A Phase 2/3, Randomized, Double-Blind, Multicenter, Multinational, 4-Arm, Controlled, Dose-Ranging Study to Evaluate Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus

Published: 18-09-2008
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Primary:The primary objective of this study is to assess, relative to placebo, the efficacy, tolerability, andsafety of teplizumab when administered according to 3 different teplizumab dosing regimens insubjects with recent-onset (onset within past...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON33995

Source
ToetsingOnline

Brief title
Protégé 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 Endpoint

This study has two primary endpoints. The first primary endpoint is a composite endpoint. It is the proportion of subjects, who at 52 weeks after randomization, have both a total daily insulin dose of less than 0.5 U/kg/day and HbA1c level of less than 6.5%. The second primary endpoint is the mean HbA1c level at 52 weeks after randomization.

The two primary endpoints will be assessed in a hierarchical manner with the composite being assessed first. The mean HbA1c will only be assessed if a statistically significant difference is obtained with the composite endpoint.

Safety Endpoints

Evaluations of safety will be based on adverse event (AE) and serious adverse event (SAE) rates,

as well as other safety parameters. AEs will be described by system organ class and MedDRA

term, severity, and relationship to teplizumab.

Secondary outcome

Secondary Efficacy Endpoints

The secondary endpoints of this study are:

•To compare, relative to placebo, the capacity of teplizumab to preserve C-peptide secretory responses following a mixed meal eaten by the subject 104 weeks after randomization, and

•To compare the proportion of subjects, who at 104 weeks after randomization, have both a total daily insulin dose of less than 0.5 U/kg/day and HbA1c level of less than 6.5%

•To compare the proportion of subjects, who at 52 weeks after randomization, have both a total daily insulin dose of less than 0.5 U/kg/day and HbA1c level of less than 7.0%

•To compare, relative to placebo, mean HbA1c level at 104 weeks after randomization.

Other Endpoints

Exploratory endpoints include:

•Supportive analyses of the primary endpoints (including subgroups)

•Time course of effect of teplizumab on the primary endpoint and on C-peptide

• Analyses of the time course of insulin requirements, HbA1c level, glucose

levels, and hypoglycemic episodes

•Various pharmacodynamic and immunologic parameters, biomarkers and potential

new surrogate endpoints

•The examination of potential dose-response relationships among AEs and

therapeutic outcomes

Study description

Background summary

Type 1 diabetes mellitus (T1DM) is a serious and potentially life-threatening condition that
results from progressive, autoimmune destruction by T lymphocytes of the insulin-producing β-
cells of the pancreas. There are no approved therapies that prevent progressive and irreversible
destruction of the insulin-producing β-cells of the pancreas.

During this studie the Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR
Non-Binding, Anti-CD3 Monoclonal Antibody, will be evaluated.

Study objective

Primary:
The primary objective of this study is to assess, relative to placebo, the efficacy, tolerability, and
safety of teplizumab when administered according to 3 different teplizumab dosing regimens in
subjects with recent-onset (onset within past 12 weeks) type 1 diabetes. All regimens will be
administered in addition to standard of care.

Secondary:
The secondary objectives are to assess the durability of clinical benefit and the pharmacokinetics,

pharmacodynamics, and immunogenicity of teplizumab.

Study design

This Phase 2/3 clinical trial has 3 segments. Just patients form North America will be included in segment 1. If enrollment is slow, the study will be conducted in other countries as well, after the required regulatory approvals. In the Netherlands patients will only be included in segment 2 and 3.

Segment #1
* Open-label administration of teplizumab for 14 days to 30 subjects (ages 18-35 [n=10]; ages 12-17 [n=10]; ages 8-11 [n=10]) with recent-onset (within 12 weeks of the first visit to any physician for symptoms or signs) type 1 diabetes to assess safety and tolerability of teplizumab.
* Subjects aged 18-35 will be enrolled first and evaluated through Study Day 28 before the enrollment of children begins.
* Children aged 8-17 will be enrolled after all subjects aged 18-35 have completed their evaluations through Study Day 28 and after the Data Monitoring Committee (DMC) reviews and approves the data. This part of Segment #1 will be conducted as two cohorts (ages 12-17 and 8-11) that will proceed in parallel, but each cohort will be evaluated separately by the DMC for safety and tolerability.

Segment #2
* Double-blind, double-dummy administration of teplizumab or placebo for 14 days to 500 subjects with recent-onset (within 12 weeks of the first visit to any physician for symptoms or signs) type 1 diabetes, randomly assigned to 1 of 4 study arms, to assess safety and efficacy of teplizumab. To maintain the blind, all subjects in Arms #1, #2, and #3 will receive both teplizumab and placebo. Subjects in Arm #4 will receive placebo only (i.e., double-dummy design).
* After DMC review and approval of data through Study Day 28 for subjects aged 18-35 in Segment #1, subjects aged 18-35 will be enrolled.
* After DMC review and approval of data through Study Day 28 for subjects aged 12-17 in Segment #1, children aged 12-17 will be enrolled.
* After DMC review and approval of data through Study Day 28 for subjects aged 8-11 in Segment #1, children aged 8-11 will be enrolled.

* Arm #1--Herold Regimen (n=200): Subjects will receive a 14-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 4-13. The total dose for a 14-day course is approximately 9034 µg/m2. This regimen is comparable to the Herold Regimen. For subjects weighing 70 kg and having
a body surface area (BSA) of 1.92 m2, this dosing schedule delivers ~17 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 comparable to the Herold Regimen 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
IND 100,262 Page 10 of 141 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 comparable to the Herold Regimen that is
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 treatment will be repeated at Week 26.

Segment #3
* Follow-up of subjects in Segments #1 and #2 to Week 104 to assess long-term safety and durability of clinical benefit.

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 29 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. Written informed consent obtained from the subject (assent will be obtained for subjects under age 18, according to country-specific requests) including consent for the use of research-related health information.
2. Enrollment (Segment #1) or randomization (Segment #2) on Study Day 0 within 12 weeks of first visit to any physician for symptoms or signs of diabetes.
3. Diagnosis of type 1 diabetes mellitus, according to the American Diabetes Association and must have adiagnosis of type 1 diabetes mellitus.
4. Requirement for injected insulin therapy currently or in recent past.
5. Have a detectable fasting or stimulated C-peptide level (above the lower limit of detection of the assay).
6. One positive result on testing for any of the following antibodies:
a. islet-cell autoantibodies (ICA512/IA-2),
b. glutamic acid decarboxylase autoantibodies, or
c. insulin autoantibodies (if present during first 2 weeks, but not beyond 2 weeks, of insulin treatment)
7. Male or female.
8. Subject must be in one of the following age groups:
· Age 18-35 years (initiation of enrollment in Segment #2 requires approval by DMC and, if required, other authorities according to all applicable regulations); or
· Age 12-17 years pending approval by DMC and, if required, other authorities according to all applicable regulations; or
· Age 8-11 years pending approval by DMC and, if required, other authorities according to all applicable regulations.
9. Body weight >= 36 kg.
10. Body surface area (BSA) <=2.4 m2 (Interactive Voice Response System [IVRS] will be used to calculate BSA using Mosteller formula) (see Appendix B).
11. Sexually active females, unless surgically sterile, must use 2 forms of contraception (including oral, transdermal, injectable, or implanted contraceptives, IUD, female condom, diaphragm with spermicide, cervical cap, abstinence, use of a condom by the sexual partner

or sterile sexual partner) for 30 days before the first dose of study drug and must agree to continue using such precautions through the end of the study (Study Day 728). Cessation of birth control after this point should be discussed with a responsible physician. Male subjects with parners of child-bearing potential should use barrier contraception in addition to having their partners use another method of contraception.
*Abstinence is only an acceptable form of contraception if it is the subject's preexisting normal status.
12. Willing to forego other forms of experimental treatment during the study, particularly immunomodulatory agents and agents that stimulate pancreatic beta cell regeneration or insulin secretion.

Exclusion criteria

1. Prior administration of a monoclonal antibody*within the 1 year before enrollment or randomization at Study Day 0* that could potentially prevent or confound a therapeutic response to teplizumab.
2. Participation in any type of therapeutic drug or vaccine clinical trial within the last 12 weeks before enrollment or 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 at any time before enrollment or randomization.
6. Current or planned therapy with Exenatide or any other agents that stimulate pancreatic beta cell regeneration or insulin secretion, or any oral antibiabetic agents
7. Current or planned therapy with inhaled insulin, if it becomes available
8. Uncompensated heart failure, fluid overload, myocardial infarction or evidence of ischemic heart disease or other serious cardiac disease within the 12 weeks before enrollment or randomization.
9. History of epilepsy, cancer, cystic fibrosis, sickle cell anemia, neuropathy, peripheral vascular disease or cerebrovascular disease.
10. Newly diagnosed hypothyroidism (not currently being treated but which, in the opinion of the investigator, should be treated) or active Graves* disease. Subjects with preexisting hypothyroidism may join the study if their medication is stable with no expected change in dosage or status of disease.
11. Eczema, asthma or severe atopic disease requiring treatment, including tpoical or inhales coricosteroids, within the 12 weeks before enrollment or randomization.
12. Evidence of active infection, such as fever >= 38.0oC (100.5oF).
13. Known or suspected infection with human immunodeficiency virus (HIV).
14. Evidence of active hepatitis B (HBV) or hepatitis C virus (HCV), such as positive hepatitis B surface antigen (HBsAg) or anti-hepatitis C antibody.
15. Total bilirubin >1.5 x upper limit of normal (ULN).
16. AST or ALT >1.5 x ULN.
17. Evidence of active or latent tuberculosis, which may include a positive purified protein derivative (PPD) skin test result (>=10 mm induration); a chest X-ray consistent with

tuberculosis; or household contact with a person with active tuberculosis, unless appropriate isoniazid (INH) prophylaxis for tuberculosis was previously given
18. Vaccination with a live virus within the 8 weeks before enrollment or randomization or planned live virus vaccination continuing through Week 52 of the study. Vaccination with an antigen or killed organism must not be given within 8 weeks before or planned within 8 weeks after each dosing cycle. (For additional information on vaccines see section 3.3.5.2).
19. Any infectious mononucleosis-like illness within the 6 months before enrollment or randomization.
20. Serologic and clinical evidence of acute infection with Epstein-Barr virus (EBV), including a positive EBV IgM. (Viral load does not have to be positive).
21. Serologic evidence of acute infection with cytomegalovirus (CMV), defined as a positive CMV IgG and a positive viral load.
22. Lymphopenia (<1000 lymphocytes/µL).
23. Neutropenia (<1000 PMN/µL on 2 consecutive evaluations performed on different days).
24. Thrombocytopenia (<150,000 platelets/µL).
25. Anemia (Hgb <10 g/dL).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-05-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	Teplizumab
Generic name:	NAp

Ethics review

Approved WMO Date:	18-09-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-03-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-06-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-06-2009
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	EUCTR2006-002457-69-NL
ClinicalTrials.gov	NCT00385697
CCMO	NL22283.078.08