A Phase 3, Randomized, Double-Blind Study Comparing ABT-494 to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti- Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs

Published: 10-11-2015
Last updated: 19-04-2024

Period 1:The first objective, of period 1, is to compare the efficacy of ABT-494 15 mg QD and 30 mg QD versus placebo for the treatment of signs and symptoms of subjects with active RA who are on a stable dose of conventional synthetic disease-…

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

Summary

ID

NL-OMON43941

Source
ToetsingOnline

Brief title
M13-549 (csDMARD-IR)

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: JAK-inhibitor, Placebo, Rheumatoid Arthritis

Outcome measures

Primary outcome

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20

response (US/FDA regulatory purposes) or the proportion of subjects achieving

LDA (EU/EMA regulatory purposes) at Week 12.

Secondary outcome

Ranked secondary endpoints (at Week 12) are:

1. Change from baseline in DAS28 (CRP);

2. Change from baseline in HAQ-DI;

3. ACR50 response;

4. ACR70 response;

5. Change from baseline in Short Form-36 (SF-36) Physical Component Score (PCS);

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

7. Proportion of subjects achieving clinical remission (CR) based on DAS28

(CRP);

8. Change from baseline in FACIT-F (Functional Assessment of Chronic Illness

Therapy-Fatigue);

9. Change from baseline in RA-WIS (Work Instability Scale for Rheumatoid Arthritis);

10. Change from baseline in morning stiffness (severity).

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]);

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

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

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

* Change from baseline in SF-36.

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for above-mentioned measures at
Weeks 16, 20, 24, 36, 48 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 and 30 mg QD versus placebo for the treatment of signs and symptoms of subjects with active RA who are on a stable dose of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and have an inadequate response to csDMARDs.

The second objective, of period 1, is to compare the safety and tolerability of ABT-494 15 mg QD and 30 mg QD versus placebo in subjects with active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs.

Periode 2:
The objective of this study in periode 2, is to evaluate the long-term safety, tolerability, and efficacy of ABT-494 30 mg QD and 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 to periods. Period 1 is a randomized, double-blind, placebo-controlled treatment period of 12 weeks. Period 2 is a blinded long-term extension period for subjects who completed period 1.

Subjects will be randomized in a 2:2:1:1 ratio to one of 4 treatment groups:
- Group 1: ABT-494 30 mg QD (period 1) --> ABT-494 30 mg QD (period 2)
- Group 2: ABT-494 15 mg QD (period 1) --> ABT-494 15 mg QD (period 2)
- Group 3: Placebo (period 1) --> ABT-494 30 mg QD (period 2)
- Group 4: Placebo (period 1) --> ABT-494 15 mg QD (period 2)

The study will be conducted in approximately 230 research centers and approximately 600 subjects will be enrolled.

Intervention

Subjects who are randomized in the ABT-494 treatment groups will start their dose ABT-494 30 mg QD or ABT-494 15 mg QD orally at Baseline and must take their oral dose of medication once daily for 12 weeks (period 1). Subjects who are randomized in the Placebo treatment groups will receive matching placebo for ABT-494 to remain the blind and must take their oral dose of medication oral once daily for 12 weeks (period 1).

Subjects who complete their visit in week 12 (end of period 1) will enter the blinded long-term extension portion of the study (period 2). Subjects who are assigned to ABT-494 treatment groups in period 1 will continue to receive ABT-494 30 mg QD or ABT-494 15 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to Placebo in period 1 will be switched to receive ABT-494 30 mg QD or ABT-15 mg QD in a blinded fashion per pre-specified randomization assignments.

Subjects must have been on a stable dose of csDMARD(s) for * 4 weeks prior to the first dose of study drug and must remain on a stable dose until week 24. Starting at Week 24, initiation of or change in corticosteroids, NSAIDs, acetaminophen, or adding or increasing doses of csDMARDs is allowed.

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 have been receiving csDMARD therapy * 3 months and on a stable dose for * 4 weeks prior to the first dose of study drug:
**Subjects must have failed at least one of the following: MTX, sulfasalazine, or leflunomide.
**Subjects with inadequate response to hydroxychloroquine and/or chloroquine can only be included if they have also failed MTX, sulfasalazine, or leflunomide.
**The following csDMARDs are allowed (stable dose for * 4 weeks prior to the first dose of study
drug): oral or parenteral MTX (15 to 25 mg/week; or * 10 mg/week in subjects who are intolerant of MTX at doses * 15 mg/week), sulfasalazine (* 3000 mg/day), hydroxychloroquine (* 400 mg/day), chloroquine (* 250 mg/day), and leflunomide (* 20 mg/day).
**A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.;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 * 3 mg/L (central lab) at Screening Visit.;5. Subjects with prior exposure to at most one bDMARD may be enrolled (up to 20% of study
population) if they have documented evidence of intolerance to the bDMARD or limited

exposure
(* 3 months).

Exclusion criteria

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib);2. Subjects 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:	24
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ABT-494
Generic name:	ABT-494

Ethics review

Approved WMO Date:	10-11-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-01-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Not approved Date:	03-03-2016
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	EUCTR2015-003332-13-NL
CCMO	NL54443.091.15
Other	nog niet bekend