A randomized, double-masked, placebo-controlled, efficacy and safety study of RV 001, an insulin-like growth factor-1 receptor (IGF-1R) antagonist antibody (fully human), administered every 3 weeks (q3W) by intravenous (iv) infusion in patients suffering from active thyroid eye disease (TED)

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

Summary

ID

NL-OMON41037

Source
ToetsingOnline

Brief title
Study on efficacy and safety of RV001 in Graves' eye disease

Condition

- Thyroid gland disorders
- Vision disorders

- Autoimmune disorders

Synonym
Graves Orbitopathy, Thyroid Eye Disease

Research involving
Human

Sponsors and support

Primary sponsor: River Vision Development Corporation
Source(s) of monetary or material Support: River Vision Development Corporation

Intervention

Keyword: Antibody, Eye disease, Insuline-like, RV 001

Outcome measures

Primary outcome

The primary efficacy endpoint is the assessment of whether the patient is a

responder or not (yes or no) at the end of the 6 month treatment phase

(week 24). A responder is defined as a patient with a decrease in overall CAS *

2 points, OR an improvement in ductions of * 10 degrees, OR a reduction in

proptosis * 2 mm. All responses must be observed in the study eye without

deterioration of CAS in the fellow eye (i.e. increase in CAS * 2 points).

Abbrevation:

CAS = Clinical Activity Score

Secondary outcome

Clinical activity score (7 pont scale), proptosis, motility restriction,

Clinical measure of severity score, time to respond, and Graves' Ophthalmopathy

Quality of Life (GO-QOL)

Study description

Background summary

Thyroid eye disease (TED) also called Graves' orbitopathy or ophthalmopathy (GO) and thyroid- associated ophthalmopathy (TAO), is an autoimmune condition usually associated with Graves' disease (GD). In the US, the annual incidence rate of TED has been estimated to be 16 cases per 100,000 population for women and 2.9 cases for men.

Multiple lines of evidence indicate that IGF-1R is a major auto-antigen responsible for triggering and driving TED. RV 001 is an antagonist mAb with low nanomolar affinity for human IGF-1R. Binding of RV 001 to IGF-1R blocks receptor activation by agonists and also causes direct inactivation of the receptor through antibody-induced internalization. RV 001 has no agonist activity at IGF-1R and is highly selective; in particular, it does not recognize the insulin receptor. Systemic administration of RV 001 to patients with moderate to severe active TED should therefore attenuate all disease symptoms that are contingent on IGF-1R activation. This argument holds whether the IGF-1R is being activated by GD-IgG or endogenous ligands IGF-1R and IGF2, or whether the receptor function with an antibody may also attenuate signaling through the TSHR, another autoantigen that has been implicated in TED, because IGF-1R and TSHR are physically and functionally coupled. RV 001 therefore has the potential to treat TED at multiple different molecular and cellular levels and administering RV 001 early in the active phase of TED will potentially minimize the severity and duration of the active phase, have a beneficial effect on long-term outcome, and minimize the need for corrective surgeries. Previous preclinical and clinical experience indicates that RV 001 has an acceptable safety profile following iv infusion and is therefore a suitable drug candidate to be investigated in the TED indication.

Study objective

The primary objective is to investigate the efficacy, safety and tolerability of RV 001 (a fully human anti-IGF-1R antibody) administered q3W for 6 months, in comparison to placebo, in the treatment of patients suffering from active TED.

Secondary objectives:
- to assess clinical measures of severity
- to assess the effect of treatment on quality of life (QOL)

Exploratory objectives:
- to explore the effects of RV 001 over time on candidate plasma biomarkers, to assess the correlation between changes for baseline in plasma biomarkers and

efficacy, and to evaluate the effects of treatment on markers of inflammation an immunity considered related to the disease pathophysiology, relative to pre- and post-treatment profiles.
- to evaluate pharmacokinetic (PK) parameters to estimate exposures and understand PK-pharmacodynamic (PD) relationships.
and understand PK-pharmacodynamic (PD) relationships.

Study design

This multicenter study has a randomized, double-masked, placebo-controlled, parallel-group, design.

The study consists of three parts:

1) A screening phase of 4 weeks duration (+/- 2 weeks) within no treatment. Patients will attend the clinic on 1-2 occasions or as required during the screening period.
2) A double-masked treatment phase of 6 months. Patients will attend clinic visits at week 0 (1st infusion, baseline visit), week 1, 3 (2nd infusion), 4,6 (3rd infusion), 9 (4th infusion), 12 (5th infusion), 15 (6th infusion), 18 (7th infusion),21 (8th infusion) and 24 (final assessment visit). Phone contact by research staff focusing on safety and tolerability aspects will be made the day after infusion for the first and second infusions, and thereafter as required. Patients experiencing an infusion associated event will also be contacted by phone by research staff after the infusion.
3) A follow-up phase of 12 months with no additional treatment during at least the first 3 months. Patients will attend clinic visits at months 7,9,12,15 and 18.

During the screening period patients will complete eligibility criteria assessments; eligible patients meeting the study criteria will be randomly assigned to the double-masked treatment phase, using a 1:1 ratio, to receive a starting dose of 10 mg/kg of RV 001 or placebo q3W by iv infusion. At week 3, the dose will be escalated to 20 mg/kg iv q3W. Following dose escalation, patients will continue at this dose level for all subsequent infusions. The active treatment phase of the study has a duration of 6 months (8 infusions). Randomization will be stratified by smoking status. During the treatment period patients will be evaluated at clinic visits every 3 weeks and, if appropriate, by phone contact by research staff. Measurements for efficacy, tolerability, safety, biomarkers and PK will be performed according to the assessment schedule.

Patients must be withdrawn if optic neuropathy or any condition requiring surgical intervention develops or if the clinical activity score (CAS) increases by 2 or more points.

Data and Safety Monitoring Board (DSMB): a DSMB will be assembled to review

data on a regular basis. All details relating to the constitution of the DSMB, the scope of the data review, and timing of the meetings, are described separately in the DSMB Charter.

Intervention

RV 001 or placebo will be administered q3W by iv infusion over 6 months for a total of 8 infusions. All patients will start RV 001 treatment at a dose of 10 mg/kg. At week 3, the dose will be escalated to 20 mg/kg and then kept constant for the remaining period of the trial. In case of intolerable AEs, patients should be withdrawn from the study. To maintain the mask, placebo patients will similarly have the "dose" doubled at week 3. The duration of the infusion can be adjusted if infusion related AEs emerge.

Study burden and risks

Patients will have to return to the clinic up to a maximum of 19 times and will have to undergo the following procedures:

- Administration of RV 001 or placebo every three weeks by iv infusion over 6 months for a total of 8 infusions
- Medical history assessment (questions about health, current medications, and any allergies).
- Physical examination, vital signs (respiratory rate, pulse rate, blood pressure and body temperature), height and weight. - every visit
- Electrocardiograms (ECG) - at weeks 0, 3, 6, 12, 24, 72
- Blood samples will be drawn for blood chemistry, blood cell counts, biomarker assessment - every visit
- Patients need to fasten 8 hours before blood sample is drawn at week 1 and 4
- Urine test for chemistry and cells - every visit
- Serum (at screening) and urine pregnancy tests (every three weeks) will be performed, for women able to have children, or who's onset of menopause was within the past 2 years
- Eye examinations to assess the Clinical Activity Score/ Clinical Measures of Severity Score: Assessment of pain, swelling, redness, space between eyelids, range of eye movement and any protrusion of the eyes - every visit
- Completion of a short questionnaire to show how the eye problems affect the daily life (a quality of life assessment) - at weeks 6 and 12, 24, 28, 48, 72
- Color eye photos will be taken - at weeks 0, 6, 12, 18, 24, 28, 72

The main ethical concerns with study design are the potential risks imposed by exposure to the investigational drug RV 001. RV 001 is a fully human IgG monoclonal antibody that is a high potency, high specificity antagonist of the insulin like growth factor type 1 receptor (IGF1R).
Unlike some first generation antiIGF1R monoclonal antibodies, RV 001has no partial agonist activity and does not interact with insulin receptors, to which

IGF1R is most closely related. RV 001 does not stimulate antibody dependent cell mediated cytotoxicity and is not immunogenic. Good laboratory practice toxicology studies in cynomolgus monkeys showed that RV 001, dosed to 75 mg/kg/week IV for up to 39 weeks, produced no target organ histopathology or adverse safety pharmacology.
Most importantly from a risk assessment perspective, RV 001 has been previously administered to greater than 730 human cancer patients in trials for a number of oncology indications. The doses used in the oncology studies are comparable to the dose that is being used in the TED study. The extensive clinical safety database generated from these previous trials confirms that RV 001 is generally well tolerated. The safety data from a RV 001 monotherapy study conducted in 310 late stage sarcoma patients indicated the only potentially drug related SAEs (Grade > 3) anticipated in the TED patients are hyperglycemia (< 3 %), thrombocytopenia (< 1 %) and infusion related side effects (< 1 %).
These AEs were all reversible and will be specifically monitored for, and managed, if observed in TED patients.
Multiple procedures have been put in place to ensure the safety of patients in the TED01RV study. These include:
(i) Patients with potential risk factors for RV 001 therapy are excluded from the study. This covers poorly controlled diabetics (i.e. change in the diabetes medication * oral or insulin * greater than 10% over the past 60 days) and subjects with platelet count less than 100 x 109/L at screening or baseline, or hemoglobin values greater than 2 gr/dL below the lower limit of the reference range.
(ii) Ongoing assessment of adverse events (AEs), including serious adverse events (SAEs), premature withdrawals for AEs and rates of AEs (severity, relationship) and regular measurement of ECGs, vital signs, and laboratory parameters (hematology, biochemistry, urinalysis), together with physical examinations. The assessment of AEs and SAEs will be conducted by an independent Data and Safety Monitoring Board (DSMB) who meets monthly during the duration of the trial.
iii) Immediate withdrawal of patients from the study in cases of unacceptable AEs within 2 weeks of the next scheduled dose (defined as inability to work or perform daily activity), or if optic neuropathy (defined by a decrease in vision of two lines of Snellen chart, new visual field defect or color defect secondary to optic nerve involvement), or any condition requiring surgical intervention develops, or if the clinical activity score (CAS) increases by 2 or more points.
(iv) Non fasted blood glucose levels will be evaluated prior to each RV 001 infusion and under fasting conditions at weeks 1, 4, 15, and 21. In the event of hyperglycemia, the decision whether to withdraw a patient from the trial is at the discretion of the investigator. If hyperglycemia is mild and the patient remains in the study the investigator can control the condition by modifying the patient*s diet or by treatment with standard antidiabetic drugs such as metformin and sulphanylureas. Since a referral for treatment of hyperglycemia may take some time, if the investigator considers it appropriate to continue the patient in the study, the next scheduled infusion visit may be skipped to

allow anti-diabetic treatment to show its activity and hyperglycemia to return to mild/moderate level before dosing. The patient would then be dosed at the next scheduled visit (i.e. 6 weeks after the previous infusion). Fasting blood glucose levels must return to mild/moderate severity before the next scheduled infusion. The above process of withholding a scheduled infusion will be permitted only twice during the study.
(v) Platelet levels will also be assessed by the investigator prior to each RV 001 infusion. Patients with severe thrombocytopenia (i.e. < 35 x 109/l platelets) will be withdrawn from the study and treated, for example with corticosteroids, or blood / platelet transfusions.
(vi) If adverse events develop during an infusion (e.g. nausea, injection site pain), the rate of infusion may be slowed, or stopped, as required. Symptomatic treatment, e.g. antipyretics, antihistamines, beta agonists, oxygen, IV fluid, will be administered as needed. Following an immediate infusion associated event, vital signs (temperature, blood pressure, pulse and respiratory rate) will be determined every 5 minutes until stable, and then every 15 minutes for two additional determinations. The infusion may be restarted upon complete resolution of symptoms, except for patients who experienced an anaphylactic reaction assessed to be severe in intensity. Patients experiencing an immediate infusion associated event will also be contacted by phone by a research nurse the day after the infusion.
(vii) To monitor for delayed infusion reactions, phone contacts by a research nurse focusing on safety and tolerability will be made the day after infusion for the first and second infusions, and thereafter as required. Patients with a skin rash which worsens following repeated infusions of study drug, or who present other signs of serum sickness (e.g. delayed fever, myalgias, arthralgias), will be withdrawn.
(viii) The first infusion for all patients is a * dose (10 mg/kg IV). This is an additional safety measure included to take account of the fact that only cancer patients have previously been exposed to RV 001.
(ix) To obviate risk to a developing fetus, women of childbearing age (including women with onset of menopause of < 2 years) must be willing and able to use two different methods of contraception, one of which must be an oral (or depot) contraceptive. Assurances of abstinence will not be acceptable. Pregnancy tests will be performed at screening, baseline, all visits during dosing and at follow up visits 1 and 2. If pregnancy occurs the patient will be withdrawn from the study. Male patients must agree to use a barrier contraceptive method or must be surgically sterile.
(x) Samples for measuring anti RV 001 antibodies will be taken at baseline and at weeks 0, 3, 9, 24, 36, and 72.
Analysis will only be performed at week 72 (study completion), but any patient with treatment emergent antidrug antibodies will be followed up.
Note, treatment induced anti RV 001 antibodies were not detected in previous oncology studies.

Several lines of evidence suggest that IGF1 is involved in the pathophysiology

of thyroid eye disease.
RV001 is specifically blocking the IGF1 receptor therefore the study has been designed to answer the question: Is RV 001 superior to placebo in treating active thyroid eye disease and what is RV 001*s safety profile in the TED population? In addition, positive efficacy results would indicate that:
(i) IGF1R plays important roles in regulating the autoimmune response in TED. This could have implications for other autoimmune conditions, such as rheumatoid arthritis, Crohn*s disease and multiple sclerosis, raising the possibility that these diseases may likewise be successfully treated with IGF1R antagonists (Smith 2010). The result would also promote the discovery and development of orally active IGF1R antagonists as 2nd generation therapies for TED.
(ii) Blocking the underlying autoimmune pathophysiology of TED is a viable means of treating the disease. This would strengthen arguments that other targets believed to be important in TED autoimmunity, in particular thyroid stimulating hormone receptor (TSHR), may also be viable targets for treating TED (Bahn, 2010).

In addition, irrespective of the efficacy outcome, TED01RV will provide valuable information about the time course of TED by following disease progression in 42 placebo treated patients over 18 months, starting within 9 months of the first diagnosis of eye symptoms. Moreover, thyroid biomarker analysis may provide useful data about TED disease mechanism at both the molecular and cellular levels.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet each of the following inclusion criteria to be eligible take part in the study:
1. Aged 18-75 years (inclusive).
2. Clinical diagnosis of Graves' disease associated with active TED with a clinical activity score (CAS) * 4 (on the 7 point version of the scale) for the most severely affected eye.
3. Fewer than 9 months from onset of TED as determined by patient records.
4. No previous medical or surgical therapy for TED, excluding local supportive measures and oral steroids if the maximum cumulative dose is less than 1000 mg methylprednisolone or equivalent. There must be at least 6 weeks between last administration of steroids and study randomization.
5. Patients must be euthyroid or with mild hypo- or hyperthyroidism defined as free thyroxine (FT4) and free triiodothyronine (FT3) levels less than 50% above or below the normal limits. Every effort should be made to correct the mild hypo- or hyperthyroidism promptly.
6. Not requiring immediate surgical ophthalmological intervention.
7. ALT/AST * 3 x the upper limit of normal (ULN) for the reference laboratory; serum creatinine < 1.5 x ULN according to age.
8. Diabetic patients must have a well controlled disease, demonstrated by no change in the diabetes medication (oral or insulin) greater than 10% for the past 60 days
9. Women of child bearing potential, including women with an onset of menopause within the past 2 years (women who have not had at least 12 months of non-therapy-induced amenorrhea or who are not surgically sterile (absence of ovaries and/or uterus), will require a negative pregnancy test at screening and at all treatment visits up to follow up visit 2 (month 9) post randomization and must be willing and able to use two different methods of contraceptive, one of which must be an oral contraceptive. Male patients must be surgically sterile or must agree to use a barrier contraceptive method. Contraception must be continued for 3 months after the last dose of study drug.

Exclusion criteria

Patients meeting any of the following exclusion criteria will not be eligible to take part in the study.

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision within the last 6 months of two lines of Snellen chart, new visual field defect or color defect secondary to optic nerve involvement.
2. Corneal decompensation unresponsive to medical management.
3. Improvement in CAS of * 2 points between screening and baseline.
4. Treatment with oral or intravenous (IV) steroids within the previous 3 months except oral steroids for the treatment of TED with a cumulative dose less than 1000 mg methylprednisolone or equivalent providing there is a 6 week washout prior to study randomization. Administration of any other immunosuppressive agent for any indication in the previous 3 months. Topical steroids for dermatological conditions are not excluded.
5. Any treatment with any investigational agent for any condition in the past 60 days, or treatment with an investigational agent for any condition during the trial.
6. Any previous treatment with rituximab (Rituxan® or MabThera®).
7. Previous orbital irradiation.
8. Identified preexisting ophthalmic disease which, in the judgment of the investigator, would preclude study participation or complicate interpretation of study results.
9. Platelet count < 100 x 109/L at screening or baseline. Patients with platelet count < 35 x 109/L following dosing will be withdrawn.
10. Bleeding diathesis.
11. Hemoglobin concentration > 2 gr/dL below the lower limit of the local laboratory reference range.
12. Malignant condition in the past 12 months (with the exception of successfully treated basal cell carcinoma of the skin).
13. Pregnant or lactating women.
14. Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the investigator or as reported by the patient.
15. Poorly controlled diabetes.
16. Known hypersensitivity to any of the components of RV 001 or prior hypersensitivity reactions to monoclonal antibodies.
17. Any other condition which, in the opinion of the investigator, would preclude inclusion in the study.
18. Patients who have already been randomized and received treatment under this protocol. Under no circumstances are patients who enroll in this study permitted to be re-randomized to this study and enrolled for a second course of treatment.

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:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Not yet assigned
Generic name:	Teprotumumab

Ethics review

Approved WMO Date:	30-09-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2014-000113-31-NL
ClinicalTrials.gov	NCT01868997
CCMO	NL50281.018.14