A Phase 3, Randomized, Double-Blind Study Comparing ABT-494 to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)

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Period 1: The first objective, of period 1, is to compare the efficacy of ABT-494 15 mg QD versus placebo and versus adalimumab for the treatment of signs and symptoms of rheumatoid arthritis in subjects with moderately to severely active RA who are...

Ethical review	Not approved
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON44070

Source
ToetsingOnline

Brief title
M14-465 (MTX-IR Structure)

Condition

- Autoimmune disorders
- Joint disorders

Synonym
'Rheumatoid Arthritis' and 'Rheumatism'

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: AbbVie

Intervention

Keyword: Adalimumab, JAK-inhibitors, Placebo, Rheumatoid Arthritis

Outcome measures

Primary outcome

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20 response at Week 12 (US/FDA regulatory purposes) or the proportion of subjects achieving CR based on DAS28 (CRP) at Week 12 (EU/EMA regulatory purposes).

Secondary outcome

Ranked secondary endpoints of this study are:

1. Proportion of subjects achieving LDA at Week 12;

2. Change from baseline in DAS28 (CRP) at Week 12;

3. Change from baseline in HAQ-DI at Week 12;

4. ACR20 response rate at Week 12;

5. ACR50 response rate at Week 12;

6. ACR70 response rate at Week 12;

7. Proportion of subjects achieving LDA based on based on DAS28 (CRP) * 3.2 at Week 12

8. Change from baseline in SF-36 PCS at Week 12;

9. Proportion of subjects achieving CR based on DAS28 (CRP) at Week 12;

10. Change from baseline in FACIT-F at Week 12;

11. Proportion of subjects with no radiographic progression at Week 26;

12. Change from baseline in RA-WIS at Week 12;

13. Change from baseline in morning stiffness (severity) at Week 12.

Additional endpoints at all visits are:

* Change from baseline in individual components of ACR response;

* ACR20/50/70 response rates;

* Change from baseline in DAS28(CRP) and DAS28 (erythrocyte sedimentation rate [ESR]);

* Proportion of subjects achieving LDA or CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and CDAI criteria;

* Change from baseline in morning stiffness (severity and duration).

Additional endpoints (at Weeks 12, 26, and 48) are:

* Change from baseline in EQ-5D-5L.

Additional endpoints (at Weeks 26 and 48) are:

* Change from baseline in SF-36;

* Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS * 0)

* Change from baseline in joint space narrowing score and joint erosion score.

Asessments to evaluate efficacy of treatment in Period 2 will be analyzed for

above-mentioned measures at

Weeks 60, 72, 84, 96 and every 12 weeks thereafter until completion of the

study.

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease characterized by inflammation of the articular synovial membrane. The hallmark feature of patients affected by RA is an inflammatory process manifested by persistent symmetric polyarthritis of synovial joints. Early therapy with disease-modifying antirheumatic drugs (DMARDs) is the standard of care, although a significant proportion of patients either do not achieve disease remission or become refractory to available therapies as the disease progresses. Novel therapies are therefore required to complement the available interventions to address the unmet need in the treatment of patients with RA. Evidence suggests that inhibition of Janus kinase (JAK)-mediated pathways is a promising approach for the treatment of patients with this chronic disease. AbbVie is developing a small molecule inhibitor of JAK, ABT-494, that may address the current medical needs.

Study objective

Period 1:
The first objective, of period 1, is to compare the efficacy of ABT-494 15 mg QD versus placebo and versus adalimumab for the treatment of signs and symptoms of rheumatoid arthritis in subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX.

The second objective is to compare the efficacy of ABT-494 15 mg QD versus placebo for the prevention of structural progression in RA subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX.

The third objective is to compare the safety and tolerability of ABT-494 15 mg QD versus placebo, and versus ADA in subjects with moderately to severely active RA subjects who are on a stable background of MTX and who have an inadequate response to MTX.

Period 2:
The objective of this study, of period 1, is to evaluate the long-term safety, tolerability, and efficacy of ABT-494 15 mg QD in subjects with RA who have completed Period 1.

Study design

This is a Phase 3 multicenter study that includes two periods. Period 1 is a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period. Period 2 is a long-term for subjects who have completed Period 1.

Subjects will be randomized in a 2:2:1 ratio to one of 3 treatment groups:
- Group 1: ABT-494 15 mg QD
- Group 2: Placebo
- Group 3: Adalimumab

The study will be conducted in approximately 370 research centers and approximately 1500 subjects will be enrolled.

Intervention

Subjects will receive both oral study drug QD (either ABT-494 15 mg or matching placebo) and subcutaneous study drug eow (either ADA 40 mg or matching placebo).

Subjects must have been on oral or parenteral MTX therapy for * 3 months, on a stable MTX dose for * 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or * 10 mg/week in subjects who are intolerant of MTX at doses * 15 mg/week), and must remain on a stable dose throughout the study.

Subjects in the placebo group who do not achieve a * 20% improvement in TJC and SJC at Weeks 14, 18, or 22 will be switched to blinded ABT-494 treatment. At Week 26, all remaining subjects in the placebo group will be switched to the blinded ABT-494 treatment regardless of clinical response.

Subjects in the ADA group who do not achieve a * 20% improvement in TJC and SJC at Weeks 14, 18, 22, or Week 26 will be switched to blinded ABT-494 treatment.

Subjects in the ABT-494 treatment group who do not achieve a * 20% improvement in TJC and SJC at Weeks 14, 18, 22, or Week 26 will be switched to blinded ADA treatment.

Subjects who complete the Week 48 visit (end of Period 1) will enter the long-term extension portion of the study (period 2). Subjects who are assigned to the ABT-494 15 mg QD treatment group at the end of period 1 will continue to

receive ABT-494 15 mg QD in a blinded manner. Subjects who are assigned to adalimumab 40 mg eow at the end of period 1 will continue to receive adalimumab 40 mg eow in a blinded manner.

Study burden and risks

Subjects participating in this study are required to come to all scheduled visits and complete the procedures, as described in section E.4.

Risks of participating in this study are:
- higher dose and/or frequency of drug administration
- extra time
- (extra) procedures)
- come to all scheduled visits
- adverse events (described in section E.9)
- discomfort of tests that will be conducted during study

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. Adult male or female, at least 18 years old.;2. Diagnosis of RA for * 3 months.;3. Subjects must have been on oral or parenteral MTX therapy * 3 months and on a stable prescription of 15 to 25 mg/week (or * 10 mg/week in subjects intolerant of MTX at doses * 15 mg/week) for
* 4 weeks prior to the first dose of study drug. In addition, all subjects should take a dietary supplement of folic acid or folinic acid throughout the study participation.;4. Subject meets both of the following disease activity criteria:
a. * 6 swollen joints (based on 66 joint counts) and * 6 tender joints (based on 68 joint counts) at
Screening and Baseline Visits; and
b. hsCRP * 5 mg/L (central lab, ULN 2.87 mg/L) at Screening Visit.;5. Subject has at least one of the following at Screening:
a. * 3 bone erosions on x-ray; or
b. * 1 bone erosion and a positive rheumatoid factor; or
c. * 1 bone erosion and a positive anti-cyclic citrullinated peptide autoantibody.;6. Subjects with prior exposure to only one bDMARD (except ADA) may be enrolled (up to 20% of total study population) if they have documented evidence of intolerance to the bDMARD or limited
exposure (< 3 months).;7. Except for MTX, subject must have discontinued all csDMARDs. The washout period for
csDMARDs prior to the first dose of study is specified below or should be at least five times the
mean terminal elimination half-life of a drug:
*** 4 weeks prior to first dose of study drug for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;
*** 8 weeks prior to first dose of study drug for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal or as per local label).

Exclusion criteria

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).;2. Subjects who have been exposed to adalimumab or who are considered inadequate responders to bDMARD therapy as determined by the Investigator.;3. History of inflammatory joint disease other than RA. History of secondary Sjogren's Syndrome is permitted.

Study design

Design

Study phase:	3
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:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ABT-494
Generic name:	ABT-494
Product type:	Medicine
Brand name:	Adalimumab
Generic name:	Adalimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	10-11-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	09-02-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-07-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Not approved Date:	11-07-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2015-003333-95-NL
ClinicalTrials.gov	NCT02629159
CCMO	NL54444.091.15