EU-RISK MANAGEMENT PLAN FOR TEIZEILD® (TEPLIZUMAB)

Risk Management Plan (RMP) Version number	**Version 1.1**
Data Lock Point (DLP)	**31-AUG-2024**
Date of final sign-off	**10-NOV-2025**

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Not applicable
Summary of significant changes in this RMP	Not applicable

RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	Not applicable
Approved with procedure	Not applicable
Date of approval (opinion date)	Not applicable

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted]*a*,[redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ADA:	Anti-Drug Antibody
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
AF:	Attributable Fraction
AID:	Autoimmune Diabetes
ALT:	Alanine Transaminase
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area-Under the Curve
BSA:	Body Surface Area
CD:	Cluster of Differentiation
CGM:	Continous Glucose Monitoring
CHO:	Chinese Hamster Ovary
CI:	Confidence Interval
CKD:	Chronic Kidney Disease
CMV:	Cytomegalovirus
CNS:	Central Nervous System
COVID-19:	Coronavirus Disease-2019
CRS:	Cytokine Release Syndrome
CTCAE:	Common Terminology Criteria for Adverse Event
CV:	Cardiovascular
DKA:	Diabetic Ketoacidosis
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
DoO:	Delay of Onset
EBV:	Epstein-Barr Virus
ECG:	Electrocardiogram
e-CTD:	Electronic-Common Technical Document
EEA:	European Economic Area
EFD:	Embryo Foetal Development
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
EU:	European Union
GP:	General Practitioner
GPRD:	General Practice Research Database
HbA1c:	Glycated Hemoglobin
HCP:	Healthcare Professional
HIV:	Human Immunodeficiency Virus
HLA:	Human Leukocyte Antigen
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN-γ:	Interferon Gamma
IgG:	Immunoglobulin G

IgM:	Immunoglobulin M
IL:	Interleukin
INN:	International Nonproprietary Name
IP:	Intraperitoneal
IRR:	Incidence Rate Ratio
IV:	Intravenous
KLH:	Keyhole Limpet Hemocyanin
mAb:	Monoclonal Antibody
MAH:	Marketing Authorization Holder
MedDRA:	Medical Dictionary for Regulatory Activities
mRNA:	Messenger Ribonucleic Acid
NCA:	National Competent Authority
NOAEL:	No Observed Adverse Effect Level
NOD:	Non Obese Diabetic
NSAID:	Non-Steroidal Anti-Inflammatory Drug
OGTT:	Oral Glucose Tolerance Test
PAF:	Platelet Activating Factor
PASS:	Post-Authorization Safety Study
PBMC:	Peripheral Blood Mononuclear Cells
PI:	Product Information
PIP:	Paediatric Investigation Plan
PL:	Package Leaflet
PND:	Postnatal Day
PPND:	Pre and Post Natal Develpoment
PRAC:	Pharmacovigilance Risk Assessment Committee
PRO:	Patient Reported Outcome
PTPN22:	Protein Tyrosine Phosphatase Non-Receptor Type 22
QPPV:	Qualified Person Responsible for Pharmacovigilance
RMM:	Risk Minimization Measure
RMP:	Risk Management Plan
SAE:	Serious Adverse Event
SC:	Subcutaneous
SmPC:	Summary of Product Characteristics
SMR:	Standardized Mortality Ratio
SOC:	System Organ Class
T1D:	Type 1 Diabetes
T2D:	Type 2 Diabetes
TB:	Tuberculosis
TDAR:	T-cell Dependent Antibody Response
TEAE:	Treatment Emergent Adverse Event
TNF-α:	Tumor Necrosis Factor Alpha
UK:	United Kingdom
ULN:	Upper Limit of Normal
US:	United States
WHO:	World Health Organization

PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Teplizumab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	A10XX01
Marketing Authorization Applicant	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Teizeild
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Teplizumab is a cluster of differentiation (CD)3-directed mAb.
	Summary of mode action: Teplizumab preserves beta cell function by binding to CD-3, which involves partial agonistic signaling and exhaustion of pancreatic beta cell autoreactive T lymphocytes. Studies that evaluated the mechanisms of teplizumab have shown a number of effects on specific subpopulations of T cells that are integral to the initiation and propagation of the autoimmune process causing beta cell destruction. In addition to reduced effector function of T cells, presumably including autoreactive T cells given observed increased beta cell survival, and as a result of CD3 partial agonism, teplizumab appears to increase the number and function of regulatory T cells. [1, 2,3, 4] More recent studies indicate that teplizumab also induces immunologic "exhaustion" in a subset of effector CD8+ T cells believed to be previously autoreactive. [5, 3] Importantly, the increase in exhausted CD8+ T cells has been associated with delayed progression to clinical type 1 diabetes (T1D) in the natural course of the disease [6] and correlates with clinical response to teplizumab. [3] Collectively, these mechanistic data 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, leading to the re-establishment of beta cell self-tolerance [7] for extended periods of time in many treated patients.
	Important information about its composition: Teplizumab is expressed from a recombinant Chinese Hamster Ovary (CHO) cell line. Teplizumab is a sterile, preservative-free solution for intravenous (IV) infusion.

	Excipients: dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 80, sodium chloride, and water for injection.
Hyperlink to the product information	Refer to electronic common technical document (e-CTD) sequence 0000, Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	Current: Teizeild *is indicated to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D.*
	Proposed: Not applicable
Dosage in the EEA	Current: *Teizeild 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 as follows:* *Day 1: 65 micrograms/m^2* *Day 2: 125 micrograms/m^2* *Day 3: 250 micrograms/m^2* *Day 4: 500 micrograms/m^2* *Days 5 through 14: 1030 micrograms/m^2*
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: *One mL of concentrate for solution for infusion contains 1 mg of teplizumab.* *Each vial contains 2 mg of teplizumab in 2 mL (2 mg/2 mL).*
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the European Union (EU)	Yes

ATC: Anatomical Therapeutic Chemical; BSA: Body Surface Area; CD: Cluster of Differentiation; CHO: Chinese Hamster Ovary; e-CTD: Electronic-Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; IV: Intravenous; mAb: Monoclonal Antibody: RMP: Risk Management Plan; T1D: Type 1 Diabetes.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Diabetes is a common disease with more than half a billion people affected worldwide in 2021. Estimates released by the International Diabetes Federation in 2021 showed that prevalence of diabetes varied between 5 and 18% by region among adults aged 20-79 years. [8]

There are 2 forms of diabetes mellitus with distinct pathophysiology and affected populations. Type 2 diabetes (T2D) is the most common form of diabetes accounting for over 90% of all diabetes cases worldwide and T1D, the lesser common form accounting for the residual 10% cases.

Teplizumab *is indicated to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D.*

Epidemiological data on stage 2 T1D is not available as it was previously rarely identified. Recent approval of teplizumab in the United States (US) and recognition of avoidance of diabetic ketoacidosis (DKA) have highlighted the importance of screening for T1D. These patients are now being identified and better characterized. It is anticipated that data will increase with time. However, the epidemiology of T1D (stage 3) in adult and in pediatric populations is summarized in the following tables.

Table 6 - Epidemiology of type 1 diabetes in the adult population

Indication	Type 1 diabetes in the adult population
Incidence	Fewer data are available on incidence of T1D in the adult population, due to prior understanding that T1D is a disease that most often starts in childhood or early adulthood. Misdiagnosing adult-onset T1D as T2D has been reported and would result in an under estimation of the T1D burden. [9] A recent epidemiology study showed that, there is a paucity of data, particularly in low- and middle-income countries. The incidence of adult-onset T1D is lowest in Asian and highest in Nordic countries. [10,11] In Sweden, in 1998-2001, the incidence of T1D was 27.1 per 100 000 person-year in the 20 to 100 years old population. [12] In a longitudinal study (2001-2015) in the US, the annual incidence rate of T1D was 18.6 per 100 000 persons for ages 20-64 years. [13] Despite the incidence of childhood-onset T1D in China being among the lowest in the world, prevalence data show similar trends across the life span. Between 2010 and 2013, the yearly incidence was 1.28/100 000 among individuals 15–29 years of age versus 0.69/100 000 among older adults. [10]
Prevalence	In adults, data from a General Practice Research Database (GPRD) study suggested that the prevalence of T1D in United Kingdom (UK) was 0.3% in 2003. [14] In another study, the prevalence of T1D in 2000 was estimated to be 0.15% in France, 0.14% in Italy, 0.21% in Spain, 0.21% in Germany, and 0.33% in the UK. [15,16] In France according to Santé Publique France agency, the prevalence of T1D in adults was 0.3 to 0.5 % in 2019. [17]

Indication	Type 1 diabetes in the adult population
Demographics of the population in the authorized or proposed indication(s), as applicable	Type 1 diabetes most often begins at young age (<20 years) and is mainly due to autoimmune destruction of the pancreatic β-cells that produce insulin. However, more recent data suggest that only about 50% to 60% of those with T1D are younger than 16-18 years at presentation and that such disease occurs at a low incidence level throughout adulthood. [18] In Sweden, the incidence of T1D in age group 20-49 years was lower (11.7 to 19.7 per 100 000 person-years) compared to 50-80 years (27.3 to 55.0 per 100 000 person-years). [12] In the US the incidence rate of T1D was greatest in youth aged 10-14 years, at 45.5 cases per 100 000 person-years. The annual incidence rate of T1D was 34.3 per 100 000 persons for ages 0-19 years and 18.6 per 100 000 persons for ages 20-64 years in this cohort. [13] Risk factors for the disease: The cause of autoimmune destruction of the pancreatic β-cells in T1D is multifactorial and incompletely understood. The current model holds that T1D arises in genetically susceptible children exposed to environmental triggers. Nevertheless, approximately 90% of individuals who develop T1D do not have a family history of T1D. [19] • Genetic Susceptibility to T1D Genotype plays an important role in the development of T1D. The lifetime risk of developing T1D in the general population is approximately 0.4%, and this risk increases significantly with a first-degree relative with T1D. Siblings have a 3% to 6% risk of developing T1D and children have a 1% to 2% risk if the mother has T1D and a 3% to 5% risk if the father has T1D. Siblings of children with T1D diagnosed before age 7 years have the highest risk. In a large study of twin pairs in Finland, the concordance rates for T1D were 27.3% in monozygotic twins and 3.8% in dizygotic twins. The risk of T1D increased with younger age of onset in the index twin. In the 1970s, T1D was recognized as being associated with genetic variants in the human leukocyte antigen (HLA) on chromosome 6p21.3. Human leukocyte antigen class II DR4 and DR3 are most closely associated with T1D, and the combination of the 2 alleles, DR3/DR4, produces the highest genetic susceptibility. Those children with the highest risk genotype have a 5% risk of getting diabetes by age 15 years. Human leukocyte antigen variants account for approximately 50% of T1D genetic susceptibility. More than 40 genes account for the remaining 50% genetic risk. After the HLA alleles, polymorphisms in insulin (encoding proinsulin) and protein tyrosine phosphatase non-receptor type 22 (PTPN22) (involved in T-cell regulation) contribute the most genetic risk for T1D. [20] • Environmental Factors The role of environmental risk factors in the development of T1D is suggested by the modest concordance rates between twins and studies of migrant populations. Studies have demonstrated that being born in a high-incidence country increases the risk of T1D in children of parents who have migrated from low-incidence regions. [21,22] Furthermore, higher socioeconomic status is associated with increased T1D risk in the SEARCH cohort. [23] This correlation is behind the hygiene hypothesis, which proposes that improved living standards and decreased infectious burden drive the increase in autoimmune diseases in industrialized countries.
Main existing treatment options	Lifelong insulin treatment is needed after diagnosis of stage 3 T1D. The central precept in the management of stage 3 T1D is that some form of insulin be given in a defined treatment plan tailored to the individual to prevent DKA and minimize clinically relevant hypoglycemia while achieving the individual's glycemic goals in order to reduce the incidence of micro and macrovascular complications. [24] Teplizumab is currently the only approved therapy to delay the onset of stage 3 T1D. Higher C-peptide levels have been associated with lower risk of DKA events, lower daily insulin dose, lower risk of retinopathy, lower risk of nephropathy, and lower risk of severe hypoglycemia. [24,25]

Indication	Type 1 diabetes in the adult population
Natural history of the indicated condition in the untreated population including mortality and morbidity	High-risk individuals (stage 2) have a 75% risk of progression to symptomatic (stage 3) T1D within 5 years, close to 100% risk of progressing to stage 3 in their lifetime. [26,27] Approximately 40% of T1D patients present with DKA at diagnosis [28] • Diabetic Ketoacidosis is a medical emergency and can be fatal without prompt treatment. • Diabetic Ketoacidosis is the leading cause of death in people under 50 years with T1D, contributed to 29 % of male deaths and 22 % in women. [29] Individuals with T1D have a ten-times higher risk for cardiovascular (CV) events (eg, myocardial infarction, stroke, angina, and the need for coronary-artery revascularization) than age-matched nondiabetic populations. [30,31] The GPRD study reported that annual mortality rates in the UK during 1992-1999 were 8.0 per 1000 person-years in T1D subjects compared with 2.4 in those without diabetes (hazard ratio = 3.7, 95% confidence interval (CI) 3.2 4.3). The increased mortality rates in these patients were apparent across all age groups. The predominant cause of death in patients with T1D was CV disease. [32] In Sweden, it was also reported a significant excess mortality (all causes) in T1D patients before development of late complications: the mean age and sex (standardized mortality ratio [SMR] = observed numbers of death/expected numbers of death) were 2.2 and was higher in females than in males (2.7 versus 1.9). [33] Age at disease onset is an important determinant of survival and CV disease. Patients with T1D with disease onset before 10 years of age had a 30 times increased risk of coronary heart disease and acute myocardial infarction in their early adult years. Women with onset of T1D before 10 years of age had a 60 times increased risk of coronary heart disease and 90 times increased risk of acute myocardial infarction, in the same early adult period. [18] In Norway it was found a higher SMR in a T1D cohort (4.0) without significant difference between males and females. [34]
Important co-morbidities	Co-morbidities: T1D typically presents as a monoglandular autoimmune condition, however, it can also present concomitantly, either at diagnosis or later, with a variety of other non-glandular and glandular autoimmune diabetes (AID). T1D-associated AID include autoimmune thyroid diseases (15%-30%), type A gastritis (15%), celiac disease (3%-12%), vitiligo (1%-7%), rheumatoid arthritis (1.2%), systemic lupus erythematosus (1.15%), and Addison disease (0.5%). [35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51] It has been established in stage 3 T1D that uncontrolled, high levels of blood glucose due to loss of beta cell function is a risk factor for short term (such as DKA, chronic kidney disease [CKD]) and longer-term complications, including chronic microvascular and macrovascular, that can result in retinopathy, nephropathy, neuropathy and premature CV morbidity and mortality. Hypoglycemia may occur in stage 3 T1D patients who are treated with exogenous insulin due to the side effect of insulin treatment. Concomitant medications: Stage 3 T1D patients require lifelong administration of insulin. Insulin therapy includes continuous subcutaneous (SC) insulin infusion via a pump or multiple daily doses of prandial (injected or inhaled) and basal insulin injection. It is possible, though less common, for recent-onset adult stage 3 T1D for patients to require anti-hypertensives or cholesterol-lowering medications. [52]

AID: Autoimmune Diabetes; CI: Confidence Interval; CKD: Chronic Kidney Disease; CV: Cardiovascular; DKA: Diabetic Ketoacidosis; GPRD: General Practice Research Database; HLA: Human Leukocyte Antigen; PTPN22: Protein Tyrosine Phosphatase Non-Receptor Type 22; SC: Subcutaneous; SMR: Standardized Mortality Ratio; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; UK: United Kingdom; US: United States.

Table 7 - Epidemiology of type 1 diabetes in the pediatric population

Indication	Type 1 diabetes in the pediatric population
Incidence	Type 1 diabetes is a disease that often starts in childhood or early adulthood. It is estimated that the incidence of T1D among children and adolescents is increasing in many countries, particularly in the age group of under 15 years, and the overall annual increase is estimated to be around 3% with strong indications of geographic differences. [53] There is a wide range of the incidence of T1D reported globally, and this incidence varies from country to country. The first global diabetes incidence study, the World Health Organization (WHO) Multinational Project for Childhood Diabetes (The DIAMOND Project Group), collected data between 1990 and 1999 and reported incidence data for children younger than 14 years of age. The study suggested that, during the period 1990-1999, in children aged 14 years or under, the overall age-adjusted incidence rates of T1D varied more than 350 fold among countries in the same region and between regions, from 0.1/100 000 per year in China and Venezuela to 37.8/100 000 per year in Sardinia to 40.9/100 000 per year in Finland. [54] Most of the new cases diagnosed in Southeast Asia are from India, with an overall annual estimated incidence rate of 4.2/100 000. [55] The EURODIAB study reported in 2012 that, during 2004-2008, the annual incidence rate of T1D among children aged 15 years or under ranged from 10.4 per 100 000 per year in Croatia to 36.6 per 100 000 per year in Sweden. Incidence rates were high in northern and northwestern Europe and low in central, southern, and Eastern Europe. [56] The results of the EURODIAB Study Group also showed that the overall annual increase in incidence was 3.4% per annum in 1989-2013. [57] In France, the incidence rate of T1D in children aged younger than 15 years rose significantly between 1988 and 2004, from 8.9 to 13.5 per 100 000 person years, indicating an annual increase in incidence of 3.3%. The annual increase was greatest in the youngest children (0-4 years: 7.6%; 5-9 years: 4.1%; 10-14 years: 1.3%). [58] A similar trend was continuously observed over the following period between 2010 and 2015 from 15.4 to 19.1 per 100 000 person-years, with an annual increase of 4.0%. This trend was observed in both sexes and in all age groups. [59] The SEARCH for Diabetes in Youth study (the SEARCH study) evaluated youth younger than 20 years of age who were newly diagnosed with diabetes, between 2002 and 2018 in the US, and reported that the age-, sex- and ethnicity-adjusted incidence of T1D increased by 2.02% annually, from 19.5 per 100 000 in 2002-2003 to 21.7 per 100 000 in 2011-2013, to 22.2 per 100 000 in 2017-2018. After adjustment for age, sex, and race or ethnic group, significant annual increases were identified in age groups of 5-9, 10-14, and 15-19 years in both sexes. [60,61] A modelling study published in 2022, hypothesized a large underestimation of T1D diagnosis worldwide and estimated a global annual incidence rate of 13.66/100 000 in ages 0 to 19 years. [62] Despite the increase in incidence observed in a number of countries, some countries including Sweden, Norway, Finland, Italy, Ireland, Australia, and Japan have reported stable or declining incidence rates of T1D in pediatric population in recent years. [63,64,65,66,67,68,69,70] Changes in the environment such as prevalence of childhood obesity, chronic viral infections, and latitude ultraviolet B-vitamin D pathway may contribute to the current evolving pattern observed of regional disparity of T1D incidence. [71]
Prevalence	The global distribution of T1D varies significantly by region. Europe is estimated to have the largest number of prevalent T1D cases, followed closely by Southeast Asia, including India. The West Pacific region, including China, has the lowest number of prevalent T1D cases. [55] The SEARCH study of the US population estimated the prevalence of T1D at 1.5 cases/1000 in youths aged younger than 20 years in 2001 and 1.9 cases/1000 in 2009, representing an increase of 30.0% over the 8-year period. The greatest prevalence increase was observed in those aged 15-19 years. [72] In 2009, prevalence was highest among non-Hispanic whites, with

Indication	Type 1 diabetes in the pediatric population
	2.6 cases/1000 youths, followed by blacks, with 1.6 cases/1000 youths. Overall, no gender differences in the prevalence of T1D were found. [72,73] Another study, using the US MarketScan database, also reported that the annual prevalence of T1D increased from 1.5 to 2.3 per 1000 during 2002-2013 in children younger than 18 years of age. [74] Other regions that have published data on T1D prevalence in youths include Spain (2.1/1000 in children 0-16 years), Germany (1.5/1000 in children 0-14 years), Sardinia (4.6/1000), Manitoba, Canada (1.2/1000), Saudi Arabia (1.1/1000), and Turkey (0.8/1000 in children 0-17 years), and Japan (0.1/1000 in children 0-14 years). [55,70,75,76,77] In total, in 2021, 1 211 900 children and adolescents below 20 years of age were estimated to have T1D globally. [8]
Demographics of the population in the in the authorized or proposed indication(s), as applicable	Type 1 diabetes remains a major disease of childhood and early adulthood. Most people develop this disease at younger than 20 years of age. However, more recent data suggest that only about 50% to 60% of those with T1D are younger than 16-18 years at presentation and that such disease occurs at a low incidence level throughout adulthood. [78] More than 96 000 children and adolescents under 15 years are estimated to be diagnosed with T1D annually and the number is estimated to be more than 132 600 when the age range extends to 20 years. [8] It is generally accepted that hormonal changes at puberty are responsible for the highest incidence in 10-14 years old children compared with other age groups. The peak incidence for girls seems to occur 3 years before the peak incidence for boys. [55] The SEARCH study of the US population estimated that the prevalence of T1D was highest among non-Hispanic whites aged 10 to 19 years, with 2.9 cases/1000 youths, followed by blacks aged 10 to 19 years, with 2.1 cases/1000 youths. Overall, no gender differences in the prevalence of T1D were found. However, higher rates in girls were noted in 3 racial/ethnic groups, Blacks, Asian/Pacific Islanders, and American Indians. [55] Despite these findings, another study, using the US MarketScan dataset, reported that prevalence of T1D was higher in male than in female youths (0-17 years). [74] In Germany, the prevalence was estimated to be 1.5 per 1000 in children (0-14 years old) in 2008. The prevalence rates were 0.4, 1.5, and 2.6 per 1000 for the age groups 0-4 years, 5-9 years, and 10-14 years, respectively. [76] In the UK, data from the population-based Yorkshire Register of Diabetes in Children and Young People showed that the incidence for non-south Asians (21.5 per 100 000) was significantly higher than for South Asians (14.7 per 100 000). [79] On a larger scale, EURODIAB analyzed the incidence trends during 15 years and found a more rapid increase in girls aged 5 to 9 years and a slower increase in girls aged 10 to 14 years compared with boys. Boys aged 10 to 14 years tended to have had a higher risk than same age girls of being newly diagnosed with diabetes in central and eastern European countries, with a more accelerated increase in incidence rates than the rest of Europe. [55] Risk factors for the disease: The risk factors for the development of T1D in children remain incompletely understood. The current model holds that T1D arises in genetically susceptible children exposed to environmental triggers. The role of viral infections in the pathogenesis of T1D is supported by epidemiological, serological, and histological studies (Primavera M, et al.). [80] Studies further investigated multiple environmental factors, as potential triggers, such as dietary factors (cow's milk protein), vitamin D, and obesity, with conflicting results. [55] For more details see data in the adult table (Table 6).
Main existing treatment options	Lifelong insulin treatment is needed after diagnosis of stage 3 T1D. The central precept in the management of stage 3 type 1 diabetes is that insulin therapy is mandatory in a patient tailored regimen to prevent DKA and minimize clinically relevant hypoglycemia while achieving the individual's glycemic targets without hypoglycemia in order to reduce the incidence of long-term micro and macrovascular complications. [24]

Indication	Type 1 diabetes in the pediatric population
	Teplizumab is currently the only approved therapy to delay the onset of stage 3 T1D. Higher C-peptide levels have been associated with lower risk of DKA events, lower daily insulin dose, lower risk of retinopathy, lower risk of nephropathy, and lower risk of severe hypoglycemia. [25,81,82]
Natural history of the indicated condition in the untreated population including mortality and morbidity	High-risk individuals (stage 2) have a 75% risk of progression to symptomatic (stage 3) T1D within 5 years, close to 100% risk of progressing to stage 3 in their lifetime. [26] Approximately 40% of T1D patients present with DKA at diagnosis. [28] • Diabetic ketoacidosis is a medical emergency and can be fatal without prompt treatment. • Diabetic ketoacidosis is the leading cause of death in people under 50 years with T1D, contributed to 29% of male deaths and 22% in women. [29] Approximately 80% of adolescents do not achieve glycemic goals, [83] poorly controlled T1D significantly increases mortality. • On average, life expectancy is reduced by approximately 16 years for children diagnosed before the age of 10 and reduced by approximately 10 years if diagnosed with T1D later in life. [84] The EURODIAB study demonstrated that a significant excess mortality (all causes) persisted in European countries in the years following the diagnosis of T1D in childhood, and before the onset of late complications. The SMR was 2.0 and varied from 0 to 4.7 between countries. It was higher in females (2.7) than in males (1.8) but without significant difference by age groups. [85] In the US, data from the Pittsburgh Epidemiology of Diabetes Complications study revealed that the overall mortality in patients with type 1 diabetes was 7.9 per 1000 person-years. [86] In the UK, data from the population-based Yorkshire Register of Diabetes in Children and Young People showed the SMR was 4.1 in T1D patients with early onset (under 15 years). [87] Ischemic heart disease deaths began to emerge in young adulthood for T1D patients with early onset, with an SMR of 13.8 and median age at death of 35 years. [88]
Important co-morbidities	Type 1 diabetes typically presents as a monoglandular autoimmune condition, however, it can also present concomitantly either at diagnosis or later with a variety of other non-glandular and glandular AID. Pediatric T1D-associated AID include autoimmune thyroid diseases (15%-30%), type A gastritis (15%), celiac disease (3%-12%), vitiligo (1%-7%), and Addison disease (0.5%). [35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,89] It has been established in stage 3 T1D that uncontrolled, high levels of blood glucose due to beta cell function loss is a risk factor for short term (such as DKA, CKD) and longer-term complications including chronic microvascular and macrovascular complications that can result in retinopathy, nephropathy, neuropathy and premature CV morbidity and mortality. Hypoglycemia may occur in stage 3 T1D patients who are treated with insulin due to the side effect of insulin treatment. Concomitant medications: Type 1 diabetes patients require lifelong administration of insulin. Insulin therapy includes continuous SC insulin infusion via a pump or multiple daily doses of prandial (injected or inhaled) and basal insulin injection.

AID: Autoimmune Diabetes; CKD: Chronic Kidney Disease; CV: Cardiovascular; DKA: Diabetic Ketoacidosis; SC: Subcutaneous; SMR: Standardized Mortality Ratio; T1D: Type 1 Diabetes; UK: United Kingdom; US: United States; WHO: World Health Organization.

PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical toxicology studies summarized in this document are intended to assess nonclinical safety of teplizumab and support registration for the delay of onset of stage 3 type 1 diabetes of T1D in at-risk individuals. Teplizumab is a humanized immunoglobulin G1 (IgG1) mAb, specifically binds to human CD3+ T cells and cross-reacts with chimpanzee CD3+ T cells. Teplizumab does not cross-react with CD3+ T cells of commonly used animal species (rodents and non-rodents). Due to ethical concerns and restrictions, the toxicology package for teplizumab is limited to a single-dose study in chimpanzees (Study T-2002-009) and additional toxicology studies were conducted using a mouse surrogate anti-CD3 in CD-1 mice (see below). In chimpanzee, the primary pharmacologic effect was a reduction in circulating CD3+ T cells after a single SC administration of teplizumab at doses of 0.1, 1, or 10 mg/kg and were returned to baseline values by 42 days post-dose at the low and mid doses. There were no injection site observations and treatment-related effects on safety pharmacology endpoints, including body temperature, electrocardiogram (ECGs), heart rate, blood pressure, or respiratory rate, following a single-dose up to 10 mg/kg SC. At the highest tested dose (10.0 mg/kg SC) there was profound suppression of cells that led to non-neoplastic B-cell lymphoproliferative disease in chimpanzees followed by mortality approximately 30 days later due to a recurrent viral infection (Epstein-Barr Virus [EBV]-like lymphocryptovirus infection). Teplizumab-treated chimpanzees also showed transient dose-dependent increases in circulating levels of tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-10 and interferon gamma (IFN-γ).

To evaluate the nonclinical safety profile, single and repeat-dose toxicology studies, reproductive and developmental toxicology studies, and a cytokine release study were performed in CD-1 mice using the anti-CD3 mouse surrogate antibody. The surrogate antibody was well tolerated in mice in single-dose studies up to 60 mg/kg SC or 30 mg/kg IV, and in repeat-dose studies following 6 consecutive daily doses up to 20 mg/kg SC or 0.3 mg/kg IV. No target organ toxicity was identified in the single or repeat-dose studies unrelated to the known anti-CD3+ activity of the surrogate antibody. Lymphocyte counts were reduced in the 6-day study at all dose levels, which was correlated microscopically with a decrease in the cellularity of the thymus. The decrease in thymic cellularity was still present after a 6-week recovery period, but at a lower incidence and severity.

In a 1-month (dose given once every 3 days) repeat-dose study of the surrogate anti-CD3 mouse antibody in CD-1 mice was terminated by the prior sponsor due to pause of clinical program. There were anaphylactic reactions including mortality after the 4^{th} dose at 0.3 mg/kg IV and after the 5^{th} dose at 3.0 mg/kg IV. Clinical signs in the decedents, including swollen nose, irregular breathing, hypoactivity, and recumbency, occurred within minutes of injection. No anaphylactic reactions or mortality were observed at 20 mg/kg IV. The no observed adverse effect level (NOAEL) in the 1-month study was not established.

An invitro study of the cytokine release potential of teplizumab in normal peripheral blood mononuclear cells (PBMC) from healthy subjects versus PBMC from psoriatic patients (Study MGA031-HL003) demonstrated no difference between the two groups, suggesting no enhanced cytokine release to teplizumab in subjects with an altered immune response. In a single dose cytokine release study in mice given surrogate by SC, there was a slight increase in serum concentrations of IL-6 and IL-12, consistent with a mild induction of cytokine release.

In the fertility studies, surrogate antibody did not affect fertility or reproductive performance in male or female CD-1 mice. In embryo-foetal development toxicity in mice, the NOAEL for the embryo-fetal development was 0.3 mg/kg. In the pre and postnatal development (PPND) study, maternally-exposed F1 progeny, decreased fertility and decreased antibody titers for the primary immunoglobulin M (IgM) and IgG responses and secondary IgG response to keyhole limpet hemocyanin (KLH).

Juvenile animal studies were not conducted for teplizumab or surrogate and the toxicity profile was not characterized in juvenile animals.

Genotoxicity and carcinogenicity studies were not conducted with teplizumab or the surrogate antibody, consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S6R1 guidance for biological pharmaceuticals because of their biological activity as immunosuppressive agents. Due to lack of target expression in rodent species, it is not possible to conduct carcinogenicity studies with teplizumab. As it is a protein, no genotoxic/mutagenicity risk expected to humans.

Table 8 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Key issues identified from acute or repeat-dose toxicity studies. • **Reduction in circulating lymphocyte sub-sets (CD3+ cells)**, a primary pharmacology effect, seen with ***teplizumab*** and ***surrogate***.	
Teplizumab: After a single SC administration of teplizumab to chimpanzees at doses of 0.1, 1, or 10 mg/kg. Effects at 0.1 and 1 mg/kg were recovered during treatment-free period, however at the highest test dose marked suppression of T-cells led to non-neoplastic B-cell lymphoproliferative disease in chimpanzees followed by mortality approximately 30 days later due to a recurrent viral infection (EBV-like lymphocryptovirus infection). 1 mg/kg was considered as NOAEL dose in the study and the exposure (Area-Under the Curve [AUC]) at this dose was approximately 17 x higher than clinical dose in the PROTECT (clinical Phase-3) study.	• Reduction in circulating lymphocytes is a known pharmacology effect for teplizumab, an anti-CD3 antibody and this effect is relevant to humans. Decreased lymphocyte count was seen with teplizumab at clinical dose in T1D patients (see [Part II SVII]). • Lymphopenia is considered as an important identified risk (see [Part II SVII]).
Surrogate: After single (60 mg/kg SC or 30 mg/kg IV) and repeated doses (once daily SC (0.03, 0.3 or 20 mg/kg) OR IV (0.3 mg/kg) for 6 days), surrogate was well tolerated in mice up to 6 days. Mainly pharmacology mediated effects (reduction in lymphocyte counts) were seen and are consistent with those seen with teplizumab. In the 6-day study, myeloid hyperplasia was observed in the bone marrow of the femur and sternum but was not considered adverse and this finding were resolved during the recovery period. The NOAELs for the surrogate antibody were 20 mg/kg SC and 0.3 mg/kg IV based on the absence of adverse toxicity at the highest tested dose levels. • **Decreased T-cell dependent antibody response (TDAR):** TDAR was not studied in adult animals either with teplizumab or surrogate. In the PPND mice study with	• Although TDAR measurements were not performed in adult animals following teplizumab or surrogate, due to decreased lymphocyte count (pharmacology effect)

Key Safety Findings	Relevance to human usage
surrogate, TDAR was assessed in maternally (F0)-exposed F1 progeny by administration of KLH antigen via intraperitoneal (IP), on Postnatal Day (PND) 28 and rechallenged again on PND70 and blood samples collected on PND35 and PND84 to measure TDAR. F1 mice from the highest test dosed F0 (20 mg/kg) showed a significantly decreased antibody titres for the primary IgM and IgG responses and secondary IgG response to KLH. These changes were accompanied by dose dependent decreased lymphocyte counts (pharmacological effect).	decreased TDAR may be expected in adult animals. Decreased TDAR can be considered potentially relevant finding to humans and this effect can have an impact on the effectiveness of vaccine in humans if given after teplizumab dosing but there are no safety concerns. All age-appropriate vaccinations can be administered prior to teplizumab is initiated and therefore is not considered for inclusion in the list of safety concerns.
• **Increased cytokine release:** ***Teplizumab***- treated chimpanzees also showed transient dose-dependent increases in circulating concentrations of TNF-α, IL-6, IL-10, and IFN-γ. Similarly, in a single dose cytokine release study in mice given ***surrogate*** by SC, there was a slight increase in serum concentrations of IL-6 and IL-12, consistent with a mild induction of cytokine release. In an **in vitro study, *teplizumab*** did not show difference in cytokine profile between normal PBMC from healthy subjects versus PBMC from psoriatic patients, suggesting no enhanced response to teplizumab in subjects with an altered immune response.	• No major difference in cytokine induction profile in PBMCs from healthy and patients with altered immune response is promising but the risk of increased cytokine concentrations with teplizumab in patients cannot be excluded. Cytokine release syndrome (CRS) (including serious cases) has occurred in teplizumab-treated patients. Mechanism of action of teplizumab, class effect together with nonclinical findings, clinical and postmarketing experience provide sufficient evidence to support the causal association with teplizumab and CRS (see [Part II SVII]). The risk of increased cytokine concentrations is thus relevant to humans and CRS is considered as an important identified risk (see [Part II SVII]).
• **Anaphylaxis:** In a 1-month repeat-dose study of the ***surrogate*** given once every 3 days to CD-1 mice, there were anaphylactic reactions including mortality after the 4th dose at 0.3 mg/kg IV and after the 5th dose at 3.0 mg/kg IV. Clinical signs in the decedents, including swollen nose, irregular breathing, hypoactivity, and recumbency, occurred within minutes of injection. No anaphylactic reactions or mortality were observed in the vehicle (buffer/saline) and high (20 mg/kg IV) groups. Similar findings of anaphylaxis followed by morbidity was observed in a pharmacodynamic study following repeated administration of the surrogate or isotype control (same mouse construct as surrogate with a different Fv that does not bind CD3) to non-obese diabetic (NOD) mice for 5 days followed by resumption of dosing 6 weeks after the non-dosing period. Mortality was observed when dosing was resumed with surrogate or isotype control 6 weeks after the non-dosing period. Significant levels of anti-drug antibody (ADA) were detected in all test animals. Mortality in animals given the isotype control implied that ADA were at least partly directed to the shared Fc regions of the surrogate and isotype control and not directly related to pharmacology of the surrogate. In NOD mice study, pre-treatment with platelet activating factor (PAF) antagonist prevented anaphylaxis suggests that anaphylaxis in mice was mediated through IgG1, a mechanism that is common to rodents but not observed in humans.	• The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. The occurrence of serious anaphylactic responses to recombinant proteins is rare in humans. Therefore, observed anaphylaxis in mice after treating with surrogate is not relevant to humans.

Key Safety Findings	Relevance to human usage
Reproductive/developmental toxicity studies: Surrogate was used in the reproductive and developmental (male and female fertility, embryo-foetal, pre- and post-natal) toxicity studies in mice. The following are the identified issues: • In the ***embryo-foetal development*** (EFD) study, highest (20 mg/kg) surrogate dose was identified as maternally toxic and *embryo-foetal toxic* dose in mice. Increased incidence of post-implantation loss is a key finding in the EFD. NOAEL dose for maternal and EFD was 0.3 mg/kg (mid dose). • In the ***pre- and post-natal development*** (PPND) toxicity study in mice (F0) given ***surrogate***, maternally-exposed F1 progeny there was test article-related findings of *decreased male and female fertility and conception/copulation* indices of F1 progeny. The NOAEL for F1 generation reproductive toxicity was 3.0 mg/kg SC.	• Embryo Foetal Development toxicity is an identified hazard based on the findings with surrogate. Due to surrogate use, safety multiples cannot be calculated, therefore, EFD risk cannot be excluded for teplizumab. While extrapolation of safety findings in reproductive and development toxicity studies in mice to humans are unknown and cannot be confirmed in clinical studies, the findings in mice is considered potentially relevant to humans. The use in pregnancy is thus considered a missing information [Part II SVII]. • No relevant fertility findings for humans from nonclinical safety studies in adult (Fo) mice. • Identified hazard (decreased male and female fertility and conception/copulation indices) limited to F1 progeny with surrogate. Translation of observed finding in mouse F1 progeny with use of mouse surrogate to teplizumab in humans is unclear and thus considered missing information.
Safety pharmacology **Cardiovascular (CV) system, including potential effect on the QT interval:** • No formal CV safety study was conducted. However, CV safety parameters (heart rate, ECG) monitored in chimpanzees following a single SC teplizumab dose did not reveal concerns for CV safety. **Respiratory system:** • No formal respiratory safety study was conducted. However, no effects on the respiratory rate in chimpanzees following a single SC teplizumab dose. **Central Nervous system (CNS):** • No formal CNS safety study was conducted. However no neurological effects noted in chimpanzees following a single SC teplizumab dose. **Other toxicity-related information or data** • **Local tolerance:** No specific studies conducted to assess local tolerance of teplizumab. However, neither inflammation nor irritation were observed at the injection site in chimpanzees following a single SC injection of teplizumab.	• Based on nonclinical toxicology/safety pharmacology studies, no relevant safety pharmacology (CV, respiratory, CNS) findings for human. • No relevant findings for humans.

ADA: Anti-Drug Antibody; AUC: Area-Under Curve; CD: Cluster of Differentiation; CNS: Central Nervous System; CRS: Cytokine Release Syndrome; CV: Cardiovascular; EBV: Epstein-Barr Virus: ECG: Electrocardiogram; EFD: Embryo Foetal Development; IFN-γ: Interferon Gamma; IgG: Immunoglobulin G: IgM: Immunoglobulin M: IL: Interleukin; IP: Intraperitoneal; IV: Intravenous; KLH: Keyhole Limpet Hemocyanin; NOAEL: No Observed Adverse Effect Level; NOD: Non Obese Diabetic; PAF: Platelet Activating Factor; PBMC: Peripheral Blood Mononuclear Cells: PND: Postnatal Day; PPND: Pre and Post Natal Development; SC: Subcutaneous: T1D: Type 1 Diabetes; TDAR: T-cell Dependent Antibody Response; TNF-α: Tumor Necrosis Factor Alpha.

No additional nonclinical data have been collected on the use of teplizumab in any special population.

The European Medicines Agency (EMA) Decision on agreement of Paediatric investigation plan (PIP) was on 25 October 2024 for delay the onset of stage 3 T1D indication (P/0386/2024) and indicated that a Juvenile Animal Study or further non-clinical studies were not considered warranted.

In conclusion, nonclinical safety/toxicity profile of teplizumab was characterized in CD-1 mice and chimpanzees either with teplizumab or its mouse surrogate as per ICHS6(R1) guidelines. Nonclinical safety findings such as decreased lymphocyte counts, decreased immune response, increased cytokine concentrations were also identified as risks in clinical studies with teplizumab and considered for inclusion in the list of safety concerns [Part II SVII].

PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

Teplizumab has been in clinical development in T1D for over 20 years with eleven Phase 1/2, 2 and 3 completed clinical trials in T1D, including one Phase 2 in stage 2 T1D (to delay stage 3 clinical T1D) and ten Phase 1/2, 2 and 3 in stage 3 T1D (to delay progression of disease, for regimen selection and characterization of pharmacological properties). One pediatric Phase 2 study in stage 2 T1D is ongoing. In these studies, teplizumab was administered intravenously over a 6, 12, or 14-day dosing regimen in either a single course or two courses separated by 6 or 12 months. Dosing was based on BSA. There is also one observational Phase 3 study ongoing on patients with stage 3 T1D previously treated in one of the completed studies.

Seven phase 2 and 3 completed studies contribute to teplizumab safety data: Protégé, Encore, AbATE, Delay, TN-10, Protégé Extension (no drug administered), and PROTECT.
1008 participants were exposed to teplizumab in these studies. The study regimen and the number of patients exposed to teplizumab in each study are shown in Table 9 below:

Table 9 - Teplizumab dose regimens per study

Study	Total dose (per course)	Duration	Courses of treatment	Total number of participants
PROTECT	9034 µg/m²	12 days	2	217
Protégé	9034 µg/m²	14 days	2	245
	2985 µg/m²	14 days	2	102
	2426 µg/m²	6 days	2	106
Encore	9034 µg/m²	14 days	2	63
	2985 µg/m²	14 days	2	66
	2426 µg/m²	6 days	2	63
Delay[a]	9034 µg/m2	14 days	1	28
	9034 µg/m2	14 days	2	22
AbATE	9034 µg /m²	14 days	2	52
TN-10	9034 µg /m²	14 days	1	44

a The 32 Subjects randomized in this trial were offered 14-day course of open-label Teplizumab treatment after completion of 12-month follow-up: 18 from placebo group and 22 from teplizumab group initiated this second course.

Table 10 - Exposure by planned total dose - Safety population - Teplizumab treatment group

	Patients (%)
One[a] 14-days course of 9034 µg/m²	94 (9.3)
Two 14-days courses of 9034 µg/m²	360 (35.7)
Two 14-days courses of 2985 µg/m²	168 (16.7)
Two 12-days courses of approx. 9.0 mg/m²	217 (21.5)
Two 6-days courses of 2426 µg/m²	169 (16.8)
Total	**1008**

	Patients (%)

a 32 Subjects who completed 12-months of follow-up were offered 14-day course of open-label Teplizumab treatment and 22 initiated this second course.

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OUT=REPORT/OUTPUT/rmp_ex_dosing_s_t_x.rtf (31-MAY-2024 14:46)

Table 11 - Exposure by planned total dose and stage of T1D - Safety population - Teplizumab treatment group

	Patients (%)
Stage 2	
One 14-days course of 9034 µg/m²	44 (100)
Two 14-days courses of 9034 µg/m²	0
Two 14-days courses of 2985 µg/m²	0
Two 12-days courses of approx. 9.0 mg/m²	0
Two 6-days courses of 2426 µg/m²	0
Total	**44**
Stage 3	
One[a] 14-days course of 9034 µg/m²	50 (5.2)
Two 14-days courses of 9034 µg/m²	360 (37.3)
Two 14-days courses of 2985 µg/m²	168 (17.4)
Two 12-days courses of approx. 9.0 mg/m²	217 (22.5)
Two 6-days courses of 2426 µg/m²	169 (17.5)
Total	**964**

a The 32 Subjects who completed 12-months of follow-up were offered 14-day course of open-label Teplizumab treatment and 22 initiated this second course.

Percentages are calculated based on the total number of patients in each stage of type 1 diabetes.
PGM=PRODOPS/SAR446681/OVERALL/RMP/REPORT/PGM/rmp_ex_dosing_s_t.sas
OUT=REPORT/OUTPUT/rmp_ex_dosing_by_stage_s_t_x.rtf (31-MAY-2024 14:46)
T1D: Type 1 Diabetes.

In Protégé and Encore studies, to ensure double-blind, double-dummy design, participants randomized in the 6-day regimen received additionally 8 injections (8 days) of Placebo. For the number of injections summary below Table 12 and Table 13 all injections are counted for the participants randomized in teplizumab arm (teplizumab and placebo).

Table 12 - Exposure - Safety Population - Teplizumab Treatment Group

Number of Teplizumab injections	Patients (%)
Course 1	
6-days courses	
1	2 (1.2)
2	3 (1.8)
4	3 (1.8)

Number of Teplizumab injections	Patients (%)
5	10 (5.9)
6	151 (89.3)
Total	169
12-days courses	
1	1 (0.5)
2	6 (2.8)
3	4 (1.8)
6	1 (0.5)
8	2 (0.9)
9	1 (0.5)
11	13 (6.0)
12	189 (87.1)
Total	217
14-days courses	
1	5 (0.8)
2	5 (0.8)
3	7 (1.2)
4	5 (0.8)
5	9 (1.5)
6	6 (1.0)
7	6 (1.0)
8	3 (0.5)
9	4 (0.7)
11	8 (1.3)
12	11 (1.8)
13	30 (5.0)
14	505 (83.6)
Total	604
Course 2	
6-days courses	
2	2 (2.0)
3	1 (1.0)
4	2 (2.0)
5	4 (3.9)
6	93 (91.2)
Total	102
12-days courses	
4	1 (0.5)
5	1 (0.5)
7	1 (0.5)
8	1 (0.5)
11	5 (2.6)
12	182 (95.3)
Total	191
14-days courses	

Number of Teplizumab injections	Patients (%)
1	4 (1.0)
2	2 (0.5)
3	3 (0.8)
5	5 (1.3)
6	3 (0.8)
7	3 (0.8)
8	2 (0.5)
9	2 (0.5)
10	2 (0.5)
12	6 (1.5)
13	24 (6.0)
14	342 (85.9)
Total	398

18 patients from the placebo arm of the Delay study received an open-label course of Teplizumab, which is summarized in course 2. A total of 1008 patients received at least one injection of Teplizumab.
Percentages are based on the total number of patients receiving at least one dose in each course and within each planned course duration.
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OUT=REPORT/OUTPUT/rmp_ex_injections_s_t_x.rtf (31-MAY-2024 14:46)

Table 13 - Exposure by stage of T1D - Safety population - Teplizumab treatment group

Number of Teplizumab injections	Patients (%)
Stage 2	
Course 1	
14-days courses	
13	3 (6.8)
14	41 (93.2)
Total	44
Stage 3	
Course 1	
6-days courses	
1	2 (1.2)
2	3 (1.8)
4	3 (1.8)
5	10 (5.9)
6	151 (89.3)
Total	169
12-days courses	
1	1 (0.5)
2	6 (2.8)
3	4 (1.8)
6	1 (0.5)
8	2 (0.9)
9	1 (0.5)
11	13 (6.0)
12	189 (87.1)

Number of Teplizumab injections	Patients (%)
Total	217
14-days courses	
1	5 (0.9)
2	5 (0.9)
3	7 (1.3)
4	5 (0.9)
5	9 (1.6)
6	6 (1.1)
7	6 (1.1)
8	3 (0.5)
9	4 (0.7)
11	8 (1.4)
12	11 (2.0)
13	27 (4.8)
14	464 (82.9)
Total	560
Course 2	
6-days courses	
2	2 (2.0)
3	1 (1.0)
4	2 (2.0)
5	4 (3.9)
6	93 (91.2)
Total	102
12-days courses	
4	1 (0.5)
5	1 (0.5)
7	1 (0.5)
8	1 (0.5)
11	5 (2.6)
12	182 (95.3)
Total	191
14-days courses	
1	4 (1.0)
2	2 (0.5)
3	3 (0.8)
5	5 (1.3)
6	3 (0.8)
7	3 (0.8)
8	2 (0.5)
9	2 (0.5)
10	2 (0.5)
12	6 (1.5)
13	24 (6.0)
14	342 (85.9)

Number of Teplizumab injections	Patients (%)
Total	398

18 patients from the placebo arm of the Delay study received an open-label course of Teplizumab, which is summarized in course 2. A total of 1008 patients received at least one injection of Teplizumab.

For each stage of type 1 diabetes, percentages are based on the total number of patients receiving at least one dose in each course and within each planned course duration.

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OUT=REPORT/OUTPUT/rmp_ex_injections_by_stage_s_t_x.rtf (31-MAY-2024 14:46)
T1D: Type 1 Diabetes.

Table 14 - Exposure by age group and gender - Safety population - Teplizumab treatment group

	Patients (%)	
Age group(years)	**Female**	**Male**
8 to <12	123 (32.1)	141 (22.6)
12 to <18	156 (40.7)	292 (46.7)
≥18	104 (27.2)	192 (30.7)
Total	**383**	**625**

PGM=PRODOPS/SAR446681/OVERALL/RMP/REPORT/PGM/rmp_ex_age_gender_s_t.sas
OUT=REPORT/OUTPUT/rmp_ex_age_gender_s_t_x.rtf (14-MAY-2024 16:12)

Table 15 - Exposure by age group, gender and stage of T1D - Safety population - Teplizumab treatment group

	Patients (%)	
Age group(years)	**Female**	**Male**
Stage 2		
8 to <12	8 (42.1)	5 (20.0)
12 to <18	3 (15.8)	13 (52.0)
≥18	8 (42.1)	7 (28.0)
Total	**19**	**25**
Stage 3		
8 to <12	115 (31.6)	136 (22.7)
12 to <18	153 (42.0)	279 (46.5)
≥18	96 (26.4)	185 (30.8)
Total	**364**	**600**

Percentages are calculated based on the total number of patients in each stage of type 1 diabetes.

PGM=PRODOPS/SAR446681/OVERALL/RMP/REPORT/PGM/rmp_ex_age_gender_s_t.sas
OUT=REPORT/OUTPUT/rmp_ex_age_gender_by_stage_s_t_x.rtf (14-MAY-2024 16:12)
T1D: Type1 Diabetes.

Table 16 - Exposure by racial or ethnic origin - Safety population - Teplizumab treatment group

	Patients (%)
Racial origin	
White	761 (75.5)
Black or African American	13 (1.3)
Asian	204 (20.2)
American Indian or Alaska native	3 (0.3)
Multiple	6 (0.6)
Other	11 (1.1)

	Patients (%)
Racial origin	
Not reported	8 (0.8)
Unknown	2 (0.2)
Total	**1008**
Ethnic origin	
Hispanic or Latino	55 (5.5)
Non-Hispanic or Latino	943 (93.6)
Not reported	10 (1.0)
Total	**1008**

PGM=PRODOPS/SAR446681/OVERALL/RMP/REPORT/PGM/rmp_ex_race_ethnic_s_t.sas
OUT=REPORT/OUTPUT/rmp_ex_race_ethnic_s_t_x.rtf (14-MAY-2024 16:15)

Table 17 - Exposure by racial or ethnic origin and stage of T1D - Safety population - Teplizumab treatment group

	Patients (%)
Stage 2	
Racial origin	
White	44 (100)
Total	**44**
Ethnic origin	
Hispanic or Latino	1 (2.3)
Non-Hispanic or Latino	43 (97.7)
Total	**44**
Stage 3	
Racial origin	
White	717 (74.4)
Black or African American	13 (1.3)
Asian	204 (21.2)
American Indian or Alaska native	3 (0.3)
Multiple	6 (0.6)
Other	11 (1.1)
Not reported	8 (0.8)
Unknown	2 (0.2)
Total	**964**
Ethnic origin	
Hispanic or Latino	54 (5.6)
Non-Hispanic or Latino	900 (93.4)
Not reported	10 (1.0)
Total	**964**

Percentages are calculated based on the total number of patients in each stage of type 1 diabetes.
PGM=PRODOPS/SAR446681/OVERALL/RMP/REPORT/PGM/rmp_ex_race_ethnic_s_t.sas
OUT=REPORT/OUTPUT/rmp_ex_race_ethnic_by_stage_s_t_x.rtf (14-MAY-2024 16:15)
T1D: Type 1 Diabetes.

PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 18 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnant women	To avoid potential harm to an unborn fetus through exposure of drug.	Yes	Not applicable
Breastfeeding women	To avoid potential harm to a newborn through exposure of drug from breast milk.	Yes	Not applicable
Patient has a medical condition of serious inter-current illness including significant cardiac disease, significant liver disease, concurrent autoimmune disease, or any other underlying condition, aside from well-controlled asthma, thyroid, or celiac disease, that may significantly interfere with study compliance including all prescribed evaluations and follow-up activity, and measurement of safety and clinical endpoints.	Possibility that these medical conditions may significantly interfere with study compliance including all prescribed evaluations and follow-up activity, and measurement of safety and efficacy endpoints.	No	No relevant safety pharmacology (CV, respiratory, CNS) findings were reported from animal studies [Part II SII]). Teplizumab exposure in patients having these medical conditions does not constitute an additional safety concern.
Patient has a history of malignancy	Immunomodulation could theoretically predispose to recurrence of prior malignancy or viral infections which may lead to *de novo* malignancy (lymphoproliferative disorders).	No	Malignancy has been included as an important potential risk in the list of safety concerns ([Part II SVII]). Information on carcinogenic potential of teplizumab is included in SmPC section 5.3 (Preclinical safety data).
Patient is treated concomitantly by non-investigational products known to affect diabetes (eg, any oral antidiabetic agents, any agents that might stimulate pancreatic beta cell regeneration or insulin secretion) or immunological status (eg, any	Efficacy assessments could be impaired by these medications.	No	The absence of safety data in this patient population does not constitute a safety concern. Teplizumab was not studied in patients taking these drugs as the efficacy results may have been impacted in this population, but

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
immunosuppressive agents including high-dose, extensive topical, or systemic glucocorticoid therapy short courses, ie, approximately 2 weeks or less, for transient conditions is allowed).			no specific safety issues are foreseen. In stage 3 T1D studies, patients who received standard of care treatment for T1D (eg, standard of care insulin replacement therapy), had no additional safety concerns. Information related to interaction of Teizeild with other medicinal products is provided in Summary of Product Characteristics (SmPC) section 4.5 Interaction with other medicinal products and other forms of interactions.
Patient has active infection including active or latent tuberculosis (TB), serologic evidence of acute infection with EBV and Cytomegalovirus (CMV) or any infectious mononucleosis-like illness, serologic evidence of current or past infection with Human Immunodeficiency Virus (HIV), Hepatitis B, and Hepatitis C.	Teplizumab may lower the ability of the immune system to fight infections.	No	Serious infections are considered as an important identified risk [Part II SVII]. Warnings and precautions relative to serious infections are made in the labelling SmPC section 4.4 Special warnings and precautions of use; Package Leaflet [PL] sections 2 What you need to know before you are given Teizeild and 4 Possible side effects).
Patient has either received/planned to receive a live-attenuated vaccination within 8 weeks prior treatment, or up to 12 months after last dose. Patient has either received/planned to receive an inactivated/messenger ribonucleic acid (mRNA) vaccine within 2 weeks prior treatment or 6 weeks after each treatment course.	Safety with live-attenuated vaccines has not been studied. Teplizumab may interfere with immune response and decrease vaccine efficacy.	No	Due to the immunomodulatory nature of teplizumab, it is possible to time vaccinations around treatment course to minimize these effects. Patients will be administered all age-appropriate vaccinations prior to starting teplizumab treatment. Warnings / precautions and recommendations relative to vaccinations are made in the labelling (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).

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patient has Baseline Laboratory Abnormalities in Complete Blood Counts or Liver Enzyme tests, such as: • Lymphocyte counts less than 10^9 lymphocytes/L • Hemoglobin less than 100 g/L • Platelet count less than 150 x 10^9 platelets/L • Absolute neutrophil count less than 1.5 x 10^9 neutrophils/L • Elevated alanine transaminase (ALT) or aspartate aminotransferase (AST) greater than 2 times the upper limit normal (ULN) or bilirubin greater than 1.5 times ULN	Teplizumab may cause transient decrease of certain blood cells levels (or counts) and increased liver enzymes due to its mechanism of action.	No	Lymphopenia and CRS are considered as important identified risks (Part II SVII). Warnings/precautions and recommendations are made in the labelling (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).

ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; CMV: Cytomegalovirus; CNS: Central Nervous System; CRS: Cytokine Release Syndrome; CV: Cardiovascular; EBV: Epstein-Barr Virus; HIV: Human Immunodeficiency Virus; mRNA: Messenger Ribonucleic Acid; PL: Package Leaflet; SmPC: Summary of Product Characteristics;T1D: Type 1 Diabetes; TB: Tuberculosis; ULN: Upper Limit of Normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as: rare or very rare adverse reactions, adverse reactions with a long latency, adverse reactions caused by cumulative exposure beyond two courses.

The clinical development programme can detect adverse drug reactions that are uncommon (≥1/1000 to <1/100) or more frequent. Indeed, with approximately 1000 patients exposed in the Phase 2/3 clinical program, the probability to observe at least one occurrence of an adverse event (AE) in the teplizumab group is 95%, if this event truly occurs in at least 0.003% of the population, meaning that AEs with a frequency greater than 1 in 333 could be detected in the teplizumab group with a 95% probability.

Cumulative effects are not anticipated due to the short half-life of teplizumab, extensive metabolism and lack of tissue accumulation.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 19 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. However, a total of 13 pregnancies occurred in clinical development with possible exposure to teplizumab. Twelve pregnancies occurred in 10 patients exposed to teplizumab; two of these pregnancies were during teplizumab treatment. One pregnancy occurred in a female partner of a male patient exposed to teplizumab.
Breastfeeding women	Breastfeeding women were not included in clinical development program.
Patients with relevant comorbidities • Patients with renal impairment • Patients with CV impairment • Patients with hepatic impairment • Patients with pulmonary impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials.	Patients with comorbidities such as significant cardiac, vascular, pulmonary, gastrointestinal, neurologic, hematologic, rheumatologic, oncologic, psychiatric diseases, or immune deficiency, or any condition that may interfere with study compliance, measurement of safety and clinical endpoint, were not included in controlled clinical studies.
Populations with relevant different ethnic origin	Type 1 diabetes incidence has been known to typically occur in a predominantly Caucasian population and this is reflected in teplizumab clinical program. Although no racial or ethnic groups were excluded from clinical studies, most participants (93.4%) exposed to teplizumab were not Hispanic or Latino ethnicity. The race most represented were white (75.1%) followed by Asian (20.6%), black or African American (1.3%), and other races with lower than 1% representation.
Paediatric population	In clinical studies, 70.1% of participants exposed to teplizumab were older than 8 and younger than 18 years-old (n = 694). (see Table 14 and Table 15) The safety and effectiveness of teplizumab have not been yet established in pediatric patients younger than 8 years of age.
Elderly population	Elderly population (65 years and older) has not been included in clinical development. Stage 2 T1D is largely a condition that occurs in pediatric and non-elderly adult patients.
Subpopulations carrying known and relevant genetic polymorphisms	Not applicable
Other	Not relevant.

CV: Cardiovascular; T1D: Type 1 Diabetes.

Pregnant and breastfeeding women

Very limited data are available concerning the use of teplizumab in pregnant or breastfeeding women. Outcomes for the 12 pregnancies which occurred in 10 patients exposed to teplizumab in the development program (Protégé, Encore, Study 1, Protégé extension, PROTECT) include

7 normal neonates, 2 elective terminations, 1 spontaneous abortion, 1 premature labor, and 1 unknown lost to follow-up. One pregnancy in a female partner of a male patient exposed to teplizumab had no complications. In the subject with the spontaneous abortion, the time from last dose of teplizumab to time of conception was approximately 20 months. The investigator assessed the event of spontaneous abortion as unlikely related to the study drug and suggested the subject's T1D and Grave's disease as an alternate cause of the event.

Data is also available from pre-clinical animal studies [Part II SII]. In animal reproduction studies, mice were given an anti-CD3 mouse surrogate antibody SC during organogenesis through lactation. Pups born to dams administered the murine surrogate antibody during pregnancy showed a reduction in the adaptive immune response consistent with the expected pharmacology. In an embryo-fetal developmental toxicity study, increase in post-implantation loss occurred in the 20 mg/kg group of pregnant mice, in the presence of maternal toxicity. The 20 mg/kg dose is equivalent to a BSA-based dose of 743 800 mcg/m^2.

However, pregnant and breastfeeding women are part of the target population. Therefore, the use of teplizumab in pregnant or breastfeeding women is considered as missing information. (see Section SVII.3.2).

Patients with relevant comorbidities

Teplizumab has not been studied in patients with underlying medical conditions aside from well controlled asthma, thyroid disease, or celiac disease. Patients with relevant comorbidities were excluded from clinical trials due to methodological reasons and use of teplizumab in these populations was not considered a safety concern.

Metabolism and clearance of teplizumab do not depend on renal or hepatic function. It is not anticipated that exposure to teplizumab will affect patients with hepatic and renal impairment differently from the studied population.

Population with relevant different ethnic origin and different race

To date, there is no information to suggest that patients of specific age, racial or ethnic origins are adversely affected by teplizumab.

Pediatric population

Use of teplizumab in children 8-years-old and older has been studied in the development program. However, long-term safety in this population aged 8 to < 18 is considered as missing information (see Section SVII.3.2). Use of teplizumab in children younger than 8 years-old has not been established yet.

Elderly population

Use of teplizumab in patients older than 65-years-old has not been studied. Stage 2 type 1 diabetes is largely a condition that occurs in pediatric and younger adult patients. Treatment of elderly is thus expected to be less common. Based on data in exposure of older adults to teplizumab, it is not anticipated that the risks in elderly population would differ from the known safety profile.

Subpopulations carrying known and relevant genetic polymorphisms

To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of teplizumab in the currently proposed indication(s).

PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

Exposure has been calculated based on sales figures (weighted average of 17 vials = 1 patient, assuming that approximately 25% of adult patients with BSA >1.94 m^2 required the use of 24 vials, as opposed to 14). This method of calculation is susceptible to mild stocking effect.

SV.1.2 Exposure

Table 20 - Exposure by indication and <gender><age group>

Indication	Sex			Age (years)				
	Male	Female	Unknown	<8	8 to ≤ 16	>16 to ≤65	>65	Unknown
Overall	119	151	29	1	67	183	5	43[a]
Stage 2 T1D, (DoO)	117	147	28	1	66	178	5	42
Stage 3 T1D, (off-label)	2	4	1	0	1	5	0	1

a Among the Unknown age, 18 cases have reported age groups as follows: 1 adolescent, 10 adult, 7 child. Because the brackets for those age groups in the database are different from the brackets in the table (ex. Adults are up to 18 not 16), those cases are included in the unknown age despite having age group reported.

±The total estimated exposure based on the method described above [Section SV.1.1] is 347. The numbers in this Table 20 are from the 299 cases available in the pharmacovigilance safety data base through the DLP. Data on age and gender of patients who reported AEs in solicited and spontaneous postmarketing sources are reported, if captured.

AE: Adverse event; DLP: Data Lock Point; DoO: Delay of onset; T1D: Type 1 Diabetes.

Table 21 - Exposure by indication and <dose> <formulation> <region>

Indication	Dose	Formulation	Region	
	Single course of 11240 mcg/m^2	**Intravenous**	**USA**	**EU and non-EU country**
Overall	**299**	**299**	**293**	**6**
Stage 2 T1D, (DoO)	**292**	**292**	**286**	**6**
Stage 3 T1D (off label)	**7**	**7**	**7**	**0**

±The total estimated exposure based on the method described above [Section SV.1.1] is 347. The numbers in this Table 21 are from the 299 cases available in the pharmacovigilance safety data base through the DLP. Data on age and gender of patients who reported AEs in solicited and spontaneous postmarketing sources are reported, if captured.

AE: Adverse Event; DLP: Data Lock Point; DoO: Delay of Onset; EU: European Union; T1D: Type 1 Diabetes; USA: United States of America.

From the initial approval of teplizumab on 17 November 2022 in the US (to delay the onset of stage 3 T1D in adults and pediatric patients aged 8 years and older with stage 2 T1D, with only one approved dosing regimen) to the DLP of this RMP date, 31 August 2024, a total of 347 patients were estimated to have been exposed to teplizumab.

PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

The properties of teplizumab do not indicate a potential for misuse for illegal purposes.

A drug abuse liability assessment study was not performed with teplizumab as the compound has no or only a limited ability to cross the blood-brain barrier with negligible exposure in the brain and has shown no propensity for eliciting any neurological effects in toxicology studies. Potential for misuse of teplizumab for illegal purposes is considered low as this product is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use, such as known pharmacological addictive effects.

PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

- **Neutropenia** associated with the use of teplizumab was transient and rarely severe. The main clinical consequence of severe neutropenia would be a risk of serious infection which is already an important identified risk for teplizumab. Patient with early stage or new-onset T1D are typically not at higher risk for serious infections, as this is more associated with longer latency and complications from poor glycemic control, [90,91] which do not apply to the target population for teplizumab treatment. Neutropenia is addressed in SmPC sections 4.2 Posology and Method of administration and 4.8 Undesirable effects: obtain a complete blood count, which includes absolute neutrophil count, prior to initiating teplizumab. White blood cell monitoring (including neutrophils count) is also required during the treatment (SmPC section 4.4 Special warnings and precautions of use).

  In clinical development, neutropenia occurred in 36.9% of teplizumab treated patients, the majority were grade 1 or 2 in severity and resolved spontaneously with a nadir around day 8 of treatment and resolved within 4 weeks of treatment; 0.3% of subjects experienced neutropenia of grade 4 in severity. Serious adverse events (SAEs) of neutropenia occurred in 0.2% of teplizumab treated patients, 0.3% of patients interrupted and 1.1% permanently discontinued teplizumab treatment due to AEs of neutropenia.

  Serious clinical consequences in association with neutropenia, such as febrile neutropenia, have not been reported in clinical development or postmarketing setting. All postmarketing cases of neutrophil count decrease were non-serious and there has been only one serious case of white blood cell count decrease (not specifically neutropenia) associated with CRS leading to hospitalization.

  Therefore, based on the above, neutropenia is not considered important for inclusion in the list of safety concerns in the RMP.

- **Anemia** associated with the use of teplizumab was transient and rarely severe. In clinical development, anemia occurred in 7.8% of teplizumab treated patients, 0.2% were grade 3 in severity. 1.2% of patients required treatment discontinuation due to hemoglobin decrease and 0.2% due to anemia. Anemia/hemoglobin decrease resolved within 2-4 weeks of treatment with rare exceptions. Few non-serious cases of anemia have been reported in postmarketing data. Serious clinical consequences have not been reported as a result of anemia in either clinical development or postmarketing data. Anemia is addressed in SmPC section 4.2 Posology and method of administration: obtain complete blood count, which includes red blood cell count and laboratory parameters for hemoglobin, is required prior to initiating teplizumab.

  Therefore, based on the above, anemia is not considered important for inclusion in the list of safety concerns in the RMP.

- **Thrombocytopenia** associated with the use of teplizumab was transient and rarely severe. In clinical development, thrombocytopenia occurred in 17.3% of teplizumab treated patients, the majority were grade 1 in severity, and none were reported beyond grade 3 (n = 1) in severity and resolved within 2-4 weeks (median duration 3 days) post treatment, with rare exceptions. 0.9% of thrombocytopenia events led to discontinuation and 0.3% led to interruption of therapy. Similarly, only a few cases of thrombocytopenia have been reported in postmarketing data and all were non-serious. Serious clinical consequences have not been reported in clinical development or postmarketing data as a consequence of thrombocytopenia. Thrombocytopenia is addressed in SmPC section 4.2 Posology and method of administration: obtain complete blood count, which includes platelet count, prior to initiating teplizumab.

  Therefore, based on the above, thrombocytopenia is not considered important for inclusion in the list of safety concerns in the RMP.

- **Vaccinations:** due to the immunomodulatory nature of teplizumab, it is possible that teplizumab may interfere with the immune response to vaccination and decrease vaccine efficacy. In addition, the safety of immunization with live-attenuated (live) vaccines in teplizumab-treated patients has not been studied. Due to the short duration of administration (14-day) and short half-life of teplizumab, it is possible to time vaccinations around treatment course. Patients will be administered all age-appropriate vaccinations prior to starting teplizumab treatment as follows:

  - Live-attenuated vaccinations are not recommended within the 8 weeks prior to starting teplizumab treatment, during treatment, between treatment courses, or up to 52 weeks after completion of final treatment course.
  - Inactivated or mRNA vaccinations are not recommended within the 2 weeks prior to any teplizumab treatment course, during treatment, or up to 6 weeks after completion of any treatment course.

  Therefore, vaccination is not considered important for inclusion in the list of safety concerns in the RMP. Warnings and precautions and recommendations relative to vaccinations prior to, during and after treatment with teplizumab are made in the labelling (SmPC sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions of use).

- **Liver function tests abnormalities**: Liver enzymes (ALT, AST) and bilirubin elevations were observed in teplizumab-treated patients, both in the context of CRS and in patients without CRS, however presumably due to release of cytokines. In the pool of 7 clinical trials, ALT or AST elevations were reported in approximately 24% of teplizumab-treated patients (ALT increased 23.6%, AST increased 24%) compared to approximately 10% (ALT increased 7.9%, AST increased 14.3%) of placebo-treated patients during the treatment course. On laboratory analysis, 7.8% of teplizumab-treated patients experienced a peak ALT >3 x ULN compared to 1.7% in placebo-treated patients. For AST, 5.3% of teplizumab-treated patients experienced a peak AST >3 x ULN compared to 1.1% in placebo-treated patients. It should be noted that, per label, teplizumab treatment should be discontinued in patients who develop elevated ALT or AST more than 5 x ULN or bilirubin more than 3 x ULN. Most liver enzyme elevations were transient and resolved within weeks of drug discontinuation or treatment without evidence of long-term sequelae. In addition, pattern of liver enzyme elevation is consistent with that seen from effect of cytokine release

during partial agonism of T-cells with AST, ALT, and bilirubin increasing simultaneously, rather than a delayed rise in bilirubin seen with drug-induced liver injury.

Postmarketing data demonstrated non-serious events of hepatic enzyme increase in <10% of exposed population and blood bilirubin increase in <1% of exposed population in line with clinical experience as far as severity, association with release of cytokine symptomatology, and time to resolution.
Liver function test abnormality indicative of CRS symptoms will be followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, with the risk minimization messages in the product information (PI): liver enzymes and bilirubin will be monitored prior to and during the treatment with teplizumab, with specific recommendation to treat CRS, pause and resume or discontinue the treatment with teplizumab based on baseline laboratory parameters (SmPC sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions of use) are adhered by prescribers.

Therefore, liver function test abnormality is not considered important for inclusion in the list of safety concerns in the RMP.

- **Hypersensitivity:** Hypersensitivity reactions have been observed in teplizumab-treated patients in clinical trials at rates 2 to 3-fold higher than in placebo/control patients. Most common symptoms included rash, urticaria and peripheral or generalized edema. A case of anaphylaxis (with hypoxia and bronchospasm) was observed in one teplizumab-treated patient who was hospitalized. Hypersensitivity reactions have also been reported in teplizumab-treated patients in postmarketing. Although hypersensitivity reactions (including severe and serious events) may occur with teplizumab, it is considered sufficient to reflect those in the SmPC and no further specific characterisation is considered necessary, by adequate information in the SmPC - sections 4.4 Special warnings and precautions of use and 4.8 Undesirable effects- and prescription medicine only.

  Additionally, teplizumab is contraindicated in patients who have had severe hypersensitivity reactions, including anaphylaxis, to teplizumab or any of its excipients (SmPC section 4.3 Contraindications). The risk is outweighed by the benefits from the use of teplizumab. Therefore, based on the above, hypersensitivity is not considered important for inclusion in the list of safety concerns in the RMP.

- **Potential harm from medication errors or overdose:** Thus far, no cases of overdose with teplizumab have occurred in clinical trials or postmarketing. The currently approved dosing regimen(s) and suggested pre-medications have been optimized in development to improve tolerability and reduce the frequency of CRS and lymphopenia. Preparing the infusion solution according to the instructions detailed in SmPC section 6.6 (Special precautions for disposal and other handlings) is also recommended to avoid any medication error that could potentially increase the risk of CRS and lymphopenia depending on severity and timing. CRS and lymphopenia can occur in any treated patient without predictive factors on the approved regimen (see Table 29 for CRS and for Table 30 Lymphopenia). CRS and lymphopenia from overdose with clinical consequences, even serious, are expected to occur at a low frequency considered to be acceptable in relation to the severity of the indication treated. In addition, CRS and lymphopenia will be followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting.

Information and recommendation related to CRS and lymphopenia are provided in the SmPC (sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions of use).

- **Potential for off-label use**: Off-label use to date has been infrequent, occurring in two scenarios thus far: stage 2 patients younger than 8 years of age and in patients 8 years and older with stage 3 T1D receiving the stage 2 regimen. In stage 3 T1D patients, safety has been extensively assessed: teplizumab's safety profile is known based on the large established clinical safety database that includes approximately 700 teplizumab-treated children 8 years and older in completed clinical T1D trials [Part II SIII]. The safety profile is consistent and predictable across age groups, potential safety risks in children can be mitigated through clinical measures. Safety data are currently being generated in children 0 to <8 years of age in an ongoing study (PETITE-T1D study protocol, CTD 5.3.5.2). Currently treatment of patients <8 years of age are not approved for marketing authorization in any territory. Potential for off-label use is not considered important for inclusion in the list of safety concerns in the RMP.
- **Potential for transmission of infectious agents:** The aseptic manufacture of teplizumab is validated and carried out in accordance with the "EU Guidelines to Good Manufacturing Practice for Medicinal Products for Human Use, Annex 1". However, this product requires preparation (dilution), and infusion within a specified time frame (SmPC sections 4.2 Posology and method of administration and 6.6 Special precautions for disposal and other handling) to lower the risk of transmission of any infectious agent introduced during the preparation process. Given these known risks, no further characterization is needed. This risk can be followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. Therefore, potential for transmission of infectious agents is not considered important for inclusion in the list of safety concerns in the RMP.
- **Immunogenicity:** Teplizumab is a humanized mAb characterized as low to moderate risk of immunogenicity potential. Potential benefits of teplizumab treatment outweigh the possible immunogenic risks. While 50%-92% of clinical trial subjects who received a single treatment course developed ADAs, many of which appear to be neutralizing based on the limited data, the benefit of teplizumab in delaying onset to clinical diagnosis of T1D as well as preservation of c-peptide levels in both at-risk and in newly diagnosed subjects has been shown to be superior to that of control subjects. Safety risks from immunogenicity are low as most of the AEs (which are transient and manageable) appear to be related to drug treatment and not related to immunogenicity. Therefore, immunogenicity is not considered important for inclusion in the list of safety concerns in the RMP.
- **Risks related to the administration procedure:** Administration of teplizumab requires IV infusion. Known risks related to obtaining IV access apply as result of route of administration (bruising, bleeding, clotting, risk of infection). However, they do not impact the risk-benefit profile of teplizumab treatment, and therefore this risk is not considered important for inclusion in the list of safety concerns in the RMP.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table 22 - Important identified risk considered for inclusion in the list of safety concerns: Cytokine release syndrome

Cytokine release syndrome	
Scientific evidence that has led to the inclusion	Class effect: Drugs known to cause CRS [92,93,94] include anti-CD3 or anti-T cell mAbs, particularly T cell-depleting and T cell-agonistic antibodies (muromonab, visilizumab, blinatumomab) and other immune modulatory antibodies such as tocilizumab (anti-IL-6 receptor) and rituximab (B cell depleting anti-CD19). Mechanism of action: teplizumab causes partial T cell CD3 agonism which leads to increased cytokine secretion as part of its immunomodulatory mechanism of action. Clinical evidence: Cytokine release syndrome (6.4% including 0.9% serious cases) has occurred in teplizumab-treated patients. From the postmarketing experience, 2.6% of patients reported CRS, 0.8% of cases were serious. Mechanism of action of teplizumab, together with pre-clinical findings, and clinical and postmarketing experience provided evidence to support the causal association with teplizumab and CRS.
Risk-benefit impact	Serious CRS may occur with teplizumab. This risk can be minimized by following proper dosing regimen and risk minimization measures such as premedication and laboratory monitoring. No cases of life-threatening (grade 4) CRS have been reported in teplizumab-treated patients. The risk is outweighed by the benefits from the use of teplizumab.

CD: Cluster of Differentiation; CRS: Cytokine Release Syndrome; IL: Interleukin; mAb: Monoclonal Antibody.

Table 23 - Important identified risk considered for inclusion in the list of safety concerns: Lymphopenia

Lymphopenia	
Scientific evidence that has led to the inclusion	Mechanism of action: Due to its mechanism of action, ie, partial T-cell activation, release of cytokines and expression of integrins in lymphocytes and cell-adhesion molecules in endothelial cells, teplizumab is expected to cause transient lymphopenia believed to be the result of lymphocytes margination (not depletion). Clinical evidence: Lymphopenia (including serious cases) have been observed in patients treated with teplizumab in both clinical trials and postmarketing settings. In clinical trials, lymphopenia (including serious events, grade 3 and 4) was the most reported AEs with higher frequency in teplizumab-treated patients compared to placebo/controls. From the postmarketing experience, approximately 15% of patients reported lymphopenia.
Risk-benefit impact	Lymphopenia is considered an important identified risk due to its frequency and relation with the mechanism of action of teplizumab. However, vast majority of cases of lymphopenia observed in teplizumab-treated patients were non-serious, transient, and self-resolving. This risk can be minimized by following proper dosing regimen and risk minimization measures such as laboratory monitoring. The risk is outweighed by the benefits from the use of teplizumab.

AE: Adverse Event.

Table 24 - Important identified risk considered for inclusion in the list of safety concerns: Serious Infections

Serious Infections	
Scientific evidence that has led to the inclusion	Clinical evidence: Serious bacterial and viral infections have occurred in teplizumab-treated patients. In clinical trials, teplizumab-treated patients had a higher rate of serious infections (3.1%) than placebo/control patients (2.2%), including gastroenteritis, cellulitis, pneumonia, abscess, sepsis. In addition, 2 cases of serious of infection (0.6%) were reported in postmarketing.
Risk-benefit impact	The risk is considered manageable and outweighed by the benefits resulting from the use of teplizumab.

Table 25 - Important potential risk considered for inclusion in the list of safety concerns: Malignancies

Malignancies	
Scientific evidence that has led to the inclusion	Immunosuppressive therapies carry a theoretical concern for carcinogenic potential or lack of adequate tumour suppression. Teplizumab is not an immunosuppressant but rather a non-depletive immune modulator. Current safety data available do not support a causal association between teplizumab treatment and malignancy. This constitutes a theoretical risk classified as important potential, as per EMA's request, that will be further characterized in a long-term safety study, Global Registry Study ([Part III]; [Annex 3]).
Risk-benefit impact	There are currently no data from clinical trials and postmarketing indicating an increased risk of cancer in patients treated with teplizumab. Long-term studies are needed to assess the carcinogenic potential of teplizumab.

EMA: European Medicines Agency.

Table 26 - Missing information considered for inclusion in the list of safety concerns: Long-term safety, including growth, in patients aged 8 to <18 years

Long-term safety, including growth, in patients aged 8 to <18 years	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	There are no specific safety concerns in children, as compared to the adult population. However, long-term safety data have not been studied in this population. In such case, 'long term safety in children' may be included as missing information. As limited data have been available at the time of marketing authorization, a pediatric PASS can be considered as a suitable method of collecting post-approval safety data in children. Additional data will be collected through a long-term Global Registry Study which will follow safety, and growth as per routine clinical practice ([Part III]; [Annex 3]).
Risk-benefit impact	Additional safety data, including growth, are needed to characterize the long-term safety profile in this pediatric population.

PASS: Post Authorization Safety Study.

Table 27 - Missing information considered for inclusion in the list of safety concerns: Use during pregnancy

Use during pregnancy	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	Although there is insufficient data on teplizumab, monoclonal antibodies can be actively transported across the placenta, and teplizumab may cause immunosuppression in the utero-exposed infant.
Risk-benefit impact	Available case reports from clinical trials with teplizumab are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. As a precautionary measure, the use of teplizumab is not recommended during pregnancy and in women of childbearing potential not using contraception. Additional data are needed to characterize the safety profile in this population.

Table 28 - Missing information considered for inclusion in the list of safety concerns: Use during breastfeeding

Use during breastfeeding	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	Although there are no data on teplizumab, endogenous maternal IgG and monoclonal antibodies are transferred into human milk.
Risk-benefit impact	There are no data on the presence of teplizumab in either human or animal milk, the effects on the breastfed child, or the effects on milk production. As a precautionary measure breastfeeding should be discontinued during treatment with teplizumab and for 30 days after the last dose of treatment to minimize drug exposure to a breastfed infant. Additional data are needed to characterize the safety profile in this population.

IgG: Immunoglobulin G.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable since first RMP.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for teplizumab:

- Important identified risks:
  - Cytokine release syndrome
  - Lymphopenia
  - Serious infections

- Important potential risk:
  - Malignancies
- Missing information:
  - Long-term safety, including growth, in patients aged 8 to <18 years
  - Use during pregnancy
  - Use during breastfeeding

SVII.3.1 Presentation of important identified risks and important potential risks

Table 29 - Important identified risk: Cytokine release syndrome

<table>
<tr><th>Important Identified Risk</th><th>Cytokine release syndrome</th></tr>
<tr><td>Potential mechanism</td><td>The moderate cytokine increase observed with teplizumab is consistent with the mechanism of action, ie, partial T cell CD3 activation in the initial days of infusion until the T cells become deactivated (anergic or exhausted). Endothelial cells can also be activated, resulting in some of the more severe manifestations. To reduce cytokine-mediated toxicity, in comparison to other anti-CD3 compounds, teplizumab has the Fc portion of the humanized IgG1 engineered, as to disrupt both FcR and complement component C1q binding.</td></tr>
<tr><td>Evidence source (s) and strength of evidence</td><td>Cytokine release syndrome events, including serious, have been observed in teplizumab-treated patients in clinical trials and postmarketing settings. This risk is expected, based on the pharmacologic mode of action of teplizumab.</td></tr>
<tr><td>Characterization of the risk</td><td>The clinical presentation of CRS may include fever, rigors, malaise, fatigue, nausea, vomiting, headache, rash, and diarrhea. There may be involvement of the respiratory (tachypnea, hypoxemia), CV (tachycardia, hypotension), coagulation (elevated D-dimer, decreased fibrinogen), renal (azotemia), hepatic (elevation of transaminases, hyperbilirubinemia) and neurologic (headache, confusion, mental status changes) systems. The timing and magnitude of the effect depends upon the inducing agent and the magnitude of immune cell activation.
Clinical Trial Development
<u>Frequency:</u>
Cytokine release syndrome (Medical Dictionary for Regulatory Activities [MedDRA] Preferred Term “cytokine release syndrome”): 6.4% (65/1008) of teplizumab-treated patients and 1.1% (4/356) of control patients.
• Cytokine release syndrome during course 1: 5.3% of teplizumab-treated patients and 0.8% of control patients.
• Cytokine release syndrome during course 2: 2.0% of teplizumab-treated patients and 0.3% of control patients.
<u>Severity and nature of the risk:</u>
Cytokine release syndrome is usually mild to moderate in severity. No grade 4 or grade 5 CRS events have been observed.
Severity of CRS in 1008 teplizumab-treated and 356 control patients (subject count, number [%]):
<table>
<tr><th>CTCAE grade</th><th>Teplizumab</th><th>Control</th></tr>
<tr><td>Grade 1</td><td>28 [2.8]</td><td>2 [0.6]</td></tr>
<tr><td>Grade 2</td><td>30 [3.0]</td><td>2 [0.6]</td></tr>
</table>
</td></tr>
</table>

Important Identified Risk	Cytokine release syndrome

Grade 3	10 [1.0]	0 [0.0]

CTCAE: Common Terminology Criteria for Adverse Event.

Most often, CRS was observed during the first 3-5 days of dosing. Symptoms, generally mild, included rash, headache, nausea, vomiting, fever and chills/rigors, arthralgias, myalgia, fatigue, and malaise, all considered manageable, transient and reversible.

Management of CRS symptoms was performed using supplementary therapy such as use of locally approved non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and antihistamines or modification of study drug administration. Patients that experienced severe and prolonged CRS symptoms may also have received high potency NSAIDs (eg, ketorolac), acetaminophen with codeine or meperidine, Ondansetron and saline boluses when needed. Glucocorticoids were used for intractable symptoms or ≥grade 3 that could not be relieved with the previously described medication.

CRS caused dose interruption in 0.5% and permanent treatment discontinuation in 1.3% of teplizumab-treated patients.

Teplizumab can cause an increase in liver enzymes, including ALT and AST, with or without elevations in bilirubin, commonly seen in the context of release of cytokine.

Majority of cases were mild to moderate in severity. Only 1 event grade 4 and no grade 5 events were observed.

Alanine transaminase, AST and bilirubin elevations reported in 1008 teplizumab-treated and 356 control patients by Preferred Term (subject count, number [%]):

Preferred Term	Teplizumab	Control
Aspartate aminotransferase increased	242 [24.0]	51 [14.3]
Grade 1	205 [20.3]	48 [13.5]
Grade 2	49 [4.9]	6 [1.7]
Grade 3	14 [1.4]	1 [0.3]
Alanine aminotransferase increased	238 [23.6]	28 [7.9]
Grade 1	196 [19.4]	23 [6.5]
Grade 2	50 [5.0]	6 [1.7]
Grade 3	20 [2.0]	1 [0.3]
Grade 4	1 [<0.1]	0 [0.0]
Transaminases increased	1 [<0.1]	0 [0.0]
Grade 1	1 [<0.1]	0 [0.0]
Blood bilirubin increased	68 [6.7]	10 [2.8]
Grade 1	54 [5.4]	9 [2.5]
Grade 2	19 [1.9]	2 [0.6]
Grade 3	2 [0.2]	0 [0.0]
Bilirubin conjugated increased	37 [3.7]	3 [0.8]
Grade 1	36 [3.6]	2 [0.6]

<table>
<tr><th>Important Identified Risk</th><th>Cytokine release syndrome</th></tr>
<tr><td></td><td>
<table>
<tr><td>Grade 2</td><td>3 [0.3]</td><td>1 [0.3]</td></tr>
<tr><td>Hyperbilirubinaemia</td><td>59 [5.9]</td><td>14 [3.9]</td></tr>
<tr><td>Grade 1</td><td>47 [4.7]</td><td>9 [2.5]</td></tr>
<tr><td>Grade 2</td><td>21 [2.1]</td><td>6 [1.7]</td></tr>
<tr><td>Grade 3</td><td>1 [<0.1]</td><td>0 [0.0]</td></tr>
</table>
Elevations in ALT, AST and bilirubin were mostly transient.

Peak ALT >ULN but <3 x ULN was noted in 513 (50.9%) and 77 (21.6%) of teplizumab-treated and control subjects, respectively. 11 (1.1%) teplizumab subjects and 1 (0.3%) of control had peak ALT >10 x ULN.

Five participants met the criteria of ALT or AST >3 x ULN plus total bilirubin >2 x ULN: 3 were from the Protégé study and 2 were from the PROTECT study. All cases that occurred during treatment (n = 3) were associated with CRS and met the criteria of ALT/AST >3 x ULN plus total bilirubin >2 x ULN by day 3 or 4 after first dose. All events resolved without any long-term sequelae. The two other cases had an alternative etiology (Hepatitis A [n = 1], Biloma [n = 1]).
Seriousness and outcomes:
Serious CRS was reported in 9 (0.9%) of teplizumab-treated patients. All but 1 case occurred during the first course of treatment. All cases of serious CRS resolved without long-term sequelae.
Postmarketing experience
There have been reports of CRS, 6 non-serious (1.7%) and 3 serious (0.8%), consistent with what has been observed in clinical trials.
Background incidence/prevalence
Cytokine release syndrome is a systemic inflammatory syndrome which occurs in response to infections agents or immunotherapy drugs. To date, no observational study estimates specifically the incidence of CRS in the T1D population. However, publications have reported a higher risk for coronavirus disease-2019 (COVID-19) infected diabetic patients to develop a cytokine storm due to the hyperinflammatory microenvironment. 95,96,97,98

Cytokine release syndrome has been associated with multiple mAb treatments, among other treatments, in clinical trials (such as odronextamab, teclistamab, muronomab, rituximab), mostly anti-CD3, CD19, CD20, but not exclusively. No observational study however published CRS incidence data in mAb treated patients. 92,93,94
</td></tr>
<tr><td>Risk factors and Risk groups</td><td>Unknown</td></tr>
<tr><td>Preventability</td><td>Risk minimization measures for this risk include both routine (information in the SmPC/PL, prescription only medicine) and additional measures (Healthcare professional [HCP] and patients guides), (for details see Part V).

It is important to follow strictly the instructions when preparing the infusion solution (detailed in the SmPC) and to administer teplizumab according to the dosing regimen. Teplizumab dose is gradually increased over the first days of infusion (ramping period) and for a 30-minute minimum infusion time to increase tolerability and minimize the risk of CRS development (Part I).

Premedicate with antipyretics, antihistamine and, or antiemetics prior to teplizumab treatment for the first 5 days of dosing.

Teplizumab is not recommended for patients with elevated ALT or AST greater than 2 times the ULN or bilirubin greater than 1.5 times ULN at baseline.</td></tr>
</table>

Important Identified Risk	Cytokine release syndrome
	Monitor liver enzymes, discontinue in those that develop elevated ALT or AST more than 5 times the ULN, and if severe CRS develops consider temporarily pausing dosing or discontinuing treatment.
Impact on the benefit-risk balance of the product	When used in accordance with the label, this risk is considered manageable and outweighed by the benefits resulting from the product's use.
Public health impact	Public health impact is expected to be minimal when used as recommended.

ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; CD: Cluster of Differentiation; COVID-19: Coronavirus Disease-2019; CRS: Cytokine Release Syndrome; CTCAE: Common Terminology Criteria for Adverse Event; CV: Cardiovascular; HCP: Healthcare Professional; IgG: Immunoglobulin G; mAb: Monoclonal Antibody; MedDRA: Medical Dictionary for Regulatory Activities; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PL: Package Leaflet; SmPC: Summary of Product Characteristics; ULN: Upper Limit of Normal.

Table 30 - Important identified risk: Lymphopenia

<table>
<tr><th>Important Identified Risk</th><th>Lymphopenia</th></tr>
<tr><td>Potential mechanism</td><td>Lymphopenia is consistent with the mechanics of action of teplizumab and is believed to be related to margination (expression of integrins in lymphocytes and cell-adhesion molecules in endothelial cells), as a result of the partial agonistic activity of teplizumab, rather than depletion.</td></tr>
<tr><td>Evidence source (s) and strength of evidence</td><td>In clinical trials, lymphopenia was observed in the majority of teplizumab-treated patients (approximately 75%). Serious lymphopenia occurred in only 0.2% of participants in the teplizumab group. This risk is expected, based on the pharmacologic mode of action of teplizumab.
Postmarketing data have not shown increased frequency.</td></tr>
<tr><td>Characterization of the risk</td><td>Clinical trial development
<u>Frequency:</u>
Lymphopenia (MedDRA preferred terms “lymphopenia”, “lymphocyte count decrease”), was the most common AE, reported in 74.5% (751/1008) teplizumab and 12.9% (46/356) control subjects.
• Lymphopenia during days 1-29 of course 1: 70.9% in teplizumab, 2.9 % in control
• Lymphopenia during days 1-29 of course 2: 36.7% in teplizumab, 6.7 % in control
Lymphopenia led to dose interruption in 2.3% of teplizumab-treated patients and rarely led to study drug discontinuation (4 teplizumab [0.4%] and 1 control [0.1%] subjects).
<u>Severity and nature of the risk:</u>
Overall, majority of teplizumab-treated patients (66.5%) experienced mild to moderate lymphopenia. Severe (grade 3) lymphopenia occurred in 42.3% while grade 4 was observed in 3.8% of teplizumab patients.
Severity of lymphopenia in 1008 teplizumab-treated and 356 control patients (subject count, number [%])
<table>
<tr><th>CTCAE grade</th><th>Teplizumab</th><th>Control</th></tr>
<tr><td>Grade 1</td><td>281 [27.9]</td><td>30 [8.4]</td></tr>
<tr><td>Grade 2</td><td>389 [38.6]</td><td>14 [3.9]</td></tr>
<tr><td>Grade 3</td><td>426 [42.3]</td><td>9 [2.5]</td></tr>
<tr><td>Grade 4</td><td>38 [3.8]</td><td>1 [0.3]</td></tr>
<tr><td>Missing</td><td>1 [<0.1]</td><td>0</td></tr>
</table>
</td></tr>
</table>

Important Identified Risk	Lymphopenia
	CTCAE: Common Terminology Criteria for Adverse Event. Lymphopenia was transient in nature. Onset occurred early during the dosing course, peaked around day 5, began to resolve while treatment continued and returned to baseline by day 28. Severe lymphopenia (0.5 X 10^9 cells/L) that lasted for 7 days or longer was uncommon and occurred in 1.9% of subjects receiving teplizumab. The transient lymphopenia was not associated with increased infection risk, which is in line with the drug's mechanism of action. Teplizumab does not lead to T cell depletion. Instead, teplizumab leads to margination of T cells (expression of integrins in lymphocytes and endothelial cells because of the partial agonistic activity of teplizumab). Seriousness and outcomes: Serious lymphopenia was reported in 2 (0.2%) teplizumab-treated patients and occurred during the first course of treatment. **Postmarketing experience** Approximately 15% of patients reported non-serious cases of lymphopenia. One serious case of lymphopenia has been reported. **Background incidence/prevalence:** To date, no observational study estimated specifically the incidence of lymphopenia in the T1D population, as AEs are reported in clinical trials.
Risk factors and Risk groups	Unknown
Preventability	Risk minimization measures for this risk include both routine (information in the SmPC/PL, prescription only medicine) and additional measures (HCP and patients guides), (for details see [Part V]). Teplizumab is not recommended for subjects with preexisting lymphopenia (<10^9 lymphocytes/L). It is important to follow strictly the instructions when preparing the infusion solution and to administer teplizumab according to the dosing regimen. The dosing regimen has been optimized to avoid more prolonged lymphopenia. If prolonged severe lymphopenia (<0.5 x 10^9 cells/L lasting 1 week or longer) develops, the treatment should be discontinued. Monitoring of white blood cells count before and during treatment with teplizumab is required.
Impact on the benefit-risk balance of the product	When used in accordance with the label, this risk is considered manageable and outweighed by the benefits resulting from the product's use.
Public health impact	Minimal

AE: Adverse Event; CTCAE: Common Terminology Criteria for Adverse Event; HCP: Healthcare Professional; MedDRA: Medical Dictionary for Regulatory Activities; PL: Package Leaflet; SmPC: Summary of Product Characteristics; T1D: Type 1 Diabetes.

Table 31 - Important identified risk: Serious infections

Important Identified Risk	Serious infections
Potential mechanism	Immunosuppressive and immunomodulatory agents may enhance the risk for developing infections. Teplizumab is an immunomodulatory agent rather than immunosuppressive. However, immunomodulatory/immunosuppressive agents can enhance the risk of infections. Transient increase in the risk of developing infections may occur.
Evidence source (s) and strength of evidence	Individual diagnosis of serious bacterial and viral infections has occurred in teplizumab-treated patients in clinical trials and postmarketing.

<table>
<tr><th>Important Identified Risk</th><th>Serious infections</th></tr>
<tr><td>Characterization of the risk</td><td>
Clinical trial development

Frequency:
In the safety pool, teplizumab-treated patients had a higher rate of serious infections (3.1%) than control-treated patients (2.2%), including gastroenteritis, cellulitis, pneumonia, abscess, and sepsis.
Infections Grade 3 or above were considered adverse event of special interest (AESI) in clinical trials and occurred in 58 (5.8%) participants exposed to teplizumab versus 12(3.4%) for control participants.
Severity and nature of risk:
In clinical trials, the majority of infections were Grade 1 and 2.
Severity of treatment emergent adverse events (TEAEs) by the Infections and infestations system organ class (SOC) in 1008 teplizumab-treated and 356 control patients (subject count, number [%]):
<table>
<tr><th>CTCAE grade</th><th>Teplizumab</th><th>Control</th></tr>
<tr><td>Grade 1</td><td>456 [45.2]</td><td>167 [46.9]</td></tr>
<tr><td>Grade 2</td><td>198 [19.6]</td><td>65 [18.3]</td></tr>
<tr><td>Grade 3</td><td>23 [2.3]</td><td>7 [2.0]</td></tr>
<tr><td>Grade 4</td><td>2 [0.2]</td><td>0</td></tr>
<tr><td>Missing</td><td>0</td><td>2 [0.6]</td></tr>
</table>
CTCAE: Common Terminology Criteria for Adverse Event.

No fatal cases of serious infections were reported.
Viral infections are important safety events to monitor with immunomodulatory therapy, particularly reactivation of latent deoxyribonucleic acid (DNA) viruses, such as EBV. Due to a younger population enrolled in the teplizumab T1D studies, only 75% (compared to 90% of what would be expected in adults) were EBV seropositive for a history of prior infection at baseline; therefore, new EBV infections were expected in the seronegative participants. Overall, there was no increase of primary EBV infections with teplizumab treatment. However, reactivation of EBV occurred more commonly in teplizumab participants, but they were generally asymptomatic, and viremia, if present, was transient and typically occurred at a single study visit. No serious events of EBV reactivation occurred in clinical trials. Herpes zoster, all non-serious events, were reported in 1.3% of teplizumab-treated patients and 0.3% in control participant.
New asymptomatic CMV infection occurred rarely and was observed at comparable rates in teplizumab and control participants.
Seriousness and outcome:
No specific serious infections occurred at clearly greater frequencies with teplizumab. Many of the uncommon infections reflect the global nature of the T1D population.

Postmarketing experience
Postmarketing data have not shown increased frequency. Two cases of serious of infection (0.6%) were reported: one case of gastrointestinal infection and one case of serious EBV reactivation was reported with prolonged fever and lymphadenopathy.

Background incidence/prevalence:
Patients with T1D and poor glycaemic control had a significantly higher risk for infection (Incidence rate ratio [IRR] 8.47; 95% CI [5.86-12.24]) compared to patients with T2D. Even after accounting for duration of diabetes, patients with T1D showed higher rates of hospitalisation (IRR 1.12; 95% CI [1.01-1.24]) and death because of infection (IRR 1.42; 95% CI [1.03-1.96]).
</td></tr>
</table>

Important Identified Risk	Serious infections
	Serious infections considered for inclusion in the list of safety concerns are documented as following: gastrointestinal infection (Attributable fraction [AF] 8.0%; 95% CI [2.6-12.8]), cellulitis (14.0%; 95% CI [11.3-17.0]) and other skin infections (12.1%; 95% CI [9.5-14.4]), pneumonia (15.3%; 95% CI [11.9-18.5]) and sepsis (20.8%; 95% CI [15.2-26.2]). [90]
Risk factors and Risk groups	Unknown
Preventability	Risk minimization measures for this risk include both routine (information in the SmPC/PL, prescription only medicine) and additional measures (HCP and patients guides), (for details see Part V). Teplizumab is not recommended for patients with: • Laboratory or clinical evidence of acute infection with EBV or CMV • Active serious infection or chronic active infections other than localized skin infections • Absolute neutrophil counts less than $1.5x10^9$ neutrophils/L. Administer all age-appropriate vaccinations prior to starting teplizumab. • Live-attenuated vaccinations are not recommended within the 8 weeks prior to starting teplizumab treatment, during treatment, between treatment courses, or up to 52 weeks after completion of final treatment course. • Inactivated or mRNA vaccinations are not recommended within the 2 weeks prior to any teplizumab treatment course, during treatment, or up to 6 weeks after completion of any treatment course. Monitor patients for signs and symptoms of infection during and after teplizumab treatment. If serious infection develops, treat appropriately, and discontinue teplizumab.
Impact on the benefit-risk balance of the product	When used in accordance with the label, this risk is considered manageable and outweighed by the benefits resulting from the product's use.
Public health impact	Minimal

AESI: Adverse Event of Special Interest; AF: Attributable Fraction; CI: Confidence Interval; CMV: Cytomegalovirus; CTCAE: Common Terminology Criteria for Adverse Event; DNA: Deoxyribonucleic Acid; EBV: Epstein-Barr Virus; HCP: Healthcare Professional; IRR: Incidence Rate Ratio; mRNA: Messenger Ribonucleic Acid; PL: Package Leaflet; SmPC: Summary of Product Characteristics; SOC: System Organ Class; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; TEAE: Treatment Emergent Adverse Event.

Table 32 - Important potential risk: Malignancies

Important Potential Risk	Malignancies
Potential mechanism	Immunosuppressive therapies carry a theoretical concern for carcinogenic potential or lack of adequate tumor suppression. However, teplizumab is not an immunosuppressant, but rather a non-depletive immune modulator.
Evidence source (s) and strength of evidence	Three cases of malignancies were reported during clinical development. Currently, there is insufficient evidence from clinical studies and postmarketing data to establish a relationship between teplizumab and malignancies. The longest trial follow-up duration available in publication is the 7-years follow-up of the AbATE trial (n = 43), and this trial reported no malignancy among the 43 patients treated with two courses of teplizumab (given 1 year apart)[99].
Characterization of the risk	**Clinical trial development** Frequency: Through the DLP (31-Aug-2024), during which teplizumab was used in over 1000 patients with T1D and 1800 patient years follow-up, 1 case of metastatic

Important Potential Risk	Malignancies
	melanoma in a pre-existing lesion has been reported. After the DLP of this document (31-Aug-2024) till cut-off date (28-Feb-2025), a case of low-grade glioneuronal neoplasm was reported and a signal evaluation was performed and adjudicated not to be a risk. Two cases were reported in clinical studies involving indications other than T1D, both in transplant patients undergoing concomitant immunosuppressive treatment: 1 case of a recurrent squamous cell carcinoma and 1 case of non-malignant lymphoproliferative syndrome associated with EBV reactivation. Severity and nature of risk: The case of squamous cell carcinoma was grade 2, while metastatic melanoma, lymphoproliferative syndrome and low-grade glioneuronal neoplasm were grade 3. There were no cases of grade 4 and no fatalities reported. The case of squamous cell carcinoma was reported in a clinical trial entitled "Phase 1 Trial of Humanized Non-activating Anti-CD3 Monoclonal Antibody in the Treatment of Renal Allograft Rejection (Study 8223)". The participant developed squamous cell carcinoma about 5 months after receiving 10 out of 14 protocol stipulated teplizumab infusions of 5 mg/day for a total cumulative dose of 50 mg. The participant was on multiple concomitant immunosuppressant medications for the treatment of renal transplant rejection. The investigator indicated that this event was a recurrence and was assessed as not related to teplizumab. The metastatic melanoma case was reported from the Protégé study (CP-MGA031-01). During participation, the participant received 4 out of the 14 scheduled study drug infusions (cumulatively approximately 0.484 mg) and was permanently discontinued from the study due to bilirubin elevation. The participant had a long-standing history of multiple nevi with diagnosis of dysplastic nevus syndrome. The lesion of interest was first noted approximately 2 years prior to participating in the trial without any prior consultations and had changed appearance over the year prior to the diagnosis of metastatic melanoma, 189 days after teplizumab treatment. The participant underwent excision of the lesion and was in full remission 2 years post-excision, and there has been no recurrence of metastatic malignant melanoma. The investigator has assessed the relationship as 'not related' to the study drug and indicated prior sun exposure as an alternative cause. The case of low-grade glioneuronal neoplasm was reported in the PETITE study, 1 year and 4 days after a full 14-day course of teplizumab (cumulatively approximately 10.12 mg). No imaging of the spinal cord is available from before enrollment to the study, therefore the true latency time is not known. As a result, the investigator assessed the event as "possibly related" to teplizumab. An independent external expert in pediatric neuro-oncology, who has been involved in the treatment of more than 1000 pediatric patients with low-grade glioma, assessed the case as not related in congruence with the sponsor assessment. Low-grade gliomas typically exhibit very slow growth rate; therefore, based on the size of the tumor, extending from the cervical cord down to thoracic cord T7 level, it was likely present before the trial started. No known factors accelerate growth apart from molecular drivers. Seriousness and outcomes: All cases were serious. The non-malignant case of lymphoproliferative syndrome resolved after discontinuation of immunosuppressives and with anti-viral therapy. All other cases were treated with non-drug therapy/surgical treatment and ongoing surveillance for recurrence. **Postmarketing experience** No case of malignancy has been reported in postmarketing setting to cut-off date (28-Feb-2025). **Background incidence/prevalence**

Important Potential Risk	Malignancies
	To date, no observational study estimated specifically the incidence of malignancies in the T1D pediatric population. A moderate overall cancer excess risk of 17% to 20% [100,101,102] has been described in the T1D adult population as compared to the general population. However, this risk was not confirmed in a large recent UK study which observed decreased overall cancer risk. [103] With consistency, higher overall cancer risks were reported in women as compared to men, [102,104,105,106] including in non-sex specific cancer. [106]
Risk factors and Risk groups	Risk of malignancies may increase with immunosuppression.
Preventability	Avoidance of concomitant immunosuppression.
Impact on the benefit-risk balance of the product	There is currently no data indicating an increased risk of cancer in patients treated with teplizumab. Long-term studies are needed to assess the carcinogenic potential of teplizumab.
Public health impact	Minimal.

CD: Cluster of Differentiation; DLP: Data Lock Point; EBV: Epstein-Barr Virus; T1D: Type 1 Diabetes; UK: United Kingdom.

SVII.3.2 Presentation of the missing information

Table 33 - Missing information: Long-term safety, including growth, in patients aged 8 to <18 years

Missing information	Long-term safety, including growth, in patients aged 8 to <18 years
Evidence source(s) and strength of evidence	While nearly 700 participants exposed in the development program were under the age of 18 years, the follow up was for two years on average. An additional 48 months of follow up is ongoing in the PROTECT-Extension study. Aside from this, the longest trial follow-up duration available in publication is the 7-years retrospective follow-up of the AbATE trial (n = 43), and no new safety concerns were identified among the 43 patients treated with two courses of teplizumab (given 1 year apart). Additional data will be collected through a long-term Global Registry Study ([Part III]; [Annex 3]) which will follow safety, and growth obtained as per routine clinical practice.
Population in need for further characterization	Additional data are needed to characterize the long-term safety profile in this pediatric population. The Marketing Authorization Holder (MAH) is also planning to conduct PIPs to further characterize the safety profile of teplizumab in this population (P/0386/2024; EMA/PE/0000221282).

EMA: European Medicines Agency; MAH: Marketing Authorization Holder; PIP: Paediatric Investigation Plan

Table 34 - Missing information: Use during pregnancy

Missing information	Use during pregnancy
Evidence source(s) and strength of evidence	No sufficient evidence from clinical studies and postmarketing data reported exists.

Missing information	Use during pregnancy
Population in need for further characterization	Pregnant women exposed to teplizumab. The safety profile in female patients, including pregnant women will be characterized through routine pharmacovigilance.

Table 35 - Missing information: Use during breastfeeding

Missing information	Use during breastfeeding
Evidence source(s) and strength of evidence	No sufficient evidence from clinical studies and postmarketing data reported exists.
Population in need for further characterization	Breastfeeding women exposed to teplizumab. The safety profile in female patients, including breastfeeding women will be characterized through routine pharmacovigilance.

PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Table 36 - Summary of the safety concerns

Important identified risks	Cytokine release syndrome
	Lymphopenia
	Serious Infections
Important potential risk	Malignancies
Missing information	Long-term safety, including growth, in patients aged 8 to <18 years
	Use during pregnancy
	Use during breastfeeding

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of teplizumab.

The safety profile of teplizumab will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints relating to AEs, and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 37 - Additional pharmacovigilance activities (category 1 to 3) summary

GLOBAL REGISTRY study (OBS18565) summary (Cat. 3)
Study short name and title
A prospective observational study to describe long-term clinical outcomes in patients with stage 2 T1D, treated with teplizumab or standard of care.
Rationale and study objectives
In the teplizumab development programme, the pharmacokinetics, pharmacodynamics, efficacy, and safety of teplizumab among participants in clinical trials were evaluated. The clinical studies conducted to date have demonstrated a positive benefit-risk balance of the product. To further evaluate the safety and effectiveness of teplizumab among patients in a real-world setting, the Applicant is proposing an observational global registry study as a postmarketing measure. The objective of this study in approximately 200 patients (150 exposed/50 control) is to characterise 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. Safety will be assessed based on the following and will be further specified in the final protocol: • Adverse event of special interest (AESIs) (including pregnancies and malignancies) • Adverse events (AEs) • Serious adverse events (SAEs) Effectiveness will be assessed based on elapsed time from study treatment to the development of Stage 3 T1D, change in glycaemic parameters such as glycaemia, glycated hemoglobin (HbA1c), continuous glucose monitoring (CGM), C-peptide, oral glucose tolerance test (OGTT) (as available in routine practice), and data from patient reported outcomes (PROs) and will be further specified in the final protocol.
Study design
This is a prospective, multicentre, observational, study in patients diagnosed with stage 2 T1D, prescribed with teplizumab as per standard of care. Teplizumab will not be provided by the applicant.
Observation period
The planned observation period per patient will be approximately 5 years from enrolment. To enrol approximately 200 patients, a period of 3 years is estimated. The overall duration of the study is estimated as 8 years.

Study populations

Adults or paediatric patients aged ≥8 years diagnosed with stage 2 T1D who have received / started teplizumab treatment within 6 weeks to study entry (whatever the duration of treatment, even 1 single dose) or intended to initiate teplizumab treatment according to product label within 6 weeks from study entry.

Milestones

Protocol planned to be submitted to Pharmacovigilance Risk Assessment Committee (PRAC): 31-Dec-2025

First patient enrolled:	6 months after Protocol approval
Study completion:	Approximately 8 years after first patient enrolled
Final report of study results submitted to PRAC:	12 months after study completion

TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717) summary (Cat. 3)

Study short name and title

Survey among HCPs and Patients to assess dissemination, knowledge, and behaviour with respect to the RMMs for teplizumab use in Europe.

Rationale and study objectives

Following the inclusion of additional risk minimization measures (RMMs) in the RMP, this study is designed to assess the effectiveness of the RMMs' tools dissemination and the HCPs' and patients' risks knowledge and behavioural outcome, to ensure the RMMs, committed to in the RMP, are effective and address appropriately the risks it was proposed and implemented for: Educating HCPs on the safe use of teplizumab, Educating patients on the risks related to teplizumab use, identifying the signs and symptoms indicative of those risks and the related actions to be taken.

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.

Objectives among HCPs:

- To assess dissemination of RMMs towards HCPs including receipt and reading of HCP and patient guides for teplizumab.
- To assess HCPs knowledge with regards to the RMMs including prescribing/dispensing conditions and risks associated with exposure to teplizumab.
- To assess HCPs behaviour with regards to the RMMs including prescription/dispensation of teplizumab.

Objectives among Patients[a]:

- To assess dissemination of RMMs towards patients[a] treated with teplizumab including receipt and reading of the educational materials provided by the HCPs.
- To assess the knowledge of patients[a] treated with teplizumab with regards to the risks associated with the use of teplizumab, identification of the signs and symptoms indicative of those risks and the related actions to be taken.

To assess the behaviour of patients[a] treated with teplizumab with regards to identification of the signs and symptoms indicative of the risks associated with teplizumab and the related actions to be taken.

Study design

This is a prospective, primary data collection, cross-sectional, multi-country, non-interventional online Survey conducted among HCPs and patients.

Study populations

Approximately 270 HCPs (diabetologists, endocrinologists, paediatric endocrinologists, nurses [delivering the infusions]), having prescribed or delivered teplizumab in the last 6 months, will be surveyed.

Approximately 270 patients, treated with teplizumab in the last 6 months, will be surveyed. Patients will be identified through the HCPs enrolled. Recruitment will ensure an adequate proportion of minor of age participants is included.

Children-in-care and patients in an ongoing clinical trial of any investigational product or who had ended participation within 6 months prior to study enrolment will be excluded.

Milestones	
Protocol planned to be submitted to PRAC:	30-Sep-2026
First patient enrolled:	12 months after Market Access granted
Study completion:	12 months after First Patient Enrolled
Final report of study results submitted to PRAC:	12 months after study completion

a For patients between 8 to 14 years of age, the survey shall be filled out by their parent, guardian or caregiver. Upper age limit might vary according to local regulation.

AE: Adverse Event; AESI: Adverse Event of Special Interest; CGM: Continuous Glucose Monitoring; HbA1c: Glycated Hemoglobin; HCP: Healthcare Professional; OGTT: Oral Glucose Tolerance Test; PRAC: Pharmacovigilance Risk Assessment Committee; PRO: Patient Reported Outcome; RMM: Risk Minimization Measure; RMP: Risk Management Plan; SAE: Serious Adverse Event; T1D: Type 1 Diabetes.

III.3 SUMMARY TABLE OF 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

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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	30-Sep-2026
			First patient enrolled	12 months after Market Access granted
			Study completion	12 months after First Patient Enrolled
			Final report of study results submitted to PRAC	12 months after study completion

HCP: Healthcare professional; PRAC: Pharmacovigilance Risk Assessment Committee; RMM: Risk Minimization Measure; T1D: Type 1 Diabetes.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for teplizumab.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Given the overall safety profile of teplizumab and the considered important identified risks, which have been characterized based on a clinical and postmarketing safety database, the risk management strategy for teplizumab consists of routine risk minimization measures (labeling information which includes communication on the risks, specific clinical measures and legal status reported in the PI aimed to patients and HCPs) (see Table 39), and additional risk minimization measures (educational/safety advice tools) (see Table 40).

V.1 ROUTINE RISK MINIMIZATION MEASURES

Teplizumab is a prescription only medicine and detailed information regarding safety information is being provided in the SmPC with this information in patient friendly language for patients in the PL.

Table 39 - 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: Prior to initiating the treatment: 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). During the course of the treatment: 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 warnings and precautions of use) and PL section 3 (How Teizeild is given).

Safety concern	Routine risk minimization activities
	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 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: Prior to initiating the treatment: 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).

Safety concern	Routine risk minimization activities
	During and after the course of the treatment: 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). In case of serious infection: 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 (Preclinical safety data). **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.
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).

Safety concern	Routine risk minimization activities
	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.

CMV: Cytomegalovirus; CRS: Cytokine Release Syndrome; EBV: Epstein-Barr Virus; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

The following educational/safety advice tools are implemented for teplizumab:

Guide for risk minimization for healthcare professionals:

- **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.

Guide for risk minimization for patients:

- **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 PL thoroughly.

Table 40 - Additional risk minimization measures

Healthcare Professional (HCP) guide	
Objectives	The overall objective is to provide information related to the safety concerns CRS, lymphopenia and severe infections that may be observed in patients treated with teplizumab, and how to manage them. Important recommendation includes requirements for premedication, monitoring of laboratory values and clinical examination prior to, during and after the treatment with teplizumab, and treatments to use should signs and symptoms of these risks be observed. These recommendations include: Premedication prior infusion, Laboratory evaluation of total blood count, liver enzyme tests prior to, during and after the treatment, Laboratory and/or monitoring for signs and symptoms of the risks related to the use of teplizumab, Management of the risks related to the use of teplizumab including medications to use, lab tests, pausing / discontinuation and resuming the treatment, Recommendation related to all age-appropriate vaccinations to be administered prior to or after the treatment.
Rationale for the additional risk minimization activity	Healthcare professionals should be informed and educated on the risks related to the use of this mAb to treat T1D. Healthcare professionals should also inform and ensure patient compliance with testing and vigilance for signs and symptoms associated with those risks.
Target audience and planned distribution path	The target audience should include physician prescribers (such as diabetologists, pediatricians, pediatric/adult endocrinologists) and all HCPs managing patients with T1D (nurses, general practitioners [GPs]), hospital pharmacists) and HCPs in charge of laboratory analysis (biologists, laboratory assistants, laboratory technicians) according to national healthcare system. The HCP guide should be distributed at launch. Ad-hoc redistribution could occur in line with local regulation and national health systems. Electronic and/or hard copies distribution is supported by the company in addition to the most appropriate means including electronic channels (emails, internet websites such as company website, NCA website, HCPs websites and any other local website where feasible).
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness would be indirectly measured by routine pharmacovigilance through reporting rate analysis.

	In addition: RMM EFFECTIVENESS SURVEY (OBS21717 [Part III]; [Annex 3]) is planned: "Survey among HCPs and Patients to assess dissemination, knowledge, and behavior with respect to the RMMs for teplizumab use in Europe." Criteria for success: Monitoring the reporting rate of AEs. For the RMM EFFECTIVENESS SURVEY (OBS21717): • HCPs' dissemination of RMMs'tools, knowledge and behavior with regards to the RMMs based on results from the study • Patients' dissemination of RMMs'tools, knowledge and behavior related to the risks based on results from the study
Patient Guide	
Objectives	The overall objective is to inform patients/legal representative on the risks of CRS, lymphopenia and serious infections that may happen when treated with teplizumab. Patients/legal representatives should be aware of signs and symptoms related to those risks and understand the need to urgently seek medical advice /contact their treating HCP. Important information includes: Premedication prior infusion, Laboratory evaluation of total blood count, liver enzyme tests prior to, during and after the treatment, Laboratory and/or monitoring for signs and symptoms of the risks related to the use of teplizumab, Information on the risks related to the use of teplizumab including medication to use, pausing/resuming and or discontinuing the treatment, Information related to all age-appropriate vaccinations that can be administered prior to or after the treatment.
Rationale for the additional risk minimization activity	Patients/legal representatives should be aware of all the prescribing conditions before, during and after the treatment; the signs and symptoms of the risks related to the use of teplizumab, and understand the recommendation provided by their treating HCP. The guide emphasizes the importance of premedication, lab testing and vigilance for signs and symptoms and to rapidly seek medical advice / contact their prescribing physician to receive an appropriate treatment, pause or discontinue the treatment with teplizumab.
Target audience and planned distribution path	The target audience include patients/legal representative through their HCP. This patient guide should be provided by the HCPs to any new patient treated with teplizumab. The patient guide should be distributed at launch. Ad-hoc redistribution could occur in line with local regulation and national health systems. Electronic and/or hard copies distribution is supported by the company in addition to the most appropriate means including electronic channels (emails, internet websites such as company website, NCA website, HCPs websites, Patients' websites and any other local website where feasible).

Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness would be indirectly measured by routine pharmacovigilance through reporting rate analysis. In addition: • RMM EFFECTIVENESS SURVEY (OBS21717 [Annex 3]) is planned: "Survey among HCPs and Patients to assess dissemination, knowledge, and behaviour with respect to the RMMs for teplizumab use in Europe." Criteria for success: Monitoring the reporting rate of AEs. For the RMM EFFECTIVENESS SURVEY (OBS21717): • HCPs' dissemination of RMMs' tools, knowledge and behavior with regards to the RMMs based on results from the study. • Patients' dissemination of RMMs' tools, knowledge and behavior related to the risks based on results from the study.

AE: Adverse Event; CRS: Cytokine Release Syndrome; GP: General Practitioner; HCP: Healthcare Professional; mAb: Monoclonal Antibody; NCA: National Competent Authority; RMM: Risk Minimization Measure; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 41 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cytokine release syndrome	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.2 (Posology and method of administration) • Section 4.4 (Special warnings and precautions of use) • Section 4.8 (Undesirable effects), Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) • Section 3 (How Teizeild is given) • Section 4 (Possible side effects) Prescription only medicine. **Additional risk minimization measures:** Healthcare Professional Guide Patient guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) • TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717)
Lymphopenia	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.2 (Posology and method of administration) • Section 4.4 (Special warnings and precautions of use)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Section 4.8 (Undesirable effects) • Section 5 (Pharmacological properties) Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) • Section 4 (Possible side effects) Prescription only medicine. **Additional risk minimization measures:** Healthcare Professional Guide Patient guide	• TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717)
Serious Infections	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.2 (Posology and method of administration) • Section 4.4 (Special warnings and precautions of use) • Section 4.8 (Undesirable effects) Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) • Section 4 (Possible side effects) Prescription only medicine. **Additional risk minimization measures:** Healthcare Professional Guide Patient guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) • TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717)
Malignancies	**Routine risk minimization measures:** Labeled in SmPC: • Section 5.3 (Preclinical safety data) Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** GLOBAL REGISTRY study (OBS18565)
Long-term safety, including growth, in patients aged 8 to < 18 years	**Routine risk minimization measures:** Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** GLOBAL REGISTRY study (OBS18565)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use during pregnancy	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.6 (Fertility, pregnancy and lactation) • Section 5.3 (Preclinical safety data) Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** GLOBAL REGISTRY study (OBS18565)
Use during breastfeeding	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.6 (Fertility, pregnancy and lactation) • Section 5.3 (Preclinical safety data) Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) Prescription only medicine. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** GLOBAL REGISTRY study (OBS18565)

PL: Package Leaflet; RMM: Risk Minimization Measure; SmPC: Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Teizeild (Teplizumab)

This is a summary of the RMP for Teizeild. The RMP details important risks of Teizeild, how these risks can be minimized, and how more information will be obtained about Teizeild's risks and uncertainties (missing information).

Teizeild's SmPC and its PL give essential information to HCPs and patients on how Teizeild should be used.

This summary of the RMP for Teizeild should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Teizeild's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Teizeild is authorized *to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D.*

It contains Teplizumab as the active substance and it is given by IV infusion.

Further information about the evaluation of Teizeild benefits can be found in Teizeild's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

<link to the EPAR summary landing page>

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Teizeild, together with measures to minimize such risks and the proposed studies for learning more about Teizeild risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Teizeild, these measures are supplemented with additional risk minimization measures (Educational/Safety advice tools for HCPs and patients) mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions from solicited, spontaneous, and literature sources are collected continuously and regularly analyzed, including regular aggregate signalling activities, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Teizeild is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of Teizeild are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Teizeild. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 42 - List of important risks and missing information

Important identified risks	Cytokine release syndrome
	Lymphopenia
	Serious Infections
Important potential risk	Malignancies
Missing information	Long-term safety, including growth, in patients aged 8 to <18 years
	Use during pregnancy
	Use during breastfeeding

II.B Summary of important risks

Table 43 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Cytokine release syndrome

Cytokine release syndrome	
Evidence for linking the risk to the medicine	Cytokine release syndrome events, including serious, have been observed in teplizumab-treated patients in clinical trials and postmarketing settings. This risk is expected, based on the pharmacologic mode of action of teplizumab.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.2 (Posology and method of administration) • Section 4.4 (Special warnings and precautions of use) • Section 4.8 (Undesirable effects) Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) • Section 3 (How Teizeild is given) • Section 4 (Possible side effects) Prescription only medicine. **Additional risk minimization measures** • Healthcare Professional Guide • Patient guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) • TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717) See [Section II.C.2] of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; RMM: Risk Minimization Measure; SmPC: Summary of Product Characteristics.

Table 44 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Lymphopenia

Lymphopenia	
Evidence for linking the risk to the medicine	In clinical trials, lymphopenia was observed in the majority of teplizumab-treated patients (approximately 75%). Serious lymphopenia occurred in only 0.2% of participants in the teplizumab group. This risk is expected, based on the pharmacologic mode of action of teplizumab. Postmarketing data have not shown increased frequency.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.2 (Posology and method of administration) • Section 4.4 (Special warnings and precautions of use)

Lymphopenia	
	• Section 4.8 (Undesirable effects) • Section 5 (Pharmacological properties) Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) • Section 4 (Possible side effects) Prescription only medicine. **Additional risk minimization measures** • Healthcare Professional Guide • Patient guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) • TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717) See [Section II.C.2] of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; RMM: Risk Minimization Measure; SmPC: Summary of Product Characteristics.

Table 45 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious Infections

Serious Infections	
Evidence for linking the risk to the medicine	Individual diagnosis of serious bacterial and viral infections has occurred in teplizumab-treated patients in clinical trials and postmarketing.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.2 (Posology and method of administration) • Section 4.4 (Special warnings and precautions of use) • Section 4.8 (Undesirable effects) Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) • Section 4 (Possible side effects) Prescription only medicine. **Additional risk minimization measures** • Healthcare Professional Guide • Patient guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) • TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717) See [Section II.C.2] of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; RMM: Risk Minimization Measure; SmPC: Summary of Product Characteristics.

Table 46 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Malignancies

Malignancies	
Evidence for linking the risk to the medicine	Three cases of malignancies were reported during clinical development. Currently, there is insufficient evidence from clinical studies and postmarketing data to establish a relationship between teplizumab and malignancies. The longest trial follow-up duration available in publication is the 7-years follow-up of the AbATE trial (n = 43), and this trial reported no malignancy among the 43 patients treated with two courses of teplizumab (given 1 year apart). Additionally, no malignancy has been reported in postmarketing to cut-off date (28-Feb-2025). [99]
Risk factors and risk groups	Risk of malignancies may increase with immunosuppression.
Risk minimization measures	**Routine risk minimization measures:** Labeled in SmPC: • Section 5.3 (Preclinical safety data) Prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) See [Section II.C.2] of this summary for an overview of the post-authorization development plan.

SmPC: Summary of Product Characteristics.

Table 47 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Long-term safety, including growth, in patients aged 8 to <18 years

Long-term safety, including growth, in patients aged 8 to <18 years	
Risk minimization measures	**Routine risk minimization measures:** Prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) See [Section II.C.2] of this summary for an overview of the post-authorization development plan.

Table 48 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use during pregnancy

Use during pregnancy	
Risk minimization measures	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.6 (Fertility, pregnancy and lactation) • Section 5.3 (Preclinical safety data) Labeled in PL: • Section 2 (What you need to know before you are given Teizeild) Prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) See [Section II.C.2] of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 49 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use during breastfeeding

Use during breastfeeding	
Risk minimization measures	**Routine risk minimization measures:** Labeled in SmPC: • Section 4.6 (Fertility, pregnancy and lactation) • Section 5.3 (Preclinical safety data) Labeled in PL: Section 2 (What you need to know before you are given Teizeild) Prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • GLOBAL REGISTRY study (OBS18565) See [Section II.C.2] of this summary for an overview of the post-authorization development plan.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization of Teizeild.

II.C.2 Other studies in post-authorization development plan

Table 50 - Other studies in post-authorization development plan

GLOBAL REGISTRY study (OBS18565) (Cat. 3)
Purpose of the study: The objective of this study in approximately 200 (150 exposed/50 control patients) is to characterise 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.
TEPLIZUMAB RMM EFFECTIVENESS SURVEY study (OBS21717) (Cat. 3)
Purpose of the study: 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.

HCP: Healthcare Professional; RMM: Risk Minimization Measure; T1D: Type 1 Diabetes.

REFERENCES

1. Ablamunits V, Bisikirska B, Herold KC. Acquisition of regulatory function by human CD8(+) T cells treated with anti-CD3 antibody requires TNF. Eur J Immunol. 2010 Oct;40(10):2891-901.
2. Bisikirska B, Colgan J, Luban J, Bluestone JA, Herold KC. TCR stimulation with modified anti-CD3 mAb expands CD8+ T cell population and induces CD8+CD25+ Tregs. J Clin Invest. 2005 Oct;115(10):2904-13.
3. Long SA, Thorpe J, Herold KC, Ehlers M, Sanda S, Lim N, et al. Remodeling T cell compartments during anti-CD3 immunotherapy of type 1 diabetes. Cell Immunol. 2017 Sep;319:3-9.
4. Waldron-Lynch F, Henegariu O, Deng S, Preston-Hurlburt P, Tooley J, Flavell R, et al. Teplizumab induces human gut-tropic regulatory cells in humanized mice and patients. Sci Transl Med. 2012 Jan 25;4(118):118ra12.
5. Long SA, Thorpe J, DeBerg HA, Gersuk V, Eddy J, Harris KM, et al. Partial exhaustion of CD8 T cells and clinical response to teplizumab in new-onset type 1 diabetes. Sci Immunol. 2016 Nov;1(5):eaai7793.
6. Wiedeman AE, Muir VS, Rosasco MG, DeBerg HA, Presnell S, Haas B, et al. Autoreactive CD8+ T cell exhaustion distinguishes subjects with slow type 1 diabetes progression. J Clin Invest. 2020 Jan 2;130(1):480-90.
7. Lebastchi J, Deng S, Lebastchi AH, Beshar I, Gitelman S, Willi S, et al. Immune therapy and β-cell death in type 1 diabetes. Diabetes. 2013 May;62(5):1676-80.
8. Magliano DJ, Boyko EJ; IDF Diabetes Atlas 10th edition scientific committee. IDF DIABETES ATLAS [Internet]. 10th ed. Brussels: International Diabetes Federation; 2021. PMID: 35914061.
9. Fang M, Wang D, Echouffo-Tcheugui JB, Selvin E. Age at Diagnosis in U.S. Adults With Type 1 Diabetes. Ann Intern Med. 2023 Nov;176(11):1567-8.
10. Leslie RD, Evans-Molina C, Freund-Brown J, Buzzetti R, Dabelea D, Gillespie KM, et al. Adult-Onset Type 1 Diabetes: Current Understanding and Challenges. Diabetes Care. 2021 Nov;44(11):2449-56.
11. Harding JL, Wander PL, Zhang X, Li X, Karuranga S, Chen H, et al. The Incidence of Adult-Onset Type 1 Diabetes: A Systematic Review From 32 Countries and Regions. Diabetes Care. 2022 Apr 1;45(4):994-1006.
12. Thunander M, Petersson C, Jonzon K, Fornander J, Ossiansson B, Torn C, et al. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. Diabetes Res Clin Pract. 2008 Nov;82(2):247-55.
13. Rogers MAM, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC Med. 2017 Nov 8;15(1):199.

14. Hippisley-Cox J, Pringle M. Prevalence, care, and outcomes for patients with diet-controlled diabetes in general practice: cross sectional survey. Lancet. 2004 Jul 31-Aug 6;364(9432):423-8.

15. Holman N, Young B, Gadsby R. Current prevalence of Type 1 and Type 2 diabetes in adults and children in the UK. Diabet Med. 2015 Sep;32(9):1119-20.

16. Passa P. Diabetes trends in Europe. Diabetes Metab Res Rev. 2002 Sep-Oct;18 Suppl 3:S3-8.

17. Briet C, Piffaretti C, Fosse S, Denis P, Allix I, Campagna AF, et al. Epidemiology of type 1 diabetes and its complications. Rev Prat. 2018 Jun;68(6):607-10.

18. Rawshani A, Sattar N, Franzen S, Rawshani A, Hattersley AT, Svensson AM, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet. 2018 Aug 11;392(10146):477-86.

19. Cherubini V, Chiarelli F. Autoantibody test for type 1 diabetes in children: are there reasons to implement a screening program in the general population? A statement endorsed by the Italian Society for Paediatric Endocrinology and Diabetes (SIEDP-ISPED) and the Italian Society of Paediatrics (SIP). Ital J Pediatr. 2023 Jul 19;49(1):87.

20. Steck AK, Rewers MJ. Genetics of type 1 diabetes. Clin Chem. 2011 Feb;57(2):176-85.

21. Norris JM, Johnson RK, Stene LC. Type 1 diabetes-early life origins and changing epidemiology. Lancet Diabetes Endocrinol. 2020 Mar;8(3):226-38.

22. Gan MJ, Albanese-O'Neill A, Haller MJ. Type 1 diabetes: current concepts in epidemiology, pathophysiology, clinical care, and research. Curr Probl Pediatr Adolesc Health Care. 2012 Nov-Dec;42(10):269-91.

23. Hamman RF, Bell RA, Dabelea D, D'Agostino RB Jr, Dolan L, Imperatore G, et al; SEARCH for Diabetes in Youth Study Group. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. Diabetes Care. 2014 Dec;37(12):3336-44.

24. ElSayed NA, Grazia Aleppo, Bannuru RR, Bruemmer D, Collins B, Laya Ekhlaspour, et al. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2024. Diabetes Care. 2023 Dec 11;47(Supplement):S158-78.

25. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care. 2003 Mar;26(3):832-6.

26. Sims EK, Besser RJ, Dayan C, Geno Rasmussen C, Greenbaum C, Griffin KJ, et al. Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective. Diabetes. 2022 Apr 1;71(4):610-23.

27. Insel R, Dutta S, Hedrick J. Type 1 Diabetes: Disease Stratification. Biomed Hub. 2017 Nov 21;2(Suppl 1):111-26.

28. Rewers A, Dong F, Slover RH, Klingensmith GJ, Rewers M. Incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado youth, 1998-2012. JAMA. 2015 Apr 21;313(15):1570-2.

29. Livingstone SJ, Levin D, Looker HC, Lindsay RS, Wild SH, Joss N, et al. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. JAMA. 2015 Jan 6;313(1):37-44.

30. Melendez-Ramirez LY, Richards RJ, Cefalu WT. Complications of type 1 diabetes. Endocrinol Metab Clin North Am. 2010 Sep;39(3):625-40.

31. Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. Diabetes Care. 2006 Nov;29(11):2528-38.

32. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. Diabetologia. 2006 Apr;49(4):660-6.

33. Dahlquist G, Kallen B. Mortality in childhood-onset type 1 diabetes: a population-based study. Diabetes Care. 2005 Oct;28(10):2384-7.

34. Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia. 2006 Feb;49(2):298-305.

35. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. Autoimmun Rev. 2016 Jul;15(7):644-8.

36. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014 Jan 4;383(9911):69-82.

37. Anaya JM. The diagnosis and clinical significance of polyautoimmunity. Autoimmun Rev. 2014 Apr-May;13(4-5):423-6.

38. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010 Apr 29;464(7293):1293-300.

39. Gillespie KM. Type 1 diabetes: pathogenesis and prevention. CMAJ. 2006 Jul 18;175(2):165-70.

40. Todd JA. Etiology of type 1 diabetes. Immunity. 2010 Apr 23;32(4):457-67.

41. Triolo TM, Armstrong TK, McFann K, Yu L, Rewers MJ, Klingensmith GJ, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. Diabetes Care. 2011 May;34(5):1211-3.

42. Biondi B, Kahaly GJ, Robertson RP. Thyroid Dysfunction and Diabetes Mellitus: Two Closely Associated Disorders. Endocr Rev. 2019 Jun 1;40(3):789-824.

43. Troncone R, Discepolo V. Celiac disease and autoimmunity. J Pediatr Gastroenterol Nutr. 2014 Jul;59 Suppl 1:S9-11.

44. Cohn A, Sofia AM, Kupfer SS. Type 1 diabetes and celiac disease: clinical overlap and new insights into disease pathogenesis. Curr Diab Rep. 2014 Aug;14(8):517.

45. Alonso N, Soldevila B, Sanmartí A, Pujol-Borrell R, Martínez-Cáceres E. Regulatory T cells in diabetes and gastritis. Autoimmun Rev. 2009 Jul;8(8):659-62.

46. Frommer L, Kahaly GJ. Autoimmune Polyendocrinopathy. J Clin Endocrinol Metab. 2019 Oct 1;104(10):4769-82.

47. Kahaly GJ, Frommer L. Polyglandular autoimmune syndromes. J Endocrinol Invest. 2018 Jan;41(1):91-8.

48. Yoshioka K, Ohsawa A, Yoshida T, Yokoh S. Insulin-dependent diabetes mellitus associated with Graves' disease and idiopathic hypoparathyroidism. J Endocrinol Invest. 1993 Sep;16(8):643-6.

49. Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabet Med. 1995 Jul;12(7):622-7.

50. Barera G, Bonfanti R, Viscardi M, Bazzigaluppi E, Calori G, Meschi F, et al. Occurrence of celiac disease after onset of type 1 diabetes: a 6-year prospective longitudinal study. Pediatrics. 2002 May;109(5):833-8.

51. Barker JM. Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab. 2006 Apr;91(4):1210-7.

52. Zaharia OP, Lanzinger S, Rosenbauer J, Karges W, Mussig K, Meyhofer SM, et al. Comorbidities in Recent-Onset Adult Type 1 Diabetes: A Comparison of German Cohorts. Front Endocrinol (Lausanne). 2022 Jun 3;13:760778.

53. International Diabetes Federation [Internet]. IDF Diabetes Atlas, 8th ed. Brussels, Belgium: International Diabetes Federation, 2017.

54. DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Diabet Med. 2006 Aug;23(8):857-66.

55. Stanescu DE, Lord K, Lipman TH. The epidemiology of type 1 diabetes in children. Endocrinol Metab Clin N Am. 2012;41:679-94.

56. Patterson CC, Gyurus E, Rosenbauer J, Cinek O, Neu A, Schober E, et al. Trends in childhood type 1 diabetes incidence in Europe during 1989-2008: evidence of non-uniformity over time in rates of increase. Diabetologia. 2012;55:2142-7.

57. Patterson CC, Harjutsalo V, Rosenbauer J, Neu A, Cinek O, Skrivarhaug T, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989-2013: a multicentre prospective registration study. Diabetologia. 2019 Mar;62(3):408-17.

58. Barat P, Valade A, Brosselin P, Alberti C, Maurice-Tison S, Levy-Marchal C. The growing incidence of type 1 diabetes in children: the 17-year French experience in Aquitaine. Diabetes Metab. 2008;34:601-5.

59. Piffaretti C, Mandereau L, Guilmin S, Choleau C, Coutant R, Fosse S. Trends in childhood type 1 diabetes incidence in France, 2010-2015. Diabetes Res Clin Pract. 2019 Mar;149:200-7.

60. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. N Engl J Med. 2017 Apr 13;376(15):1419-29.

61. Wagenknecht LE, Lawrence JM, Isom S, Jensen ET, Dabelea D, Liese AD, et al; SEARCH for Diabetes in Youth study. Trends in incidence of youth-onset type 1 and type 2 diabetes in the USA, 2002-18: results from the population-based SEARCH for Diabetes in Youth study. Lancet Diabetes Endocrinol. 2023 Apr;11(4):242-50.

62. Ward ZJ, Yeh JM, Reddy CL, Gomber A, Ross C, Rittiphairoj T, et al. Estimating the total incidence of type 1 diabetes in children and adolescents aged 0-19 years from 1990 to 2050: a global simulation-based analysis. Lancet Diabetes Endocrinol. 2022 Dec;10(12):848-58.

63. Berhan Y, Waernbaum I, Lind T, Mollsten A, Dahlquist G. Thirty Years of Prospective Nationwide Incidence of Childhood Type 1 Diabetes: The Accelerating Increase by Time Tends to Level Off in Sweden. Diabetes. 2011 Jan 26;60(2):577-81.

64. Skrivarhaug T, Stene LC, Drivvoll AK, Strom H, Joner G. Incidence of type 1 diabetes in Norway among children aged 0-14 years between 1989 and 2012: has the incidence stopped rising? Results from the Norwegian Childhood Diabetes Registry. Diabetologia. 2013 Oct 23;57(1):57-62.

65. Harjutsalo V, Sund R, Knip M, Groop PH. Incidence of type 1 diabetes in Finland. JAMA. 2013;310(4):427-8.

66. Bruno G, Pagano E, Rossi E, Cataudella S, De Rosa M, Marchesini G, et al. Incidence, prevalence, costs and quality of care of type 1 diabetes in Italy, age 0-29 years: The population-based CINECA-SID ARNO Observatory, 2002-2012. Nutr Metab Cardiovasc Dis. 2016 Dec;26(12):1104-11.

67. Roche EF, McKenna AM, Ryder KJ, Brennan AA, O'Regan M, Hoey HM. Is the incidence of type 1 diabetes in children and adolescents stabilising? The first 6 years of a National Register. Eur J Pediatr. 2016;175(12):1913-9.

68. Haynes A, Bulsara MK, Bower C, Jones TW, Davis EA. Regular peaks and troughs in the Australian incidence of childhood type 1 diabetes mellitus (2000-2011). Diabetologia. 2015 Jul 31;58(11):2513-6.

69. Haynes A, Bulsara MK, Jones TW, Davis EA. Incidence of childhood onset type 1 diabetes in Western Australia from 1985 to 2016: Evidence for a plateau. Pediatr Diabetes. 2018;19(4):690-2.

70. Onda Y, Sugihara S, Ogata T, Yokoya S, Yokoyama T, Tajima N, et al. Incidence and prevalence of childhood-onset Type 1 diabetes in Japan: the T1D study. Diabet Med. 2017 Jul;34(7):909-15.

71. Xia Y, Xie Z, Huang G, Zhou Z. Incidence and trend of type 1 diabetes and the underlying environmental determinants. Diabetes Metab Res Rev. 2018:e3075.

72. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA. 2014 May 7;311(17):1778-86.

73. Pettitt DJ, Talton J, Dabelea D, Divers J, Imperatore G, Lawrence JM, et al. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. Diabetes Care. 2014 Feb;37(2):402-8.

74. Li L, Jick S, Breitenstein S, Michel A. Prevalence of Diabetes and Diabetic Nephropathy in a Large U.S. Commercially Insured Pediatric Population, 2002-2013. Diabetes Care. 2016 Feb;39(2):278-84.

75. Giralt P, Santillana L, Madrigal D, Merlo A, Toledo B, Anaya F. Incidence of diabetes mellitus and prevalence of type 1a diabetes mellitus in children younger than 16 years old from the province of ciudad real (spain). An Esp Pediatr. 2001 Sep;55(3):213-8.

76. Manuwald U, Salzsieder E, Holl RW, Schoffer O, Stahl-Pehe A, Giani G, et al. Trends in Incidence Rates during 1999-2008 and Prevalence in 2008 of Childhood Type 1 Diabetes Mellitus in Germany--Model-Based National Estimates. PLoS One. 2015 Jul 16;10(7):e0132716.

77. Yesilkaya E, Cinaz P, Andiran N, Bideci A, Hatun S, Sarı E, et al. First report on the nationwide incidence and prevalence of Type 1 diabetes among children in Turkey. Diabet Med. 2017;34(3):405-10.

78. Daneman D. Type 1 diabetes. Lancet. 2006 Mar 11;367(9513):847-58.

79. Harron KL, McKinney PA, Feltbower RG, Bodansky HJ, Norman PD, Campbell FM, et al. Incidence rate trends in childhood type 1 diabetes in Yorkshire, UK 1978-2007: effects of deprivation and age at diagnosis in the South Asian and non-South Asian populations. Diabet Med. 2011;28:1508-13.

80. Primavera M, Giannini C, Chiarelli F. Prediction and Prevention of Type 1 Diabetes. Front Endocrinol (Lausanne). 2020 Jun 2;11:248.

81. Jeyam A, Colhoun H, McGurnaghan S, Blackbourn L, McDonald TJ, Palmer CNA, et al; SDRNT1BIO Investigators. Clinical Impact of Residual C-Peptide Secretion in Type 1 Diabetes on Glycemia and Microvascular Complications. Diabetes Care. 2021 Feb;44(2):390-8.

82. Sorensen JS, Johannesen J, Pociot F, Kristensen K, Thomsen J, Hertel NT, et al; Danish Society for Diabetes in Childhood and Adolescence. Residual β-Cell function 3-6 years after onset of type 1 diabetes reduces risk of severe hypoglycemia in children and adolescents. Diabetes Care. 2013 Nov;36(11):3454-9.

83. Faulds ER, Grey M, Tubbs-Cooley H, Hoffman RP, Militello LK, Tan A, et al. Expect the unexpected: Adolescent and pre-teens' experience of diabetes technology self-management. Pediatr Diabetes. 2021 Nov;22(7):1051-62.

84. Rawshani A, Sattar N, Franzén S, Rawshani A, Hattersley AT, Svensson AM, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet. 2018 Aug 11;392(10146):477-86.

85. Patterson CC, Dahlquist G, Harjutsalo V, Joner G, Feltbower RG, Svensson J, et al. Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetologia. 2007 Dec;50(12):2439-42.

86. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes. 2006 May;55(5):1463-9.

87. Evans-Cheung TC, Bodansky HJ, Parslow RC, Feltbower RG. Mortality and acute complications in children and young adults diagnosed with Type 1 diabetes in Yorkshire, UK: a cohort study. Diabet Med. 2018;35(1):112-20.

88. Evans-Cheung TC, Bodansky HJ, Parslow RC, Feltbower RG. Early deaths from ischaemic heart disease in childhood-onset type 1 diabetes. Arch Dis Child. 2018;103(10):981-3.

89. Warncke K, Frohlich-Reiterer EE, Thon A, Hofer SE, Wiemann D, Holl RW, et al. Polyendocrinopathy in children, adolescents, and young adults with type 1 diabetes: a multicenter analysis of 28,671 patients from the German/Austrian DPV-Wiss database. Diabetes Care. 2010 Sep;33(9):2010-2.

90. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care. 2018 Oct;41(10):2127-35.

91. Chaudhry UAR, Carey IM, Critchley JA, DeWilde S, Limb ES, Bowen L, et al. A matched cohort study evaluating the risks of infections in people with type 1 diabetes and their associations with glycated haemoglobin. Diabetes Res Clin Pract. 2024 Jan;207:111023.

92. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. Expert Rev Clin Immunol. 2009 Sep;5(5):499-521.

93. Martin TG, Mateos MV, Nooka A, Banerjee A, Kobos R, Pei L, et al. Detailed overview of incidence and management of cytokine release syndrome observed with teclistamab in the MajesTEC-1 study of patients with relapsed/refractory multiple myeloma. Cancer. 2023 Jul 1;129(13):2035-46.

94. Bannerji R, Arnason JE, Advani RH, Brown JR, Allan JN, Ansell SM, et al. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. Lancet Haematol. 2022 May;9(5):e327-39.

95. Nassar M, Nso N, Baraka B, Alfishawy M, Mohamed M, Nyabera A, et al. The association between COVID-19 and type 1 diabetes mellitus: A systematic review. Diabetes Metab Syndr. 2021 Jan-Feb;15(1):447-54.

96. George TP, Joy SS, Rafiullah M, Siddiqui K. Cytokines Involved in COVID-19 Patients with Diabetes: A Systematic Review. Curr Diabetes Rev. 2023;19(3):e180122200321.

97. Nassar M, Daoud A, Nso N, Medina L, Ghernautan V, Bhangoo H, et al. Diabetes Mellitus and COVID-19: Review Article. Diabetes Metab Syndr. 2021 Nov-Dec;15(6):102268.

98. Erener S. Diabetes, infection risk and COVID-19. Mol Metab. 2020 Sep;39:101044.

99. Perdigoto AL, Preston-Hurlburt P, Clark P, Long SA, Linsley PS, Harris KM, et al. Treatment of type 1 diabetes with teplizumab: clinical and immunological follow-up after 7 years from diagnosis. Diabetologia. 2019 Apr;62(4):655-64.

100. Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K. Cancer risk among patients hospitalized for Type 1 diabetes mellitus: a population-based cohort study in Sweden. Diabet Med. 2010 Jul;27(7):791-7.

101. Zendehdel K, Nyren O, Ostenson CG, Adami HO, Ekbom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. J Natl Cancer Inst. 2003 Dec 3;95(23):1797-800.

102. Fredriksson M, Persson E, Dahlquist G, Mollsten A, Lind T. Risk of cancer in young and middle-aged adults with childhood-onset type 1 diabetes in Sweden-A prospective cohort study. Diabet Med. 2022 Mar;39(3):e14771.

103. Swerdlow AJ, Jones ME, Slater SD, Burden ACF, Botha JL, Waugh NR, et al. Cancer incidence and mortality in 23 000 patients with type 1 diabetes in the UK: Long-term follow-up. Int J Cancer. 2023 Aug 1;153(3):512-23.

104. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. Diabetes Care. 2015 Feb;38(2):264-70.

105. Hsu PC, Lin WH, Kuo TH, Lee HM, Kuo C, Li CY. A Population-Based Cohort Study of All-Cause and Site-Specific Cancer Incidence Among Patients With Type 1 Diabetes Mellitus in Taiwan. J Epidemiol. 2015;25(9):567-73.

106. Carstensen B, Read SH, Friis S, Sund R, Keskimaki I, Svensson AM, et al. Cancer incidence in persons with type 1 diabetes: a five-country study of 9,000 cancers in type 1 diabetic individuals. Diabetologia. 2016 May;59(5):980-8.

PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Prior to the launch of Teizeild in each country the marketing authorization holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority (NCA).

The educational materials are aimed at minimizing specific safety concerns for a safe use of Teizeild in patients.

The MAH shall ensure that in each country where Teizeild is marketed, all healthcare professionals, patients/carers who are expected to prescribe / dispense / use Teizeild have access to/are provided with the following educational package to be disseminated through professional bodies:

1. Physician tools of risk minimization measures and,
2. Patient tools of risk minimization measures

1. Physician tools of risk minimization measures

- Product Information
- Guide for risk minimization for healthcare professionals

<u>Guide for risk minimization for healthcare professionals</u>:

<u>HCPs guide, key elements</u>:

- 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.

2. The patient tools of risk minimization measures:

- Patient information leaflet
- Guide for risk minimization for patients

<u>Guide for risk minimization for patients</u>:

<u>Patients guide, key elements</u>:

- 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.