A Phase 3, Randomized, Double-Blind Study Comparing ABT-494 Once Daily Monotherapy to Methotrexate (MTX) Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis

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Period 1: The first objective, of period 1, is to compare the safety and efficacy of ABT-494 15 mg QD monotherapy, and 30 mg QD monotherapy versus weekly methotrexate (MTX) monotherapy for the treatment of signs and symptoms of rheumatoid arthritis...

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

Summary

ID

NL-OMON43652

Source
ToetsingOnline

Brief title
M13-545 (MTX-naïve)

Condition

- Autoimmune disorders
- Joint disorders

Synonym
'Rheumatoid Arthitis' and 'Rheumatism'

Research involving
Human

Sponsors and support

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

Intervention

Keyword: JAK-inhibitors, Monotherapy, MTX, Rheumatoid Arthritis

Outcome measures

Primary outcome

The primary endpoint in Period 1 is the proportion of subjects achieving ACR50 response (US/FDA regulatory purposes) or the proportion of subjects achieving Clinical Remission (CR) (EU/EMA regulatory purposes) at Week 24. For Japan/PMDA regulatory purposes, the primary endpoints are the proportion of subjects achieving ACR20 response and change from baseline in modified Total Sharp Score (mTSS) at Week 24.

Secondary outcome

Ranked secondary endpoints are:

1. Change from baseline in DAS28 (CRP);

2. Change from baseline in HAQ-DI;

3. ACR20 response rate;

4. ACR50 response rate;

5. Change from baseline in modified Total Sharp Score (mTSS);

6. ACR70 response rate;

7. Proportion of subjects achieving LDA based on DAS28 (CRP) * 3.2;

8. Change from baseline in SF-36 PCS;

9. Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS * 0) at Weeks 24 and 48.

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 by DAS28(CRP), DAS28(ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI);

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

Additional endpoints (at Weeks 12, 24, and 48) are:

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

* Change from baseline in FACIT-F;

* Change from baseline in WPAI;

* Change from baseline in SF-36.

Additional endpoints (at Weeks 24 and 48) are:

* Change from baseline in mTSS;

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

* Change from baseline in radiographic joint space narrowing and erosion scores.

Assessments 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 safety and efficacy of ABT-494 15 mg QD monotherapy, and 30 mg QD monotherapy versus weekly methotrexate (MTX) monotherapy for the treatment of signs and symptoms of rheumatoid arthritis (RA) in MTX-naïve subjects with moderately to severely active RA. The second objective is to compare the efficacy of ABT-494 15 mg QD monotherapy and ABT-494 30 mg QD monotherapy versus weekly MTX monotherapy for prevention of structural progression.

Period 2:
The objective of this study, of period 1, is to evaluate the long-term safety, tolerability, and efficacy of ABT-494 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 and is blinded until the last subject completes the last visit of 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: ABT-494 30 mg QD
- Group 3: MTX once a week

The study will be conducted in approximately 300 research centers and approximately 975 subjects will be enrolled.

Intervention

Subjects who are assigned to ABT-494 15 mg will start oral at 15 mg/day at Baseline. Subjects who are assigned to ABT-494 30 mg will start oral at 30 mg/day at Baseline. Subjects who are assigned to the MTX treatment group will start oral MTX treatment at 10 mg/week.

To maintain the blind, subjects will be provided with matching placebo. In addition, all subjects should take a dietary supplement of oral folic acid (or equivalent) throughout study participation.

1) Subjects who are originally randomized to MTX:
- those who achieve clinical remission by CDAI (clinical disease activity index < 2.8) at week 26 will continue blinded treatment with MTX.
- those who do not achieve clinical remission by CDAI but achieve * 20% improvement in both TJC and SJC compared to baseline will continue on blinded TMX and the investigator should initiate or increase background RA medication.
- those who do not achieve clinical remission by CDAI and do not achieve * 20% improvement in both TJC and SJC compared to baseline will be re-randomized in a 1:1 ratio to receive blinded ABT-494.

2: Subjects who were originally randomized to ABT-494:
- those who achieve clinical remission by CDAI (clinical disease activity index < 2.8) at week 26 will continue blinded treatment with ABT-494.
- those who do not achieve clinical remission by CDAI but achieve * 20% improvement in both TJC and SJC compared to baseline continue on blinded ABT-494 and the investigator should initiate or increase background RA medications.
- those who do not achieve clinical remission by CDAI and do not achieve * 20% improvement in both TJC and SJC compared to baseline will add MTX to ABT-494 in a blinded matter.

Subjects who complete the Week 48 visit (end of period 1) will enter the

long-term extension of the study (period 2). Subjects will continue the same treatment per assignment at the end of period 1 in a blinded fashion. When the last subject completes the last visit of period 1 (week 48), study drug assignment may be unblinded and subjects would then be dispensed study drug in an open-label fashion until completion of period 2.

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. Naïve to MTX or, if already on MTX, have received no more than 3 weekly MTX doses with requirement to complete a 4-week MTX washout before the first dose of study drug.;4. Subjects with prior exposure to csDMARDs other than MTX may be enrolled if completed the
washout period as 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.;5. 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.

Exclusion criteria

1. Intolerant to MTX.;2. Prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).;3. Prior exposure to any bDMARD(s).;4. 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:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ABT-494
Generic name:	ABT-494
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Methotrexate
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:	21-03-2016
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:	13-07-2016
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	EUCTR2015-003334-27-NL
ClinicalTrials.gov	NCT02706873
CCMO	NL54442.091.15