A multicenter, double-blind, randomized, active controlled, parallel-group study to evaluate the efficacy, safety, tolerability, and pharmacodynamic profiles of TL011 infusions compared with MabThera® (rituximab) in subjects with severe, active rheumatoid arthritis treated with methotrexate (MTX)

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Primary objective: to demonstrate equivalence of the efficacy of TL011 in comparison with the reference product MabThera(rituximab) in subjects with severe, active RA treated with MTX.• Secondary objective: To assess the pharmacodynamics (PD),...

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

Summary

ID

NL-OMON37109

Source
ToetsingOnline

Brief title
ALTO

Condition

- Immune disorders NEC

Synonym
rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: TEVA Pharma
Source(s) of monetary or material Support: pharmaceutisch bedrijf

Intervention

Keyword: rheumatoid arthritis

Outcome measures

Primary outcome

Primary efficacy endpoint:

Proportion of subjects (%) who meet the ACR20 criteria defined as at least a

20% improvement from baseline values in swollen joint count,

tender joint count, and 3 of the following 5 (core set items) disease activity

measures at Week 24:

• Subject*s assessment of pain using a visual analog scale (VAS).

• Subject*s global assessment of disease activity (VAS).

• Physician*s global assessment of disease activity (VAS).

• Health Assessment Questionnaire (HAQ).

• Acute phase reactant value (CRP will be used for analysis. ESR can be used if

CRP data is missing).

Secondary outcome

Secondary efficacy endpoints:

• ACR20 response at Week 48.

• Proportion of subjects (%) who meet the ACR response criteria for ACR50

defined as at least 50% improvement from baseline values

in swollen joint count, tender joint count, and 3 of the 5 (core set items)

disease activity measures (see primary efficacy endpoint)

from baseline at Weeks 24 and 48.

• Proportion of subjects (%) who meet the ACR response criteria for ACR70

defined as at least 70% improvement from baseline values

in swollen joint count, tender joint count, and 3 of the 5 (core set items)

disease activity measures (see primary efficacy endpoint) at

Weeks 24 and 48.

• Disease activity will be measured at Weeks 24 and 48 using DAS28(a 28-joint

assessment for swelling and tenderness).

• Individual parameters of ACR improvement:

* The number of tender joints, the number of swollen joints.

* Subject*s global assessment of disease activity on a VAS.

* Physician*s global assessment of disease activity on a VAS.

* Subject*s assessment of pain on a VAS.

* Subject assessment of disability on the HAQ.

* Acute phase reactant (CRP or ESR if CRP result is missing)

Other secondary efficacy endpoints: Health related quality of life assessment

using the SF-36 questionnaire, Simplified Disease Activity

Index (SDAI), Clinical disease Activity Index (CDAI), the proportion of

subjects discontinuing the study due to lack of efficacy.

Pharmacodynamics parameters:

• Mean CD19+ B cells (absolute as well as % reduction from baseline).

• % of subjects with CD19+ B cell depletion at each time point.

Safety endpoints:

• Adverse events (AEs).

• Vital signs.

• Laboratory tests, including CRP and ESR.

• Immunogenicity: HACA.

• ECG.

Tolerability endpoints:

• Proportion of subjects (%) who prematurely discontinue the study.

• Proportion of subjects (%) who prematurely discontinue the study due to AEs

following 1 or 2 courses of the study drug.

Study description

Background summary

Rheumatoid arthritis is a relatively common chronic inflammatory disease characterized by joint swelling, pain, stiffness, damage and ultimately loss of joint function that is estimated to affect 0.8% of the population. Current therapies target the immune system early in the disease process before joint

damage occurs, and include such drugs as methotrexate,tumour necrosis factor inhibitor agents and rituximab, a diseasemodifying antirheumatic drug approved by the European Medicines agency and the Food and Drug Administration for use in combination with methotrexate for treatment of severely active rheumatoid arthritis in subjects who have had an inadequate response to tumour necrosis factor inhibitor agents. TL011 is developed to be a biosimilar product to rituximab. This is a randomized, doubleblind, multicenter, activecontrolled, parallelgroup study with 2 treatment groups

Study objective

Primary objective: to demonstrate equivalence of the efficacy of TL011 in comparison with the reference product MabThera
(rituximab) in subjects with severe, active RA treated with MTX.
• Secondary objective: To assess the pharmacodynamics (PD), immunogenicity, safety, and tolerability of TL011 in comparison
with MabThera (rituximab) in subjects with severe, active RA treated with MTX.

Study design

This is a randomized, double-blind, multicenter, active-controlled, parallel-group study to compare MabThera (rituximab) with the biosimilar product TL011.
After a screening period of up to 21 days, subjects will be randomly assigned with equal probability to 1 of the 2 treatment groups. During the 24-week core study period, data will be collected for safety, efficacy, and PD. Subjects will be followed up for an additional 24
weeks for the assessment of long-term efficacy and safety (to the end of the follow-up period).
Each subject will receive 2 infusions during the study treatment period (intravenous infusions of 1000 mg of either TL011 or MabThera
(rituximab), as randomized under double-blind conditions) the first infusion on Day 1 and the second on Day 15. If a repeat course of
treatment is required per Investigator*s medical judgment, the additional course of treatment (2 infusions) of open-label TL011
(1000 mg/infusion) will be given at Day 169 (Week 24; end of the core study period) and at Day 183 (Week 26). No further re-treatments will
be allowed during the study. As specified in the Summary of Product Characteristics (SmPC) for MabThera (rituximab), all subjects will
receive concomitant MTX at a stable dosage of 10 to 25 mg/week throughout the study (until Week 48).
The unblinding of the study database and analysis of efficacy, safety, tolerability and PD will be performed after all subjects have either completed the 24-week core study period or discontinued the study and will include all parameters from the follow up period that can be
calculated up to this time point. A further, final analysis of efficacy,

safety, tolerability, PD, and safety from the open-label, extended follow-up period will be done at study end (Week 48, end of the extended follow-up period).

Intervention

Each subject will receive 2 infusions during the study treatment period (intravenous infusions of 1000 mg of either TL011 or MabThera (rituximab), as randomized under double-blind conditions) the first infusion on Day 1 and the second on Day 15. If a repeat course of treatment is required per Investigator*s medical judgment, the additional course of treatment (2 infusions) of open-label TL011 (1000 mg/infusion) will be given at Day 169 (Week 24; end of the core study period) and at Day 183 (Week 26).

Study burden and risks

Rituximab is classified pharmaceutically as a biologic response modifier and has been approved globally for the treatment of subjects with various types of NHL and for subjects with RA who have had an inadequate respose or intolerance to other diseasemodifying antirheumatic drugs (DMARDs), including one or more tumor necrosis factor (TNF) inhibitor therapies.
This phase III study is a pivotal confirmatory study, TL011 is being developed as biosimilar to Rituximab, the same benefits of Rituximab are expected to be for TL011
For the same reason, all risks and AEs of TL011 are expected to be similar to MabThera, as of today no unexpected safety considerations were raised from other clinical trials
There is no placebo arm in this study

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Aged 18-80 years (inclusive) at screening.
2. Rheumatoid arthritis for at least 6 months, as defined by the Revised Criteria ACR 1987 (adult onset RA).
3. Severe, active, seropositive (plasma RF level of at least 20 IU/mL and/or ACPA/anti-CCP positive) disease as defined by the following, revealed in screening tests:
• Active disease defined as presence of at least 8 swollen and 8 tender joints (at the screening visit).
• A serum CRP level of >=15 mg/L (>=1.5 mg/dL) and/or an ESR (Westergren method) of >=28 mm per hour at screening.
4. Inadequate response or intolerance DMARDs other than MTX and/or TNFi therapies (1 or more).
5. Treatment with MTX (10 to 25 mg/week) for at least 12 weeks prior to screening, with at least 4 weeks before screening at a stable dosage that will remain stable throughout the study period
(up to Week 48).
6. Willing and able to provide written informed consent prior to performing study procedures.
7. Women or men of reproductive potential must use (or have his/her partner use) effective contraceptive methods starting from screening and until 12 months following the last infusion (acceptable methods of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner*s vasectomy or double-barrier method [condom or diaphragm with spermicide]).

Exclusion criteria

1. Documented rheumatic autoimmune disease or inflammatory joint disease other than RA (eg, psoriatic arthritis or ankylosing spondylitis).
2. Significant systemic involvement secondary to RA (eg, vasculitis, pulmonary fibrosis, or

Felty*s syndrome) or American Rheumatism Association (ARA) functional class IV disease.
3. Hypersensitivity to active ingredients, excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections) and murine proteins.
4. Active uncontrolled infection (viral, bacterial or fungal infection) requiring systemic therapy or clinically significant infection, at screening and/or at Day 1 (baseline), or a history of recurring or
chronic infections or with underlying conditions that may, according to the Investigator*s judgment, further predispose subjects to serious infection.
5. Known immunodeficiency syndrome, including total immunoglobulins (IgG, IgA and IgM) lower than the lower limit of normal (LLN).
6. Positive human immunodeficiency virus (HIV) serology (in case of positive result an additional HIV RNA test should be performed), positive hepatitis B surface antigen or positive hepatitis C antigen (in case of positive result an additional hepatitis C virus [HCV] RNA test should be performed).
7. History of cancer in the past 5 years prior to screening (except basal-cell carcinoma of the skin that has been excised).
8. Immunization with live viral vaccines less than 4 weeks prior to Day 1 (baseline) and/or planned live viral vaccination during the core study period and/or the anticipated B cell depletion period.
9. Use of oral/intravenous/intramuscular systemic corticosteroids
• Oral corticosteroids at a dose higher than 10 mg prednisone daily (or an equivalent dose of other oral steroids) within the 4 weeks prior to screening and between screening and Day 1 (baseline)
OR
• Oral corticosteroids at a dose equal to or lower than 10 mg prednisone daily (or an equivalent dose of other oral steroids) that were not kept at a stable dose within 4 weeks prior to screening and between screening and Day 1 (baseline).
• Use of intravenous/intramuscular/intra-articular or parenteral glucocorticoids <4 weeks prior to screening.
10. Use of any cytotoxic therapies and immunosuppressants, (except for allowed dosage of MTX) or other DMARDs within the 4 weeks prior to screening or between screening and Day 1 (baseline).
11. Prior use of MabThera (rituximab) and/or participation in a previous clinical trial with the investigational study drug TL011.
12. Use of TNFi and any other biological agent for the treatment of autoimmune diseases less than 8 weeks prior to Day 1 (baseline) or use of etanercept and anakinra less than 4 weeks prior to Day 1.
13. Participation in a previous clinical trial and/or use of an investigational drug within 90 days of screening.
14. Clinically significant or unstable medical or surgical condition that may preclude safe and complete study participation based on the Investigator*s judgment. Conditions may include cardiovascular disease (including severe heart failure of New York Heart Association [NYHA] class IV or severe, uncontrolled cardiac disease) pulmonary, hepatic, renal, or neurological disease as determined by medical history, physical examination, laboratory tests, chest X-ray, or ECG.
15. Likely to be non-compliant or uncooperative during the study in the judgment of the Investigator.

16. History of tuberculosis, latent tuberculosis tested as required by the local regulations, and/or positive chest X-ray for tuberculosis at screening or within the previous 6 months.
17. Pregnant, lactating, or intending to become pregnant during the study or within 12 months following the last infusion.
18. History of and/or current drug and/or alcohol abuse.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Mabthera
Generic name:	rituximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TL011
Generic name:	Rituximab

Ethics review

Approved WMO Date:	05-06-2012
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	07-06-2012
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

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	EUCTR2011-005021-48-NL
ClinicalTrials.gov	NCT01123070
CCMO	NL40529.048.12