Safety and Efficacy of BI 695500 in patients with moderately to severely active rheumatoid arthritis: an open-label extension trial

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Primary objective:To evaluate the long-term safety of BI 695500 in adult patients with moderate tosevere active rheumatoid arthritis (RA) who have successfully completed treatment inTrial 1301.1.Secondary objective:* To assess the long-term efficacy…

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

Summary

ID

NL-OMON40517

Source
ToetsingOnline

Brief title
BI1301.4 BI695500 extension

Condition

- Autoimmune disorders
- Joint disorders

Synonym
Reumatoid Arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: BI695500, extension study, RA

Outcome measures

Primary outcome

Primary efficacy endpoint:

The primary endpoint of Trial 1301.4 is safety; efficacy will be evaluated as secondary and other endpoints.

Primary safety endpoint:

The primary endpoint is defined as the number (proportion) of patients with drug related adverse events during the treatment phase

Secondary outcome

Secondary efficacy endpoints:

* The change from Baseline in Trial 1301.1 in DAS28 (erythrocyte sedimentation rate [ESR]) at Week 48 of Trial 1301.4;

* The proportion of patients meeting the American College of Rheumatology 20% (ACR20) response criteria (based on improvement since Baseline in Trial 1301.1) at Week 48 of Trial 1301.4;

* The proportion of patients who meet the ACR/European League Against Rheumatism (EULAR) definition of remission (based on improvement since Baseline in Trial 1301.1) at Week 48 of Trial 1301.4;

* The proportion of patients who meet the EULAR response (good response, moderate response, or no response) (based on DAS28 improvement since Baseline in Trial 1301.1) at Week 48 of Trial 1301.4.

Other efficacy endpoints:

* The change from Baseline in Trial 1301.1 in DAS28 (ESR) at Week 24 of Trial 1301.4;

* The proportion of patients meeting ACR20 response criteria (based on improvement since Baseline in Trial 1301.1) at Week 24 of Trial 1301.4;

* The proportion of patients who meet the ACR/EULAR definition of remission (based on improvement since Baseline in Trial 1301.1) at Week 24 of Trial 1301.4;

* The proportion of patients who meet the EULAR response (good response, moderate response, or no response) (based on DAS28 improvement since Baseline in Trial 1301.1) at Week 24 of Trial 1301.4;

* ACR50 and ACR70 responders (based on improvement since Baseline in Trial 1301.1) at Week 24 of Trial 1301.4;

* ACR50 and ACR70 responders (based on improvement since Baseline in Trial 1301.1) at Week 48 of Trial 1301.4;

* The change from Baseline in Trial 1301.1 in DAS28 (C-reactive protein [CRP]) at Week 24 of Trial 1301.4;

* The change from Baseline in Trial 1301.1 in DAS28 (CRP) at Week 48 of Trial 1301.4;

* Individual parameters of the ACR improvement criteria (based on improvement

since Baseline in Trial 1301.1): swollen joint count, tender joint count, patient*s
and physician*s global assessments of disease activity, patient*s assessment of pain, Health Assessment Questionnaire - Disability Index (HAQ-DI) and acute phase reactant (CRP) at Week 24 of Trial 1301.4;
* Individual parameters of the ACR improvement criteria (based on improvement since Baseline in Trial 1301.1): swollen joint count, tender joint count, patient*s
and physician*s global assessments of disease activity, patient*s assessment of pain, HAQ-DI and acute phase reactant (CRP) at Week 48 of Trial 1301.4;
* The change from Baseline in Trial 1301.1 in 36-item Short Form Health Survey (SF-36) at Week 24 of Trial 1301.4;
* The change from Baseline in Trial 1301.1 in SF-36 at Week 48 of Trial 1301.4;
* The change from Baseline in Trial 1301.4 in DAS28 (ESR) at Week 24 of Trial 1301.4;
* The change from Baseline in Trial 1301.4 in DAS28 (ESR) at Week 48 of Trial 1301.4;
* The proportion of patients meeting ACR20 response criteria (based on improvement since Baseline in Trial 1301.4) at Week 24 of Trial 1301.4;
* The proportion of patients meeting ACR20 response criteria (based on improvement since Baseline in Trial 1301.4) at Week 48 of Trial 1301.4;
* The change from Baseline in Trial 1301.4 in SF-36 at Week 24 of Trial 1301.4;
* The change from Baseline in Trial 1301.4 in SF-36 at Week 48 of Trial 1301.4.

Other endpoints/parameters of interest:

* Immunogenicity (proportion of patients with ADAs) at Weeks 24 and 48;

* Pharmacodynamic analysis of CD19+ B-cells, CD3+, CD4+, and CD8+ T-cells, total RF, RF immunoglobulin (Ig) isotypes, Igs (total Ig, IgG, IgA and IgM).

* A PPK analysis with sparse blood sampling throughout the treatment period and at follow-up will be carried out to assess the PK of BI 695500 in the underlying population.

Other safety endpoints include:

* Infusion reaction adverse events

* Rate of infections/serious infections (seriousness of infection defined as requirement of IV antibiotics for treatment and/or meeting seriousness criteria to be qualified as an SAE)

Additional safety criteria include physical examination, vital signs (blood pressure, pulse rate, respiratory rate, body temperature), 12-lead electrocardiogram, laboratory tests, concomitant medication, and tolerability.

Relevant findings in these safety assessments will be reported as adverse events.

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by synovial inflammation in the joints and consequently, progressive joint destruction. Depending on the severity of the disease, systemic manifestations may occur including lung disease, rheumatoid nodules and cardiovascular system effects. If left untreated, RA may lead to severe functional disabilities, and therefore a considerable reduction in quality of life for the patient. The prevalence of RA varies with factors such as gender, race and smoking status and is approximately 0.5-1%.

B lymphocytes (B-cells) are thought to play a crucial role in the pathogenesis of RA. B-cells are highly efficient antigen-presenting cells and therefore contribute to the auto-immune response through downstream activation of T-cells via co-stimulatory molecules. B-cells respond to, and produce, chemokines and cytokines that facilitate lymphocyte infiltration into joints, formation of ectopic lymphoid structures (e.g., the formation of T-cell * B-cell follicles with germinal center reactions in the synovium of affected joints), angiogenesis, and synovial hyperplasia that characterize the pathology observed in the rheumatoid joint. They are also the primary source of rheumatoid factors (RFs) and anti-cyclic citrullinated peptide (anti-CCP) antibodies which contribute to the formation of immune complexes and complement activation in inflamed joints. Thus, B-cell targeted therapy could play an important role in RA through a reduction in the B-cell count as well as a reduction in B-cell-mediated downstream effects on other cell types involved in the inflammatory response.

BI 695500 is a monoclonal antibody being developed as a proposed biosimilar to rituximab (MabThera® in the European Union [EU]; Rituxan® in the United States [US]). BI 695500 is a genetically engineered chimeric mouse/human monoclonal antibody (mAb) representing a glycosylated immunoglobulin (Ig) with human IgG1 constant

regions and murine light-chain and heavy-chain variable region sequences. The active
substance of BI 695500 is rituximab and, like MabThera® and Rituxan®, BI 695500 has been
shown, in vitro, to lead to the elimination of B-cells by means of several different
mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complementdependent
cytotoxicity (CDC), and apoptosis. Rituximab causes rapid peripheral B-cell depletion in vivo.

BI 695500, as a proposed biosimilar product, may be seen to provide comparable PK,
efficacy, safety and tolerability in patients with RA and may present an opportunity to
improve healthcare.

In conclusion, these data support the continued evaluation of the PK, efficacy and safety of
BI 695500 in patients with RA over an additional 48 weeks.

Study objective

Primary objective:
To evaluate the long-term safety of BI 695500 in adult patients with moderate to severe active rheumatoid arthritis (RA) who have successfully completed treatment in
Trial 1301.1.
Secondary objective:
* To assess the long-term efficacy of BI 695500 in patients with moderately to severely active RA. These analyses will be displayed by the groups the patients were randomized in Trial 1301.1 as well as overall.
Other objectives:
* To assess population pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of BI 695500 in patients with moderately to severely active RA.
* To evaluate the safety, efficacy and tolerability of BI 695500 in patients with
moderately to severely active RA, who were initially randomized to receive Rituxan®/MabThera® in the clinical Trial 1301.1 compared with patients who continued to receive BI 695500. For this analysis baseline as measured in Trial 1301.4 will be considered.

Study design

To assess the continued safety and efficacy of repeated courses with BI 695500, patients from the initial randomized controlled Trial 1301.1 who are eligible

for
further treatment courses, will receive two 1000 mg drug infusions of BI 695500: the
first on Day 1 and the second on Day 15. This includes patients who were initially
randomized to receive Rituxan®/MabThera® in Trial 1301.1, who will be transitioned
to treatment with BI 695500 in Trial 1301.4.
Patients are eligible to receive another course of treatment at 24 weeks if the investigator considers the patient as having benefited from previous treatment course(s).
The second course of treatment will consist of one infusion of BI 695500 at Week 24
and one infusion of BI 695500 at Week 26.

Intervention

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further treatment courses, will receive two 1000 mg drug infusions of BI 695500: the
first on Day 1 and the second on Day 15. This includes patients who were initially
randomized to receive Rituxan®/MabThera® in Trial 1301.1, who will be transitioned
to treatment with BI 695500 in Trial 1301.4.

Patients are eligible to receive another course of treatment at 24 weeks if the investigator considers the patient as having benefited from previous treatment course(s).

The second course of treatment will consist of one infusion of BI 695500 at Week 24
and one infusion of BI 695500 at Week 26.

Study burden and risks

Rituximab causes rapid peripheral B cell depletion in vivo. Therefore, CD19+ B cell counts will be monitored at frequent
intervals throughout the trial for each of the trial medications.
Common adverse reactions reported in greater than 10% of patients include infusion related reactions, upper respiratory tract
infections and urinary infections. Overall, infusion-related reactions in clinical trials with MabThera and Rituxan occurred in up
to one third of patients approximately, with the first infusion and decreased with subsequent infusions. Serious infusion-related

reactions were uncommon (<1% of patients) and were predominantly seen during the initial course.
Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators.
The use of MabThera and Rituxan has been shown to be associated with an increased risk of progressve multifocal leukoencephalopathy (PML). On the basis of limited experience with MabThera and Rituxan in RA patients the present data do not suggest an increased risk of malignancy, however, the possible risk for the development of solid tumors cannot be excluded.
BI695500, as a proposed biosimilar product, may be seen to provide comparable PK, efficiacy, safety and tolerability in patients with RA and may present an opportunity to improve healthcare.

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

1. Must give written informed consent and be willing to follow this CTP.;2. Male or female patients, with moderately to severely active RA who have previously participated in the double-blind randomized clinical Trial 1301.1.;3. Current treatment for RA on an outpatient basis: ;a) Patients must continue to receive and tolerate oral or parenteral methotrexate (MTX) therapy at a dose of 15-25 mg per week (dose may be as low as 10 mg per week if the patient is unable to tolerate a higher dose). The dose must have been stable for at least 4 weeks prior to Day 1. ;b) Patients must be willing to receive oral folic acid (at least 5 mg/week or as per local practice) or folinic acid (at least 1 mg per week or as per local practice) or equivalent during the entire trial (mandatory co-medication for MTX treatment).;c) If receiving current treatment with oral corticosteroids (other than intra-articular or parenteral), the dose must not exceed 10 mg/day prednisolone or equivalent. During the 4 weeks prior to Baseline (Day 1) the dose must remain stable.;d) Intra-articular and parenteral corticosteroids are not permitted throughout the trial, with the exception of IV administration of 100 mg methylprednisolone 30 to 60 minutes prior to each infusion as this is part of the trial procedures.;e) Any concomitant non-steroidal anti-inflammatory drugs (NSAIDs) must be stable throughout the trial.;f) Patients may be taking oral hydroxychloroquine provided that the dose is not greater than 400 mg/day, or chloroquine provided that the dose is not greater than 250 mg/day. These doses must have been stable for a minimum of 12 weeks prior to Day 1. The hydroxychloroquine or chloroquine treatment will need to be continued at a stable dose with the same formulation until the end of the trial.;4. For participants of reproductive potential (males and females), use of a medically acceptable method of contraception during the trial, i.e., a combination of 2 forms of effective contraception (defined as hormonal contraception, intrauterine device, condom with spermicide, etc.). Females of childbearing potential must also agree to use an acceptable method of contraception (see above) for 12 months following completion or discontinuation from the trial medication.

Exclusion criteria

1. Patients receiving current treatment with corticosteroids must not be receiving a dose exceeding 10 mg/day prednisone or equivalent.;2. Serious underlying medical conditions, which, per the investigator*s discretion, could impair the ability of the patient to participate in the trial (including but not limited to ongoing severe infection, severe immunosuppression, severe heart failure, uncontrolled hypertension, uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease).;3. Pregnancy or breast feeding. For women of childbearing potential, a positive serum pregnancy test at the Screening Visit.;4. Patients who have significant cardiac disease, including but not limited to congestive heart failure of Class III or IV of the New York Heart Association (NYHA) classification; uncontrolled angina or arrhythmia; any uncontrolled or severe cardiovascular or cerebrovascular disease; or uncontrolled hypertension. ;5. Treatment with IV or intramuscular corticosteroids. The only exception will be the administration of 100 mg IV methylprednisolone 30 to 60 minutes before each infusion

as part of the trial procedures.;6. Any condition or treatment (including biologic therapies) that, in the opinion of the investigator, may place the patient at unacceptable risk during the trial.;7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times upper limit of normal (ULN).;8. Hemoglobin <8.0 g/dL.;9. Levels of IgG <5.0 g/L.;10. Absolute neutrophil count <1500/*L.;11. Platelet count <75000/*L.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-08-2014
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BI695500 10mg/ml
Generic name:	BI695500

Ethics review

Approved WMO

Date:	13-02-2014
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

Approved WMO

Date:	24-06-2014
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	06-11-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	14-11-2014
Application type:	Amendment
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	EUCTR2013-002622-23-NL
ClinicalTrials.gov	NCT01955733
CCMO	NL47012.048.14