Efficacy, pharmacokinetics, and safety of BI 695500 versus rituximab in patients with moderately to severely active rheumatoid arthritis: a randomized, double-blind, parallel arm, multiple dose, active comparator trial.

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Primary objectives:The primary objectives of this trial are:• To show PK similarity of BI 695500 to MabThera® and Rituxan® and of Rituxan® to MabThera® (three-way PK similarity).• To establish statistical equivalence of efficacy of BI 695500 and...

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

Summary

ID

NL-OMON41649

Source
ToetsingOnline

Brief title
Bio-sequetia RA study

Condition

- Autoimmune disorders
- Central nervous system infections and inflammations

Synonym
rheuma, rheumatoid arthritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BI 695500, phase I/III, Rheumatoid arthritis (RA)

Outcome measures

Primary outcome

PK (Part I only): AUC0-tz, AUC0-*. pred (determined after the second drug

infusion)

Efficacy co-primary endpoints: Change in DAS28 (ESR) from Baseline to Week 24.

Secondary outcome

• PK (part I only): AUC 0-336 (dertermined after the first drug infusion) and

observed Cmax (determined after the second drug infusion).

• The proportion of patients meeting American College of Rheumatology 20

response criteria at Week 48;

• American College of Rheumatology 50% and American College of Rheumatology 70%

responders at Weeks 24 and 48;

• The proportion of patients who meet the ACR/EULAR definition of

remission at Weeks 24 and 48.

• The change from Baseline in DAS28 (CRP) at Week 24 and Week 48;

• The change from Baseline in DAS28 (ESR) at Week 48

• European League Against Rheumatism response at Weeks 24 and 48;

• Individual parameters of the ACR improvement criteria: 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 Weeks 24 and 48;

• The change from Baseline in 36-item Short Form Health Survey at Weeks 24 and 48;

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

* ACR20 responsor rate at Week 24.

Other PK endpoints:

• Part I only: time from dosing to maximum measured concentration (tmax), area under the plasma concentration versus time curve from time zero to infinity extrapolated from observed Clast (AUC0-*_obs), the percentage of the AUC0-* that is obtained by extrapolation (%AUCtz-*_pred and obs), terminal rate constant in plasma (*z), terminal elimination half-life of the analyte in plasma (t1/2), all determined after the second drug infusion, as well as total clearance of the analyte in plasma following intravascular administration (CL) and apparent volume of distribution (Vz) during the terminal phase *z following an intravascular dose, all determined after the second drug infusion determined based on the complete exposure.

If feasible, further PK endpoints will be derived, such as AUC0-t. Timepoints at which ADA development has a clear impact on PK will be excluded.

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.

Study objective

Primary objectives:
The primary objectives of this trial are:
• To show PK similarity of BI 695500 to MabThera® and Rituxan® and of Rituxan® to MabThera® (three-way PK similarity).
• To establish statistical equivalence of efficacy of BI 695500 and Rituxan®/ MabThera®, in patients with moderately to severely active RA, based on the change in Disease Activity Score 28 (DAS-28) score measured at 24 weeks compared to Baseline and the American College of Rheumatology 20% (ACR20) response at Week 24.

Secondary objectives:
•The secondary objectives of this trial are to compare the efficacy, safety and tolerability of BI 695500 and Rituxan®/MabThera® in patients with moderately to severely active RA.

Study design

150 patients with moderately to severely active RA who have had an inadequate response or intolerance to conventional disease modifying ant-rheumatic drug (DMARD) therapy including at least one tumor necrosis factor (TNF) inhibitor, will be randomized into part I of the trial . Patients will be allocated to treatment 1:1:1 ratio to receive BI 695500 (n=50), Rituxan (n=50) or MabThera (n=50). Each patient will receive two 1000 mg intravenous (IV) drug infusions: the first on day 1 and the second on Day 15. Patients randomized to part 1 will undergo up to 19 visits over the duration of the trial (48 weeks).

If the PK data support equivalent bioavailability among the treatment groups, and no safety concerns are identified by IDMC then a further 150 patients will be randomized into Part II.

In Part II, patients (with moderately to severely active RA who had an inadequate response or intolerance to conventional DMARD therapy including at least one TNF inhibitor) will be allocated to treatment in a 1:1 ratio to receive BI 695500 (n=75) or MabThera (n=75). Each patient will receive two 1000 mg drug infusions: the first on Day 1 and the second on day 15. Patients randomized to Part II will undergo up to 15 visits over the duration of the trial (48 weeks).

Intervention

Part I (Phase 1 study) contains three groups:
1) 50 patients receiving BI 695500. each patient will receive two 1000 mg intravenous (IV) drug infusions: the first on day 1 and the second on Day 15. Patients randomized to part 1, BI 695500 group will undergo up to 19 visits over the duration of the trial (48 weeks).

2) 50 patients receiving Rituxan. each patient will receive two 1000 mg intravenous (IV) drug infusions: the first on day 1 and the second on Day 15. patients randomized to part 1, Rituxan group will undergo up to 19 visits over the duration of the trial (48 weeks).

3)50 patients receiving MabThera. each patient will receive two 1000 mg intravenous (IV) drug infusions: the first on day 1 and the second on Day 15. patients randomized to part 1, mabThera group will undergo up to 19 visits over the duration of the trial (48 weeks).

Part II (phase 3 study) contains 2 groups:
1) 75 patients receiving BI 695500. each patient will receive two 1000 mg intravenous (IV) drug infusions: the first on day 1 and the second on Day 15. patients randomized to part II, BI 695500 group will undergo up to 15 visits over the duration of the trial (48 weeks).

2) 75 patients receiving MabThera: each patient will receive two 1000 mg

intravenous (IV) drug infusions: the first on day 1 and the second on Day 15. patients randomized to part II, mabThera group will undergo up to 15 visits over the duration of the trial (48 weeks).

Part I and part II patients are eligible to receive a second course of treatment at 24 weeks if they have shown a minimum improvement of DAS28 of 1.2 or higher from baseline at 16 weeks after initial treatment This treatment will consist of one infusion of trial medication at week 24 and one infusion of trial medication 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

Adult patients, between 18 and 80 years of age, with moderately to severely active RA for at least 6 months as defined by at least six swollen joints (66 joint count) and at least eight tender joints (68 joint count) at Screening and Baseline (Day 1), and either an erythrocyte sedimentation rate (ESR) of > 28 mm/hour OR a C-reactive protein (CRP) level > 1.0 mg/dL (normal: < 0.4 mg/dL) at Screening. Patients must have had an inadequate response or intolerance to conventional disease modifying anti-rheumatic drug (DMARD) therapy including at least one tumor necrosis factor (TNF) inhibitor.
Must be currently receiving and tolerating oral or parenteral 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) for at least 12 weeks immediately prior to Day 1. The dose should be stable for at least 4 weeks prior to Day 1 (for all inclusion criteria see also page 35-36 of the protocol).

Exclusion criteria

Patients with active infection, severe immunosuppression or severe heart failure will be excluded (for all exclusion criteria see page 36-38 of the protocol).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-08-2013
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BI 695500 10 mg/mL
Generic name:	BI 695500
Product type:	Medicine
Brand name:	MabThera
Generic name:	rituximab 10 mg/mL
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rituxan
Generic name:	rituximab 10 mg/mL

Ethics review

Approved WMO

Date:	13-12-2011

Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	10-09-2012
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	04-03-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	18-03-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	01-05-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	02-05-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	28-08-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	04-09-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	18-09-2014

Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	23-09-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	18-03-2015
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	EUCTR2011-002894-48-NL
ClinicalTrials.gov	NCT01682512
CCMO	NL38383.048.11