.3.1. Deviations from the protocol-specified dose and time window are documented in EOT Listing 1.1.6. Most subjects received study drug treatment as planned. Few doses were withheld or reduced for protocol-specified reasons (see Section 12.1.2).

Outcomes and estimation

Primary objective

The primary objective of the study was to determine whether treatment of at-risk subjects with teplizumab resulted in a delay of T1D. The primary endpoint was the time from randomisation to T1D diagnosis or last contact. The cumulative incidence of diabetes onset over time from randomisation within each treatment group was estimated using the Kaplan-Meier method (proportion surviving diabetes-free as a function of time), see Figure 15.

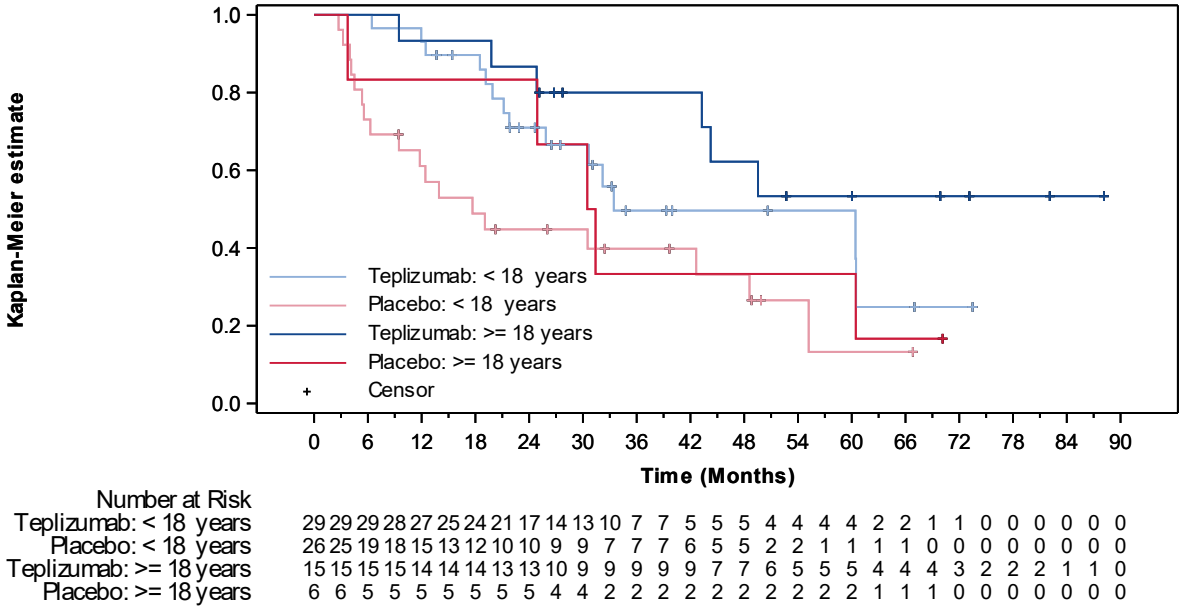
Figure 14 Kaplan-Meier curve of time to T1D diagnosis by treatment group (ITT population)



Abbreviations: ITT=intent to treat, T1D=type 1 diabetes
Source: EOT Figure 2.1.1

Sub-groups analyses were conducted based on age (<18 years; ≥18 years) for the primary efficacy endpoint of time to onset of Stage 3 T1D. Figure 16 presents a comparison of all subgroups by age (<18 years; ≥18 years) and treatment allocation (teplizumab versus placebo). In both age subgroups, teplizumab demonstrated greater delay in progression to Stage 3 T1D compared to placebo (HR=0.47 [95% CI: 0.23 to 0.96] in participants <18 years of age; HR=0.40 [95% CI: 0.12 to 1.31] in participants ≥18 years of age). The limited sample size, particularly in participants >18 years of age, warrants cautious interpretation.

Figure 15. TN-10 study: Kaplan-Meier curves of time to onset by age and treatment group - ITT population



Criteria for T1D onset were based on glucose testing or the presence of unequivocal hyperglycemia with acute metabolic decompensation, such as DKA. For glucose testing, one of the following criteria had to be met on 2 occasions as soon as possible but ≥1 day apart:

• Symptoms of diabetes plus a casual plasma glucose concentration >200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

• Fasting plasma glucose ≥126 mg/dL (7 mmol/L). Fasting was defined as no caloric intake for at least 8 hours.

• 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L). The test had to be performed using a glucose load containing the equivalent of 1.75 g/kg body weight to a maximum of 75 g anhydrous glucose dissolved in water. It was preferred that at least one of the 2 testing occasions involved an OGTT.

Subjects who were lost to follow- up before developing T1D or were being followed at the study closure were censored at the last OGTT measurement or physical examination, whichever was later.

The final analysis was conducted through the cut-off date of 30 November 2018, after a sufficient number of events (40 or more), i.e., onset of T1D, had occurred and the last subject had had at least 1 post-baseline visit, in order to achieve the planned 80% statistical power for the primary analysis (see Section 9.7.2). The median times to T1D were 24.9 months in the placebo group and 49.5 months in the teplizumab groups (EOT Table 2.1.1). The hazard ratio obtained from the Cox model was 0.41 (95% CI: 0.22, 0.78, p=0.0066) (EOT Table 2.1.2). The yearly interval and cumulative hazard ratios are shown in Table 25.

Table 15 Yearly interval and cumulative hazard ratios of time to T1D onset (ITT population)

	No. (%) T1D diagnosed			Hazard Ratio (95% CI)	
Year	Teplizumab	Placebo	Chi Square Test	Cumulative	Interval
1	4 (9.1)	13 (40.6)	9.16	0.177 (0.0576, 0.5432)	0.177 (0.0576, 0.5432)
2	8 (18.2)	3 (9.4)	5.92	0.394 (0.1859, 0.8340)	1.215 (0.3224, 4.5806)
3	3 (6.8)	3 (9.4)	6.58	0.411 (0.2087, 0.8108)	0.502 (0.1012, 2.4868)
4	3 (6.8)	2 (6.3)	6.09	0.452 (0.2404, 0.8491)	0.853 (0.1426, 5.1067)
5	2 (4.5)	2 (6.3)	7.16	0.440 (0.2409, 0.8026)	0.338 (0.0474, 2.4025)

Abbreviations: CI=confidence interval, ITT=intent to treat, T1D=type 1 diabetes
Source: EOT Table 2.1.3

Table 26 provides the demographics and baseline characteristics of the 8 subjects in the placebo group who were diagnosed with Stage 3 T1D <6 months, compared to the rest of the placebo group and to the teplizumab treatment group.

Table 16 TN-10 study: Demographics and baseline characteristics in the placebo (with Stage 3 T1D diagnosis before or after 6 months) and teplizumab group - ITT population

Variable (Unit) Characteristic/Statistic	Teplizumab N = 44	Placebo with Stage 3 T1D diagnosis after 6 months N = 24	Placebo with Stage 3 T1D diagnosis before 6 months N = 8	Total N = 76
Age (years)				
n	44	24	8	76
Mean	19.24	18.12	15.77	18.52
SD	11.871	11.500	10.297	11.507
Min	8.5	8.6	9.2	8.5
Median	14.21	14.35	12.53	13.90
Max	49.5	45.0	41.0	49.5
Age group [n (%)]				
n	44	24	8	76
< 18	29 (65.9)	19 (79.2)	7 (87.5)	55 (72.4)
>= 18	15 (34.1)	5 (20.8)	1 (12.5)	21 (27.6)
Strata [n (%)]				
n	44	24	8	76
< 18 & Confirmed OGTT	24 (54.5)	16 (66.7)	7 (87.5)	47 (61.8)
< 18 & Unconfirmed OGTT	5 (11.4)	3 (12.5)	0	8 (10.5)
>= 18 & Confirmed OGTT	15 (34.1)	5 (20.8)	1 (12.5)	21 (27.6)
Sex [n (%)]				
n	44	24	8	76
Female	19 (43.2)	11 (45.8)	4 (50.0)	34 (44.7)
Male	25 (56.8)	13 (54.2)	4 (50.0)	42 (55.3)
Ethnicity [n (%)]				
n	44	24	8	76
Hispanic or Latino	1 (2.3)	1 (4.2)	0	2 (2.6)
Not Hispanic or Latino	43 (97.7)	22 (91.7)	7 (87.5)	72 (94.7)
Unknown	0	1 (4.2)	1 (12.5)	2 (2.6)
Race [n (%)]				
n	44	24	8	76
White	44 (100)	23 (95.8)	7 (87.5)	74 (97.4)
Asian	0	1 (4.2)	0	1 (1.3)
Multiple	0	0	1 (12.5)	1 (1.3)
Weight (kg)				
n	44	24	8	76
Mean	57.86	57.85	54.41	57.49
SD	24.704	21.104	14.733	22.536
Min	26.6	27.2	38.9	26.6
Median	51.95	64.45	50.75	55.43
Max	143.5	117.1	83.2	143.5
Height (cm)				
n	44	24	8	76
Mean	159.633	158.768	156.450	159.025
SD	15.5724	16.8328	9.7251	15.3524
Min	128.00	129.90	137.50	128.00
Median	161.200	161.000	158.000	160.400
Max	193.90	184.00	170.00	193.90
BMI (kg/m2)				
n	44	24	8	76
Mean	21.95	22.09	22.03	22.00
SD	6.377	4.496	4.357	5.594
Min	14.7	16.0	17.1	14.7
Median	19.95	21.75	21.40	21.00
Max	43.7	34.6	28.8	43.7
BMI group [n (%)]				

Variable (Unit) Characteristic/Statistic	Teplizumab N = 44	Placebo with Stage 3 T1D diagnosis after 6 months N = 24	Placebo with Stage 3 T1D diagnosis before 6 months N = 8	Total N = 76
n	44	24	8	76
< Median	26 (59.1)	9 (37.5)	3 (37.5)	38 (50.0)
>= Median	18 (40.9)	15 (62.5)	5 (62.5)	38 (50.0)
Relationship to person with T1D [n (%)]				
n	44	24	8	76
Sibling	30 (68.2)	12 (50.0)	7 (87.5)	49 (64.5)
Offspring	7 (15.9)	5 (20.8)	1 (12.5)	13 (17.1)
Parent	7 (15.9)	5 (20.8)	1 (12.5)	13 (17.1)
Sibling and another first-degree relative	3 (6.8)	2 (8.3)	1 (12.5)	6 (7.9)
Second-degree relative	5 (11.4)	7 (29.2)	0	12 (15.8)
Third-degree relative or further removed	1 (2.3)	2 (8.3)	0	3 (3.9)
Autoantibodies				
Anti-GAD65				
n	44	24	8	76
Negative	4 (9.1)	3 (12.5)	1 (12.5)	8 (10.5)
Positive	40 (90.9)	21 (87.5)	7 (87.5)	68 (89.5)
Micro insulin				
n	44	24	8	76
Negative	25 (56.8)	17 (70.8)	4 (50.0)	46 (60.5)
Positive	19 (43.2)	7 (29.2)	4 (50.0)	30 (39.5)
Anti-IA-2				
n	44	24	8	76
Negative	18 (40.9)	5 (20.8)	3 (37.5)	26 (34.2)
Positive	26 (59.1)	19 (79.2)	5 (62.5)	50 (65.8)
ICA				
n	44	24	8	76
Negative	15 (34.1)	2 (8.3)	2 (25.0)	19 (25.0)
Positive	29 (65.9)	22 (91.7)	6 (75.0)	57 (75.0)
Anti-ZnT8				
n	44	24	8	76
Negative	12 (27.3)	5 (20.8)	3 (37.5)	20 (26.3)
Positive	32 (72.7)	19 (79.2)	5 (62.5)	56 (73.7)
Autoantibodies titer				
Anti-GAD65 (harmonized)				
n	44	24	8	76
Mean	320.9	407.4	157.6	331.0
SD	297.46	374.43	240.30	322.87
Min	4	1	9	1
Median	240.0	309.0	62.0	221.5
Max	1047	1278	730	1278
Micro insulin				
n	44	24	8	76
Mean	0.0307	0.0157	0.0276	0.0256
SD	0.07966	0.03946	0.03281	0.06529
Min	-0.001	-0.003	0.002	-0.003
Median	0.0070	0.0030	0.0105	0.0055
Max	0.517	0.190	0.082	0.517
Anti-IA-2 (harmonized)				
n	44	24	8	76
Mean	153.6	190.3	146.0	164.4
SD	190.35	157.67	199.14	180.05
Min	0	0	0	0

Variable (Unit) Characteristic/Statistic	Teplizumab N = 44	Placebo with Stage 3 T1D diagnosis after 6 months N = 24	Placebo with Stage 3 T1D diagnosis before 6 months N = 8	Total N = 76
Median	52.0	187.5	35.0	101.5
Max	667	556	462	667
ICA				
n	44	24	8	76
Mean	270.0	122.1	217.5	217.8
SD	647.05	148.38	434.17	518.57
Min	0	0	0	0
Median	20.0	80.0	60.0	40.0
Max	2560	640	1280	2560
Zinc Transporter				
n	44	24	8	76
Mean	0.2662	0.2284	0.1539	0.2425
SD	0.30308	0.24457	0.21303	0.27654
Min	-0.004	-0.004	-0.012	-0.012
Median	0.1565	0.1160	0.0785	0.1295
Max	1.029	0.817	0.583	1.029
Number of Autoantibodies Positive				
n	44	24	8	76
1	1 (2.3)	0	0	1 (1.3)
2	12 (27.3)	5 (20.8)	2 (25.0)	19 (25.0)
3	11 (25.0)	3 (12.5)	2 (25.0)	16 (21.1)
4	12 (27.3)	11 (45.8)	3 (37.5)	26 (34.2)
5	8 (18.2)	5 (20.8)	1 (12.5)	14 (18.4)
HLA alleles present				
n	44	24	8	76
Neither DR3 or DR4	5 (11.4)	3 (12.5)	0	8 (10.5)
DR3 only	10 (22.7)	6 (25.0)	2 (25.0)	18 (23.7)
DR4 only	16 (36.4)	9 (37.5)	5 (62.5)	30 (39.5)
Both DR3 and DR4	11 (25.0)	6 (25.0)	1 (12.5)	18 (23.7)
Missing	2 (4.5)	0	0	2 (2.6)
HLA-DR3				
n	42	24	8	74
Absent	21 (50.0)	12 (50.0)	5 (62.5)	38 (51.4)
Present	21 (50.0)	12 (50.0)	3 (37.5)	36 (48.6)
HLA-DR4				
n	42	24	8	74
Absent	15 (35.7)	9 (37.5)	2 (25.0)	26 (35.1)
Present	27 (64.3)	15 (62.5)	6 (75.0)	48 (64.9)
Glucose level at baseline (mg/dL)				
n	44	24	8	76
Mean	162.5	151.9	165.5	159.5
SD	22.29	19.73	29.87	22.70
Min	115	103	110	103
Median	164.6	151.8	172.7	160.4
Max	207	190	200	207
C-peptide AUC in 2-hour OGTT at baseline (nmol/L)				
n	44	24	8	76
Mean	1.98	1.98	1.64	1.94
SD	0.846	0.788	0.416	0.792
Min	0.6	0.7	1.1	0.6
Median	1.77	1.80	1.68	1.76

Variable (Unit) Characteristic/Statistic	Teplizumab N = 44	Placebo with Stage 3 T1D diagnosis after 6 months N = 24	Placebo with Stage 3 T1D diagnosis before 6 months N = 8	Total N = 76
Max	4.4	3.8	2.3	4.4
HbA1c at baseline (%)				
n	44	24	8	76
Mean	5.16	5.18	5.28	5.18
SD	0.334	0.297	0.089	0.305
Min	4.6	4.3	5.1	4.3
Median	5.20	5.20	5.30	5.20
Max	6.1	5.6	5.4	6.1

Secondary objectives

Regarding efficacy, the secondary objective of the study was to determine whether treatment with teplizumab was superior to placebo with respect to C-peptide responses to oral glucose, as obtained from timed collections during longitudinal tests. Assessment of treatment on mechanistic outcomes was another secondary objective.

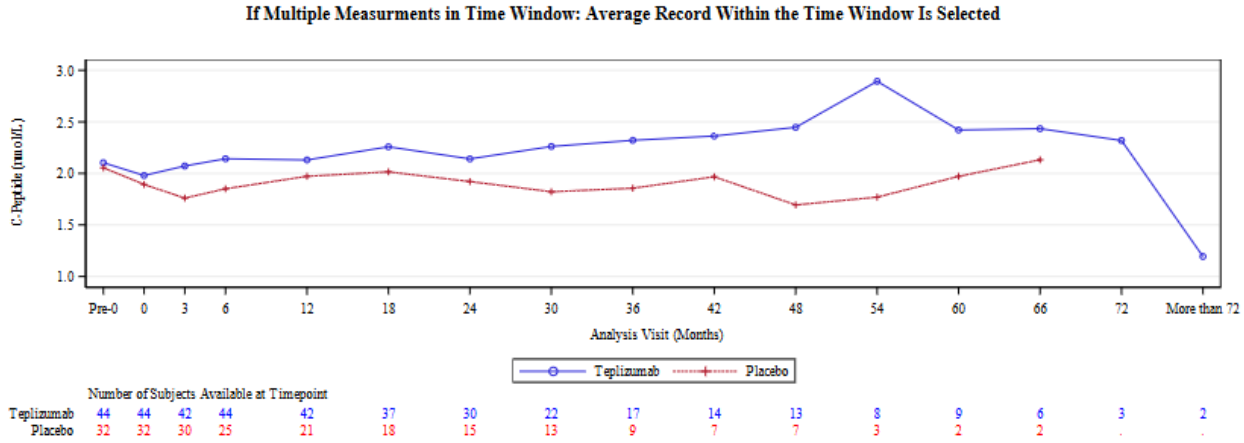
The effect of teplizumab on C-peptide response to oral glucose, was measured as the C-peptide AUC in a 2-hour OGTT (measurements at timepoints 0, 30, 60, 90, and 120 minutes). This assessment was performed at 3 months and 6 months after randomization, and then every 6 months or more frequently if clinically indicated. The C-peptide and insulin data from the OGTT were used to measure insulin secretion. The insulin, glucose, and C-peptide data from the OGTT were used to measure insulin sensitivity. Measure of glycemic control was made by HbA1c.

Subjects who were diagnosed with T1D ended study participation once diagnosed with T1D or shortly thereafter and no longer underwent further assessments. Exogenous insulin use was therefore not captured. These participants were invited to participate in the TrialNet TN01 Pathway to Prevention Study (Stage 2 T1D participants), TrialNet Long-Term Investigative Follow-Up in TrialNet (LIFT) (Stage 3 T1D participants), or the TN-10 Extension study (participants who developed Stage 3 T1D within 1 year and wished to receive open-label course of teplizumab). For the TrialNet TN10 study the applicant has only access to published data and the amount of exogenous insulin use was not reported in the publication by Sims et al.

The TN-10 Extension study enrolled 6 participants who developed Stage 3 T1D after the completion of the TN-10 study. Mean (SD) baseline average daily use of exogenous insulin was 0.32 (0.19) units/kg/day in 3 of 5 participants who had received teplizumab prior in the TN-10 study, and 0.41 units/kg/day in the participant who had received placebo. Mean (SD) average daily use of exogenous insulin was 0.43 (0.34) units/kg/day in 3 of the participants who had received teplizumab prior in the TN-10 study at Day 546, and 0.88 units/kg/day in the participant who had received placebo at Day 546.

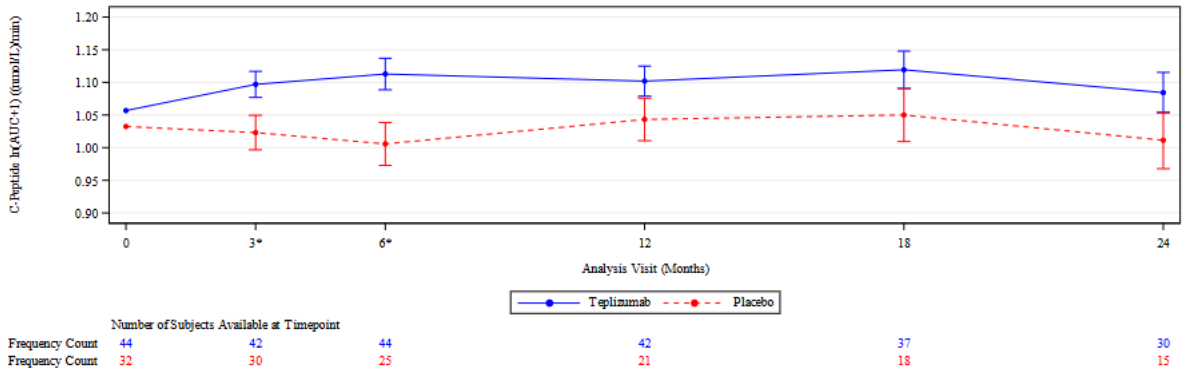
Subjects who were not diagnosed with T1D had OGTTs at 3 months after randomization and then every 6 months thereafter until the study cut-off date or withdrawal. Figure 17 shows the absolute mean C-peptide AUC values over time, including the pre-baseline value.

Figure 16 2-hour C-peptide AUC by time window



Abbreviations: AUC=area under the time-concentration curve, ITT=intent to treat, OGTT=oral glucose tolerance test Note: If multiple data points were available within a study visit time window, the average value was used. Source: EOT Figure 2.4.4

Figure 17 C-peptide (ln(AUC + 1)) least square means estimates (with standard error) by treatment and time window from the 2-year model (ITT population)



*Statistical significance between teplizumab and placebo was found at Month 3 and Month 6.
Abbreviations: AUC=area under the time-concentration curve, CI=confidence interval, ITT=intent to treat, SE=standard error.
Source: EOT Figure 2.4.3

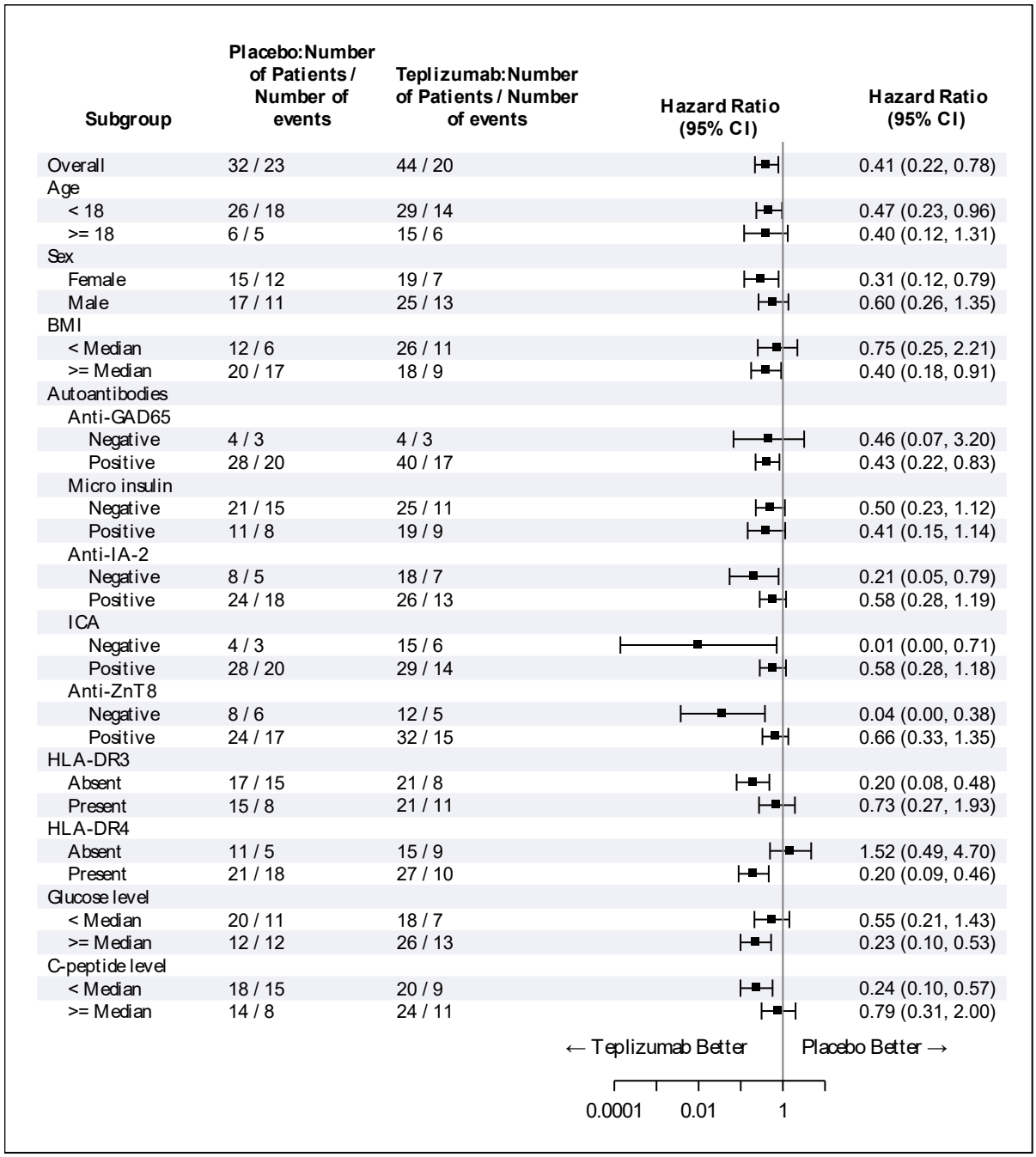
The MMRM analyses of C-peptide ln(AUC+1) data for 24 months indicated that teplizumab treatment was associated with higher C-peptide levels (i.e., more beta cell preservation) than placebo.

Mechanistic Outcome Assessments

TrialNet performed immune and genetic assays to further understand mechanisms that may be underlying the T1D disease process and response to therapy. For this purpose, samples for peripheral blood mononuclear cell (PBMC), DNA, RNA, plasma, and serum were obtained. Human leukocyte antigen (HLA) testing could also be done as needed.

Pre-defined and ad-hoc subgroup analyses

Figure 18. TN-10 study: Subgroup analyses - Forest plot of time to Stage 3 T1D onset - ITT Population



PGM=PRODOPS/SAR446681/MGA031_005/QREG/REPORT/PGM/eff_sub_forest_i_f.sas
OUT=REPORT/OUTPUT/eff_sub_forest_i_f_i.rtf (30JUN2025 18:38)

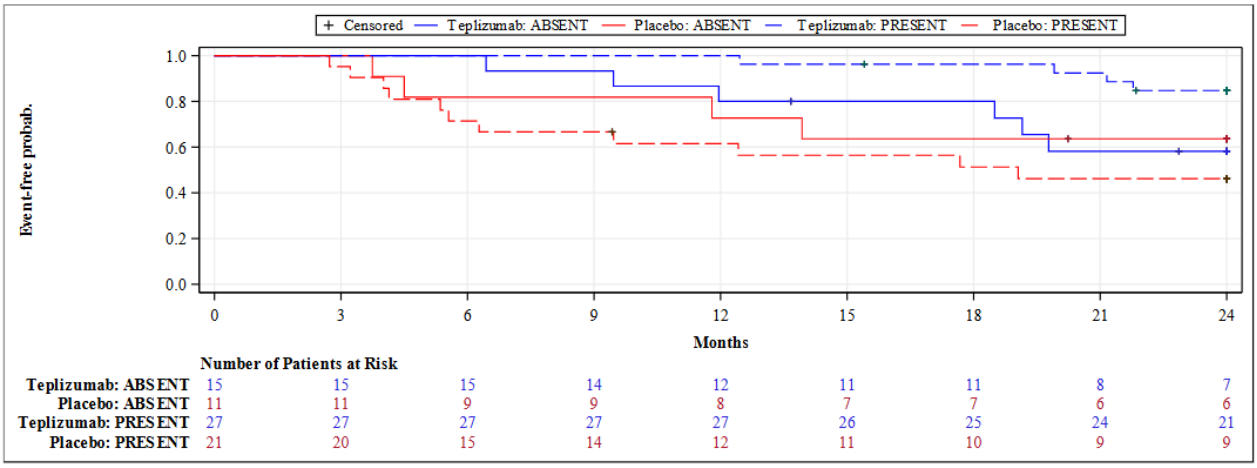
The effects of teplizumab was compared with placebo in sub-groups based on age at baseline, sex, body mass index (BMI) at baseline (< median and ≥ median), autoantibodies (anti-GAD65, micro-insulin, anti-IA-2, ICA, anti-ZnT8), HLA type (HLA DR3, HLA DR4), pre-treatment C-peptide (< median, ≥ median), and glucose levels (< median, ≥ median) during OGTT. Results were presented in a forest plot as hazard ratios and 95% confidence intervals (CIs) of T1D onset between teplizumab and placebo for each subgroup.

According to the applicant, the number of events in each subgroup was small and no adjustment for multiplicity was made, precluding definitive conclusions.

The Cox model (primary endpoint Cox model was used as a base) was adjusted for age, with the exception of the interaction test for age (<18 years versus ≥18 years) but was not adjusted for multiple testing.

Additionally, Kaplan-Meier graphs (over the first 24 months on study) were presented for the 4 subgroups (anti-ZnT8 antibody status, HLA types [DR3 and DR4], pre-treatment C-peptide [<median and ≥ median]) by treatment, see Figure 20 for HLA type DR4 as one example.

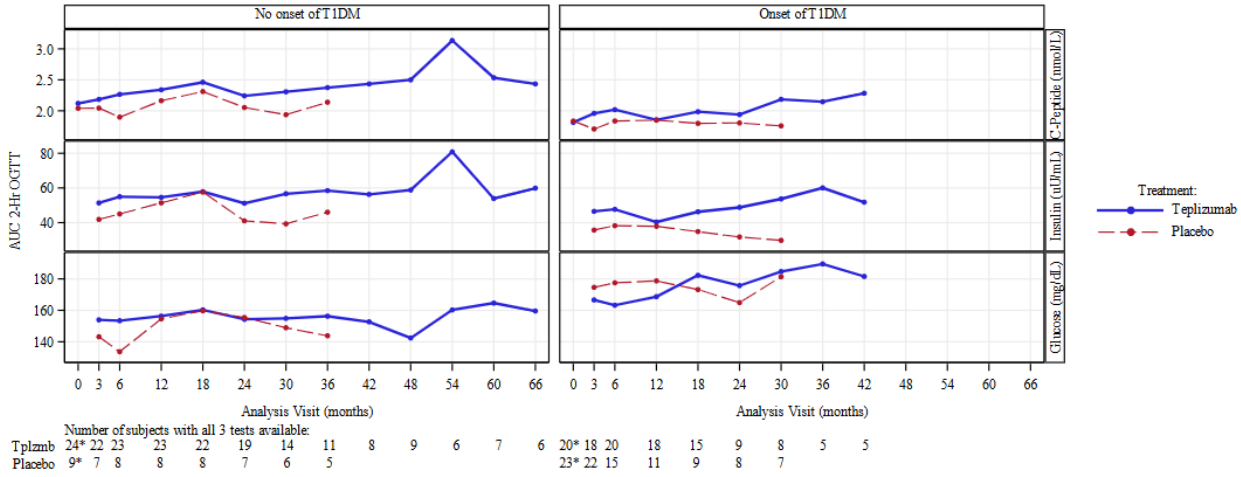
Figure 19 HLA DR4 allele (presence versus absence)



Ancillary analyses

In order to assess whether C-peptide and other metabolic parameters (endogenous insulin and glucose levels) differed between those who were free of T1D and those who developed T1D, a facet plot was developed (Figure 21).

Figure 20 Facet plot of AUCs of C-peptide, glucose, and insulin levels in the 2-hour OGTT over time by treatment group and T1D diagnosis (ITT population)



Abbreviations: AUC=area under time-concentration curve, ITT=intent to treat, OGTT=oral glucose tolerance test, T1D=type 1 diagnosis.
Source: EOT Figure 2.4.2

Among subjects who received a T1D diagnosis in the study, the treatment effect of teplizumab was also statistically significant (top right panel, p=0.030, EOT Table 2.3.2). These results are consistent with the observations in the MMRM analysis described above. Furthermore, those who ultimately develop T1D during the study had lower C-peptide and endogenous insulin levels and higher blood glucose compared with those who did not develop T1D.

The C-peptide, glucose and insulin levels in the 2-hour OGTT differed over time by treatment group and by the fact if diagnosed with T1D during the study or not.

Teplizumab serum concentration does not differ by T1D diagnosis or not in the study. But the study subjects who did not get a T1D diagnosis had greater variability and higher median concentrations compared to those who got a T1D diagnosis. Since the variability is high, and the number of participants in the study is low, no conclusions can be drawn from these results.

At the 3-month visit, 24 of 42 subjects had anti-teplizumab antibodies, and of those, 11 had neutralising antibodies. The presence of anti-teplizumab antibodies was not associated with drug concentration, nor with the fact if T1D was diagnosed during the study or not.

6.3.2.2. PROTECT - PRV-031-001

6.2.2.2.1. Study title

PROTECT: A Phase 3, randomized, double-blind, multinational, placebo-controlled study to evaluate efficacy and safety of teplizumab (PRV-031), a humanized, FcR non-binding, anti-

CD3 monoclonal antibody, in children and adolescents with newly diagnosed type 1 diabetes (T1D)

6.3.2.2.2. Study design

This was a Phase 3, randomized, double-blind, multinational, placebo-controlled study. Enrolled participants were randomly assigned with a ratio of 2:1 to either teplizumab or placebo (saline infusion) group.

Study treatment
Teplizumab or placebo were administered by intravenous infusion in addition to the standard of care (insulin treatment and titration).
Active group: Two 12-day courses of teplizumab (administered by intravenous infusion) starting at Week 1 and Week 26 consisting of daily IV doses of 106 µg/m^2, 425 µg/m^2, and 850 µg/m^2, on Study Days 1, 2, and 3-12, respectively. The total dose for each 12-day course was 9.0 mg/m^2. A modified dosing schedule was introduced due to COVID-19 pandemic. Participants who were unable to receive the second 12-day course at Week 26 due to COVID-19 pandemic restrictions were given the second course on approximately Day 364 (Week 52 visit), approximately 12 months after randomization. Those who received the modified dosing schedule were given the second course after 52 weeks, followed by 26 weeks of observation, compared to the original dosing schedule with second course after 26 weeks followed by 52 weeks of observation time. Placebo group: Two 12-day courses of saline infusion for 12 days starting at Week 1 and Week 26 or Week 52.

Compared to a 14-day dosing regimen adopted in the other studies with teplizumab (TN10 and supportive studies in Stage 3 T1D), the 12-day teplizumab regimen in PROTECT was chosen as more convenient for the participants and their families. Based on calculations, the amount of teplizumab given in the 12- and 14-day approach differs by 0.005 mg/m^2.

Figure 21: Schematic Overview of the Study

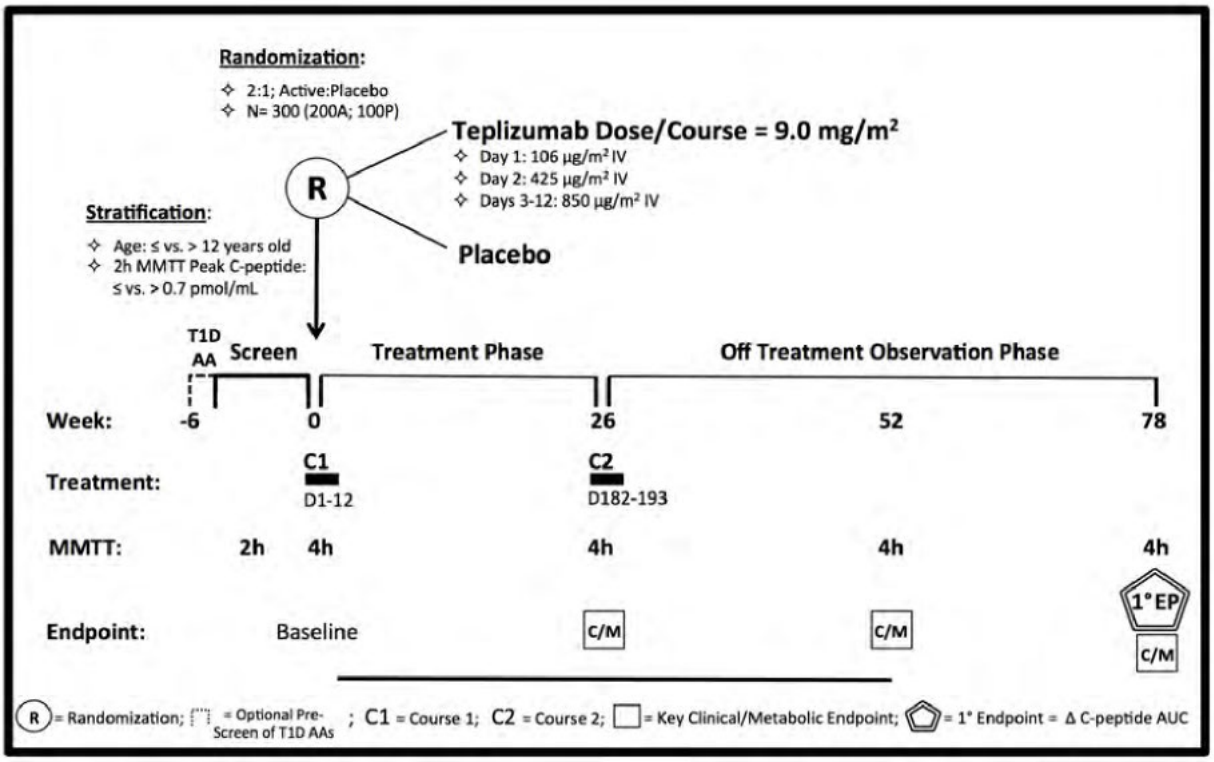
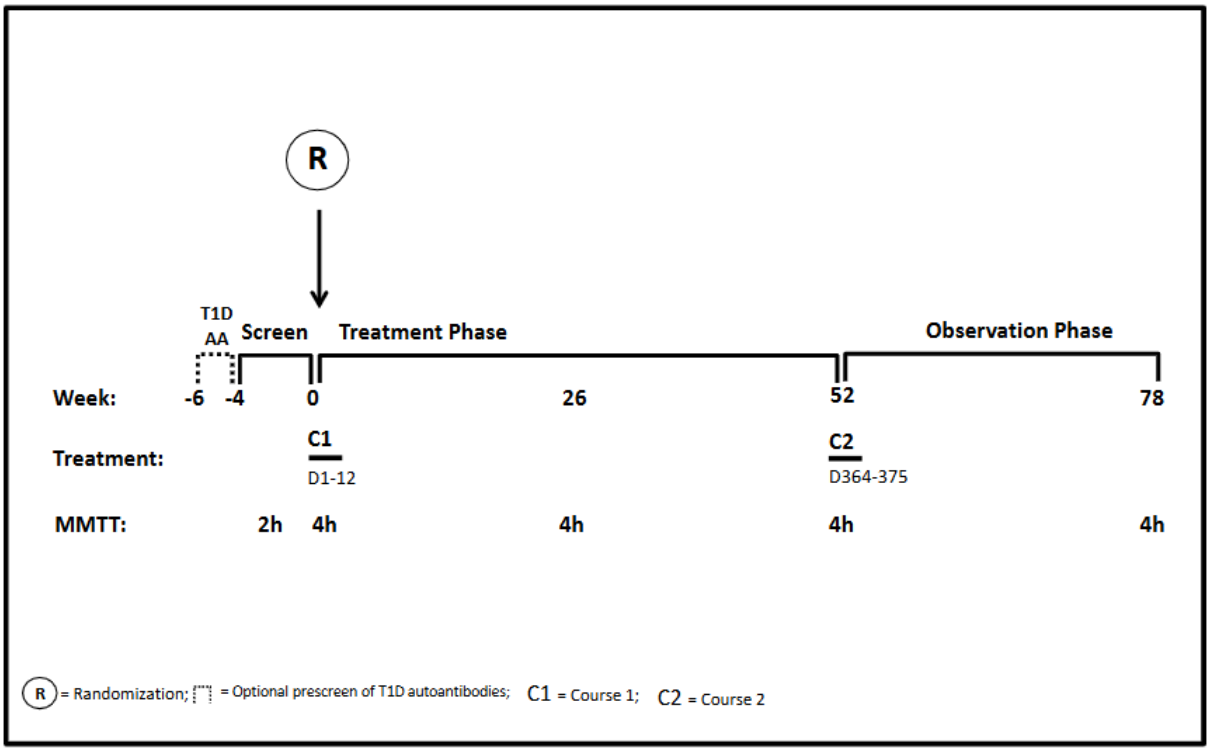


Figure 22 Modified Dosing Schedule for Participants Affected by COVID-19 Pandemic Restrictions



Randomisation

Participants were to be randomly assigned in a 2:1 ratio for the teplizumab group and the placebo group, respectively. The randomisation was to be balanced by using randomly permuted blocks. The stratification variables used in the randomisation were peak C-peptide level at screening (0.2 to <=0.7 and >0.7 pmol/mL) and age at randomisation (8-12 and >12-17 years).

The interactive web response system (IWRS) was to assign a unique treatment code, which dictated the treatment assignment and matching study drug kit for the participant. For each stratification stratum, the range for the randomisation numbers was pre-defined and the IWRS system was to fill each block with randomised participants until the block size was met. In addition, the randomisation number a participant received from the list was random compared to the sequence in which the participant was assigned. Each block contained active and placebo participants based on the allocation ratio and block size. A requestor had to use his or her own user identification and personal identification number when contacting the IWRS and then give the relevant details to uniquely identify the participant.

Blinding

This was a double-blind study. Blinding was to be maintained for all study participants, investigators, and study coordinators throughout the study. In addition, all personnel at the sites, the CRO, third-party laboratory vendors, and the Sponsor were to be blinded to the treatment assignment through the completion of the study. Teplizumab and placebo were to be supplied to the sites in vials and kits that appeared identical. Each kit had a unique number printed on all labels, including the outer carton label and the label of each vial inside the kit. Detailed instructions for handling the blinded study drug kits were to be provided in the Pharmacy Manual. Teplizumab was supplied in 2 mL type 1 glass vials with rubber stoppers and flip-off seals. The formulation of teplizumab consisted of 10 mM sodium phosphate, 150 mM sodium chloride, and 0.05 mg/mL Tween 80 with pH 6.1. The placebo formulation consisted of the same formulation buffer without teplizumab.

Teplizumab may cause transient reductions in WBC (including lymphocytes and neutrophils). Central laboratory results for WBC total and differential counts and platelet counts, as well as TBNK panel, were to be reported to study sites in a blinded fashion. If, at any time, the investigator had any concern about the health or safety of a participant and request the participant’s current or previous WBC or platelet count from the central laboratory, they were to be provided with the unblinded laboratory results.

During the study treatment courses (except the last day of dosing), WBC and differential and platelet counts were to be measured by local laboratories at the study site and reviewed by the investigator prior to dosing; these results were not blinded. If a result were to meet a stopping rule, the investigator was to contact the Medical Monitor and conduct appropriate clinical and laboratory follow-up.

The treatment designation codes were to be available to members of the DMC, the supporting independent statistician, the vendor for study product labelling, packaging and distribution, the IWRS vendor, select individuals at Provention Bio, Inc. and other study associated personnel as indicated above.

Patient population

The study subjects were 8-17 years of age and had recently received a diagnosis of T1D according to the ADA (American Diabetes Association) criteria. Time from diagnosis to initiation of study drug should not exceed 6 weeks.

The study was conducted at 61 active sites in Belgium, Czech Republic, Germany, France, Poland, Canada, United States and the United Kingdom.

In addition to above mentioned study participant facts, **main inclusion criteria** consisted of:

- Participant had a peak stimulated C-peptide of ≥0.2 pmol/mL from a 2-hour mixed meal tolerance test (2h MMTT) at screening.
- Participant had a positive result on testing for at least one of the following T1D-related autoantibodies before randomization: Glutamic acid decarboxylase 65 (GAD65) autoantibodies, Islet antigen 2 (IA-2) autoantibodies, Zinc transporter 8 (ZnT8) autoantibodies, Islet cell cytoplasmic autoantibodies (ICA) or Insulin autoantibodies.

Main exclusion criteria consisted of**:**

Known allergies, severe reaction, intolerance, hypersensitivity, or anaphylaxis to human, humanized, or murine monoclonal antibodies, teplizumab or any of its components or its excipients.

Active participation in a therapeutic drug, invasive medical device, or vaccine clinical trial within 12 weeks before the first dose of study drug or has received an investigational treatment with the potential for T1D disease modification.

Significant renal, cardiac, vascular, pulmonary, gastrointestinal, neurologic, hematologic, rheumatologic, oncologic, psychiatric disease, or immune deficiency.

Any autoimmune disease other than T1D (e.g., rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, multiple sclerosis, systemic lupus erythematous), with the exception of clinically stable thyroid or celiac disease.

Participant had an active infection within the 48 hours prior to randomization, was prone to infections.

History of or serologic evidence at screening of current or past infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).

Objectives and estimands

Primary objective

The primary objective was to determine whether 2 courses of teplizumab slow the loss of beta cell function over 18 months (78 weeks) in children and adolescents 8-17 years old who had been newly diagnosed with T1D (within 6 weeks of randomization). C-peptide (or C-peptide AUC after stimulation with a 4h MMTT) was used as a marker for beta cell activity.

The study was designed to test for superiority. The null hypothesis for the primary and secondary efficacy endpoints is that there is no difference between teplizumab and placebo in the efficacy measurements. The alternative hypothesis was that there is a treatment difference between teplizumab and placebo. The hypothesis for each endpoint will be tested separately.

Estimand for the primary objective

Table 17: Estimands for primary objective

	Children and adolescents (8-17 years old) with newly diagnosed Type 1 Diabetes (within 6 weeks) as defined by the protocol inclusion/exclusion criteria.
Treatment conditions	Not defined by the applicant.
Primary endpoint	Week 78 time-concentration curve (AUC) of C-peptide after a 4-hour mixed meal tolerance test.
Population-level summary	The mean change from baseline to week 78 in C-peptide ln(AUC+1) between teplizumab group and placebo groups.
Intercurrent events and strategy to handle them	
ICEs	• use of medications disallowed according to the protocol, • modified dosing schedule due to COVID-19, • premature discontinuation of study treatment, • non-adherence to the planned treatment regimen. All ICEs were to be handled by means of the treatment policy strategy.
Population	Children and adolescents (8-17 years old) with newly diagnosed Type 1 Diabetes (within 6 weeks) as defined by the protocol inclusion/exclusion criteria.

The primary objective of the study was to determine whether teplizumab treatment, compared to placebo, could preserve beta cell function over 18 months (78 weeks). This was studied in children and adolescents 8-17 years old who had been diagnosed with T1D in the previous 6 weeks.
The change from baseline to week 78 in C-peptide ln(AUC+1) after a 4-hour (4h) mixed meal tolerance test (MMTT) was to be used as a measurement of beta cell function.

The primary endpoint, the area under time-concentration curve (AUC) of C-peptide after a 4-hour (4h) mixed meal tolerance test (MMTT), is recognised as a marker of beta cell function. Change from baseline C-peptide secretory activity (eg, C-peptide AUC) is considered as a relevant co-primary endpoint when assessed along with a relevant clinical endpoint (e.g, HbA1c, reduction in insulin use, or severe hypoglycemic episodes) for studies designed to evaluate preservation of beta cell function in newly diagnosed clinical T1D. Clinically relevant endpoints were defined and analysed as secondary endpoints.

The primary efficacy endpoint was evaluated in children and adolescents (8-17 years old) with newly diagnosed TID. All ICEs, including use of medications disallowed according to the protocol, modified dosing schedule due to COVID-19, premature discontinuation of study treatment, and non-adherence to the planned treatment regimen, were handled by the treatment policy strategy. Four out of five attributes for the primary estimand were defined.

Statistical methods for estimation and sensitivity analysis on primary estimand

Analysis sets

The ITT population was used for primary analyses on efficacy and was to consist of all randomised subjects. The per-protocol (PP) population was to be used in supportive analyses.

Multiplicity control

To control the family-wise Type 1 error at the 0.05 level, inference on four predefined secondary efficacy endpoints (see Secondary objective) was to be drawn only if the primary efficacy endpoint reached statistical significance and in applying the Hochberg procedure.

Main analysis methods for primary endpoint

The primary efficacy endpoint was tested at two-sided 0.05 level. The change from baseline in C-peptide ln(AUC+1) at week 78 had been planned to be and was analysed using an analysis of covariance (ANCOVA) model with treatment, age group at randomisation, and baseline C-peptide ln(AUC+1) as covariates. The estimated mean change from baseline in ln(AUC+1) and the associated 95% CI for each treatment group, as well as the estimated mean difference in ln(AUC+1) between the treatment groups and the associated 95% CI, were to be presented together with the corresponding p-value.

Descriptive statistics and graphical presentation of the change from baseline C-peptide ln(AUC+1) by visit and treatment group was also to be provided.

All ICEs were handled by the treatment policy strategy.

Handling of missing data

Missing data at week 78 for the primary efficacy endpoint were imputed using multiple imputation (MI), regardless of the reasons for dropouts (including missing data due to ICEs). Four patterns were used:

- Patterns 1 and 2: missing values at week 78 among participants who discontinued the study treatment early (separated by those who discontinued and completed the study, respectively) were to be imputed using data from retrieved dropouts (i.e., participants who discontinued treatment before week 78 but still had an efficacy measurement at week 78).
- Patterns 3 and 4: missing values at week 78 among participants who completed the study treatment (separated by those who discontinued and completed the study, respectively) were to be imputed using data from treatment completers.

The MI was to be carried out by 1) generating 100 sets of data and applying linear regression models with the covariates treatment, age, gender, C-peptide ln(AUC+1) at previous time points, and baseline C-peptide ln(AUC+1) to generate each imputed dataset, 2) applying the primary efficacy analysis model in each of the imputed datasets, and 3) combining the results using Rubin's rule (Rubin, 1987).

Sensitivity analyses

Four sensitivity analyses for the primary efficacy endpoint were prespecified and have been performed. Among them,

- A control-based imputation applying the MI procedure described above, but where missing data of C-peptide ln(AUC+1) in the teplizumab group was imputed based on the available data from the placebo group.
- A tipping point analysis incorporating the MI procedure described above, used in 1) imputing missing data at each visit, 2) deriving the change from baseline ln(AUC+1) from the imputed values at week 78 in the teplizumab and placebo groups, adjusted by a pair of shift parameters, (Δt, Δp), 3) applying the primary efficacy analysis model in each of the imputed

datasets, 4) combining the results using Rubin's rule, and 5) repeating steps 2-4 for a range of (Δt, Δp) to fine-tune the tipping point until the p-value ≥ 0.05. The shift parameters (Δt, Δp) for each run were to be empirically determined.

Subgroup analyses

Subgroup analyses on the primary efficacy endpoint were prespecified in the final SAP and were to be displayed graphically using forest plots.

Sample size

The determination of sample size was based on C-peptide ln(AUC+1). Assumptions were based on results from previous studies on teplizumab. Using an estimate of 0.25 nmol/L, the transformation to geometric mean in the placebo group is exp(0.25)-1 = 0.28. This study was designed to show a difference of at least a 40% in C-peptide response between teplizumab and placebo. In geometric means this translates to a value of (1.4*0.28) = 0.392. Consequently, approximately 300 participants were planned for enrolment, assuming 2-sided α=0.05, 90% power, 2:1 randomisation, and a 10% dropout rate.

Secondary objective

Secondary key efficacy objectives were to evaluate participant improvements in clinical parameters of diabetes management, including daily insulin use, glycemic control (as measured by HbA1c and time in range [TIR]), and clinically important hypoglycemic episodes.

Other secondary objectives were:

- To determine the safety and tolerability of two courses of teplizumab, administered intravenously (IV)
- To evaluate the pharmacokinetics (PK) and immunogenicity of two courses of IV teplizumab.

The study is designed to test for superiority. The null hypotheses for the primary and secondary efficacy endpoints will be that there is no difference between teplizumab and placebo in the efficacy measurements. The alternative hypotheses will be that there is a treatment difference between teplizumab and placebo. The hypothesis for each endpoint will be tested separately.

Estimands for the secondary objective

No estimands were defined for the secondary objective.

Statistical methods for estimation and sensitivity analysis on the secondary estimand

The below secondary endpoints were included in the MTP (see Statistical methods for estimation and sensitivity analysis on primary estimand). The analyses were performed on the ITT population. No estimands were defined for the secondary objective.

Average exogenous insulin use at week 78, change from baseline in average HbA1c (%) at week 78, and time in glycaemic target range (TIR) at week 78 had been planned to be and were analysed using ANCOVA. The models included treatment group and randomisation stratification factors (age group and screening peak C-peptide category) as covariates. The ANCOVA model on HbA1c also included baseline HbA1c (%). Missing values at week 78 (including missing data due to ICEs) were to be imputed in the same way as for the primary efficacy endpoint.

The event rate of clinically important hypoglycaemic episodes had been planned to be and was analysed using a negative binomial model. The negative binomial model included treatment group and randomisation stratification factors as covariates.

6.3.2.2.3. Results

Participant flow and numbers analysed

The study initiation date is 5 April 2019, which is the date for the enrolment of the first participant. The last subject completed the 1st May 2023.

A total of 328 eligible participants were enrolled and randomized in the study, with 61.6% of participants in the United States and Canada, 34.7% in the EU, and 3.7% in UK.

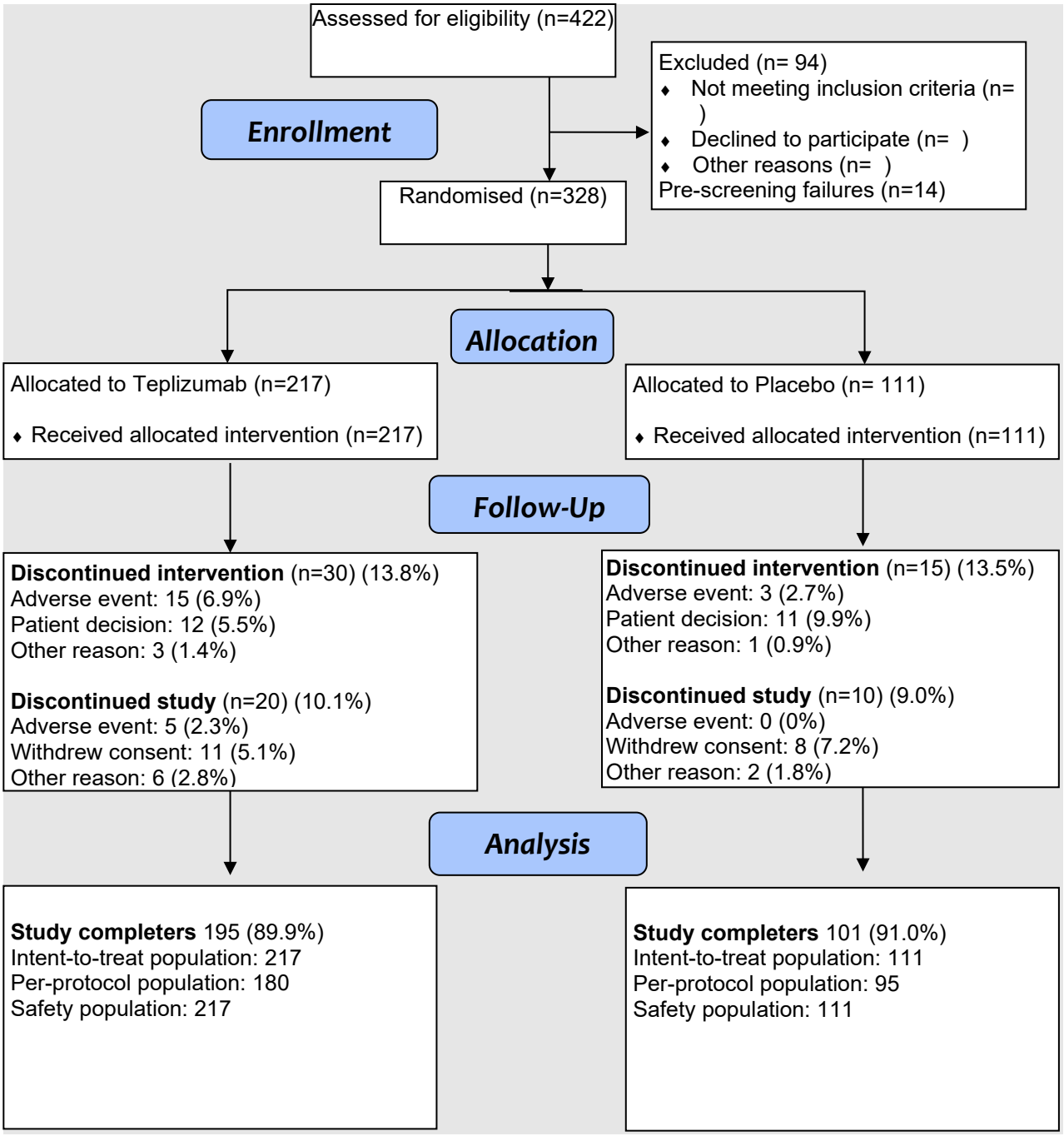
The number of randomised subjects by country and by treatment arm include the below:

- 5 were randomised in Belgium (1 teplizumab / 4 placebo)
- 27 were randomised in Czech Republic (17 teplizumab / 10 placebo)
- 14 were randomised in France (9 teplizumab / 5 placebo)
- 20 were randomised in Germany (12 teplizumab / 8 placebo)
- 48 were randomised in Poland (33 teplizumab / 15 placebo)
- 182 were randomised in US (126 teplizumab / 56 placebo)
- 20 were randomised in Canada (13 teplizumab / 7 placebo)
- 12 were randomised in United Kingdom (6 teplizumab / 6 placebo)

In addition, 2 participants were screened in Hungary, but none were randomised.

All randomized participants received study treatment (Figure 24). Thus, the ITT and Safety populations were the same. The PP population included 275 (83.8%) participants. Sixteen (14.4%) and 37 (17.1%) participants in the placebo and teplizumab groups, respectively, were excluded from the PP population. The most common reason for this exclusion was treatment compliance <80%, which accounted for the exclusion of 15 of the 16 participants in the placebo group and 32 of the 37 participants in the teplizumab group.

Figure 23: Participant flow



Ninety-four (94) subjects were screened but not randomised. 14 of these individuals are noted as pre-screening failures, and 80 as screen failures. The reasons for screen failures are noted in Table 28.

Table 18 Summary of all screen failures

All participants screened	422	
Pre-screening failures	14	(3.3)
Screen failures	80	(19.0)
Inclusion		
Able to be randomized and initiate study drug within 6 weeks (42 days) of the formal T1D diagnosis according to the ADA criteria.	8	(1.9)
Has a peak stimulated C-peptide of >=0.2 pmol/mL from a 2-hour mixed meal tolerance test (2h MMTT) at screening.	7	(1.7)
Has a positive result on testing for at least one T1D-related autoantibodies before randomization.	16	(3.8)
Has received a diagnosis of T1D according to ADA criteria	1	(0.2)
Participant and/or appropriate legal guardian must sign an informed consent form (ICF).	19	(4.5)
Up to date with and/or agree to receive immunizations.	1	(0.2)
Exclusion		
A stated condition related to TB.	6	(1.4)
Current or prior (within 30 days before screening) use of drugs other than insulin to treat hyperglycemia.	1	(0.2)
Has a clinically active infection with CMV.	1	(0.2)
Has a clinically active infection with EBV.	1	(0.2)
Has a diagnosis of significant liver disease.	3	(0.7)
Has a history of alcohol, drug, or chemical abuse within 12 months prior to study screening.	1	(0.2)
Has a history of or serologic evidence at screening of current or past infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).	1	(0.2)
Has a medical, psychological or social condition that would interfere with safe and proper completion of the trial.	13	(3.1)
Has an active infection and/or fever within 48 hours prior to randomization or prone to infections.	4	(0.9)
Has any of the stated hematologic laboratory results within 10 days before randomization.	6	(1.4)
Has significant renal, cardiac, vascular, pulmonary, gastrointestinal, neurologic, hematologic, rheumatologic, oncologic, psychiatric disease, or immune deficiency.	2	(0.5)
Recent or planned vaccinations.	1	(0.2)
Unknown	3	(0.7)

Note: Percentages are based on the number of all screened participants. All Screened includes participants who signed screening informed consent/assent or pre-screening informed consent/assent.

Source: Listing 16.2.1.3

The majority of participants received 2 courses of study drug (88.4%), and most (79.9%) participants received the study drug according to the normal dosing schedule, i.e., the second treatment course was initiated at Week 26. Twenty-eight (8.5%) participants received the study drug according to MDS, i.e., the second course was initiated at Week 52. Disposition of study participants, including reasons for discontinuing study drug and discontinuing from the study, is provided in Table 29.

In the teplizumab group, 5 (2.3%) participants discontinued from the study due to AEs, including 3 participants who discontinued the study due to protocol-defined liver aminotransferase elevations and 2 due to cytokine release syndrome.

Table 19 Disposition of Participants (All Randomized)

	Placebo N=111	Teplizumab N=217	Total N=328
	n (%)	n (%)	n (%)
Received any study drug			
Course 1	111 (100)	217 (100)	328 (100)
Course 2	99 (89.2)	191 (88.0)	290 (88.4)
Received full course			
Course 1	105 (94.6)	189 (87.1)	294 (89.6)
Course 2	91 (82.0)	182 (83.9)	273 (83.2)
Courses 1 & 2	88 (79.3)	172 (79.3)	260 (79.3)
Normal dosing schedule	87 (78.4)	175 (80.6)	262 (79.9)
MDS	12 (10.8)	16 (7.4)	28 (8.5)
Discontinued study drug	15 (13.5)	30 (13.8)	45 (13.7)
Adverse event	3 (2.7)	15 (6.9)	18 (5.5)
Participant decision	11 (9.9)	12 (5.5)	23 (7.0)
Other[a]	1 (0.9)	3 (1.4)	4 (1.2)
Discontinued study drug but completed study	6 (5.4)	18 (8.3)	24 (7.3)
Discontinued study drug and study	9 (8.1)	12 (5.5)	21 (6.4)
Completed study	101 (91.0)	195 (89.9)	296 (90.2)
Discontinued from study	10 (9.0)	22 (10.1)	32 (9.8)
Adverse event	0	5 (2.3)	5 (1.5)
Withdrew consent	8 (7.2)	11 (5.1)	19 (5.8)
Lost to follow-up	0	5 (2.3)	5 (1.5)
Other	2 (1.8)	1 (0.5)	3 (0.9)
Pregnancy	0	1 (0.5)	1 (0.3)

Abbreviations: MDS=modified dosing schedule.
Note: Participants received Course 2 treatment at Week 26 in the normal dosing schedule and at Week 52 in the MDS.
Source: Table 14.1.1.1, Listing 16.2.1.1

All 328 randomized participants were included in the ITT and Safety populations (Table 30). The ITT and Safety populations were the same, each included 111 participants in the placebo group and 217 in the teplizumab group. The PP population included 275 (83.8%) participants. Sixteen (14.4%) and 37 (17.1%) participants in the placebo and teplizumab groups, respectively, were excluded from the PP population. The most common reason for this exclusion was treatment compliance <80%, which accounted for the exclusion of 15 of the 16 participants in the placebo group and 32 of the 37 participants in the teplizumab group (Table 14.1.1.4).

Table 20 Data Sets Analyzed (All Randomised)

	Placebo N=111	Teplizumab N=217	Total N=328
	n (%)	n (%)	n (%)
ITT Population	111 (100)	217 (100)	328 (100)
Safety Population	111 (100)	217 (100)	328 (100)
Per Protocol Population	95 (85.6)	180 (82.9)	275 (83.8)

Abbreviations: ITT=intent to treat, PK=pharmacokinetic(s).
Source: Table 14.1.1.1

Deviations from study plan

Protocol amendments

The original protocol (version 1.0, dated 31 December 2018), implemented at the time of study initiation, was amended to version 2.0 (dated 02 September 2019), version 3.0 (12 May 2020), and version 4.0 (10 December 2020). Minor regional variations in study procedures in compliance with specific regulatory authorities' requirements were documented in country-specific protocol versions. All versions of the study protocol are included in Appendix 16.1.1. The substantive changes to the study in each protocol amendment are listed in the CSR. Changes included:

Version 1.0 to 2.0:

- Time in glycemic target range was added as a part of the assessments of glycemic control along with HbA1c.
- The primary efficacy analysis was changed from repeated measures analysis to ANCOVA

Version 2.0 to 3.0:

- As some participants were unable to receive the second course of treatment as scheduled because of the COVID-19 pandemic restrictions, the MDS was implemented to allow these participants to receive the second treatment course starting at the Week 52 visit instead of the Week 26 visit.
- New Schedule of Events tables were added for participants on the MDS due to COVID-19 pandemic restrictions.
- An electrocardiogram (ECG) substudy in approximately 45 participants at selected US sites was added to evaluate ECG data at time points when teplizumab serum concentrations reach peak levels.

Version 3.0 to 4.0:

- A pharmacokinetic (PK) sample was added on Day 9 of Treatment Course 1 to better characterize the PK profile of teplizumab. The blood draw volume was updated to account for this additional sample.
- Requirement for polyvinyl chloride (PVC) infusion bag was removed based on updated compatibility data that became available in October 2020
- A pharmacodynamic (PD) substudy was added to evaluate the PD effects of teplizumab treatment at time points concurrent with PK sampling during and after Treatment Course 1. The substudy was to be conducted at all North American study sites

- The ECG substudy, added in version 3.0, was removed, as the FDA granted a waiver. The previous Appendix 4 was replaced by the description of a PD substudy (see above).

Protocol deviations

Major protocol deviations are listed in Listing 16.2.2.1 in the Clinical Study Report (CSR) and summarized in Table 14.1.2.1. A total of 201 (61.3%) participants had one or more major protocol deviations during the entire study, with comparable proportions between the placebo (64.9%) and teplizumab (59.4%) groups. The major protocol deviations were primarily related to procedures and tests (placebo group 33.3% vs teplizumab group 24.4%), informed consent (27.0% vs 21.7%), treatment deviations (10.8% vs 12.9%), and other (9.0% vs 12.4%).

Protocol deviations related to COVID-19 are listed in Listing 16.2.2.2 of the CSR and summarized in Table 14.1.2.2. A total of 46 (14.0%) participants had one or more COVID-19-related deviation during the study, including 28 (8.5%) with COVID-related major protocol deviations. The proportions of participants who had COVID-19-related deviations were comparable between the placebo (15.3%) and teplizumab (13.4%) groups.

Treatment compliance

Treatment compliance (ITT Population) was listed (CSR section 16.2.5.1). Records of study drug administration were used to assess compliance. Treatment compliance within a treatment course was calculated as [total amount of study drug administered (µg) / total amount of study drug prescribed (µg)] x 100 during the dosing period.

Treatment compliance, i.e., having received 80% to 100% of planned doses of study drug, was generally high in the study. In Course 1, the mean compliance rates were 98.2% in the placebo group and 92.2% in the teplizumab group. In Course 2 (including the normal dosing schedule and MDS), the mean compliance rates were 86.5% and 86.2%, respectively. For both courses combined, the mean compliance rates were 86.5% and 85.3%, respectively.

Two participants in the teplizumab group received more than 100% of the planned number of doses because their originally planned Course 2 treatment at Week 26 was suspended after initiation due to possible COVID-19 exposure. These participants' Course 2 treatment was rescheduled according to the MDS (i.e., starting at Week 52).

Baseline data

A summary of demographic and other characteristics for the ITT population is presented in Table 31. Individual listings of demographic and baseline data, medical history, and historical diagnostic tests were included in Appendix 16.2.4.

The demographics at randomisation were generally balanced between the placebo and teplizumab groups. Overall, the mean (SD) age was 12.1 (2.54) years, with 41.5% of participants in the 8 to 11 years subgroup and 58.5% in the 12 to 17 years subgroup. The proportion of male participants was slightly higher in the placebo group (62.2%) than the teplizumab group (54.8%).

The mean (SD) daily dose of exogenous insulin at baseline was 0.426 (0.2928) U/kg/day, slightly higher in the teplizumab group (0.447 U/kg/day) than in the placebo group (0.383 U/kg/day). The mean (SD) HbA1c level was 9.00% (1.797%), which was slightly higher in the placebo group (9.18%) than in the teplizumab group (8.90%).

The majority of the study population race was noted as white. 3.4% and 2.1% were noted as black and asian, respectively. The BMI Z-score median is higher for the teplizumab group than for the placebo group.

Table 21 Demographics and Other Characteristics (ITT Population)

	Placebo N=111	**Teplizumab N=217**	**Total N=328**
Age at randomization (years)			
Mean (SD)	12.3 (2.55)	12.0 (2.53)	12.1 (2.54)
Median	12.0	12.0	12.0
Min, max	8, 17	8, 17	8, 17
Age group at randomization, n (%)			
8 to 11 years	46 (41.4)	90 (41.5)	136 (41.5)
12 to 17 years	65 (58.6)	127 (58.5)	192 (58.5)
Sex, n (%)			
Male	69 (62.2)	119 (54.8)	188 (57.3)
Female	42 (37.8)	98 (45.2)	140 (42.7)
Race			
White	94 (84.7)	189 (87.1)	283 (86.3)
Black or African American	6 (5.4)	5 (2.3)	11 (3.4)
Asian	3 (2.7)	4 (1.8)	7 (2.1)
American Indian or Alaskan Native	0	1 (0.5)	1 (0.3)
Native Hawaiian or Other Pacific Islander	1 (0.9)	0	1 (0.3)
Multiple[a]	0	6 (2.8)	6 (1.8)
Other	1 (0.9)	4 (1.8)	5 (1.5)
Not reported	6 (5.4)	8 (3.7)	14 (4.3)
Ethnicity			
Hispanic or Latino	4 (3.6)	14 (6.5)	18 (5.5)
Not Hispanic or Latino	101 (91.0)	193 (88.9)	294 (89.6)
Not reported	6 (5.4)	10 (4.6)	16 (4.9)
Height at baseline (cm)			
Mean (SD)	158.48 (14.977)	155.35 (15.358)	156.41 (15.279)
Median	157.80	155.00	156.00
Min, max	126.0, 189.0	118.5, 191.5	118.5, 191.5
Weight at baseline (kg)			
Mean (SD)	49.19 (15.889)	46.68 (14.992)	47.53 (15.323)
Median	48.50	45.90	46.75
Min, max	21.5, 92.0	21.6, 104.3	21.5, 104.3
BMI at baseline (kg/m^2)			
Mean (SD)	19.063 (3.6415)	18.868 (3.4517)	18.934 (3.5127)
Median	18.360	18.130	18.175
Min, max	12.74, 33.25	10.36, 34.18	10.36, 34.18
BMI z-score at baseline			
Mean (SD)	0.0557 (1.0957)	0.0627 (1.0723)	0.0603 (1.0786)
Median	0.0305	0.0631	0.0581
Min, max	-3.832, 2.494	-6.317, 2.491	-6.317, 2.494

	Placebo N=111	Teplizumab N=217	Total N=328
Time from T1D diagnosis to randomization (weeks)			
Mean (SD)	5.20 (0.812)	5.37 (0.730)	5.31 (0.762)
Median	5.40	5.60	5.60
Min, max	2.6, 6.1	2.6, 6.6	2.6, 6.6
Stratification: Peak C-peptide group, n (%)			
0.2-0.7 pmol/mL	47 (42.3)	91 (41.9)	138 (42.1)
>0.7 pmol/mL	64 (57.7)	126 (58.1)	190 (57.9)
Stratification: Age group, n (%)			
8-12 years	62 (55.9)	120 (55.3)	182 (55.5)
>12-17 years	49 (44.1)	97 (44.7)	146 (44.5)
Mean C-peptide AUC (pmol/mL) at baseline			
n	111	217	328
Mean (SD)	0.7237 (0.3190)	0.7445 (0.3653)	0.7375 (0.3499)
Median	0.6516	0.6744	0.6678
Min, max	0.223, 1.987	0.193, 2.384	0.193, 2.384
Insulin use at baseline (U/kg/day)[b]			
n	63	126	189
Mean (SD)	0.383 (0.2535)	0.447 (0.3093)	0.426 (0.2928)
Median	0.334	0.392	0.373
Min, max	0.00, 1.02	0.00, 1.80	0.00, 1.80
HbA1c (%) at baseline			
n	110	217	327
Mean (SD)	9.18 (1.918)	8.90 (1.729)	9.00 (1.797)
Median	9.10	8.80	8.90
Min, max	5.3, 14.3	4.8, 14.6	4.8, 14.6

Abbreviations: BMI=body mass index, ITT=intent to treat, SD=standard deviation, T1D=type 1 diabetes.
[a]Participants who marked multiple race categories were counted once and summarized as "multiple."
[b]Insulin use at baseline was calculated as the average daily use for participants who had at least 3 days of data recorded in the insulin diary before the start of study drug.
Note: Percentages were based on the number of non-missing observations in each treatment group.
Source: Table 14.1.3.1

The participants' T1D disease characteristics at baseline are summarized in Table 32. Approximately 80% of all participants were positive for 3 or more T1D-related autoantibodies. The proportion of study subjects having different autoantibodies is balanced for all autoantibodies but anti-insulin. The differences in HLA-types between treatment groups are 5-6 percentage points.

Table 22 Disease Characteristics at Baseline (ITT Population)

	Placebo N=111	Teplizumab N=217	Total N=328
History of DKA, n (%)	4 (3.6)	0	4 (1.2)
History of ketoacidosis, n (%)	0	2 (0.9)	2 (0.6)
T1D-related autoantibodies, n (%)			
n	111	217	328
anti-GAD65	96 (86.5)	183 (84.3)	279 (85.1)
anti-IA-2	87 (78.4)	165 (76.0)	252 (76.8)
anti-ZnT8	83 (74.8)	162 (74.7)	245 (74.7)
anti-insulin	85 (76.6)	144 (66.4)	229 (69.8)
anti-ICA	54 (48.6)	112 (51.6)	166 (50.6)
Number of positive T1D autoantibodies, n (%)			
n	111	217	328
0	0	1 (0.5)[a]	1 (0.3)
1	3 (2.7)	10 (4.6)	13 (4.0)
2	13 (11.7)	38 (17.5)	51 (15.5)
3	30 (27.0)	47 (21.7)	77 (23.5)
4	39 (35.1)	66 (30.4)	105 (32.0)
5	26 (23.4)	55 (25.3)	81 (24.7)
HLA genotype: DR3, n (%)			
n	109	215	324
Positive	56 (51.4)	96 (44.7)	152 (46.9)
Negative	53 (48.6)	119 (55.3)	172 (53.1)
HLA genotype: DR4, n (%)			
n	109	215	324
Positive	75 (68.8)	137 (63.7)	212 (65.4)
Negative	34 (31.2)	78 (36.3)	112 (34.6)

Abbreviations: AUC=area under the concentration-time curve, DKA=diabetic ketoacidosis, GAD=glutamic acid decarboxylase, HbA1c=hemoglobin A1c, HLA=human leukocyte antigen, IA=islet antigen, ICA=islet cell cytoplasmic autoantibody, ITT=intent to treat, SD=standard deviation, T1D=type 1 diabetes, ZnT8=zinc transporter 8.
[a]Participant 826903138 was randomized after testing positive for autoantibodies by the local laboratory. However, the central laboratory result was negative.
Note: Percentages were based on the number of non-missing observations in each treatment group.
Source: Table 14.1.3.1, Table 14.1.3.2, Table 14.1.4.1

Concerning the participants' medical history, the most common SOCs reported were immune system disorders (23.8%), skin and subcutaneous tissue disorders (15.9%), and infections and infestations (15.5%). The most common types of prior medications were long-acting insulins and analogs (32.0%) and fast-acting insulins and analogs (18.3%). The medical history and prior medications in the study participants were broadly consistent with the peadiatric population with newly diagnosed T1D. According to the applicant, no notable differences were observed between the placebo and teplizumab groups.

The most common types of concomitant medications were propionic acid derivatives (99.4%), fast-acting insulins and analogs (97.6%), long-acting insulins and analogs (86.0%), aminoalkyl ethers (64.9%), and anilides (39.9%). Participants in the teplizumab group were more likely to have used

concomitant aminoalkyl ethers (placebo 58.6% vs teplizumab 68.2%) and anilides (placebo 27.0% vs teplizumab 46.5%).

Outcomes and estimation

Primary Efficacy Endpoint

The result of the primary analysis of the change in C-peptide ln(AUC+1) from baseline to Week 78 is shown in Table 33.

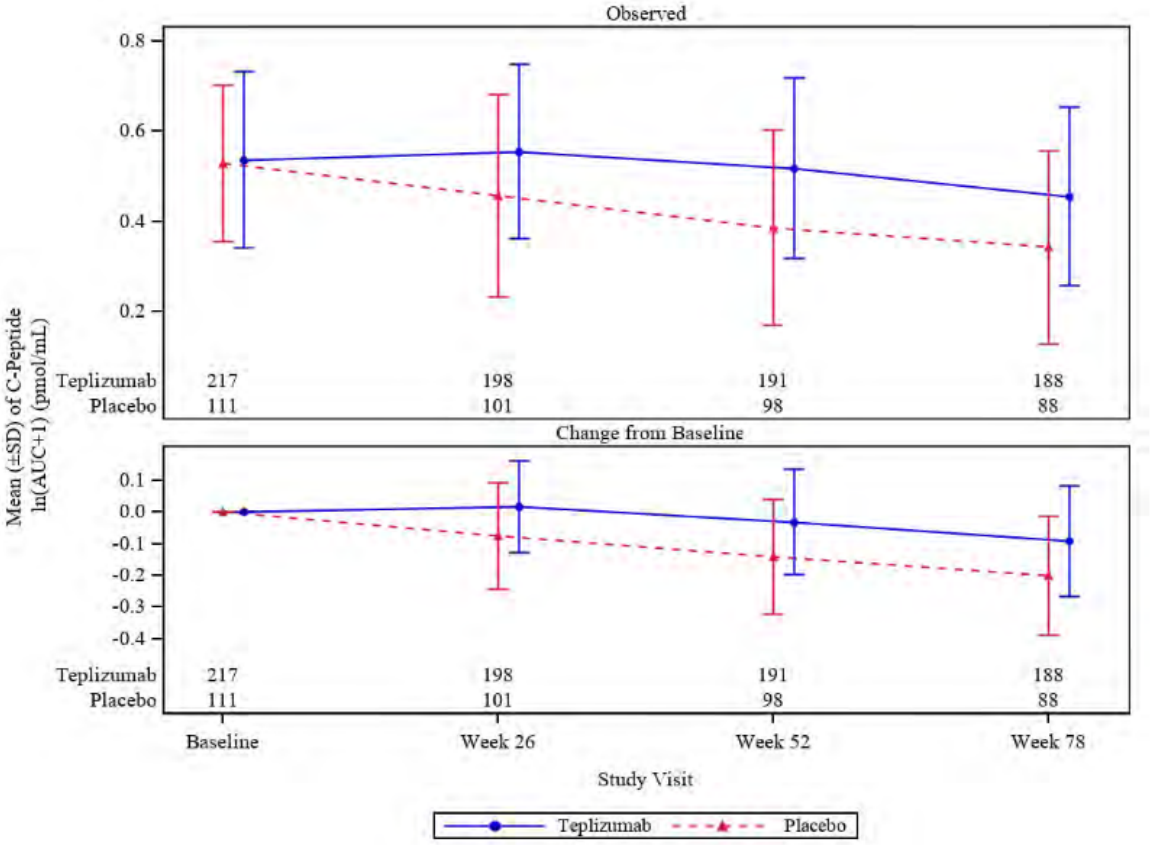
Table 23 Primary Analysis of Change from Baseline in C-peptide ln(AUC+1) (pmol/mL) at Week 78 (ITT Population)

	Placebo N=111	Teplizumab N=217
Baseline C-peptide ln (AUC+1)		
n	111	217
Mean (SD)	0.5290 (0.1732)	0.5367 (0.1955)
Median	0.5017	0.5154
Min, max	0.201, 1.094	0.177, 1.219
Week 78		
n	88	188
Mean (SD)	0.3426 (0.2147)	0.4560 (0.1983)
Median	0.3154	0.4568
Min, max	0.023, 0.972	0.047, 0.988
Change from baseline at Week 78		
n	88	188
Mean (SD)	-0.1999 (0.1883)	-0.0908 (0.1750)
Median	-0.1909	-0.0839
Min, max	-0.804, 0.238	-1.152, 0.320
LS mean (95% CI)	-0.2112 (-0.2437, -0.1786)	-0.0859 (-0.1090, -0.0628)
LSmean difference (95% CI)		0.1253 (0.0852, 0.1653)
p value		<0.001

Abbreviations: ANCOVA=analysis of covariance, AUC=area under the concentration-time curve, CI=confidence interval, ITT=intent to treat, LS=least square, SD=standard deviation
Note: Baseline is defined as the most recent value collected prior to the first dose of study drug.
Note: Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption.
Note: Estimates and the p-value were obtained from an ANCOVA model that included treatment, age group at randomization, and baseline C-peptide ln(AUC+1) as independent variables.
Note: LSmean difference = teplizumab – placebo.
Source: Table 14.2.1.1

The observed values of C-peptide ln(AUC+1) in 4h MMTT over time and changes from baseline are displayed in Figure 25. The placebo group showed a decline in the mean ln(AUC+1) value. At all post-baseline time points, the teplizumab group had a higher mean ln(AUC+1) value than the placebo group.

Figure 24 Observed Values and Change from Baseline in C-peptide ln(AUC+1) (pmol/mL) over time (ITT Population)



Abbreviations: AUC=area under the concentration-time curve, ITT=intent to treat, SD=standard deviation
Note: Baseline is defined as the most recent value collected prior to the first dose of study drug.
Source: Figure 14.2.1.1

Secondary Efficacy Endpoints

Secondary efficacy endpoints included the following:

• Exogenous insulin use: defined as a daily average in units per kilogram per day (U/kg/day), at Week 78

• HbA1c levels: expressed in % and mmol/mol, at Week 78

• TIR: expressed as a daily average of the percentage of time in a 24-hour day a Participant's blood glucose (BG) is ≥ 70 but ≤180 mg/dL (≥ 3.9 to ≤10.0 mmol/L), assessed using continuous glucose monitoring (CGM), at Week 78

• Clinically important hypoglycemic episodes: defined as the total number of episodes of a BG reading of <54 mg/dL (3.0 mmol/L) and/or episodes of severe cognitive impairment requiring external assistance for recovery, from randomization through Week 78.

Exogenous insulin use

The ANCOVA analysis of average exogenous insulin use, derived from insulin diary records, is shown in Table 34. The teplizumab group showed a numerically lower average daily insulin dose at Week 78 than the placebo group, but statistical significance was not reached. The reasons for missingness of the insulin use at week 78 are shown in Table 35.

Table 24 Analysis of Average Daily Use of Exogenous Insulin (U/kg/day) at Week 78 (ITT Population)

	Placebo N=111	**Teplizumab N=217**
Baseline		
n	63	126
Mean (SD)	0.383 (0.2535)	0.447 (0.3093)
Median	0.334	0.392
Min, max	0.00, 1.02	0.00, 1.80
Week 78		
n	50	98
Mean (SD)	0.598 (0.3268)	0.446 (0.2675)
Median	0.557	0.409
Min, max	0.10, 1.75	0.00, 1.47
LS mean (95% CI)	0.593 (0.470, 0.716)	0.463 (0.363, 0.562)
LSmean difference (95% CI)		-0.131 (-0.280, 0.018)
p value		0.085

Abbreviations: ANCOVA=analysis of covariance, CI=confidence interval, ITT=intent to treat, SD=standard deviation.
Note: Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption.
Note: Estimates and the p-value were obtained from an ANCOVA model that included treatment, age group at randomization, and screening peak C-peptide category as independent variables.
Note: Insulin use was calculated as the average daily use for participants who had at least 3 days of insulin use recorded in the Insulin Use eDiary for each visit. Data were obtained from the Insulin Use eDiary.
Note: LSmean difference = teplizumab − placebo.
Source: Table 14.2.2.1

Table 25. PROTECT: Missingness reasons for the insulin use at Week 78 - ITT Population

n %	**Teplizumab (N=217)**	**Placebo (N=111)**
Total number of participants with insulin dose at W78	98 (45.2)	50 (45.0)

n %	Teplizumab (N=217)	Placebo (N=111)
Total number of participants with missing insulin dose at W78	119 (54.8)	61 (55.0)
Participants who had discontinued the study at W78	22 (10.1)	10 (9.0)
Participants who were on-study but did not report any insulin dose at W78	97 (44.7)	51 (45.9)
Patients reported fewer than 3 days	29 (13.4)	12 (10.8)
Did not report any insulin data at W78	68 (31.3)	39 (35.1)
Did not report any insulin data in eDiary during the study	5 (2.3)	10 (9.0)

Participants who were on study but had discontinued insulin at W78 are counted in participants with insulin dose at W78, with a dose of 0.
PGM=DEVOPS/SAR446681/EFC18118/QREG/REPORT/PGM/eff_ins_miss_i_t.sas
OUT=REPORT/OUTPUT/eff_ins_miss_i_t_i.rtf (24JUN2025 13:05)

Hemoglobin A1c at Week 78

The ANCOVA analysis of HbA1c showed an improvement in the mean HbA1c levels from baseline to Week 78 In both treatment groups. The LS mean (95% CI) difference between teplizumab and placebo was -0.09% (-0.42%, 0.24%) (p=0.606). The change in HbA1c at Week 78 was similar between the 2 groups.

TIR for Glycemic Control from CGM at Week 78

The ANCOVA analysis of TIR for glycemic control, defined as the percentage of time blood glucose, was between 70 and 180 mg/dL, at Week 78. The LS mean (95% CI) difference between teplizumab and placebo in TIR for glycemic control was 4.71% (-1.72%, 11.15%) (p=0.151). The teplizumab group showed a numerically higher TIR at Week 78 compared with the placebo group, but statistical significance was not reached.

Rate of Clinically Hypoglycemic Events Through Week 78 (eDiary Data)

Analysis of the rate of clinically important hypoglycemic events (which included Level 2 and Level 3 events reported in the Hypoglycemic Events eDiary), showed that the rate of clinically important hypoglycemic events during the study was similar between the 2 groups. According to the SAP-specified criteria for Level 3 events, none of the hypoglycemic events reported in the eDiary were classified as Level 3. Thus, the efficacy analysis of clinically important hypoglycemic events included only Level 2 events.

Explorative endpoints

Explorative endpoints included:

Participants Not Using Exogenous Insulin or Met Criteria for Insulin Discontinuation. Participants who met the insulin discontinuation criteria were numerically higher in the teplizumab group than in the placebo group for all post-baseline timepoints. However, p-values were between 0.136 and 0.634, with one exception.

White Blood Cell Subsets Analyses of quantitative lymphocyte subsets (TBNK panel) in blood showed that in the teplizumab group, the percentage of circulating CD3+CD4+ T cells decreased after each

course of treatment was initiated. The absolute numbers of other white blood cells (B cells and NK cells) were not markedly affected by teplizumab.

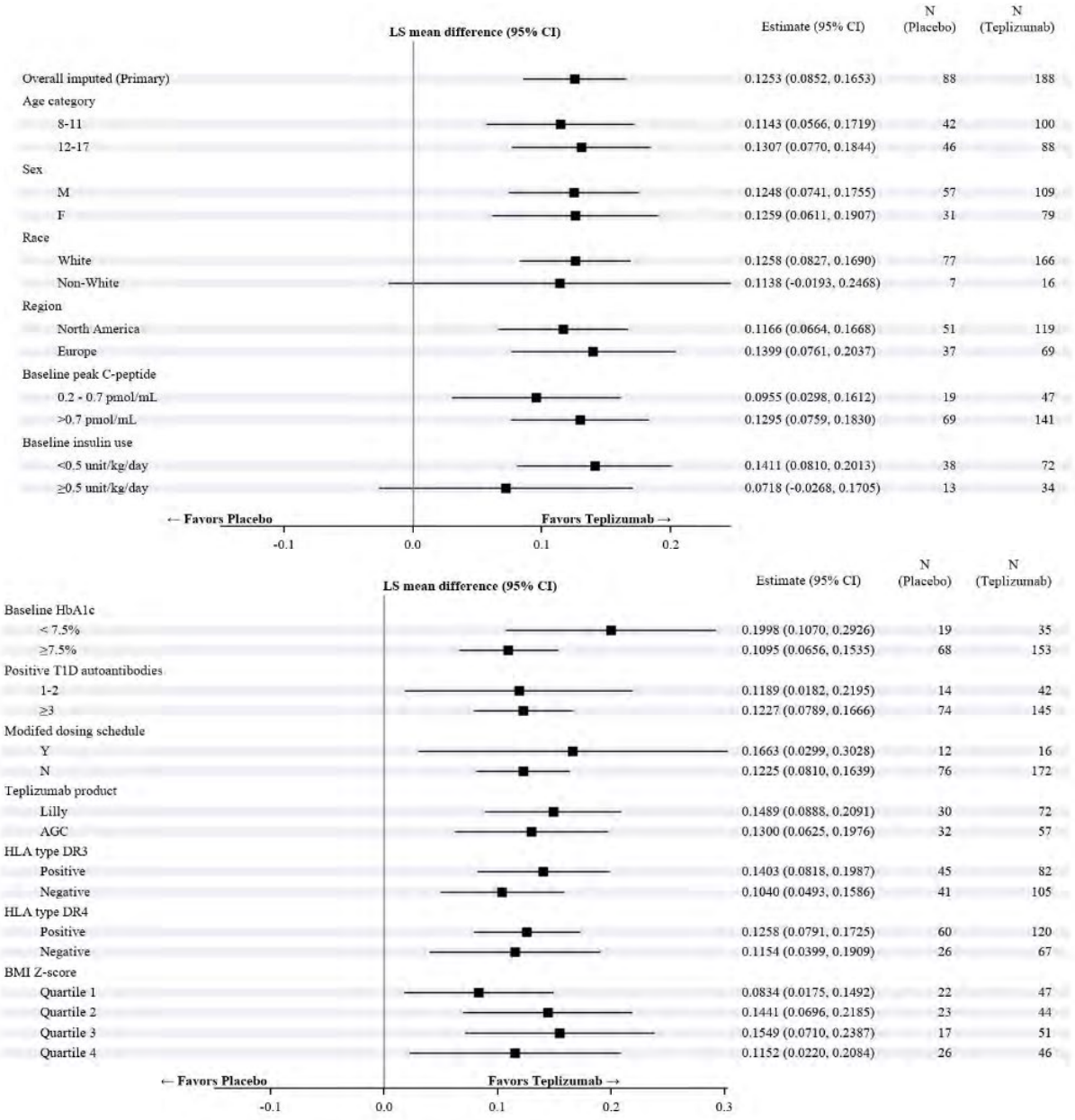
T1D Autoantibodies The proportions of participants who tested positive for T1D autoantibodies over time remained generally unchanged from baseline during the study and were comparable between the placebo and teplizumab groups.

Pre-defined and ad-hoc subgroup analyses

Primary efficacy endpoint

Sub-groups analyses of the primary endpoint by age group, sex, race, geographic region, baseline insulin use, baseline peak C-peptide category, baseline HbA1c category, dosing schedule category, number of positive autoantibodies, HLA genotype DR3, HLA genotype DR4, teplizumab manufacturer, and BMI z-score were performed. The sub-group analysis results are displayed in Figure 26.

Figure 25 Forest Plot of Subgroup Analysis of Change from Baseline in ln(AUC+1) C-peptide (pmol/mL) at Week 78 (ITT Population)



Abbreviations: AUC=area under the concentration-time curve, BMI=body mass index, F=female, HbA1c=hemoglobin A1c, HLA=human leukocyte antigen, ITT=intent to treat, M=male, T1D=type 1 diabetes
Note: Baseline was defined as the most recent value collected before the first dose of study drug.
Note: Missing data were multiply imputed using a pattern-mixture model under the assumption of missing not at random.
Source: Figure 14.2.1.4

Pre-defined and post-hoc sensitivity analyses

Post-hoc analysis: Sensitivity Analysis of Primary Efficacy Endpoint with Redefined Below-Detection Levels

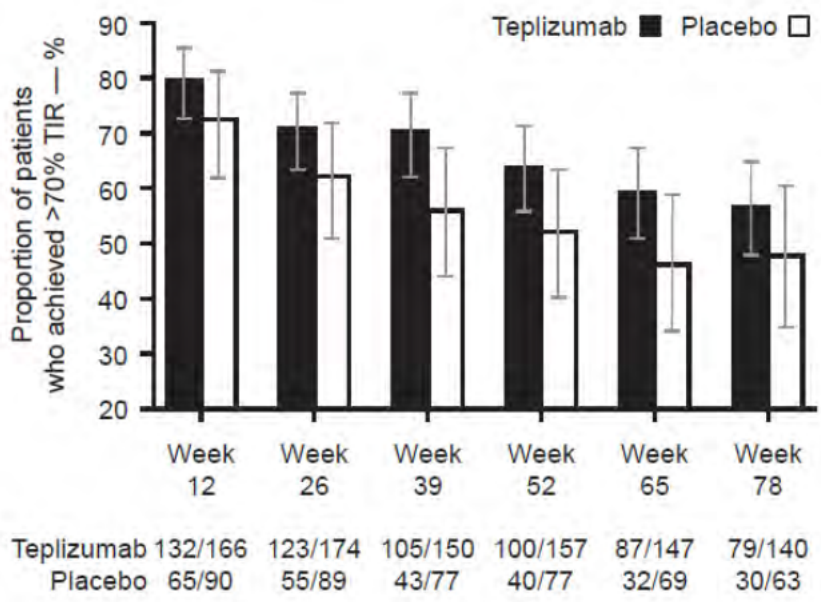
In the planned analysis, the numeric values of C-peptide level that were below the level of detection were set to blank when the character results reported in the source data were converted to numeric

results. Therefore, those blank C-peptide values were imputed according to the statistical analysis plan. A post-hoc sensitivity analysis was conducted in which the threshold of the detectable value was applied for those data points. A total of 16 participants (11 in the placebo group and 5 in the teplizumab group) had at least one C-peptide sample with below-detection value at Week 78. The LS mean (95% CI) of change from baseline in C-peptide ln(AUC+1) at Week 78 were -0.2201 (-0.2526, -0.1877) pmol/mL for the placebo group and -0.0877 (-0.1108, -0.0646) pmol/mL for the teplizumab group. The LS mean difference (95% CI) between the teplizumab and placebo group was 0.1324 (0.0927, 0.1721) pmol/mL (p<0.001), which was slightly larger than the difference seen in the planned analysis.

Post-hoc analysis: Proportion of Participants with TIR >70%

The proportion of participants who had TIR >70% over time is displayed in Figure 27.

Figure 26 Proportion of Participants with TIR >70% for Glycemic Control by Visit (ITT Population)



Abbreviations: CGM=continuous glucose monitoring, ITT=intent to treat, TIR=time in range
Note: Percentages are based on the number of non-missing observations in each treatment group.
Note: Clopper-Pearson exact CIs are reported.
Source: Table 14.2.6.9.1a

Post-Hoc Analysis: Sensitivity Analysis of Clinically Important Hypoglycemic Events (explorative endpoint)

The prespecified analysis of clinically important hypoglycemic events was performed based on the data reported in the Hypoglycemic Event eDiary completed by the participants and their caregivers. Hypoglycemic events were also reported as AEs by investigators in the AE CRF. To address the potential underreporting of clinically important hypoglycemic events in the eDiary, a sensitivity analysis integrating the eDiary and AE CRF data was conducted, in which clinically important hypoglycemic events were defined as follows:

• Level 2 events: Level 2 events from the eDiary or hypoglycemia AEs Grade 2 from the AE CRFs

• Level 3 events: Level 3 events from the eDiary or hypoglycemia adverse events Grade 3 or above from the AE CRFs

In the analysis, duplicate or overlapping hypoglycemic events in the eDiary and AE CRF were removed. The total number of clinically important hypoglycemic events was identified using the above criteria throughout the study. For the overall rate of clinically important hypoglycemic events, the estimated ratio (95% CI) of teplizumab/placebo was 0.90 (0.64, 1.27) (p=0.538). For Level 3 hypoglycemic events, the estimated ratio (95% CI) was 0.29 (0.13, 0.62) (p=0.002).

6.3.3. Clinical studies in special populations

Table 26 Clinical studies in special populations

	Controlled Trials	***Non-controlled trials***
Renal impairment* patients (Subjects number /total number)	none	SDRNT1BIO: Objective 1: 631/5630 participants Objective 2: 59/407 participants
Hepatic impairment** patients (Subjects number /total number)	none	SDRNT1BIO: Objective 1: 34/5630 participants Objective 2: ≤5/407 participants
Paediatric patients <18 years (Subjects number /total number)	TN-10: 55/76 PROTECT: 328/328 Protégé: 163/305 Encore: 73/125 Study 1: 31/ 42 AbATE: 72/77 Delay: 55/60	Fr1da: 152/152 Objective 1: 64/5630 participants Objective 2: ≤5/407 participants
Older patients; Age 65-74 (Subjects number /total number)	none	SDRNT1BIO: Objective 1: 379/5630 participants Objective 2: 30/407 participants
Age 75-84 (Subjects number /total number)	none	SDRNT1BIO: Objective 1: 109/5630 participants Objective 2: 7/407participants
Age 85+ (Subjects number /total number)	none	SDRNT1BIO: Objective 1: ≤5/5630 participants Objective 2: ≤5/407 participants
Other (Subjects number /total number)	none	

* Renal impairment is defined as having CKD Stage 3 or worse (eGFR less than 60ml/min or RRT)
** Hospital record with ICD10 codes for "Diseases of Liver (K70-K77) within 10 years prior to enrolment
Note: No participants received teplizumab in the SDRNT1BIO and Fr1da studies.
Objective 1 SDRNT1BIO: To examine the association of baseline C-peptide with incident complications of diabetes, including: diabetic ketoacidosis (DKA), severe hospitalised hypoglycaemia (SHH), retinopathy and maculopathy, chronic kidney disease and estimated Glomerular Filtration Rate (eGFR), cardiovascular disease (CVD) and its

components myocardial infarction (MI), heart failure and stroke, and death in the Scottish Diabetes Research Network Type 1 Bioresource. Association of C-peptide at baseline with glycaemic control, as measured by HbA1c, during follow up was also examined.
Objective 2 SDRNT1BIO: To examine the association of C-peptide during follow up, and change from baseline in C-peptide during follow up, with incident complications and HbA1c during follow up in a subset of patients in the Scottish Diabetes Research Network Type 1 Bioresource in whom post-baseline blood samples are available for analysis.

No study participant was 65 years or older. The number of paediatric study participants per clinical trial is specified above. No participants with impaired renal function or with impaired hepatic function were included in controlled trials.

6.3.4. Supportive studies

Two completed extension studies TN-10 Extension (PRV-031-002) and Protégé Extension (CP-MGA031-02) are included in the dossier. For details on the studies, see Table 11 (section 6.1.2).

TN-10 extension was a single-arm, multicenter, open-label clinical study to evaluate the safety of teplizumab in participants with clinical (Stage 3) T1D. Teplizumab-treated and placebo participants in the TN-10 study who had developed Stage 3 T1D after the conclusion of that study, were eligible to enroll and receive teplizumab treatment within one year of clinical T1D diagnosis. All participants were to receive a 12-day course of teplizumab given through daily IV infusions. Secondary objectives included to evaluate beta-cell function, using the endpoint C-peptide AUC after a 4h MMTT. The study was conducted in the US from February 2020 to January 2024. There were 6 study participants. The sample size was too small for statistical conclusions to be made, thus no meaningful results evaluation for any efficacy endpoint was possible.

Protégé Extension The study was started in Feb 2009 (first subject enrolled), and the sponsor decided to terminate the study (based on study CP-MGA031-01 results) in Nov 2010. The primary objective of the extension study was to assess longer-term safety. The secondary objectives planned for the extension study were to assess longer-term efficacy of teplizumab, evaluate immunologic effects (in Canada and the United States [US] only), measure anti-teplizumab antibody levels, and assess patient-reported outcomes (PRO) in adults and children with recent-onset T1DM. Of the 497 subjects eligible for the extension study, 219 subjects were enrolled, and none completed this extension study. All 219 enrolled subjects were analysed for safety.

The original composite endpoint (HbA1c<6.5% and insulin<0.5U/kg/day) as well as C- peptide, insulin use, HbA1c, and the new composite (HbA1c<7.0% and insulin<0.25U/kg/day) were to be assessed as was done in Protégé. Because the study was terminated early with a limited number of subjects and subject visits the data were only summarised. Too few data were available for meaningful results evaluation for any efficacy endpoint.

6.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

The Integrated Summary of Efficacy includes the statistical analysis plan for C-peptide meta-analysis, of 18 June 2020, describing the meta-analysis plan for the assessment of C-peptide levels across multiple studies in subjects with newly diagnosed T1D (i.e., Stage 3) in support of indication 1, and the

Statistical analysis plan Integrated summary of effectiveness (ISE) for stage 3 Type 1 Diabetes (T1D) of 19 April 2024, in support of the initially claimed indication 2.

Meta analysis in support for Indication 1 is based on individual data from 5 clinical studies: Protégé (randomised segment), Encore, Study 1, AbATE (=study 4), and Delay. For the initially claimed Indication 2, the meta-analyses are based on 6 clinical studies: Protégé (randomised segment), Encore, Study 1, AbATE (=study 4), Delay and the pivotal study PROTECT. For details concerning these studies, see Table 11 (section 6.1.2).

A brief summary is provided in Table 37. Baseline characteristics and demographics are presented in Table 38.

Table 27 Study Entry Criteria and Dosing Schedule

	PROTECT	**Protégé**	**Encore**	**Study 1**	**AbATE**	**Delay**
Age at entry (years)	8-17	8-35	8-35	7.5–30	8-30	8-30
Time from diagnosis to treatment	≤6 weeks	≤12 weeks	≤12 weeks	≤6 weeks	≤8 weeks	4-12 months
Baseline C-peptide	≥0.2 pmol/mL	Detectable level	Detectable level	≥0.2 nmol/L	≥0.2 nmol/L	≥0.2 nmol/L
Autoantibodies	At least 1 T1D-associated autoantibody	At least 1+ a. islet-cell autoantibodies (ICA512/IA-2) b. anti-GAD65+, or c. insulin autoantibodies (if present during first 2 weeks, but not beyond 2 weeks, of insulin treatment)	At least 1+ a. islet-cell autoantibodies (ICA512/IA-2) b. anti-GAD65+, or c. insulin autoantibodies (if present during first 2 weeks, but not beyond 2 weeks, of insulin treatment	presence of anti-GAD65+, anti-ICA512+, and/or anti-insulin autoantibodies	anti-GAD65+, anti-ICA512+, or ICA+.	at least 1+ autoantibody (islet cell antibody [ICA], anti-GAD65+ or anti-ICA512+
Dosing schedule	12 days, 2 courses	14 days, 2 courses	14 days, 2 courses	12 or 14 days, 1 course	14 days, 2 courses	14 days, 1 course
Dose schedule	Baseline, 6 months (or 12 months for modified dosing schedule (due to COVID-19 pandemic))	Baseline, 6 months	Baseline, 6 months	Baseline	Baseline, 12 months	Baseline

PROTECT

The PROTECT study is described in detail in section 6.3.2.2.

Protégé

The primary objective of the Phase 2/3 study was to assess, compared to placebo, the efficacy, tolerability, and safety of teplizumab when administered according to 3 different teplizumab dosing regimens in subjects with newly diagnosed T1D (clinical diagnosis within past 12 weeks). The secondary objectives included to assess the preservation of beta cell reserve as measured by C-peptide, durability of clinical benefit. After all subjects completed dosing and follow-up through Day 364, the independent Data Monitoring Committee (DMC) performed a planned analysis of 1-year unblinded safety and efficacy data from this study. No significant differences were observed between the teplizumab and placebo treatment groups in the primary endpoint (HbA1c<6.5% and insulin<0.5 units/kg/day at Week 52 [Day 364]).

Encore

The primary objective of this Phase 3 study was to assess, compared to placebo, the efficacy, tolerability, and safety of teplizumab when administered according to 3 different teplizumab dosing regimens in subjects with newly diagnosed T1D. All regimens were administered in addition to standard of care (i.e., insulin treatment). The secondary objectives were to assess the preservation of beta cell reserve as measured by C- peptide, durability of clinical benefit, and the pharmacokinetics, pharmacodynamics, and immunogenicity of teplizumab. A total of 400 planned subjects were randomised into 4 treatment groups in a 1:1:1:1 ratio and dosed for 14 consecutive days in 2 courses, the first at randomisation and the other at 26 weeks. The 4 treatment groups were: (1) full 14-day regimen; (2) 6-day regimen; (3) 1/3 dose regimen; and (4) placebo. Subjects in all 4 treatment groups underwent a 4-hour MMTT throughout 2 years.

Enrollment and dosing under this protocol was suspended based on the results from the Protégé study when the primary endpoint was not met in the interim analysis (composite of HbA1c<6.5% and Insulin<0.5units/kg/day). As a result of the early termination of this study, only 29,1% of the participants were followed for 24 months as originally planned.

Study 1

This study was a Phase 1/2, randomized, controlled, open-label study to test the safety and course of teplizumab on the loss of insulin production over 2 years in subjects with newly diagnosed T1D (within 6 weeks of clinical diagnosis). The control group underwent the same metabolic and immunologic assessments as in the drug-treated group, but the subjects did not receive study drug (standard of care only) and were not hospitalized. Subjects randomly assigned to drug treatment received either a 12-day (n = 9) or 14-day (n = 12) course of teplizumab. The subjects in both groups returned for a 4-hour MMTT every 6 months.

AbATE

This was a randomized, open-label study which enrolled individuals diagnosed with T1D (clinical diagnosis within 8 weeks of randomization), and were positive for anti-GAD65+, anti-ICA512+, or ICA+ at 6 medical centers in the US. Subjects were randomized to teplizumab treatment or a control group (standard of care) in a 2:1 ratio. The study was open label. The drug treatment group received two 14-day courses of teplizumab, with the first course occurring at randomization and the second course 12 months later. Subjects in both groups underwent a 4-hour MMTT every 6 months for 2 years.

Delay

The study was a randomized, double-blind, placebo-controlled trial with a 1:1 randomization to teplizumab or placebo infusions. Sixty subjects were enrolled and dosed from 4 to 12 months from the clinical diagnosis of T1D, at 4 academic centers in the US. Randomization was stratified by time from diagnosis (4-8 months and 9-12 months). The primary outcome was a comparison of C-peptide responses to a 4-hour MMTT after 1 year. Subjects received a 14-day course of either intravenous teplizumab or saline.

Table 28 Baseline characteristics and demographics

	PROTECT		Protégé		Encore		Study 1		AbATE		Delay	
	Teplizumab N=217	Placebo N=111	Teplizumab[1] N=207	Placebo N=98	Teplizumab[1] N=63	Placebo N=62	Teplizumab N=21	Placebo N=21	Teplizumab N=52	Placebo N=25	Teplizumab N=32	Placebo N=28
Age mean (SD)	12.0 (2.53)	12.3 (2.55)	18.8 (7.4)	18.2 (7.3)	17.3 (6.4)	18.4 (7.9)	13.9 (5.4)	14.9 (6.0)	12.7 (4.9)	12.3 (4.1)	12.7 (4.1)	11.9 (4.0)
Sex (% Male)	54.8	62.2	62.8	62.2	60.3	66.1	61.9	61.9	53.8	64	56.3	60.7
HbA1c (%) mean (SD)	8.90 (1.729)	9.18 (1.918)	8.32 (2.01)	8.19 (2.03)	8.09 (2.0)	8.40 (2.0)	8.98 (1.7)	8.05 (1.1)	7.43 (0.99)	7.7 (1.23)	6.4 (0.8)	7.14 (1.2)
C-peptide (nmol/L) mean (SD)	0.7445 (0.3653)	0.7237 (0.3190)	0.65 (0.53)	0.65 (0.43)	0.68 (0.56)	0.58 (0.35)	0.49 (0.2)	0.48 (0.2)	0.72 (0.29)	0.67 (0.28)	0.62 (0.30)	0.59 (0.42)
Insulin Use (units/kg/day) mean (SD)	0.447 (0.3093)	0.383 (0.2535)	0.61 (0.40)	0.64 (0.31)	0.59 (0.29)	0.61 (0.33)	0.51 (0.25)	0.44 (0.21)	0.39 (0.26)	0.39 (0.17)	0.41 (0.14)	0.39 (0.20)
Time from diagnosis, weeks, mean (SD)	5.37 (0.730)	5.20 (0.812)	8.5 (2.6)	8.5 (2.6)	9.1 (2.3)	8.6 (2.4)	<6 weeks	<6 weeks	5.8 (1.2)	5.4 (1.3)	30.9 (10.7)	30.7 (10.5)

Abbreviation: SD=standard deviation

[1] Including subjects who received the full 14-day regimen only.

Meta analyses to support the stage 2 data (indication 1)

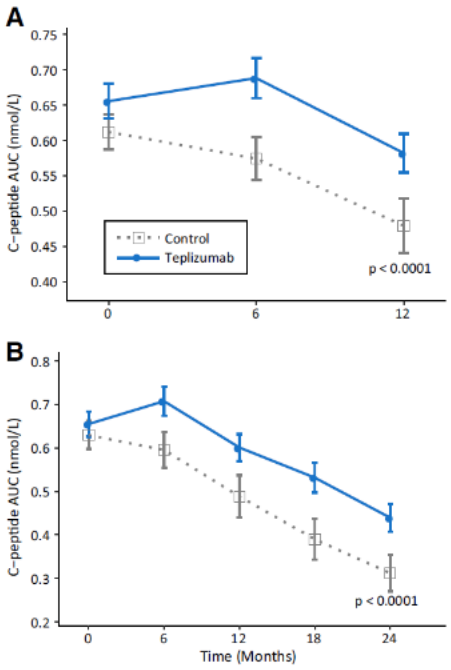
According to the applicant, the rationale for the use of C-peptide data in Stage 3 patients as supportive evidence stems from the observation that Stage 2 disease is a contiguous phase in the continuum of T1D. Among the 5 studies included in this meta-analysis, C-peptide was the primary endpoint in three studies (AbATE, Delay, Study 1) and a key secondary endpoint in two studies Protégé and Encore. The At-Risk (TN-10) study was not included in the meta-analysis due to differences in patient population (stage 2 pre-diabetics) and assessment for C-peptide (2-hour OGTT).

A one-stage meta-analysis using individual patient data was performed. In the one-stage approach, a random effects model that incorporated both within-study and between-study variance was used due to heterogeneity amongst the studies. ANCOVA with a random treatment effect was used for the analyses, which included ln(AUC+1) as the dependent variable, and baseline C-peptide, the random treatment effect, age, study, and # of courses of treatment (1 vs 2) as covariates. Estimates of treatment effect and between- study variability were derived along with 95% CIs. One analysis concerned 5 studies based on pooled 12-month data (one year follow-up) and another analysis was

based on 3 studies based on pooled 24-month data (2 year follow up). Encore was only included in the first analysis.

Observed mean C-peptide AUC for 1- and 2-year follow-up are shown in Figure 28.

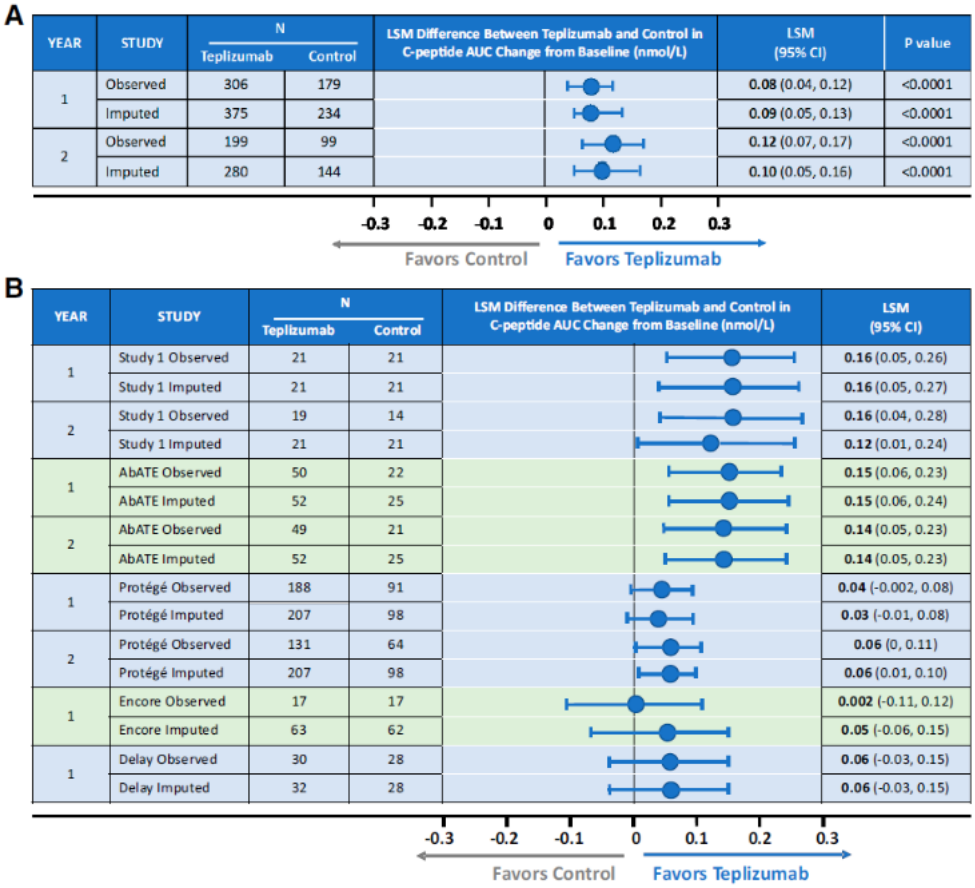
Figure 27 Stage 3 T1D - Meta-analysis of the 5 supportive studies: Mean (SE) observed C-peptide or 1- and 2-year follow-up



Modified from Herold et al. Diabetes Care 2023 (68). **A:** C-peptide AUC levels at 1 year from the 5 studies with 1-year data; p-value at 1 year was derived from the ANCOVA model for the 1-year integrated observed data. **B:** C-peptide AUC levels at 2 years from the 3 studies with 2-year data; p-value at 2 years was derived from ANCOVA for the observed 2-year integrated data.

Forest plots of the LS mean differences (observed and imputed values) between teplizumab and control groups in the change from baseline in C-peptide AUC are presented in Figure 29.

Figure 28 Stage 3 T1D - Meta-analysis of the 5 supportive studies: Forest plot of LSM differences in the change from baseline in C-peptide AUC between teplizumab and control groups



A

YEAR	STUDY	N		LSM Difference Between Teplizumab and Control in C-peptide AUC Change from Baseline (nmol/L)	LSM (95% CI)	P value
		Teplizumab	Control			
1	Observed	306	179		**0.08** (0.04, 0.12)	<0.0001
	Imputed	375	234		**0.09** (0.05, 0.13)	<0.0001
2	Observed	199	99		**0.12** (0.07, 0.17)	<0.0001
	Imputed	280	144		**0.10** (0.05, 0.16)	<0.0001

B

YEAR	STUDY	N		LSM Difference Between Teplizumab and Control in C-peptide AUC Change from Baseline (nmol/L)	LSM (95% CI)
		Teplizumab	Control		
1	Study 1 Observed	21	21		**0.16** (0.05, 0.26)
	Study 1 Imputed	21	21		**0.16** (0.05, 0.27)
2	Study 1 Observed	19	14		**0.16** (0.04, 0.28)
	Study 1 Imputed	21	21		**0.12** (0.01, 0.24)
1	AbATE Observed	50	22		**0.15** (0.06, 0.23)
	AbATE Imputed	52	25		**0.15** (0.06, 0.24)
2	AbATE Observed	49	21		**0.14** (0.05, 0.23)
	AbATE Imputed	52	25		**0.14** (0.05, 0.23)
1	Protégé Observed	188	91		**0.04** (-0.002, 0.08)
	Protégé Imputed	207	98		**0.03** (-0.01, 0.08)
2	Protégé Observed	131	64		**0.06** (0, 0.11)
	Protégé Imputed	207	98		**0.06** (0.01, 0.10)
1	Encore Observed	17	17		**0.002** (-0.11, 0.12)
	Encore Imputed	63	62		**0.05** (-0.06, 0.15)
1	Delay Observed	30	28		**0.06** (-0.03, 0.15)
	Delay Imputed	32	28		**0.06** (-0.03, 0.15)

Extracted from Herold et al. Diabetes Care 2023 (68). **A:** Analysis includes the 5 clinical studies with 1-year data. Analysis is with and without the imputed data for missing values. **B:** Analysis includes the 3 clinical studies for which 1- and 2-year data were available. Analysis is with and without the imputed data for missing values. LSM= Least Square Mean.

Meta analyses to support the indication 2

Five of the 6 studies were pooled for the original BLA ISE. For the sBLA, data from the PROTECT study was added to the original BLA pooled data. The 6 completed studies integrated were: (1) PROTECT; (2) Protégé; (3) Encore; (4) Study 1; (5) AbATE; and (6) Delay. For the Protégé and Encore studies, only subjects who received the full 14-day teplizumab regimen or placebo were included in the pooled data. HbA1c and insulin use were secondary or exploratory endpoints in these studies. Hypoglycemic event was a secondary efficacy endpoint in the PROTECT study and an important safety assessment in all 6 studies. Additional study pooling was performed for placebo-controlled studies (PROTECT, Protégé, Encore, Delay) and standard-of-care- controlled studies (AbATE, Study 1).

In the PROTECT study, C-peptide was assessed through 4-hour MMTTs at prespecified time points from baseline to Week 78. In AbATE, Encore, Protégé, and Study 1, MMTTs were taken through 24 months and in Delay, MMTTs were taken through 12 months. Due to the early termination of the Encore study, few subjects had C-peptide data collected post 18 months. HbA1c (%) data were collected over the course of each study. Insulin use (units/kg/day) over the course of study conduct was documented in each study using a diary. Hypoglycemic events were reported by subjects in the eDiary and by

Investigators in the adverse event form in the PROTECT study. For the other 5 studies, hypoglycemic events were only reported by the investigators in the adverse event form.

Integrated analyses of efficacy endpoints

Due to the limited number of studies and the large amount of missing data in Protégé at Month 24, results were presented on the description of Month 18 data.

Peak C-peptide: In the 6 studies a trend was observed with higher proportions of participants with post-baseline peak C-peptide ≥0.2 pmol/mL in the teplizumab group compared to the control group.

HbA1c: In the 6 Stage 3 T1D studies, HbA1c (%) was collected for up to 12 months for Delay, 18 months for PROTECT, 24 months for Protégé, Encore, AbATE and Study 1.

Daily insulin use: Mean observed values and changes from baseline in daily insulin use are presented by study for the 6 studies. Participants treated in India used higher insulin doses than in other countries.

Participants meeting insulin discontinuation criteria: At baseline, the percentage of participants in the integrated analyses ITT population who met the insulin discontinuation criteria was similar in the 2 treatment groups. At Month 18, the proportions were 11.2% (43/385 participants) in the teplizumab versus 2.7% (6/222 participants) in the control group.

Hypoglycemic adverse events: Mean rates of severe (Grade ≥3) hypoglycemic adverse events (according to CTCAE) are reported by study and the event rates were evaluable for PROTECT and Protégé studies only. Due to the small sample size and the low number of participants with events, the event rates were not estimable for the other 3 studies. In PROTECT, the estimated mean rate of severe hypoglycemic adverse events was 0.20 events/patient-year in the teplizumab group and 0.67 in the control group. In Protégé, the estimated mean rate of severe hypoglycemic adverse events was 0.01 events/patient-year in the teplizumab group and 0.02 events/patient-year in the control group.

Correlation of C-peptide and metabolic endpoints: According to the applicant, scatter plots based on integrated observed data suggest that higher mean C-peptide AUC was associated with larger decrease from baseline in HbA1c, lower average daily insulin, and a lower rate of Grade ≥3 hypoglycemic events (according to CTCAE) at Month 18.

6.3.6. Data from registries

Two real-world evidence (RWE) studies, the Fr1da study (indication 1) and the SDRNT1BIO (indication 2) were included in the dossier. Details on the studies are presented in Table 39.

Table 29 Overview of completed RWE studies that support the clinical development program of teplizumab

Table 2 - Overview of completed RWE studies that support the clinical development program of teplizumab

Study (Study number)	Objectives	Study Population Number of Participants	Study Design Follow-up Duration	Key endpoints
Assessment of generalizability of TN-10 trial results to an European population (European population from the Fr1da Study) (CS-00910)	**Primary:** -To assess the similarity of times to progression from Stage 2 T1D to Stage 3 T1D observed between the TN-10 placebo arm and a cohort of European participants with Stage 2 T1D, overall, and for the TN-10 placebo arm and European study participants aged between 8-15 years only. -To assess the similarity of times to progression from Stage 2 T1D to Stage 3 T1D observed between the European study subgroups based on whether participants did or did not have a first degree relative with T1D.	TN-10 participants: 76 Total 32 placebo 44 teplizumab Stage 2 T1D Fr1da study participants: 152	Retrospective study based on secondary use of pre-existing data gathered from a clinical trial (TN-10) and a screening cohort (Fr1da). TN-10: August 2010 (beginning of inclusion) to 30 November 2018 (end of follow-up) Fr1da: February 2015 (beginning of screening) to February 2024 (end of follow-up)	Primary endpoint: Stage 3 T1D as defined using the ADA criteria Other evaluated variables were: age, gender, BMI, T1D-related antibodies (number and type of antibody[ies]), HLA-DR3 and HLA-DR4 presence, HbA1c, glucose tolerance, T1D staging, age at first and confirmatory test for diagnosis of Stage 2 T1D and Stage 3 T1D, age at last visit, time between index/age at Stage 2 T1D and Stage 3 T1D diagnosis, existence of a FDR with diagnosed T1D, relationship to relative with diagnosed T1D.
Relationship of residual C-peptide secretion to clinical outcomes in a large T1D Cohort from Scotland (SDRNT1BIO) (ESC-2024ESR0000218)	**Objective 1:** To examine the association of C-peptide at enrolment into the Scottish Diabetes Research Network Type 1 Bioresource with incident complications of diabetes, including: severe hospitalized hypoglycemia, diabetic ketoacidosis, microvascular complications (retinopathy and maculopathy, chronic kidney disease and estimated Glomerular Filtration Rate), macrovascular complications (cardiovascular disease and its components myocardial infarction, heart failure and stroke), and death.	Scottish Diabetes Research Network Type 1 Bioresource Objective 1: 5630 participants	Secondary data analysis of T1D participants included an observational, longitudinal, cohort study. Enrolment: 1 December 2010-29 November 2013 Follow-up till: 31 December 2022	Key endpoints: age, gender, autoantibody status for anti-GAD65, IA2 and ZnT8, baseline and follow-up of: • random (non-fasting) serum C-peptide • plasma glucose • diabetes duration • HbA1c • eGFR • CKD Stage 3 or worse status, hospitalization or death from DKA • hospitalization or death from hypoglycemia • CVD • death Other evaluated variables were: self-reported insulin dose at baseline, start date of using an insulin pump and a CGM, retinal eye screening status, CKD worsening by 1 or more stage, transition to CKD Stage 3, renal dialysis and transplantation status, transition by at least 1 retinopathy grade or incident Grade 2 maculopathy.

Abbreviations (not included in the abbreviation list of this document): CKD= chronic kidney disease; CVD= cardiovascular disease; FDR= first degree relative.

Fr1da study

The Fr1da study, started in Germany in 2015, is the largest population-based screening study of early diagnosis of T1D in children (17). Currently, 194 696 children aged 1-21 years have been enrolled into the study. The same definition of dysglycemia Stage 2 T1D as applied in the TN-10 study was adopted to select the Fr1da participants for comparison (diagnosed by OGTT or any relevant alternative test [e.g, fasting plasma glucose] within 7 weeks before the date of Stage 2 T1D confirmation or at Stage 2 T1D confirmation). Stage 3 T1D was defined using the American Diabetes Association criteria for diabetes diagnosis.

The Fr1da study was not limited to participants with a family history of T1D.

The primary analyses included: • 32 participants in the TN-10 placebo group (median age 13 years, interquartile range [IQR]: 11-16); • 152 participants from the Fr1da study (median age 5 years, IQR: 3-8).

The sub-group analyses for the primary objective included: • 45 participants from the Fr1da study with first degree relatives; • 107 participants from the Fr1da study without first degree relatives. The TN-10 placebo group had a similar risk of progression from Stage 2 to Stage 3 T1D compared with the Fr1da group (Table 40).

Table 30 Hazard ratios for progression to Stage 3 T1D for TN10 placebo group and Fr1da group

Group	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
TN-10 placebo group	1.3 (0.8-2.1)	1.1 (0.6-2.1)
Fr1da group	Reference	Reference

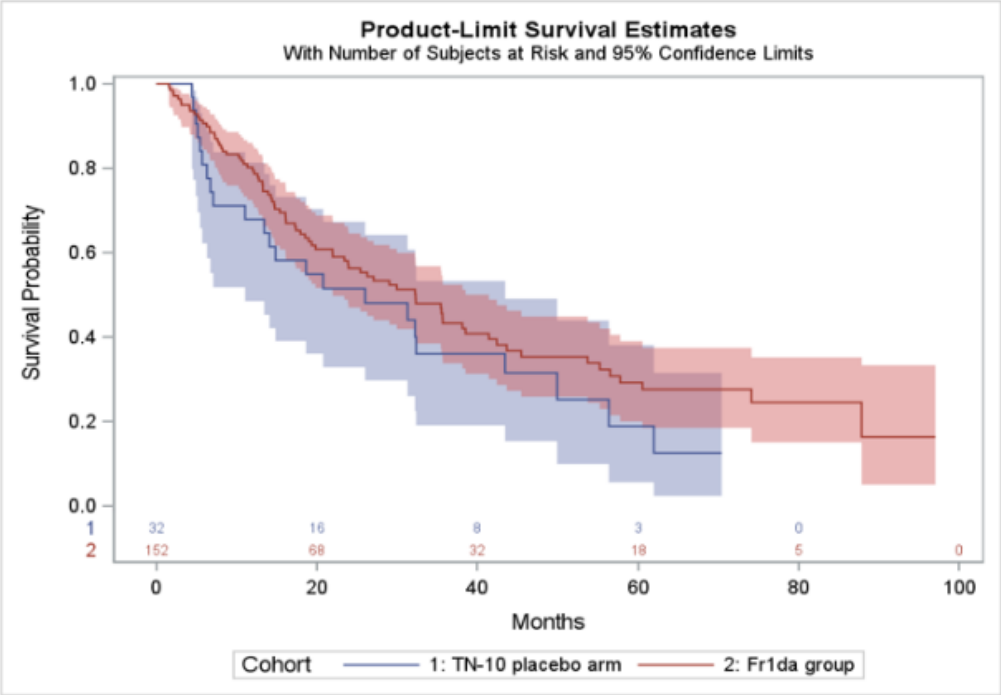
a Adjusted for anti-IA-2 status, HbA1c >5.7%, and 120-minute OGTT results (prognostic factors of progression to Stage 3 T1D identified from univariate Cox proportional hazard models)

Reference = reference group.

Source: 5.3.5.4 Study CS-00910, Table 5.

Kaplan-Meier curves for progression are shown in Figure 30. Having a first degree relative with T1D had little impact on the Kaplan-Meier curves between the Fr1da participants sub-grouped by first degree relative diagnosed with T1D status.

Figure 29 Stage 3 T1D progression-free survival probability in TN-10 placebo group and Fr1da group



Analyses were unadjusted.

Source: Source: 5.3.5.4 Study CS-00910, Figure 2.

From this cohort, when inclusion criteria for TN-10 were applied, 152 subjects were selected for comparison to the TN-10 placebo group (32 subjects).

SDRNT1BIO - Relationship of residual C-peptide secretion to clinical outcomes in a Type 1 Diabetes Cohort from Scotland

Data from 5630 SDRNT1BIO participants showed that higher random C-peptide for a given age, gender and diabetes duration was associated with a lower incidence of DKA and severe hospitalized hypoglycemia and incident or worsening retinal status (analysis of Objective 1 of the study). There was also an inverse association with HbA1c. These associations remained across 11 years from the C-peptide measurement, and whether C-peptide was used as a categorical or continuous variable. Mean C-peptide was also inversely associated with recurrent DKA and severe hospitalized hypoglycemia

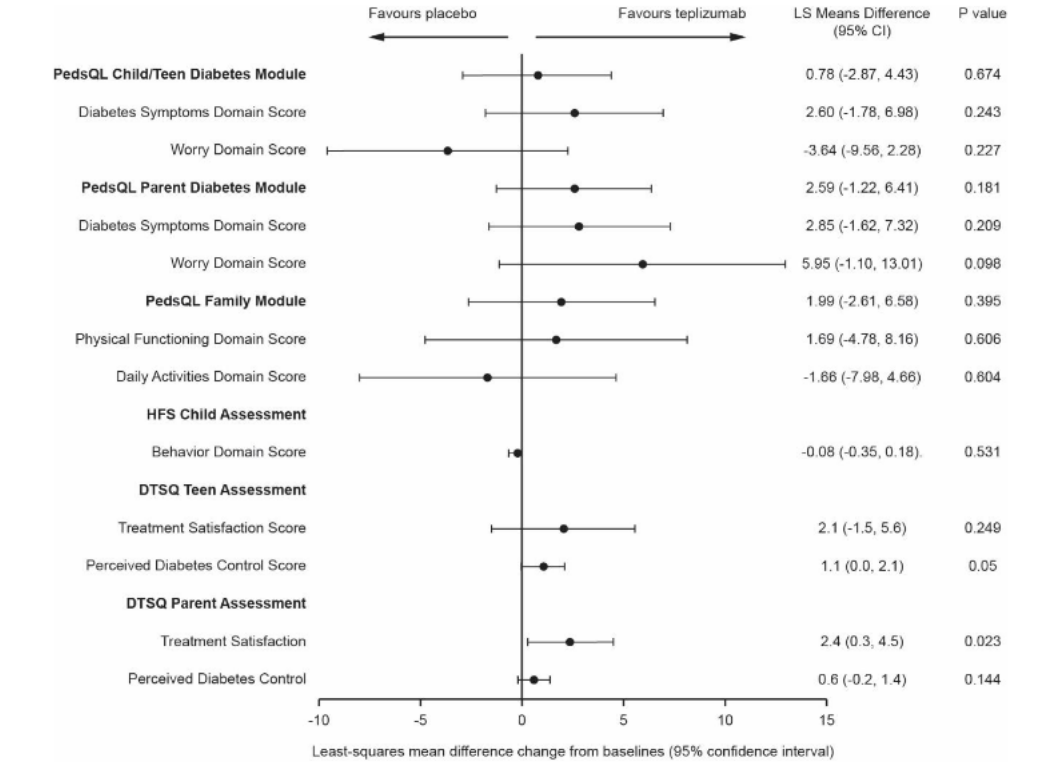
and there was some evidence that a non-linear model fitted better than a linear model. Association of current C-peptide with other outcomes examined (microvascular and macrovascular complications and death) were not observed.

6.3.7. Patient experience data (PED)

In order to incorporate participants and/or caregivers' opinions, several patient-reported outcomes (PROs) were administered during the PROTECT study. Results from PRO analyses are shown in Figure 31.

Teens in the teplizumab group experienced less decline in perceived diabetes control at Week 78 and greater improvement in treatment satisfaction compared to the placebo group as measured by the DTSQ. This was supported by parents/caregivers as measured by the DTSQ-parent version.

Figure 30 PROTECT study - Forest plot of LS mean difference in patient-centered outcomes - ITT population



Source: 5.3.5.1 Study PRV-031-001, Figure 27.
P-values are nominal p-values for descriptive purpose only.

>

Early dialogue with CHMP

In addition, in the framework of early dialogue with patients, the CHMP has received input from the organisation "The International Diabetes Federation (IDF)", answering from a patient perspective. In their response, the IDF state that there is an unmet medical need for a curative treatment for T1D. A drug that delays the onset and progression of type 1 diabetes (T1D) would represent a significant

advancement in diabetes care. Each additional year without reaching stage 3 T1D enhances quality of life since it may help prevent severe acute complications and lower the risk of chronic complications over time and reduce the daily burden of blood sugar management. Many individuals with T1D experience treatment fatigue due to the constant demands of self-management, despite technological and pharmacological advancements.

A therapy that delays progression to stage 3 T1D could also allow children to develop T1D at an older age when they are more emotionally mature and better equipped to manage their condition independently. It would also provide a more gradual psychological adjustment for them and their families. The duration of onset delay for this type of medicinal product is particularly important in this context.

Side effects as mild issues like fatigue, headaches, or temporary immune suppression may be tolerable if the benefits are substantial. However, severe side effects, such as severe migraines, significant gastrointestinal distress, kidney damage, or long-term immune dysfunction, must be avoided.

Structured psychological support would need to be provided to alleviate anxiety stemming from the uncertainty of how long the disease onset may be delayed.

The IDF concludes that the treatment's overall acceptability would depend on several key factors, including the duration of the delay period before onset, method of administration, side effects, cost, accessibility and the need for ongoing monitoring.

6.3.8. Healthcare professional engagement

Early dialogue with CHMP

In the framework of early dialogue with healthcare professional, the CHMP has received input from the European Association for the Study of Diabetes (EASD). According to the EASD, the call for a disease modifying therapy is loud. There are presently no disease modifying therapies for T1D stage 2 or 3. They suggest that it should be explored further (in post-marketing setting) whether such a long infusion (12-14 days) is needed and whether a second course is needed in the setting of stage 3 T1D. According to EASD, the side effects described for teplizumab are manageable. The way of administration is an Achilles heel, with need for intravenous (IV) administration over several days, but should not be an absolute hurdle.

6.3.9. Overall discussion and conclusions on clinical efficacy

Discussion

Delaying the onset of stage 3 T1D in patients with stage 2 T1D – Indication 1

Design and conduct of clinical study TN-10

TN-10 was a multicenter, double-blind, randomized (1:1), placebo-controlled study to determine treatment effect of teplizumab treatment compared to placebo (saline solution) in persons at risk of developing T1D. The randomisation with a placebo treatment arm, is considered adequate for examination of treatment efficacy. Both participants and investigators were masked to the treatment assignment.
76 participants were included in the study. Study subjects who had a first degree relative with T1D, and at least two different T1D-related autoantibodies, among other inclusion criteria, were selected. Since the Applicant seeks an indication not restricted to persons with first degree relatives nor with two autoantibodies or more, the question if study results can be extrapolated to the general population, was raised. There were also other aspects like e.g. HLA group that may influence the effect of the treatment. Justifications have been provided with respect to generalisability of the results to patients in the EU and ethnicity. Generalisability to persons without a first degree relative and only one autoantibody is assumed from supporting data taking into account of the method of action of teplizumab and the physiopathology of T1D.

In the CSP issued 22 June 2010 (the last finalised version before start of enrolment), it was stated that subjects were to be randomly assigned 1:1 to teplizumab or placebo based on age strata (<18 and ≥18 years) and TrialNet study site. The stratification factors used in the randomisation are agreed and the applicant has clarified that these were not changed during the study. According to the NEJM publication (Herold, 2019), the randomisation of subjects was stratified by study site, categorised age, and second OGTT result before treatment while according to the CSR, eligible subjects were categorised into three strata based on age and OGTT status (ages 8-17 with a confirmed abnormal OGTT, ages 8-17 with an abnormal OGTT that was not confirmed, and 18 or older with a confirmed abnormal OGTT, respectively). The Applicant has explained that the modified inclusion criteria in the protocol amendment issued 25 June 2014 led to the adjustment of the covariates included in the primary efficacy analysis model as well as to the alterations presented in Herold (2019) and the analyses presented in the CSR, as compared to what was stated in the CSP issued 22 June 2010.

There were imbalances with regards to the planned 1:1 allocation to treatment arms (n=44 participants were randomised to teplizumab and n=32 to placebo arm), and with regards to the stratification variables used in the randomisation (e.g. age). The Applicant has provided information regarding the number of randomised subjects per TrialNet study site in each treatment arm, respectively. The Applicant argues that these imbalances were likely due to the low-enrolling sites in which the number of participants in each treatment group was not completely balanced (8 out of 14 sites randomised <= 3 participants), and that in these small sites, the block randomisation (block size n=4) could not prevent the observed imbalances in numbers randomised between treatment arms. It is concluded that that this is a likely explanation.

The estimand framework was not used for the primary objective, nor for the secondary objective in the study TN-10. Since the study started in 2010, and the last study subject was completed in 2018, it is fully understood that the estimand framework from 2019 was not applied.

The primary objective was defined by the applicant as: *To determine whether treatment with teplizumab of at-risk subjects resulted in delaying or preventing the onset of clinical Stage 3 T1D*. The design of the study made it possible to investigate if teplizumab delays the onset of T1D. But it is not possible to answer the question whether teplizumab completely prevents the onset of T1D, since the study length is not enough to determine if an effect on prevention is probable. Since the prevention of T1D is not included in the indication claimed, this issue is not further pursued.

The primary endpoint, the elapsed time to onset of T1D, is considered clinically relevant and is in line with the EMA guidance for T1D prevention studies that recommends cumulative diabetes incidence as primary efficacy endpoint. The onset of T1D was defined by clinically recognised blood glucose levels, and measured by clinically relevant laboratory tests, including OGTT. In case of early termination due to lost-to-follow-up or similar, the timepoint of last contact is considered equal to timepoint of onset of T1D. These strategies for managing primary endpoint are acknowledged.

The secondary endpoint consisted of C-peptide AUC after stimulation with a 2-h OGTT, obtained from timed collections during longitudinal tests. C-peptide is recognised since 2012 as an important marker of beta cell function that can be used in pharmacological intervention trials to assess the preservation of endogenous insulin secretory capacity. In this study, the possibility of the secondary endpoint to support the primary endpoint results is limited because the secondary endpoint is not type 1 error protected due to the fact that the study was event-driven.

Statistical considerations

The final SAP was issued 27 March 2018, which was before the data cut-off (30 November 2018). An SAP addendum was issued 9 April 2020.

According the CSP amendment dated 25 June 2014, an interim analysis was planned to be performed when 50% of the expected number of T1D events had been observed, which was performed after observing n=18 events (45%). More details and clarifications on the interim analysis and study integrity were requested. After reviewing the applicant’s response and the documents provided (such as the DMSB charter and DSMB meeting minutes), it is concluded that the integrity of study TN-10 can be considered maintained. As also discussed below, the study would have been claimed as positive even if the primary efficacy analysis would have been analysed as an interim efficacy analysis with 62% information fraction. This is concluded to strengthen study integrity as the primary efficacy analysis is considered to be Type 1 error controlled.

The primary efficacy endpoint, time to T1D, was evaluated at a 0.025 one-sided significance level. The ITT population was used in all efficacy analyses. The primary efficacy analysis was based on a Cox PH model with treatment group, design strata (defined as a combination of categorised age and OGTT status at enrolment), as well as continuous age at enrolment as covariates. Subjects who were lost to follow-up before developing T1D or were followed up to study closure, were censored at the last OGTT measurement or physical examination, whichever occurred later. The minimum and maximum time of follow-up for subjects in the teplizumab arm was 6.4 and 88.1 months, respectively. The corresponding figures in the placebo arm were 2.7 and 70.1 months.

The covariates included in the primary efficacy analysis model were not unambiguously pre-specified, but as stated earlier in the discussion, the applicant has explained that this was due to the modified inclusion criteria in the protocol amendment issued 25 June 2014. The results of several additional

analyses on the primary efficacy endpoint were requested, e.g. as pre-specified in the CSP issued 2010 and in the final SAP, and with reference to what is stated regarding the adjustment of stratification variables used in the randomisation in the Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013). The results of these additional analyses are consistent with the primary analysis result.

The applicant was also asked to reanalyse the n=43 endpoint events as an interim efficacy analysis in which the type 1 error is controlled at a 5% (two-sided) significance level using the pre-specified Lan-DeMets O'Brien-Fleming spending function at 43/69=62% information fraction. The result of this analysis has been provided, and it is concluded that the study would have been claimed as positive even if the primary efficacy analysis would have been analysed as an interim efficacy analysis, when also taking into account the (first) interim analysis conducted at n=18 events.

The sensitivity analyses presented in the CSR included a worst-case imputation (i.e., imputation of T1D event) for subjects who withdrew consent or were lost to follow-up as well as imputation of a follow-up time of 12 months for subjects with <12 months of follow-up. These sensitivity analyses were not pre-specified but are acknowledged as having limited impact on the primary effect estimate and its corresponding p-value. The pre-specified tipping point analysis was not performed; however, this was not requested as the performed sensitivity analyses involved worst case imputation. One pre-specified and performed sensitivity analysis was planned to deal with the potential loss of drug effect, but it is understood to have involved external data from the TN-01 study and is therefore not deemed relevant.

For the exploratory secondary endpoint C-peptide AUC, the study design led to changes in the planned analyses. Furthermore, the handling of missing data was not pre-specified before start of enrolment, and the methodology used is neither consistent nor agreed. This is not further pursued, as this is an exploratory endpoint and its results are not crucial for the benefit-risk evaluation, nor will the results be presented in the PI.

Results

There were amendments to the protocol initial study protocol (dated 13 November 2009). Due to slower enrolment rate, the original protocol (n= 144 subjects) with an estimated minimum of T1D events (n=69), was revised in June 2014 to reduce the estimated minimum number of events to n=40 and sample size to 71.

According to the applicant, 146 subjects who were identified through the TN-01 study were assessed for eligibility in the current TN-10 study. Seventy subjects were screen failures. The 30 screen failure subjects for whom the inclusion/exclusion criteria form was completed were described. For the 40 remaining "screen failures", this form was not completed. The applicant has upon request provided the reasons for screen failure for these 40 subjects. Of these subjects, 30 subjects did not meet inclusion criteria, 3 met exclusion criteria, 5 were lost to follow-up and 2 withdrew consent. The reasons for screen failure do not seem remarkable, and although a total high number of screen failures, this is not considered to have an absolute impact on the validity of the results.

The baseline characteristics are not considered balanced. There is a difference in the BMI between the study groups. In the teplizumab group, a bigger proportion of study subjects have a BMI < median (59.1%) than in the placebo group (37.5%). Since the study subjects are assumed to have developed T1D by symptoms of high blood sugar or a confirming OGTT, there is a possibility that some individuals have developed type 2 diabetes (although having anti-antibodies according to inclusion criteria), especially if overweight. Therefore, possible cases of type 2 diabetes might influence the results, and the risk is higher in the placebo group.

The applicant states that within each age group, the mean body weight and BMI were generally similar between treatment arms. This is agreed. But for children, the median body weight and median BMI were not similar between treatment arms. A higher proportion of children in the teplizumab group had a weight < 50 kg and fewer had a weight 50 kg – 100 kg, than in the placebo group. This imbalance in weight distribution between teplizumab and placebo groups observed can possibly have affected the study results. For adults, imbalances are noted between the teplizumab and placebo groups when looking at the different BMI groups. The teplizumab group contained 7 individuals (46,7%) with BMI 18,5 to <25 compared to 1 individual (16,7%) in the placebo group. The teplizumab group contained 5 individuals (33,3%) with BMI ≥30 kg/m^2, compared to 1 individual in the placebo group. Maximum BMI was markedly higher in the teplizumab group. Adult patients with BMI ≥30 kg/m^2 can be suspected of having diabetes type 2 instead of type 1. If some of the adult patients were misdiagnosed with stage 2 T1D when included in the study, and instead had T2D or "pre-T2D", this might explain the absence of insulin treatment for these patients. Partial remission of T1D was seen in higher frequency for patients with higher BMI in a study from 2019 (Chobolt et al). In both cases, this is suspected to influence the results for the adult population of the study. But since the adult group is small, conclusions are difficult to draw from the results in this group.

It is agreed that the observed overall imbalance in baseline BMI and body weight at baseline was mainly due to the imbalance in age group.

The presence of autoantibodies and the HLA types are not considered entirely balanced. E.g., IAA, IA-2, ICA and DR3 only and DR4 only, differ between study groups. The imbalances are not considered crucial, since the study is small and the sub-groups even smaller, which makes the interpretation of results of sub-group analyses unclear.

It is noted that in one table (Table 19), ethnicity is divided in two groups: "Hispanic or Latino" and "Not Hispanic or Latino". Race is divided in white, asian and multiple. A study subject can therefore be hispanic and white. In another table (Table 22), the race is divided in three groups: asian, hispanic and white and a subject can only belong to one of these three groups. There is obviously a discrepancy between the two classification systems. It is also noted that none of the study participants were classified as black or afro-american. Since the study is small, and the sub-groups even smaller, and sub-group analyses regarding ethnicity or race will not be meaningful, this issue is not further pursued.

The medical history is considered balanced. The medication is assumed to be balanced, since the medical history is.

The primary objective of the study was to determine whether treatment of at-risk subjects with teplizumab resulted in a delay of stage 3 T1D. The primary endpoint was the time from randomisation to T1D diagnosis or last contact. Criteria for T1D onset were based on glucose testing or the presence of unequivocal hyperglycemia with acute metabolic decompensation, such as DKA.

Since glucose criteria for inclusion in the study and onset Stage 3 were very close, the baseline values for the inclusion criteria were of interest. Baseline data for fasting plasma glucose and plasma glucose after OGTT (30, 60, 90 and 120 min) were provided per treatment group. According to the applicant, these values were balanced between groups, which is agreed. Interestingly, some individuals had a 2-hour plasma glucose meeting the criteria for T1D onset (≥200 mg/dL (11.1 mmol/L)) already at baseline. Maximum OGTT 120 min glucose is 240 for the teplizumab group and 217 for the placebo group, according to the tables provided by the applicant. None of the 8 participants in the placebo group who were diagnosed with T1D <6 months had a 120 min OGTT glucose value >200 mg/dL at baseline.

For the 8 participants in the placebo group who were diagnosed with T1D <6 months, fasting plasma glucose and plasma glucose after OGTT (30, 60, 90 and 120 min), both at inclusion and at onset of

Stage 3 T1D, were presented and compared to both the rest of the placebo group and to the teplizumab treatment group. The group of 8 participants had higher glucose values than the rest of the placebo group, and the rest of the placebo group had lower glucose values than the teplizumab treated group. This is expected. Individual fasting plasma glucose and plasma glucose after OGTT (30, 60, 90 and 120 min) were presented for baseline and at T1D onset. For all but one of them, the criteria on which inclusion and onset were based on, is understood from the data presented. The onset data do not differ from the onset data for the other groups (teplizumab, and placebo with T1D > 6 months). For one participant, the T1D onset does not seem to be based on the glucose data. This is the only case which is not explained by the data provided by the applicant, and since it is not expected to have a major impact on the results of the study, the issue is not further pursued. The glucose data do not raise further questions concerning the group of placebo-treated participants who were diagnosed with T1D within 6 months.

The glucose testing criteria for onset of Stage 3 T1D are agreed, but the true benefit for the patient is if the need for exogenous insulin is postponed. Unfortunately, participants were not followed after the onset of Stage 3 T1D, and no data on exogenous insulin use were collected. In an extension study, 6 patients were enrolled. Exogenous insulin was lower in 3 of the participants who had received teplizumab prior in the TN-10 study at day 546, than for the participant that was placebo-treated at day 546. No value can be attributed to these data, since enrolment in the Extension study was optional, and since the study size was very small, with only one previously placebo-treated patient.

For recent-onset Stage 3 T1D patients, decrease in the use of exogenous insulin has been demonstrated for the teplizumab-treated group versus control group, according to a publication by Harold et al 2023. The results in the study published 2023 are not questioned, but the benefit of absence of insulin treatment or lower insulin doses is not considered proven in the TN-10 study population.

Kaplan-Meier curves showing proportion surviving diabetes-free as a function of time, were presented. The applicant states that the largest difference between teplizumab and placebo was observed in the first year and that the cumulative hazard ratios showed continued advantage of teplizumab over placebo through Year 5. According to the Kaplan-Meier curve of time to T1D diagnosis by treatment group and the table presenting yearly interval and cumulative hazard ratios of time to T1D onset, a difference between the teplizumab and placebo groups is indicated for the 6-12 months post-treatment. The latter statement on continued advantaged of teplizumab, is partly agreed. For years 3-5 post-treatment, the number of subjects getting T1D diagnoses during these years are 2-3 in each group, therefore these data are considered unreliable. It is assumed that teplizumab-treatment results in fewer subjects developing T1D during the first 6-12 months post-treatment, and that during the following years (years 2-5 post-treatment), subjects in the teplizumab arm and the placebo arm develop T1D at approximately the same rate. A long-term continuous treatment effect cannot be concluded from the data, but there are indications of maintained differences in T1D Stage 3 development during the next 4 years.

Extended follow-up data, as reported by Sims et al. 2021, demonstrated a median delay of approximately three years in the progression to clinical T1D. However, due to study design, the extended follow-up of additional 16 months only affects the subjects not diagnosed with Stage 3 T1D at the timepoint for analysis when n=43, according to the revised study protocol. Mean time to diagnosis after extended follow-up is strongly driven by a few subjects in the teplizumab group which had not yet been diagnosed after 72 months. Moreover, the overall study size was small (N=76). The results from the extended follow-up are not reflected in the SmPC.

The baseline characteristics for the 8 subjects in the placebo group who were diagnosed with TID <6 months, compared to the other study subjects, per treatment arm, were demonstrated. The

characteristics of these 8 individuals did not raise suspicion of imbalance that would impact the validity of the study.

Sensitivity analyses were conducted to address potential imbalances in baseline characteristics, a concern previously raised. Sensitivity analyses were not pre-specified, which is discussed under statistical considerations (see above). The applicant concludes that the outcomes of all 3 sensitivity analyses were consistent with the primary analysis outcome, which is agreed.

The secondary objective of the study was to determine whether treatment with teplizumab was superior to placebo with respect to C-peptide responses to oral glucose, as obtained from timed collections during longitudinal tests.

There was no Type 1 error control with respect to secondary endpoints. Also, there were changes in the planned analysis with respect to C-peptide, due to study design. The lack of Type 1 error control with respect to secondary endpoints is accepted in exploratory phase 2 trials but is not recommended in confirmatory trials, as it affects the statistical evaluation that can be made regarding any secondary endpoints intended to support the primary endpoint results.

The effect of teplizumab on C-peptide response to oral glucose was measured at a 2-hour OGTT. The C-peptide assessments were performed at 3 months and 6 months after randomisation, and then every 6 months or more frequently if clinically indicated. Once a subject was diagnosed with T1D, no additional OGTTs were performed.

The exploratory (i.e., not Type 1 error controlled) endpoint C-peptide AUC over time is higher for the teplizumab group than for the placebo group for timepoints up to 66 months according to the data provided. But at 54 months, the placebo group consisted of only 3 patients, and at 66 months 2 patients. The supportive C-peptide data indicate that patients treated with teplizumab had higher level of insulin secretion (both as assumed equimolar to C-peptide, and as measured) than the placebo group. But it is not agreed that prolonged effect can be seen throughout the study. The difference between groups in C-peptide ln (AUC +1) was maintained from month 12 visit to month 24 visit, but no additional effect was seen from month 12. Furthermore, due to a small number of participants from start, imbalanced baseline characteristic and even smaller number of available patients after 48 months (as a result of study design), it is not known if the positive effect of treatment with teplizumab corresponds to a true clinical treatment effect, and if so, for how long this treatment effect can be assumed to be maintained. The issue of how long C-peptide AUC can be maintained is not further pursued since this is an explorative endpoint and does not constitute a claim in the product information.

Sub-group analyses of time to onset of T1D were made. Sub-groups were based on baseline data: age, sex, BMI, autoantibodies, HLA type, C-peptide, and glucose levels during OGTT. Although underpowered, it did not reveal any distinct treatment effect for specific markers.

At randomisation, the study subjects were stratified by study site and by age. Therefore, the response to teplizumab treatment in the two different age subgroups <18 years and ≥18 years, is of great interest. The applicant provided a Kaplan-Meier curve showing time to onset by age and treatment group (Figure 16). The number of patients in each subgroup and treatment group was presented, stating the number of patients at risk along the timeline. The randomisation was planned to be 1:1 (teplizumab versus placebo). However, as earlier shown by the applicant, 44 participants received teplizumab and 32 participants received placebo, with a pronounced difference from planned ratio occurred in the subgroup divided by age. Thus, the subgroup of patients ≥18 years is small.

However, while the evidence of an effect in adults is based on a small number of patients, given that the mechanism of action (modulation of CD3+ T cells to preserve β-cell function) is consistent

regardless of age, a positive treatment effect of teplizumab in adults with stage 2 T1D is reasonably expected.

The applicant has provided an updated forest plot with specified number of subjects per study arm, number of events, and estimates for all sub-groups. Difference in median time to diagnosis for teplizumab was found to be 2 years. However, the baseline data are not balanced between study groups, and the small number of study participants does not allow for firm conclusions on the event-driven primary endpoint, nor for sub-group analyses.

Meta-analysis was made of C-peptide data in Stage 3 T1D patients from 5 studies. The meta-analysis showed greater decline from baseline for the placebo pool than for the teplizumab pool for the 12-month analysis. The 24-month analysis, also showing the same pattern, was based on only 3 studies. However, there were differences between the individual studies included in the meta-analysis with respect to study design, e.g. C-peptide AUC being primary or secondary endpoint, inclusion criteria, size, and early termination/modification due to study failure. Therefore, the meta-analysis data are not considered supportive of indication 1. As C-peptide data from the study PROTECT (Stage 3 T1D) also showed greater decline from baseline for the placebo group than for the teplizumab group, these study data could be considered as supportive for indication 1, rather than the meta-analysis data.

Real world evidence (RWE) data from study Fr1Da were presented to support generalisability. In the Fr1Da study, the TN-10 placebo treated group was compared with an untreated population (European participants, 2-15 years of age, with Stage 2 T1D). The outcomes for the two groups were similar. This shows that the placebo population of TN-10 had a similar natural progression of T1D as the European cohort. Whether the European cohort would react in the same way to teplizumab treatment, as the teplizumab population of TN-10 study, is not proven. But since the baseline characteristics of the European cohort resembled those of TN-10, it could be assumed that the results of TN-10 are generalisable to a European population.

Similarity, treatment effect is assumed for patients having different combinations of auto-antibodies, or only one autoantibody, and for different HLA types. Generalisability to individuals without a first degree relative with T1D is agreed.

The proposed dosing regimen for Stage 2 T1D is based on the pivotal TN-10 study. During the development, the manufacturing process for drug substance was changed. The drug substances from the different processes resulted in different drug exposure levels between the product used in the trial and the to-be-marketed product. Therefore, doses were suggested to be modified for indication 1, to adjust for these differences. This adjustment is supported by safety data from the PROTECT study and by post-marketing experience. Proposed dosing regimen in Stage 2 T1D indication is acceptable.

There is currently no coordinated EU-wide strategy for screening or harmonised policy for early T1D detection. Identification of stage 2 T1D, characterised by the presence of multiple islet autoantibodies and abnormal glucose tolerance but without clinical symptoms, is still largely research-based or opportunistic, rather than part of routine clinical care across EU Member States, thus varies widely by country. The Applicant provided an overview of several current and emerging screening initiatives for early-stage T1D across Europe and internationally (such as TEDDY, Fr1da, EDENT1FI, INNODIA DETECT, and national programs in Italy, France, Spain, Germany, and others). The cited initiatives demonstrate increasing support for early detection of T1D, however continued harmonization across Member States will be important to support broader implementation and integration into clinical practice.

In summary, for the claimed indication 1, the single pivotal phase 2 study TN-10 was small in size. However, the results are considered robust from a statistical point of view. Further, the mechanism of action is supported by other studies in the T1D population. The external validity could be questioned,

but based on the mechanism of action, the pathophysiology of T1D and results in sub-groups in other studies (in patients with stage 3) no major differences in sub-groups are expected. Therefore, it is considered that a clinically meaningful effect has been appropriately documented for subjects with Stage 2 T1D.

A SAG (Scientific advisory group) on Cardiovascular Issues convened on 9th of September 2025. The experts confirmed the clinical relevance of delaying the onset of stage 3 T1D in stage 2 patients. Postponing the onset of the disease will also delay the onset of the "honeymoon period" with less treatment requirements.

The Applicant had received a CHMP scientific advice in 2020 in which a confirmatory Phase 3 study in the stage 2 T1D population was recommended. The Applicant does not consider that such a study is feasible. Instead, in order to capture more data in the target population, a Global Registry including an untreated control arm will be initiated post-approval of the product. A synopsis is included in the RMP. A secondary objective of this study is to assess effectiveness of teplizumab in the stage 2 population. The study will include 200 patients (150 treated with teplizumab / 50 not treated). The approach proposed by the Applicant to set-up a global registry is considered acceptable however the applicant is urged to seek scientific advice to increase the size of the study and optimize the protocol.

Delaying further progression of Stage 3 T1D - Indication 2

For the initially claimed indication 2, efficacy results were based on the pivotal study PROTECT and the applicant mentions 5 other studies as supportive. In the pivotal study, the primary endpoint consisted of the area under concentration-time curve for C-peptide.

During the assessment procedure, the Applicant withdrew their claim for this indication.

Design and conduct

The PROTECT study was a Phase 3, randomized, double-blind, multinational, placebo-controlled study to determine the effect of teplizumab treatment compared to placebo (saline infusion) in preserving beta cell function. Study subjects were children and adolescents, aged 8-17 years, diagnosed with T1D within 6 weeks. The inclusion and exclusion criteria were considered adequate. Important inclusion criteria were peak stimulated C-peptide of ≥0.2 pmol/mL from a 2-hour mixed meal tolerance test (2h MMTT) at screening and at least one autoantibody associated with T1D.

C-peptide (or C-peptide AUC after stimulation with a 4h MMTT) is acknowledged as a measurement of beta-cell activity. But it is not evident that a difference in beta-cell activity between teplizumab treated group vs placebo group translates into a clinically relevant effect. Within a scientific advice procedure, the CHMP did not consider that the change in C-peptide AUC at 18 months was sufficient as a primary endpoint by itself. According to EMA guideline for clinical studies aiming at preservation of beta-cell function, the primary outcome should preferably consist of co-primary endpoints including not only the change from baseline in C-peptide (e.g. C-peptide AUC) but also HbA1c, frequency of hypoglycemic episodes, or with another relevant clinical marker.

Enrolled participants (N=328) were randomly assigned with a ratio of 2:1 to either teplizumab or placebo (saline infusion) group. The stratification variables used in the randomisation were to be peak C-peptide level at screening (0.2 to 0.7 pmol/mL inclusive, versus >0.7 pmol/mL) and age at

randomisation (8 to 12 years, versus >12 to 17 years). This design is in principle considered adequate, although age groups usually are divided at the age of 11 years.

A block size of 6 appeared to have been used in the randomisation. The randomisation procedure is considered appropriate and was adhered to, in terms of actual numbers of subjects randomised into the treatment arms. The stratification variables are accepted and were balanced across treatment arms.

Teplizumab or placebo was administered by intravenous infusion in addition to the standard of care (insulin treatment and titration). The study participants received two 12-day courses of teplizumab (as iv infusion) or saline infusion (placebo group) starting at week 1 and week 26. A modified dosing schedule was introduced due to COVID-19 pandemic. Participants who were unable to receive the second 12-day course at Week 26 due to COVID-19 pandemic restrictions were given the second course on approximately Day 364 (Week 52 visit), approximately 12 months after randomisation. The question of if this modified schedule had had an impact on study results was raised.

The applicant referred to the open-label study AbATE (Study 4), in which newly diagnosed (within ≤8 weeks) patients received two treatment courses 12 months apart. This study included 52 teplizumab treated participants and 25 control subjects receiving standard care only. In the AbATE study, no increase in the safety risk was seen and the C-peptide decline was smaller in the teplizumab group than in the control group. Of note is that the treatment effect seen in an open-label study cannot be directly compared to that of a double-blind study. Nevertheless, a treatment effect was observed in the AbATE study, and the number of participants who received the modified dosing schedule in the PROTECT study is considered small (28/328). Therefore, it is assumed that the modified schedule did not markedly affect study results.

In stage 3 disease, where more intensive dosing was used, the clinical benefit remains unproven, and the justification for repeat dosing was requested. It is not clear if and when a second dose cycle should be administered. Moreover, there is variation in the dosing regimens used across trials, and consequently, different dosing is suggested for the first and second indications; and the rational supporting these dosing choices was requested. The Applicant provides a multi-study rationale for the selected dosing regimen in Stage 3 T1D, primarily based on historical data from Protégé, Encore, AbATE, and PROTECT, but the variability in dosing schedules across trials and the lack of harmonization in endpoint definitions limit the strength of the justification. While the data suggest that the choice of a 12-day course administered 6 months apart may be optimal to provide the effect on C-peptide levels, the justification remains partially exploratory. The failure to meet secondary endpoints in the PROTECT trial after the second course raises concerns about the clinical benefit.

The proposed dosing regimen differs slightly from that used in TN-10 due to differences in bioavailability between the product used in the TN-10 trial and for some participants in the PROTECT study, and the to-be-marketed product. This adjustment is supported by safety data from the PROTECT study and by post-marketing experience.

The issue related to the dosing regimen and justification for repeat dosing in Stage 3 T1D remains unresolved and further robust justification of dosing is deemed necessary.

The primary objective was to determine whether 2 courses of teplizumab slow the loss of beta cells and preserve beta cell function over 18 months (78 weeks) in children and adolescents 8-17 years old who had been newly diagnosed with T1D (within 6 weeks of randomisation). The statistical hypothesis was superiority over placebo for the primary efficacy endpoint change from baseline to week 78 in C-peptide ln(AUC+1).

All intercurrent events (ICEs), including use of medications disallowed according to the protocol, modified dosing schedule due to COVID-19, premature discontinuation of study treatment, and non-

adherence to the planned treatment regimen, were handled by the treatment policy strategy. Four out of five attributes for the primary estimand were defined. The modified dosing schedule due to COVID-19 is considered a special ICE, and the applicant's treatment policy strategy for this ICE was motivated by the fact that it provides a conservative estimate to the treatment effect, which is acknowledged.

There were no definitions of additional estimands in the documentation, although this was previously advised by the EMA scientific advice. It is also noted that the primary estimand and ICEs were not pre-specified in the CSP, but in the final SAP that was finalised close to study end.

The secondary objective included an evaluation of participant improvements in key clinical parameters of diabetes management after 2 courses of teplizumab vs. placebo. The clinical secondary endpoints were daily insulin use, glycaemic control (as measured by HbA1c and TIR), and clinically important hypoglycaemic episodes. The statistical hypothesis was superiority over placebo for these endpoints. Estimands for the secondary objective were not defined.

In principle, the data quality assurance measures put in place seem adequate. Audit Certificates were provided for 11 site inspections. According to CSR, there were 61 sites treating patients. It is considered that there is no need for an inspection.

Statistical considerations

The final SAP (v. 5.0) was issued 17 March 2023, which is prior to the completion of the last participant (01 May 2023). No previous versions of the SAP were found in the documentation.

The primary efficacy endpoint change from baseline in C-peptide ln(AUC+1) to week 78 was evaluated at a 0.05 two-sided significance level. The ITT population was used in all efficacy analyses. The primary efficacy endpoint was tested using an ANCOVA model including the covariates treatment group, age group at randomisation, and baseline C-peptide ln(AUC+1). There were some changes in the planned analyses, but these were either implemented at early phase of enrolment or perceived as minor. For completeness, and although this may introduce collinearity, the applicant was asked to provide the results of an ANCOVA model in which both randomisation stratification factors were included. The result of this additional analysis is consistent with the primary efficacy analysis result.

Sensitivity analyses on the primary efficacy endpoint included, for example, a control-based imputation according to jump-to-reference and a tipping point analysis. These are appreciated. However, clarifications were requested regarding the handling of missing data at week 78 in the primary efficacy analysis, which concern 13.4% and 20.7% of the subjects in the teplizumab and placebo arm, respectively. The applicant was asked to clarify how many participants with, and without, ICEs that did, and did not, have week 78 measurements, respectively. The applicant has provided the requested information and overall, the information presented is not concerning. For example, the number of participants with premature treatment discontinuation was relatively similar in both treatment arms. The ICE 'modified dosing schedule' was slightly less prevalent in the teplizumab arm, compared to placebo arm. Furthermore, n=3 participants in teplizumab arm and n=1 in control arm had taken prohibited medication according to protocol. It is also noted that missing C peptide data at week 78 was somewhat more prevalent in the placebo arm, both among participants with and without an ICE. Missing values, regardless of if resulting from an ICE or due to other reasons, were handled by the same pattern-mixture model in which MI was applied.

To control for the family-wise Type 1 error at the 0.05 level, a Hochberg procedure was used for inference on the clinically relevant secondary efficacy endpoints exogenous insulin use at week 78, change from baseline in HbA1c (%) at week 78, TIR at week 78, and event rate of clinically important

hypoglycaemic episodes through week 78. Given that none of the secondary endpoints would have been statistically significant according to any multiple testing procedure, but also that a co-primary endpoint has been previously recommended in the Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus as well as in EMA scientific advice, it would have been better if at least one of the Type 1 error controlled secondary efficacy endpoints would have been incorporated in the sample size calculation.

Results

The protocol amendment considered to have highest potential impact on study results and the validity of the results is the introduction of modified dosing schedule due to COVID-19. Information on protocol deviations was provided. The teplizumab group and the placebo group were reasonably equally affected by protocol deviations. It is noted that a majority of the study subjects who received less than prescribed doses were in the teplizumab group. A possible explanation could be the AEs, and this will be discussed in the Safety section. Subjects who received a full Course 1 (12 infusions, full dose) but not the second Course, were predominantly subjects belonging to the placebo group (10 of 19).

Baseline characteristics

The placebo group had a higher proportion of male subjects than the teplizumab group. This is not assumed to affect the reliability of the results. The majority of the study population race was noted as white. Only 3.4% and 2.1% were noted as black and asian, respectively. This small representation in the study is not ideal. But, at present, there is no indication that the study results are not valid for non-white patients.

It is noted that the BMI Z-score median is higher for the teplizumab group than for the placebo group. Since the age distribution seems balanced between groups, the BMI imbalance is not considered to affect the study results. In the randomisation, study subjects were stratified for age and for peak C-peptide level. The study subjects considered balanced between the treatment groups, regarding these stratification parameters.

Insulin use at baseline is slightly higher for the teplizumab group than for the placebo group. It is not known if the insulin use represents degree of disease development, and that the disease thereby can be assumed slightly more advanced in the teplizumab group. As the primary endpoint is defined as difference from baseline of AUC stimulated C-peptide, having a more advanced disease could either lead to less difference from baseline or a larger difference from baseline, depending on the assumptions on the natural disease development. At this stage of the assessment, the difference in insulin use at baseline between groups is considered rather small and is not assumed to affect the results.

The proportion of study subjects having different autoantibodies is balanced for all autoantibodies but anti-insulin. The difference in anti-insulin is not prominent, and therefore not considered to have an impact on the results. The differences in HLA-types between treatment groups are 5-6 percentage points, which is not considered to have an impact on the results.

Additionally, the association between ADA development and specific patient characteristics, such as genotype or immunological background, should be explored and clarified, given the immunologic nature of the disease and possible inter-individual differences in immune response.

Primary endpoint

C-peptide is acknowledged as a marker of beta cell function considered relevant as a co-primary endpoint when assessed along with a relevant clinical endpoint/s. In this study, C-peptide was used as a single primary endpoint. The analyses of C-peptide ln(AUC+1) in 4h MMTT over time and changes from baseline showed that teplizumab group had a higher mean ln(AUC+1) value than the placebo group. The difference between teplizumab and placebo in the change from baseline in C-peptide ln(AUC+1) was statistically significant ($p<0.001$). The performed sensitivity analyses on the primary efficacy endpoint were pre-specified and consistent with the primary analysis results.

In order to determine a clinically relevant treatment effect of teplizumab, the use of a co-primary endpoint is considered necessary, especially in this case of an MAA with a single pivotal trial.

Secondary endpoints

The four key secondary endpoints were Type 1 error controlled for the ITT population, but none of these secondary endpoints showed statistically significant treatment effect of teplizumab in comparison to placebo.

The failure to meet the clinical secondary endpoints after the second course of administration, for which a contribution of ADA to the reduced efficacy cannot be excluded, remains a critical concern. Whether the secondary efficacy endpoints were met after the first course is unclear. Hypothetically, if the secondary endpoints were met after the first course of treatment, and not after the second course, this would support the hypothesis of ADA-related loss of efficacy. In such a scenario, the second course of treatment would not be supported. However, the clinical benefit of a single-course treatment in the Stage 3 T1D population would need to be confirmed through long-term efficacy data from an additional dedicated study.

Exogenous insulin use was defined as a daily average in units per kilogram per day (U/kg/day), at Week 78. It was calculated from the participants´self-reported eDiary data. The participants were to report their daily insulin use for 7 separate days. Based on these data, the average daily use of insulin (U/kg/day) was determined. Participants needed to have insulin data for at least 3 days in order to calculate the average daily use. The teplizumab group showed a numerically lower average daily insulin dose at Week 78 than the placebo group, but the difference did not reach statistical significance. Exogenous insulin use is considered a highly valuable clinical endpoint, which in this study failed to contribute to the evidence of a treatment effect.

The number of participants reporting insulin use according to insulin diary records was considered low. It is assumed that some participants were not on insulin treatment, but also that many participants were on insulin but did not complete their diary, especially at week 78. It is noted that 126/217 participants in the teplizumab group and 63/111 in the placebo group were on insulin treatment at baseline. This is the exact number of participants from each group on which the average exogenous insulin dose at baseline is based on. For week 78, the insulin use was based on data from only approximately 45% of the participants (98/217 for teplizumab, 50/111 for placebo). The low reporting could reflect participants not complying to eDiary reporting, or patients for some reason discontinued

the study. Ultimately, the diagnosis of Stage 3 T1D could also be questioned for some participants, if they were not on insulin treatment at week 78, since a honeymoon period is typically not expected to last until week 78.

The secondary endpoint **TIR** expressed as a daily average of the percentage of time in a 24-hour day a participant's blood glucose (BG) is within defined range was assessed using continuous glucose monitoring (CGM), at Week 78. The applicant states that the mean TIR for glycemic control was numerically higher in the teplizumab group than the placebo group at all timepoints during the study. This is agreed, but since the analyses do not show statistical significance, the value of observed differences is uncertain. It is noted that the data for TIR are based on 63 of 111 (57 %) participants in the placebo group and 140 of 217 (65 %) participants in the teplizumab group. The missing participants are assumed to be due to fewer than 3 days of CGM data recorded for each visit and/or a range of fewer than 8 hours on a given day. The reasons for missing CGM metrics data were explained and are understood. But as the study lacked statistical power for the endpoint, the CGM metrics data are not considered supportive.
The applicant provided data from post-hoc analyses on the per protocol population (PP). Although some confusion regarding the figure numbers presented in the text, the figures show data on differences in percentage of TIR and minutes in TIR, between the teplizumab group and placebo group, with $p < 0.05$ (figures 9 and 10, respectively).

The PP population, the analyses of which were pre-specified as supportive, included 83.8% of the ITT population (82.9% of the teplizumab group and 85.6% of the placebo group). As such, these results cannot replace the analyses based on the primary analysis population, i.e., ITT, and can at most be attributed supportive value.

No difference was seen in **HbA1c at Week 78** between the teplizumab and the placebo groups. HbA1c could be interpreted as a measurement of disease management, and a disease deterioration could make it more difficult to obtain a good disease management. Therefore, HbA1c is agreed to be a clinically relevant endpoint.

The secondary endpoint **Clinically important hypoglycemic episodes**, was defined as the total number of episodes of a BG reading of <54 mg/dL (3.0 mmol/L) and/or episodes of severe cognitive impairment requiring external assistance for recovery, from randomization through Week 78. The rate of clinically important hypoglycemic events during the study was similar between the 2 groups. According to the SAP-specified criteria for Level 3 events, none of the hypoglycemic events reported in the eDiary were classified as Level 3. Thus, the efficacy analysis of clinically important hypoglycemic events included only Level 2 events.

In summary, the relevance of the treatment effect of teplizumab in comparison to placebo is questioned for the secondary endpoints.

Explorative endpoints

A number of explorative endpoints were examined. For most of them, no difference was shown for the teplizumab group compared to placebo. The rate of clinically important hypoglycemic events appeared to be lower in the second period than in the first period for both treatment groups. The proportions of participants who tested positive for T1D autoantibodies over time remained generally unchanged from

baseline during the study and were comparable between the placebo and teplizumab groups. Thus, teplizumab did not seem to have a negative impact on T1D autoantibodies.

Differences between the treatment groups were seen for 4h MMTT C-peptide AUC, participants with Peak C-peptide ≥0.2 pmol/mL and participants not using exogenous Insulin or met criteria for Insulin discontinuation, with higher values in the teplizumab group. These observations are considered indicative, but no conclusions can be drawn.

Analyses of quantitative lymphocyte subsets (TBNK panel) in blood showed that in the teplizumab group, the percentage of circulating CD3+CD4+ T cells decreased after each course of treatment was initiated.

The objective of the performed meta-analyses to support the initially claimed indication 2 was to show the effect of teplizumab on clinically relevant metabolic markers of diabetes management such as insulin use, HbA1c levels, and hypoglycaemic events. The SAP was finalised approximately one year after completion of the PROTECT study, i.e., at a time point when the results of the PROTECT study, which failed to show statistically significant differences with regards to clinically relevant secondary endpoints, were already known. As such, the credibility of the performed meta-analyses was assessed by means of pre-requisites for retrospective meta-analysis detailed in "Points to consider on application with meta-analyses". Some of these requirements were not fulfilled.

Both the PROTECT and Protégé study contributed to the majority of the participants included in the performed analyses.

For HbA1c and mean daily insulin dose, the results of the primary meta-analysis models showed no statistically significant differences between treatment groups. It could be possible that mean daily insulin doses and the percentage of participants who met the insulin discontinuation criteria at month 18 may be more favourable in the teplizumab group, but the current level of evidence is not convincing.

For Peak C-peptide, a trend was observed in the 6 studies with higher proportions of participants with post-baseline peak C-peptide ≥0.2 pmol/mL in the teplizumab group compared to the control group. The event rates of hypoglycaemic adverse events were evaluable for PROTECT and Protégé studies only. In Protégé, the estimated mean rates of severe hypoglycaemic adverse events were considered very small, and hardly evaluable. Due to the small sample size and the low number of participants with events, the event rates were not estimable for the other 3 studies.

According to the applicant, the performed scatter plots based on integrated observed data suggest that higher mean C-peptide AUC may be associated with larger decrease from baseline in HbA1c, lower average of daily insulin use and a lower rate of Grade ≥3 hypoglycaemic events (according to CTCAE) at Month 18. However, the correlation coefficients varied from -0.1 to close to -0.5 and it is not agreed that these associations can be concluded based on the results provided.

Data from the RWE SDRNT1BIO indicate that higher C-peptide was associated with a lower number of DKA, severe hospitalized hypoglycemia and retinopathy events, during a median of 11 years of follow-up in 5630 participants. This possible correlation of the C-peptide marker to clinically important events is considered valuable to investigate further. But at present, no conclusions with respect to teplizumab treatment or the possible clinical benefits of C-peptide in the context of teplizumab treatment, can be drawn.

In summary, the difference at week 78 between teplizumab and placebo in the change from baseline in C-peptide ln(AUC+1) was statistically significant ($p<0.001$). It is agreed that the primary objective of the study was met. However, C-peptide is acknowledged as a marker of beta cell function considered

relevant as a co-primary endpoint when assessed along with a relevant clinical endpoint(s). But C-peptide ln (AUC+1) in 4h MMTT was used as a single primary endpoint in this study, and the clinically relevant endpoints as secondary endpoints. As type 1 error controlled secondary endpoints, they could possibly have contributed to the totality of evidence for a treatment effect of teplizumab. But, as all secondary endpoints failed to show treatment effect, no contribution from clinical endpoints is added to the knowledge on treatment effect.

The applicant has presented a range of analyses and contextual data; however, these data cannot be considered sufficient to support the establishment of clinical benefit. Therefore, the clinical relevance of C-peptide preservation in stage 3 T1D remains unproven.

Even if the results of some of the exploratory and/or post-hoc analyses provided may indicate beneficial effects, convincing results for the pre-planned type 1 error controlled clinical endpoints in the PROTECT study would have been expected in order to confirm a clinically relevant effect of teplizumab treatment in the patient population in question. The performed meta-analysis was not robustly showing treatment effect in favour of teplizumab with regards to clinically relevant variables. Thus, it cannot compensate for, or replace, analyses of multiplicity adjusted clinical secondary efficacy endpoints in the PROTECT study, as pivotal evidence.

The target population is broader than the study population in the PROTECT trial. E.g., only study subject 8-17 years of age and subjects with T1D diagnosis within 6 weeks and having remaining C-peptide levels were included. Therefore, the effect in patients with respect to age, other times from diagnose or remaining C-peptide levels at diagnose, is questioned.

Conclusions on the clinical efficacy

Based on the results of the pivotal and supportive clinical studies, treatment with teplizumab results in a delay of beta-cell destruction as measured by C-peptide compared to placebo.

With regards to the proposed first indication "to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D", it is acknowledged that results are available from one small, phase 2 trial. However, the results are considered robust from a statistical point of view. Further, the mechanism of action is supported by other studies in the T1D population. Based on the mechanism of action, the pathophysiology of T1D and results in sub-groups in other studies (in patients with stage 3) no major differences in sub-groups are expected. Therefore, it is considered that a clinically meaningful effect has been appropriately documented for subjects with Stage 2 T1D.

In addition, the Applicant will set up a global registry study in patients with stage 2 TID that is included in the RMP. A secondary objective of this study is to assess effectiveness of teplizumab in this population. The study will include 200 patients (150 treated with teplizumab / 50 not treated). To ensure that the registry study is adequate to evaluate the effectiveness of the product, the applicant is urged to seek EMA scientific advice to discuss the assessment of effectiveness including the size of the study.

There is currently no coordinated EU-wide strategy for screening or harmonised policy for early T1D detection. Identification of stage 2 T1D, characterised by the presence of multiple islet autoantibodies and abnormal glucose tolerance but without clinical symptoms, is still largely research-based or opportunistic, rather than part of routine clinical care. Several current and emerging screening

initiatives exist across Europe and internationally (such as TEDDY, Fr1da, EDENT1FI, INNODIA DETECT, and national programs in Italy, France, Spain, Germany, and others). These initiatives demonstrate increasing support for early detection of T1D, however continued harmonization across EU Member States will be important to support broader implementation and integration into clinical practice.

For the initially claimed second indication "to delay the progression of stage 3 T1D in adults and children with recently diagnosed stage 3 T1", no conclusions are drawn as the applicant withdrew the claim for this indication.

6.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

6.4.1. Safety data collection

Safety data is derived from the clinical trials previously described under the efficacy section of the report. Adverse events were collected throughout these studies. The pooled safety dataset for teplizumab (the 'all studies pool') encompass one study with participants with stage 2 T1D (the pivotal TN-10 study) and 6 studies in patients recently diagnosed stage 3 T1D (including the pivotal PROTECT study) of which one is an extension study (Table 41). The bio-compatibility study conducted on healthy patients with sub-therapeutic doses and the TN-10 extension study that was finalized after the data lock data (23 August 2024) of the integrated safety analysis are excluded. Furthermore, no safety data was available from Study 1. The pooling is considered acceptable.

Table 31. Studies providing safety data to safety summary

Study	Study Title	Pooled in ISS?
PROTECT (PRV-031-001)	A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (PRV-031), a Humanized, FcR Non-Binding, anti-CD3 Monoclonal Antibody, in Children and Adolescents with Newly Diagnosed Type 1 Diabetes (T1D)	Yes
Protégé (CP-MGA031-01)	A Phase 2/3, Randomized, Double-Blind, Multicenter, Multinational, 4-Arm, Controlled, Dose-Ranging Study to Evaluate Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus	Yes
Protégé Extension[a] (CP-MGA031-02)	A Multicenter, Multinational Extension of Study CP-MGA031-01 to Evaluate the Long-Term Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus.	Yes
Encore[a] (CP-MGA031-03)	A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus	Yes
AbATE (ITN027AI) (Study 4)	Phase II Multiple-Dose Treatment of Type 1 Diabetes Mellitus With hOKT3γ1 (Ala-Ala) (Autoimmunity-blocking Antibody for Tolerance study)	Yes
Delay (ISCT-MGA031-001) (Study 5)	Phase 2 trial of hOKT3γ1(Ala-Ala), teplizumab, for treatment of patients with recent onset Type 1 diabetes mellitus	Yes
TN-10 (ISCT-MGA031-005)	Anti-CD3 monocloncal antibody (teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus (TrialNet-10 study)	Yes
TN-10 Extension (PRV-031-002)	An Open-Label Study to Evaluate the Safety of Teplizumab (PRV-031) in At-Risk Relatives Who Develop Type 1 Diabetes	No
Single dose bio-comparability study (PRV-031-004)	A Phase 1, Randomized, Double-Blind, Parallel Group, Single-Dose Study in Healthy Subjects to Evaluate the Biocomparability of Teplizumab (PRV-031) Manufactured at Two Sites	No

Abbreviations: ISS=integrated summary of safety.
a Protégé Extension and Encore were terminated early by the Sponsor (primary efficacy endpoint not met).

The specific safety monitoring approach for each study is detailed below and an overview of the schedule of safety assessments for TN-10, PROTECT, Protégé, Encore, Protégé Extension, AbATE, and Delay is provided in Table 42.

TN-10: The follow-up duration was defined by time to protocol-specified number of T1D events observed; the median duration of follow-up was approximately 24.5 months for all participants (approximately 27.5 months for teplizumab-treated participants and approximately 17.8 months for placebo-treated participants). Participants were evaluated at regular intervals at on-site visits or via telephone call. All participants had regular contact with study personnel for formal inquiry about adverse events, and monitoring for possible diagnosis of T1D (i.e., presence or absence of blurred vision, polyuria, polydipsia, unintended weight loss).

PROTECT study: The follow-up duration was 18 months. Throughout this study, participants were assessed regularly via in-person and remote interviews, physical exams, self-reports, and laboratory examinations. Assessments occurred daily during the two 12-day treatment courses and regularly between the courses and the post-treatment follow-up period. Participants/caregivers used an eDiary to collect data related to insulin use, hypoglycaemic events, intermittent (e.g., spot-check or fingerstick) glucose measurements, AEs and internal medical and social history to be reviewed at clinical trial visits.

Protégé, Protégé Extension, and Encore: The follow-up duration was 24 months in Protégé, and 3 years in Protégé Extension. The planned follow-up duration was 24 months in Encore; on 20 October 2010, approximately 13 months after the first participant enrolled, the sponsor prematurely terminated the study and continued to follow participants for 18 months after their first dose of their last cycle of study medication. Participants were evaluated at regular intervals at on-site visits or via telephone call. Participants reported on a diary card insulin use, glucose and mealtimes.

AbATE: The follow-up duration was 24 months. Participants were evaluated at regular intervals at on-site visits. Immunologic testing could occur for up to 5 years post-study initiation. Participants received "intensive" management of their diabetes. Glucose levels were to be checked at least 4 times daily and records of the glucose levels were to be communicated to the certified diabetes educator every 2 weeks.

Delay: The follow-up duration was 12 months. Participants were evaluated at regular intervals at on-site visits.

Table 32. Schedule of safety visits (on-site or phone calls) in studies from the all studies pool

	Adverse events	**Laboratory parameters (Haematology +/- Chemistry)**
TN-10	Throughout the study including at following visits: Screening Each day of treatment course Day 20, Week 6, Months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, and then every 6 months	Screening Days 0, 1, 2, 3, 4, 5, 6, 8, 11, 13, 20, Week 6, Months 3, 6, 12, 18, 24, 36, 48, 60, 66, 72, and then every 6 months
PROTECT	Throughout the study including at following visits Screening Each day Course 1, Course 2 Weeks 4, 8,12, 20, 26 (MDS), 30, 34, 39, 52, 56 (MDS), 60 (MDS), 65, 78, EOT	Screening, Course1: Days 1, 2, 4, 6, 9, 12 Course 2: Days 182, 183, 185, 187, 190, 193 Weeks 4, 8, 12, 20, 26 (MDS), 30, 34, 39, 52, 56 (MDS), 60 (MDS), 65, 78, EOT
Protégé	Throughout the study including at following visits Each day Course 1, Course 2 Weeks 4, 5, 8, 13,16, 20, 28, 30, 32, 36, 39, 44, 48, 52, 56, 60, 64, 68, 72, 78, 80, 84, 88, 92, 96, 104	Screening, Course 1: Days 0, 1, 2, 3, 4, 5, 6, 7, 9, 11 Course 2: Days 182, 183, 184, 185, 186, 187, 188, 189, 191, 193 Weeks 3, 5, 13, 20, 28, 30, 39, 52, 104
Encore	Throughout the study including at following visits Each day Course 1, Course 2 Weeks 2, 3, 4, 8, 13, 16, 20, 28, 30, 32, 36, 39, 44, 48, 52, 56, 60, 64, 68, 72, 78, 80, 84, 88, 92, 96, 104 After 20 Oct 2010: If 1 course: Weeks 4, 8, 13, 26, 39, 52, 64, 78, If 2 courses: Weeks 30, 39, 52, 64, 78, 88, 104	Screening Course 1: Days 0, 1, 2, 3, 4, 5, 6, 7, 9, 11, 13 Course 2: Days 182, 183, 184, 185, 186, 187, 188, 189, 191, 193, 195 Weeks 2, 4, 13, 20, 28, 30, 39, 52 After 20 Oct 2010: If 1 course: Weeks 4, 13, 26, 39, 52, 78, If 2 courses: Weeks 30, 39, 52, 78, 104
Protégé Extension	Throughout the study including at following visits Day 0, Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36	Day 0, Months 6, 12, 18, 24, 30, 36
AbATE	Throughout the study including at following visits Screening Each day Course 1, Course 2 Months 1, 2, 3, 6, 9, 12, 13, 15, 18, 21, 24	Screening Course 1: Days 0, 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 14, 30 Course 2: Days 0, 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 14, 30 Months 2, 3, 6, 9, 12, 15, 18, 24
Delay	Throughout the study	Screening Days 0, 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 30 Months 2, 3, 6, 9, 12, 14, 15, 18, 21, 24

6.4.2. Patient exposure

In total, 1008 patients in the 'all-studies' pool were exposed to Teplizumab and 356 patients to control treatment. Of those, 900 patients received teplizumab in a placebo-controlled setting. The open label AbATE study (52 patients) did not employ placebo and Teplizumab was compared with standard of

care, the open label extension of the Delay study encompassed 18 patients exposed to teplizumab and the open label segment of the Protegé study encompassed 38 patients.

The number of participants by study in the "all studies pool" is listed in Table 43. While the participant disposition and exposure tables indicate 990 participants in the teplizumab group, most safety tables indicate 1008 participants exposed to teplizumab. The difference of 18 participants reflects the way Delay study participants were analysed: 18 participants who were initially randomly assigned to the placebo group and completed one-year follow-up elected to receive open-label teplizumab at Year 2 (Course 2). In addition, 22 participants in the teplizumab group who completed one-year follow up elected to receive a second course of open-label teplizumab treatment.

Table 33. Numbers of participants by study - All studies pool

Study ID	Number of Participants Exposed to Teplizumab	Number of Participants Exposed to Placebo	Number of Participants Exposed to Other[a]	Total
PROTECT	217	111	0	328
Protégé	453	98	0	551
Protégé Extension[b]	0	0	0	0
Encore	192	62	0	254
Delay	32/50[c]	28	0	60
AbATE	52	0	25	77
TN-10	44	32	0	76
Total	990/1008	331	25	1346

a "Other" refers to standard of care, no placebo infusion.
b A total of 219 participants from the Protégé study were enrolled in the Protégé Extension study. No treatment was given.
c In the Delay study, 32 participants were randomized to the teplizumab group in the double-blind part. In the open-label part, 18 participants initially in the placebo group received teplizumab treatment and are counted in both the teplizumab and placebo groups.
Source: 5.3.5.3 ISS Tables All Studies Pool, Table 1.1.

The PROTECT study was completed in May 2023, PROTEGÉ Feb 2011, PROTÉGÉ Ext Feb 2011, ENCORE Ext April 2012, AbATE July 2011, DELAY 2011 and TN-10-005 2018.

The duration of follow-up for the all studies pool is summarized in Table 44. Safety data above 1 year is available from >90% of patients, and data above 2 years is available from 38.9% of patients.

For the first indication (to delay the onset of stage 3 T1D in patients with stage 2 T1D), 44 patients have been exposed to teplizumab in the clinical trials.

Table 34. Summary of study follow-up duration - All studies pool

	Teplizumab N = 990	Control N = 356	Total N = 1346
Cumulative study follow up (patient-years)	1865.6	631.6	2497.2
Duration of study follow up (days) n	990	356	1346
Mean	688.3	648.0	677.6
SD	260.70	246.68	257.59
Median	724.5	571.0	722.0
Min	3	47	3
Max	2684	2136	2684
Duration of study follow up categories – n (%)			
<1 year	65 (6.6)	33 (9.3)	98 (7.3)
≥1 year	925 (93.4)	323 (90.7)	1248 (92.7)
≥2 years	385 (38.9)	122 (34.3)	507 (37.7)
≥3 years	53 (5.4)	12 (3.4)	65 (4.8)

Abbreviation: SD=standard deviation.
Note: Duration of study follow-up (days) is calculated as (end of study day – first dose day) + 1.
Source: 5.3.5.3 ISS Tables All Studies Pool, Table 1.4.1.

The demographic and baseline characteristics in the all studies pool are summarized in Table 45. Demographics in the 'all-studies' pool were overall comparable in the teplizumab and the control group. The overall median age was 14 years, 72% of participants were below 18 years. 62% of the population were male and 38% female. 76% were white and 19% asian. Demographics in the TN-10 study was comparable to the overall 'all-studies' pool.

Table 35. Demographic and baseline characteristics - All studies pool

	Teplizumab N = 990 n (%)	Control N = 356 n (%)	Total N = 1346 n (%)
Age (years)			
Mean	16.34	15.44	16.10
SD	7.007	7.025	7.020
Min	8.0	8.0	8.0
Median	14.00	13.00	14.00
Max	49.5	45.0	49.5
Age group,n (%)			
<18 years	694 (70.1)	276 (77.5)	970 (72.1)
≥18 years	296 (29.9)	80 (22.5)	376 (27.9)
Sex, n (%)			
Female	376 (38.0)	135 (37.9)	511 (38.0)
Male	614 (62.0)	221 (62.1)	835 (62.0)

	Teplizumab N = 990	Control N = 356	Total N = 1346
	n (%)	n (%)	n (%)
Ethnicity n (%)			
Hispanic or Latino	55 (5.6)	17 (4.8)	72 (5.3)
Not Hispanic or Latino	925 (93.4)	331 (93.0)	1256 (93.3)
Unknown	0	2 (0.6)	2 (0.1)
Not Reported	10 (1.0)	6 (1.7)	16 (1.2)
Race n (%)			
White	743 (75.1)	282 (79.2)	1025 (76.2)
Asian	204 (20.6)	54 (15.2)	258 (19.2)
Black or African American	13 (1.3)	10 (2.8)	23 (1.7)
American Indian or Alaska Native	3 (0.3)	0	3 (0.2)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	1 (<0.1)
Multiple	6 (0.6)	1 (0.3)	7 (0.5)
Other	11 (1.1)	2 (0.6)	13 (1.0)
Unknown	2 (0.2)	0	2 (0.1)
Not Reported	8 (0.8)	6 (1.7)	14 (1.0)
BMI (kg/m^2)			
Mean	20.62	20.25	20.52
SD	4.162	4.019	4.127
Min	10.4	12.7	10.4
Median	19.81	19.72	19.77
Max	43.7	42.3	43.7
Region n (%)			
North America	494 (49.9)	201 (56.5)	695 (51.6)
Europe	268 (27.1)	97 (27.2)	365 (27.1)
Rest of the world	228 (23.0)	58 (16.3)	286 (21.2)

Abbreviations: BMI=body mass index, BSA=body surface area, SD=standard deviation
Source: 5.3.5.3 ISS Tables All Studies Pool, Table 1.2.

6.4.3. Adverse events

An overview of TEAEs in the all studies pool is presented in Table 46 and an overview of TEAEs in study TN-10 is presented in Table 47.

Table 36. Overview of TEAEs - All studies pool

	Teplizumab N = 1008 n (%)	Control N = 356 n (%)	Total N = 1346 n (%)
Participants with at least 1 type of event			
TEAE	1003 (99.5)	341 (95.8)	1327 (98.6)
Treatment-emergent AESI	265 (26.3)	60 (16.9)	325 (24.1)
Treatment-emergent SAE	119 (11.8)	26 (7.3)	145 (10.8)
TEAE leading to study treatment interruption	103 (10.2)	11 (3.1)	114 (8.5)
TEAE leading to study treatment withdrawal	128 (12.7)	12 (3.4)	140 (10.4)
TEAE by CTCAE grade			
Grade 1	958 (95.0)	317 (89.0)	1258 (93.5)
Grade 2	883 (87.6)	232 (65.2)	1105 (82.1)
Grade 3	582 (57.7)	79 (22.2)	660 (49.0)
Grade 4	79 (7.8)	6 (1.7)	85 (6.3)
Grade 5	3 (0.3)	0	3 (0.2)
Missing	3 (0.3)	3 (0.8)	6 (0.4)
TEAE by relationship to study drug			
Definitely related	233 (23.1)	19 (5.3)	251 (18.6)
Probably related	747 (74.1)	102 (28.7)	847 (62.9)
Possibly related	807 (80.1)	224 (62.9)	1015 (75.4)
Probably not related	798 (79.2)	231 (64.9)	1016 (75.5)
Definitely not related	762 (75.6)	267 (75.0)	1021 (75.9)
Missing	2 (0.2)	1 (0.3)	3 (0.2)
TEAEs leading to death	3 (0.3)	0	3 (0.2)

Abbreviations: AESI=adverse event of special interest, CTCAE=Common Terminology Criteria for Adverse Events, SAE=serious adverse event, TEAE=treatment-emergent adverse event,

Source: 5.3.5.3 ISS Tables All Studies Pool, Table 2.1.1.

Table 37. Overview of TEAEs (Safety population) in study TN-10

	Teplizumab N=44	**Placebo** N=32	**Total** N=76
	n (%)	n (%)	n (%)
Subjects with at least 1:			
TEAE	43 (97.7)	22 (68.8)	65 (85.5)
Treatment-emergent AESI	4 (9.1)	0	4 (5.3)
Treatment-emergent SAE	7 (15.9)[a]	1 (3.1)	8 (10.5)
TEAE leading to treatment interruption	1 (2.3)	0	1 (1.3)
TEAE leading to treatment withdrawal	1 (2.3)	2 (6.3)	3 (4.0)
TEAE related to study drug	42 (95.5)	11 (34.4)	53 (69.7)
Death	0	0	0

[a]A total of 8 SAEs occurred in 7 subjects in the teplizumab group.

In the pooled dataset ("all studies pool"), almost all participants reported any TEAE in both the teplizumab group (99.5%) and the control group (95.8%), however TEAEs related to the study drug were more frequent in the teplizumab compared to the control group (definitely related: 23.1% vs 5.3%; probably related: 74.1% vs. 28.7%). SAEs occurred more frequently in the teplizumab group than in the placebo group (26.3% vs. 16.9%). TEAEs leading to study treatment interruption and withdrawal were more frequent in the teplizumab group. 3 fatal TEAEs occurred in the teplizumab group in the pooled dataset, and an additional case occurred in the TN-10 study extension. No fatal events were reported in the placebo group.

Grade 3 (severe) TEAEs were more frequent in the teplizumab group than control (7.8% vs. 1.7%), aa well as grade 4 (life-threatening) TEAEs were more frequent (7.8% vs. 1.7%). These reactions occurred mainly in the PTs lymphopenia, leukopenia and neutropenia.

In the TN-10 study performed in 44 individuals, the overall summary of adverse events were similar as for the 'all studies pool'

Common adverse events by preferred term

TEAEs with an incidence of ⩾5% for the pooled dataset are summarized by SOC and PT in Table 48. The five most common TEAEs with a higher incidence in the teplizumab group than the control group included lymphopenia (74.5% [teplizumab] versus 12.9% [control]), leukopenia (57.5% versus 20.5%), neutropenia (36.9% versus 18.3%), blood bicarbonate decreased (30.2% versus 19.1%) and rash (35.6% versus 8.4%).

Table 38. TEAEs with incidence ⩾5% by SOC and PT - All studies pool

System Organ Class Preferred Term	Teplizumab N = 1008		Control N = 356		Total N = 1346	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Participants with at least one TEAE	1003 (99.5)	6461.12	341 (95.8)	783.63	1327 (98.6)	2291.34
Blood and lymphatic system disorders	853 (84.6)	287.51	138 (38.8)	35.14	986 (73.3)	143.44
Lymphopenia	751 (74.5)	158.94	46 (12.9)	8.49	797 (59.2)	78.58
Leukopenia	580 (57.5)	72.90	73 (20.5)	14.60	650 (48.3)	50.25
Neutropenia	372 (36.9)	30.01	65 (18.3)	12.59	437 (32.5)	24.93
Thrombocytopenia	174 (17.3)	11.05	24 (6.7)	4.20	198 (14.7)	9.22
Anaemia	79 (7.8)	4.55	22 (6.2)	3.79	101 (7.5)	4.36
Investigations	705 (69.9)	116.57	190 (53.4)	61.68	888 (66.0)	97.89
Blood bicarbonate decreased	304 (30.2)	22.40	68 (19.1)	13.41	372 (27.6)	19.98
Aspartate aminotransferase increased	242 (24.0)	16.72	51 (14.3)	9.61	293 (21.8)	14.83
Haemoglobin decreased	235 (23.3)	16.17	57 (16.0)	10.97	291 (21.6)	14.77
Alanine aminotransferase increased	238 (23.6)	16.23	28 (7.9)	4.92	266 (19.8)	13.08
Blood sodium decreased	129 (12.8)	7.76	36 (10.1)	6.46	165 (12.3)	7.44
Blood alkaline phosphatase increased	108 (10.7)	6.36	35 (9.8)	6.26	142 (10.5)	6.30
Blood calcium decreased	102 (10.1)	5.95	20 (5.6)	3.42	122 (9.1)	5.31
Blood potassium increased	66 (6.5)	3.71	18 (5.1)	3.05	84 (6.2)	3.54
Blood bilirubin increased	68 (6.7)	3.85	10 (2.8)	1.67	78 (5.8)	3.30
Blood albumin decreased	66 (6.5)	3.75	12 (3.4)	2.01	77 (5.7)	3.26
Metabolism and nutrition disorders	570 (56.5)	60.93	196 (55.1)	61.55	765 (56.8)	61.11
Hypoglycaemia	206 (20.4)	12.74	96 (27.0)	19.70	302 (22.4)	14.37
Hyponatraemia	172 (17.1)	10.97	52 (14.6)	9.86	224 (16.6)	10.69
Hypocalcaemia	138 (13.7)	8.45	37 (10.4)	6.71	175 (13.0)	8.01
Hyperkalaemia	77 (7.6)	4.41	16 (4.5)	2.72	93 (6.9)	3.98
Hypoalbuminaemia	56 (5.6)	3.16	15 (4.2)	2.54	71 (5.3)	3.00
Infections and infestations	557 (55.3)	51.52	196 (55.1)	54.31	746 (55.4)	51.98
Upper respiratory tract infection	195 (19.3)	12.02	66 (18.5)	12.29	257 (19.1)	11.92
Nasopharyngitis	108 (10.7)	6.17	38 (10.7)	6.66	146 (10.8)	6.29
Skin and subcutaneous tissue disorders	620 (61.5)	81.51	101 (28.4)	21.24	712 (52.9)	57.68
Rash	359 (35.6)	29.35	30 (8.4)	5.23	384 (28.5)	21.40
Pruritus	135 (13.4)	8.22	23 (6.5)	3.96	157 (11.7)	7.07
Rash maculo-papular	55 (5.5)	3.07	4 (1.1)	0.66	59 (4.4)	2.45

System Organ Class Preferred Term	Teplizumab N = 1008		Control N = 356		Total N = 1346	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Gastrointestinal disorders	459 (45.5)	41.22	129 (36.2)	29.13	582 (43.2)	37.53
Nausea	247 (24.5)	16.74	55 (15.4)	10.12	299 (22.2)	14.82
Vomiting	179 (17.8)	11.17	40 (11.2)	6.97	215 (16.0)	9.90
Diarrhoea	90 (8.9)	5.18	27 (7.6)	4.63	116 (8.6)	5.00
Abdominal pain	87 (8.6)	4.94	22 (6.2)	3.74	109 (8.1)	4.65
Abdominal pain upper	78 (7.7)	4.41	28 (7.9)	4.83	105 (7.8)	4.47
General disorders and administration site conditions	448 (44.4)	39.56	127 (35.7)	28.56	567 (42.1)	36.04
Pyrexia	241 (23.9)	16.21	52 (14.6)	9.45	290 (21.5)	14.26
Fatigue	102 (10.1)	5.96	29 (8.1)	5.02	131 (9.7)	5.73
Chills	80 (7.9)	4.60	8 (2.2)	1.33	88 (6.5)	3.76
Nervous system disorders	374 (37.1)	29.18	103 (28.9)	22.07	470 (34.9)	27.00
Headache	309 (30.7)	22.38	82 (23.0)	16.40	385 (28.6)	20.55
Respiratory, thoracic and mediastinal disorders	238 (23.6)	15.71	90 (25.3)	17.95	323 (24.0)	16.06
Oropharyngeal pain	97 (9.6)	5.58	37 (10.4)	6.45	133 (9.9)	5.76
Cough	89 (8.8)	5.05	24 (6.7)	4.05	113 (8.4)	4.81
Nasal congestion	63 (6.3)	3.52	20 (5.6)	3.38	82 (6.1)	3.44
Musculoskeletal and connective tissue disorders	176 (17.5)	10.92	42 (11.8)	7.46	218 (16.2)	10.05
Pain in extremity	51 (5.1)	2.82	11 (3.1)	1.82	62 (4.6)	2.57
Injury, poisoning and procedural complications	141 (14.0)	8.27	41 (11.5)	7.18	182 (13.5)	8.01
Renal and urinary disorders	125 (12.4)	7.33	32 (9.0)	5.54	155 (11.5)	6.79
Proteinuria	90 (8.9)	5.15	18 (5.1)	3.03	108 (8.0)	4.61
Psychiatric disorders	93 (9.2)	5.31	40 (11.2)	7.13	129 (9.6)	5.59
Vascular disorders	90 (8.9)	5.15	28 (7.9)	4.89	117 (8.7)	5.05
Immune system disorders	98 (9.7)	5.68	16 (4.5)	2.69	114 (8.5)	4.92
Cytokine release syndrome	65 (6.4)	3.67	4 (1.1)	0.66	69 (5.1)	2.90
Hepatobiliary disorders	63 (6.3)	3.57	14 (3.9)	2.37	77 (5.7)	3.27
Hyperbilirubinaemia	59 (5.9)	3.34	14 (3.9)	2.37	73 (5.4)	3.09

Abbreviations: IR=incidence rate; PT=preferred term, SOC=system organ class.

Note: The denominator in percent calculation is the number of participants in each treatment group for subject count. System organ classes and preferred terms are based on MedDRA version 26.0. Total study follow-up time is calculated as the sum of duration in study (from first dose to the end of study) of individual participants in each treatment group.

Source: 5.3.5.3 ISS Tables All Studies Pool, Table 2.3.4.1.

TEAEs with an incidence of ≥5% from the TN-10 study are summarized by SOC and PT in Table 49. In this study, the most common Preferred Terms (PTs) reported in the teplizumab group were

lymphopenia (72.7%), leukopenia (20.5%), rash pruritic (15.9%), and nasopharyngitis (15.9%). When all rash-related terms (including rash, rash erythematous, rash macular, rash maculo-papular, rash popular, rash pruritic, and urticaria) are combined, 19 of 44 (43.2%) subjects in the teplizumab group had rash-related AEs.

Table 39. TEAEs with incidence ⩾5% by SOC and PT – TN-10 study

SOC	PT	Teplizumab N=44	Placebo N=32	Total N=76
		n (%)	n (%)	n (%)
Subjects with at least 1 TEAE		43 (97.7)	22 (68.8)	65 (85.5)
Blood and lymphatic system disorders		33 (75.0)	4 (12.5)	37 (48.7)
	Leukopenia	9 (20.5)	0	9 (11.8)
	Lymphopenia	32 (72.7)	2 (6.3)	34 (44.7)
	Neutropenia	3 (6.8)	1 (3.1)	4 (5.3)
Infections and Infestations		23 (52.3)	8 (25.0)	31 (40.8)
	Nasopharyngitis	7 (15.9)	2 (6.3)	9 (11.8)
	Pneumonia	4 (9.1)	1 (3.1)	5 (6.6)
	Sinusitis	4 (9.1)	1 (3.1)	5 (6.6)
	Upper respiratory tract infection	4 (9.1)	1 (3.1)	5 (6.6)
Skin and subcutaneous tissue disorders		20 (45.5)	3 (9.4)	23 (30.3)
	Rash	6 (13.6)	0	6 (7.9)
	Rash pruritic	7 (15.9)	0	7 (9.2)
Nervous system disorders		9 (20.5)	5 (15.6)	14 (18.4)
	Headache	5 (11.4)	3 (9.4)	8 (10.5)
Gastrointestinal disorders		7 (15.9)	3 (9.4)	10 (13.2)
	Vomiting	2 (4.5)	2 (6.3)	4 (5.3)
Respiratory, thoracic and mediastinal disorders		7 (15.9)	1 (3.1)	8 (10.5)
	Bronchospasm	3 (6.8)	0	3 (3.9)
	Cough	3 (6.8)	0	3 (3.9)

Within the SOC 'blood and lymphatic system disorders', PTs reported with higher frequencies in the teplizumab group compared to control were lymphopenia (74.5% vs. 12.9%), leukopenia (57.5% vs 20.5%), neutropenia (36.9% vs. 18.3%).

Imbalance in AEs related to liver function were observed within the SOC 'Investigations' where PTs

reported with higher frequencies for teplizumab were aspartate aminotransferase increased (24.0% vs. 14.3%), alanine aminotransferase increased (23.6% vs. 7.9%), blood bilirubin increased (6.7% vs. 2.8%) and blood albumin decreased (6.5% vs. 3.4%). Within the SOC 'hepatobiiliary disorders', there was a small increased frequency of hyperbilirubinaemia for teplizumab (5.9% vs. 3.9%).

Also, within SOC 'Metabolism and nutrition disorders' an imbalance in hypoalbuminaemia is noted (5.6% vs. 4.2% in teplizumab vs. control).

Furthermore, within the SOC 'Investigations' the PT 'haemoglobin decreased' was more frequent in the teplizumab than control (23.3% vs. 16.0%). There was also an increased occurrence in anaemia (7.8% vs. 6.2%) within the SOC 'Blood and lymphatic system disorders.

Within the SOC 'Skin and subcutaneous disorders' PTs reported with higher frequencies in the teplizumab group compared to control were rash (35.6% vs. 8.4%), pruritus (13.4% vs. 6.5%) and rash maculo-papilar (5.5% vs. 1.1%). The TEAEs were in general mild to moderate in intensity (CTCAE grade 1 and 2). Three grade 3 cases of rash and 1 grade 3 case of rash popular were reported.

With the SOC 'gastrointestinal disorders' PTs reported with higher frequencies in the teplizumab group compared to control were nausea (24.5% vs. 15.4%), vomiting (17.8% vs. 11.2%), abdominal pain (8.6% vs. 6.2%) and gastritis (1.7% vs. 0.6%).

For the SOC "Infections and infestations", TEAEs were in general balanced in the 'all studies pool' (55% in both groups). A slight imbalance for Epstein Barr viraemia was noted however (2.6% vs. 0.8% in teplizumab vs. control). In the TN-10 study, the frequency of TEAEs for the SOC was increased in the teplizumab group compared to control (52.3% vs. 25.0%) however given the few cases, the estimate is less reliable. Imbalances in the TN-10 study were noted in the PTs nasopharyngitis (15.9% [7 cases] vs. 6.3% [2 cases]), pneumonia (9.1% [4 cases] vs. 3.1% [1 case]), sinusitis 9.1% [4 cases] vs. 3.1% [1 case]) and upper respiratory tract infection (9.1% [4 cases] vs. 3.1% [1 case]). The frequency of cough was increased in teplizumab vs. control (8.8% vs. 6.7%).

Within the SOC 'General disorders and administration site conditions' PTs with higher frequencies in the teplizumab group compared to control were pyrexia (23.9% vs. 14.6%) and chills (7.9% vs. 2.2%).

The PT headache was more frequent in the teplizumab group than control (30.7% vs. 23.0%).

Proteinuria was more frequent in the teplizumab group than control (8.9% vs. 5.1%). Most cases were grade 1 proteinuria and were resolved within the same timeframe in both treatment groups. The cases were in general not considered related to treatment by investigators and had no clear temporal relation with teplizumab administration. The imbalance is thus not assessed as clinically significant.

The PT 'cytokine release syndrome' was more frequent in the teplizumab group than control (6.4% vs. 1.1%).

The frequency of hypoglycaemia was lower in the teplizumab group (20.4% vs. 27.0%). In the studies in the safety database, hypoglycaemia was classified according to CTCAE given that the standardisation by the International Hypoglycaemia Study Group was not yet published when the studies were conducted. In the all-studies pool, hypoglycaemia was reported in 20.4% vs. 27.0% in teplizumab vs. control. For grade 3 or higher hypoglycaemia (i.e. below 2.17 mM), the frequencies were 4.4% vs. 5.9% in teplizumab vs. control. In participants ≥18 years of age, the incidence was 6.4% in the teplizumab group and 5.0% in the control group. For grade 3 hypoglycaemia, the incidence was 1.0% in the teplizumab group and 1.3% in the control group. For paediatric

participants 12 to <18 years of age, the incidence of hypoglycaemia was 23.9% in the teplizumab group and 32.5% in the control group and in participants 8 to <12 years of age the incidence was 30.3% in the teplizumab group and 34.5% in the control group. For grade 3 hypoglycaemia, in participants 12 to <18 years of age, the incidence of Grade 3 or higher Hypoglycaemia (PT) was 5.8% in the teplizumab group and 7.2% in the control group and in participants 8 to <12 years of age the incidence was 5.7% in the teplizumab group and 7.3% in the control group.

The PT 'Blood bicarbonate decreased' was more frequent in the teplizumab group than the control in the overall safety pool (30.2% vs. 19.1%). As commented by the applicant, there were very few cases in the PROTECT study (a single case in each group), and there were no case in the TN-10 study. Cases were however reported with a high frequency across all treatment arms in the Protegé and the Encore study. The apparent overall imbalance thus appears to be an artefact when the studies are pooled.

TEAEs during treatment course and through 28 days after the last dose

The applicant has provided a separate summary of the incidence of TEAEs that occurred during either the treatment course or through 28 days after the last dose was administered. The imbalances in TEAEs found in the full all studies pool were also present in this summary, thus indicating that it may be a temporal relationship with the administration of teplizumab and the TEAEs. Furthermore, imbalances in abdominal pain (7.1% vs. 4.2% in teplizumab vs. control) and oropharyngeal pain (5.9% vs. 2.8% in teplizumab vs. control) was found. The frequency of hypoglycaemia was reduced in teplizumab vs. control (13.6% vs. 20.2%).

Adverse drug reactions

The ADRs proposed for inclusion in the SmPC is provided in Table 50.

Table 40: ADRs proposed for inclusion in the SmPC

Infections and infestations	Link to data*
Uncommon	Infections
Not known	Epstein-Barr virus reactivation
Blood and lymphatic system disorders	
Very Common	Lymphopenia
	Thrombocytopenia
	Leukopenia
	Neutropenia
	Haemoglobin decreased
Common	Blood bilirubin increased
	Eosinophilia
Immune system disorders	
Common	Cytokine release syndrome
Uncommon	Hypersensitivity
Nervous system disorders	
Very Common	Headache
Gastrointestinal disorders	
Very Common	Vomiting

Common	Nausea
	Diarrhoea
	Abdominal pain
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased
	Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	
Very Common	Rash
	Pruritus
Common	Rash maculo-papular
	Rash pruritic
	Urticaria
	Skin exfoliation
General disorders and administration site conditions	
Very Common	Pyrexia
	Fatigue
Common	Chills
Not Known	Pain
	Illness

* include the link to source data

6.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Deaths

Four deaths occurred during the studies, all in the teplizumab group (Table 51). The cases were related to diabetic ketoacidosis and glomerulosclerosis leading to uraemia, acute myocardial infarction, unknown death related to gastrointestinal disorders and suicide, respectively. No case occurred in relation to administration of teplizumab (earliest case 9 months after administration) and the cases are thus unlikely considered related to teplizumab.

Table 41. List of participant deaths - All studies safety pool

Study	Age at enrollment Sex	Adverse event Time to onset post last dose	Cause of death	Relationship to study drug
Protégé	19 years Female	Diabetic ketoacidosis/ intercapillary glomerulosclerosis 9 months	Diabetic ketoacidosis	Unlikely
Protégé	27 years Male	Acute myocardial infarction/ cardio-respiratory arrest/ ventricular tachycardia 15 months	Anterior myocardial infarction; Ventricular tachycardia; cardiopulmonary arrest	Not related

Study	Age at enrollment Sex	Adverse event Time to onset post last dose	Cause of death	Relationship to study drug
Protégé Extension	24 years Female	Death 26 months	Unknown Death preceded by abdominal pain, vomiting and loose stools; admitted due to vomiting. Records could not be obtained from clinical site.	Not related
TN-Extension[a]	21 years Female	Completed suicide 9 months	Completed suicide, major depressive disorder	Not related

a TN10-Extension was not included in the pooled analyses.

Serious Adverse Events

A summary of SAEs for the pooled dataset is provided in Table 52.

Table 42. Summary of TESAEs by SOC and PT - All studies pool

System Organ Class Preferred Term	Teplizumab N = 1008		Control N = 356		Total N = 1346	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Subjects with at least one TESAE	119 (11.8)	6.84	26 (7.3)	4.45	145 (10.8)	6.24
Metabolism and nutrition disorders	38 (3.8)	2.06	6 (1.7)	0.99	44 (3.3)	1.79
Diabetic ketoacidosis	21 (2.1)	1.13	1 (0.3)	0.16	22 (1.6)	0.89
Hyperglycaemia	6 (0.6)	0.32	3 (0.8)	0.49	9 (0.7)	0.36
Hypoglycaemia	6 (0.6)	0.32	2 (0.6)	0.33	8 (0.6)	0.32
Diabetes mellitus inadequate control	4 (0.4)	0.21	0	0.00	4 (0.3)	0.16
Dehydration	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Diabetic ketosis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Ketoacidosis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Ketosis	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Infections and infestations	31 (3.1)	1.69	8 (2.2)	1.32	39 (2.9)	1.60
Gastroenteritis	4 (0.4)	0.21	4 (1.1)	0.65	8 (0.6)	0.32
Cellulitis	2 (0.2)	0.11	2 (0.6)	0.33	4 (0.3)	0.16
Gastroenteritis viral	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Infection	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Pneumonia	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Anal abscess	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Appendicitis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Appendicitis perforated	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Arthritis bacterial	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04

System Organ Class Preferred Term	Teplizumab N = 1008		Control N = 356		Total N = 1346	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Bronchitis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Dengue fever	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Device related bacteraemia	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Epididymitis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Gastritis viral	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Hepatic amoebiasis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Hepatitis A	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Infectious mononucleosis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Paronychia	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Peritonitis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Pharyngotonsillitis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Pilonidal disease	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Pulmonary tuberculosis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Pyelonephritis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Renal abscess	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Sepsis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Staphylococcal sepsis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Tuberculosis	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Urinary tract infection	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Varicella	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Wound infection	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Nervous system disorders	11 (1.1)	0.59	3 (0.8)	0.49	14 (1.0)	0.56
Hypoglycaemic seizure	7 (0.7)	0.37	0	0.00	7 (0.5)	0.28
Hypoglycaemic unconsciousness	2 (0.2)	0.11	1 (0.3)	0.16	3 (0.2)	0.12
Hypoglycaemic coma	1 (<0.1)	0.05	1 (0.3)	0.16	2 (0.1)	0.08
Central nervous system haemorrhage	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Dizziness	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Syncope	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Gastrointestinal disorders	11 (1.1)	0.59	1 (0.3)	0.16	12 (0.9)	0.48
Gastritis	4 (0.4)	0.21	0	0.00	4 (0.3)	0.16
Vomiting	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Abdominal pain	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Abdominal pain upper	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Constipation	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Diarrhoea	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Intestinal obstruction	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Nausea	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04

System Organ Class Preferred Term	Teplizumab N = 1008		Control N = 356		Total N = 1346	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Immune system disorders	12 (1.2)	0.64	0	0.00	12 (0.9)	0.48
Cytokine release syndrome	9 (0.9)	0.48	0	0.00	9 (0.7)	0.36
Drug hypersensitivity	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Hypersensitivity	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Serum sickness	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Injury, poisoning and procedural complications	9 (0.9)	0.48	2 (0.6)	0.33	11 (0.8)	0.44
Concussion	1 (<0.1)	0.05	1 (0.3)	0.16	2 (0.1)	0.08
Splenic rupture	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Ankle fracture	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Craniocerebral injury	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Facial bones fracture	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Fall	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Fibula fracture	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
First degree chemical burn of skin	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Foot fracture	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Skull fracture	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Spinal compression fracture	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Upper limb fracture	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Psychiatric disorders	5 (0.5)	0.27	2 (0.6)	0.33	7 (0.5)	0.28
Suicide attempt	3 (0.3)	0.16	0	0.00	3 (0.2)	0.12
Suicidal ideation	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Anxiety	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Hallucination	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Mental disorder	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
General disorders and administration site conditions	4 (0.4)	0.21	2 (0.6)	0.33	6 (0.4)	0.24
Non-cardiac chest pain	0	0.00	2 (0.6)	0.33	2 (0.1)	0.08
Pyrexia	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Death	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Pain	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Blood and lymphatic system disorders	4 (0.4)	0.21	1 (0.3)	0.16	5 (0.4)	0.20
Neutropenia	2 (0.2)	0.11	1 (0.3)	0.16	3 (0.2)	0.12
Lymphopenia	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Renal and urinary disorders	3 (0.3)	0.16	2 (0.6)	0.33	5 (0.4)	0.20
Intercapillary glomerulosclerosis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Ketonuria	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Microalbuminuria	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04

System Organ Class Preferred Term	Teplizumab N = 1008		Control N = 356		Total N = 1346	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Nephrolithiasis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Pelvi-ureteric obstruction	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Cardiac disorders	3 (0.3)	0.16	0	0.00	3 (0.2)	0.12
Acute myocardial infarction	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Angina pectoris	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Cardio-respiratory arrest	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Coronary artery disease	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Palpitations	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Ventricular tachycardia	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Eye disorders	3 (0.3)	0.16	0	0.00	3 (0.2)	0.12
Cataract subcapsular	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Corneal erosion	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Iritis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Hepatobiliary disorders	3 (0.3)	0.16	0	0.00	3 (0.2)	0.12
Biliary dyskinesia	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Biloma	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Cholecystitis acute	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Hepatosplenomegaly	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Skin and subcutaneous tissue disorders	3 (0.3)	0.16	0	0.00	3 (0.2)	0.12
Rash	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Dermatitis atopic	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Investigations	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Alanine aminotransferase increased	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Aspartate aminotransferase increased	2 (0.2)	0.11	0	0.00	2 (0.1)	0.08
Pregnancy, puerperium and perinatal conditions	1 (<0.1)	0.05	1 (0.3)	0.16	2 (0.1)	0.08
Abortion spontaneous	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Complication of pregnancy	0	0.00	1 (0.3)	0.16	1 (<0.1)	0.04
Ear and labyrinth disorders	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Deafness neurosensory	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Musculoskeletal and connective tissue disorders	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Musculoskeletal chest pain	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Metastatic malignant melanoma	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04

System Organ Class Preferred Term	Teplizumab N = 1008		Control N = 356		Total N = 1346	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Vascular disorders	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04
Subclavian vein thrombosis	1 (<0.1)	0.05	0	0.00	1 (<0.1)	0.04

Abbreviations: IR = Incidence Rate, PY = Patient-Year, TESAE = Treatment-Emergent Serious Adverse Event.

Note: The denominator on percent calculation is the number of participants in each treatment group. The denominator on the IR per PY calculation is the total study follow-up time at risk for the event for each treatment group. Total study follow-up time at risk is calculated as the sum of individual participants at risk duration, defined as time from first dose to first occurrence of event for participants with the event, or time from first dose to the end of study for participants without the event. For participants receiving Placebo in the Delay double-blind period and teplizumab in the open-label period this calculation is done separately for each period for treatment arm columns. Delay participants initially randomized to the Placebo arm, who were later also eligible for the open-label Course 2 administration of teplizumab, are counted once for each treatment arm and once in the total column of participant count. Adverse events for these participants are counted in one treatment arm only (Teplizumab or Control) and once in the total column, according to the treatment at adverse event onset. SOCs and PTs are based on MedDRA version 26.0.

Source: 5.3.5.3 ISS Tables All Studies Pool, Table 2.11.1.2.

The frequencies of SAEs in the pooled dataset were in general low and balanced between the teplizumab and control group.

SAEs related to glucose metabolism were registered. Hyper and hypoglycaemia occurred at low frequencies (0.6-0.8%) in both treatment groups. Cases of diabetic ketoacidosis were registered, which predominantly occurred in the teplizumab group (2.1% [21 cases] vs. 0.3% [1 case]). The cases occurred several months after drug administration, and they appear to be related to the underlying development of diabetes.

7 cases of hypoglycaemic seizures (0.7%) were registered in the teplizumab group, with no cases occurring in the control group. The reported hypoglycaemic events appear to be related to the insulin treatment rather than teplizumab.

For the SOC 'immune system disorders' all occurring SAEs were registered within the teplizumab group (12 cases [1.2%]). For the PT 'cytokine release syndrome', 9 cases (0.9%) were registered in the teplizumab group with no cases in the control group. A single case each was registered for 'drug hypersensitivity', 'hypersensitivity' and 'serum sickness'. The SmPC contains information to mitigate the risk for cytokine release syndrome which includes premedication during the first 5 administration days.

For the SOC 'Infections and infestations' there was a slightly increased occurrence in the teplizumab group compared to control (3.1% [31 cases] vs. 2.2% [8 cases] without any obvious difference in the PT pattern. The slightly higher frequency of reported PTs within the SOC "infections and infestations" most probably reflects the known immunosuppressive effect of teplizumab. The risk for serious infections is reflected in the SmPC sections 4.4 and 4.8.

For the SOC 'gastrointestinal disorders' there was an overall imbalance (1.1% [11 cases] vs. 0.3% [1 case]). The SAEs occurred within several PTs with no clear pattern. Nausea and vomiting are included as Adverse reactions in SmPC section 4.8.

Three SAEs of suicide attempt and two cases of suicidal ideation were registered in the teplizumab group with no cases in the control group. Furthermore, one fatal event due to suicide occurred in the teplizumab group.

In the TN-10 study, eight subjects (18.2%) had a total of 9 SAEs during the study, including 7 (15.9%) subjects in the teplizumab group and 1 (3.1%) subject in the placebo group.

In the teplizumab group, 1 subject had 2 SAEs (dizziness and ankle fracture). Furthermore, 4 of the SAEs, which occurred in 4 subjects, were infections (pneumonia, cellulitis, wound infection, and gastroenteritis).

AEs of Special Interest

AESIs in the all studies pool are summarized by SOC and PT and in Table 54. The incidence of AESIs was higher in the teplizumab group (26.3%) than in the control group (16.9%). Data adjusted according to study size were provided and showed similar results.

Table 43. Search criteria applied for adverse events of special interest (AESI)

Type of event	Search criteria
≥Grade 3 infections (includes all opportunistic infections)	SOC - 'Infections and infestations'; ≥Grade 3
Acute mononucleosis-like illness (eg, 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', EBV IgM antibody positive
Lymphomas or other malignancies	SOC - 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' and HLT - includes 'malignant' or 'lymphomas
≥Grade 3 hypoglycemic adverse events (severe)	PT - 'Hypoglycemia', 'Hypoglycemic seizure', 'Hypoglycemic coma'; 'Hypoglycemic unconsciousness'; ≥Grade 3
≥Grade 3 liver function abnormalities (AST, ALT, bilirubin), ie, an AST or ALT value >5.0 x ULN or a bilirubin value >3.0 x ULN.	HLT - 'Liver function analyses'; ≥Grade 3
≥Grade 3 thrombocytopenia (platelet counts less than 50 000/μL)	PT - 'Thrombocytopenia'; ≥Grade 3
≥Grade 3 neutropenia (<1000 PMN/μL on 2 consecutive evaluations performed on different days	PT - 'Neutropenia'; ≥Grade 3
≥Grade 4 allergic/hypersensitivity reaction (through Study Day 365), ie, 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 (through Study Day 365), ie, 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

Abbreviations: ALT= alanine aminotransferase; AST=aspartate aminotransferase; EBV=Epstein-Barr virus, HLT=high level term, PMN=polymorphonuclear leukocytes; PT=preferred term, SOC=system organ class; ULN=upper limit of normal.

Source: 5.3.5.3 ISS SAP 05Jul2024, Table 5.

Table 44. AESIs by category, SOC and preferred term - Safety population - All studies pool

AESI category System Organ Class Preferred Term	Teplizumab N=1008 n(%)	 IR per 100 PY	Control N=356 n(%)	 IR per 100 PY	Total N=1346 n(%)	 IR per 100 PY
Subjects with at least one AESI	265(26.3)	17.66	60(16.9)	11.04	325(24.1)	15.90
Acute mononucleosis-like illness	102(10.1)	5.91	19(5.3)	3.21	121(9.0)	5.22
Investigations	50(5.0)	2.78	12(3.4)	2.00	62(4.6)	2.59
Epstein-Barr virus antibody positive	31(3.1)	1.69	11(3.1)	1.83	42(3.1)	1.72
Cytomegalovirus test positive	10(1.0)	0.54	2(0.6)	0.33	12(0.9)	0.48
Epstein-Barr virus test positive	9(0.9)	0.48	0	0.00	9(0.7)	0.36
Epstein-Barr virus antigen positive	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Infections and infestations	34(3.4)	1.85	5(1.4)	0.82	39(2.9)	1.59
Epstein-Barr viraemia	26(2.6)	1.41	3(0.8)	0.49	29(2.2)	1.18
Infectious mononucleosis	4(0.4)	0.21	1(0.3)	0.16	5(0.4)	0.20
Epstein-Barr virus infection	2(0.2)	0.11	1(0.3)	0.16	3(0.2)	0.12
Epstein-Barr virus infection reactivation	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Mononucleosis syndrome	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Blood and lymphatic system disorders	21(2.1)	1.13	3(0.8)	0.49	24(1.8)	0.97
Lymphadenopathy	21(2.1)	1.13	3(0.8)	0.49	24(1.8)	0.97
Major hypoglycemia	53(5.3)	2.90	23(6.5)	3.88	76(5.6)	3.14
Metabolism and nutrition disorders	44(4.4)	2.39	21(5.9)	3.53	65(4.8)	2.67
Hypoglycaemia	44(4.4)	2.39	21(5.9)	3.53	65(4.8)	2.67
Nervous system disorders	9(0.9)	0.48	2(0.6)	0.33	11(0.8)	0.44
Hypoglycaemic seizure	6(0.6)	0.32	0	0.00	6(0.4)	0.24
Hypoglycaemic unconsciousness	3(0.3)	0.16	1(0.3)	0.16	4(0.3)	0.16
Hypoglycaemic coma	1(<0.1)	0.05	1(0.3)	0.16	2(0.1)	0.08
>=Grade 3 neutropenia	55(5.5)	3.06	8(2.2)	1.33	63(4.7)	2.62
Blood and lymphatic system disorders	55(5.5)	3.06	8(2.2)	1.33	63(4.7)	2.62
Neutropenia	55(5.5)	3.06	8(2.2)	1.33	63(4.7)	2.62
>=Grade 3 infections	25(2.5)	1.35	7(2.0)	1.15	32(2.4)	1.30
Infections and infestations	25(2.5)	1.35	7(2.0)	1.15	32(2.4)	1.30
Cellulitis	3(0.3)	0.16	3(0.8)	0.49	6(0.4)	0.24
Gastroenteritis	1(<0.1)	0.05	2(0.6)	0.33	3(0.2)	0.12
Gastroenteritis viral	3(0.3)	0.16	0	0.00	3(0.2)	0.12
Herpes zoster	2(0.2)	0.11	1(0.3)	0.16	3(0.2)	0.12
Infection	2(0.2)	0.11	0	0.00	2(0.1)	0.08
Pneumonia	2(0.2)	0.11	0	0.00	2(0.1)	0.08
Anal abscess	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Appendicitis	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Appendicitis perforated	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Arthritis bacterial	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Conjunctivitis	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Dengue fever	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Hepatic amoebiasis	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Liver abscess	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Malaria	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04

AESI category System Organ Class Preferred Term	Teplizumab N=1008 n(%)	Teplizumab N=1008 IR per 100 PY	Control N=356 n(%)	Control N=356 IR per 100 PY	Total N=1346 n(%)	Total N=1346 IR per 100 PY
Peritonitis	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Pilonidal disease	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Staphylococcal sepsis	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Tuberculosis	0	0.00	1(0.3)	0.16	1(<0.1)	0.04
Wound infection	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Wound infection staphylococcal	0	0.00	1(0.3)	0.16	1(<0.1)	0.04
>=Grade 3 liver function abnormalities	28(2.8)	1.52	3(0.8)	0.49	31(2.3)	1.26
Investigations	28(2.8)	1.52	3(0.8)	0.49	31(2.3)	1.26
Alanine aminotransferase increased	21(2.1)	1.14	1(0.3)	0.16	22(1.6)	0.89
Aspartate aminotransferase increased	14(1.4)	0.75	1(0.3)	0.16	15(1.1)	0.61
Gamma-glutamyltransferase increased	2(0.2)	0.11	2(0.6)	0.33	4(0.3)	0.16
Blood bilirubin increased	2(0.2)	0.11	0	0.00	2(0.1)	0.08
Lymphomas or other malignancies	23(2.3)	1.24	5(1.4)	0.82	28(2.1)	1.14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23(2.3)	1.24	5(1.4)	0.82	28(2.1)	1.14
Skin papilloma	19(1.9)	1.02	5(1.4)	0.82	24(1.8)	0.97
Anogenital warts	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Dysplastic naevus	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Lipoma	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Melanocytic naevus	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Lymphocyte count <500 mm3 for 7 days or longer	19(1.9)	1.03	0	0.00	19(1.4)	0.77
Blood and lymphatic system disorders	19(1.9)	1.03	0	0.00	19(1.4)	0.77
Lymphopenia	19(1.9)	1.03	0	0.00	19(1.4)	0.77
>=Grade 3 rash	6(0.6)	0.32	0	0.00	6(0.4)	0.24
Skin and subcutaneous tissue disorders	6(0.6)	0.32	0	0.00	6(0.4)	0.24
Rash	3(0.3)	0.16	0	0.00	3(0.2)	0.12
Dermatitis atopic	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Pruritus	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
Rash papular	1(<0.1)	0.05	0	0.00	1(<0.1)	0.04
>=Grade 3 thrombocytopenia	1(<0.1)	0.05	1(0.3)	0.16	2(0.1)	0.08
Blood and lymphatic system disorders	1(<0.1)	0.05	1(0.3)	0.16	2(0.1)	0.08
Thrombocytopenia	1(<0.1)	0.05	1(0.3)	0.16	2(0.1)	0.08

Note: AESI = Adverse Event of Special Interest, IR = Incidence Rate, PY = Patient-Year
Note: The denominator on percent calculation is the number of subjects in each treatment group. The denominator on the incidence rate per patient-year calculation is the total study follow-up time at risk for the event for each treatment group
Note: Total study follow-up time at risk is calculated as the sum of individual subjects at risk duration, defined as time from first dose to first occurrence of event for subjects with the event, or time from first dose to the end of study for subjects without the event. For subjects receiving Placebo in the Delay double-blind period and Teplizumab in the open-label period this calculation is done separately for each period for treatment arm columns.
Note: Delay subjects initially randomized to the Placebo arm, who were later also eligible for the open-label course 2 administration of Teplizumab, are counted once for each treatment arm and once in the total column of subject count. Adverse events for these subjects are counted in one treatment arm only (Teplizumab or Control) and once in the total column, according to the treatment at adverse event onset
Note: System organ classes (SOCs) and preferred terms are based on MedDRA version 26.0
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/ae_aesi_cat_ir_s_t.sas
OUT=REPORT/OUTPUT/ae_aesi_cat_ir_s_t_i.rtf (04JUN2025 10:03)

For the TEAI '≥Grade 3 infections' the frequency was similar in both groups (2.5% vs. 2.0%). For the AESI 'Acute mononucleosis-like illness', the frequency was higher in teplizumab vs. control (10.1% vs. 5.3%).

For the TEAI '≥Grade 3 neutropenia' the frequency was higher in the teplizumab group than in control (5.5% vs. 2.2%).

For the TEAI '≥Grade 3 liver function abnormalities' the frequency was higher in the teplizumab group than in the control group (2.8% vs. 0.8%).

For the TEAI 'Lymphomas and other malignancies', the frequency was 2.3% in teplizumab and 1.4% in the control group. The difference is mainly related to increased number of cases of skin papilloma in the teplizumab group. No lymphoma was reported. One patient was diagnosed with metastatic melanoma that developed in a dysplastic nevi already present when the patient entered the study.

For the TEAI 'Severe (≥Grade 3) hypoglycaemic adverse events' the frequency was lower in the teplizumab than in the control group (5.3% vs. 6.5%).

6.4.5. Discontinuation due to adverse events

A higher proportion of participants discontinued study drug in the teplizumab group compared to control (12.7% vs. 3.4%), see Table 55. The most common reason for discontinuation were AEs related to the SOC Investigations (7.1% vs 0.8%).

Within the SOC investigations, increased frequencies in the teplizumab vs. control group were noted for the PTs alanine aminotransferase (ALAT) increased (4.5% vs. 0.3%), aspartate aminotransferase (ASAT) increased (2.2% vs. 0.3%) and haemoglobin decreased (1.2% vs 0%).

For the SOC blood and lymphatic system disorders, the overall frequency of discontinuations was 2.5% in the teplizumab group and 0.3% in the control group. Among the PTs, imbalances were noted for neutropenia (1.1% vs. 0%) and thrombocytopenia (0.9% vs. 0%).

Within the SOC immune system disorders, there was an imbalance in the PT cytokine release syndrome (1.3% vs. 0%). Furthermore, 2 discontinuations due to hypersensitivity occurred in the teplizumab group with no cases in the control group.

For the other SOCs, the events were few and no clear differences were noted between the treatment arms.

Table 45. TEAEs causing permanent discontinuation of study drug by SOC and preferred term Safety population - All Studies Pool

System Organ Class	Preferred Term	Teplizumab N = 1008 n (%)	Control N = 356 n (%)	Total N = 1346 n (%)
Subjects with at least one type of event of interest		128 (12.7)	12 (3.4)	140 (10.4)
Investigations	-Total	72 (7.1)	3 (0.8)	75 (5.6)
	Alanine aminotransferase increased	45 (4.5)	1 (0.3)	46 (3.4)
	Aspartate aminotransferase increased	22 (2.2)	1 (0.3)	23 (1.7)
	Haemoglobin decreased	12 (1.2)	0	12 (0.9)
	Blood bilirubin increased	4 (0.4)	1 (0.3)	5 (0.4)
	CD4 lymphocytes decreased	3 (0.3)	0	3 (0.2)
	Epstein-Barr virus antibody positive	2 (0.2)	1 (0.3)	3 (0.2)
	Gamma-glutamyltransferase increased	3 (0.3)	0	3 (0.2)
	International normalised ratio increased	2 (0.2)	0	2 (0.1)
Investigations (continued)	Bilirubin conjugated increased	1 (<0.1)	0	1 (<0.1)
	Blood calcium decreased	1 (<0.1)	0	1 (<0.1)
	Mean cell haemoglobin concentration increased	1 (<0.1)	0	1 (<0.1)
	Red blood cell count decreased	1 (<0.1)	0	1 (<0.1)
Blood and lymphatic system disorders	-Total	25 (2.5)	1 (0.3)	26 (1.9)
	Neutropenia	11 (1.1)	0	11 (0.8)
	Thrombocytopenia	9 (0.9)	0	9 (0.7)
	Lymphopenia	4 (0.4)	1 (0.3)	5 (0.4)
	Anaemia	2 (0.2)	0	2 (0.1)
	Leukopenia	1 (<0.1)	0	1 (<0.1)
Immune system disorders	-Total	15 (1.5)	0	15 (1.1)
	Cytokine release syndrome	13 (1.3)	0	13 (1.0)
	Hypersensitivity	2 (0.2)	0	2 (0.1)
Infections and infestations	-Total	10 (1.0)	4 (1.1)	14 (1.0)
	Herpes zoster	3 (0.3)	1 (0.3)	4 (0.3)
	COVID-19	1 (<0.1)	1 (0.3)	2 (0.1)
	Nasopharyngitis	2 (0.2)	0	2 (0.1)
	Cellulitis	0	1 (0.3)	1 (<0.1)
	Device related bacteraemia	0	1 (0.3)	1 (<0.1)
	Hepatitis A	1 (<0.1)	0	1 (<0.1)
	Infection	1 (<0.1)	0	1 (<0.1)
	Pharyngitis	1 (<0.1)	0	1 (<0.1)
	Rhinitis	1 (<0.1)	0	1 (<0.1)
	Tuberculosis	0	1 (0.3)	1 (<0.1)
	Upper respiratory tract infection	1 (<0.1)	0	1 (<0.1)
Hepatobiliary disorders	-Total	7 (0.7)	2 (0.6)	9 (0.7)
	Hyperbilirubinaemia	6 (0.6)	2 (0.6)	8 (0.6)
	Hepatosplenomegaly	1 (<0.1)	0	1 (<0.1)
General disorders and administration site conditions	-Total	4 (0.4)	0	4 (0.3)
	Pyrexia	4 (0.4)	0	4 (0.3)
	Pain	1 (<0.1)	0	1 (<0.1)
Vascular disorders	-Total	3 (0.3)	0	3 (0.2)
	Hypotension	1 (<0.1)	0	1 (<0.1)
	Phlebitis	1 (<0.1)	0	1 (<0.1)
	Subclavian vein thrombosis	1 (<0.1)	0	1 (<0.1)
Skin and subcutaneous tissue disorders	-Total	2 (0.2)	0	2 (0.1)
	Rash	1 (<0.1)	0	1 (<0.1)
	Rash pruritic	1 (<0.1)	0	1 (<0.1)
	Urticaria	1 (<0.1)	0	1 (<0.1)
Metabolism and nutrition disorders	-Total	0	1 (0.3)	1 (<0.1)
	Hyponatraemia	0	1 (0.3)	1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-Total	1 (<0.1)	0	1 (<0.1)
	Anogenital warts	1 (<0.1)	0	1 (<0.1)
Nervous system disorders	-Total	1 (<0.1)	0	1 (<0.1)
	Headache	1 (<0.1)	0	1 (<0.1)
Pregnancy, puerperium and perinatal conditions	-Total	0	1 (0.3)	1 (<0.1)
	Complication of pregnancy	0	1 (0.3)	1 (<0.1)
Renal and urinary disorders	-Total	1 (<0.1)	0	1 (<0.1)
	Proteinuria	1 (<0.1)	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	-Total	1 (<0.1)	0	1 (<0.1)
	Dysphonia	1 (<0.1)	0	1 (<0.1)

Note: TEAE = Treatment-Emergent Adverse Event.
Note: The denominator in percent calculation is the number of subjects in each treatment group for subject count.
Note: Delay subjects initially randomized to the Placebo arm, who were later also eligible for the open-label course 2 administration of Teplizumab, are counted once for each treatment arm and once in the total column of subject count. Adverse events for these subjects are counted in one treatment arm only (Teplizumab or Control) and once in the total column, according to the treatment at adverse event onset.
Note: System organ classes (SOCs) and preferred terms are based on MedDRA version 26.0.

6.4.6. Safety in special populations

TEAEs/TESAEs were generally comparable between the age groups. It is noted that TESAEs of diabetic ketoacidosis predominantly occurred in the age group <18 years. In patients <18 years the frequency was 2.4% (17 cases) in teplizumab vs. 0.4% (1 case) in control whereas in patients ≥18 years the frequency was 1.4% (4 cases) vs. 0%. Of note the statistical estimate in patients ≥18 years may be less reliable given the fewer number of patients. There are 712 <18 and 296 ≥18 subjects in the Teplizumab group and 276 and 80 respectively in the control group. The frequency was not increased in patients aged 8 to <12 compared to 12 to <18.

Given the indication of teplizumab, the tables summarizing AEs in patients above 65 years are not considered relevant and thus omitted.

For race, only the white (75.1%) and asian (20.6%) sub-groups had enough number of participants for comparison of adverse events. The applicant has not identified any major differences between the groups.

The safety of teplizumab during pregnancy or lactation has not been studied in the clinical studies. Monoclonal antibodies in general can be transported across the placenta and be present in human milk but no data is available for teplizumab. 12 pregnancies occurred in patients treated with teplizumab during the studies of which 8 resulted in normal neonates, 2 were medically terminated, 1 spontaneous abortion and 1 was lost to follow-up. The conception in the case leading to spontaneous abortion occurred approximately 20 months after the last dose was given.

No data on use in patients with renal and hepatic impairment is available from the clinical studies. In the SmPC section 4.2, use of teplizumab in patients with ALT or AST >2XULN or bilirubin >1.5XULN is not recommended.

6.4.7. Immunological events

Data on development of ADAs and TEAEs in patients developing ADAs has been summarized by the applicant for the TN-10, PROTECT, Protegé and Encore studies. Encore is not discussed here given the limited dataset.

In the TN-10 study where teplizumab was administered as a single 14-day course (according to the proposed dosing scheme for stage 2 T1D), 60% were ADA positive. No major differences in TEAEs related to ADA status was observed in the limited dataset (26 positive and 18 negative).

In the PROTECT study where teplizumab was administered as two 12-day courses (according to the proposed dosing schema for stage 3 T1D), 94% were positive after the first treatment course and 98% were positive after the second treatment course. Due to the few ADA negative subjects (n=12), no firm conclusions can be drawn from the dataset.

In the Protegé study, across the treatment regimens, 60-70% developed ADAs after the first treatment course and 80-90% after the second course. No major differences were noted for immune-related TEAEs depending on ADA status. The frequency of TEAEs within the SOC Skin & Subcutaneous disorders was increase in the first treatment course for patients receiving the full 14 day regimen and the 1/3 regimen whereas no differences were noted in after the second treatment course.

In summary, the proportion of patients developing ADAs was high (60% in the TN-10 study after the single treatment course; 98% in the PROTECT study after the second treatment course). When safety data was reviewed based on ADA status, no clear differences between the groups could be discerned for immune-related TEAEs. Given that most patients develop ADAs, this group is well-

covered by the overall safety database for the product.

6.4.8. Safety related to drug-drug interactions and other interactions

There are no described interactions between teplizumab and other drugs or food. However, caution is advised in considering treatment with concomitant medications with safety profiles that may overlap with those of teplizumab, such as drugs associated with liver function abnormalities, cytopenias or other immune modulators.

6.4.9. Vital signs and laboratory findings

Hematology

Laboratory values for leukocytes, lymphocytes, and neutrophils at selected visits are summarized in *Table 56* and a shift plot for lymphocytes is shown in *Figure 32.*

Different blood cell counts were used in different studies, therefore all values could not be pooled, thus the number of participants with available data at each timepoint in the tabulations differs between the assessments of the different cell types.

Table 46. Summary of leukocyte and lymphocyte counts at selected time points - All studies pool

Hematology parameter	Timepoint	Teplizumab (N=990)[a]		Control (N=356)	
		N[b]	Mean (SD)	N[b]	Mean (SD)
Leukocytes (10^3 cells/µL)	Baseline	990	6.059 (1.7282)	356	5.958 (1.6664)
	Course 1 Day 5 (nadir)	954	4.473 (1.6363)	326	6.167 (1.7897)
	Course 1 Day 11	897	5.324 (1.7290)	312	5.948 (1.5627)
	Course 1 F/U Week 3-6[c]	831	5.933 (1.6968)	292	5.899 (1.5867)
	Course 2 Day 5 (nadir)	670	4.437 (1.5607)	205	5.996 (1.4822)
	Course 2 Day 11	621	5.568 (1.6488)	191	5.801 (1.6591)
	Course 2 F/U Week 3-6[c]	556	5.673 (1.5799)	156	5.637 (1.3968)
Lymphocytes (10^3 cells/µL)	Baseline	990	2.143 (0.6357)	356	2.164 (0.6190)
	Course 1 Day 5 (nadir)	951	0.760 (0.5012)	325	2.159 (0.6515)
	Course 1 Day 11	896	1.387(0.5769)	311	2.107 (0.6383)
	Course 1 F/U Week 3-6[c]	814	2.189 (0.8719)	288	2.150 (0.5723)
	Course 2 Day 5 (nadir)	670	1.042 (0.6093)	205	2.063 (0.6164)
	Course 2 Day 11	621	1.711 (0.6604)	188	2.038 (0.6228)
	Course 2 F/U Week 3-6[c]	544	2.012 (0.6692)	129	2.013 (0.5795)

Hematology parameter	Timepoint	Teplizumab (N=990)[a]		Control (N=356)	
		N[b]	Mean (SD)	N[b]	Mean (SD)
Neutrophils (10^3 cells/µL)	Baseline	916	3.309 (1.3892)	313	3.178 (1.3881)
	Course 1 Day 5	879	3.110 (1.5004)	306	3.374 (1.5219)
	Course 1 Day 11	827	3.316 (1.4367)	292	3.258 (1.2571)
	Course 1 F/U Week 3-6[c]	746	3.135 (1.2357)	270	3.104 (1.2759)
	Course 2 Day 5	608	2.814 (1.2956)	205	3.295 (1.2806)
	Course 2 Day 11	559	3.298 (1.3737)	188	3.235 (1.3785)
	Course 2 F/U Week 3-6[c]	485	3.063 (1.2774)	153	3.004 (1.518)

Abbreviations: F/U=follow up, SD=standard deviation.

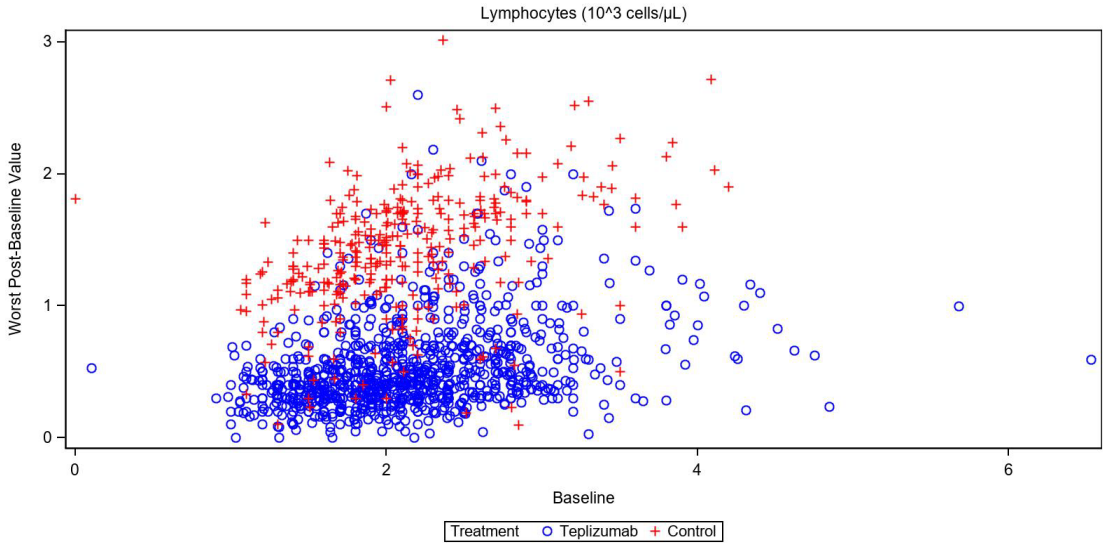
a Participants in Delay who were initially randomized to the control arm and later eligible for the open-label Course 2 treatment of teplizumab are not included.

b Number of participants with available data at each timepoint.

c Follow-up started after the end of treatment course.

Source: 5.3.5.3 ISS Tables All Studies Pool, Table 3.1.

Figure 31. Hematology shift plots from baseline to highest post-baseline values of laboratory tests - All studies pool



The mean leukocyte, lymphocyte and neutrophil count decreased during the treatment course in the teplizumab group but return to baseline at the follow-up 3-6 weeks after the treatment. The most pronounced effect was on the lymphocyte count which is expected given the mode of action. 90.5% and 57.5% of participants in the teplizumab group had lymphocyte counts below 1x103 and 0.5x103 cells/µL, respectively, compared with 15.4% and 3.7%, respectively, in the control group.

A summary of haemoglobin values at selected timepoints is provided in Table 57. Data indicate stable values and no differences between the treatment arms.

Table 47. Summary of haemoglobin values at selected time points - All studies pool

Hematology parameter	Timepoint	Teplizumab (N=990)[a]		Control (N=356)	
		N[b]	Mean (SD)	N[b]	Mean (SD)
Haemoglobin (g/dL)	Baseline	990	13.436 (1.2895)	356	13.476 (1.6901)
	Course 1 Day 5	954	13.091 (1.3611)	326	13.132 (1.2510)
	Course 1 Day 11	897	12.972 (1.3677)	312	13.009 (1.2682)
	Course 1 F/U Week 3-6[c]	831	13.427 (1.2866)	292	13.498 (1.2262)
	Course 2 Day 5	670	13.351 (1.3670)	205	13.304 (1.4368)
	Course 2 Day 11	621	13.174 (1.3364)	191	13.247 (1.3601)
	Course 2 F/U Week 3-6[c]	557	13.666 (1.4068)	156	13.684 (1.2538)

Abbreviations: F/U=follow up, SD=standard deviation.

d Participants in Delay who were initially randomized to the control arm and later eligible for the open-label Course 2 treatment of teplizumab are not included.

e Number of participants with available data at each timepoint.

f Follow-up started after the end of treatment course.

Source: 5.3.5.3 ISS Tables All Studies Pool, Table 3.1.

Liver function

The number and percentage of participants who had elevated ALT, AST, ALP, and total bilirubin at any time during the studies in the all studies safety pool are summarized by times of upper limit of normal (ULN) in Table 58, Table 59, Table 60 and Table 61.

*Table 48. ALT by *ULN (Safety population, All Studies Pool)*

Criteria	Teplizumab N=1008	Control N=356	Total N=1346
> 1*ULN	418 (41.5)	70 (19.7)	486 (36.1)
> 2*ULN	150 (14.9)	15 (4.2)	165 (12.3)
> 3*ULN	79 (7.8)	6 (1.7)	85 (6.3)
> 4*ULN	49 (4.9)	5 (1.4)	54 (4.0)
> 5*ULN	30 (3.0)	2 (0.6)	32 (2.4)
> 6*ULN	21 (2.1)	1 (0.3)	22 (1.6)
> 7*ULN	15 (1.5)	1 (0.3)	16 (1.2)
> 8*ULN	14 (1.4)	1 (0.3)	15 (1.1)
> 9*ULN	11 (1.1)	1 (0.3)	12 (0.9)
> 10*ULN	11 (1.1)	1 (0.3)	12 (0.9)

Note: ALT = Alanine Aminotransferase
Note: The denominator in percent calculation is the number of subjects in each treatment group (N) for subject count
Note: Only post-baseline values are included in the calculation of this table
Note: Delay subjects initially randomized to the Placebo arm, who were later also eligible for the open-label course 2 administration of Teplizumab, are counted once for each treatment arm and once in the total column. Laboratory results for these subjects during course 1 are summarized in the Control arm and during course 2 in the Teplizumab arm
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/lab_liv_uln_s_t.sas OUT=REPORT/OUTPUT/lab_liv_uln_alt_s_t_x.rtf (29SEP2025 19:07)

*Table 49. AST by *ULN (Safety population, All Studies Pool)*

Criteria	Teplizumab N=1008	Control N=356	Total N=1346
> 1*ULN	404 (40.1)	94 (26.4)	492 (36.6)
> 2*ULN	100 (9.9)	14 (3.9)	114 (8.5)
> 3*ULN	53 (5.3)	4 (1.1)	57 (4.2)
> 4*ULN	31 (3.1)	2 (0.6)	33 (2.5)
> 5*ULN	18 (1.8)	1 (0.3)	19 (1.4)
> 6*ULN	11 (1.1)	1 (0.3)	12 (0.9)
> 7*ULN	9 (0.9)	1 (0.3)	10 (0.7)
> 8*ULN	7 (0.7)	0	7 (0.5)
> 9*ULN	6 (0.6)	0	6 (0.4)
> 10*ULN	4 (0.4)	0	4 (0.3)

Note: AST = Aspartate Aminotransferase, ULN = Upper Limit of Normal
Note: The denominator in percent calculation is the number of subjects in each treatment group (N) for subject count
Note: Only post-baseline values are included in the calculation of this table
Note: Delay subjects initially randomized to the Placebo arm, who were later also eligible for the open-label course 2 administration of Teplizumab, are counted once for each treatment arm and once in the total column. Laboratory results for these subjects during course 1 are summarized in the Control arm and during course 2 in the Teplizumab arm
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/lab_liv_uln_s_t.sas OUT=REPORT/OUTPUT/lab_liv_uln_ast_s_t_x.rtf (30SEP2025 17:18)

*Table 50. ALP by *ULN (Safety population, All Studies Pool)*

Criteria	Teplizumab N=1008	Control N=356	Total N=1346
> 1*ULN	310 (30.8)	118 (33.1)	422 (31.4)
> 2*ULN	31 (3.1)	13 (3.7)	44 (3.3)
> 3*ULN	4 (0.4)	2 (0.6)	6 (0.4)
> 4*ULN	1 (0.1)	0	1 (0.1)
> 5*ULN	1 (0.1)	0	1 (0.1)
> 6*ULN	0	0	0
> 7*ULN	0	0	0
> 8*ULN	0	0	0
> 9*ULN	0	0	0
> 10*ULN	0	0	0

Note: ALP = Alkaline Phosphate, ULN = Upper Limit of Normal
Note: The denominator in percent calculation is the number of subjects in each treatment group (N) for subject count
Note: Only post-baseline values are included in the calculation of this table
Note: Delay subjects initially randomized to the Placebo arm, who were later also eligible for the open-label course 2 administration of Teplizumab, are counted once for each treatment arm and once in the total column. Laboratory results for these subjects during course 1 are summarized in the Control arm and during course 2 in the Teplizumab arm
PGM=PRODOPS/SAR446681/OVERALL/QREG SBLA/REPORT/PGM/lab liv uln s t.sas OUT=REPORT/OUTPUT/lab liv uln alp s t x.rtf (30SEP2025 17:19)

*Table 51. Total bilirubin by *ULN (Safety population, All Studies Pool)*

Criteria	Teplizumab N=1008	Control N=356	Total N=1346
> 1*ULN	185 (18.4)	44 (12.4)	228 (16.9)
> 2*ULN	22 (2.2)	5 (1.4)	26 (1.9)
> 3*ULN	6 (0.6)	2 (0.6)	7 (0.5)
> 4*ULN	2 (0.2)	2 (0.6)	4 (0.3)
> 5*ULN	1 (0.1)	1 (0.3)	2 (0.1)
> 6*ULN	1 (0.1)	0	1 (0.1)
> 7*ULN	1 (0.1)	0	1 (0.1)
> 8*ULN	0	0	0
> 9*ULN	0	0	0
> 10*ULN	0	0	0

Note: ULN = Upper Limit of Normal
Note: The denominator in percent calculation is the number of subjects in each treatment group (N) for subject count
Note: Only post-baseline values are included in the calculation of this table
Note: Delay subjects initially randomized to the Placebo arm, who were later also eligible for the open-label course 2 administration of Teplizumab, are counted once for each treatment arm and once in the total column. Laboratory results for these subjects during course 1 are summarized in the Control arm and during course 2 in the Teplizumab arm
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/lab_liv_uln_s_t.sas OUT=REPORT/OUTPUT/lab_liv_uln_bili_s_t_x.rtf (30SEP2025 17:19)

The duration of ≥Grade 2 ALT increases is provided in Table 62.

75 events of ≥grade 2 ALT increases were registered in the teplizumab group, and the mean duration was 44.4 days (median 20.0 days). For ≥grade 3 ALT increases, 22 events were registered, and the mean duration was 73.6 days (median 23.0 days).

Except in one case who had sequalae of ALT and AST increased after treatment during the second round, the liver function abnormalities were resolved without any clinical sequalae or indications of associated hepatic injury.

The dataset was searched for cases of Hy's law (ALT or AST > 3*ULN) and TBIL > 2*ULN). ULN for bilirubin was defined as 1 mg/dL for adults and 1.5 mg/dL for paediatric participants.

Two cases fulfilled Hy's law using the separate bilirubin reference values for adults and children. The first case (10-year male) was clearly related to hepatitis A infection and is thus not a valid Hy's law case. The second case (34-year male) may have been confounded by biliary dyskinesia.

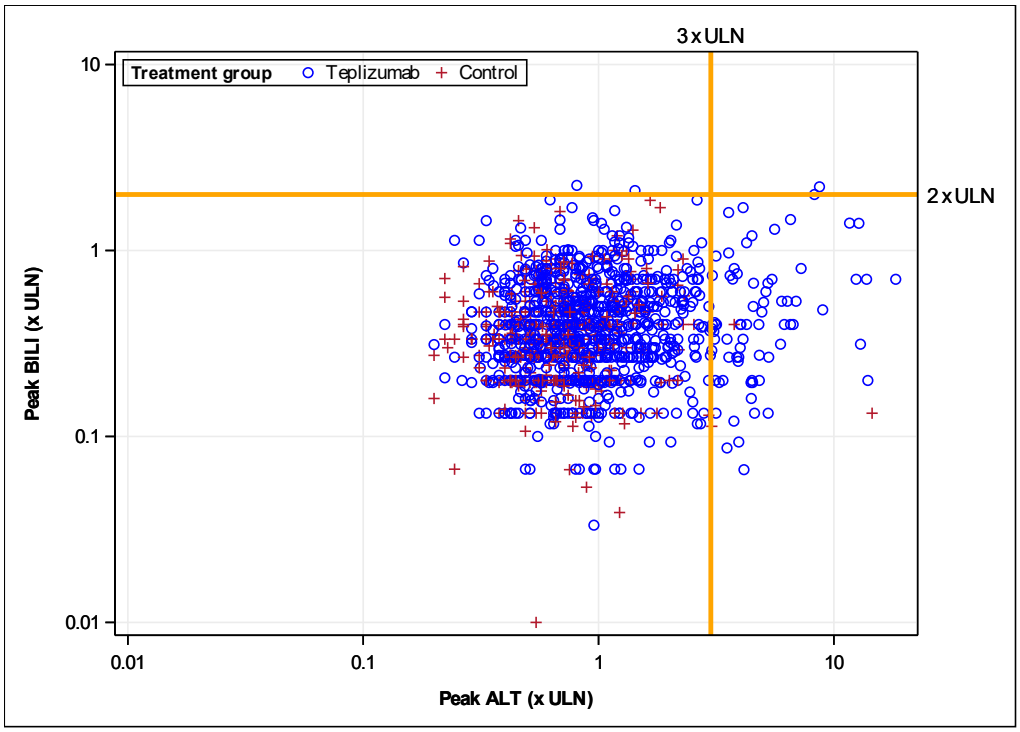
An eDISH plot of peak ALT by peak total bilirubin is provided in Figure 33.

Table 52. Duration of ≥Grade 2 ALT increases - Safety population - All Studies Pool

	Teplizumab N=1008	**Control N=356**
Duration of ≥grade 2 ALT increase (days) - Course 1		
Number [1]	60	5
Mean (SD)	47.8 (96.6)	100.2 (112.3)
Median	20.5	37.0
Min ; Max	2 ; 637	6 ; 228
Duration of ≥grade 2 ALT increase (days) - Course 2		
Number [1]	15	2
Mean (SD)	30.5 (45.6)	48.5 (37.5)
Median	16.0	48.5
Min ; Max	2 ; 186	22 ; 75
Duration of ≥grade 2 ALT increase (days) - Overall		
Number [1]	75	7
Mean (SD)	44.4 (88.8)	85.4 (96.3)
Median	20.0	37.0
Min ; Max	2 ; 637	6 ; 228

ALT: Alanine aminotransferase
[1] Number of events
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/ae_liv_dur_s_t.sas
OUT=REPORT/OUTPUT/ae_liv_dur_alt_s_t_i.rtf (28MAY2025 12:44)

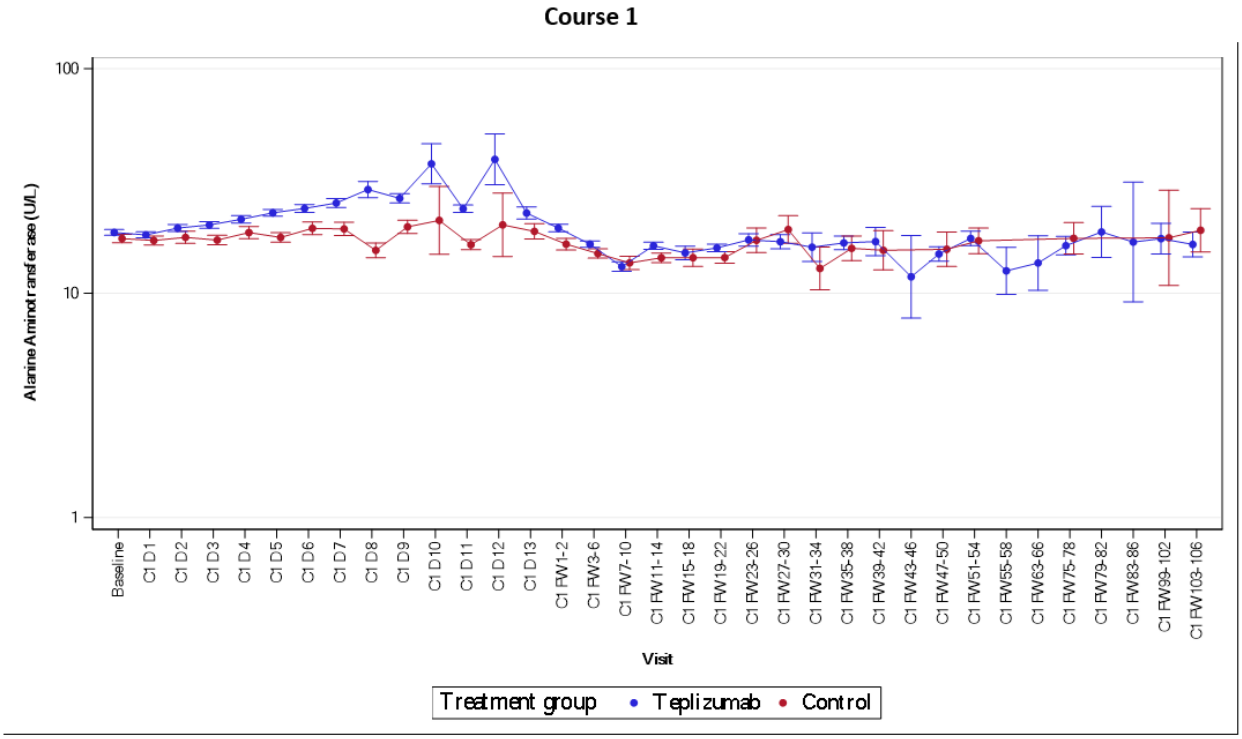
Figure 32. eDISH plot of peak ALT by peak total bilirubin (with ULN=1 mg/dL in adults and ULN=1.5 mg/dL in paediatric participants) - All courses - Safety population - All studies pool

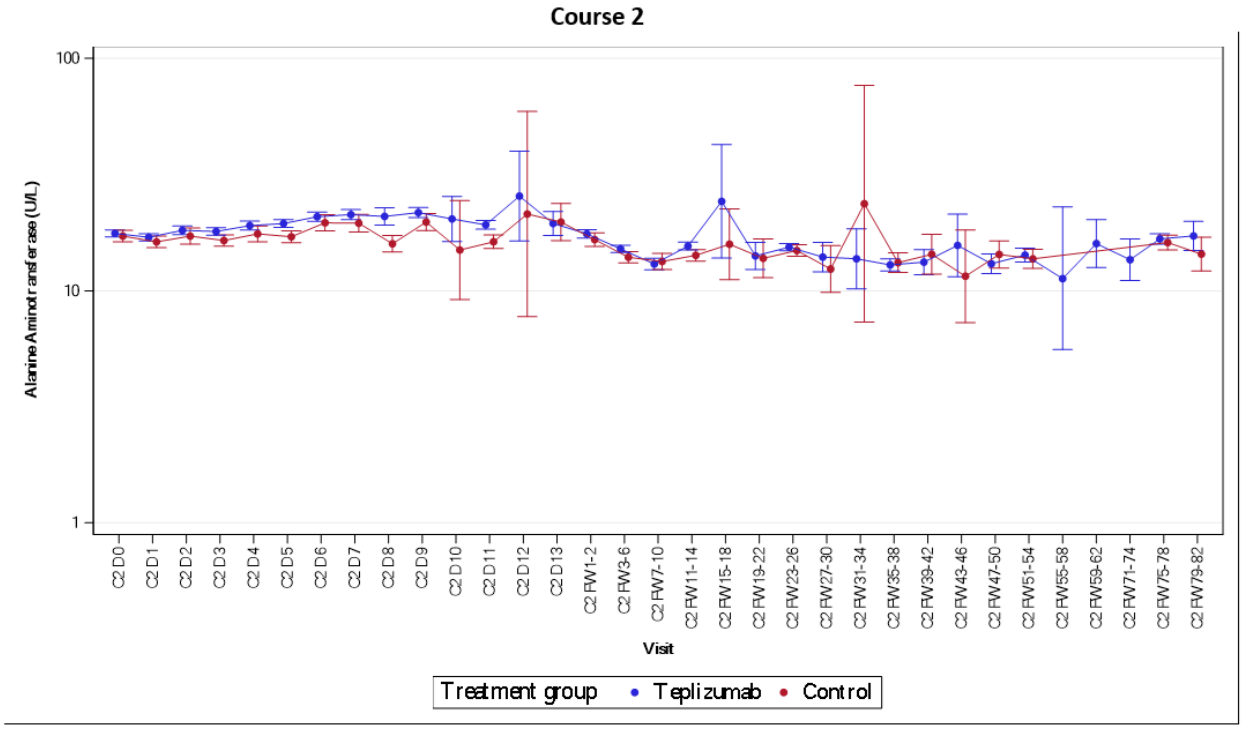


Due to log scale axes 0.01 value is assigned if the analysis value equals 0.

Plots of mean ALT during Course 1 and Course 2 show that the increase in ALT in the teplizumab group was primarily observed between Day 3 until Day 13 in Course 1 (Figure 34). In Course 2, no evident increase in ALT was observed in the teplizumab group. The elevation in ALT in the teplizumab group is thus transient, concomitant with the first days of treatment in Course 1, and elevation in ALT did not increase with repeated dose administration (i.e. Course 2). The data might however be affected by bias due to discontinuations of study drug in the teplizumab group. The small peaks observed on Day 10 and Day 12 in Course 1 may be due to the difference in the timing of sample collections during the different studies. In most of the studies, samples were collected on Days 9, 11 and 13 while in the PROTECT study, samples were collected on Days 9 and 12 but not on Day 11.

Figure 33. Mean curve with 95% CI for ALT by treatment, timepoint and course - Safety population - All Studies Pool





Virology

The applicant followed antibodies for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) in the clinical studies. During the follow-up period, positive IgM for EBV that may indicate an acute or recent infection, occurred in 6.8% of participants in the teplizumab group and 3.9% in the control group. For CMV, antibodies were found in few patients and no clear differences between the groups.

Vital signs and physical findings

There was no difference in patients regarding blood pressure and heart rate between the study groups. Slightly more patients displayed body temperatures above 37.5 °C in the teplizumab group compared to control (29.8% vs. 24.4%) which is in line with an increased frequency of TEAEs of pyrexia in the teplizumab group. Cardiac safety was specifically studied in the Encore study which revealed no ECG findings.

Data on growth is available from the clinical studies and indicate no differences concerning length and weight development between the study groups (Table 63, Table 64, Table 65, Table 66).

Table 53. Body height across visits, by age group and by arm, excluding outliers - Safety population (<18 years) - All studies pool

	8 - 11 years old (N=315)		12 - 17 years old (N=556)	
	Teplizumab (N=218)	**Control (N=97)**	**Teplizumab (N=401)**	**Control (N=155)**
Baseline				
Number	211	93	395	154
Mean (SD)	143.826 (8.380)	144.614 (9.004)	165.246 (10.250)	165.283 (10.280)
Median	143.900	143.000	165.100	165.400
Min ; Max	118.50 ; 165.00	126.00 ; 167.60	136.50 ; 196.80	141.50 ; 189.00
Week 26				
Number	180	74	346	129
Mean (SD)	147.273 (8.159)	148.860 (9.015)	167.250 (10.169)	167.902 (10.193)
Median	147.000	148.880	167.200	167.000
Min ; Max	127.00 ; 167.60	128.40 ; 174.00	136.50 ; 197.50	141.50 ; 193.00
Change from Baseline to Week 26				
Number	180	74	346	129
Mean (SD)	3.367 (1.813)	3.225 (1.608)	2.108 (2.123)	2.192 (2.051)
Median	3.250	3.000	2.000	2.000
Min ; Max	-0.50 ; 12.20	-0.50 ; 8.10	-3.00 ; 9.10	-2.50 ; 7.00
Week 52				
Number	186	79	359	136
Mean (SD)	150.536 (8.584)	150.156 (9.688)	169.053 (9.985)	169.110 (9.898)
Median	150.000	148.000	169.000	169.000
Min ; Max	130.70 ; 175.00	131.10 ; 181.60	141.00 ; 199.10	141.50 ; 193.00
Change from Baseline to Week 52				
Number	186	79	359	136
Mean (SD)	6.401 (2.407)	6.147 (2.460)	3.744 (3.439)	3.674 (3.214)
Median	6.100	6.000	3.000	3.100
Min ; Max	-0.50 ; 14.10	0.00 ; 14.00	-2.90 ; 16.50	-2.50 ; 11.70

	8 - 11 years old (N=315)		12 - 17 years old (N=556)	
	Teplizumab (N=218)	Control (N=97)	Teplizumab (N=401)	Control (N=155)
Week 78				
Number	168	67	337	123
Mean (SD)	153.374 (8.633)	154.382 (9.390)	170.430 (10.019)	170.660 (10.101)
Median	153.000	153.000	171.000	170.100
Min ; Max	132.60 ; 177.00	135.70 ; 177.30	141.50 ; 199.00	141.50 ; 193.00
Change from Baseline to Week 78				
Number	168	67	337	123
Mean (SD)	9.426 (3.198)	9.509 (2.779)	5.083 (4.583)	4.824 (4.330)
Median	9.450	9.500	4.000	3.600
Min ; Max	0.00 ; 18.10	0.90 ; 16.20	-3.00 ; 18.50	-0.80 ; 17.00

Note: AbATEstudy has been excluded from this analysis since no post baseline data are available in the database.
PROTEGE Open Label (Segment 1) study has been excluded from this analysis since there is no control arm for this study.
Note: Outliers were defined as participants with any value < 100 cm or with any decrease > 5cm between two consecutive visits
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/osa_vs_desc_allvis_byage_outl_s_t.sas
OUT=REPORT/OUTPUT/osa_vs_byage_hgt_outl_s_t_i.rtf (29SEP2025 17:31)

Table 54. Body weight across visits, by age group and by arm, excluding outliers - Safety population (<18 years) - All studies pool

	8 - 11 years old (N=315)		12 - 17 years old (N=556)	
	Teplizumab (N=218)	Control (N=97)	Teplizumab (N=401)	Control (N=155)
Baseline				
Number	216	94	400	155
Mean (SD)	38.548 (8.942)	38.491 (9.846)	55.935 (13.940)	56.568 (13.023)
Median	37.285	36.500	54.050	54.400
Min ; Max	21.60 ; 80.20	21.50 ; 86.20	25.80 ; 116.60	32.10 ; 92.00
Week 26				
Number	184	73	351	130
Mean (SD)	40.849 (9.733)	41.096 (10.415)	58.379 (13.725)	59.991 (12.739)
Median	39.000	38.100	56.400	59.650
Min ; Max	23.10 ; 88.90	25.20 ; 91.50	27.50 ; 110.80	35.10 ; 95.50
Change from Baseline to Week 26				
Number	184	73	351	130
Mean (SD)	2.150 (2.790)	2.076 (2.809)	2.688 (3.792)	3.080 (3.919)
Median	1.900	1.800	2.900	3.000
Min ; Max	-5.50 ; 16.30	-8.10 ; 12.60	-9.60 ; 17.00	-6.70 ; 14.80
Week 52				
Number	192	80	364	138
Mean (SD)	43.462 (10.721)	42.528 (11.019)	60.961 (13.600)	62.088 (13.080)
Median	41.000	39.450	59.000	61.000
Min ; Max	24.20 ; 90.40	25.30 ; 94.10	30.70 ; 111.50	37.30 ; 101.00

	8 - 11 years old (N=315)		12 - 17 years old (N=556)	
	Teplizumab (N=218)	Control (N=97)	Teplizumab (N=401)	Control (N=155)
Change from Baseline to Week 52				
Number	192	80	364	138
Mean (SD)	4.623 (3.949)	4.439 (3.484)	5.069 (5.084)	5.186 (5.649)
Median	4.350	4.000	4.900	5.000
Min ; Max	-5.80 ; 27.00	-3.00 ; 17.80	-13.80 ; 28.80	-7.70 ; 26.50
Week 78				
Number	172	66	343	125
Mean (SD)	45.927 (11.069)	44.761 (10.082)	63.173 (13.931)	63.715 (12.716)
Median	43.150	42.700	61.900	62.600
Min ; Max	25.50 ; 93.10	26.20 ; 74.90	33.80 ; 114.00	37.90 ; 98.20
Change from Baseline to Week 78				
Number	172	66	343	125
Mean (SD)	7.226 (5.357)	7.359 (4.049)	7.196 (6.649)	6.897 (6.696)
Median	6.750	7.450	6.700	7.100
Min ; Max	-4.00 ; 38.80	-0.40 ; 19.00	-13.80 ; 35.60	-8.00 ; 26.60

Note: AbATE study has been excluded from this analysis since no post baseline data are available in the database.
PROTEGE Open Label (Segment 1) study has been excluded from this analysis since there is no control arm for this study.
Note: Outliers were defined as participants with any weight decrease > 20% between two consecutive visits
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/osa_vs_desc_allvis_byage_outl_s_t.sas
OUT=REPORT/OUTPUT/osa_vs_byage_wgt_outl_s_t_i.rtf (26SEP2025 10:05)

Table 55. Height Z-score across visits, by age group and by arm, excluding outliers - Safety population (<18 years) - All studies pool

	8 - 11 years old (N=315)		12 - 17 years old (N=556)	
	Teplizumab (N=218)	Control (N=97)	Teplizumab (N=401)	Control (N=155)
Baseline				
Number	211	93	395	154
Mean (SD)	1.004 (1.029)	1.005 (0.961)	0.462 (1.130)	0.597 (1.007)
Median	1.000	1.004	0.475	0.552
Min ; Max	-1.65 ; 3.73	-1.33 ; 3.26	-2.93 ; 4.33	-2.05 ; 4.05
Week 26				
Number	180	74	346	129
Mean (SD)	1.043 (0.977)	1.101 (0.942)	0.442 (1.153)	0.610 (1.041)
Median	0.991	1.106	0.456	0.626
Min ; Max	-1.21 ; 3.92	-1.14 ; 3.63	-2.93 ; 4.20	-2.21 ; 3.47
Change from Baseline to Week 26				
Number	180	74	346	129
Mean (SD)	0.488 (0.271)	0.460 (0.221)	0.278 (0.278)	0.293 (0.274)
Median	0.457	0.467	0.261	0.266
Min ; Max	-0.07 ; 1.91	-0.08 ; 1.14	-0.46 ; 1.28	-0.39 ; 1.08

	8 - 11 years old (N=315)		12 - 17 years old (N=556)	
	Teplizumab (N=218)	Control (N=97)	Teplizumab (N=401)	Control (N=155)
Week 52				
Number	186	79	359	136
Mean (SD)	1.078 (0.993)	0.995 (0.983)	0.440 (1.137)	0.512 (1.035)
Median	1.087	0.842	0.484	0.517
Min ; Max	-1.27 ; 4.22	-1.08 ; 4.09	-2.81 ; 4.27	-2.31 ; 3.23
Change from Baseline to Week 52				
Number	186	79	359	136
Mean (SD)	0.903 (0.327)	0.868 (0.325)	0.499 (0.447)	0.494 (0.422)
Median	0.874	0.865	0.426	0.454
Min ; Max	-0.07 ; 1.91	0.00 ; 1.72	-0.40 ; 2.19	-0.39 ; 1.57
Week 78				
Number	168	67	337	123
Mean (SD)	1.049 (0.999)	1.057 (0.941)	0.395 (1.116)	0.495 (1.082)
Median	1.127	1.022	0.421	0.532
Min ; Max	-1.21 ; 3.40	-0.98 ; 3.10	-2.93 ; 4.05	-2.63 ; 3.40
Change from Baseline to Week 78				
Number	168	67	337	123
Mean (SD)	1.303 (0.420)	1.312 (0.357)	0.676 (0.590)	0.647 (0.559)
Median	1.298	1.311	0.563	0.532
Min ; Max	0.00 ; 2.43	0.12 ; 2.13	-0.42 ; 2.62	-0.12 ; 2.17

Note: AbATE study has been excluded from this analysis since no post baseline data are available in the database.
PROTEGE Open Label (Segment 1) study has been excluded from this analysis since there is no control arm for this study.
Note: Outliers were defined as participants with any value < 100 cm or with any decrease > 5cm between two consecutive visits
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/osa_vs_desc_allvis_byage_outl_s_t.sas
OUT=REPORT/OUTPUT/osa_vs_byage_hgt_outl_s_t_zsc_i.rtf (29SEP2025 17:31)

Table 56. Body weight Z-score across visits, by age group and by arm, excluding outliers - Safety population (<18 years) - All studies pool

	8 - 11 years old (N=315)		12 - 17 years old (N=556)	
	Teplizumab (N=218)	Control (N=97)	Teplizumab (N=401)	Control (N=155)
Baseline				
Number	216	94	400	155
Mean (SD)	0.810 (0.923)	0.733 (0.894)	0.272 (1.112)	0.473 (1.020)
Median	0.768	0.726	0.253	0.607
Min ; Max	-1.51 ; 3.18	-1.91 ; 3.04	-4.21 ; 3.36	-3.58 ; 2.60
Week 26				
Number	184	73	351	130
Mean (SD)	0.759 (0.912)	0.683 (0.798)	0.318 (1.066)	0.552 (0.997)
Median	0.735	0.609	0.302	0.681
Min ; Max	-1.52 ; 3.27	-1.24 ; 3.08	-4.03 ; 3.23	-3.00 ; 2.82

	8 - 11 years old (N=315)		12 - 17 years old (N=556)	
	Teplizumab (N=218)	Control (N=97)	Teplizumab (N=401)	Control (N=155)
Change from Baseline to Week 26				
Number	184	73	351	130
Mean (SD)	0.247 (0.313)	0.272 (0.321)	0.270 (0.383)	0.278 (0.335)
Median	0.205	0.222	0.243	0.250
Min ; Max	-0.77 ; 1.68	-0.57 ; 1.28	-1.13 ; 2.36	-0.42 ; 1.35
Week 52				
Number	192	80	364	138
Mean (SD)	0.758 (0.916)	0.665 (0.832)	0.366 (1.061)	0.548 (0.983)
Median	0.799	0.720	0.379	0.688
Min ; Max	-1.46 ; 3.15	-1.53 ; 3.07	-4.29 ; 3.22	-2.78 ; 2.89
Change from Baseline to Week 52				
Number	192	80	364	138
Mean (SD)	0.511 (0.401)	0.552 (0.415)	0.507 (0.498)	0.478 (0.487)
Median	0.488	0.522	0.438	0.452
Min ; Max	-0.66 ; 1.77	-0.23 ; 1.63	-0.95 ; 2.76	-0.52 ; 1.88
Week 78				
Number	172	66	343	125
Mean (SD)	0.748 (0.888)	0.566 (0.811)	0.378 (1.068)	0.513 (1.002)
Median	0.746	0.637	0.390	0.596
Min ; Max	-1.55 ; 3.12	-1.67 ; 2.28	-2.57 ; 3.20	-3.01 ; 2.67
Change from Baseline to Week 78				
Number	172	66	343	125
Mean (SD)	0.804 (0.511)	0.902 (0.464)	0.715 (0.635)	0.649 (0.607)
Median	0.821	0.863	0.636	0.657
Min ; Max	-0.44 ; 2.37	-0.09 ; 2.19	-0.81 ; 2.60	-0.60 ; 2.19

Note: AbATE study has been excluded from this analysis since no post baseline data are available in the database.
PROTEGE Open Label (Segment 1) study has been excluded from this analysis since there is no control arm for this study.
Note: Outliers were defined as participants with any weight decrease > 20% between two consecutive visits
PGM=PRODOPS/SAR446681/OVERALL/QREG_SBLA/REPORT/PGM/osa_vs_desc_allvis_byage_outl_s_t.sas
OUT=REPORT/OUTPUT/osa_vs_byage_wgt_outl_s_t_zsc_i.rtf (26SEP2025 10:05)

6.4.10. Post-marketing experience

The applicant estimates based on sales data that approximately 414 patients have been exposed (up to November 2024). The reported SAEs and AEs are in general in line with the pattern observed in the clinical trials.

6.4.11. Overall discussion and conclusions on clinical safety

Discussion

a. Overall assessment of available safety data

The pooled safety dataset for teplizumab (the 'all studies pool') encompass one study with participants with stage 2 T1D (the pivotal TN-10 study) and 6 studies in patients recently diagnosed with stage 3 T1D (including the pivotal PROTECT study) of which one (CP-MGA031-02) is an extension study. In this dataset, 1008 patients were exposed to Teplizumab and 356 patients to control treatment. Of those, 900 patients received teplizumab in a placebo-controlled setting.

Safety data beyond 1 year is available from >90% of patients, and data beyond 2 years is available from 385 patients. The size of the safety database is overall deemed sufficient. The population with stage 2 T1D is limited and only 44 patients have been exposed in clinical trials, however post-marketing data is available from an estimate of 414 exposed patients. Furthermore, safety data from the 6 studies in patients recently diagnosed with stage 3 T1D are supportive as the safety profile is expected to be similar between the 2 populations.

The median age in the pooled safety dataset was 14 (8-49.5) years, 72% of participants were below 18 years and 62% of the population were male. Demographics in the TN-10 study was comparable to the overall 'all-studies' pool (72% of participants < 18 years).

Overview of adverse events

In the pooled dataset ('all-study' pool) almost all participants reported any TEAE in both the teplizumab group (99.5%) and the control group (95.8%) however TEAEs related to the study drug were more frequent in the teplizumab compared to the control group (definitely related: 23.1% vs 5.3%; probably related: 74.1% vs. 28.7%).

In the TN-10 study any TEAEs were reported by 97.7% in the teplizumab group vs 68.8% in the placebo group and TEAEs related to the study drug were reported by 95.5% (teplizumab) vs 34.4% (placebo). In the pooled dataset, SAEs occurred more frequently in the teplizumab group than in the placebo group (11.8% vs. 7.3%). The most common SAE in the teplizumab group were diabetes ketoacidosis (reported by 2.1% vs 0.3% in the placebo group). Overall, in the All-study pool, a higher proportion of participants discontinued study drug due to adverse events in the teplizumab group compared to control (12.7% vs. 3.4%), mainly due to AST/ALT increases. Four fatal TEAEs occurred in the teplizumab group, none of the cases occurred in relation to administration of teplizumab (earliest case 9 months after administration) and the cases are thus not likely considered related to teplizumab.

Grade 3 (severe) TEAEs were more frequent in the teplizumab group than control (7.8% vs. 1.7%), also grade 4 TEAEs (urgent intervention required) were more frequent (7.8% vs. 1.7%). These reactions occurred mainly in the PTs lymphopenia, leukopenia and neutropenia.

Among the SOCs, the most pronounced imbalances in AEs were noted in 'Blood and lymphatic system disorders', 'Investigations' and 'Skin and subcutaneous tissue disorders'.

The applicant has provided a separate summary of the incidence of TEAEs and SAEs that occurred during either the treatment course or through 28 days after the last dose was administered, which shows that most TEAEs are temporary related to teplizumab administration. A separate summary of AEs occurring 28 days after the exposure of the drug up to the next administration still show

imbalances for some TEAEs but the differences between the groups is smaller and the frequencies lower.

At the time of submission of the application, teplizumab was approved for the indication to delay the onset of Stage 3 T1D in adult and peadiatric patients 8 years of age and older with Stage 2 T1D by the Food and Drug Administration (FDA) in the United States (US) in November 2022 and in the United Arab Emirates (UAE) and Israel in 2024.

The applicant estimates that approximately 414 patients have been exposed. The reported SAEs and AEs are in general in line with the pattern observed in the clinical trials.

Non-clinical safety studies identified decreased lymphocyte counts, reduced immune response, and elevated cytokine levels as risks. AEs pertaining to these risks were also observed in clinical studies involving teplizumab.

Allergic/hypersensitivity reactions

Within the SOC 'Skin and subcutaneous disorders', PTs reported with higher frequencies in the teplizumab group compared to control were rash (35.6% vs. 8.4%), pruritus (13.4% vs. 6.5%) and rash maculo-papilar (5.5% vs. 1.1%). The TEAEs were in general mild to moderate in intensity (CTCAE grade 1 and 2. Three grade 3 cases of rash and one grade 3 case of rash popular was reported. The skin reactions were transient and did not result in any clinical sequela.

Within the SOC 'General disorders and administration site conditions' PTs with higher frequencies in the teplizumab group compared to control were pyrexia (23.9% vs. 14.6%) and chills (7.9% vs. 2.2%).

The PT 'cytokine release syndrome' may present in symptoms such as rash, headache, nausea, vomiting, fever, and chills/rigors, arthralgias, myalgia, fatigue, and malaise and was more frequent in the teplizumab group than control (6.4% vs. 1.1%) of which 9 were classified as SAEs, all in the teplizumab group (0.9%). The manifestations typically occurred during the first 5 days of teplizumab treatment. Related to this PT, 1.3% of patients discontinued study drug with no patients in control.

The SmPC contains information to mitigate the risk for cytokine release syndrome which includes premedication during the first 5 administration days. Premedication was introduced after the completion of Study 1 based on the experience from that study and has been used in the subsequent studies. There is no controlled data on the efficacy of the premedication and the exact premedication used could be determined on individual basis. The frequencies of adverse reactions related to cytokine release syndrome in the following studies have in general been lower which could be indicative of an effect. Given that most studies have been conducted using premedication, the information provided in the current SmPC is considered acceptable.

The risk for hypersensitivity reactions (including cytokine release syndrome) is reflected in SmPC sections 4.4 and 4.8 and is also included in the RMP as an important identified risk. It is also noted that the product will be under restricted medical prescription.

One case of anaphylaxis and one case of generalised skin reaction were registered and are reflected in the hypersensitivity reactions in section 4.4 of the SmPC.

Infections

Teplizumab is an immunomodulator, and infectious complications were monitored in all clinical trials. Frequencies of TAEs within the SOC 'Infections and infestations' were similar in both treatment arms

(55.2% vs. 55.1% in teplizumab vs. control). For SAEs within this SOC, there was a slightly increased occurrence in the teplizumab group compared to control (3.1% [31 cases] vs. 2.2% [8 cases] without any obvious difference in the PT pattern. In the TN-10 study, 9.1% (n=4) reported events (all SAEs) within the SOC Infections and infestations compared to none in the placebo group. The slightly higher frequency of reported PTs within the SOC "infections and infestations" most probably reflects the known immunosuppressive effect of teplizumab. The AESI 'Acute mononucleosis-like illness' was more frequent in teplizumab vs. control (10.1% vs. 5.3%). The risk for serious infections is reflected in SmPC section 4.4 and 4.8 and included as an important identified risk in the RMP. Infectious mononucleosis and Epstein-Barr virus reactivation are reflected in section 4.8 of the SmPC.

Haematology

Within the SOC 'blood and lymphatic system disorders', TEAEs were reported with higher frequencies in the teplizumab group compared to control for the PTs lymphopenia (74.5% vs. 12.9%), leukopenia (57.5% vs 20.5%), neutropenia (36.9% vs. 18.3%). An imbalance is also noted for TEAEs of eosinophilia (4.7% vs. 1.1%).

Furthermore, within the SOC 'Investigations' the PT 'haemoglobin decreased' was more frequent in the teplizumab than control (23.3% vs. 16.0%) which may be related to a small directionally similar increased occurrence in anaemia (7.8% vs. 6.2%) within the SOC 'Blood and lymphatic system disorders.

The TEAI '≥Grade 3 lymphopenia for 7 days or longer' occurred in 1.9% of patients in the teplizumab group vs. no patients in the control.

The mean leukocyte, lymphocyte and neutrophil count decreased during the treatment course in the teplizumab group but return to baseline at the follow-up 3-6 weeks after the treatment. The most pronounced effect was on the lymphocyte count which is expected given teplizumab's mechanism of action. 90.5% and 57.5% of participants in the teplizumab group had lymphocyte counts below $1x10^3$ and $0.5x10^3$ cells/µL, respectively, compared with 15.4% and 3.7%, respectively, in the control group. Information on lymphopenia is adequately provided in the SmPC and included as an important identified risk in the RMP. Thus, transient lymphopenia is a key identified risk observed in participants treated with teplizumab. Teplizumab causes a transient reduction in the number of circulating lymphocytes due to margination, which is directly related to the mechanism of action of the drug. However, the development of transient lymphopenia does not appear to be associated with an overall increase in infections (all studies pool: 55.3% in the teplizumab group and 55.1% in the control group), consistent with the lack of T cell depletion, however as previously discussed, the AESI 'Acute mononucleosis-like illness' was more frequent in teplizumab vs. control (10.1% vs. 5.3%).

Hepatic safety

Imbalance in AEs related to liver function were observed within the SOC 'Investigations' where PTs reported with higher frequencies for teplizumab were aspartate aminotransferase increased (24.0% vs. 14.3%), alanine aminotransferase increased (23.6% vs. 7.9%), blood bilirubin increased (6.7% vs. 2.8%) and blood albumin decreased (6.5% vs. 3.4%). Within the SOC 'hepatobiliary disorders', there was a small increased frequency of hyperbilirubinemia for teplizumab (5.9% vs. 3.9%). 3 patients reported SAEs within this SOC (biliary dyskinesia, biloma, cholecystitis acute, Hepatosplenomegaly) for teplizumab and no cases in the control group.

For the TEAI '≥Grade 3 liver function abnormalities' the frequency was higher in the teplizumab group than in the control group. Adjusted frequencies were 2.7% in teplizumab and 1.0% in the control group.

A higher proportion of participants discontinued study drug in the teplizumab group compared to control related to the PTs 'alanine aminotransferase increased' (7.1% vs. 0.8%) and 'aspartate aminotransferase increased' (2.2% vs. 0.3%).

Administration of teplizumab was related to increases in laboratory values of transaminases. Increases >3XULN were registered for ALT (7.8% vs. 1.7%) and AST (5.3% vs. 1.1%) in teplizumab vs. control. Increases in ALT >5XULN in 3.0% vs. 0.6% in teplizumab vs. control. 11 patients (1.1%) displayed increases >10XULN in teplizumab vs. 1 patient (0.3%) in control. The liver function abnormalities were resolved without any clinical sequalae or indications of associated hepatic injury. The ULN for bilirubin was defined as 1 mg/dL for adults and 1.5 mg/dL for paediatric participants. One patient in the teplizumab group fulfilled Hy's law (ALT or AST > 3*ULN) and TBIL > 2*ULN) using these reference values for bilirubin (a 34-year-old patient) however considered confounded by alternative aetiology (biliary dyskinesia); (Another case, 10-year male, was clearly related to hepatitis A infection and is thus not a valid Hy's law case).

The transaminase elevations may be secondary to cytokine release syndrome, however only 17.7% (14 patients) of patients with ALT>3X also displayed CRS and the mechanism is thus not clear. Monitoring of liver function in relation to the treatment course is included in section 4.4 of the SmPC.

Metabolic

Imbalances in SAEs related to glucose metabolism were registered. While SAEs of hyper- and hypoglycaemia occurred at low frequencies (0.6-0.8%) in both treatment groups, imbalances in SAEs of diabetic ketoacidosis and hypoglycaemic seizures were noted.

SAEs of diabetic ketoacidosis were registered (including one fatal case), which predominantly occurred in the teplizumab group (2.1% [21 cases] vs. 0.3% [1 case]). Four cases occurred within 6 months after teplizumab administration, but the majority of cases occurred after one year of administration, and they appear to be related to the underlying development of diabetes. No cases of DKA were observed in the PROTECT study which may have been due to closer glucose monitoring using CGM. In the TN-10 study, patients were not followed after their onset of stage 3 T1D. Upon review of the cases it is concluded that in all these cases, well-known precipitating factors are described (such as infections, insulin compliance or insulin delivery issues). The patients in general had poor metabolic control during the study and at the time of the event. Even though the observed imbalance is notable, a causal relationship to teplizumab seems unlikely and it is not warranted to be reflected in the SmPC. Cases of DKA would be reported through routine pharmacovigilance activities.

The frequency of AEs of hypoglycaemia was reduced in teplizumab vs. control (13.6% vs. 20.2%) however 7 SAEs of hypoglycaemic seizures (0.7%) were registered in the teplizumab group, with no cases occurring in the control group. The reported hypoglycaemic events appear to be related to the insulin treatment rather than teplizumab.

Gastrointestinal

Within the SOC 'gastrointestinal disorders' PTs reported with higher frequencies in the teplizumab group compared to control were nausea (24.5% vs. 15.4%), vomiting (17.8% vs. 11.2%) and abdominal pain (8.6% vs. 6.2%). For SAEs within this SOC, there was an overall imbalance (1.1% [11 cases] vs. 0.3% [1 case]) within several PTs.

Malignancies

Long term safety remains an uncertainty. Based on the mechanism of action, an increased risk of malignancy (e.g. leukaemia) cannot be entirely ruled out, however currently there are no evident data indicating an increased risk of cancer associated with teplizumab. As long-term data continue to be collected, this will be further evaluated. For the TEAI "Lymphomas and other malignancies", the adjusted frequency was 2.4% in teplizumab and 1.2% in the control group. The difference appears mainly be related to increased number of cases of skin papilloma in the teplizumab group but the data was not clearly presented in the application. The applicant explained that events in the AESI category "lymphomas and other malignancies" predominantly consisted of skin papilloma, a benign exophytic growth common in children. All events were non serious and generally mild in intensity. Most of the events occurred more than 1 month after the last IMP dose, resolved, and were assessed by the investigators as not related to the IMP. No lymphoma was reported.

Suicide/suicide attempts

Three SAEs of suicide attempt and two cases of suicidal ideation were registered in the teplizumab group with no cases in the control group. Furthermore, one fatal event due to suicide occurred in the teplizumab group. The applicant has reviewed the 4 cases of suicide attempts and the completed suicide. The cases in general occurred a significant time after treatment with teplizumab. One suicide attempt occurred 1 month after administration, but this patient had a documented history of depression prior to treatment. The case of completed suicide occurred 9 months after teplizumab administration. This patient was first treated in the TN-10 study and was subsequently enrolled in the TN-10 extension study where he received an additional course of teplizumab 9 years after the first treatment course. One year and 7 months prior to the last treatment course the patient was diagnosed with major depressive disorder. Thus, given the significant time between the events and teplizumab administration and/or history of depression, the cases are not considered likely related to teplizumab.

Immunogenicity

The proportion of patients developing ADAs was high (60% in the TN-10 study after the single treatment course; 98% in the PROTECT study after the second treatment course). Based on the whole clinical and POPPK package, further analysis was requested to support the comparison of the immunogenic profiles as well as the overall immunogenicity profile of teplizumab. A summarizing table was requested with the ADA levels (mean, median, range, missing data), ADA and Nab occurrence observed in each clinical study, by treatment course and by product as well as pooled data. The demographic characteristics of participants were also requested. In addition, a tabulated summary was requested comparing daily ADA levels (mean, median, range, missing data), ADA and Nab occurrence (i.e. across all time points) for each study by product and pooled data.

The Applicant provided rationale with regards to the unfeasibility of pooling of immunogenicity data from all studies together due to non-comparable study designs and the use of different bioanalytical methods across studies and has added the requested updates in the ISI:

a/ The Applicant did create tables and figures pooling data for ADA/NAb occurrence, ADA titer levels and impact of ADAs/NAbs on PK/PD and efficacy. These tables and figures will be included in the updated ISI in addition to the already available tables by product. The provided additional information does not indicate any clear influence of ADAs on efficacy, or safety.

b/ The Applicant did create tables for the studies Protégé, TN-10 and PROTECT to assess the impact of maximum quartile titers on immune-related TEAEs. These tables and figures will be included in the updated ISI in addition to the already provided tables by ADA status.

c/ With regards to POPPK modelling analysis, the Applicant has also added the following information in the ISI for the PROTECT study:

"The updated population PK model (Model 454) indicated that clearance was influenced by ADA titers in the PROTECT study. Clearance increased linearly with time-dependent value of log(titer) above the estimated threshold of 6.05 (corresponding to the log10 ADA titer of 2.63).

d/ The Applicant has provided the requested summarizing table for the PROTECT study with demographic data and immunogenicity results across treatment courses and by type of product (Eli Lilly/AGC Biologics), including products pooled together. Similar demographic data are observed across courses and products. Similar increase in ADA titers across courses for each product. An increase in Nab status is also observed across treatment courses but a bioanalytical artefact linked to the sensitivity of the Nab assay cannot be ruled out.

Furthermore, the Applicant was asked to discuss why the profiles of ADA occurrence differ between the clinical study TN-10 and the clinical study PROTECT. According to the Applicant, several issues compromise the comparability of immunogenicity across the clinical study TN 10 and the clinical study PROTECT: the different sampling schedule, the difference in the number of participants and the potential differences in Human Leukocyte Antigen (HLA) genes across subjects. Finally, in the ISI, beside protocol specified collection days, spurious unscheduled visit samples for ADA, Nab and lymphocytes are mentioned. The Applicant was asked to further elaborate on the rationale behind the collection of these spurious immunogenicity samples, their results and their correlation with the PK/PD and clinical outcomes. The Applicant has clarified that spurious unscheduled samples could be collected at the Early Termination/End of Study Visit (spurious unscheduled visits) for participants who either discontinued study treatment early or experienced AEs suspected to be related to immunogenicity (e.g., infusion reactions, injection site reactions, or hypersensitivity) but they were not planned to be used for the assessment of their correlation to PK/PD and clinical outcomes. However, they included the identification of ADA and NAb status for each treatment course.

When safety data was reviewed based on ADA status, no clear differences between the groups could be discerned for immune-related TEAEs. Given that most patients develop ADAs, clinical safety is considered well-described in the population developing ADAs.

Special populations

TEAEs/TESAEs were generally comparable between the age groups. The safety of teplizumab during pregnancy or lactation has not been studied in the clinical studies. Monoclonal antibodies in general can be transported across the placenta and be present in human milk, but no data is available for teplizumab. 12 pregnancies occurred in patients treated with teplizumab during the studies of which 8 resulted in normal neonates, 2 were medically terminated, 1 spontaneous abortion and 1 was lost to follow-up. The conception in the case leading to spontaneous abortion occurred approximately 20 months after the last dose was given. No data on use in patients with renal and hepatic impairment is available from the clinical studies.

b. Adverse drug reactions in the SmPC

The ADRs proposed for inclusion in the SmPC are described below in Table 50.

Table 57: ADRs proposed for inclusion in the SmPC

Infections and infestations	Link to data*
Uncommon	Infections
Not known	Epstein-Barr virus reactivation
Blood and lymphatic system disorders	
Very Common	Lymphopenia
	Thrombocytopenia
	Leukopenia
	Neutropenia
	Haemoglobin decreased
Common	Blood bilirubin increased
	Eosinophilia
Immune system disorders	
Common	Cytokine release syndrome
Uncommon	Hypersensitivity
Nervous system disorders	
Very Common	Headache
Gastrointestinal disorders	
Very Common	Vomiting
	Nausea
Common	Diarrhoea
	Abdominal pain
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased
	Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	
Very Common	Rash
	Pruritus
Common	Rash maculo-papular
	Rash pruritic
	Urticaria
	Skin exfoliation
General disorders and administration site conditions	
Very Common	Pyrexia
	Fatigue
Common	Chills
Not Known	Pain
	Illness

Conclusions on clinical safety

The size of the safety database is overall deemed sufficient. The population with stage 2 T1D is more limited and only 44 patients have been exposed in clinical trials, however post-marketing data is available from an estimate of 414 exposed patients. The reported SAEs and AEs are in general in line

with the safety profile observed in the clinical trials. Furthermore, safety data from the 6 studies in patients recently diagnosed with stage 3 T1D are supportive as the safety profile is expected to be similar between the 2 populations.

Most TEAEs were mechanism-based or related to the transient release of cytokines and occurred within the first month of treatment.

Rash and pruritus were frequently reported in relation to teplizumab.

Cytokine release syndrome was reported in 6.4% of patients. One case of anaphylaxis and one case of generalized skin reaction were observed.

In line with the mechanism of action, decreases in lymphocyte count were registered but values returned to baseline 3-6 weeks after treatment.

Increases in transaminases were registered and one case in the teplizumab group fulfilled Hy's criteria, however considered confounded by alternative aetiology (Another case, 10-year male, was clearly related to hepatitis A infection and is thus not a valid Hy's law case). Monitoring of liver function in relation to the treatment course is included in section 4.4 of the SmPC and cases of hepatotoxicity should be followed in the PSURs.

The overall frequency of infections was similar in both treatment arms however the frequency of serious infections was slightly increased (3.1% vs. 2.2%) in the teplizumab group.

Imbalances in SAEs of diabetic ketoacidosis (including one fatal case) were noted (2.1% vs. 0.3%). Upon review of the cases it is concluded that in all cases, well-known precipitating factors are described (such as infections, insulin compliance or insulin delivery issues). The patients in general had poor metabolic control during the study and at the time of the event. In addition, four cases occurred within 6 months after teplizumab administration, but the majority of cases occurred after one year of administration and appear to be related to the underlying development of diabetes. Even though the observed imbalance is notable, a causal relationship to teplizumab seems unlikely and therefore, it is not warranted to be reflected in the SmPC. Cases of DKA would be reported through routine pharmacovigilance activities.

In the RMP, cytokine release syndrome, lymphopenia and serious infections are included as important identified risks.

Malignancies are included as an important potential risk.

Use during pregnancy and breastfeeding and long-term safety, including growth, in patients aged 8 to <18 years are included as missing information.

A PASS (Global registry study) will be initiated post approval. It is included in the RMP as a category 3 PASS. The primary objective is to assess safety data in patients with Stage 2 type 1 diabetes treated with teplizumab, which will provide further information on long-term safety in the target population.

7. Risk management plan

7.1. Safety specification

7.1.1. Proposed safety specification

The summary of safety concerns in the RMP is the following:

Summary of safety concerns	
Important identified risks	Cytokine release syndrome Lymphopenia Serious Infections
Important potential risks	Malignancies
Missing information	Long term safety, including growth, in patients aged 8 to <18 years Use during pregnancy Use during breastfeeding

7.2. Pharmacovigilance plan

7.2.1. Proposed pharmacovigilance plan.

Routine Pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting/ PSURs and signal detection are deemed necessary to monitor the risks related to teplizumab.

Additional Pharmacovigilance activities

In addition, the applicant has proposed the following additional pharmacovigilance activities:

Table 38 - Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit risk)				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances (key to benefit risk)				
Not applicable				
Category 3 - Required additional pharmacovigilance activities (by the competent Authority)				
GLOBAL REGISTRY study (OBS18565) Planned	To characterize the long-term safety and effectiveness profile of teplizumab in patients with stage 2 T1D treated with teplizumab under real-world conditions in a multinational postmarketing setting.	• Cytokine release syndrome • Lymphopenia • Serious infections • Malignancies • Long-term safety, including growth, in patients aged 8 to <18 years • Use during pregnancy • Use during breastfeeding	Protocol planned submission to PRAC First patient enrolled Study completion Final report of study results submitted to PRAC	31-Dec-2025 6 months after Protocol approval Approximately 8 years after first patient enrolled 12 months after study completion
TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717) Planned	To assess the effectiveness of RMMs' dissemination towards HCPs prescribing/dispensing teplizumab and patients treated with teplizumab and assess their knowledge and behaviour with respect to the RMMs for teplizumab use in Europe.	• Cytokine release syndrome • Lymphopenia • Serious infections	Protocol planned submission to PRAC First patient enrolled Study completion Final report of study results submitted to PRAC	30-Sep-2026 12 months after Market Access granted 12 months after First Patient Enrolled 12 months after study completion

HCP: Healthcare professional; PRAC: Pharmacovigilance Risk Assessment Committee; RMM: Risk Minimization Measure; T1D: Type 1 Diabetes.

7.2.2. Discussion on the Pharmacovigilance Plan

Routine Pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting/PSUR and signal detection are deemed necessary to monitor the risks related to teplizumab. This is acceptable.

Additional Pharmacovigilance activities

The additional pharmacovigilance activities proposed above are acceptable.

7.3. Risk minimisation measures

7.3.1. Proposed risk minimisation measures

Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Cytokine release syndrome	**Routine risk minimization communication:** Labeled in SmPC: sections 4.4 (Special warnings and precautions of use) and 4.8 (Undesirable effects), and PL: sections 2 (What you need to know before you are given Teizeild), 3 (How Teizeild is given) and 4 (Possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** Specific requirements prior to initiating the treatment, recommendation during the course of the treatment and in case of severe CRS: <u>Prior to initiating the treatment</u>: Requirement to obtain a complete blood count and to test liver enzymes and bilirubin - SmPC sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions of use), and PL section 4 (Possible side effects). Premedication prior to teplizumab infusion for the first 5 days of dosing required and as needed- SmPC sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions of use) and PL section 3 (How Teizeild is given). <u>During the course of the treatment</u>: Progressive dosing increase for the first few days - SmPC section 4.2 (Posology and method of administration). Monitoring of liver enzymes and bilirubin- SmPC sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions of use) and PL section 4 (Possible side effects). Monitoring for signs and symptoms of CRS- SmPC section 4.4 (Special warnings and precautions of use) and PL section 4 (Possible side effects). Medications to be administered to treat CRS - SmPC sections 4.2 (Posology and method of administration) and 4.4 (Special

Safety concern	Routine risk minimization activities
	warnings and precautions of use) and PL section 3 (How Teizeild is given). In case of severe CRS: Recommendation to pause and resuming or discontinuing the treatment - SmPC sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions of use), and PL section 4 (Possible side effects). **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Lymphopenia	**Routine risk communication:** Labeled in SmPC sections 4.4 (Special warnings and precautions of use), 4.8 (Undesirable effects) and section 5 (Phamacological properties), and PL sections 2 (What you need to know before you are given Teizeild) and 4 (Possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** Specific requirements prior to initiating the treatment, recommendation during the course of the treatment and in case of prolonged severe lymphopenia: Prior to initiating the treatment: Requirement to obtain a complete blood count - SmPC section 4.2 (Posology and method of administration), and PL section 4 (Possible side effects). During the course of the treatment: Monitoring of white blood cell counts - section 4.8 (Undesirable effects), and PL section 4 (Possible side effects). In case of prolonged severe lymphopenia: Recommendation for discontinuing teplizumab – SmPC section 4.4 (Special warnings and precautions of use) and PL section 4 (Possible side effects). **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Serious Infections	**Routine risk communication:** Labeled in SmPC sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions of use) and section 4.8 (Undesirable effects), and PL sections 2 (What

Safety concern	Routine risk minimization activities
	you need to know before you are given Teizeild) and 4 (Possible side effects). **Routine risk minimization activities recommending specific clinical measures to address the risk:** Specific requirements prior to initiating the treatment, recommendation during the course of the treatment and in case of serious infection: <u>Prior to initiating the treatment</u>: Obtain complete blood counts: SmPC section 4.2 (Posology and method of administration) and PL section 4 (Possible side effects), Obtain laboratory or clinical evidence of acute infection with EBV or CMV: SmPC section 4.2 (Posology and method of administration), Check patients for active serious infection or chronic active infection: SmPC section 4.2 (Posology and method of administration) and PL section 2 (What you need to know before you are given Teizeild) Recommendation for vaccinations, labeled in SmPC sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions of use), and PL section 2 (What you need to know before you are given Teizeild). <u>During and after the course of the treatment</u>: Monitoring for signs and symptoms of serious infections - SmPC section 4.4 (Special warnings and precautions of use) and PL section 2 (What you need to know before you are given Teizeild). <u>In case of serious infection</u>: Recommendation to treat appropriately and discontinue teplizumab - SmPC section 4.4 (Special warnings and precautions of use) and PL section 4 (Possible side effects). **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Malignancies	**Routine risk communication:** Labeled in SmPC Section 5.3 (Pre-clinical safety data) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Prescription only medicine
Long-term safety, including growth, in patients aged 8 to <18 years	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Use during pregnancy	**Routine risk communication:** Use of teplizumab during pregnancy is labeled in SmPC Section 4.6 (Fertility, pregnancy and lactation) and section 5.3 (Preclinical safety data), and PL section 2 (What you need to know before you are given Teizeild). Patients should inform their healthcare provider in case of a known or planned pregnancy - PL section 2 (What you need to know before you are given Teizeild). **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Use during breastfeeding	**Routine risk communication:** Breastfeeding during teplizumab treatment is labeled in SmPC Section 4.6 (Fertility, pregnancy and lactation) and section 5.3 (Preclinical safety data), and PL section 2 (What you need to know before you are given Teizeild). Breastfeeding woman should be informed they may interrupt breastfeeding – labeled in PL section 2 (What you need to know before you are given Teizeild). **Routine risk minimization activities recommending specific clinical measures to address the risk:** None

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Prescription only medicine.

CMV: Cytomegalovirus; CRS: Cytokine Release Syndrome; EBV: Epstein-Barr Virus; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Planned additional risk minimisation measures

In addition, the applicant has proposed the following additional risk minimisation measures:

Healthcare Professional Guide

Healthcare professional (HCP) guide available in hard/ electronic copy and web-based (depending on agreement with National Competent Authority [NCA]) to inform, educate HCPs to the safe use of teplizumab in stage 2 T1D patients. The objective is also to ensure (at prescription and initiation of the treatment with teplizumab) a conversation between the prescribing/treating HCPs and the patient/legal representative around specific information and important recommendation related to the treatment with teplizumab.

These are pertaining to the following safety concerns:

- Cytokine Release Syndrome,
- Lymphopenia,
- Severe infections

The HCP guide includes the following key elements:

- Information related to the requirement to premedicate patients, to monitor total blood count, liver enzymes prior to, during or after the treatment,
- Guidance for vaccination prior to or after the treatment,

Patient Guide

Patient guide available in hard/electronic copy and web-based (depending on agreement with NCA). Objective of this guide is for patients treated with teplizumab and their legal representative to know the risks related to the use of teplizumab and to be able to recognize the signs and symptoms indicative of those risks.

At the time of treatment initiation, the patient guide will be given by the HCPs to the patient/legal representative (which the patient should keep and be able to share with other HCPs involved with their treatment). HCPs can download this patient guide in countries, where available.

The patient guide helps the patient identify the following safety concerns:

- Cytokine Release Syndrome,
- Lymphopenia,
- Severe infections

The patient guide includes the following key elements:

- Information to educate patient about signs/symptoms which could be indicative of these risks and to tell their doctor or nurse immediately if these occur,
- Guidance for vaccinations prior to or after the treatment,
- Recommendation for the patients/legal representative to read the package leaflet (PL) thoroughly.

7.3.2. Discussion on the risk minimisation measures

Routine risk minimisation measures

The proposed routine risk minimisation measures are acceptable.

Additional risk minimisation measures

The proposed additional risk minimisation measures are acceptable and considered sufficient to minimise the risks of the product in the proposed indication.

7.4. RMP Summary and RMP Annexes overall conclusion

The RMP Summary and RMP Annexes are acceptable.

7.5. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.1 is acceptable.

8. Pharmacovigilance

8.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

8.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 17.11.2022.

9. Product information

9.1. Summary of Product Characteristics (SmPC)

9.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical trial and also in line with was originally proposed by the Applicant.

9.1.2. SmPC section 5.1 justification

Information on the single pivotal study TN-10, supporting the indication, is included in the SmPC section 5.1.

9.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

9.3. Quick Response (QR) code

A request to include a QR code in the labelling for the purpose of directing the user to a website with statutory information, i.e. SmPC and PL as well as contact and side effect reporting information has been submitted by the applicant and has been found acceptable.

9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Teizeild (teplizumab) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

10. Benefit-risk assessment

10.1. Therapeutic context, proposed therapeutic indication

The proposed indication for Teizeild is:

- to delay the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D.

Teizeild should be administered by intravenous infusion, using a body surface area (BSA)-based dosing, once daily for 14 consecutive days.

At the time of submission of the application, teplizumab was approved for the indication to delay the onset of Stage 3 T1D in adult and peadiatric patients 8 years of age and older with Stage 2 T1D by the Food and Drug Administration (FDA) in the United States (US) in November 2022 and in the United Arab Emirates (UAE) and Israel in 2024.

10.1.1. Disease or condition

Type 1 diabetes (T1D) is a chronic autoimmune disease. It leads to the destruction of insulin-producing pancreatic beta cells by autoimmune mechanism, resulting in life-long dependence on exogenous insulin.

T1D occurs in both children and adults. T1D is commonly initially diagnosed in children, with more than half of T1D patients diagnosed before the age of 14 years. In 2022, there were 8.75 million individuals worldwide with T1D. Europe carries the largest burden of the world's T1D with 31 000 new cases of T1D in children and adolescents (0-19 years) each year.

The burden placed on patients and their families/caregivers when clinical T1D is diagnosed is multifaceted, including social and emotional aspects.

Symptoms which lead to the diagnosis of T1D typically include thirst, polydipsia, polyuria, fatigue, weakness, and weight-loss. Not seldom, both for children and adults, the acute symptoms of abdominal pain, thirst and weakness lead to the diagnosis of high blood sugar and T1D.

The autoimmune destruction of beta cells may initially be clinically silent, but it can be identified by the detection of autoantibodies such as islet cell antibodies (ICA), anti-glutamic acid decarboxylase (GAD) 65 antibody, anti-ICA512 (also termed islet antigen 2 [IA-2]) antibodies, insulin autoantibodies (IAA) and antibodies to zinc transporter 8 (ZnT8).

- T1D can be divided into 3 stages:
- Stage 1: emergence of 2 or more T1D-related autoantibodies, which reflects the initiation of the autoimmune process; this stage is associated with normoglycemia.
- Stage 2: persistence of T1D-related autoantibodies with further loss of beta cell function and development of dysglycemia. This represents a more advanced but still pre-symptomatic stage of the disease.
- Stage 3: symptomatic or clinical T1D, when remaining beta cell capacity is insufficient to maintain glucose metabolism and exogenous insulin replacement is needed.

The progression to clinical T1D (Stage 3) is not a matter of "if" but "when" as >95% of patients in Stage 1 and virtually all of patients in Stage 2 will progress to Stage 3 and become insulin dependent. For Stage 2 T1D, the diagnosis of this early stage is highly depending on the implementation of screening programs and thus may vary across countries and even regions.

10.1.2. Available therapies and unmet medical need

For a detailed description, please see section 3.1 of this report.

T1D is treated with exogenous insulin once it reaches stage 3.

Allogenic pancreas islet cell transplantation or islet cellular therapy used in conjunction with concomitant immunosuppression has been recently introduced and exists as non-standard treatment for clinically overt T1D which represents a more advanced population than early-T1D. Such treatments may be considered when people experience severe hypoglycemia despite intensive diabetes management and education. No therapeutic agents with the possibility to modify the progression of T1D are approved in the EU and therefore there is an unmet need for such treatment options.

10.2. Main clinical studies

For a detailed description of the clinical studies supporting this application, please refer to section 6.3.2 of this document.

Study TN-10

Study TN-10, a phase 2 study, is the single pivotal study for the indication "to delay the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D". TN-10 was a multicenter, double-blind, randomized (1:1), placebo-controlled study to determine whether a single 14-day course of teplizumab treatment compared to placebo (saline solution) in participants at high risk for T1D (in Stage 2) resulted in delaying the diagnosis of clinical Stage 3 T1D. Primary endpoint was the elapsed time to onset of T1D stage 3 (based on glucose testing with an OGTT or the presence of unequivocal hyperglycemia with acute metabolic decompensation, such as DKA). Secondary endpoint was change in C-peptide responses as indicator of beta cell function. C-peptide was measured on several occasions during an OGGT, resulting in an AUC C-peptide measurement. Enrolled participants were aged 8 to 45 years and were identified through the TrialNet TN-01 Pathway to Prevention Trial. The participants were at high risk of developing T1D on the basis of indicators including having a relative who had been diagnosed with T1D, abnormal glucose tolerance at baseline and presence of 2 or more T1D-related autoantibodies.

10.3. Favourable effects

The primary endpoint of study TN-10 was the elapsed time to onset of T1D stage 3 (based on glucose testing with an OGTT or the presence of unequivocal hyperglycemia with acute metabolic decompensation, such as DKA). The final analysis was conducted through the cut-off date of 30 November 2018, after a sufficient number of events (40 or more), i.e., onset of T1D, had occurred and the last subject had at least 1 post-baseline visit. The median times to T1D were 24.9 months in the placebo group and 49.5 months in the teplizumab groups. In study TN-10, 20 (45%) of the 44 teplizumab-treated subjects and 23 (72%) of the 32 placebo-treated subjects were diagnosed with stage 3 T1DM. The hazard ratio obtained from the Cox model was 0.41 (95% CI: 0.22, 0.78,

p=0.0066) resulting in a statistically significant delay in the development of stage 3 T1DM. The primary endpoint of the study was met.

Secondary endpoint was change in C-peptide responses as indicator of beta cell function. C-peptide was measured as the C-peptide AUC in a 2-hour OGTT (measurements at timepoints 0, 30, 60, 90, and 120 minutes). This assessment was performed at 3 months and 6 months after randomization, and then every 6 months or more frequently if clinically indicated. The MMRM analyses of C-peptide ln(AUC+1) data for 24 months indicated that teplizumab treatment was associated with higher C-peptide levels (i.e., more beta cell preservation) than placebo.

Meta-analyses on C-peptide data in patients with stage 3 T1D showed a greater decline from baseline for the placebo pool than for the teplizumab pool, both for the 12-month (5 participating studies) and the 24-month (3 participating studies) analyses. P values<0.001 at 1 year and 2 years, respectively, was derived from the ANCOVA model for the 1-year and 2-year integrated data, respectively.

10.3.1. Uncertainties and limitations about favourable effects

There were imbalances with regards to the planned 1:1 allocation to treatment arms (44 participants were randomised to teplizumab and 32 to placebo arm), and also with regards to the stratification variables used in the randomisation (e.g. age). However, no major impact on the study results is expected.

The results of the meta-analysis of C-peptide data is associated with uncertainties since the analysis was based on 5 studies with various different designs, some studies small in size, and some studies failed to reach primary endpoint, in patients with newly diagnosed T1DM (ie. Stage 3).

A Global Registry covering the proposed target population and including an untreated control arm will be initiated post approval. A synopsis is included in the RMP. Planned primary objective is to assess safety data in patients with Stage 2 T1D treated with teplizumab. As secondary objective, the effectiveness will be assessed and measured as elapsed time from teplizumab treatment or enrolment (control group) to the development of Stage 3 T1D.

10.4. Unfavourable effects

The pooled safety dataset for teplizumab (the 'all studies pool') encompass one study with participants with stage 2 T1D (the pivotal TN-10 study where 44 subjects were exposed to teplizumab, including 29 subjects < 18 years) and 6 studies in patients recently diagnosed with stage 3 T1D (including the pivotal PROTECT study) of which one is an extension study. In this dataset, 1008 patients were exposed to Teplizumab and 356 patients to control treatment. Of those, 900 patients received teplizumab in a placebo-controlled setting. Safety data beyond 1 year is available from >90% of patients, and data beyond 2 years is available from 38.9% of patients.

The population with stage 2 T1D is limited as 44 patients have been exposed in clinical trials, however post-marketing data is available from an estimate of 414 exposed patients. The reported SAEs and AEs are in general in line with the safety profile observed in the clinical trials. Furthermore, safety data from the 6 studies in patients recently diagnosed with stage 3 T1D are supportive as the safety profile is expected to be similar between the 2 populations.

Allergic/hypersensitivity reactions

Rash was reported with higher frequencies in the teplizumab group compared to control (35.6% vs.

8.4%). The TEAEs were in general mild to moderate in intensity (CTCAE grade 1 and 2). Three grade 3 cases of rash and one grade 3 case of rash popular were reported. The events were resolved without clinical sequalae.

The PT 'cytokine release syndrome' was more frequent in the teplizumab group than control (6.4% vs. 1.1%) of which 9 were classified as SAEs, all in the teplizumab group (0.9%).

Haematology

Within the SOC 'blood and lymphatic system disorders', TEAEs were reported with higher frequencies in the teplizumab group compared to control for lymphopenia (74.5% vs. 12.9%), leukopenia (57.5% vs 20.5%), neutropenia (36.9% vs. 18.3%). The mean leukocyte, lymphocyte and neutrophil count decreased during the treatment course in the teplizumab group but return to baseline at the follow-up 3-6 weeks after the treatment.

Hepatic safety

Administration of teplizumab was related to increases in laboratory values of transaminases. Increases >3XULN were registered for ALT (7.8% vs. 1.7%) and AST (5.3% vs. 1.1%) in teplizumab vs. control. Increases in ALT >5XULN in 3.0% vs. 0.6% in teplizumab vs. control. 11 patients (1.1%) displayed increases >10XULN in teplizumab vs. 1 patient (0.3%) in control. Except in one case (reported sustained ALT and AST increase), the liver function abnormalities were resolved without any clinical sequalae or indications of associated hepatic injury. The dataset was searched for cases of Hy's law (ULN for bilirubin was defined as 1 mg/dL for adults and 1.5 mg/dL for paediatric participants); One case (10 year male) was clearly related to hepatitis A infection and is thus not a valid Hy's law case and one other case (a 34-year old patient) in the teplizumab group fulfilled the criteria (ALT or AST > 3*ULN) and TBIL > 2*ULN) however upon review, the case is considered confounded by an alternative aetiology (biliary dyskinesia).

Imbalances in reported AEs related to liver function were observed for the PTs 'aspartate aminotransferase increased' (24.0% vs. 14.3%), 'alanine aminotransferase increased' (23.6% vs. 7.9%), 'blood bilirubin increased' (6.7% vs. 2.8%). Within the SOC 'hepatobiliary disorders', there was a small increase in hyperbilirubinemia for teplizumab (5.9% vs. 3.9%).

Metabolic

Imbalances in SAEs related to glucose metabolism were registered. While SAEs of hyper and hypoglycaemia occurred at low frequencies (0.6-0.8%) in both treatment groups, imbalances in SAEs of diabetic ketoacidosis and hypoglycaemic seizures were noted.

SAEs of diabetic ketoacidosis were registered (including one fatal case), which predominantly occurred in the teplizumab group (2.1% [21 cases] vs. 0.3% [1 case]). The cases occurred several months after drug administration, and they appear to be related to the underlying development of diabetes. In all cases, well-known precipitating factors are described (such as infections, insulin compliance or insulin delivery issues). The patients in general had poor metabolic control during the study and at the time of the event. Even though the observed imbalance is notable, a causal relationship to teplizumab seems unlikely. Cases of DKA would be reported through routine pharmacovigilance activities.

The frequency of TEAEs of hypoglycaemia was reduced in teplizumab vs. control (13.6% vs. 20.2%) however 7 SAEs of hypoglycaemic seizures (0.7%) were registered in the teplizumab group, with no cases occurring in the control group.

Gastrointestinal

Within the SOC 'gastrointestinal disorders' PTs reported with higher frequencies in the teplizumab group compared to control were nausea (24.5% vs. 15.4%), vomiting (17.8% vs. 11.2%) and

abdominal pain (8.6% vs. 6.2%).

Infections

Frequencies of TAEs within the SOC 'Infections and infestations' were similar in both treatment arms (55.2% vs. 55.1% in teplizumab vs. control). For SAEs within this SOC, there was a slightly increased occurrence in the teplizumab group compared to control (3.1% [31 cases] vs. 2.2% [8 cases] without any obvious difference in the PT pattern. The AESI 'Acute mononucleosis-like illness' was more frequent in teplizumab vs. control (10.1% vs. 5.3%).

10.4.1. Uncertainties and limitations about unfavourable effects

The size of the safety database is overall deemed sufficient; however the stage 2 T1D population is limited where only 44 patients have been exposed in clinical trials. Furthermore, based on exposure differences between the product used in the TN-10 study and the commercial product, the proposed posology is ~25% higher than the doses used in the TN-10 study. However, experience from the labelled dose is available from the US where 414 patients are estimated to have been exposed to Teplizumab for the stage 2 indication. The reported SAEs and AEs are in general in line with the safety profile observed in the clinical trials.

TEAEs within the SOC 'Skin and subcutaneous disorders' PTs reported with higher frequencies in the teplizumab group. The skin reactions were transient and did not result in any clinical sequela. One case of anaphylaxia and one case of generalised skin reaction were however reported.

Cytokine release syndrome has been identified. Section 4.4 of the SmPC includes information on how this should be adequately managed, emphasizing the importance of careful patient monitoring during the initial days of infusion, appropriate dose escalation (particularly during the ramp-up period), and prompt symptomatic treatment. In cases of non-resolved CRS despite a drug pause, discontinuation of treatment may be warranted. It is also noted that the product is under restricted medical prescription.

Administration of teplizumab was related to increases in laboratory values of transaminases and one case of Hy's law was observed, however considered confounded by alternative aetiology (biliary dyskinesia) (Another case, 10-year male, was clearly related to hepatitis A infection and is thus not a valid Hy's law case). The applicant views the transaminase elevations as secondary to cytokine release syndrome. The transaminase elevations may be secondary to cytokine release syndrome, however only 17.7% (14 patients) of participants with ALT>3X also displayed CRS and the mechanism is thus not clear. Instructions to monitor liver function in relation to the treatment course is included in section 4.4 of the SmPC.

Transient lymphopenia is observed in participants treated with teplizumab. Teplizumab causes a transient reduction in the number of circulating lymphocytes due to margination, which is directly related to the mechanism of action of the drug. This has been observed in approximately 80% of participants. The development of transient lymphopenia does not appear to be associated with an overall increase in infections (all studies pool: 55.3% in the teplizumab group and 55.1% in the control group), consistent with the lack of T cell depletion, however the AESI 'Acute mononucleosis-like illness' was more frequent in teplizumab vs. control (10.1% vs. 5.3%).

In order to mitigate the risks related to teplizumab, routine risk minimisation measures are in place including restricted medical prescription status. Moreover, additional risk minimisations measures in the form of healthcare professional guide and patient guide will be implemented. A study to assess the effectiveness of these measures will also be conducted post approval.

Teplizumab introduces a new therapeutic concept in otherwise healthy children and the long-term impact of immune modulation in this population is not fully understood. These uncertainties are especially relevant in the stage 2 population, where individuals are asymptomatic and do not yet require treatment. Long-term safety, including growth, in patients aged 8 to <18 years is included as missing information in the RMP and will be followed in the category 3 PASS (global registry).

Based on the mechanism of action, an increased risk of malignancy (e.g., leukaemia) cannot be entirely ruled out, however currently there are no evidence indicating an increased risk of cancer associated with teplizumab. 'Malignancies' is included as an important potential risk in the RMP. As long-term data continue to be collected, this will be further evaluated as part of the category 3 PASS (global registry) included in the RMP.

10.5. Effects Table

Effect (short description)	*Treatment*	*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable Effects				
Indication 1: Onset of Stage 3 T1D mean time from randomisation (95% CI)	Teplizumab Infusion course 14 d (study participants 44/76) 49.5 months	Placebo (study participants 32/76) 24.9 months	**SoE:** Hazard ratio: 0.41 (95% CI: 0.22, 0.78, p=0.0066) **Unc:** small study, Few participants after 24 m Unbalanced baseline Target population	TN-10 Single pivotal phase II
Indication 1: Response in C-peptide AUC to oral glucose 2-h OGTT C-peptide (ln (AUC +1)) (secondary endpoint)	Teplizumab Infusion course 14 d	placebo	**SoE:** Change from baseline Difference teplizumab-placebo, LSmean (95% CI) 0.06924 (-0.02977, 0.16826) p= 0.1675 **Unc:** no type 1 error control due to study design	TN-10
Indication 1 Changes in C-peptide from Baseline (nmol/L) (Difference teplizumab – control, LS mean)	n = 375 teplizumab Course 1 +2 Various 12 d-14 d + 0d-12d	n = 234 control (placebo or standard care) blinded or OL	**SoE:** 0.08 nmol/L (0.04, 0.12) at year 1 0.12 nmol/L (0.07, 0.17) at year 2 **Unc:** retroactively designed meta-analyses, various designs, small studies, early termination etc.	Meta-analysis of 5 studies
Unfavourable Effects				
Any TEAE	1003 (99.5%)	341 (95.8%)		All studies pool
Any TEAE	43 (97.7%)	22 (68.8%)		TN-10 study
Any TESAE	119 (11.8%)	26 (7.3%)		All studies pool
Any TESAE	7 (15.9%)	1 (3.1%)	9 SAEs (0.9%), all in treatment group	TN-10 study

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Rash	359 (35.6%)	30 (8.4%)		All studies pool
Cytokine release syndrome	65 (6.4%)	4 (1.1%)		
Alanine aminotransferase increased	238 (23.6%)	28 (7.9%)	ALT>3XULN (7.8% vs. 1.7%) ALT>5XULN (3.0% vs. 0.6%)	
Lymphopenia	751 (74.5%)	46 (12.9%)	Values return to baseline at the follow-up 3-6 weeks after the treatment	

Abbreviations: ALT: Alanine aminotransferase; AUC: Area under curve; CGM: continuous glucose monitoring; CI: confidence interval; LS: Least square; MMTT: mixed meal tolerance test; OGTT: oral glucose tolerance test; Ref: reference; SAE: Serious adverse event; SD: Standard deviation; SoE: strength of evidence; T1D: Type 1 Diabetes mellitus; TEAE: treatment emergent adverse event; TESAE: Treatment-emerging serious adverse event; U: units; ULN: upper limit of normal; Unc: uncertainties

10.6. Benefit-risk assessment and discussion

10.6.1. Importance of favourable and unfavourable effects

Teplizumab is a humanized monoclonal antibody (IgG1 subclass) that binds to the CD3ε chain of the T-cell receptor complex on human T cells, which leads to internalisation of the teplizumab/CD3 complex. The claimed mechanism of action of teplizumab (to prevent beta-cell destruction in T1D) is not fully understood but is thought to involve partial agonistic signalling and deactivation of pancreatic beta-cell autoreactive T lymphocytes.

Based on the results of the pivotal and supportive clinical studies, treatment with teplizumab results in a delay of beta-cell destruction as measured by C-peptide compared to placebo.

The proposed indication *to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D* is mainly supported by one small, placebo-controlled Phase 2 study (TN-10). The results show that the median time to progression to stage 3 T1D was 49.5 months in the Teizeild group, compared with 24.9 months in the placebo group. These results are also supported by results from studies in the stage 3 T1D population with respect to delaying destruction of beta-cells. Delaying the onset of stage 3 TID would be of clinical benefit since it would delay the start of insulin treatment. Especially for young children and their caregivers, T1D management including insulin injections and blood glucose monitoring can be stressful, and therefore each year of postponement is assumed to be beneficial.

The study population is small which raises questions about the external validity of the results and there were imbalances with regards to the planned 1:1 allocation to treatment arms (44 participants were randomised to teplizumab and 32 to placebo arm), and with regards to the stratification variables used in the randomisation (e.g. age). However, based on the mode of action of teplizumab, the pathophysiology of T1D and results in sub-groups in other studies (in patients with stage 3) no major differences in sub-groups are expected and a positive treatment effect across sub-groups is supported.

Therefore, the CHMP considered that a clinically meaningful effect has been appropriately

documented for subjects with Stage 2 T1D based on the pivotal trial to support a full marketing authorisation.

A SAG (Scientific advisory group) on Cardiovascular Issues convened on 9th of September 2025. The experts confirmed the clinical relevance of delaying the onset of stage 3 T1D in stage 2 patients. Postponing the onset of the disease will also delay the onset of the "honeymoon period" with less treatment requirements (Minutes of the SAG meeting are appended to this report).

In order to capture more data in the target population, a Global Registry including an untreated control arm will be initiated post-approval of the product. A synopsis is included in the RMP. The approach proposed by the Applicant to set-up a global registry is considered acceptable. The Applicant is urged to seek scientific advice to optimize the protocol.

With respect to safety, teplizumab was primarily associated with transients AEs.

Administration of teplizumab was related to increases in laboratory values of transaminases; increases >3XULN were very common and increases >5XULN were common. Monitoring of liver function in relation to the treatment course is included in section 4.4 of the SmPC and any cases of hepatotoxicity should be followed in the PSURs.

Rash was reported with higher frequencies in the teplizumab group compared to control.

The PT 'cytokine release syndrome' was more frequent in the teplizumab group than control of which 9 were classified as SAEs, all in the teplizumab group. One case of anaphylaxis was observed.

Lymphopenia was frequently observed and is related to the mode of action. It has potential to increase the risk for serious infections. However, the frequency of serious infections was only slightly increased in the teplizumab group.

The long-term impact of immune modulation in this population is not fully understood. These uncertainties are especially relevant in the stage 2 population, where individuals are asymptomatic and do not yet require treatment.

Appropriate routine and additional risk minimisation measures will be implemented. A PASS (survey) will assess the effectiveness of the risk minimisation measures. A PASS (global registry) will investigate the long-term safety and effectiveness of teplizumab.

10.6.2. Balance of benefits and risks

With respect to the proposed indication to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D, the results are available from one small, phase 2 trial. However, the results are considered robust from a statistical point of view. Furthermore, the mechanism of action is supported by other studies in the T1D population. Based on the mechanism of action, the pathophysiology of T1D and results in sub-groups in other studies (in patients with stage 3) no major differences in sub-groups are expected. Therefore, it is considered that a clinically meaningful effect has been appropriately documented for subjects with Stage 2 T1D.

Teplizumab was associated with increases in transaminases and Lymphopenia. Cases of cytokine release syndrome occurred, and also one case of anaphylaxis. These issues are not considered to outweigh the proven benefits of teplizumab provided that the routine and additional risk minimisation measures are implemented and followed.

Considering all favourable and unfavourable effects, the benefit-risk balance of Teizeild for the

indication *to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D* is considered positive.

10.6.3. Additional considerations on the benefit-risk balance

Input from additional experts

A SAG on Cardiovascular Issues was convened on 9th of September 2025. The minutes from the SAG meeting are appended to this report.

Early dialogue with CHMP

In the framework of the CHMP early dialogue, input from patients and healthcare professionals was provided. Details are included in sections 6.3.7 and 6.3.8 of this report.

10.7. Benefit-risk conclusions

10.7.1. Final CHMP conclusions

Considering all favourable and unfavourable effects described above, the CHMP considered that the benefit-risk balance of Teizeild in the indication *to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D* is positive.

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