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Teplizumab (TEIZEILD®) for stage 2 type 1 diabetes

Health Technology Assessment

Final Report

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Project Team

Project leader: Sarah Wolf, MSc

AIHTA Appraisal Board Author Group: Alba Colicchia, MPH
Daniel Fabian, MSc
Naomi Linton-Romir, MPH
PharmDr. Eva Malíková, PhD
Dr. Tatiana Marschik
Michaela Riegelnegg, MA
Dr. med. Eleen Rothschedl
Diana Szivakova, MA
Priv.-Doz. Dr. phil. Claudia Wild
Sarah Wolf, MSc

Project Support

Systematic literature search: Tarquin Mittermayr, MA

External review: OA Univ. Prof. Dr. Thomas C. Wascher (Österreichische Gesundheitskasse Mein Hanusch-Krankenhaus)
Ass.-Prof. Priv.-Doz. Dr. Elke Fröhlich-Reiterer (LKH-Universitätsklinikum Graz)
Ao. Univ. Prof. Dr. Birgit Rami-Merhar, MBA (Universitätsklinikum – AKH Wien)

Internal review: Dr. MMag. Sabine Geiger-Gritsch

Correspondence: HTA-Austria Appraisal Board Team, bewertungsboard@aihta.at

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Dr. rer. soc. oec. Ingrid Zechmeister-Koss, managing director

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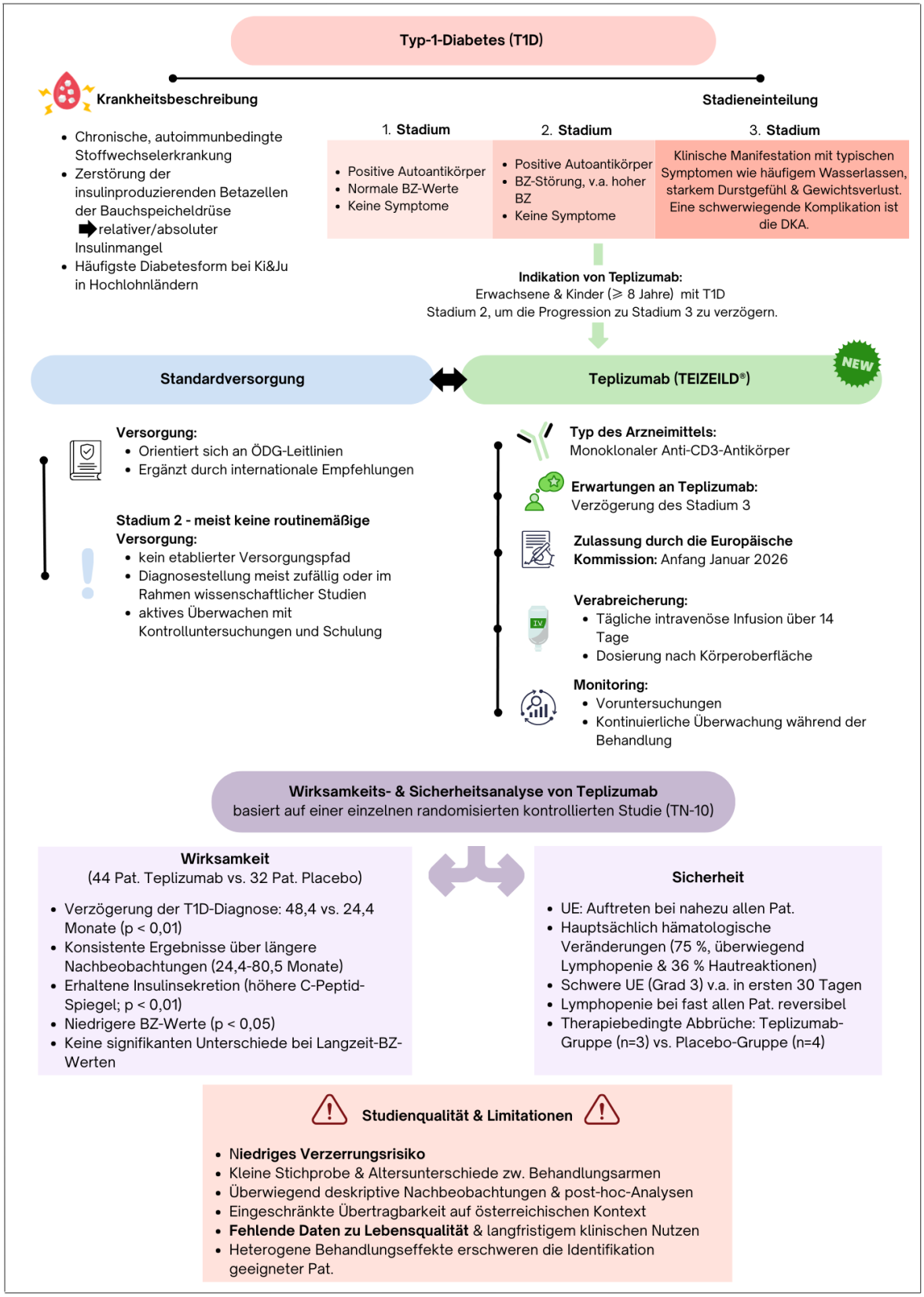
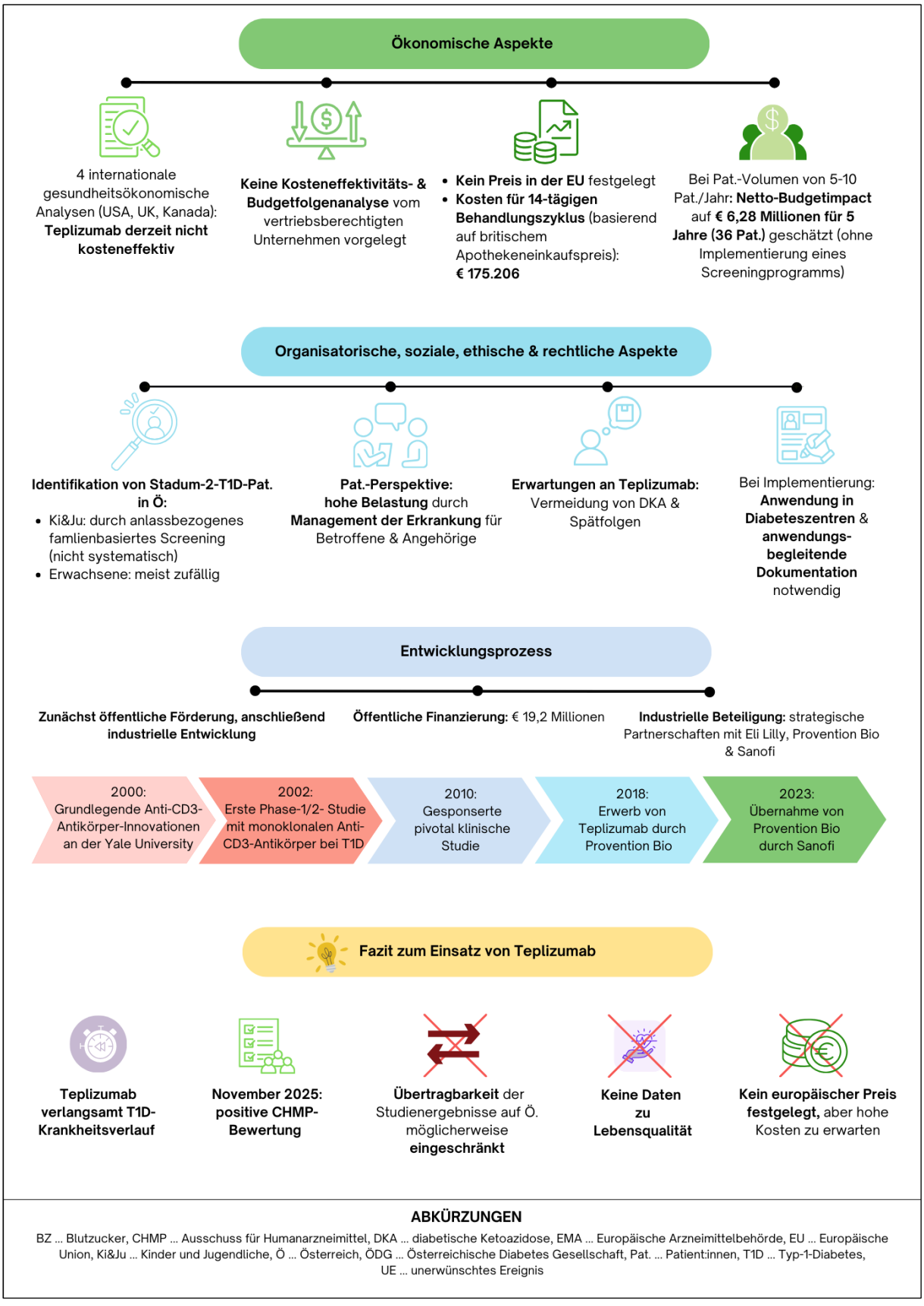




ABKÜRZUNGEN

BZ ... Blutzucker, CHMP ... Ausschuss für Humanarzneimittel, DKA ... diabetische Ketoazidose, EMA ... Europäische Arzneimittelbehörde, EU ... Europäische Union, Ki&Ju ... Kinder und Jugendliche, Ö ... Österreich, ÖDG ... Österreichische Diabetes Gesellschaft, Pat. ... Patient:innen, T1D ... Typ-1-Diabetes, UE ... unerwünschtes Ereignis

Zusammenfassung

Der vorliegende Health Technology Assessment (HTA)-Bericht evaluiert Teplizumab (TEIZEILD®) zur Verzögerung der Progression zu Typ-1-Diabetes (T1D) im Stadium 3 bei Erwachsenen und Kindern (≥ 8 Jahre) mit T1D im Stadium 2.

Beschreibung der Erkrankung und Behandlungsoptionen

T1D ist eine chronische autoimmunbedingte Stoffwechselerkrankung, bei der insulinproduzierende Betazellen des Pankreas zerstört werden, was zu einem relativen oder absoluten Insulinmangel führt. Die Erkrankung entwickelt sich häufig über präsymptomatische Stadien mit nachweisbarer Betazellautoimmunität und schreitet zu einer klinisch manifesten Hyperglykämie fort. Dabei werden drei Stadien unterschieden: (1) Vorliegen ≥2 Autoantikörper bei normoglykämischem Stoffwechsel ohne Symptome; (2) Autoantikörpernachweis (≥2 Autoantikörper) mit Dysglykämie im Sinne einer gestörten Glukosetoleranz, weiterhin ohne klinische Symptome; (3) klinische Manifestation mit typischen Symptomen wie vermehrter Harnausscheidung (Polyurie), vermehrtem Durstgefühl (Polydipsie) und Gewichtsverlust, wobei in mehreren Fällen eine diabetische Ketoazidose auftreten kann.

T1D macht etwa 5-10 % aller Diabetesfälle aus, ist jedoch die häufigste Diabetesform im Kindes- und Jugendalter in Hochlohnländern. In Österreich beträgt die Inzidenz bei Kindern unter 15 Jahren 28,6 pro 100.000 Personenjahre; etwa 3.500 Kinder und Jugendliche leben mit T1D. Nationale Prävalenzdaten für Erwachsene liegen nicht vor.

Die Behandlung von T1D in Österreich orientiert sich an den Leitlinien der Österreichischen Diabetes-Gesellschaft sowie an internationalen Empfehlungen. Präsymptomatische Stadien (Stadien 1 und 2) sind mangels klinischer Manifestation nicht Teil eines etablierten Versorgungspfads. Mit Erreichen des klinischen Stadiums 3 beginnt die strukturierte Diabetesversorgung mit dem Ziel einer möglichst normoglykämischen Einstellung, der Vermeidung akuter Komplikationen und der Prävention langfristiger Folgeerkrankungen. Die lebenslange Insulintherapie bildet die Grundlage der Behandlung im Stadium 3 und erfolgt mittels multipler täglicher Injektionen, der Insulinpumpentherapie oder auch über automatisierte Insulinabgabesysteme (AID-Systeme). Die kontinuierliche Glukosemessung ist Standard der Therapieanpassung; ergänzend sind strukturierte Schulungsprogramme, multidisziplinäre Betreuung und psychosoziale Unterstützung feste Bestandteile der Versorgung, insbesondere im pädiatrischen Bereich

Überblick über das neue Arzneimittel

Teplizumab ist ein monoklonaler Antikörper, der die Autoimmunreaktion bei T1D im Stadium 2 moduliert. Er wirkt auf CD4+ und CD8+ T-Zellen und reduziert deren autoreaktive Aktivität gegenüber insulinproduzierenden Betazellen, wodurch die endogene Insulinsekretion länger erhalten bleibt und der Übergang in Stadium 3 verzögert werden kann. Die Behandlung erfolgt als einmaliger Therapiezyklus mit täglichen intravenösen Infusionen über 14 Tage und einer Dosierung nach Körperoberfläche. Vor Behandlungsbeginn sind umfassende Voruntersuchungen erforderlich; während der Therapie ist eine engmaschige klinische und laborchemische Überwachung vorgesehen.

Im November 2025 erhielt Teplizumab vom Ausschuss für Humanarzneimittel (CHMP) der Europäischen Arzneimittelagentur (EMA) eine positive Bewertung für Patient:innen ab 8 Jahren mit T1D im Stadium 2 zur Verzögerung des Fortschreitens in das Stadium 3. Die Bewertung erfolgte im Rahmen des Priority-

Medicines-(PRIME)-Programms für Arzneimittel mit hohem ungedecktem medizinischem Bedarf. Die Zulassung durch die Europäische Kommission wird im ersten Quartal 2026 erwartet[1].

Wirksamkeit und Sicherheit

Der Nachweis der Wirksamkeit und Sicherheit von Teplizumab bei Stadium-2-T1D basieren auf einer einzelnen randomisierten kontrollierten Studie (TN-10), die den Übergang von Stadium 2 zu Stadium 3 untersuchte. Insgesamt wurden 76 Patient:innen randomisiert: 44 erhielten Teplizumab, 32 Placebo. Die Mehrheit war unter 18 Jahre alt und Träger:innen von ≥ 3 Autoantikörpern. Die medianen Langzeitblutzuckerwerte (HbA1C-Werte) lagen im Normbereich (5,2 % vs. 5,3 %).

Teplizumab verzögerte die klinische Manifestation von T1D signifikant: Nach einer medianen Nachbeobachtungszeit von 24,5 Monaten betrug die mediane Zeit bis zur Diagnose 48,4 Monate in der Teplizumab-Gruppe gegenüber 24,4 Monaten unter Placebo ($p < 0,01$). Die Ergebnisse blieben in Analysen mit längeren Nachbeobachtungszeiten von 24,4 bis 80,5 Monaten konsistent. Die C-Peptid-Spiegel als Marker der körpereigenen Insulinproduktion waren nach medianen 30,3 Monaten in der Teplizumab-Gruppe höher (1,94 vs. 1,72 pmol/ml; $p < 0,01$), was auf eine erhaltene Insulinsekretion hinweist. Unter Placebo nahm die Insulinproduktion ab. Die durchschnittlichen Blutzuckerwerte über die Zeit waren unter Teplizumab niedriger (164 vs. 177 mg/dl; $p < 0,05$), während sich die HbA1C-Werte nicht signifikant unterschieden.

Unerwünschte Ereignisse traten bei nahezu allen Patient:innen der Teplizumab-Gruppe auf. Es wurden 112 Ereignisse berichtet, hauptsächlich hämatologische Veränderungen (75 %, überwiegend Lymphopenie) und Hautreaktionen (36 %). Schwere unerwünschte Ereignisse (Grad 3) traten hauptsächlich in den ersten 30 Tagen auf; betroffen war vor allem die Lymphopenie, die bei fast allen Patient:innen wieder reversibel war. In der Teplizumab-Gruppe (n=3) sowie in der Placebo-Gruppe (n=4) kam es zu Abbrüchen des 14-tägigen Behandlungszyklus. Die Gründe hierfür waren Laborveränderungen, Schwierigkeiten beim intravenösen Zugang sowie Hautausschlag. Es wurden keine Todesfälle in der TN-10-Studie berichtet.

Das Gesamtverzerrungspotenzial der TN-10-Studie wurde als niedrig eingestuft. Dennoch bestehen relevante methodische Limitationen: Die kleine Stichprobe, Unterschiede im Altersprofil zwischen den Behandlungsarmen sowie überwiegend deskriptive Nachbeobachtungen und post-hoc Analysen schränken die Aussagekraft ein. Zudem fehlen Daten zur Lebensqualität und zum langfristigen klinischen Nutzen. Weiters ist die Übertragbarkeit der Ergebnisse auf österreichische Versorgungsstrukturen eingeschränkt. Beispielsweise wäre in Österreich wahrscheinlich ein stationärer Krankenhausaufenthalt erforderlich, da die vorgesehenen ambulanten Versorgungsstrukturen für einen Therapiezyklus von über 14 Tagen nicht in allen Zentren verfügbar sind.

Ökonomische Aspekte

Das vertriebsberechtigte Unternehmen hat für Teplizumab keine Preisangabe für Österreich, keine gesundheitsökonomische Evaluation und keine Budgetfolgeanalyse eingereicht. Basierend auf dem britischen Apothekeneinkaufspreis von € 12.515 pro 2-ml-Ampulle ergeben sich geschätzte Kosten von etwa € 175.206 für einen 14-tägigen Behandlungszyklus. Die 5-Jahres-Kosten pro Patient:in werden auf € 180.946 geschätzt, gegenüber € 10.971 für die Standardversorgung. Das ergibt inkrementelle Kosten von € 169.975. Bei einem geschätzten Patient:innen-Volumen von fünf bis zehn Personen pro Jahr wird der Netto-Budgetimpakt über fünf Jahre bei ambulanter Verabreichung auf € 6,28 Millionen geschätzt. Eine Szenarioanalyse zeigte, dass sich die Verabreichungskosten jedoch um ca. das Neunfache erhöhen, wenn Teplizumab stationär verabreicht wird, was zu einem Netto-Budgetimpakt von € 6,9 Millionen für

[1] Nachtrag: Teplizumab wurde am 8. Jänner 2026 von der Europäischen Kommission zugelassen.

fünf Jahre führt. Generell sind die Hauptkostentreiber der Erwerb des Arzneimittels und die Verabreichung im stationären Setting.

Darüber hinaus ergaben vier internationale gesundheitsökonomische Analysen, dass Teplizumab mit höheren inkrementellen Kosten im Vergleich zur Standardbehandlung von T1D verbunden ist, während die geschätzten inkrementellen Gesundheitsgewinne gering sind. Die inkrementellen Kosten pro behandelte Person liegen im Bereich von mehreren hunderttausend Euro, wohingegen inkrementelle Gesundheitsgewinne im Allgemeinen auf etwa 0,3-0,5 qualitätsadjustierten Lebensjahren geschätzt werden und in einigen Unteranalysen sogar noch niedriger. Unter Berücksichtigung der Unsicherheiten in den Effektabschätzungen sowie der begrenzten Evidenzbasis erscheint das Verhältnis der berichteten Kosten-zu-Nutzen-Ergebnisse (ICERs) ungünstig. In Bezug auf den für das jeweilige Land relevanten Schwellenwert für die Kosteneffektivität kann Teplizumab auf Grundlage der vorliegenden Daten daher als nicht kosteneffektiv eingestuft werden. Eine Ausnahme wurde in einer explorativen Subgruppenanalyse beobachtet, die auf Personen beschränkt war, die ZnT8-Antikörper-negativ waren. Hierbei lag der ICER innerhalb der üblicherweise für die Zahlungsbereitschaft herangezogenen Schwellenwerte. Dieser Befund basiert jedoch auf einer einzelnen explorativen Subgruppenanalyse, beruht auf starken Modellannahmen und wurde in nachfolgenden Evaluationen oder in anderen Zuständigkeitsbereichen nicht bestätigt.

Soziale, organisatorische, ethische und rechtliche Aspekte

Für eine erfolgreiche Implementierung von Teplizumab sind strukturelle und personelle Ressourcen erforderlich. In Österreich werden geeignete Patient:innen im Stadium 2 des T1D derzeit überwiegend zufällig identifiziert, da systematische Screeningprogramme fehlen. Im Vergleich dazu haben andere Länder z. T. bereits Screeninginitiativen gestartet (z. B. Italien mit gesetzlich verankertem Screening, Deutschland mit der Fr1da-Studie).

Die Verabreichung und Implementierung von Teplizumab erfordern spezialisierte (pädiatrische) diabetologische Teams sowie die Integration in die bestehende Versorgung der Diabeteszentren. Die Erwartungen der Patient:innen an Teplizumab sind ambivalent: Einerseits bestehen Hoffnungen auf eine Verzögerung des Krankheitsbeginns und eine Reduktion krankheitsbedingten Stresses, andererseits gibt es Bedenken hinsichtlich möglicher Nebenwirkungen, der Langzeitsicherheit sowie der emotionalen Belastung während der Behandlung.

Ethische Aspekte bei der Implementierung von Teplizumab umfassen den Ausschluss von Kindern unter 8 Jahren, potenzielle Ungleichheiten im Zugang aufgrund begrenzter Ressourcen sowie die Notwendigkeit, Investitionen in neue Therapien mit etablierten Interventionen abzuwägen. Weitere soziale Aspekte betreffen die Stigmatisierung von Diabetes und Herausforderungen bei der schulischen Integration.

Bestehende Register, etwa das österreichisches Diabetes Inzidenzregister für Kinder und Jugendliche, die Diabetes-Patient:in-Verlaufsdokumentation oder das Tiroler Diabetesregister, bieten potenziell eine Grundlage für die anwendungsbegleitende Dokumentation von Teplizumab.

Öffentliche Investition

Teplizumab geht auf akademische Forschung an der Yale University zurück und basiert auf frühen Arbeiten zu anti-CD3-monoklonalen Antikörpern zur Immunmodulation bei T1D. Die Entwicklung wurde über einen Zeitraum von mehr als drei Jahrzehnten mit rund € 19,2 Millionen an öffentlichen Fördermitteln unterstützt. Die kommerzielle Entwicklung erfolgte in mehreren Etappen: MacroGenics lizenzierte die Rechte von Yale, arbeitete mit Eli Lilly zusammen und übertrug das Produkt später an Provention Bio, das die Entwicklung bis zur FDA-Zulassung im Jahr 2022 vorantrieb. Damit wurde Teplizumab zur ersten zugelassenen Therapie zur Verzögerung der Progression in Stadium 3 bei T1D. Im Jahr 2023 erwarb Sanofi Provention Bio für $ 2,9 Milliarden, was den Abschluss eines langen Innovationsprozesses von öffentlich finanzierter Forschung bis zur globalen Kommerzialisierung markiert.

Weitere Entwicklungen

Die klinische Forschung zu Teplizumab ist umfangreich und umfasst derzeit sechs laufende Studien von Phase 1 bis Phase 4. Drei Studien rekrutieren aktiv, darunter Untersuchungen zu metabolischen Endpunkten im Stadium 2 (NCT06338553), zur Wirksamkeit und Sicherheit in japanischen Populationen (NCT06791291) und zum Erhalt der Betazellfunktion im Stadium 3 (NCT07088068). Die geplanten Studienabschlüsse liegen zwischen 2027 und 2028. Zwei weitere aktive Studien ohne Rekrutierung betreffen die Langzeitsicherheit (NCT04598893) sowie das Stadium 2 bei pädiatrischen Patient:innen (NCT05757713). Zusätzlich ist eine Plattformstudie zum Vergleich von Teplizumab mit Anti-Thymozyten-Globulin (NCT07216391) geplant, deren Abschluss für 2029 vorgesehen ist. Darüber hinaus wird Teplizumab in den USA derzeit von der FDA im Rahmen eines Zulassungsverfahrens für T1D im Stadium 3 geprüft, was potenziell auch für die weitere europäische Entwicklung und die Zulassungserweiterung relevant sein könnte. Neben Teplizumab befinden sich auch neun weitere Wirkstoffe zur Behandlung von T1D in der Entwicklung, davon zwei für T1D im Stadium 2 und sieben für neudiagnostiziertes Stadium 3. Zulassungsentscheidungen der EC werden zwischen 2030 und 2033 erwartet.

Schlussfolgerung

Teplizumab stellt die erste krankheitsmodifizierende Therapie für T1D im Stadium 2 dar und zeigt in der verfügbaren Evidenz eine Verzögerung der Progression zur klinischen Manifestation (Stadium 3). Dieser Wirksamkeitsnachweis basiert jedoch ausschließlich auf einer einzelnen randomisierten kontrollierten Studie mit kleiner Stichprobe und erlaubt keine belastbaren Aussagen zum patient:innenrelevanten Nutzen über den Zeitpunkt der klinischen Manifestation hinaus. Insbesondere fehlen Nachweise für klinisch relevante Vorteile wie die Vermeidung akuter Komplikationen, eine verbesserte Stoffwechsellage oder eine nachhaltige Reduktion der Krankheitslast. Obwohl Daten zur Anwendung von Teplizumab fehlen, würde eine Verlängerung der Stadium-2-Phase des T1D voraussichtlich die Stoffwechsellage verbessern und das Auftreten einer DKA verzögern. Die verfügbaren Sicherheitsdaten beschränken sich auf einen einzelnen Behandlungszyklus und eine abschließende Beurteilung der Langzeitsicherheit ist derzeit nicht möglich.

Die ökonomische Bewertung ist aufgrund hoher initialer Kosten, fehlender österreichischer Preisinformationen und weitgehender Annahmen zur Größe der Patient:innenpopulation mit hoher Unsicherheit behaftet. Darüber hinaus bestehen organisatorische Hürden, insbesondere hinsichtlich der frühen Identifikation geeigneter Patient:innen sowie des Fehlens etablierter Screening- und Versorgungspfade sowie begrenzter personeller Kapazitäten und struktureller Voraussetzungen in der Diabetesversorgung.

Obwohl eine Verzögerung des Krankheitsbeginns insbesondere im Kindes- und Jugendalter grundsätzlich von hoher klinischer Relevanz sein kann, bleibt der patient:innenrelevante Zusatznutzen von Teplizumab darüber hinausgehend bislang nicht ausreichend belegt. Da Langzeitdaten fehlen, ist derzeit keine abschließende Nutzen-Risiko-Bewertung möglich, insbesondere vor dem Hintergrund, dass Teplizumab den Krankheitsbeginn verzögert, jedoch das Auftreten einer chronischen Erkrankung nicht verhindert. Der Stellenwert von Teplizumab ist daher gesamtheitlich im Kontext der österreichischen Diabetesversorgung zu bewerten.

Executive summary

This Health Technology Assessment (HTA) report evaluates teplizumab (TEIZEILD®) for delaying the onset of stage 3 type 1 diabetes (T1D) in adults and children (≥ 8 years) with stage 2 T1D.

Disease background

T1D is a chronic, immune-mediated metabolic disease characterised by destruction of insulin-producing pancreatic beta cells, resulting in relative or absolute insulin deficiency. The disease commonly develops through presymptomatic stages with detectable beta-cell autoimmunity and progresses to clinically manifest hyperglycaemia. Three stages are distinguished: (1) the presence of multiple autoantibodies with normoglycaemia and no symptoms; (2) autoantibody positivity with dysglycaemia in the sense of impaired glucose tolerance, still without clinical symptoms; and (3) clinical manifestation with typical symptoms such as increased urine output (polyuria), excessive thirst (polydipsia) and weight loss, with diabetic ketoacidosis (DKA) occurring in multiple cases.

T1D accounts for approximately 5-10% of all diabetes cases but represents the most common form of diabetes in children and adolescents in high-income countries. In Austria, the incidence among children under 15 years of age is 28.6 per 100,000 person-years; approximately 3,500 children and adolescents are living with T1D. National prevalence data for adults are not available.

The management of T1D in Austria adheres to the Austrian Diabetes Association guidelines and international recommendations. Presymptomatic stages (stages 1 and 2) are not part of an established care pathway because there is no clinical disease. Upon reaching clinical stage 3, structured diabetes care is initiated to achieve stable glycaemic control, prevent acute complications, and reduce the risk of long-term sequelae. Lifelong insulin therapy is the cornerstone of treatment in stage 3 and is administered via multiple daily injections or insulin pump therapy, with increasing use of automated insulin delivery systems. Continuous glucose monitoring (CGM) is standard for treatment adjustment, and structured education programmes, multidisciplinary care, and psychosocial support are integral components of care, particularly in paediatric settings.

Overview of the new medicinal product

Teplizumab is a monoclonal antibody that modulates the autoimmune response in stage 2 T1D. It targets CD4+ and CD8+ T cells and reduces their autoreactive activity against insulin-producing beta cells, thereby preserving endogenous insulin secretion for a longer period and delaying progression to stage 3 T1D. Treatment is administered as a single 14-day intravenous course with body-surface-area-adjusted dosing. Comprehensive baseline assessments are required prior to treatment initiation, and close clinical and laboratory monitoring is recommended during therapy.

In November 2025, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion for teplizumab for patients aged 8 years and older with stage 2 T1D to delay progression to stage 3. The assessment was conducted under the Priority Medicines (PRIME) programme for medicines addressing high unmet medical need. The final marketing authorisation by the European Commission is expected in the first quarter of 2026[2].

Clinical effectiveness and safety

The clinical effectiveness and safety assessment of teplizumab in stage 2 T1D is based on a single randomised controlled trial (TN-10), which investigated the medicinal product for delaying progression from stage

[2] Addendum: Teplizumab was approved by the European Commission on 8 January 2026.

2 to stage 3 T1D in patients aged 8 years and older. A total of 76 patients were randomised, with 44 receiving teplizumab and 32 receiving placebo. Most participants were younger than 18 years and had ≥3 autoantibodies. Mean long-term blood glucose values (HbA1c values) were within the normal range (5.2% vs 5.3%).

After a median follow-up of 24.5 months, teplizumab significantly delayed the onset of clinical T1D. Median time to diagnosis was 48.4 months in the teplizumab group compared to 24.4 months in the placebo group ($p<0.01$), with consistent results in extended follow-up, ranging from 24.5 up to 80.5 months. C-peptide levels, as a marker of endogenous insulin production, were higher in the teplizumab group after a median of 30.3 months (1.94 vs 1.72 pmol/ml; $p<0.01$), indicating preserved insulin secretion compared with placebo. Average glucose exposure over time was lower with teplizumab (164 vs 177 mg/dl; $p<0.05$), while HbA1c values showed no significant difference. The safety analysis included all randomised patients. Adverse events occurred in nearly all patients in the teplizumab group, where 112 events were reported, primarily haematological disorders (75%, predominantly lymphopenia) and skin reactions (36%). Severe adverse events (Grade 3) were primarily observed within the first 30 days, mostly lymphopenia, which resolved in nearly all cases. Discontinuations of the 14-day treatment course occurred in both the teplizumab group (n=3) and the placebo group (n=4). The reasons were laboratory abnormalities, inabilities to establish intravenous access, and rash. No deaths were reported in the TN-10 study.

The risk of bias in the TN-10 was rated as low. However, the validity is limited by the small sample size, differences in the age profiles of the treatment arms, the descriptive follow-up, the post-hoc analyses, and the restricted generalisability to the Austrian population. Additionally, data on quality of life and long-term clinical benefit are lacking.

Economic aspects

The marketing authorisation holder did not submit a price proposal for Teplizumab, nor a health economic evaluation, or budget impact analysis (BIA) for Austria. Based on the UK pharmacy purchase price of €12,515 per 2-ml vial, the estimated overall acquisition cost is €175,206 for a 14-day treatment course. The 5-year direct healthcare cost per patient treated in an outpatient clinic with teplizumab is estimated at €180,948, compared to €10,971 for standard care, resulting in a net incremental cost of €169,975. Assuming five to ten patients treated annually, the net budget impact over five years is estimated at €6.28 million. However, a scenario analysis showed that administration costs increase approximately ninefold when teplizumab is administered in an inpatient setting, resulting in a net budget impact of around €6.9 million. In general, the main cost drivers are drug acquisition and administration.

Furthermore, four international health economic analyses found that teplizumab is associated with higher incremental costs than standard treatment for T1D, while the estimated incremental health gains are small. The incremental costs per person treated are in the range of several hundred thousand euros, whereas incremental health gains are generally estimated at around 0.3-0.5 quality-adjusted life years, and even lower in some sub-analyses. Given the uncertainties in the effect estimates and the limited evidence base, the reported cost-effectiveness ratios (ICERs) appear unfavourable. With respect to the country-specific cost-effectiveness threshold, teplizumab is not cost-effective based on the available data. An apparent exception was observed in an exploratory subgroup analysis limited to individuals who were ZnT8 antibody-negative. Here, the ICER was within the commonly used willingness-to-pay thresholds. However, this finding is based on a single exploratory subgroup analysis, relies on strong model assumptions, and has not been confirmed in subsequent evaluations or in other jurisdictions.

Social, organisational, ethical and legal aspects

The successful implementation of teplizumab depends not only on clinical outcomes but also on organisational readiness to deliver screening, diagnosis, treatment, and follow-up in an equitable and coordinated way. Identifying eligible patients at stage 2 T1D is challenging in the absence of systematic screening, as detection in Austria is predominantly incidental, whereas several other countries have begun implementing screening initiatives for early identification (e.g., Italy, with a legally mandated screening programme for T1D, and Germany, through the Fr1da study). Administration and implementation require specialised

paediatric diabetology teams and integration into existing care pathways. Teplizumab is intended to be administered in diabetes centres. Managing T1D imposes a substantial burden on children, young people, and caregivers, affecting mental health, family dynamics, and occupational and financial stability. Patient and caregiver expectations regarding teplizumab are mixed: while many express hope for delaying disease onset and reducing stress, concerns remain about potential side effects, long-term safety, and emotional responses during treatment. Ethical considerations include the exclusion of children under 8 years from treatment, potential inequalities in access due to resource constraints, and the need to balance investment in emerging therapies with established interventions. Additional social aspects include diabetes stigma and challenges in educational integration. Registry structures exist for documenting T1D in Austria and could be adapted for the application of teplizumab (e.g., the national incidence register for children and young people, the Diabetes Patient Follow-up Documentation Registry, or the Tyrol Diabetes Register).

Public investment aspect

Originating from academic research at Yale University, teplizumab emerged from early investigations into anti-CD3 monoclonal antibodies for immune modulation in T1D. The development was supported by approximately €19.2 million in public funding over more than three decades, primarily from US federal agencies for basic, preclinical, and clinical research. Commercial development progressed through several stages: MacroGenics licensed the rights from Yale, partnered with Eli Lilly, and later transferred the asset to Provention Bio, which advanced development leading to FDA approval in 2022 as the first therapy to delay the onset of stage 3 T1D in at-risk individuals. In 2023, Sanofi acquired Provention Bio for $2.9 billion, marking the culmination of a long innovation pathway from publicly funded research to global commercialisation.

Landscape overview

The clinical development programme for teplizumab is extensive, with six ongoing studies ranging from early phase 1 to phase 4 clinical trials. Three trials are actively recruiting, including investigations into metabolic outcomes in stage 2 T1D (NCT06338553); efficacy and safety in Japanese populations (NCT-06791291); preservation of beta-cell function in stage 3 T1D (NCT07088068), with completion dates between 2027 and 2028. Two additional studies are active but not recruiting: one focusing on long-term safety (NCT04598893) and one on paediatric stage 2 T1D (NCT05757713). A planned platform trial comparing teplizumab with anti-thymocyte globulin (NCT07216391) is expected to conclude by 2029. In addition, teplizumab is currently under FDA review in the United States for stage 3 T1D, which could also inform further European development and approval expansion. Beyond teplizumab, nine therapies are in development for T1D, two targeting stage 2 and seven for newly diagnosed stage 3 disease, with anticipated EC decisions between 2030 and 2033.

Conclusion

Teplizumab represents the first disease-modifying therapy for stage 2 T1D and has been shown, in the available evidence, to delay progression to clinical manifestation (stage 3). However, this effect is based solely on a single randomised controlled trial with a small sample size and does not support robust conclusions regarding patient-relevant benefit beyond the time of clinical manifestation. In particular, evidence for clinically meaningful benefits, such as reduced acute complications, improved metabolic stability, or sustained reductions in disease burden, is lacking. Although data on teplizumab administration are unavailable, extending the duration of stage 2 T1D is expected to improve metabolic control and delay the onset of DKA.

The available safety data are limited to a single treatment course and indicate an expected short-term safety profile; long-term data are lacking. The health-economic evidence is characterised by substantial uncertainty and, across multiple international economic evaluations, consistently indicates an unfavourable cost-benefit profile and budgetary implications for the Austrian healthcare system. In addition, substantial organisational barriers exist, particularly in the early identification of eligible patients and in the absence of established screening and care pathways.

Although a delay in disease onset, particularly in children and adolescents, may be highly clinically relevant, the patient-relevant additional benefit of teplizumab has not yet been sufficiently demonstrated. Due to the lack of long-term data, a conclusive benefit–risk assessment is currently not possible, particularly given that teplizumab delays but does not prevent the onset of a chronic disease. The overall value of teplizumab, therefore, needs to be assessed holistically within the context of diabetes care in Austria.

1 Introduction

The objective of this report is to evaluate teplizumab (TEIZEILD®) for delaying the progression to stage 3 type 1 diabetes (T1D) in adult and paediatric patients aged 8 years and older with stage 2 T1D.

zu evaluierendes Medikament: Teplizumab bei Stadium 2 T1D

1.1 Disease background

Overview

Diabetes mellitus (DM) comprises a group of chronic metabolic conditions characterised by persistent hyperglycaemia resulting from inadequate insulin secretion, impaired insulin action, or both [1-3]. DM represents a major global health challenge, affecting an estimated 830 million people worldwide [3] with prevalence and incidence continuing to rise steadily over the past decades [4].

DM als zunehmende globale Krankheitslast

Within the broader group of DM conditions, T1D accounts for approximately 5-10% of all cases [4, 5]. Nevertheless, it represents the predominant form of diabetes diagnosed in children and adolescents in high-income countries [5].

Treatment of T1D requires lifelong insulin therapy, frequent glucose monitoring, and active patient self-management. Despite advances in diabetes technologies, individuals with T1D continue to face acute and long-term complications and a considerable treatment burden [4-6].

T1D: progressive Autoimmunform mit hohem Therapieaufwand

Classification

While the aetiology of DM is heterogeneous, this assessment focuses solely on T1D, the condition relevant to the technology under evaluation. According to the International Statistical Classification of Diseases and Related Health Problems (ICD), T1D is coded as 5A10 in ICD-11, classified as autoimmune beta-cell destruction leading to insulin deficiency [7].

ICD-11: T1D als autoimmune Betazellzerstörung mit Insulinmangel

Pathogenesis and disease stages

T1D develops through a T-cell-mediated autoimmune process directed against pancreatic beta cells. Autoreactive CD4+ and CD8+ T lymphocytes infiltrate the islets and interact with antigen-presenting cells, driving progressive beta-cell loss through inflammatory signalling. Diabetes-associated autoantibodies serve as markers of this autoimmune process and reliable indicators of ongoing beta-cell autoimmunity, although they are not direct mediators of cellular injury [5, 8]. Declining beta-cell function leads to impaired insulin secretion and subsequent abnormal glucose levels. Clinical onset occurs once endogenous insulin reserve becomes insufficient to maintain glucose homeostasis [4, 8].

T-Zell-getriebene Autoimmunpathogenese

The progression of T1D is characterised by presymptomatic and symptomatic stages defined by autoimmunity, glycaemic status and clinical presentation. This staging system, endorsed by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and international

international standardisiertes Drei-Stadien-Modell für T1D

paediatric societies (ISPAD), standardises the description of disease development [5, 8]:

- **Stage 1:** Presence of two or more diabetes-associated autoantibodies with normoglycaemia and no clinical symptoms. Individuals have established beta-cell autoimmunity and an increased risk of progression to clinical T1D [5, 8].
- **Stage 2:** Persistent positivity for two or more diabetes-associated autoantibodies with dysglycaemia (abnormal glucose levels not meeting thresholds for clinical T1D diagnosis) while remaining asymptomatic. This stage reflects advanced beta-cell dysfunction and is associated with faster progression to overt T1D, particularly at younger ages [4, 5, 8].
- **Stage 3:** Symptomatic T1D characterised by hyperglycaemia and meeting established biochemical diagnostic criteria described in the *Diagnosis* section [5, 6].

heterogene Progression trotz klarer Stadien

Although the staging model describes a predictable sequence from autoimunity to overt diabetes, progression is heterogeneous. In individuals with stage 1 T1D (normoglycaemia), approximately 44% progress to stage 3 within five years, with 80–90% progressing within 15 years. Evidence also indicates that individuals with positivity for more than two diabetes-associated autoantibodies have a 70% risk of developing clinical T1D within 10 years, rising to 84% within 15 years. However, not all individuals with Stage 1 or Stage 2 progress; some remain stable for many years, particularly when seroconversion occurs at older ages or when metabolic abnormalities are absent [2, 5, 8].

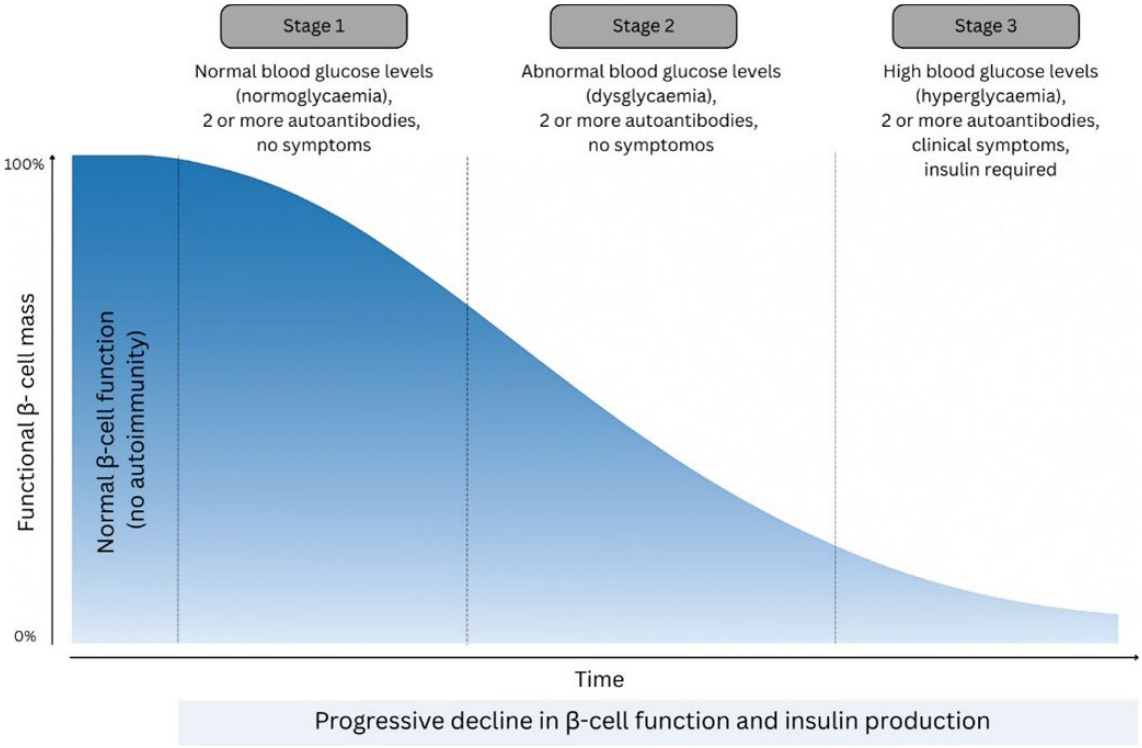


Figure 1-1: Schematic representation of the natural history and staging of T1D, illustrating the progressive decline of beta-cell function from the presymptomatic to symptomatic phase, modified according to Insel et al., 2015 [8]

Diagnosis

Stadium 1 und 2 bleiben in Österreich (Ö) meist unentdeckt

The diagnostic approach for T1D depends on the disease stage. Presymptomatic stages 1 and 2 are defined by immunological and metabolic abnormalities. Identifying these stages requires targeted screening for autoantibodies and, for stage 2, also assessment of dysglycaemia (e.g., fasting plasma glucose, oral glucose tolerance test [OGTT] or continuous glucose monitoring (CGM)). Such screening is not part of routine clinical practice in Austria and remains uncommon internationally. Although high-income countries have begun to expand screening activities in recent years, presymptomatic T1D is still mainly detected in research settings, structured family-based programmes or among individuals with elevated genetic risk [1, 2, 9].

Früherkennung derzeit nur im eingeschränkten Rahmen

Austrian clinical experts consulted for this health technology assessment (HTA) confirmed that stages 1 and 2 are currently identified only sporadically [10]. Outside of research settings, autoantibody testing is typically initiated only once clinically relevant dysglycaemia is already present. Consequently, most individuals progress from an unrecognised presymptomatic phase directly to stage 3 T1D, without access to structured monitoring or stage-specific clinical management prior to diagnosis.

Diagnose von Stadium 3 anhand biochemischer Kriterien

Stage 3 T1D is diagnosed when hyperglycaemia meets standard biochemical criteria (fasting plasma glucose ≥7.0 mmol/L, 2-h plasma glucose ≥11.1 mmol/L OGTT, Haemoglobin A1c [HbA1c] ≥6.5%, or random glucose ≥11.1 mmol/L with symptoms). Individuals typically present with polyuria, polydipsia, weight loss or fatigue, and diabetic ketoacidosis (DKA) remains a possible form of initial presentation [2, 5, 6].

Risk factors

Genetik starker Risikofaktor für T1D

T1D arises from the interaction of genetic susceptibility and environmental influences, triggering and sustaining autoimmune beta-cell destruction [5, 11]. Genetic susceptibility is a strong, established risk factor. While the absolute T1D risk in the general population is low (approximately 0.4%), first-degree relatives have substantially higher lifetime risks (around 6-7% for siblings, 6-9% for children of affected fathers, 1.3-4% for children of affected mothers, and >70% concordance in monozygotic twins) [5, 11]. High-risk human leukocyte antigen (HLA) class II haplotypes, particularly HLA-DR3-DQ2 and HLA-DR4-DQ8, confer the strongest inherited susceptibility, although fewer than 10% of individuals with these genotypes develop clinical disease [5].

Einfluss von Umweltfaktoren untersucht – Kausalität weitgehend unklar

However, most individuals diagnosed with T1D have no family history, reflecting the widespread distribution of risk alleles in the general population [11]. Environmental factors have been investigated, including viral infections, early-life exposures and microbiome-related influences, but causal pathways remain uncertain. Enteroviral infection shows the most consistent association, whereas evidence for other potential contributors remains inconclusive [4, 11]. Younger age at seroconversion is consistently associated with faster progression through the presymptomatic stages [5, 8].

Prognosis

T1D bleibt trotz Therapie komplikationsreich

Stage 3 T1D requires lifelong insulin replacement and carries a sustained risk of acute and chronic complications. Acute metabolic complications, primarily DKA and severe hypoglycaemia, are major contributors to morbidity and healthcare utilisation across all age groups [2, 5]. Chronic complications are closely linked to cumulative glycaemic exposure and may involve microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary artery disease, stroke, peripheral arterial disease) systems. Long-term evidence demonstrates that early and sustained glycaemic control reduces these risks [2, 4].

hohes Risiko für begleitende Autoimmunitäts-erkrankungen

Moreover, individuals with T1D have increased susceptibility to additional autoimmune conditions, most commonly autoimmune thyroid disease and coeliac disease, which may emerge before or after T1D diagnosis [2]. Long-term outcomes vary between individuals and are influenced by glycaemic control, diabetes duration, and access to diabetes technologies [2, 5].

früher Erkrankungsbeginn mit reduzierter Lebenserwartung assoziiert

In addition, age at onset appears prognostically relevant, with early-onset T1D associated with marked reductions in life expectancy (approximately 14 life-years lost in men and nearly 18 life-years lost in women for onset before age 10 years) [12].

Epidemiology

Ö mit moderat-bis-hoher T1D-Inzidenz

The incidence of childhood T1D varies substantially worldwide, ranging from 1.9 per 100,000 person-years (PY) in China to more than 50 per 100,000 PY in northern Europe [5]. Austria is a moderate-to-high-incidence country, with a standardised incidence of 28.6 per 100,000 PY in children under 15 years [2, 13].

Epidemiological data in Austria are mainly available for children, as national registries comprehensively cover the paediatric population but do not systematically capture adult-onset T1D. Clinical experts consulted for this HTA

confirmed that no official prevalence data are available for adults, while the number of children aged 0-14 years living with T1D in Austria is estimated at approximately 3,500 [10].

pädiatrische Daten gut erfasst: steigende T1D-Inzidenz seit 1989

The Austrian Diabetes Incidence Register (0-14 years, 1989-2021) records 5,888 paediatric DM cases, 94.3% of which are T1D. The incidence of paediatric T1D rose steadily from 1989 to 2011 (annual percentage change (APC) 4.57%, p<0.001), stabilised between 2012 and 2020 (APC 0.78%, p=0.379) and reached its highest level to date in 2021 at 28.6 per 100,000 PY (95% CI: 25.7-31.6) [2]. The increase coincided temporally with the COVID-19 pandemic; however, the registry does not record infection or vaccination histories, precluding causal interpretation. Age-specific analyses indicate that children aged 0-4 and 5-9 years experienced the steepest increases in incidence during and following this period, exceeding pre-pandemic projections [13].

Diagnosealter: Ø 8,5 Jahre, jedoch 50 % aller Neudiagnosen Erwachsene

The mean age at diagnosis in Austrian children is 8.5 years, consistent with international data showing a peak in late childhood [14]. Although T1D is commonly diagnosed in childhood, epidemiological evidence indicates that more than half of new T1D diagnoses occur in adulthood [15].

1.2 Standard of care in Austria

Overview

ÖDG-Leitlinien orientieren sich an internationalen Standards

In Austria, the clinical management of DM, including T1D, is guided by the national practice guidelines of the Austrian Diabetes Association (Österreichische Diabetes Gesellschaft, ÖDG). These guidelines cover all forms of DM and are published as a consensus document (Diabetes mellitus – Anleitung für die Praxis 2023) [2]. The recommendations adopted in Austria draw primarily from:

Empfehlungen für Kinder und Jugendliche: Orientierung hauptsächlich an ADA und ISPAD Leitlinien

- ADA Standards of Care [16]
- International Society for Paediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines [11]
- Deutsche Diabetes Gesellschaft (DDG) Guidelines [17]
- International Diabetes Federation (IDF) Guidelines [18]
- International consensus documents (e.g., European Association for the Study of Diabetes and ADA) [19]

For paediatric T1D, the ÖDG explicitly refers to the ISPAD classification and management framework, resulting in a largely harmonised international standard of care.

Standard of care for presymptomatic T1D in Austria

keine definierte Versorgung für Stadium 1 und 2 in Österreich

In Austria, individuals in stages 1 and 2 of T1D are not part of any defined clinical care pathway, as these stages do not meet the diagnostic criteria for DM and therefore fall outside the guidelines' scope. ÖDG defines DM solely by the presence of persistent hyperglycaemia, using established biochemical thresholds (see Chapter 1.1), and presymptomatic stages do not fulfil these criteria [2].

For individuals identified with stage 2 T1D, current management in Austria is limited to education and glucose monitoring. No disease-modifying treatment and no structured care pathway are available for this population, and entry

into routine diabetes care occurs only after progression to stage 3. This results in a substantial unmet need for interventions that could delay or prevent clinical disease onset.

internationale ISPAD Monitoringempfehlungen

The international consensus guidance by ISPAD outlines a structured monitoring approach for children and adolescents identified with presymptomatic autoimmune T1D [6]. According to this guidance, the purpose of the monitoring is as follows:

- *Detect metabolic progression early:* Regular assessments (e.g., HbA1c, glucose profiles, OGTT) aim to identify the transition from normoglycaemia (stage 1) to dysglycaemia (stage 2) and subsequently to overt hyperglycaemia (stage 3).
- *Prevent DKA at diagnosis:* Systematic monitoring in international programmes has been associated with a substantially lower incidence of DKA at clinical onset, reducing acute morbidity and avoiding intensive care admissions.
- *Support risk stratification and timely referral:* Monitoring enables estimation of progression risk (based on autoantibody profile, age and metabolic markers), enabling timely referral into specialist diabetes care when biochemical thresholds for stage 3 are approached.

Although this type of structured monitoring is not officially implemented in Austrian practice [2], clinical experts consulted for this HTA reported that, when presymptomatic cases are identified, components of these monitoring recommendations are generally applied. Specifically, experts consulted for this HTA indicated that the ISPAD Clinical Practice Consensus Guidelines are used as a reference [10]. These guidelines recommend monitoring glucose metabolism every three months in children and adolescents with stage 2 T1D, and every six months in adults over 18 years of age, using HbA1c and random glucose levels as core parameters [6].

General T1D treatment principles in Austria

T1D-Behandlungsziel: Stoffwechseleinstellung & Komplikationsvermeidung

Once biochemical criteria for T1D stage 3 are met, patients enter the Austrian diabetes care pathway. According to the ÖDG guideline, the overarching treatment goals are to achieve and maintain stable metabolic control, reduce glycaemic variability, prevent acute and long-term complications, and support quality of life and psychosocial well-being [2].

Insulin therapy

breites Insulinangebot ermöglicht individualisierte T1D-Therapie

Insulin is primarily administered subcutaneously via pens, syringes or insulin pumps; intravenous administration of regular insulin or rapid-acting analogues is limited to specific acute-care settings. Treatment choice is individualised based on metabolic characteristics, age, comorbidities, psychosocial context and patient preferences. The ÖDG recommends the use of modern insulin analogues and diabetes technologies when clinically appropriate and accessible. Clinical experts consulted for this HTA reported that approximately 60-70% of individuals with T1D in Austria use diabetes technologies, such as insulin pumps and CGM devices [2].

Glucose monitoring

CGM als bevorzugter Standard zur Glukoseüberwachung

CGM is considered the preferred method of glucose monitoring in routine T1D care, as it supports day-to-day insulin adjustment and contributes to

improved metabolic stability. CGM-derived metrics are used alongside HbA1c to guide therapy and assess glycaemic control [2].

Education and psychosocial care

Structured education and psychosocial support provided by multidisciplinary teams are integral components of routine T1D care in Austria, particularly at diagnosis and during adolescence and childhood [2].

Schulung & psychosoziale Betreuung integraler Bestandteil

Acute complications

Acute complications, particularly severe hypoglycaemia and DKA remain clinically relevant in T1D and contribute substantially to morbidity and healthcare utilisation, especially in children and at disease onset [2].

DKA & schwere Hypoglykämie besonders relevant

Follow-up care

Long-term management requires regular follow-up visits, ongoing monitoring of metabolic control, and structured screening for diabetes-related complications and associated autoimmune conditions [2].

regelmäßige strukturierte Nachsorge bei T1D notwendig

Paediatric aspects of care

Paediatric T1D care in Austria follows the same therapeutic principles as adult care but requires additional age-specific measures (e.g., more frequent medical visits) due to growth, puberty, variable insulin requirements and a higher risk of acute metabolic complications. Care is delivered in specialised paediatric diabetes centres by multidisciplinary teams providing age-appropriate education, psychosocial support and access to diabetes technologies, in line with national guidance from the ÖDG [2].

pädiatrische T1D-Versorgung erfordert zusätzliche altersabhängige Maßnahmen, z. B.

Insulin therapy in children often requires enhanced individualisation, particularly in infants and young children with very low insulin needs. Insulin pump therapy and hybrid closed-loop systems are therefore used more frequently in paediatric practice and are increasingly established as part of routine care. CGM is standard in paediatric T1D due to greater glycaemic variability and is used to guide ongoing therapy adjustment [2].

Pumpensysteme, hybride Systeme, Fortbildungen auch für Eltern, Erziehungsberechtigte und Lehrer:innen

In addition to medical management, structured education and psychosocial support involve not only patients but also parents, caregivers and school staff. Nutritional counselling is adapted to developmental stage and forms an integral part of care [2].

Acute complications remain an important concern in paediatric T1D. DKA at disease onset is considerably more frequent in children than in adults. Between 2012 and 2020, 44% of paediatric patients in Austria presented with DKA at diagnosis, reflecting delayed symptom recognition and the absence of early detection pathways [2].

hohe DKA-Rate bei Erstmanifestation bei Kindern

1.3 Medicinal product under evaluation

The medicinal product under evaluation in this HTA is teplizumab (TEIZEILD®), an anti-CD3 monoclonal antibody. Table 1-1 summarises the most important information on this product.

HTA-Bericht zu Teplizumab (TEIZEILD®)

Table 1-1: Pharmacological characteristics of teplizumab (TEIZEILD®) [20]

INN	
Product name	TEIZEILD®
Active substance(s)	Teplizumab
Anatomical Therapeutic Code (ATC)	A10XX01
Pharmacologic class	Anti-CD3 monoclonal antibody
MAH	Sanofi Winthrop Industrie

Abbreviation: INN ... International non-proprietary name,
MAH ... marketing authorisation holder

T-Zell-Modulation zur Erhaltung der Beta-Zell-Funktion

Teplizumab is a humanised, Fc-modified anti-CD3 monoclonal antibody that modulates the T-cell-mediated autoimmune response responsible for beta-cell destruction in stage 2 T1D. By binding to the CD3 component of the T-cell receptor on CD4+ and CD8+ T cells, it induces a controlled, transient activation phase followed by the development of partially exhausted CD8+ T cells with reduced cytotoxic activity toward pancreatic beta-cells. Subsequently, the immune system shifts toward a calmer, more regulated state, with fewer inflammatory signals and higher levels of markers associated with immune regulation. This results in reduced autoimmune attack on beta-cells and contributes to preservation of endogenous insulin secretion. Fc-engineering reduces binding to Fc receptors, minimising mitogenic signalling and cytokine-release reactions while maintaining the desired immunomodulatory effect. Overall, teplizumab modulates T-cell behaviour rather than eliminating T cells, creating a less aggressive immune response that helps slow the progression from stage 2 to stage 3 T1D [20-23].

Regulatory status

CHMP Opinion 2025; PRIME aufgrund hohen Bedarfs

Teplizumab received a positive opinion from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) in November 2025 for the treatment of individuals aged 8 years and older with stage 2 T1D with the aim of delaying the onset of stage 3 T1D. The medicine was evaluated under the Priority Medicines (PRIME) scheme because of the high unmet medical need. EMA regulatory information is summarised in Table 1-2.

Table 1-2: EMA regulatory information on TEIZEILD® [20]

Medicinal product	
Conditional marketing authorisation	No
Specific obligations of the conditional marketing authorisation	No
Additional monitoring	No
Accelerated approval	No
Exceptional circumstances	No
ATMP	No
PRIME	Yes
First approved indication	Yes; indicated to delay the onset of stage 3 T1D in adult and paediatric patients 8 years of age and older with stage 2 T1D.

Medicinal product	
Details of ongoing early access programs in the EU (as provided by the MAH)	National early access / named patient programmes reported in several European countries (including Austria)

Abbreviations: ATMP ... Advanced Therapy Medicinal Product, EU ... European Union, MAH ... Marketing Authorisation Holder, PRIME ... Priority Medicines, T1D ... type 1 diabetes

Posology and method of administration

14-tägige IV-Therapie

The final European Summary of Product Characteristics (SmPC) has not yet been published [20]. Therefore, the dosing, pre-treatment diagnostic evaluation and monitoring information presented here reflect the approved prescribing information from the US.

Teplizumab is administered as a single 14-day treatment course, given once daily by intravenous infusion (IV) over at least 30 minutes using a body-surface-area-based step-up dosing regimen (lower doses on days 1-4, followed by a higher maintenance dose on days 5-14) [24].

Requirements for pre-treatment diagnostic evaluation and monitoring

umfassende diagnostische Abklärung und engmaschiges Sicherheitsmonitoring

Premedication with an antipyretic, antihistamine and/or antiemetic is advised for at least the first five days to mitigate infusion-related symptoms. Before initiating teplizumab, a baseline clinical and laboratory assessment, including liver enzymes and a complete blood count, is recommended. Patients should also be evaluated for acute or chronic infections, and age-appropriate vaccinations should be completed prior to treatment initiation. During the 14-day treatment course, laboratory monitoring of blood counts and liver function is advised, and patients are observed for cytokine-release symptoms, infections, lymphopenia and other adverse reactions. Treatment may need to be interrupted or discontinued depending on the severity of these findings, according to the prescribing information [24].

Use in specific populations

nicht empfohlen bei Schwangerschaft, bei <8-und >65-Jährigen

Information on the use of teplizumab in specific populations, derived from the US prescribing information (as the European SmPC is not yet available), is summarised in Table 1-3.

Table 1-3: Use of teplizumab in specific populations [24]

	Teplizumab may cause fetal harm, and its use during pregnancy is not advised. For breastfeeding, the prescribing information states that a lactating woman may consider pumping and discarding breast milk during treatment and for 20 days after administration.
	Safety and efficacy have not been established for children <8 years, and use in this age group is not recommended.
	Clinical data in patients ≥65 years is limited.

2 Scope of assessment

This report aims to evaluate the clinical effectiveness, safety, and economic and other relevant aspects of teplizumab (TEIZEILD®) compared with SoC for delaying the onset of stage 3 type 1 diabetes (T1D) in adult and paediatric patients 8 years of age and older with stage 2 T1D.

Ziel: Wirksamkeits- und Sicherheitsanalyse von Teplizumab

2.1 Research questions

The following research questions will be answered in the present report:

1. **Clinical domain:**
   In patients with stage 2 T1D, is teplizumab more effective and safer compared to the current standard of care regarding patient-relevant outcomes?

   klinische Domäne: Wirksamkeit und Sicherheit

2. **Non-clinical domains:**
   What are the economic, ethical, organisational and social consequences of implementing teplizumab into the Austrian healthcare system?

   What were the key contributions of publicly funded research institutions and private companies in discovering and developing teplizumab as a therapy for the disease, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

   nicht-klin. Domänen: ökonomische, ethische, organisatorische, soziale Konsequenzen, sowie öffentliche Beiträge zu Entwicklungskosten

2.2 Inclusion criteria

Einschlusskriterien für relevante klinische Studien

zusätzlich Literatur für nicht klin. Bereiche berücksichtigt

Inclusion criteria for relevant clinical studies are summarised in Table 2-1.

Regarding the non-clinical domains, relevant economic literature was included with information about teplizumab prices, other direct medical costs and health economic evaluations. In addition, relevant literature for the organisational, ethical and social domain as well as literature on public investment, such as information on public grants, funding and contributions, was considered.

Table 2-1: Assessment scope, including the patient, intervention, comparison and outcome (PICO) question for the clinical domain

Population	Adult and paediatric patients 8 years of age and older with stage 2 diabetes mellitus type 1
Intervention	Teplizumab (TEIZEILD®)
Comparator	No treatment/placebo/active surveillance
Outcome	*Efficacy* ■ **Elapsed time from randomisation to the clinical diagnosis of diabetes** ■ **C-peptide level** ■ Glucose level ■ Oral glucose tolerance test ■ HbA1c level ■ Insulin secretion *PROs* ■ **Quality of life:** assessed with e.g., ADDQoL-19, DIDP, Diabetes QoL-Q *Safety* ■ **AEs in total** ■ **Serious AEs** ■ **Severe AEs (according to CTCAE Grade ≥3)** ■ **Death related to AEs** ■ **Treatment discontinuation due to AEs** ■ **Treatment interruption due to AEs** Rationale: Informed by clinical experts and scoping literature
Studies	Randomised controlled trials or meta-analyses If not available: non-randomised controlled studies, indirect treatment comparisons, observational studies, single-arm trials
Languages	German, English

Abbreviations: ADDQoL … Audit of Diabetes Dependent Quality of Life, AEs … adverse events, CTCAE … Common Terminology Criteria for Adverse Events, Diabetes QOL-Q … Diabetes Quality of Life Questionnaire, DIDP … DAWN-2 Impact of Diabetes Questionnaire, HbA1c … Haemoglobin A1c or glycated haemoglobin, PROs … patient-reported outcomes.

Note: Outcomes in **bold** *indicate critical efficacy and safety endpoints based on clinical expert consultation.*

3 Methods

This HTA employed a multi-domain assessment approach, following the European Network for Health Technology Assessment (EUnetHTA) methodology (see guiding questions in Chapter 3 of the Appendix) [25]. Methods were tailored to address the three research questions identified in Chapter 2, with a data cut-off of 10 December 2025.

Multi-Methoden-Ansatz: EUnetHTA-Leitfragen

Daten-Cut-off: 10. Dezember 2025

Systematic literature search and study selection

A systematic literature search was conducted on 25 November 2025, across four databases: Medline via Ovid, Embase, The Cochrane Library, and International HTA database (INAHTA). The search was limited to English and German, excluding conference abstracts (see detailed search strategies in Chapter 3 in the Appendix). After deduplication, 653 citations were identified. Additional searches in three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) yielded 55 potentially relevant hits. The marketing authorisation holder (MAH) also submitted a dossier on 10 December 2025, from which no new citations were identified.

1 systematische Literatursuche in 4 Datenbanken: 653 Treffer & Suche nach laufenden Studien

Herstellerdossier: keine zusätzlichen Infos

The study selection process followed a structured approach in which one researcher (MR) initially screened references at the abstract level, with a second reviewer (EM) reviewing the included abstracts and those with uncertainty. Full texts were screened independently, with arbitration by a third researcher (SGG) when disagreements arose. The study selection process is presented as a PRISMA flow diagram in Chapter 3 of the Appendix.

Literaturauswahl für Wirksamkeits- und Sicherheitsanalyse

Clinical effectiveness and safety assessment

Extraction of clinical effectiveness and safety data was systematically performed by one reviewer (MR) and cross-checked by a second reviewer (EM).

system. Datensynthese im 4-Augenprinzip

The risk of bias (RoB) of the included studies was assessed using the Cochrane RoB tool v.2 for randomised placebo-controlled studies [26], in duplicate by two reviewers (EM and MR), with any disagreements resolved by a third assessor (SGG).

RoB V2-Tool angewendet

As only a single randomised controlled trial was available, the evidence synthesis was conducted using a narrative approach. Consequently, the GRADE framework [27] was not applied, and the certainty of the evidence was assessed descriptively, taking into account study design, risk of bias, and precision of the reported outcomes.

keine GRADE-Bewertung

Economic evaluation methods

To collect price information on teplizumab, the Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) was contacted. In addition, the Pharmaceutical Pricing and Reimbursement Information (PPRI) network conducted a survey to gather confidential data on the economic aspects of teplizumab, including pricing and managed-entry agreements, across multiple European member states.

Preis-Infos von GÖG

Umfrage im PPRI-Netzwerk (vertraulich)

zusätzliche Handsuche nach ökonomischen Analysen zu Teplizumab

Regarding health economic evaluations of teplizumab, both the MAH's submissions and published analyses would have been considered. For the latter, we screened the literature identified through systematic and additional manual searches via Google.

Budgetfolgenanalyse für 5 Jahre

zahlreiche Annahmen getroffen, z. B. …

Moreover, according to the implementation regulation § 4(2) of the Austrian Appraisal Board, a three-year budget impact analysis (BIA), including the gross drug budget impact and additional administration-related costs, should be conducted. To accurately quantify the cost impact of the assessed therapy, a five-year time horizon was used. Additionally, the anticipated cost variations were accounted for through a scenario analysis. Overall, the following assumptions were made in the cost analysis:

- Austrian clinical experts were consulted to derive estimates of the patient population, as there are no registry data on stage 2 T1D available in Austria.
- In case the MAH does not submit an Austrian price proposal, a placeholder pharmacy purchase price from the UK, identified by the GÖG, is applied.
- In cases where the MAH does not submit an Austrian price proposal, a placeholder pharmacy purchase price from the UK, identified by the GÖG, is applied.
- For the cost calculations of teplizumab administration and stage 2 T1D management, hospital cost data from the Austrian procedure- and diagnosis-related groups (Leistungsorientierte Krankenanstaltenfinanzierung, LKF) catalogue were used. Costs of managing stage 3 T1D were adapted from the Austrian Diabetes Report 2017 [28]. The model calculations presented in this report were based on a prevalence-driven, bottom-up approach that synthesises numerous data sources from Austria (e.g., the Forum for Quality Assurance in Diabetology initiative, FQSD-Ö) and, where applicable, the international literature (primarily from Germany). Direct and indirect healthcare costs were calculated using 2014 data, whereby diabetes-specific costs were distinguished from other diabetes-related costs. Thus, the reported costs were exclusively those directly attributable to diabetes. The costs of individual therapies were also synthesised using a bottom-up approach, by linking care patterns with the respective Austrian-specific costs and tariffs or fees. Data from the LKF system, fee schedules of social insurance institutions, and the reimbursement code for drug prices were used for this purpose. Only the costs of blood sugar-lowering medication were determined using a top-down approach based on market data. For our cost analysis, the presented costs were adjusted to 2024 healthcare-specific price levels using the Austrian Consumer Price Index (CPI) health component, obtained from the Statistik Austria website [29].

… Teplizumab-Platzhalterpreis von UK

Kostendaten: LKF-Katalog & GÖG Diabetesbericht 2017 (präsentierte Kosten von 2014 auf 2024 konvertiert)

Organisational, ethical and social assessment

Bewertung nach EUnetHTA-Methodik

3 Quellen: Expert:innen, Patient:innen (Pat.), Literatur

The organisational, ethical and social aspects assessment utilised the EUnetHTA methodology. Data were gathered from three sources:

- Expert consultations with four leading clinicians (see Chapter 3 in the Appendix).
- Structured patient questionnaires (see Chapter 3 of the Appendix for details).
- Systematic literature review and manual search findings.

Development costs and public contributions

Entwicklungskosten und öffentliche Beiträge erhoben

The methodology for assessing development costs and public contributions involved several steps:

Identifizierung von: generischer oder (nicht) geschützter Bezeichnungen,

- Identifying product origins through searches for generic/non-proprietary names and trade names.

Produktherkunft & Grundlagenforschung,

- Searching for the earliest references to identify basic research and development support and research grants.
- Exploring databases on clinical trials and research funding.

Finanzierungsrunden, Fusionen & Übernahmen

- Examining company websites for information on funding rounds, sponsors, mergers, and acquisitions.
- Searching Securities and Exchange Commission (SEC) reports for information on acquisitions, patents and shareholders.
- Reviewing business news sources for additional information.
- Funding amounts were converted to € using the conversion rates as of 15 December 2025, from the Austrian National Bank [30].

zusätzlicher Überblick zu T1D-Therapien in Entwicklung

Additionally, a landscape overview of other therapies, which are in the development for stage 1 and 2 T1D, as well as recently diagnosed T1D, using the International Horizon Scanning Initiative (IHSI) database was compiled [31], supplemented by a review of other T1D medicinal products in the pipeline identified through current literature.

4 Relative clinical effectiveness and safety

This chapter evaluates the clinical effectiveness and safety of teplizumab compared to SoC for delaying the onset of stage 3 T1D in adult and paediatric patients aged 8 years and older with stage 2 T1D, addressing the clinical research question defined in Chapter 2.

4.1 Outcomes specified in the PICO

4.1.1 Efficacy outcomes

entscheidende Endpunkte für Wirksamkeit

The following outcomes were defined as ***critical***, based on expert consultation:

- Time to stage 3 T1D
- C-peptide level
- Quality of life (QoL)

Zeit bis Diagnose Diabetes Typ 1 Stadium 3

Time to stage 3 T1D refers to the time from randomisation until the T1D diagnosis is determined using an appropriate staging system (see Chapter 1).

C-Peptid-Spiegel

C-peptide level is a glycaemic control parameter that serves as a surrogate marker for endogenous insulin secretion. C-peptide is released by the pancreas in equimolar amounts with insulin, making it a reliable marker of the amount of insulin the body is still producing endogenously [32]. C-peptide can be measured using various approaches, including the area under the curve (AUC) during tolerance tests. Higher C-peptide levels indicate better residual pancreatic beta-cell function, whereas lower levels suggest that the insulin-producing beta cells are failing or have been destroyed [32].

Lebensqualität

QoL can be evaluated using patient-reported outcome measures (PROM), such as the Audit of Diabetes Dependent Quality of Life (ADDQoL-19), the DAWN-2 Impact of Diabetes Questionnaire (DIDP) and the Diabetes Quality of Life Questionnaire (Diabetes QOL-Q) [33]. QoL assessment captures the psychological burden of diagnosis, treatment-related side effects, and impact on daily functioning [34].

wichtige Endpunkte für Wirksamkeit, jedoch nicht entscheidungsrelevant

In addition, the following outcomes were defined as ***important***:

- Glucose level
- Oral glucose tolerance test (OGTT)
- Glycated haemoglobin A1c (HbA1c)
- Insulin secretion

Glukosespiegel

Glucose level is a glycaemic control parameter. Blood glucose concentration fluctuates with food intake and is controlled by insulin (which lowers it) and glucagon (which raises it) to maintain metabolic balance [35].

oraler Glukose-Toleranz-Test (OGTT)

The ***OGTT*** measures the body's capability to process glucose by administering a standard glucose dose orally while fasted and checking blood glucose levels at timed intervals (typically two hours later) [36]. This test is primarily used to diagnose diabetes and assess pancreatic beta-cell function.

HbA1c is a measure of glucose control levels and shows the average blood sugar levels over the past 90 days expressed as a percentage [37].

HbA1c-Spiegel

The ***insulin secretion*** parameter reflects pancreatic beta-cells functional capacity [35].

Insulinsekretion

1.1.1 Safety outcomes

The following safety outcomes were defined as ***critical***:

entscheidende Sicherheitsendpunkte

- Adverse events (AEs, overall)
- Serious adverse events (SAEs)
- Severe adverse events (according to CTCAE Grade ≥3)
- Death related to AEs
- Treatment discontinuation due to AEs
- Treatment interruption due to AEs

In this report, the AEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (2017), which defines an AE as any unfavourable sign, symptom, or disease temporally associated with a medical treatment, regardless of causality. Severity was graded on a scale of 1 to 5: Grade 1 (mild, asymptomatic); Grade 2 (moderate, minimal intervention indicated); Grade 3 (severe, hospitalisation or disabling); Grade 4 (life-threatening); and Grade 5 (death) [38].

unerwünschte Ereignisse (UEs) definiert nach CTCAE-Kriterien

4.2 Characteristics of the included studies

One clinical study evaluating the clinical efficacy and safety of teplizumab in adults and children (≥8 years) with stage 2 T1D was identified. The results of this study are primarily reported by Herold et al., 2019 [23], along with two follow-up publications [22, 39] and one post-hoc analysis [40]. The study was a phase 2 randomised, placebo-controlled, double-blind trial (TrialNet TN-10 anti-CD3 prevention trial).

1 Phase 2, randomisierte kontrollierte Studie identifiziert

Regarding the interventions, teplizumab or saline was administered intravenously daily for a 14-day outpatient course. The dose of teplizumab was increased until day four of treatment:

Verabreichung von Teplizumab in der Studie

- Day 0: 51 µg per m^2 of body-surface area
- Day 1: 103 µg per m^2
- Day 2: 207 µg per m^2
- Day 3: 413 µg per m^2
- Day 4 until 13: 826 µg per m^2

Abschluss der 14-tägigen Behandlung: 93 % (Teplizumab) vs. 88 % (Placebo)

Treatment was completed by 93% of teplizumab participants (41/44) and 88% of placebo participants (28/32).

The primary endpoint of the study was the time from randomisation to clinical diagnosis of T1D. The secondary endpoints included C-peptide responses to oral glucose, safety and mechanistic outcomes. Subgroup analyses were also

Primärer Studienendpunkt: Zeit bis Diagnose Diabetes Typ 1 Stadium 3

conducted based on age, HLA type, pretreatment C-peptide and glucose levels during OGTTs, and autoantibodies. OGTT was performed at three and six months and every six months thereafter (see Appendix Chapter 4.2).

medianes Follow-up bis 80,46 Monate

Across the different publications, the reported median follow-up ranged from 24.5 months in the primary analysis to 80.46 months in the longest extended follow-up. Further information on study characteristics is presented in Table 4-1.

Table 4-1: Characteristics of included study [23]

Reference/ ID	TN-10, Herold et al., 2019 [23]	TN-10, Sims et al., 2021 [22]	TN-10, Delgado et al., 2024 [39]	TN-10, Galderisi et al., 2025 [40]
Study type and design	Phase 2, randomised, placebo-controlled, double-blind trial	Extended FU of TN-10	Extended FU of TN-10	Post-hoc analysis of TN-10
Study population	Non-diabetic relatives of patients with T1D ≥8 years of age, at high risk for the development of clinical diabetes			
Study arms and sample size	Total: n=76 (Teplizumab: n=44; Placebo: n=32)	Analysis of 76 participants	Analysis of 76 participants	Analysis of 67 participants (Teplizumab: n=39; Placebo: n=28)
Study duration, data cut-off(s)	Median FU: 24.5 months 08/2010-06/2019 (primary analysis)	Median FU: 30.3 months 07/2011-03/2020	Median FU: 80.46 months Data cut-off: 07/2023	Median FU: 12 months
Locations	United States, Canada, Australia, Germany			
Primary endpoint	Delay or prevention* of the development of T1D in high-risk autoantibody-positive non-diabetic relatives of patients with T1D			
Other endpoints	C-peptide AUC Safety and tolerability Mechanistic outcomes	Glucose tolerance C-peptide AUC Insulin secretory rates	Changes in CD4+ and CD8+ T cells	OMM indices (insulin secretion, sensitivity and clearance during an OGTT) Clinical relevance and predictive capacity of OMM-estimated beta cell functional changes and insulin clearance
Documentation	*CSR: not provided* *Registry entry: NCT01030861* *Sponsoring status: sponsored (National Institute of Diabetes and Digestive and Kidney Diseases*			

Abbreviations: AUC ... area under the curve, CD ... cluster of differentiation, CSR ... clinical study report, FU ... follow-up, n ... number, NCT ... National Clinical Trial number, OGTT ... oral glucose tolerance test, OMM ... oral minimal model, T1D ... type 1 diabetes, TN-10 ... TrialNet

*Note: * Study objective stated "delay or prevention or" of T1D, though outcomes assessed delay in time to diagnosis rather than prevention.*

Ein- und Ausschlusskriterien

Eligible participants were aged 8-45 years, relatives of T1D patients, with at least two confirmed diabetes-related autoantibodies and abnormal glucose tolerance on OGTT, indicating stage 2 T1D [23]. Key exclusion criteria included overt diabetes haematologic abnormalities, immunosuppressive therapy, and pregnancy. Further eligibility criteria are described in Table 4-2 and in Chapter 4.2 of the Appendix.

Table 4-2: Inclusion and exclusion criteria [23]

Eligibility criteria	TN-10
Inclusion criteria	■ Aged between 8 and 45 years old ■ A relative of a proband with T1D ■ An abnormal glucose tolerance by OGTT confirmed within 7 weeks of baseline (visit 0) ■ At least two diabetes-related autoantibodies confirmed to be present on two occasions ■ Weigh at least 26 kg at randomisation
Exclusion criteria	■ Diabetes, or have a screening OGTT with: (1) Fasting plasma glucose ≥126 mg/dL, or (2) 2-hour plasma glucose ≥200 mg/dL ■ Lymphopenia (<1,000 lymphocytes/µL) ■ Neutropenia (<1,500 PMN/µL) ■ Thrombocytopenia (<150,000 platelets/µL) ■ Anaemia (Hgb <10 g/dL) ■ Be currently pregnant or lactating, or anticipate getting pregnant ■ Chronic use of steroids or other immunosuppressive agents ■ A history of asthma or atopic disease requiring chronic treatment

Abbreviations: Hgb ... haemoglobin, OGTT ... oral glucose tolerance test, PMN ... polymorphonuclear, T1D ... type 1 diabetes, TN-10 ... TrialNet

Study protocol amendments

Änderungen des Protokolls

The protocol underwent several amendments during the course of the trial [23]. Major changes included: revisions of sample size, enrollment period, and study duration (2012); inclusion of anti-ZnT8 as an eligible autoantibody (2012); and modified OGTT confirmation requirements for patients <18 years (single vs two abnormal tests, 2014). Additional amendments addressed safety monitoring and administrative aspects. Further details are provided in Chapter 4.2 of the Appendix.

4.3 Study population

Patient baseline characteristics

vergleichbare Baseline-Pat.-Charakteristika in den beiden Studiengruppen in der Primäranalyse

In the primary analysis, a total of 76 patients were randomised to the teplizumab (n=44) or placebo (n=32) group. Participants were positive for at least two autoantibodies, with the majority having three or more autoantibodies (73% teplizumab, 78% placebo). The majority of participants were younger than 18 years of age with 29 (66%) patients in the teplizumab and 26 (81%) in the placebo arm. Participants had to be relatives of individuals with T1D. Most patients were siblings (65% vs 50%), followed by offspring (14% vs 19%) and parents (14% vs 9%). Median HbA1c levels were in the normal range in both groups (5.2% vs 5.3%), consistent with stage 2 T1D [23]. Further details on patient baseline characteristics are presented in Table 4-3 below and in Chapter 4.3 of the Appendix. In addition, patient baseline characteristics of the post-hoc analysis distinguishing between slow and rapid progressors are also presented in the Appendix.

Table 4-3: Baseline characteristics of participants in the TN-10 trial [23]

Characteristic	TN-10	
Parameter	**Teplizumab (n=44)**	**Placebo (n=32)**
Age [years], median (IQR)	14 (12-22)	13 (11-16)
Age <18 years,n (%)	29 (66)	26 (81)
Female, n	19	15
Male, n	25	17
White, n	44	30
Asian, n	0	2
BMI [kg/m²], median (IQR)	19.6 (17.3-25.4)	21.5 (18.2-24.7)
HbA1c [%], median (IQR)	5.2 (4.9-5.4)	5.3 (5.1-5.4)
No. of autoantibodies positive (% of total)		
1	1 (2.4)	0 (0.0)
2	11 (25.0)	7 (21.9)
3	12 (27.3)	5 (15.6)
4	11 (25.0)	14 (43.8)
5	9 (20.5)	6 (18.8)

Abbreviations: BMI ... body mass index, HbA1c ... glycosylated haemoglobin, IQR ... interquartile range, n ... number, TN-10 ... TrialNet

4.4 Results on relative effectiveness and safety

4.4.1 Clinical efficacy outcomes

Time from randomisation to T1D diagnosis

stat. sign. längere mediane Zeit zur T1D-Diagnose mit Teplizumab vs. Placebo

The primary analysis of TN-10 resulted in a statistically significant delay in progression to stage 3 T1D among participants treated with teplizumab compared with placebo. After a median follow-up of 24.5 months, the estimated median time to clinical diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group (HR 0.41, 95% CI 0.22-0.78, p<0.01) [23].

Two subsequent follow-up analyses of the same cohort showed a consistent direction of effect. At a median follow-up of 30.3 months, the estimated median time to T1D diagnosis was 59.6 months with teplizumab compared with 27.1 months with placebo (HR 0.457, p<0.05) [22]. At the longest reported follow-up of 80.46 months, estimated median time to diagnosis was 52.2 months and 27.3 months, respectively (p<0.01) [39].

C-peptide levels

stat. sign. höherer C-Peptid-Spiegel mit Teplizumab

The C-peptide levels were only reported for a median follow-up of 30.3 months, with average C-peptide AUC levels of 1.94 pmol/ml in the teplizumab group compared to 1.72 pmol/ml in the placebo group (p<0.01) [22].

Additionally, the post-hoc analysis by Galderisi et al., 2025 [40] revealed no significant differences in C-peptide AUC levels between slow-progressors, who remained diabetes-free during two years after treatment and rapid-progressors who did not. While statistically significant differences in C-peptide AUC levels between the teplizumab and placebo group emerged at three and six months, these differences were no longer significant by twelve months (see Chapter 4.4 in the Appendix).

jedoch keine stat. sign. Unterschiede zw. „Slow"- und „Rapid Progressors" nach 12 Monaten

Quality of life

No data on health-related QoL were reported in the TN-10 trial or its subsequent follow-up publications.

Other glycaemic parameters

Ergebnisse zu weiteren glykäm. Parametern:

Glucose AUC was reported at a median follow-up of 30.3 months. In the teplizumab group, glucose levels were significantly lower at 164 mg/dl compared to 177 mg/dl in the placebo group (p<0.05) [41].

HbA1c levels were reported at a median follow-up of 30.3 months. No statistically significant difference was observed in HbA1c AUC in the teplizumab group compared to placebo (5.27% vs 5.42%) [41].

stat. sign. Unterschiede hinsichtlich Glukosespiegel und Insulinsekretion

Insulin secretion was reported at a median follow-up of 30.3 months and in the post-hoc analysis. In Sims et al., 2021 secretion rate modelling showed changes in the teplizumab group's slope from –1,024 pmol/month pre-treatment to +1,086 pmol/month post-treatment (p<0.001), while the placebo group's slope changed from –1,245 pmol/month to –1,037 pmol/month (p=0.95), with a statistically significant between-group difference (p=0.01) [41].

Additionally, post-hoc analysis using the Oral Minimal Model (OMM) showed total insulin secretion at month 12 increased from baseline in teplizumab-treated participants (+20.3%) compared to placebo (p<0.01). Teplizumab-treated slow-progressors (diabetes-free participants) showed increased insulin secretion (+20.3%), while placebo rapid-progressors (participants who developed T1D) showed marked declines (–61.4%; p<0.05) [40]. Details of these results are provided in Chapter 4.4 in the Appendix.

Further efficacy results of the primary and follow-up analyses are presented in Table 4-4.

Table 4-4: Efficacy results of the TN-10 trial reported by Herold et al., 2019, Sims et al., 2021, and Delgado et al., 2024 [22, 23, 39]

Outcome measure; Study reference/ID	Herold et al., 2019	Sims et al., 2021	Delgado et al., 2024
	TN-10: teplizumab (n = 44), placebo (n = 32)		
	Teplizumab vs placebo	Teplizumab vs placebo	Teplizumab vs placebo
Median follow-up, months	24.5	30.3	80.5
Critical outcomes			
Median time to T1D diagnosis, months	48.4 vs 24.4	59.6 vs 27.1	52.2 (95% CI: 30.5-86.7) vs 27.3 (95% CI: 9.5-48.4)
HR (95% CI)	**0.41 (0.22-0.78)**	**0.457**	**NR**
p-value	p<0.01	p<0.05	p<0.01
C-peptide AUC, pmol/ml	NR	1.94[a] vs 1.72[a]	NR
p-value	NR	p<0.01	NR

Outcome measure; Study reference/ID	Herold et al., 2019	Sims et al., 2021	Delgado et al., 2024
	TN-10: teplizumab (n = 44), placebo (n = 32)		
	Teplizumab vs placebo	Teplizumab vs placebo	Teplizumab vs placebo
Quality of life	NR	NR	NR
Important outcomes			
T1D diagnosis, n (%)	19 (43%) vs 23 (72%)	22 (50%) vs 25 (78%)	28 (64%) vs 28 (87.5%)
HR (95% CI)	NR	0.457 (0.24-0.87);	NR
p-value	NR	p<0.05	p<0.05
Annualised rates of T1D diagnosis, %	14.9% vs 35.9%	NR	NR
Glucose AUC, mg/dl	NR	164[b] vs 177 [b†]	NR
p-value	NR	p<0.05	NR
HbA1c AUC, mean, % (IQR)	NR	5.27 (4.99, 5.55) vs 5.42 (5.29, 5.57)	NR
p-value	NR	p=0.14	NR
Insulin secretion slope pre- vs post-treatment, pmol/month	NR	−1,024 vs +1,086; p<0.001 vs −1,245 vs −1,037; p=0.95	NR
Difference, p-valued	NR	p<0.05	NR

Abbreviations: AUC … area under the curve, CI … confidence interval, HbA1c … glycated haemoglobin, HR … hazard ratio, IQR … interquartile range, n … number, NR … not reported, T1D … type 1 diabetes, TN-10 … TrialNet, vs … versus

Notes:

[a] *Average on-study C-peptide AUC (adjusted for age and baseline C-peptide; ANCOVA),*

[b] *Average on-study glucose AUC (adjusted for age and baseline glucose; ANCOVA),*

[c] *Rate of change in total insulin secretion in two hours after oral glucose in the first six months,*

[d] *p-values based on Wilcoxon signed rank (paired) test comparing the pre- vs. post-rx slopes by subject; evaluation of how much changes in these measures changed pre- vs post-rx by subject and across those subjects in each treatment arm,*

† *values taken from the supplement.*

Subgroup analysis

Subgruppenanalyse ohne Adjustierung für multiples Testen: Hinweise für größeren Teplizumab-Effekt für HLA-DR4/3, ZnT8-Antikörper und Baseline-C-Peptide <1,75 nmol/L

Pre-specified subgroup analyses in the TN-10 trial examined treatment effects according to age, HLA type, baseline C-peptide and glucose levels, and autoantibody profile. However, these analyses were not adjusted for multiple testing. Lower HRs indicating greater relative treatment effect of teplizumab were observed in participants with HLA-DR4 presence and HLA-DR3 absence (HR 0.20, 95% CI: 0.09-0.45 and HR 0.18, 95% CI: 0.07-0.45, respectively). Similarly, greater responses were reported in patients without anti-ZnT8 antibodies (HR 0.07, 95% CI: 0.02-0.26), and in those with baseline C-peptide responses below the median of 1.75 nmol/L (HR 0.19, 95% CI: 0.08-0.47). Other autoantibodies were not associated with treatment response [23].

4.4.2 Safety outcomes

Adverse events and serious adverse events

112 UEs (alle Grade) in der Teplizumab-Gruppe vs. 23 UEs in der Placebo-Gruppe

The safety outcomes were reported only by the Herold et al., 2019. AEs of all grades were more frequent in the teplizumab group (112 events in 44 participants) than in the placebo group (23 events in 32 participants). The most common AEs with teplizumab were haematologic disorders (75%, mainly lymphopenia; vs 6% with placebo) and skin reactions (36%, primarily rash; vs 3% with placebo). Pain and infections occurred at similar rates in both groups (11% teplizumab vs 9% placebo, each). Other AEs (e.g., pulmonary,

immunologic, cardiac, gastrointestinal, metabolic) occurred in fewer than 10% of participants in either group. Endocrine AEs occurred only in the placebo group (2 participants, 6%), as did hepatobiliary or pancreatic events (1 participant, 3%) [23]. Cytokine release syndrome was reported in one patient (2.27%) treated with teplizumab [42].

Hypoglycaemia and hyperglycaemia were reported as AEs only in the case of loss of consciousness or ketoacidosis [23].

Grad 3 UE in der Teplizumab-Gruppe: Lymphopenie

Additionally, 20 grade 3 AEs occurred in the teplizumab group, of which 15 involved lymphopenia during the first 30 days, resolved by day 45 in all participants except one (resolved by day 105). In contrast, no SAEs were reported in the placebo group [23].

Hinweis für mögliche Virus-Reaktivierung

Besides, at trial entry, 30 participants (39%) were EBV-seropositive (16 teplizumab, 14 placebo) and 17 (22%) CMV-seropositive (10 teplizumab, 7 placebo). Quantifiable EBV DNA was detected only in eight teplizumab-treated participants at weeks three to six post-treatment, with one experiencing pharyngitis, rhinorrhea, and cough. EBV DNA cleared by a mean day 77 (range: 43-134 days). One teplizumab-treated participant had detectable CMV DNA at day 20, which cleared by day 42 [23].

keine Therapieabbrüche bzw. -unterbrechungen aufgrund von UEs

Abbruch des 14-Tage-Zyklus: 3 vs. 4 Pat.

Regarding discontinuation, three participants in the teplizumab group and four in the placebo group did not complete the 14-day treatment course. The reasons were laboratory abnormalities, inability to establish intravenous access and rash. Treatment interruptions and serious AEs were not reported [23]. Further details on AEs are provided in Table 4-5.

keine schweren UEs

Deaths

keine Todesfälle in TN-10 Trial berichtet

No deaths were reported during the study or extended follow-up period [23].

Table 4-5: Safety results of the TN-10 trial [23]

Adverse event category	Teplizumab		Placebo	
	Event (n = 112) n	Participants (n= 44) n (%)	Events (n = 23) n	Participants (n = 32) n (%)
Blood or bone marrow	45	33 (75)	2	2 (6)
Dermatologic or skin	17	16 (36)	1	1 (3)
Pain	11	5 (11)	5	3 (9)
Infection	8	5 (11)	5	3 (9)
Gastrointestinal	5	4 (9)	3	3 (9)
Metabolic or laboratory	7	4 (9)	2	2 (6)
Pulmonary or upper respiratory	6	4 (9)	0	0
Constitutional symptoms	3	2 (5)	0	0
Allergy or immunologic	2	2 (5)	0	0
Endocrine	0	0	2	2 (6)

Abbreviation: n ... number of participants

4.5 Certainty of the evidence

4.5.1 Risk of bias

niedriges Gesamt-Verzerrungspotential des TN-10 Trials

The RoB of the TN-10 trial was assessed using the RoB tool v.2 [43]. All domains were judged to be at low risk of bias, resulting in an overall assessment of low risk (see Chapter 4.5 of the Appendix). Protocol amendments (including sample size revisions) were noted. Still, they were not considered to substantially affect the bias assessment, as these changes were transparently reported and the pre-specified endpoints remained consistent.

4.5.2 Statistical analysis and inconsistencies

Änderungen der Einschlusskriterien: auch Personen < 18 Jahre eingeschlossen

The study protocol was amended in 2014. The target sample size was revised from 144 to 71 participants due to slower-than-expected enrollment, and patients aged <18 years were eligible for inclusion. The power calculation was adjusted to detect a 60% risk reduction (HR 0.4) rather than the originally planned 50% reduction, while maintaining 80% power with the reduced sample size. It is expected that this change has not impacted the results. However, there was a substantial difference in the proportion of patients aged <18 years between the teplizumab (66%) and placebo (81%) groups, which may have introduced bias into the results.

keine Adjustierung für multiples Testen

Statistical testing was performed in the primary analysis [23], in extended follow-up analyses [21, 37], and in a post-hoc analysis [40]. However, no preplanned alpha adjustment for multiple testing across these post-trial observational follow-up analyses was documented. While the p-values reported at extended follow-up time points remain statistically significant and support the primary findings, they should be interpreted as descriptive, given the lack of a prespecified alpha adjustment for repeated testing (see Chapter 4.5. in the Appendix).

4.5.3 Overall certainty of the evidence

The certainty of the evidence was assessed descriptively, as only a single RCT was available, and the GRADE framework was not formally applied. The assessment considered study limitations (risk of bias), inconsistency, indirectness, imprecision, and potential publication bias. While the risk of bias was judged to be low, imprecision – resulting from the small sample size (n=71 after protocol amendment), wide confidence intervals, and the lack of alpha adjustment for multiple testing across follow-up analyses – may reduce the certainty of evidence. Additionally, the substantial imbalance in the proportion of participants aged <18 years between treatment groups (teplizumab 66% vs placebo 81%) introduces potential concerns regarding the generalisability and precision of effect estimates. Overall, the certainty of the evidence for most outcomes should therefore be considered moderate rather than high.

5 Price comparisons, treatment costs and budget impact

The GÖG searched for teplizumab prices in Europe and found a list price of £10,939.12 (*converted to €12,514.72 using the European Central Bank exchange rate of 10.12.2025*) per vial for the United Kingdom (UK). For the other 15 requested countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Sweden, and Spain), no price information is available.

UK Teplizumab-Preis: € 12.515 (konvertiert) pro Einzeldosisbehälter

This part includes confidential information!

For Austria, the MAH reported that no Austrian price for teplizumab is currently available.

Angaben des Unternehmens: kein Preis für Ö verfügbar

5.1 Pharmacoeconomic model(s)

5.1.1 Submitted pharmacoeconomic model

The MAH did not submit a pharmacoeconomic model to assess the cost-effectiveness of teplizumab.

5.1.2 Published economic evaluation based on pharmaco-economic models

Characteristics of the economic evaluations and applied models

Countries and perspectives

Four economic evaluations were identified across different healthcare systems; two studies (Mital et al., 2020 and 2025) were published in peer-reviewed journals [44, 45], while the other two represent HTA reviews of pharmacoeconomic evidence submitted by the MAH to Canada's Drug Agency (CDA-AMC) [46] and the UK's National Institute for Health and Care Excellence (NICE) [47]. The two studies by Mital et al. [44, 45] adopted a US healthcare system perspective, the ongoing NICE evaluation [47] followed the UK's National Health Service and Personal Social Services perspective, while the CDA-AMC recommendation draft [46] was developed for the Canadian context using both the healthcare payer and societal perspectives. Additionally, Mital et al. (2025) [43] extended beyond the traditional healthcare payer perspective in sensitivity analyses by accounting for the time cost to the patient (or a family member for children) of receiving immunotherapy.

4 gesundheitsökonomische Studien (USA, UK, Kanada):

Mital-Studien: abgeschlossen, NICE & CDA-AMC: laufend

Besonderheit: gesellschaftliche Perspektive (Mital et al. 2025 & CDA-AMC)

Notably, because the NICE and CDA-AMC evaluations [44] are still ongoing, less detailed information was available than in the completed studies by Mital et al. [44, 45].

Intervention, comparator, and target population

Interventionen: Teplizumab vs. keine Behandlung/ Standardversorgung

The interventions varied in complexity across the included evaluations. Mital et al., 2020 compared teplizumab with no treatment [41], while Mital et al., 2025 examined six prevention-treatment strategies that combined two preventive immune therapies (teplizumab, antithymocyte globulin [ATG]) or no therapy) with two insulin management strategies (AID systems or conventional insulin management) [45]. The NICE and CDA-AMC evaluations compared teplizumab to established clinical management or no intervention [46, 47].

Zielgruppe: Stadium 2 T1D, ≥8 Jahre

All studies focused on patients with stage 2 T1D (matching our predefined PICO; see Chapter 2), although with varying inclusion criteria. The NICE evaluation, the CDA-AMC recommendation, and the Mital et al., 2025 evaluation identified adult and paediatric patients aged eight years and older at risk of T1D [45-47]. In comparison, Mital et al. (2020) uniquely examined four target groups stratified by genetic markers (HLA-DR3/DR4) and ZnT8 antibody status, without teplizumab [44].

Mital et al. 2020: 4 Subgruppen nach genetischen Markern (HLA-DR3/DR4, ZnT8)

Model structure and time horizon

Markov-Modelle: lebenslanger Zeithorizont

All studies utilised Markov models with lifetime horizons, though structures varied. Both Mital studies adapted the Sheffield T1D Policy Model: Mital et al., 2020 employed a hybrid decision tree (for genetic/antibody testing) combined with Markov microsimulation [44], while Mital et al., 2025 used Markov microsimulation to track progression from pre-T1D to diabetes, complications, and death [45]. The NICE evaluation used a simpler three-state Markov model (stage 2 T1D, stage 3 T1D, death). Cycle lengths ranged from six months for NICE [43] to one year in the studies by Mitel et al. [44, 45]. Sensitivity analyses were conducted using 10- and 20-year horizons in both studies , while Mital et al., 2025 also examined both 10- and 20-year horizons [45]. For the CDA-AMC evaluation, no information was available regarding the model and time horizon [46].

Zykluslänge: 6 Monate bis 1 Jahr

verschiedene Sensitivitätsanalysen, z. B. 10-/20-Jahres-Horizont

Cost categories and utility values

Hauptkostenkategorien: Medikament, Verabreichung, Krankheitsmanagement

Cost categories showed substantial overlap, with all studies including drug acquisition, administration costs, and disease management costs. Both Mital studies included costs for genetic/antibody testing, annual healthcare costs, insulin treatment, physician visits, and management of diabetes complications [44, 45]. Mital et al., 2025 also included AID system costs and ATG-related serum sickness treatment costs [45]. The NICE evaluation comprehensively captured diagnostic testing for pancreatic islet autoantibodies, teplizumab-related resource use, stage-specific T1D costs, and adverse event management [47]. For the CDA-AMC evaluation, no cost source information was available [46].

Nutzwerte aus Literatur, stratifiziert nach Alter/Diabetesstatus

Utility values were consistently derived from published literature and stratified by age and diabetes status. Both Mital studies applied utility-specific estimates for pre-T1D vs diabetes states and for age groups (below or above 18 years) [44, 45]. Mital et al., 2025 specified pre-T1D utilities of 0.91 (age ≤18) and 0.90 (age >18), and diabetes utilities of 0.89 (age ≤18) and 0.85 (age >18), with complication-specific decrements ranging from –0.001 to –0.208 [45]. The NICE evaluation uniquely incorporated carer disutility (–0.04) for children and modelled the stage 3 T1D impact through three distinct disutility

components: one-off initial disutility at onset, fixed disutility across all cycles, and increasing disutility over time, reflecting accumulating complications [47]. The published draft of the CDA-AMC evaluation did not report on this [46].

Uncertainty testing and discount rates

umfassende Sensitivitätsanalysen, z. B. PSA, Grenzwert- und Szenarioanalysen

All studies conducted comprehensive sensitivity analyses. Mital et al., 2020 performed two-way sensitivity analyses on key cost drivers, explored alternative time horizons and age ranges, tested scenarios for diabetes risk extrapolation beyond five years, and conducted a probabilistic sensitivity analysis (PSA) [44]. Mital et al., 2025 conducted one-way sensitivity analyses (presented as tornado diagrams), PSA, threshold analyses of teplizumab price and ATG efficacy, and scenario analyses that varied AID system assumptions and time-cost inclusion [45]. The NICE evaluation tested scenarios that excluded diagnostic test costs and used an alternative discount rate (1.5%) and mortality estimation approaches [47]. For the CDA-AMC evaluation, no information was available in the published draft [46].

Diskontraten zwischen 3 % (US-Leitlinien) und 3,5 % (UK-HTA-Leitlinien)

Discount rates varied by jurisdiction from 3% per year in Mital et al., 2025 (following updated US guidelines) [45] to 3.5% per year in Mital et al., 2020 and the NICE evaluation (consistent with UK HTA guidelines) [44], while it was not reported in the CDA-AMC evaluation draft [46].

Model assumptions

Kernannahmen, z. B.: Start im Prä-T1D-Stadium, geringeres Risiko bei Behandlung, Teplizumab-Komplikationen ausgeschlossen (Mital), etc.

All evaluations assumed that individuals start in the pre-T1D health state and that treatment reduces the risk of progression to stage 3 T1D. Both studies by Mital et al. used diabetes-related complication probabilities from the Sheffield T1D Policy Model, excluding teplizumab-induced complications [44, 45]. Mital et al., 2020 specifically assumed that the annual risk of developing T1D among individuals with combinations of HLA-DR3 and HLA-DR4 alleles was the average of the T1D risks associated with each allele and used the cost of managing ketoacidosis as a proxy for diabetes-related complications-related healthcare costs [44]. Mital et al., 2025 made several critical assumptions [45]:

- ATG efficacy in preventing T1D was half that of teplizumab (base-case) because no randomised prevention trials were available.
- The beta-cell-preserving effects of immune therapies were not sustained after clinical onset of T1D.
- The AID systems affected glycaemic outcomes similarly regardless of prior immune therapy, and neither immune therapies nor AID systems affected insulin needs.
- The AID systems provided 0.3% improvement in HbA1c and 50-95% reduction in hypoglycaemia risk, while conventional insulin management comprised specific proportions of continuous glucose monitoring/pump combinations.

NICE-spezifische Annahmen, z. B.: TN-10-Studiendaten (923 Tage Follow-up); 6-Monats-Zyklen (Trial-Intervalle + UK-Praxis) höhere Mortalität in Stadium 3 vs. 2 (Allgemeinbevölkerung)

The NICE evaluation based clinical efficacy on the TN-10 trial data with extended follow-up (median 923 days), justified the 6-month cycle length as reflecting trial intervals and UK clinical practice testing frequency, assumed higher mortality in stage 3 vs stage 2 T1D (where general population mortality was applied), and assumed that complications take ten years to manifest [47]. Unlike Mital et al., 2020, NICE did not stratify by HLA risk groups as HLA testing is not a routine UK practice, and explicitly excluded screening costs as this was outside the evaluation's remit [47].

For the CDA-AMC evaluation draft, no information on model assumptions was available [46].

Results of the economic evaluations

The four identified economic evaluations consistently demonstrated that, at the respective assumed price in the base-case analyses, teplizumab is not cost-effective for delaying the onset of stage 3 T1D in individuals with stage 2 T1D. However, the magnitude of the cost-effectiveness gap varied considerably across jurisdictions and analytical approaches.

Kernergebnis: Teplizumab nicht kosteneffektiv (alle 4 Evaluationen)

The earliest model-based evaluation by Mital et al., 2020 [44] reported that for teplizumab priced at US$100,000, for the 14-day cycle providing treatment to all at-risk individuals generated higher QALYs (19.26 vs 18.72) but at substantially higher costs (US$418,846 vs US$360,904) compared to no treatment, resulting in an ICER of US$107,300 (€91,798) per QALY gained, above the US$100,000 per QALY threshold. Cost-effectiveness varied substantially by patient subgroup, with treatment targeted to individuals with negative ZnT8 antibodies showing the most favourable results (ICER: US$4,647/€3,976 per QALY gained compared to no treatment), whereas broader treatment approaches exceeded the US$100,000 per QALY gained threshold. Threshold analysis indicated that teplizumab would need to be priced below US$48,900 for the whole 14-day cycle to be cost-effective for the broader at-risk population. The cost-effectiveness results were sensitive to diabetes management costs and assumptions about long-term disease progression, with PSA indicating considerable uncertainty. Notably, a scenario analysis showed that if teplizumab could completely prevent T1D rather than merely delay onset, it would be cost-effective even at prices up to US$284,500 per 14-day cycle [44].

Mital et al., 2020 (USA): US$ 100.000 Preis für 14-Tage-Zyklus → ICER US$ 107.300 (€ 91.798)/QALY

ZnT8-negativ Pat. am kosteneffektivsten: US$ 4.647 (€ 3.976)/QALY

hohe ICER-Sensitivität: Diabetes-managementkosten & Progressionsannahmen

A subsequent analysis by Mital et al., 2025 [45] showed that preventive ATG therapy followed by AID was the most cost-effective strategy, with total lifetime costs of US$394,250 and 19.13 QALYs. In comparison, the combination of teplizumab with AID generated 0.25 additional QALYs; however, it required an additional US$153,673 in lifetime costs, yielding an ICER of US$ 622,771 (€532,799) per QALY gained. Overall, the evaluation showed that pairing immune therapies with AID systems increased economic value relative to conventional insulin management. Nevertheless, this advantage was insufficient to render teplizumab cost-effective at the assumed market price of $194,000 per 14-day cycle. The sensitivity analyses showed that teplizumab would require a 66% price reduction (to US$65,000 per 14-day cycle) for "teplizumab-AID" to become the most cost-effective strategy [45].

Mital et al., 2025 (USA): ATG-AID kosteneffektivste Strategie (US$ 394.250, 19,13 QALYs)

Teplizumab-AID: + 0,25 QALYs, aber + US$ 153.673 → ICER US$ 622.771 (€ 532.799)/QALY

The ongoing CDA-AMC assessment evaluates teplizumab at a submitted price of CAD$257,740 per treatment course [46]. The base-case analysis found that teplizumab increased lifetime costs by CAD$221,630 compared to no intervention, primarily driven by drug acquisition costs, which are only partially offset by reduced stage 3 T1D management expenses. The analysis predicted gains of 0.24 life-years and 0.31 QALYs (healthcare payer perspective) or 0.36 QALYs (societal perspective), resulting in ICERs of CAD$747,542 (€462,624) and CAD$608,736 (€376,722) per QALY gained, respectively [46].

CDA-AMC (Kanada): ICER: CAD$ 747.542 (€ 462.624)/QALY (Zahlerperspektive) bzw. CAD$ 608.736 (€ 376.722)/QALY (Gesellschaftsperspektive)

The ongoing evaluation from NICE [47] presented divergent cost-effectiveness estimates depending on the analytical approach. In the base case submitted by the MAH using UK-specific stage 3 T1D management costs, ICERs were £29,602 (€34,160) per QALY gained (deterministic analysis) and £28,400 (€32,772) per QALY gained (probabilistic analysis). These results appear to fall within NICE's typical £20,000-£30,000 per QALY gained threshold range. However, the NICE External Assessment Group's (EAG) base case, which incorporated alternative modelling assumptions, yielded substantially higher ICERs of £165,387 (€190,850) per QALY gained (deterministic) and £171,788

NICE (UK): MAH-ICER: £ 29.602 (€ 34.160)/QALY (deterministisch) bzw. £ 28.400 (€ 32.772)/QALY (probabilistisch) → kein bevorzugter ICER wegen erheblicher Modellunsicherheiten

(€198,236) per QALY gained (probabilistic). Hence, the appraisal committee could not identify a preferred ICER due to substantial model uncertainties and the need for additional analyses. The presented cost-effectiveness results were most sensitive to stage 3 T1D disease management costs, disease-duration-based disutilities, excess-mortality risk, and teplizumab administration costs. Further scenario analyses revealed that using a lower discount rate (1.5% vs 3.5%) had the greatest impact on the ICER, as lower discounting increases the present value of long-term outcomes [47].

Hauptlimitationen: Langzeitwirksamkeit unsicher (>5 Jahre)

90 % Nutzen in Extrapolationsperiode

fehlende Evidenz: kombinierte Therapien, Komplikationsreduktion

Modellunsicherheiten: Progression, Kosten, nicht quantifizierte Vorteile

The limitations of the reported results stem primarily from considerable uncertainty surrounding teplizumab's long-term efficacy and safety beyond the 5-year trial follow-up period. Mital et al., 2020 acknowledged that efficacy data were available for only five years and that efficacy among individuals with different HLA-DR3/DR4 allele combinations was unavailable, requiring assumptions about average T1D risks [44]. Mital et al., 2025 noted the absence of clinical trials examining combined effects of immune therapies with AID systems, theoretical ATG efficacy due to lack of randomised prevention trials, unknown long-term teplizumab efficacy, and inadequate capture of heterogeneity in treatment responses [45]. The CDA-AMC evaluation highlighted that the estimated ICER was highly sensitive to the parametric distribution used to model disease progression, with approximately 90% of incremental benefit occurring in the extrapolated period beyond median 24.5-month follow-up. Healthcare resource utilisation estimates for stage 3 T1D carried significant uncertainty as the regression model did not align with clinical expectations or Canadian literature, and screening was inadequately considered [46]. The NICE evaluation reflected that uncertainties in the model prevented identification of the most likely cost-effectiveness estimate, and several benefits, such as increased preparation time for stage 3 onset, prolonged C-peptide production benefits, improved outcomes in lower socioeconomic populations, and full caregiver/family impacts, remain unquantified. In addition, the appraisal committee also disagreed with modeling approaches for disease progression, disutility estimation, and stage 3 T1D cost calculations [47].

Below, Table 5-1 presents an overview of the main results. The detailed data of the included health economic evaluations of teplizumab are presented in Chapter 5.1 in the Appendix.

Table 5-1: Overview of main results of published health economic evaluations of teplizumab

Author, year [REF]	Country	Incremental costs (base-case: teplizumab vs control)	Incremental effects (base-case: teplizumab vs control)	ICER (base-case)	Cost-effective at national threshold?
Mital et al., 2020 [44]	USA	**Teplizumab to all at-risk vs no treatment*:** +US$57,942 (+€49,571) **Teplizumab to ZnT8 negative vs no treatment:** +US$1,203 (+€1,029)	**Teplizumab to all at-risk vs no treatment*:** +0.54 QALYs **Teplizumab to ZnT8 negative vs no treatment:** +0.26 QALYs	**Teplizumab to all at-risk vs no treatment*:** US$107,300 (€91,798) per QALY gained **Teplizumab to ZnT8 negative subgroup vs no treatment:** US$4,647 (€3,976) per QALY gained	Threshold US$100,000 per QALY gained: Teplizumab to all at-risk: ✗ Teplizumab to ZnT8 negative subgroup: ✓
Mital et al., 2025 [45]	USA	**Teplizumab-AID vs ATG-AID**:** +US$153,673 (+€131,472) **Teplizumab-AID vs no therapy-AID*:** +$145,528 (+€124.504)	**Teplizumab-AID vs ATG-AID**:** +0.25 QALYs **Teplizumab-AID vs no therapy-AID*:** +0.39 QALYs	**Teplizumab-AID vs ATG-AID**:** US$622,771 (€532,799) per QALY gained **Teplizumab-with AID vs no therapy-with AID*:** $373,149 (€319,240) per QALY gained	Threshold US$100,000 per QALY gained: Teplizumab-AID vs ATG-AID*: ✗ Teplizumab-with AID vs no therapy-with AID: ✗
CDA-AMC 2025 [46]	CAN	Teplizumab vs no intervention: **Healthcare payer:** +CAD$221,630 (+€137,158) **Societal:** NR	Teplizumab vs no intervention: **Healthcare payer:** +0.31 QALYs **Societal:** +0.36 QALYs	Teplizumab vs no intervention: **Healthcare payer:** CAD$747,542 (€462,624) per QALY gained **Societal:** CAD$608,736 (€376,722) per QALY gained	Threshold CAD$50,000-100,000 per QALY gained: ✗
NICE 2025 [47]	UK	*confidential*	*confidential*	Teplizumab vs established clinical management: **MAH analysis:** **Deterministic:** £29,602 (€34,160) per QALY gained **Probabilistic:** £28,400 (€32,772) per QALY gained **EAG analysis:** **Deterministic:** £165,387 (€190,850) per QALY, **Probabilistic:** £171,788 (€198,236) QALY	**Uncertain?** (MAH's ICER within £20,000-30,000 per QALY gained threshold, but committee could not identify preferred ICER due to model uncertainties)

Abbreviations: AID … automated insulin delivery, ATG … antithymocyte globulin, CAD … Canadian dollars, CAN … Canada, CDA-AMC … Canada's Drug Agency – Agence des médicaments du Canada, EAG … external assessment group, ICER … incremental cost-effectiveness ratio, MAH … marketing authorization holder, NICE … National Institute for Health and Care Excellence, NR … not reported, QALY … quality-adjusted life-year, ZnT8 … zinc transporter 8

Notes:

** self-calculated incremental values to compare with AT standard of care (no preventive treatment)*

*** ATG-AID dominated all the other 5 strategies.*

The incremental costs and ICERs shown in the table were converted to euros for comparison.
The currency conversion was based on exchange rates valid as of the report date (8 January 2026), using the OANDA Currency Converter (https://www.oanda.com/currency-converter).
Cost-effectiveness was assessed using the national thresholds and original currencies used in the original report.

5.2 Budget impact analysis

5.2.1 Budget impact analysis submitted by the manufacturer

The MAH did not submit a budget impact analysis (BIA) of teplizumab for Austria.

5.2.2 Austrian budget impact analysis

Eligible population and market share in years 1-5

fehlende Daten zu Stadium 2 T1D in Ö mangels bevölkerungsbasiertem Screening; Diagnose meist zufällig

Expert:innen-Schätzung: 5-10 Pat. pro Jahr

In Austria, the epidemiology of stage 2 T1D is poorly understood, as there are no general-population early-detection programmes. Moreover, no empirical estimates in the literature have been identified regarding the proportion of T1D patients in the general (unscreened) population who were diagnosed at stage 2. Clinical experts confirmed that in the absence of an organised screening, pre-symptomatic detection of T1D occurs primarily incidentally. In Austrian clinical practice, patients diagnosed with pre-symptomatic (stage 1 and 2) T1D are mainly children, adolescents and pregnant women [46]. To estimate the budget impact of teplizumab in Austria, a rough expert estimate of the eligible stage 2 T1D population was used, corresponding to five to ten patients per year based on incidental diagnosis. However, this adoption rate of teplizumab following its introduction remains uncertain, constituting a significant limitation of the present BIA.

Direct medical costs of teplizumab treatment

direkte medizinische Kosten berücksichtigt

Direct medical costs of teplizumab treatment comprise drug acquisition and administration, as well as disease management costs, incurred during stage 2 T1D and subsequently during stage 3 T1D.

Acquisition cost of teplizumab

Kosten: € 175.206 für 14 Tage (basierend auf UK-Apothekeneinkaufspreis)

The UK pharmacy purchase price of £10,939.12 per 2-ml vial, obtained via the GÖG, was used as a placeholder price in the analysis. Assuming a 14-vial treatment course using single-vial packs, the overall acquisition cost is €175,206 *(converted using the European Central Bank exchange rate of 10.12.2025 and rounded to the nearest integer).*

Administration costs

ambulante intravenöse Gabe mit täglichem Monitoring

In the base scenario, teplizumab intravenous infusions are expected to be administered in a hospital setting without hospitalisation [47], which in Austria corresponds to hospital outpatient clinics. Hospital administration including hospitalisation is explored in scenario analysis.

Verabreichungskosten: € 1.806

In addition, it was assumed that complete blood counts and liver enzyme tests would be performed daily before each teplizumab dose (in line with the NICE Assessment [47]), to monitor for cytokine release syndrome and lymphopenia. Premedication costs (nonsteroidal anti-inflammatory drug or acetaminophen, antihistamine, and/or antiemetic; see section 1.3 [24]) were excluded from the analysis, given their minimal impact. The overall administrative costs amount to €1,806, with a detailed per-item breakdown presented in Table 5-2.

Table 5-2: Teplizumab administration costs (hospital outpatient clinics), per patient

Procedure	Frequency	Unit cost	Total costs	Cost source
Hospital outpatient clinic IV administration	**14**	**€49**	**€686**	LKF day-care clinic catalogue: APG00.11
Liver enzyme and complete blood count	**14**	**€3**	**€42**	LKF day-care clinic catalogue: APG24.00
Clinical consultation	**14**	**€77**	**€1,078**	LKF day-care clinic catalogue: APG18.02 (proxy)
Sum		**129**	**€1,806**	

Abbreviations: LKF ... Leistungsorientierte Krankenanstaltenfinanzierung

T1D stage 2 monitoring costs

Stadium 2 T1D-Monitoring gemäß ISPAD-Leitlinien: vierteljährliche HbA1c- und Glukosekontrollen bei Kinderarzt/ärztin

Kosten € 344/Jahr

To estimate the resource use incurred by patients with stage 2 T1D, it was assumed that incidentally detected stage 2 T1D patients in Austria are children and adolescents, who are monitored in accordance with the ISPAD Clinical Practice Consensus Guidelines 2024 [11], as recommended by Austrian clinical experts. The guideline recommends that patients with stage 2 T1D under 18 years of age have their glucose metabolism assessed using HbA1c and random glucose tests, monitored every three months [11]. Furthermore, it was assumed that this monitoring takes place during a paediatric in-person consultation, preferably in paediatric diabetes centres. Overall, the management of stage 2 T1D is estimated to cost €86 per quarter, totalling €344 per year. A detailed breakdown of disease monitoring costs for stage 2 T1D is presented in Table 5-3.

Table 5-3: Disease management costs for stage 2 T1D, per patient

Procedure	Frequency per year	Unit cost	Annual cost	Cost source
Clinical consultation	4	€77	€308	LKF day-care clinic catalogue: APG18.02
Blood sampling	4	€3	€12	LKF day-care clinic catalogue: APG24.00
Random venous glucose test	4	€3	€12	LKF day-care clinic catalogue: APG24.00
HbA1c test	4	€3	€12	LKF day-care clinic catalogue: APG24.00
Sum		**€86**	**€344**	

Abbreviations: HbA1c ... glycosylated haemoglobin, LKF ... Leistungsorientierte Krankenanstaltenfinanzierung

T1D stage 3 costs

Stadium 3 T1D Kosten aus dem Diabetes Bericht 2017 (GÖG): € 3.712/Jahr (inflationsbereinigt, ohne Produktivitätsverluste und Spätkomplikationen)

Patients treated with teplizumab eventually progress to stage 3 T1D and begin to incur monthly costs associated with blood glucose-lowering therapy, diabetes management, and acute complications. The costs for stage 3 T1D were adopted from the GÖG 2017 diabetes report, which reported the total and per-patient costs of DM in Austria from both a societal and payer perspective [28]. The average total annual healthcare costs per patient with T1D were estimated at approximately €5,095, of which around 22% and 20% were attributable to productivity losses and late complications, respectively. After excluding these cost components and adjusting for inflation using the Austrian Cost Price Index (CPI; Health component), the direct healthcare costs of stage 3 T1D management were estimated at €3,712 per year, corresponding to €309 per month. The detailed per-item breakdown is presented in Table 5-4 below.

Table 5-4: Annual disease management costs for stage 3 T1D

Cost component	Total cost for Austria	Average per patient cost*	Component description
Blood glucose-lowering therapy	€34,080,000	€840	Insulins and other drugs
Diabetes management	€100,600,000	€2,481	Doctor's visits, eye exams, foot checks, test strips, lancets, pens, pen needles, glucose sensors, insulin pumps, etc.
Acute complications	€15,840,000	€391	Hypoglycaemic and ketoacidotic episodes
Sum	**€150,520,000**	**€3,712**	

*Note: * Costs per component were self-calculated based on the per-patient total and adjusted for inflation using the Austrian CPI Health component index.*

Standard of care costs

There is no active comparator for teplizumab in Austria. T1D patients detected at stage 2 are predominantly children and adolescents, who, as noted above, are monitored in accordance with the ISPAD Clinical Practice Consensus Guidelines 2024 [11]. Consequently, they are assumed to incur only costs associated with disease management: initially at stage 2 and subsequently at stage 3 following progression.

Komparator: ISPAD-gestützte Überwachung ohne aktive Behandlung

Overall treatment costs and per-patient comparison

Teplizumab represents a preventive treatment that has demonstrated an ability to delay progression to clinical diabetes in individuals with stage 2 T1D by a median of 25 months (see detailed results in Chapter 4). From a cost perspective, this effect increases time spent in the less costly stage 2 health state, deferring the entry into the higher-cost stage 3 health state.

Progressionsverzögerung: 25 Monate; kostenrelevant da länger in Stadium 2

Within the 5-year horizon applied in the present BIA, a patient treated with teplizumab incurs one-off acquisition and administration costs in year 1. Over the following 52 months (*corresponding to the median time to stage 3 onset in the teplizumab arm of the TN-10 trial, as assessed at 80-month follow-up*), the patient incurs stage 2 T1D management costs on a quarterly basis, totalling €1,462. For the remaining eight months of the 5-year period, monthly stage 3 T1D costs are incurred, totalling €2,472. **The overall 5-year direct healthcare expenditure associated with teplizumab use is estimated at €180,948 per patient, of which €177,012 (97.8%) is attributable to drug acquisition and administration.**

5-Jahres-Kosten pro Pat. mit Teplizumab: € 180.948 (97,8 % Medikament);

52 Monate Stadium 2, dann 8 Monate Stadium 3

By contrast, under current conditions without teplizumab, patients incur only costs associated with stage 2 monitoring, followed by costs for stage 3 T1D management. They are assumed to remain in stage 2 for 27 months (*corresponding to the median time to stage 3 onset in the placebo arm of the TN-10 trial at 80-month follow-up*). During this period, they incur stage 2 costs quarterly, resulting in an overall stage 2 expenditure of €774. Over the remaining 33 months of the 5-year time horizon, they incur monthly costs associated with stage 3 management, resulting in the total stage 3 expenditure of €10,197. **The overall 5-year per-patient expenditure for T1D disease management in a patient not treated with teplizumab is therefore estimated at €10.971.**

ohne Teplizumab: 27 Monate Stadium 2 (€ 774), dann 33 Monate Stadium 3 (€ 10.197);

Gesamt 5 Jahre: € 10.971

After deducting the expenditure on the standard of care, **the reimbursement of teplizumab results in a net incremental cost of €169,975 per patient.** By delaying the onset of T1D stage 3, teplizumab offsets a portion of the upfront costs during years 3 to 5 (see Table 5-5).

inkrementelle Kosten: € 169.975/Pat. (Offset ab Jahr 3 durch Stadium-3-Verzögerung)

Table 5-5: Per-patient cost comparison

Cost categories	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Drug acquisition	€175,206					**€175,206**
Drug administration[1]	€1,806					**€1,806**
Disease management: stage 2 T1D						
With teplizumab	€344	€344	€344	€344	€86	**€1,462**
Without teplizumab (SoC)	€344	€344	€86	€0	€0	**€774**
Disease management: stage 3 T1D						
With teplizumab	€0	€0	€0	€0	€2,472	€2,472
Without teplizumab (SoC)	€0	€0	€2,781	€3,708	€3,708	€10,197
Total						
With teplizumab	**€177,356**	**€344**	**€344**	**€344**	**€2,558**	**€180,946**
Without teplizumab (SoC)	**€344**	**€344**	**€2,867**	**€3,708**	**€3,708**	**€10,971**
Net cost difference	**€177,012**	**€0**	**– €2,523**	**– €3,364**	**– €1,150**	**€169,975**

Abbreviations: SoC ... standard of care, T1D ... diabetes type 1

Note: [1] administration in hospital outpatient setting

Net drug-budget impact in years 1-5

geschätztes Pat.-Volumen: 5-10/Jahr (36 über 5 Jahre);

Netto-Budgetimpact: € 6,28 Mio. vs. Standardversorgung

The actual budget impact of reimbursing teplizumab will depend on the number of patients eligible for treatment and the rate of uptake. Applying clinical experts' estimate of five to ten patients treated per year over the 5-year time horizon, the net budget impact of reimbursing teplizumab for the total indicated population of 36 patients will be approximately €6.28 million over the first five years, compared to the amount spent on the standard of care (disease management of patients in stage 2 and stage 3). A detailed breakdown by cost categories is presented in Table 5-6.

Table 5-6: Net budget impact of teplizumab over 5 years

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Total
New pts treated p.a.	5	6	7	8	10	36
Acquisition cost	**€876,030**	**€1,051,236**	**€1,226,443**	**€1,401,649**	**€1,752,061**	**€6,307,419**
Administration costs	**€9,030**	**€10,836**	**€12,642**	**€14,448**	**€18,060**	**€65,016**
Stage 2 management	**€1,720**	**€3,784**	**€6,192**	**€8,944**	**€11,094**	**€31,734**
Stage 3 management	**€0**	**€0**	**€0**	**€0**	**€12,360**	**€12,360**
Teplizumab costs	€886,780	€1,065,856	€1,245,277	€1,425,041	€1,793,575	€6,416,529
SoC costs (stage 2+stage 3)	€1,720	€3,784	€18,807	€40,902	€67,049	€132,262
NET BUDGET IMPACT	**€885,060**	**€1,062,072**	**€1,226,470**	**€1,384,139**	**€1,726,526**	**€6,284,267**

Abbreviations: p.a. ... per annum, pts ... patients, SoC ... standard of care, T1D ... diabetes type 1

Scenario analysis

stationäre Verabreichung: Kosten steigen auf € 18.354/Pat. (Tagessatz Pädiatrie € 1.311); Budget Impact entsprechend höher

In the scenario analysis, it was assumed, based on the expert input, that teplizumab administration in Austria would require patient hospitalisation. This reflects the fact that diabetes hospital outpatient clinics, in particular paediatric ones, do not operate daily. With a per diem tariff in paediatric department corresponding to €1,311 (cost source: personal communication), per-patient administration costs would increase nine-fold, reaching €18,354. The

scenario analyses of per-patient costs and net budget impact are presented in Table 5-7 and Table 5-8, respectively.

Table 5-7: Per-patient cost scenario analysis (inpatient stay)

Cost categories	Year 1	Year 2	Year 3	Year 4	Year 5
Drug acquisition	€175,206				
Drug administration[1]	€18,354				
Disease management: stage 2 T1D					
With teplizumab	€344	€344	€344	€344	€86
Without teplizumab (SoC)	€344	€344	€86	€0	€0
Disease management: stage 3 T1D					
With teplizumab	€0	€0	€0	€0	€2,472
Without teplizumab (SoC)	€0	€0	€2,781	€3,708	€3,708
Total					
With teplizumab	**€193,904**	**€344**	**€344**	**€344**	**€2,558**
Without teplizumab (SoC)	**€344**	**€344**	**€2,867**	**€3,708**	**€3,708**
Net difference	**€193,560**	**€0**	**– €2,523**	**– €3,364**	**– € 1,150**

Abbreviations: SoC ... standard of care, T1D ... diabetes type 1

Note: [1] administration in hospital inpatient setting

Table 5-8: Net budget impact scenario analysis

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Total
New pts treated p.a.	5	6	7	8	10	36
Acquisition cost	**€876,030**	**€1,051,236**	**€1,226,443**	**€1,401,649**	**€1,752,061**	**€6,307,419**
Administration costs	**€91,770**	**€110,124**	**€128,478**	**€146,832**	**€183,540**	**€660,744**
Stage 2 management	**€1,720**	**€3,784**	**€6,192**	**€8,944**	**€11,094**	**€31,734**
Stage 3 management	**€0**	**€0**	**€0**	**€0**	**€12,360**	**€12,360**
Teplizumab costs	€969,520	€1,165,144	€1,361,113	€1,557,425	€1,959,055	€7,012,257
SoC costs (stage 2+stage 3)	€1,720	€3,784	€18,807	€40,902	€67,049	€132,262
NET BUDGET IMPACT	**€967,800**	**€1,161,360**	**€1,342,306**	**€1,516,523**	**€1,892,006**	**€6,879,995**

Abbreviations: p.a. ... per annum, pts ... patients, SoC ... standard of care, T1D ... diabetes type 1

Limitations

Limitationen:

The presented BIA is subject to several limitations, primarily attributable to the uncertainties in the Austrian eligible population and cost data:

große Unsicherheit bei Pat.-Zahlen mangels Screening

As noted previously in the relevant subchapter, without systematic screening, the size of the eligible population remains highly uncertain. The expert estimates (5-10 patients/year) applied in the presented BIA are provisional and depend on the ability of routine clinical practice to identify pre-symptomatic T1D patients incidentally. It was further assumed that the detected stage 2 patients would be children and adolescents who are monitored in accordance with the ISPAD guideline [11]; however, the disease management costs of adult patients might differ. Notably, uncertainty regarding the population eligible for teplizumab treatment was also a key issue highlighted in HTA reports from NICE [45] and Canada's Drug Agency [44], as general population-based screening programmes that could generate more reliable estimates of the eligible population are absent from their healthcare systems. In

Problem auch von NICE und CADTH betont

Screening-Implementierungskosten nicht berücksichtigt

addition, the NICE External Assessment Group raised doubts about whether the screening implementation costs should be included in the analysis as a foreseeable consequence of teplizumab reimbursement; however, the NICE Committee [45] refused to include them.

Datenunsicherheiten: GÖG-Kostenkomponenten nicht im Detail bekannt; Verabreichungssetting unsicher

Further uncertainties arise regarding the cost data used. The chosen costing approach relied on the LKF catalogue reimbursement codes associated with procedures that were deemed the best approximation of the care required for drug administration and stage 2 disease management. The disease management costs for stage 3 T1D were adopted from the GÖG diabetes report 2017, and the exact composition of the cost components is unknown, although it is presumed to have changed following the introduction of new technologies for diabetes management. Nevertheless, the adaptation of a published report was considered the preferred approach for including stage 3 management costs, given the complexity of T1D treatment. Moreover, it is uncertain whether teplizumab would be more frequently administered in hospital outpatient clinics, as assumed in the base-case analysis, or whether it would require inpatient hospitalisation, as considered in the scenario analysis.

keine indirekten Kosten berücksichtigt

Finally, standardised and widely accepted data on indirect healthcare costs are unavailable in Austria. Therefore, we followed the healthcare perspective for the analysis and did not consider indirect costs.

6 Extended perspectives

In the following chapter, relevant aspects for stakeholders are outlined, including structural and organisational requirements, patient and caregiver perspectives, as well as ethical and social considerations.

6.1 Stakeholder perspectives

Organisational aspects

Implementierung von Teplizumab erfordert strukturelle und personelle Ressourcen

A successful implementation of teplizumab depends not only on clinical outcomes but also on the readiness of the healthcare system to deliver T1D screening, diagnosis, treatment, and follow-up in an equitable and coordinated way [46]. Given the organisational effort required to administer teplizumab (see Chapter 1.3), structural resources and qualified healthcare providers (HCP) must be available to ensure safe administration and adequate aftercare.

Mangel an spez. Personal (v. a. im Bereich der Pädiatrie) führt zu strukturellen Schwächen in der Versorgung

For paediatric patients, the administration could only occur in children's hospitals under the supervision of paediatric diabetology specialists. However, Austrian clinical experts consulted for this HTA and the ÖDG highlight a shortage of multidisciplinary teams, such as paediatricians, diabetes consultants, psychologists, nutritionists, and paediatric nurses, resulting in structural deficiencies [10, 48].

Identification of eligible patients

derzeit keine reguläre Durchführung von T1D bevölkerungsbasiertes Screenings in Ö

To administer teplizumab at the indicated stage 2 T1D, eligible patients must first be identified. As previously reported, Austria lacks a population-level screening programme for T1D in children, adolescents, or adults. Adults with stage 2 T1D are typically diagnosed by chance (e.g., during gestational diabetes screening), while children and adolescents are identified through family-based opportunistic screening [10]. However, this approach captures only 15-20% of stage 2 cases, as nearly 90% of children newly diagnosed with T1D have no family history [46, 49].

Screening approaches

durch die Früherkennung von Stadium 1 oder 2 bleibt mehr Beta-Zellmasse erhalten, Pat. sind länger insulinunabhängig und weniger Komplikationen treten auf

Early detection and screening for T1D are considered essential for improving outcomes. Screening for stage 1 or 2 offers multiple benefits, including the prevention of DKA (which still occurs in up to 60% of children at diagnosis), reduction of short- and long-term complications, and preservation of beta-cell mass. This means that detecting the disease early allows patients to remain insulin-independent for a longer time and provides opportunities for initiation of therapies that can delay progression (e.g., teplizumab), timely emotional support, and education to ensure a smooth transition to insulin treatment[49, 50].

AAb-Screening ermöglicht Früherkennung und Studienteilnahme

Screening for circulating antibodies (AAbs) can be performed at any age. Importantly, T1D may occur before age one, and a younger age at seroconversion has been identified as a predictor of more rapid T1D progression and a higher

risk of DKA at diagnosis [50]. Studies suggest that repeated screening significantly increases sensitivity [51]. Finally, AAb screening can provide individuals with the opportunity to participate in clinical trials [50].

Screening implementation considerations

bevölkerungsweites Screening müsste in vorhandene Abläufe integriert werden

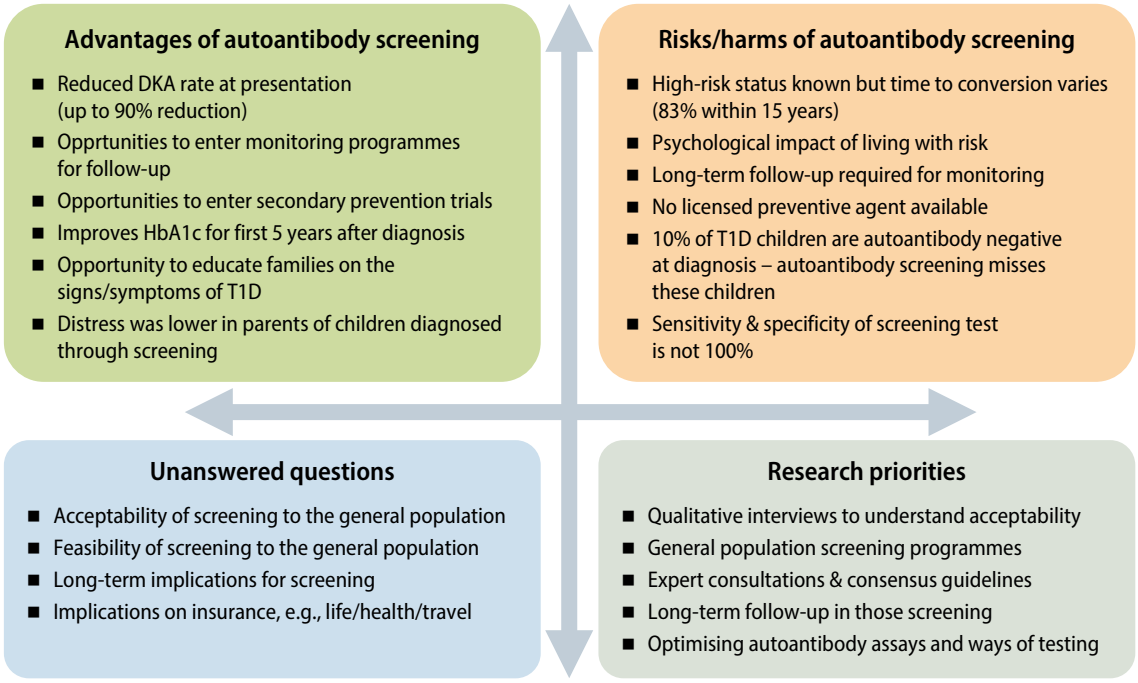
A population-wide T1D screening would be required to be integrated into existing healthcare workflows. From an organisational perspective, several steps in the screening process would need to be standardised, including communicating with individuals at risk, integration into routine procedures, and streamlining logistics, such as ordering and coding for autoantibody panels. HCPs would need to be able to interpret and communicate screening results, and ensure appropriate follow-up. A practical guide for establishing screening programmes for presymptomatic T1D is provided in the Appendix [50].

Psychosocial aspects of screening

Wissen um erhöhtes T1D-Risiko kann zu erhöhtem Stress, Unsicherheit & Ängsten führen

psychologische Unterstützung könnte im Rahmen eines Klinik-/ Ambulanzbesuchs etabliert werden

Looking at children, adolescents and their families, there are advantages to prior knowledge of a child's risk for T1D and the potential to delay diagnosis with preventative therapy; however, these must be weighed against the anxiety such information may impose on these families. Thus, although screening for T1D may induce psychological stress in children diagnosed with pre-symptomatic T1D and their parents, studies have reported that parental distress was moderately increased but returned to baseline levels with appropriate education and monitoring [49]. Hence, the integration of psychosocial support for children with early-stage T1D into routine clinical visits by HCPs with diabetes-specific training should be considered [11]. Another challenge is the uncertainty regarding the onset of stage 3 T1D and the long-term burden of living with the risk for many years [52].



Abbreviations: DKA ... diabetic ketoacidosis, HbA1c ... haemgoglobin A1c, T1D ... type 1 diabetes

Figure 6-1: Schematic representation of T1D screening in children, including status of T1D screening, outlining advantages, potential risks or harms, and unanswered questions, as well as priority research areas, adapted from [55]

Furthermore, parents frequently adopt preventive behaviours if their child is at high risk, such as increased monitoring (including capillary blood glucose checks), reducing sugar in the diet, and increasing physical activity levels [52].

When learning they have T1D-related autoantibodies, individuals of all ages and their family members can experience a range of emotional and behavioural reactions, including shock, grief, guilt, anger, depression, and anxiety [6].

Umfrage zu Motivation für Screening: Risikoabschätzung, mehr Zeit vor Manifestation der Erkrankung, Angst vor DKA, Beitrag zur Forschung

The key considerations for T1D screening identified above are reflected in a survey of 85 caregivers of children with T1D from the UK who reported strong interest in screening their children for T1D-associated antibodies [53]. Motivations of most respondents (adults ≥18 years and caregivers of children from 8-17 years) included gaining more time before disease onset and knowing their risk for T1D, both of which were rated as "important" or "very important". Additional reasons rated as "important" or "very important" by more than half of respondents included contributing to T1D research and concern about DKA [54]. Figure 6-1 depicts the advantages and disadvantages of screening children for T1D, as well as highlighting currently unanswered questions and research priorities [55].

Screening in Austria

Ö klinische Expert:innen empfehlen Diskussion über mögliches T1D-Screening

As previously noted, no population-wide screening programme for T1D is currently implemented in Austria. Clinical experts consulted for this HTA recognised the relevance of early detection and recommended discussing various T1D screening options for the Austrian context.

Access to screening for newborns

Screening-Möglichkeit für alle Neugeborenen in Wien: Freder1k-Studie

In September 2025, the Department of Paediatrics at the Medical University of Vienna and Vienna General Hospital introduced a new screening programme to detect genetic risk for T1D in newborns. This initiative, part of the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) [56] research network, is based on the Freder1k study (GPPAD-02, NCT03316261 [57]). Screening has already commenced at three hospitals in the greater Vienna area and will gradually expand to other neonatal departments. Participation is voluntary, requires parental consent, and is based on the routine newborn screening card, which involves taking a small blood sample from the infant's heel within the first days of life. Approximately 1% of children screened in this setting show an increased risk of developing T1D. In such cases, the parents receive detailed information about the results and are invited to participate in a prevention-focused study [58, 59].

Access to screening for family members of T1D patients

antikörperbezogenes Diabetesscreening für Familienangehörige von T1D-Pat.: Innodia DETECT

Through the Europe-wide research initiative Innodia, antibody-based diabetes screening for family members of T1D patients is being established in Austria under the programme "Innodia DETECT", in collaboration with the Medical Universities of Vienna, Graz, Linz, and Innsbruck [51]. The programme is planned to start in 2026 [10].

International screening efforts

IT: gesetzlich verankertes T1D-Screening für Kinder

DE: Screening regional über Fr1da-Studie möglich

Figure 6-2 provides an overview of screening programmes for T1D across Europe. Italy is currently the only European country with a legally mandated screening programme for T1D. On 27 September 2023, the Italian Ministry of Health adopted the launch of the national programme to screen children aged 1 to 17 years for T1D (and coeliac disease) [60]. In Germany, screening is available through the Fr1da study in the federal states of Bavaria, Lower Saxony, Hamburg, and Saxony for children aged 2 to 10 years. In addition, children of relatives with T1D aged 1 to 21 can participate nationwide [61].

EDENT1FI: europäische Screening-Initiative in mehreren Ländern

GPPAD: Screening-Programme

The European action for the Diagnosis of Early Non-clinical Type 1 diabetes For disease Interception (EDENT1FI) project runs local screening initiatives for children aged 1 to 17 across Europe, including Germany, Italy, Poland, Portugal, Czechia, Sweden, Denmark, and the UK [62]. The GPPAD aims to facilitate a coordinated, multidisciplinary approach to genetic screening and the conduct of primary prevention studies for T1D, with participating research sites from Belgium, Germany, Poland, Sweden, the UK, and Austria [56].

weitere Screeningmöglichkeiten in Europa, USA und Kanada

Further screening strategies have also been expanded in Denmark (DiaUnion for family members of T1D patients between 1 and 40 years), Portugal (Associação Protectora dos Diabéticos de Portugal for children aged between 2 and 10 years), the USA and Canada (TrialNet for members of T1D patients), and Australia (Type1Screen for children and young adults [62]).

The discussion of international screening efforts is particularly relevant for this assessment because the implementation of an early detection programme in Austria would be a key consideration for the potential use of teplizumab in presymptomatic individuals with T1D.

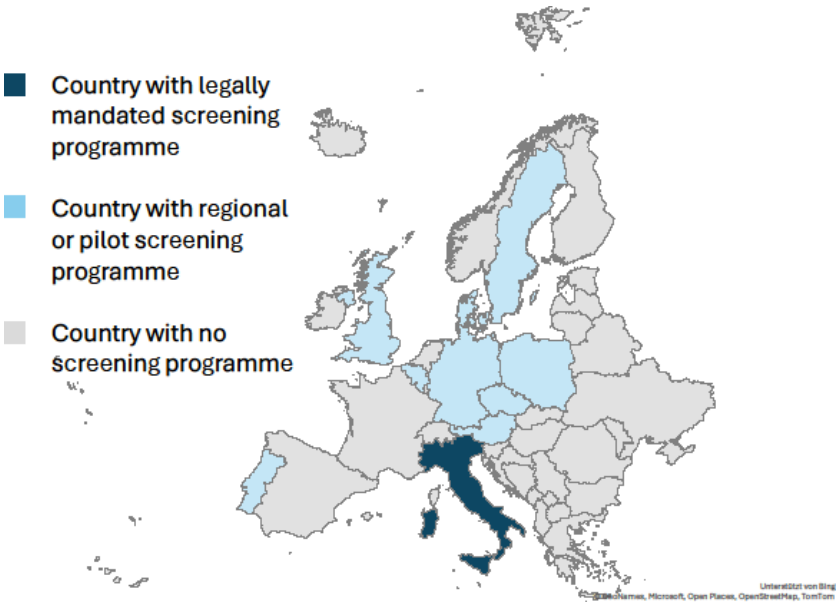


Figure 6-2: Map showing screening programmes for T1D in Europe, indicating countries with established or pilot initiatives (authors' own illustration)

6.2 Patient and caregiver perspectives

2 Pat. haben Fragebögen ausgefüllt

As part of this HTA, the patient perspective was obtained through a questionnaire, as described in the methods section (see Chapter 3). Both patients, who completed the questionnaire, were members of a patient organisation. The characteristics of the patients are described in Table 6-1.

Table 6-1: Characteristics of participants of the structured patient questionnaires (n=2)

Patient characteristics	Total number of patients (n=2)
Sex	
Female	1
Male	1
Median age (years)	62.5
Indication	
	Clinically manifest T1D
Role	
Patient	2
Carer	0
Member of patient organisation	
Yes	2

Abbreviation: T1D ... type 1 diabetes

Limitation: Befragung von nur 2 Pat.

Although the inclusion of only two participants is considered a notable limitation, the responses obtained were found to provide valuable insights into the burden of disease and the challenges related to care. Despite extensive efforts, no additional participants could be recruited, primarily due to the limited time available for identifying suitable patients.

Understanding the experiences of children, adolescents, and adults living with T1D is essential for contextualising the administration of teplizumab, particularly concerning disease burden and challenges related to disease management.

Findings from the survey

Ergebnisse der Befragung: … Alltagsbelastung

A surveyed patient with nearly 60 years of living with T1D reported a substantial burden with daily disease management. The patient highlighted the continuous effort required to maintain stable blood glucose levels, a process that requires constant monitoring, and the necessity of accepting the disease as an integral part of life. It was also described that insulin management requires constant consideration of various factors, including food intake, physical activity, and mood, and that an emergency kit must always be readily available. Additionally, dissatisfaction was expressed regarding the limited availability of new drugs and devices in Austria and their high cost [63].

… begrenzte Verfügbarkeit und hohe Kosten

… psychosoziale Unterstützungsbedarfe

… Erwartungen an neue Therapien

Furthermore, a surveyed patient expressed a need for increased psychological support. Surveyed patients also emphasised that potential negative long-term effects, especially in children and adolescents, should be carefully considered, and that any new therapy should be well tolerated and deliver on its promises [63].

Findings from the literature

Management of T1D in children and adolescents

T1D als große Herausforderung für Kinder, Jugendliche und Betreuungspersonen

Diabetes management is considered challenging and often overwhelming for children and adolescents with T1D and their caregivers. Compared with their peers, young people with diabetes appear to have a greater incidence of depression, anxiety, psychological distress, and eating disorders. Optimal treatment is regarded as requiring constant vigilance: monitoring dietary intake, counting carbohydrates, tracking trends in daily glucose values using a sensor or capillary blood glucose measurements repeatedly throughout the day, and administering insulin multiple times a day with a pen or pump. Advanced technologies and treatments may also impose burdens, which can lead young people to discontinue their use. Such treatment burdens are considered to affect their QoL significantly. Furthermore, lack of diabetes control and adequate insulin therapy is often associated with diabetes-related family conflict, poor academic performance, and/or increased interpersonal conflict. Patients with T1D face and manage the acute and life-threatening risk of hypoglycaemia daily [49].

Caregiver burden in families of children and adolescents with T1D

Organisational aspects

Belastung für Betreuende durch neuen Alltag mit T1D; Einschränkungen auch schon bei präsymptomatischen Stadien

For paediatric patients, caregiver burden is considered a particular concern, as treatment involves time off work, travel, and ongoing monitoring, also during a pre-symptomatic stage [46]. Azimi et al., 2023 [64] conducted a qualitative scoping review and found that parents experience an initial period of sadness, shock, and overwhelm following their child's diagnosis with T1D. They are required to adapt quickly to a "new normal", reorganising daily routines to accommodate care needs, and making all life decisions with T1D management as a priority.

Occupational and financial aspects

Einfluss auf Arbeitszeit der Betreuenden

Caregivers' working hours are often reduced to meet the demands of routine-based care, whereas others increase their working hours to cover the high costs associated with care [64] (e.g., expenditures related to prescription medications and medical supplies, as well as expenses associated with commuting for hospital care).

schwierige Situation für berufstätige Eltern, vor allem Mütter erfahren oft (gesundheitliche und ökonomische) Nachteile

When assessing occupational and financial situations before and in the first year after the onset of diabetes in families with a child ≤14 years of age at diagnosis and a diabetes duration of at least twelve months, Dehn-Hindenberg et al., 2021 found that mothers experienced negative consequences in their occupational situation. Their occupational status, as reflected in paid working hours, was significantly reduced in the first year after their child's diabetes diagnosis. Some mothers stopped working, while others reduced their working hours. These occupational disruptions can have long-term negative consequences for mothers' mental health and future economic situation [65].

This aligns with the observations of Austrian clinical experts consulted for this HTA, who noted that 90% of parents are affected in their professional lives due to their child's illness [10].

Psychological and social aspects

Eltern/pflegende Angehörige sind Tag und Nacht mit dem Diabetesmanagement beschäftigt → kann gesundheitliche Auswirkungen haben

Parents engage in continuous monitoring of glucose fluctuations to maintain optimal glucose levels for their child; deviations from the target range are often accompanied by feelings of guilt, shame, anxiety, and fear of future complications. This emotional strain results in constant vigilance and calculated planning during T1D care, creating a restrictive lifestyle for parents that limits opportunities for self-care, reduces social engagement, and exacerbates mental health. Concerns about unstable glucose levels, particularly fears of hypoglycaemic episodes, are especially pronounced during nighttime monitoring, leading to sleep disruption and reduced sleep quality. These factors can contribute to mood disturbances in both parent and child, marital conflict, and somatic symptoms such as headaches [64].

Grad der Belastung hängt von verfügbarer Unterstützung ab

The burden of care borne by parents is also influenced by the availability and perceived adequacy of social support they receive. A lack of reliable respite care makes it difficult for parents to travel, work extended hours, or participate in social activities. Parents frequently report frustration over family and friends' limited understanding of T1D. In contrast, connecting with other parents of children and adolescents with T1D provided comfort, relief, and practical support [64]

Management of T1D in adults

signifikante Belastung durch T1D auch bei Erwachsenen und deren Betreuungspersonen

An online survey conducted by Penfornis et al., 2024 [66] among 498 patients (≥18 years) and 54 caregivers highlighted a significant burden for both groups. Male respondents were less likely than females to experience psychological difficulty in processing their diagnosis; however, all respondents reported that T1D can hinder daily activities and contribute to fatigue and anxiety. Depression was reported by more than one-quarter of participants. In this survey, hypoglycaemia, eye disease, and kidney disease – potential complications of hyperglycaemia – were the risk factors that patients and caregivers worried about the most. The frequency of hypoglycaemic and hyperglycaemic episodes appeared to negatively impact the perception of the disease. On the other hand, the perceived risk of T1D complications was significantly associated with patients paying closer attention to disease control.

Betroffenen wünschen sich mehr Informationen & psychologische Unterstützung

Nearly one-third of patients and caregivers reported wanting more support from psychologists. Perceptions of the disease and its impacts varied, but many expressed a desire for greater knowledge about T1D, suggesting a need for enhanced diabetes education. Diabetes self-management education is key to enabling people with diabetes to achieve effective glycaemic control; patients who regularly participated in education programmes experienced fewer hypoglycaemic and hyperglycaemic episodes than those who did not [66].

Patient's expectations and wishes regarding the new therapy

Erwartungen an Teplizumab in Online-Umfrage abgefragt: >50 % einfache Entscheidung für Teplizumab

O'Donnell et al., 2025 [54] conducted a cross-sectional, observational, online survey of 47 adults (≥18 years) and caregivers of children (8-17 years) who received teplizumab, aiming to capture real-world experiences. Most respondents learned about teplizumab through their doctor. When asked about tolerating the medication, most reported feeling 'a little worried', with fewer indicating they were 'very worried'. For more than half of the respondents, the decision to take teplizumab was described as easy.

Pat. bzw. Eltern erwarten sich v. a. Vermeidung von DKA und Spätfolgen durch Teplizumab

A single-centre study by Bombaci et al., 2024 [67], involving 95 parents or caregivers of children and adolescents with T1D who had at least one additional child without T1D, evaluated parents' and caregivers' perspectives on using teplizumab. Among the 43 subjects aware of teplizumab, most (77%) learned about it at their paediatric diabetes centre. The most frequently reported benefit of delayed T1D onset was reduced disease-related stress for the family (62%), followed by postponement of insulin therapy initiation (26%) and glucose monitoring (1%). Additional perceived advantages included avoiding DKA in 40% of respondents, preventing chronic damage from hyperglycaemia in 20%, and gaining time for psychological preparation in 27%.

potenzielle Behandlung für Betreuende mit Hoffnung verbunden, aber auch Sorge bzgl. fehlender Compliance der jungen Pat.

A feeling of hope regarding the eventual use of teplizumab was expressed by 54% of respondents, while 12% reported fear of therapeutic failure or adverse reactions. Overall, expectations of a positive outcome were high in 28 %, moderate in 51%, and low in 14% of cases. Eight percent expressed concern about therapeutic failure and the development of T1D within two years. Willingness from the child to undergo treatment was expected by 28%, while reactions of fear and refusal were anticipated in 28% and 10% of cases, respectively. More than half of the respondents feared a negative emotional response from the child during treatment [67].

über 50% der Betreuenden befürworten Teplizumab-Gabe, v. a. nach einer DKA

Finally, 53% of participants indicated that they would consent to the administration of teplizumab to their child if the prescription criteria were met in the future. Parents who had previously experienced DKA with a child already affected by diabetes were more likely to consent to treatment and expected greater willingness from the at-risk child [67].

jeder weitere Tag ohne T1D wurde als bedeutsam erachtet

Quinn et al., 2025 [68] interviewed twelve parents or caregivers, nine of whom had a child aged over 8 years with stage 2 T1D and would be eligible for teplizumab treatment. Most parents expressed interest in this treatment (n=10/12). Regarding the value of delay to clinical diagnosis, any additional day without T1D was considered meaningful, and parents wanted immediate access to treatment. However, all parents requested more detailed information on side effects and risks to make an informed treatment decision and emphasised the child's role in decision-making. The authors noted that teplizumab treatment also instilled a sense of hope, as a two-year delay could provide time for additional therapies to become available to further delay progression, or potentially achieve a "cure".

Patient's experiences with the therapy

Erfahrungen mit Teplizumab:

Pat. sind zufrieden mit Entscheidung, haben trotzdem Sorge, T1D zu entwickeln

The vast majority of patients surveyed by O´Donnell et al., 2025 [54] reported that they agreed or strongly agreed with the statement 'I am glad I (or my child) did the teplizumab infusion'. Likewise, most indicated that they would recommend teplizumab to others in a similar situation. Although respondents were generally satisfied with their decision to undergo treatment, many expressed ongoing concern about developing T1D. Most participants disagreed or strongly disagreed with statements such as 'I think less about my (or the child I care for) blood glucose', 'I worry less about what I (or the child) is eating', 'I am less worried about (me or the child I care for) getting T1D', 'I think less about diabetes', and 'I check my (or the child I care for) blood glucose less often'.

Nonetheless, nearly one-third of respondents agreed or strongly agreed with the statement 'I feel more relaxed', while almost a quarter disagreed, and a few strongly disagreed. When asked about their current outlook on T1D prognosis, most respondents believed they would eventually develop clinical stage 3 T1D and were convinced that teplizumab would delay its onset in themselves or their child. In contrast, two patients each disagreed or strongly disagreed. Almost all respondents agreed or strongly agreed that they would make the same decision again if another family member required treatment [54].

6.3 Further ethical and social aspects

Beachtung ethischer und sozialer Aspekte beim Einsatz von Teplizumab

With the introduction of teplizumab, further ethical and social aspects should also be considered. These include diabetes-related stigma and possible solutions, pregnancy-related aspects of T1D, and broader questions of autonomy, justice, and equity, which are discussed in the following sections.

Diabetes stigma and possible solutions

Stigmatisierung von Pat. mit Diabetes

Diabetes stigma refers to negative attitudes, judgment, discrimination, or prejudice directed at individuals because they have diabetes. It can occur within families, schools, workplaces, and health care settings, and may be experienced internally or externally. Internal stigma involves beliefs held by a person with diabetes about themselves, including feelings of self-blame, shame, and guilt. External stigma refers to blame and judgment from others and society, which can manifest as awkward or mean looks, rejection, exclusion, and difficulty maintaining relationships and friendships [69].

Bildungseinrichtungen: Information & Aufklärung

To prevent such stigma, for example, visits from a local diabetes advisor to nurseries or schools may be helpful [48].

Herausforderungen für Kinder mit T1D bei Eintritt in Bildungseinrichtungen

Moreover, starting nursery and school poses significant challenges for both parents and children. Thus, the ÖDG emphasises that teacher education and additional mobile care are key to integrating children with diabetes into educational settings. Training educators not only facilitates greater inclusion of children in everyday life but also helps reduce fear of the disease [48, 70]. These challenges underline the importance of early diagnosis and timely intervention, such as with teplizumab, to prevent progression and mitigate the psychosocial burden associated with delayed disease recognition.

negative Wahrnehmung von Diabetes

Expert:innen fordern neue Kommunikationswege, um Vorurteile & Stigmatisierung zu verhindern

In efforts to raise awareness of diabetes in the media and encourage adherence to treatment, negative aspects (e.g., the risk of severe, life-shortening complications ranging from heart attacks to foot amputations) are often overemphasised. However, this approach reinforces negative perceptions of diabetes among the public and within organisations. Therefore, experts advocate for new communication strategies to counter prejudice and stigma. A promising approach is to highlight significant advances in medications and medical devices [71].

Pregnancy-related aspects of type 1 diabetes

Fertilität durch T1D nicht beeinträchtigt ABER schlechte Blutzuckerkontrolle erhöht Fehlbildungsrisiko

Typically, T1D does not adversely affect fertility in women. However, when planning pregnancy, it is essential to closely monitor specific parameters, including HbA1c, blood pressure, blood lipid levels, and thyroid function tests. Poor blood glucose control increases the risk of foetal malformations. In the event of an unplanned pregnancy, women with diabetes should consult their doctor as soon as possible.

Insulinbedarf variiert während der Schwangerschaft, Behandlung muss daher angepasst werden

During pregnancy, insulin requirements vary significantly: compared with the first trimester, insulin needs increase by approximately 50% in the second trimester and by up to 70-100% in the last trimester. After birth, insulin requirements drop dramatically. Hypoglycaemia may be experienced by women with T1D in the first trimester, particularly at night; treatment may therefore need to be temporarily adjusted. Later in pregnancy, blood sugar levels tend to stabilise, and the associated risk decreases [72].

In this context, treatment that delays the onset of clinical T1D, such as teplizumab, may have potential implications for women of childbearing age.

Autonomy, justice and equity

Aufschub des klin. manifesten T1D ist klinisch bedeutsam; moralischer Aspekt: Pat. < 8 Jahren können aufgrund fehlender Zulassung nicht behandelt werden

Although teplizumab does not prevent or cure T1D, treatment can delay the need for exogenous insulin therapy and its associated risks and intensive regimen. This delay is clinically meaningful not only for preserving beta cells but also because T1D often presents in patients younger than 10 years, who may face challenges with complex disease management [73]. A further moral consideration arises in this context: although often patients younger than eight years are diagnosed with T1D, the currently anticipated approval of teplizumab limits treatment to those aged eight years and older. Consequently, younger children would be excluded from receiving this therapy. Clinical experts anticipate that this limitation may cause frustration and misunderstanding among parents [10].

zeitlicher Aufschub: kein kont. Glukosemonitoring, keine Insulingabe, höhere emotionale Resilienz bei Kindern

Quinn et al., 2025 [68], reported that parents and caregivers considered the two-week single-treatment course worthwhile for achieving a two-year delay. Parents with lived experience of T1D envisioned freedom from continuous glucose monitoring, carbohydrate counting, and bolusing, alongside benefits to the child's health across the life course from two additional diabetes-free years. A delay was also sought to allow the child to become more mature and emotionally resilient, thereby improving management of T1D [68]. This observation is strongly supported by Austrian clinical experts [10].

potenziell Ungleichheiten bei Zugang zu Teplizumab

However, potential inequalities in access to teplizumab may arise due to the absence of a national screening programme, which could result in geographical variation in treatment availability. Access to treatment is more likely among individuals with greater resources and higher levels of education, for

example, through participation in research studies or by travelling to specialised centres. Whereas, the two-week treatment period, associated costs for travel, and accommodation may be prohibitive for some families. Furthermore, hospitals with limited resources may offer poorer access to this treatment [47]. This concern also applies to Austria, particularly for paediatric patients. There is a shortage of paediatric diabetologists, qualified HCP teams, and day clinic capacity to deliver treatment over 14 consecutive days; therefore, treatment would need to be administered during an inpatient hospital stay [10].

Finanzierungsentscheidungen: neue „präventive" Therapieform vs. bestehende T1D-Interventionen

The Canadian Drug Expert Committee (CDEC) examined the ethical implications of introducing teplizumab. Given uncertainty about whether delayed progression improves long-term outcomes or quality of life, discussions have arisen on whether public resources might be better spent on proven supports – such as diabetes education, insulin pumps, or continuous glucose monitors – that directly improve health for individuals already living with T1D. According to the CDEC, balancing investment in emerging therapies with established interventions remains an essential consideration for funding decisions [46].

6.4 Registries and documentation of application

anwendungsbegleitende Dokumentation in bestehenden Diabetesregistern

The absence of comprehensive epidemiological data on early-stage T1D in Austria poses significant challenges for the appropriate use of teplizumab. As described in Chapter 1 (Epidemiology), Austria lacks national data on both early-stage and diagnosed T1D [10]. This limits reliable estimates of the population potentially eligible for teplizumab. In this context, existing diabetes registries may represent a valuable infrastructure for documenting the application of teplizumab.

österreichweites Diabetesregister für Kinder seit 1989

Since 1989, Austria has maintained a diabetes incidence register for children and adolescents up to the age of 15, in which T1D, T2D and other forms of diabetes are recorded [13].

länderübergreifende Verlaufsdokumentation bei pädiatr. Pat.

In addition to this incidence-based surveillance, there is the Diabetes Patient Follow-up Documentation Registry (Diabetes-Patienten-Verlaufsdokumentation, DPV), which aims to improve treatment outcomes for people with diabetes in routine care through standardised documentation, objective comparison of quality indicators, and multicentre therapy research. Treatment facilities in Germany, Austria, Switzerland and Luxembourg are currently participating in the initiative [74].

Tiroler Diabetesregister: einziges Register für erwachsene Diabetiker:innen

While these registries provide valuable insights into paediatric diabetes, registry-based data for adults are more limited in Austria. The Tyrol Diabetes Register (Diabetesregister Tirol, DRT), established in 2006, is currently the only register of its kind for adult patients in Austria. The DRT is used to measure and improve the quality of care for diabetes patients with T1D and T2D in Tyrol. By collecting epidemiological data on patients with diabetes in Tyrol, relevant and meaningful information on risk factors, therapies, and the incidence of late complications can be provided to decision-makers and service providers. This information is used to identify and evaluate areas requiring action, as well as to inform quality assurance measures and quality improvement programmes [75]. Further information on the DRT can be found at Diabetesregister Tirol and DRT Jahresbericht 2024.

7 Development costs and public contributions

7.1 Own development costs, acquisitions and licences

Übersicht zu Entwicklungskosten

Provention Bio or Sanofi have not published the total amount of research and development (R&D) expenses attributed to TEIZEILD®. As this chapter relies wholly on publicly accessible information, any funding amounts related to the development of teplizumab may be incomplete. Table 7-1 provides a brief summary of the key development points of teplizumab.

Table 7-1: TEIZEILD® overview

Originator	Developer	Information on acquisitions	Public contribution	Type of public funding
Yale University (PI Kevan Herold)	Provention Bio Sanofi	**Initial development:** MacroGenics licensed from Yale University **2007:** Eli Lilly licensed from MacroGenics **2018:** Provention Bio acquired from MacroGenics **2023:** Sanofi acquired Provention Bio	Roughly €19.2 million in direct and indirect public funding	Basic, preclinical and clinical research

Abbreviation: PI ... Principal Investigator

Basic research and clinical development

Entwicklungsgeschichte von Teplizumab

The development of teplizumab emerged from research at Yale University, as shown in Chapter 7 in the Appendix. The fundamental research that ultimately led to teplizumab began with Kevan Herold at the Yale School of Medicine, in collaboration with immunologist Jeff Bluestone, who pioneered investigations into anti-CD3 monoclonal antibodies to modulate pathogenic T cells in T1D [76, 77]. Beginning in 2000, Herold's team conducted research into the molecular basis for different rates of T1D progression and the potential for immune intervention to preserve beta-cell function in patients with recent-onset T1D [78].

kommerzielle Entwicklung war von MacroGenics zu Eli Lilly (gescheitert) zu Provention Bio

The translation from academic research to commercial development occurred through multiple stages. MacroGenics initially purchased the rights to teplizumab and entered into a licensing agreement with Eli Lilly in 2007 with potential milestone payments. However, following a failed phase 3 trial in 2010, Eli Lilly returned the rights to MacroGenics [79]. In 2018, Provention Bio acquired teplizumab from MacroGenics through an asset purchase agreement, which Provention Bio continued developing leading to FDA approval in November 2022 as the first therapy to delay the onset of stage 3 T1D in at-risk individuals [79]. These findings are visualised in Figure 7-1.

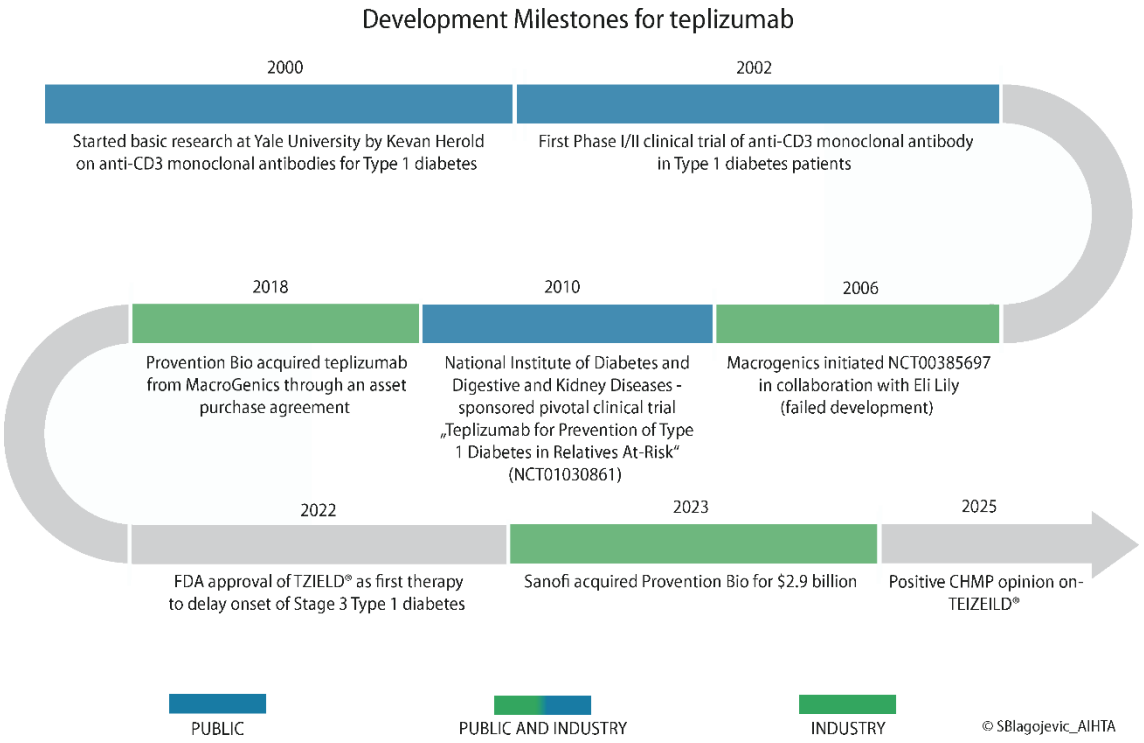


Figure 7-1: Development milestones for teplizumab

7.2 Public contributions to drug development

öffentliche Forschungsförderung von € 19,2 Mio. über 25 Jahre, hauptsächlich an der Yale University, UC und University of Chicago für Grundlagenforschung und klinische Entwicklung

Chapter 7 in the Appendix also demonstrates public research funding for the institutions and organisations that developed teplizumab. Roughly €19.2 million[3] in direct and indirect public funding were identified that contributed to the development of teplizumab in the early basic research stage, as well as in late-stage clinical development. Yale University received the largest funding amounts, with approximately €10.35 million[3] from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supporting Herold's research programme over the period from 2000 to 2025 [78]. This twenty-five-year funding commitment underscores the long-term nature of the public sector's investment in this therapeutic development. The University of California received public investment of €3.6[3] million between 2000 and 2015. Earlier foundational work was supported through €5.2[3] million in public funding directed to Jeff Bluestone's research at the University of Chicago from 1990 to 1998.

[3] All funding amounts converted to € using the exchange rates from the Austrian National Bank from 15 December 2025.

zusätzliche klinische Studien durch Immune Tolerance Network und NIDDK finanziert

Additional clinical development support was provided by the Immune Tolerance Network, primarily funded by the National Institute of Allergy and Infectious Diseases (NIAID), which sponsored three pivotal clinical trials (NCT01030861, NCT00378508, NCT00129259) [79]. The NIDDK also directly sponsored the critical "Teplizumab for Prevention of Type 1 Diabetes in Relatives At-Risk" trial from 2010-2019 [23].

Pharmapartnerschaften entscheidend: Eli Lilly 2007-2010, dann Provention Bio 2018 mit Meilensteinzahlungen; Sanofi-Übernahme 2023 für $ 2,9 Mrd. nach FDA-Zulassung von Tzield®

Strategic partnerships with pharmaceutical companies have been crucial to teplizumab's development trajectory. The 2007 Eli Lilly agreement provided $41 million up front with up to $200 million in development milestones and $250 million in sales milestones, though this partnership ended in 2010 [79]. Provention Bio's 2018 acquisition from MacroGenics involved warrants for 2,162,389 shares at $2.50/share, $170 million in regulatory milestones (including $60 million triggered by FDA approval), $225 million in sales milestones, and single-digit royalties on net sales [79]. The commercialisation of Tzield® (US-name) in 2022 marked a significant milestone as the first FDA-approved therapy to delay T1D onset in at-risk patients [80]. The 2023 Sanofi acquisition of Provention Bio for $2.9 billion marked the culmination of the development journey, with Sanofi having previously invested through a $20 million co-promotion contract and $35 million equity investment in 2022 [79].

Company structure and financials

Provention Bio 2017 gegründet mit $ 28,4 Mio. Startkapital, Börsengang 2018, weitere Finanzierungsrunden bis 2022

Provention Bio was founded in 2017 with $28.4 million in seed funding from MDB Capital Group (Venture Capital), specifically to develop therapies targeting the interception and prevention of immune-mediated diseases [81]. Provention Bio went public in 2018 with an initial public offering (IPO) raising to $50 million, followed by additional financing rounds, including a $60 million private placement in 2022 [82, 83].

MacroGenics erhielt Risikokapital ab 2001 und öffentliche Förderung

nach FDA-Zulassung $ 60 Mio. Meilensteinzahlung

MacroGenics, which held early rights to teplizumab, received substantial venture capital funding, including $13.5 million in Series A financing in 2001 from InterWest Partners, MPM Capital, and OrbiMed [84] and $25 million in Series D-2 funding in 2008 from Nextech Venture [85]. The company also received $28.6 million in public funding from HHS/NIH between 2008-2024 for various (unrelated) research programs [86]. Following FDA approval, MacroGenics earned the $60 million milestone payment from Provention Bio and remains eligible for up to $225 million in sales milestones plus single-digit royalties [79]. DRI Healthcare Trust acquired royalty rights for $100 million in 2023, while Ligand Pharmaceuticals acquired Tolerance Therapeutics for $20 million to obtain a sub-1% royalty on worldwide net sales [79].

Patents

Yale University unter Kevan Herold entwickelte grundlegende Anti-CD3-Antikörper-Innovationen für Teplizumab

Patente zunächst an MacroGenics lizenziert

The Yale University research group, led by original investigator Kevan Herold, developed crucial innovations in anti-CD3 monoclonal antibody therapy that became the foundation of teplizumab. These innovations included methods for preserving beta-cell function, protocols for immune modulation in autoimmune diabetes, and strategies for identifying at-risk patients who would benefit from early intervention. Yale Universities intellectual property was initially licensed to MacroGenics [79], creating the foundation for subsequent commercial development through multiple licensing agreements culminating in Sanofi's current ownership.

8 Landscape overview

8.1 Ongoing studies on teplizumab

6 laufende Studien zu Teplizumab von denen 4 aktiv rekrutierende Studien sind

Seven ongoing clinical studies and programmes evaluating teplizumab treatment were identified via ClinicalTrials.gov. These include three actively recruiting trials:

- the GLP-TEP study (NCT06338553), an early phase 1 trial examining GLP-1Ra impact on metabolic outcomes in stage 2 T1D patients receiving teplizumab, with estimated completion in March 2027;
- the KIBOU-T1D study (NCT06791291), a phase 2 trial assessing efficacy and safety in Japanese participants with stage 2 T1D, expected to complete in March 2028;
- the βETA PRESERVE study (NCT07088068), a phase 3 trial investigating teplizumab versus placebo in participants aged 1-25 years with stage 3 T1D, anticipated to complete in December 2028;

2 laufende Studien (Rekrutierung noch nicht begonnen) und 1 Plattformstudie geplant

Additionally, two studies are active but not recruiting:

- the PROTECT Extension study (NCT04598893), an observational trial evaluating long-term safety with completion expected in November 2026,
- the PETITE-T1D study (NCT05757713), a phase 4 trial in paediatric stage 2 T1D anticipated to complete in August 2026.

One platform trial (TN40A, NCT07216391) comparing teplizumab with ATG is not yet recruiting, with the longest timeline extending to December 2029.

The studies span early-phase through phase 4 trials, demonstrating a comprehensive clinical development programme for teplizumab across different stages of T1D (see Chapter 8 in the Appendix for a tabular overview).

8.2 Further treatments in development

2 Therapien in Entwicklung für Stage 2 T1D

Using the International Horizon Scanning Initiative (IHSI) database [26], a total of nine therapies were identified as under development for T1D indications. Two therapies are specifically targeting stage 2 T1D: Baricitinib and Glutamic Acid Decarboxylase (rhGAD65), with estimated EC decisions expected in May 2032 and November 2030, respectively.

- Baricitinib, developed by Eli Lilly, is being investigated as monotherapy for high-risk stage 1b or stage 2 T1D in patients aged 1 to 35 years.
- Glutamic Acid Decarboxylase (rhGAD65), developed by Diamyd Medical, targets stage 1 or stage 2 T1D in children aged 8 years and older and adolescents who carry the HLA DR3-DQ2 haplotype.

7 Therapien in Entwicklung für neu diagnostiziertes Stage 3 T1D

Besides, seven therapies are in development for recently diagnosed stage 3 T1D:

- Brivekimig,
- CELZ-201,
- Ladarixin,
- Autologous CD34+-enriched HSPCs,
- CNP-103,
- Frexalimab, and
- SAB-142.

For recently diagnosed T1D the expected EC decision times are as follows: CNP-103 (November 2030), CELZ-201 (December 2030), Frexalimab (March 2031), Brivekimig (July 2031), SAB-142 (October 2031), and Autologous CD34+-enriched HSPCs (May 2033). Ladarixin's EC decision date is not yet available. The therapies target various age groups, from children as young as 5 years to adults up to 45 years of age, with most focusing on adolescents and adults up to 35-40 years.

8.3 Other HTA reports

Three other HTA reports or drafts are available for Teplizumab. In August 2025, the Canadian HTA agency (CDA-AMC) published a draft report [46], and NICE also published draft guidance in the same month, with final publication expected in April 2026 [47]. Both reports evaluate the drug's effectiveness and safety for the same population: delaying the onset of stage 3 T1D. The FDA published its clinical review in November 2022, including patients with stage 2 T1D as well as patients already receiving insulin [87].

9 Discussion

Evidenzlage: Verzögerung T1D-Manifestation durch Teplizumab, jedoch Datenlimitationen zu berücksichtigen

This discussion focuses on interpreting the available evidence on teplizumab (TEIZEILD®) for individuals with stage 2 T1D and its clinical, economic, and organisational implications for the Austrian healthcare system. Although teplizumab has been shown to delay progression from stage 2 to clinical T1D, the interpretation of this effect requires careful consideration of the limited evidence base, uncertainty regarding patient-relevant benefit at diagnosis, and challenges related to implementation within existing healthcare structures.

Clinical evidence and uncertainties

Wirksamkeitanalyse basierend auf einer randomisierten Kontrollstudie: Verlängerung der Zeit bis zur T1D-Diagnose durch Teplizumab

The available clinical evidence for teplizumab in stage 2 T1D is limited to a single randomised controlled trial (TN-10), reported across several publications and analytical perspectives [22, 23, 39]. In the primary analysis, teplizumab delayed progression to clinical T1D, approximately doubling the median time to diagnosis compared with placebo (median 48.4 vs 24.4 months; HR 0.41, CI (0.22-0.78))[22, 23, 39]. Subsequent follow-up analyses of this trial population showed a sustained delay in progression over the observed follow-up periods [22, 23, 39]. These results suggest that short-term modulation of the autoimmune process may be associated with preservation of beta-cell function in a proportion of treated individuals, as reflected by higher stimulated C-peptide levels observed in the teplizumab group during follow-up [22]. Although the HR of 0.41 indicates a substantial relative reduction in progression risk, the confidence interval remains relatively wide, reflecting statistical uncertainty related to the small sample size.

heterogene Effekte – Hinweise auf Einflussfaktoren

Exploratory post-hoc metabolic analyses support heterogeneity in disease progression. Individuals classified as slow progressors maintained more stable insulin secretion and exhibited metabolic patterns consistent with compensatory mechanisms, whereas rapid progressors showed continued metabolic decline with only transient changes following teplizumab treatment [40]. Additional exploratory analyses suggested differences in treatment effect according to HLA genotype, autoantibody profile and baseline C-peptide levels [23].

niedriges Verzerrungspotential der randomisierten Kontrollstudie

trotzdem limitierte Vertrauenswürdigkeit der Evidenz: geringe Fallzahl, heterogene Effekte, etc.

Even though the risk of bias of the available clinical study was rated as low (see Chapter 4.5.1), several factors limit the certainty with which these findings can be interpreted. First, some baseline characteristics, including age distribution, were not fully balanced between treatment groups, which should be considered when interpreting results from a relatively small study population. Second, while the delay in T1D diagnosis is apparent, evidence on whether this postponement translates into measurable clinical advantages at the time of onset, such as lower risk of DKA or better metabolic stability, remains insufficient. While observational data suggest that earlier onset of T1D is associated with higher lifetime risk of complications, direct evidence demonstrating that a median delay of approximately two years translates into reduced long-term morbidity or mortality is currently lacking. Health-related QoL was not assessed in TN-10, which introduces additional uncertainty regarding the patient-perceived relevance of the observed delay [12]. Third, although exploratory analyses describe patterns associated with slower or faster progression, as well as HLA-types and autoantibodies, no validated predictors exist that reliably identify individuals most likely to benefit in clinical practice, as the extended follow-up and post-hoc analyses should be

interpreted cautiously, due to a lack of prespecified statistical hypotheses and planned adjustment for multiple testing [23, 39-41].

Generalisierbarkeit der Ergebnisse auf Ö möglicherweise eingeschränkt, z. B. TN-10 umfasst lediglich Verwandte ersten Grades

Regarding the generalisability of the available results, all data originate from first-degree relatives, a population that may not reflect individuals who would be identified through potential future screening pathways in Austria. Nevertheless, the progression risk in TN-10 was comparable to that in the European Fr1da population-based screening cohort, which included patients without first-degree relatives. This suggests that the TN-10 findings may be informative for broader European populations, although residual uncertainty regarding transferability remains [88].

eingeschränkte Umsetzbarkeit im österreichischen Versorgungssetting

In addition, the applicability of the TN-10 intervention protocol to the Austrian healthcare context is limited by differences in care delivery structures. In the trial, teplizumab was administered in an outpatient setting over 14 consecutive days. According to Austrian clinical experts, such outpatient administration would currently not be feasible in Austria, particularly in paediatric care, due to the lack of paediatric diabetes centres with daily infusion capacity. As a result, inpatient hospitalisation would likely be required, which would substantially increase treatment burden, resource use and organisational requirements. Limited availability of paediatric and diabetes care beds may further constrain implementation in routine care [10].

kurzfristige Sicherheit erwartungsgemäß

limitierte Sicherheitsdaten zu seltenen, langfristigen und wiederholten Effekten

These limitations also affect the interpretation of the safety findings, which indicate a short-term safety profile broadly consistent with expectations for an anti-CD3 monoclonal antibody [23]. Transient lymphopenia and mild to moderate infusion-related reactions, particularly rash and constitutional symptoms, were common but manageable and generally resolved without sequelae. Episodes of viral reactivation, mainly in participants with prior EBV exposure, were self-limiting and did not lead to serious clinical consequences [23]. In contrast, the narrow evidence base limits the detection of rare or delayed adverse events. The relative homogeneity of the trial population further restricts insights into how safety might vary in groups more representative of routine Austrian care. In addition, available publications report safety data for only a single treatment course. Although the possibility of repeat dosing has been raised, for example, in the PROTECT study [89], no safety data on repeated administration or long-term immunological effects are currently available.

fehlende Pat.-berichtete Endpunkte

Moreover, across the included publications, no quality-of-life outcomes or other patient-reported measures were collected. As a result, it remains unclear whether delaying the onset of clinical T1D with teplizumab affects patient well-being or perceived disease burden during the presymptomatic phase, limiting assessment of patient-relevant benefit.

Implications for early identification

Zusammenhang zwischen T1D-Erkrankungsalter und Langzeitrisiken gegeben

Since teplizumab is being investigated not only for stage 2 but also for early-stage 3 T1D, early identification of individuals along the disease continuum is becoming increasingly important. Identifying at-risk individuals at an earlier stage is relevant both for selecting appropriate candidates for disease-modifying treatment and for understanding the potential long-term impact of such interventions. Evidence from large population-based cohort studies indicates that earlier manifestation of T1D is associated with higher excess risks of cardiovascular disease and premature mortality compared with later onset, even after accounting for diabetes duration. In particular, diagnosis before age 10

has been associated with a substantial reduction in life expectancy. In contrast, onset in adulthood is associated with a smaller, though still relevant, loss of life-years. Although absolute cardiovascular event rates remain low in childhood and adolescence, earlier onset implies longer cumulative exposure to hyperglycaemia and related metabolic risk factors over the life course [12].

hohe Relevanz einer T1D-Verzögerung im Kindes- und Jugendalter

In this context, interventions targeting stages 1 and 2 T1D may be of greater potential relevance when they shift clinical onset out of early childhood. Austrian clinical experts consulted for this HTA agreed that delaying diagnosis is of greater value in children and adolescents than in adults, mainly due to psychosocial and practical considerations associated with very early disease onset [10]. However, direct evidence that a delay achieved through disease-modifying treatment translates into improved long-term clinical outcomes or reduced lifetime healthcare costs is currently lacking.

Screening programmes

internationale Programme koppeln T1D-Screening an klar definierte Versorgungspfade

International experience increasingly frames T1D as a disease continuum with identifiable presymptomatic stages, leading to the development of structured screening and monitoring programmes. Across initiatives such as INNODIA, GPPAD, and population-based programmes like Fr1da, screening is embedded within defined care pathways including confirmatory autoantibody testing, metabolic staging and structured follow-up; without such pathways, early identification does not translate into practical benefit for patients or the healthcare system [11, 59, 90-93].

INNODIA als Forschungsinfrastruktur, jedoch keine populationsbasierte Screening-Evidenz

However, not all initiatives provide evidence relevant to screening as a population-level health intervention. For example, INNODIA primarily functions as a European research infrastructure for harmonised identification, staging and longitudinal follow-up and was not designed to evaluate the effectiveness of screening programmes at the population level. Consequently, evidence on patient-relevant outcomes, such as effects on DKA at diagnosis, quality of life or healthcare resource use, remains limited [94].

Fr1da: Pat.-relevanter Nutzen bei erheblichem Organisationsaufwand

Evidence with greater direct relevance to healthcare system considerations comes from population-based autoantibody screening programmes, such as Fr1da. According to published data, screening of initially enrolled 90,000 children within routine paediatric care identified presymptomatic T1D in approximately 0.3% of participants and was associated with lower rates of DKA at clinical onset following structured follow-up. More recent information from the Fr1da programme indicates that over 200,000 children have participated in the screening initiative to date. Fr1da highlights the considerable organisational requirements associated with population-wide screening, including laboratory capacity, follow-up infrastructure and long-term monitoring [91, 95].

Abgrenzung Screeningeffekte und zusätzlicher Arzneimittelnutzen

Clinical experts consulted for this HTA noted that early detection of presymptomatic T1D combined with structured monitoring and anticipatory care may itself contribute to patient-relevant benefits, particularly lower rates of DKA at diagnosis and improved preparedness at disease onset. Such effects have been consistently observed in population-based screening programmes with defined follow-up pathways. However, no comparative evidence is available to distinguish the effects of screening and monitoring alone from those of teplizumab. Clinical studies of teplizumab were conducted in highly selected, closely monitored populations identified through research-based screening,

and observed outcomes therefore reflect the combined effects of early identification, structured follow-up and pharmacological intervention rather than the isolated effect of the medicinal product.

Screening als eigenständige gesundheitspolitische Intervention zu sehen

Screening for presymptomatic T1D, therefore, constitutes a complex health policy intervention with significant organisational and financial implications. Key questions regarding implementation procedures, financing, cost-effectiveness, and opportunity costs extend beyond the use of an individual medicinal product. Consequently, a population-based T1D screening would require a separate health technology or policy assessment and cannot be considered an extension of the present teplizumab evaluation.

Economic aspects

hohe Unsicherheit der ökonomischen Analyse für Ö

The available economic evidence for teplizumab is characterised by substantial uncertainty, driven primarily by the absence of an Austrian list price and the lack of a manufacturer-submitted pharmacoeconomic model or BIA for Austria. Consequently, the self-conducted Austrian BIA relies on a placeholder price from another jurisdiction, expert assumptions regarding the eligible population size and uptake, and partial proxies for treatment expenditures, which limit the reliability of the resulting estimates.

Budgetfolgen für Ö aus Kostenträgerperspektive für 5-Jahres-Zeithorizon und 36 erwartete Pat.: € 6,3 Mio.

Based on assumed uptake scenarios of approximately 5-10 patients per year and applying a UK placeholder price, the estimated annual net budget impact ranges from approximately €0.9 to €1.7 million. Over the five-year analysis horizon, corresponding to an estimated cumulative number of 36 treated individuals, the total budget impact amounts to approximately €6.3 million. The budget impact is driven almost entirely by drug acquisition costs. Cost offsets related to the delayed onset of stage 3 T1D are small within the analysed time horizon and do not offset treatment costs.

indirekte Kosten nicht berücksichtigt

The Austrian BIA was conducted from a healthcare payer perspective and includes only direct medical costs. Indirect costs, such as productivity losses or caregiver time, were not considered due to the adopted perspective and the absence of standardised Austrian data.

ungünstiges Kosten-Nutzen-Verhältnis in ökonomischen Modellen

Across all identified economic studies conducted in the UK, USA and Canada, teplizumab is associated with higher incremental costs than standard T1D management, while estimated incremental health gains are small. Incremental costs per treated individual are in the range of several hundred thousand euros, whereas incremental health gains are generally estimated at approximately 0.3-0.5 QALYs [42, 44], and in some sub-analyses even lower [44]. As a result, reported ICERs are highly relative to the magnitude of health gains.

Ausnahme für Subgruppe (Pat. mit negativen ZnT8-Antikörpern), jedoch unsichere Analyse

An apparent exception was observed in an exploratory subgroup analysis restricted to individuals who were ZnT8 antibody-negative, in which the ICER fell within commonly applied willingness-to-pay thresholds [44]. However, this finding is based on a single exploratory subgroup analysis, relies on strong modelling assumptions, and has not been confirmed in subsequent evaluations or other jurisdictions.

Given differences in healthcare systems, pricing structures, screening practices and population characteristics, the transferability of these international cost-effectiveness results to the Austrian healthcare context is limited.

zahlreiche Limitationen der identifizierten gesundheitsökonomischen Analysen

Several methodological limitations apply across the identified economic evaluations. The delay in progression to stage 3 T1D primarily postpones diabetes-related costs rather than reducing lifetime costs, which limits the potential for long-term cost offsets. Cost-effectiveness results are therefore highly sensitive to assumptions regarding the duration of treatment effect, long-term disease progression and discounting, as a substantial proportion of the estimated health gains, in some models more than two-thirds, accrues in extrapolated periods beyond the observed clinical follow-up [44, 45].

In addition, several potentially relevant effects are not captured in the available economic models, including improved preparation time before clinical onset, a potential reduction in DKA at diagnosis, psychological benefits of delayed insulin dependence, and impacts on education, employment and caregiving, particularly for parents (see details in Chapter 5.2.2). However, for this report, no standardised quality assessment of the included economic evaluations, e.g., using a checklist, was conducted.

Patient perspective and experience with teplizumab

begrenzte und nicht generalisierbare Pat.-Berichte

Patient-reported evidence on teplizumab is sparse and has limited transferability, as it is primarily based on small, qualitative inputs and international surveys rather than systematically collected, validated patient-reported outcome measures. Available input for this HTA indicates that the main perceived benefit relates to the delay in progression to stage 3 T1D. This delay is valued primarily as additional time for psychological adjustment and practical preparation, including planning of education, daily routines and initiation of insulin therapy.

Zeitgewinn geschätzt (Familie, Anpassung), jedoch Krankheitslast bleibt

At the same time, patient-reported data suggest that this delay does not substantially change the ongoing burden of disease management, as glucose monitoring, dietary vigilance, and concerns about disease progression largely remain unchanged. Overall, patient input supports the relevance of delayed onset at the individual and family levels but does not indicate substantial changes in daily disease management or in longer-term patient burden [54, 67].

Clinical evidence beyond presymptomatic stage 2 T1D

Teplizumab in den USA in zulassungsnaher Phase für T1D Stadium 3

Beyond its evaluation in presymptomatic stage 2 T1D, teplizumab is also being investigated in individuals with recently diagnosed stage 3 disease, reflecting broader interest in disease-modifying approaches targeting beta-cell preservation across the T1D disease continuum. In the US, teplizumab (TZIELD®) has been approved since 2022 to delay progression to stage 3 T1D in individuals aged 8 years and older with stage 2 disease, and a supplemental application for use in recently diagnosed stage 3 T1D has been accepted for expedited FDA review in October 2025 [96].

Erhalt der Betazellfunktion nach klinischem Manifestationsbeginn

The proposed use in newly diagnosed T1D aims to preserve residual beta-cell function after clinical onset, with stimulated C-peptide serving as the primary outcome. Evidence from the phase 3 PROTECT trial indicates attenuation of C-peptide decline during short- to medium-term follow-up, suggesting biological activity of teplizumab in early stage 3 T1D [89]. However, effects on secondary clinical outcomes were not consistently demonstrated, and it remains unclear whether preservation of endogenous insulin secretion translates into sustained patient-relevant benefits, such as reductions in hypoglycaemia, DKA or long-term diabetes-related complications, given the limited duration of follow-up and absence of robust clinical outcome data [89]. In parallel, reported adverse events are largely transient; however, higher rates of severe events and treatment discontinuation have been reported, stressing the need to weigh biological effects against treatment-related harms [97-100]. From an Austrian HTA perspective, these data demonstrate biological activity and regulatory progress but do not yet constitute evidence of established patient-relevant benefit in individuals with stage 3 T1D.

Ausmaß des Pat.-relevanten Nutzens unklar

UE meist transient aber erhöhte Abbruchsraten

Other aspects

akademischer Ursprung und kommerzielle Weiterentwicklung

Teplizumab originated from publicly funded academic research and was subsequently advanced through multiple stages of commercial development [76, 77, 79]. Several clinical studies for the assessed and related indications (see Chapter 8) are ongoing and may address existing evidence gaps, particularly regarding long-term safety and durability of effect. In parallel, additional therapies for presymptomatic and newly diagnosed stage 3 T1D are under development, which may further alter the therapeutic landscape. Together, these developments indicate that the current evidence base is evolving and that future reassessment may be warranted as new data become available.

weitere laufende Studien: Schließen der aktuellen Evidenzlücken?

Conclusion

nachweisbarer krankheitsmodifizierender Effekt

The available evidence indicates that teplizumab has a disease-modifying biological effect in individuals with stage 2 T1D, consistently delaying disease progression in a selected trial population. This effect is supported by mechanistic findings indicating transient preservation of beta-cell function and is accompanied by a short-term safety profile that is broadly consistent with expectations for an anti-CD3 monoclonal antibody.

hohe Unsicherheit zu Pat.-relevantem Nutzen

However, the overall certainty of patient-relevant benefit remains limited. Clinical evidence is derived from a single randomised trial with heterogeneous treatment effects and no validated predictors to identify individuals most likely to benefit. Evidence beyond delay in time to diagnosis, including effects on quality of life, metabolic stability at onset, or long-term complications, remains insufficient. In addition, available safety data are confined to a single treatment course and limited follow-up, thereby restricting conclusions regarding rare, delayed, or cumulative adverse effects.

hohe ökonomische Unsicherheit aufgrund von Kostenannahmen und Extrapolation

From an economic perspective, teplizumab is associated with high upfront costs and small estimated health gains in available models, with cost-effectiveness results mainly driven by extrapolated assumptions beyond observed clinical data. The absence of Austrian price information and manufacturer-submitted economic analyses further limits the interpretability of cost-effectiveness and budget impact estimates under Austrian healthcare conditions.

Evidenzlage mit relevanten Unsicherheiten für österreichischen Kontext

Taken together, teplizumab represents a first disease-modifying intervention for stage 2 T1D with a demonstrated effect on delaying clinical onset. At the same time, substantial uncertainty persists regarding the magnitude and durability of patient-relevant benefit, long-term safety, and organisational aspects regarding an implementation in routine care. In this context, the identification and selection of individuals with stage 2 T1D represents a critical prerequisite for the use of teplizumab, as its potential benefit is intrinsically linked to early detection and appropriate patient selection. These uncertainties are central to further decision-making in Austria and may need to be reassessed as further clinical, economic and real-world evidence becomes available.

10 References

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List of abbreviations

Aabs	Circulating antibodies
ADA	American Diabetes Association
AID	Automated insulin delivery
APC	Annual percentage change
ADDQoL	Audit of Diabetes Dependent Quality of Life
AE	Adverse events
ANCOVA	Analysis of covariance
ATMP	Advanced Therapy Medicinal Product
AUC	Area under the curve
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CD3	Cluster of differentiation 3
CDEC	Canadian Drug Expert Committee
CGM	Continuous glucose monitoring
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMV	Cytomegalovirus
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DIDP	DAWN-2 Impact of Diabetes Questionnaire
DDG	Deutsche Diabetes Gesellschaft
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPV	Diabetes-Patienten-Verlaufsdokumentation
EAG	External Assessment Group
EASD	European Association for the Study of Diabetes
EBV	Epstein-Barr virus
EDENT1FI	European action for the Diagnosis of Early Non-clinical Type 1 diabetes For disease Interception
EMA	European Medicines Agency
EU	European Union
FU	Follow-up
GPPAD	The Global Platform For The Prevention Of Autoimmune Diabetes
Hb1Ac	Glycosylated haemoglobin (Haemoglobin 1Ac)
HCP	Healthcare provider
Hgb	Haemoglobin
HLA	Human leukocyte antigen
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IDF	International Diabetes Federation
IQR	Interquartile range
ISPAD	International Society for Paediatric and Adolescent Diabetes
IV	Intravenous(ly)
Lys	Life years
MAH	Marketing authorisation holder
NCT	National Clinical Trial number
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OGTT	Oral glucose tolerance test
ÖDG	Österreichische Diabetes Gesellschaft (Austrian Diabetes Association)
ÖDV	Österreichische Diabetes Vereinigung
PMN	Polymorphonuclear neutrophils
PRIME	PRIme MEdicines
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PY	Person-years
QALY	Quality-adjusted life year
QoL	Quality of life
QOL-Q	(Diabetes) Quality of Life Questionnaire
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics

T1D ..... Type 1 diabetes
T2D ..... Type 2 diabetes
TN-10..... TrialNet 10
UK..... United Kingdom
ULN..... Upper limit of normal
US ..... United States
WHO..... World Health Organisation
ZnT8..... Zinc transporter protein 8

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