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Health Technology Briefing
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Teplizumab for the delay of clinical type-1 diabetes in at-risk patients aged 8 years and over

Company/Developer	Provention Bio

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 4053	NICE ID: 10753	UKPS ID: N/A

Licensing and Market Availability Plans

The clinical development of teplizumab for the proposed indication has been completed.

Summary

Teplizumab is in clinical development for the delay of clinical type-1 diabetes (T1D) in individuals at risk of developing the disease. T1D is a condition which usually starts early in life where the immune system (blood cells which usually defend the body from infection) attacks an organ called the pancreas. The pancreas usually makes a substance called insulin, which controls the amount of sugar in the blood. In T1D, the pancreas does not produce enough (or sometimes any) insulin. This means that blood sugar levels can become elevated which can damage many organs in the body. This type of diabetes often runs in families meaning those with relatives who have the disease may be at risk of developing it themselves. However, there is no approved disease-modifying treatment that targets the underlying cause of T1D. Some interventions have delayed the loss of insulin production in patients with type 1 diabetes, but interventions that might affect clinical progression before diagnosis are needed.

Teplizumab is an intravenously (IV) administered drug designed to recognise and exhaust autoreactive T cells: the immune cells responsible for destroying insulin-producing beta cells in T1D. This means that some beta cells are protected from the T cell attack, and people can keep on making enough of their own insulin for longer. If licenced, teplizumab will provide the first treatment for the delay of clinical T1D in individuals at risk of developing the disease.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

Delay of clinical type-1 diabetes (T1D) in individuals, at least 8 years of age, at risk of developing the disease (those with 2 or more T1D autoantibodies and dysglycaemia).[1,2]

Technology

Description

Teplizumab (PRV-031, MGA031) is a humanised IgG1k monoclonal antibody that binds to an epitope of the CD3-epsilon chain expressed on mature T lymphocytes, and thereby modulates the pathological immunologic responses underlying T1D and other autoimmune diseases.[3,4]

The clinical development of teplizumab for the proposed indication (delay of clinical T1D in individuals at risk of developing the disease) has been completed. In the phase II clinical trial (TN-10, NCT01030861), patients were given IV infusions of teplizumab for 14 consecutive days for a total cumulative dose of 9 mg/m^2 based on body surface area.[2,5]

Key Innovation

Clinical T1D is managed through insulin therapy and glucose monitoring to keep patients alive but still can reduce life expectancy for patients by a decade or more. Currently, there is no approved disease-modifying treatment that targets the underlying cause of T1D or that affects clinical progression before diagnosis.[1]

Teplizumab is genetically engineered and directed against the CD3 antigen on T cells; it selectively deactivates the immune cells responsible for beta cell destruction.[6] The results of a phase II teplizumab trial showed the treatment was able to slow down the immune system's destruction of insulin-producing beta cells, meaning those deemed at risk of T1D could keep on making enough of their own insulin for longer, delaying a diagnosis of clinical T1D.[7,8] Extended follow-up data showed that, compared to placebo, one course of teplizumab delayed insulin-dependence in presymptomatic T1D patients by a median of approximately three years.[3]

If licenced, teplizumab will provide the first immune therapy treatment for the delay of clinical T1D in at-risk individuals.

Regulatory & Development Status

Teplizumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Teplizumab was granted US Food and Drug Administration (FDA) Breakthrough Therapy designation for the prevention or delay of clinical T1D, and the European Medicines Agency (EMA) granted teplizumab PRIME designation for the prevention or delay of clinical T1D in individuals at risk of developing the disease.[3]

In July 2021 teplizumab was awarded an Innovation Passport for the delay of clinical T1D in at-risk individuals by the Medicines and Healthcare products Regulatory Agency (MHRA).[1]

Teplizumab is also in phase III clinical development for the treatment of children and adults with recent-onset T1D.[9]

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Patient Group

Disease Area and Clinical Need

T1D is an autoimmune disease characterised by T-cell mediated destruction of insulin producing beta cells within the pancreatic islets of Langerhans. Longitudinal observational studies over more than 30 years have described the progression of the autoimmune disease from the first appearance of autoantibodies until beta cell function is critically impaired and the clinical diagnosis, often with ketoacidosis, occurs. Clinical T1D is associated with a need for lifelong exogenous insulin administration for survival, increased morbidity, and mortality due to immediate (e.g., diabetic ketoacidosis, hypoglycaemia) and long-term complications (e.g., vascular, renal, and eye disease), and reduced lifespan, life impairments, and considerable health-care-related costs.[7] At risk individuals are those with two or more T1D autoantibodies and impaired glucose tolerance (dysglycaemia); these patients are still pre-symptomatic and have not yet developed the overt hyperglycaemia associated with the clinical stage of the disease. These individuals have a 75% chance of progressing to clinical T1D within 5 years and nearly a 100% lifetime risk of developing clinical T1D.[10] Research suggests that those children with an affected first-degree relative have a tenfold higher risk of T1D compared with the general population. In addition to genetic predisposition, research suggests that environmental and early-life factors may influence T1D risk.[11] Clinical T1D usually starts in children between the ages of 5 and 15 but can develop in younger children and adults too. Symptoms include increased thirst and hunger, increases urination, weight loss, fatigue and blurred vision.[1,12]

In the UK, approximately 400,000 people have T1D, including about 39,000 children 19 years and younger. The UK has one of the highest rates of T1D globally, and new diagnoses are increasing by about 4% each year.[1] In England, 2020-21, there were 39,563 finished consultant episodes (FCE) and 24,961 admissions for T1D (ICD-10 code E10), which resulted in 89,913 FCE bed days and 1,500 day cases.[13] In 2020 there were 560 deaths with T1D (ICD-10 code E10) as the underlying cause of death.[14] No UK prevalence/incidence for those at risk of T1D could be obtained from available sources.

Recommended Treatment Options

Currently, there is no National Institute for Health and Care Excellence (NICE) recommended treatment for the delay of clinical T1D in at-risk individuals. NICE recommends insulin therapy, dietary management, exercise and blood glucose control for those with clinical T1D.[15]

Clinical Trial Information

Trial	**CP-MGA031-01, NCT01030861, 2013-002248-98;** AntiCD3 Mab (Teplizumab) For Prevention of Diabetes In Relatives At-Risk for Type 1 Diabetes Mellitus **Locations:** Canada, Germany, and USA **Phase II** - Completed **Study Completion Date**: June 2019	**PRV-031-002; NCT04270942;** An Open-Label Study to Evaluate the Safety of Teplizumab (PRV-031) in At-Risk Relatives Who Develop Type 1 Diabetes **Locations:** USA **Phase II** - Recruiting **Primary Completion Date**: August 2024
Trial Design	Randomised, parallel assignment, quadruple-blind	Single group assignment, open-label
Population	76 participants, have a relative with T1D, presence of at least two confirmed	30 participants, children, adults and older adults with a diagnosis of T1D after the conclusion of the TN-10 study

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	diabetes autoantibodies, aged 8 years to 45 years.	
Intervention(s)	Teplizumab by intravenous infusion	Teplizumab by intravenous infusion
Comparator(s)	Placebo	None
Outcome(s)	Primary outcome measure: • The elapsed time from randomization to the clinical diagnosis of diabetes [Time Frame: During follow-up, median 745 days, range 74 to 2683][8]	Primary outcome measure: • Safety and tolerability of teplizumab treatment [Time Frame: 78 weeks]
Results (efficacy)	• The median time to the diagnosis of T1D was 48.4 months in the teplizumab group and 24.4 months in the placebo group; the disease was diagnosed in 19 (43%) of the participants who received teplizumab and in 23 (72%) of those who received placebo. • The hazard ratio for the diagnosis of T1D (teplizumab vs. placebo) was 0.41 (95% confidence interval, 0.22 to 0.78; P = 0.006 by adjusted Cox proportional-hazards model). • The annualized rates of diagnosis of diabetes were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group.[8]	-
Results (safety)	• A total of 15 (75%) of the 20 grade 3 events in the teplizumab group involved transient lymphopenia during the first 30 days after administration. • A spontaneously resolving rash, as previously noted, occurred in 16 (36%) of participants who received teplizumab. • The rates of infection were similar in the two treatment groups.[8]	-

Estimated Cost

The cost of teplizumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE Technology appraisal guidance. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (TA151). July 2008.

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- NICE Clinical guideline. Type 1 diabetes in adults: diagnosis and management. August 2015. Last updated: July 2021.
- NICE Clinical guideline. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). August 2015. Last updated: December 2020.
- NICE Quality Standard. Diabetes in adults (QS6). March 2011. Last updated: August 2016.
- NICE Quality standard. Diabetes in children and young people. July 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. Action for Diabetes. January 2014.
- NHS England. 2013/14 NHS Standard Contract for specialised endocrinology services (Adult) A03/S/a.

Other Guidance

- British Medical Journal. Diagnosis and management of type 1 diabetes in adults: summary of updated NICE guidance. 2015.[16]
- American Diabetes Association. Type 1 Diabetes through the life span: a position statement of the American diabetes association. 2014.[17]

Additional Information

Provention Bio did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicine.

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