A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus

Published: 07-08-2009
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Primary: The primary objective of this study is to assess relative to placebo, the efficacyof teplizumab when administered according to 3 different teplizumab dosing regimens in subjects with recent-onset T1DM (within 12 weeks of presentation of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON35199

Source
ToetsingOnline

Brief title
Protégé Encore study

Condition

- Autoimmune disorders

Synonym
diabetes

Research involving
Human

Sponsors and support

Primary sponsor: MacroGenics Inc.
Source(s) of monetary or material Support: MacroGenics;Inc.

Intervention

Keyword: diabetes mellitus type 1, monoclonal antibody, Teplizumab

Outcome measures

Primary outcome

Primary Efficacy Endpoints

This study has two primary endpoints:

• To determine the difference in the proportion of subjects who have both a total daily insulin dose < 0.5 Units (U)/kilogram (Kg)/day and hemoglobin A1c (HbA1c) level < 6.5% between teplizumab and placebo 52 weeks after randomization

• To determine the difference in mean HbA1c between teplizumab and placebo at 52 weeks after randomization

For each endpoint, groups receiving different teplizumab treatment regimens will be compared independently to the placebo group with an adjustment made for multiplicity of statistical comparisons. The primary endpoints will be tested in the sequence in which they are listed, and the first endpoint must meet the required level of statistical significance in order for the second endpoint to be tested. Inclusion of the second primary endpoint ensures that a benefit of glycemic control results from teplizumab treatment and that meeting the first

endpoint is not preferentially explained by lower insulin requirements in the teplizumab group. There will be no adjustment for multiplicity based on the two co-primary endpoints.

Secondary outcome

Secondary Efficacy Endpoints

The secondary objectives of the study are to compare teplizumab and placebo with respect to:

• The change in beta-cell function as measured by C-peptide secretory response following a mixed meal after 52 weeks of treatment.

• Incidence and rates of major, minor and nocturnal hypoglycemia at 52 weeks after randomization

• Mean number of daily insulin injections received 52 weeks after randomization

• Patient-reported outcomes (PROs) at 52 weeks after randomization

o Pediatric Quality of Life Inventory (PedsQL)

o Low Blood Sugar Survey (LBSS)

o EuroQol-5 dimensions (EQ-5D)

These secondary endpoints will be tested in the sequence in which they are listed. A gatekeeping strategy will be used in this analysis.

Other Secondary Endpoints

• The long-term safety and tolerability of teplizumab

• Proportion of subjects who have both a total daily insulin dose < 0.5 U/Kg/day and HbA1c level < 6.5% at 104 weeks after randomization

• The difference in mean HbA1c at104 weeks

• The change in beta-cell function as measured by C-peptide secretory response following a mixed meal after 104 weeks of treatment

• Incidence and rates of major, minor and nocturnal hypoglycemia at 104 weeks after randomization

• The proportion of subjects who have both a total daily insulin dose < 0.5 U/Kg/day and hemoglobin A1c (HbA1c) level < 7.0 % 52 weeks after randomization

• The difference in change in mean HbA1c from baseline to endpoint at104 weeks

• The change in beta-cell function as measured by C-peptide secretory response following a mixed meal after 104 weeks of treatment

• Incidence and rates of total and nocturnal hypoglycemia at 104 weeks after randomization

• Patient-reported outcomes (PROs) at 104 weeks after randomization

o LBSS

o EQ-5D

Exploratory Endpoints

This study has many exploratory endpoints. The methods used to analyze these endpoints will be described in the Statistical Analysis Plan. These will include, but not be limited to,

• Evaluation of the pharmcokinetics of teplizumab

• Various pharmacodynamic and immunologic parameters, biomarkers and potential new surrogate endpoints

Safety Endpoints

Safety evaluations will be based on adverse event (AE), adverse event of special interest (AESI) and serious adverse event (SAE) rates, as well as other safety parameters. AEs will be described by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) term, severity and relationship to teplizumab.

Other safety summaries will include:

• Fatalities

• Chemistry, CBC (complete blood count) with absolute lymphocyte and neutrophil counts, platelets and urinalysis (urinary protein and blood)

• Vital signs including height (centimeter [cm]), weight (kilogram [Kg])

• Hypoglycemic episodes (major, minor, nocturnal)

• Electrocardiogram (ECG) monitoring before and after drug administration

Study description

Background summary

Type 1 diabetes mellitus (T1DM) is caused by a T-lymphocyte-dependent autoimmune attack on the pancreatic ß-cells that ultimately destroys the capacity of the ß-cells to produce amounts of insulin adequate to control excessive blood glucose levels and, ultimately, to maintain life. As in other autoimmune disorders, this self-destructive process likely results from auto-reactive effector cells (e.g., natural killer and T-helper cells) that have escaped elimination or inhibition by regulatory T cells (Tregs). Unless the destruction of the pancreatic islet cells can be halted early in the course of the disease, irreversible morbidity may develop.

Teplizumab is a humanized monoclonal antibody that targets the cluster of differentiation 3 (CD3) antigen on the surface of T lymphocytes. In vitro and

in vivo data suggest that binding of teplizumab to its target triggers a cascade of events that results in a resetting of the balance between auto-reactive T cells and Tregs. A substantial body of data in experimental animals with diabetes and preliminary data in humans with T1DM indicate that the autoimmune attack on the pancreatic ß-cells can be aborted or significantly slowed with short-term intravenous (IV) treatment with teplizumab, or other anti-CD3 antibodies. A small, previously completed study suggests that treatment of individuals with recent-onset T1DM with teplizumab may produce long-term (at least 2 years) improvement in glycemic control, reduction in insulin requirements, and preservation of ß-cell function, as reflected in C-peptide response to a mixed meal stimulus. The current study is the second of two, large, randomized, placebo-controlled clinical trials to further evaluate the safety and efficacy of teplizumab in the treatment of subjects with recent-onset T1DM.

Study objective

Primary:
The primary objective of this study is to assess relative to placebo, the efficacyof teplizumab when administered according to 3 different teplizumab dosing regimens in subjects with recent-onset T1DM (within 12 weeks of presentation of first signs and symptoms of disease to a physician). All regimens will be administered in addition to standard of care.

Secondary:
The secondary objectives are to assess the durability of clinical benefit, the impact of teplizumab on health-related quality of life, and the safety and tolerability of teplizumab.

Study design

The study is a randomized, double-blind, double-dummy, multinational, 4-arm, placebo-controlled, dose-ranging study to evaluate the safety and efficacy of teplizumab in subjects (children aged 8 years or older and adults) with recent onset T1DM. The study is of two years* duration, with assessment of the primary endpoints at Week 52. The study will continue to Week 104 with investigators and subjects remaining blinded to treatment assignment.

Subjects who consent (and assent for children under age 18) and meet the entry criteria at Study Day 0 will be randomized to 1 of 4 study arms (N=400 subjects). Subjects will receive treatment with teplizumab (3 study arms of 100 each [Arms 1*3, respectively]) or placebo only (1 study arm of 100 subjects [Arm 4]). The randomization will be stratified by country and age (18-35 years, 12-17 years, and 8-11 years).

Treatment with teplizumab or placebo will be administered using a double-blind,

double-dummy design as follows:

• Arm #1--Herold Regimen (n=100): Subjects will receive a 14-day course of teplizumab consisting of daily intravenous (IV) doses of 51 micrograms/meter squared (µg/m2), 103 µg/m2, 207 µg/m2 and 413 µg/m2 on Study Days 0-3, respectively, and one dose of 826 µg/m2 on each of Study Days 4-13. The total dose for a 14-day course is approximately 9034 µg/m2. For subjects weighing 70 Kg and having a body surface area (BSA) of 1.92 m2, this dosing schedule delivers ~17 milligrams (mg) of teplizumab. The treatment will be repeated at Week 26.

• Arm #2--* Herold Regimen (n=100): Subjects will receive a 14-day course of teplizumab consisting of daily IV doses of 17 µg/m2, 34 µg/m2, 68 µg/m2 and 136 µg/m2 on Study Days 0-3, respectively, and one dose of 273 µg/m2 on each of Study Days 4-13. The total dose for a 14-day course is approximately 2985 µg/m2. This regimen is the Herold Regimen (Arm #1) divided by 3. For subjects weighing 70 Kg and having a BSA of 1.92 m2, this dosing schedule delivers ~5.6 mg of teplizumab, which is ~33% of the Herold Regimen. The treatment will be repeated at Week 26.

• Arm #3--Curtailed Herold Regimen (n=100): Subjects will receive a 6-day course of teplizumab consisting of daily IV doses of 51 µg/m2, 103 µg/m2, 207 µg/m2 and 413 µg/m2 on Study Days 0*3, respectively, and one dose of 826 µg/m2 on each of Study Days 4-5, followed by 8 days of IV placebo (Study Days 6-13). The total dose for a 14-day course is 2426 µg/m2. This regimen is the Herold Regimen (Arm #1) curtailed after 6 doses. For subjects weighing 70 Kg and having a BSA of 1.92 m2, this dosing schedule delivers ~4.6 mg of teplizumab, which is ~27% of the Herold Regimen. The treatment will be repeated at Week 26.

• Arm #4--Placebo (n=100): Subjects will receive a 14-day course of IV placebo only. The course will be repeated at Week 26.

No study drug is administered during Study Year 2. The second year of the study involves long-term follow-up through Week 104 and evaluation of all subjects randomized in Year 1.

Intervention

The study group will get the study drug administered intravenous 24 times. The control group will get the study drug administered intravenous 24 times. Both groups will undergo a venipuncture 33 times.

Study burden and risks

Because Teplizumab is an experimental drug and there might be risks that are unknown or unforeseen at the moment. The following side effects have been

reported in patients who received Teplizumab and these side effects can cause a risk for patients participating in the study:
* Blood and lymphatic system disorders such as lymphopenia and leukopenia;
* Gastrointestinal disorders such as nausea and vomiting;
* Fever, headache, skin disorders. See page 8 of the patient information and informed consent form.

The placement of an intravenous tube is a routine procedure which may cause tempory discomfort or slight bruising at the site of blood dwaing or fainting. The blood pressure cuff may cause discomfort or bruising of the upper arm.

It is unknown what the effect of Teplizumab is on pregnant woman, that is why pregnant woman are excluded from participating in the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Diagnosis of diabetes mellitus according to the American Diabetes Association (ADA) criteria
2. Written informed consent obtained from the subject (assent will be obtained for subjects under age 18 years, according to all applicable regulations) including consent for the use of research-related health information
3. Randomization on Study Day 0 within 12 weeks of first visit to any physician for symptoms or signs of diabetes
4. Requires insulin for T1DM or has required insulin at some time between diagnosis and administration of study drug.
5. Detectable fasting or stimulated C-peptide level (above the lower limit of the reportable range of the assay) at screening
6. Diagnosis of T1DM as evidenced by one positive result on testing for any of the following antibodies at screening:
a. Islet-cell autoantibodies 512 (ICA512)/islet antigen-2 (IA-2),
b. Glutamic acid decarboxylase (GAD) autoantibodies, or
c. Insulin autoantibodies (in subjects on insulin for more than 2 weeks, ICA-512/IA-2 or GAD must be positive)
7. Subjects 8-35 years old
8. Body weight > 36 Kg
9. BSA <=2.4 m2 (Interactive Voice Response System [IVRS] will be used to calculate BSA using the Mosteller formula)
10. Sexually active females, unless surgically sterile, must be willing to use 2 forms of contraception through the end of the study (Study Day 728). Acceptable forms of contraception for female subjects include: oral, transdermal, injectable or implanted contraceptives, intrauterine device (IUD), female condom, diaphragm with spermicide, cervical cap, use of a condom by the sexual partner, or sterile sexual partner. Abstinence is an acceptable form of contraception only if it is the subject*s pre-existing method of contraception. Male subjects with partners of child-bearing potential should use barrier contraception in addition to having their partners use another method of contraception
11. Willing to forego other forms of experimental treatment during the study

Exclusion criteria

1. Prior administration of a monoclonal antibody*within the 1 year before randomization at Study Day 0
2. Participation in any type of therapeutic drug or vaccine clinical trial within the last 12 weeks before randomization at Study Day 0
3. Any medical condition that, in the opinion of the investigator, would interfere with safe completion of the trial

4. Pregnant females or lactating females who intend to provide their own breast milk to the baby during the study
5. Prior murine OKT®3 treatment or other anti-CD3 treatment
6. Current therapy with GLP-1 receptor agonists (e.g., exenatide or pramlintide), or any other agents that might stimulate pancreatic beta cell regeneration or insulin secretion
7. Current treatment with oral antidiabetic agents
8. Current or planned therapy with inhaled insulin, if it becomes available
9. Uncompensated heart failure, fluid overload, myocardial infarction or evidence of ischemic heart disease or other serious cardiac disease as described in New York Heart Association (NYHA) Class III or IV criteria within the 12 weeks before randomization
10. History of epilepsy, cancer, cystic fibrosis, sickle cell anemia, neuropathy, peripheral vascular disease or cerebrovascular disease
11. Untreated hypothyroidism or active Graves* disease
12. Eczema, asthma or severe atopic disease requiring treatment, including topical or inhaled corticosteroids, within the 12 weeks before randomization
13. Treatment with systemic glucocorticoid therapy by oral, intravenous (IV), intramuscular (IM), or inhaled route within 12 weeks before randomization; patients who are likely to require treatment with corticosteroids during the trial are also excluded
14. Evidence of active infection
15. Known or suspected infection with human immunodeficiency virus (HIV)
16. History of or positive tests for hepatitis B, C of D,
17. Total bilirubin > 1.5 x upper limit of normal (ULN)
18. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 x ULN
19. Evidence of active or latent tuberculosis (TB), which may include a positive purified protein derivative (PPD) skin test result (>= 10 mm induration); a chest X-ray consistent with TB or household contact with a person with active TB, unless appropriate isoniazid (INH) prophylaxis for tuberculosis (TB) was previously given
20. Evidence of active or latent tuberculosis (TB), which may include a positive purified protein derivative (PPD) skin test result; a chest X-ray consistent with TB or household contact with a person with active TB, unless appropriate isoniazid (INH) prophylaxis for tuberculosis (TB) was previously given
21. Vaccination with a live virus or organism within the 8 weeks before randomization continuing through Week 52 of the study.
• Influenza vaccination with a killed virus, including booster vaccinations, within 4 weeks before or after each dosing cycle.
• Vaccination with other antigens or killed organisms within 8 weeks before or after each dosing cycle
22. Serologic or clinical evidence of acute infection with Epstein-Barr virus (EBV), including a positive Epstein-Barr virus (EBV) immunoglobulin M (IgM). (Viral load does not have to be positive)
23. Serologic evidence of acute infection with cytomegalovirus (CMV), defined as a positive cytomegalovirus (CMV) immunoglobulin G (IgG) and a positive viral load
24. Decreased lymphocytes (< 1000 lymphocytes/µL)
25. Decreased neutrophils (< 1000 PMN/µL on 2 consecutive evaluations performed on different days)
26. Decreased platelet count (< 150,000 platelets/µL)
27. Decreased hemoglobin (Hgb < 10 grams/deciliter [g/dL])

28. Investigative site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
29. Employees of MacroGenics, Inc. or Eli Lilly and Co., including permanent employees, temporary contract workers, or designees responsible for conducting this study. Immediate family of employees may participate in this study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-11-2009
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Teplizumab
Generic name:	NAP

Ethics review

Approved WMO

Date:	07-08-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-01-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-10-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-011606-41-NL
ClinicalTrials.gov	NCT00920582
CCMO	NL28693.078.09