A Phase 4 Trial Assessing the ImPact of Residual inflammation detected via imaging tEchniques, Drug levels and patient characteristics on the outcome of dose taperIng of adalimumab in Clinical remission rheumatoid arThritis (RA) subjects (PREDICTRA)

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The primary objective is to investigate the association between residual disease activity at Baseline as detected by magnetic resonance imaging (MRI) and the occurrence of flares in RA subjects randomized to an adalimumab dose tapering regimen...

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

Summary

ID

NL-OMON44460

Source
ToetsingOnline

Brief title
PREDICTRA

Condition

- Autoimmune disorders

Synonym
arthritis, rheumatism

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie Deutschland GmbH & Co. KG
Source(s) of monetary or material Support: AbbVie

Intervention

Keyword: Adalimumab, M14-500, RA, Rheumatoid Arthritis

Outcome measures

Primary outcome

Primary Efficacy Variables

* The primary explanatory variables are the Baseline hand and wrist synovitis

and bone marrow edema (BME) RAMRIS scores as well as a composite of both and

the dependent variable is the occurrence of flare up to Week 40 in the tapering

arm.

Secondary outcome

Secondary Efficacy Variables

* Time to flare

* Flare severity

* Proportion of subjects experiencing a flare

* Subject demographics and clinical disease characteristics at dbBaseline,

including

o Smoking status, co-morbidities, anti-citrullinated peptide antibody (ACPA)

status, Rheumatoid Factor (RF) status, disease duration, previous treatment

with conventional synthetic Disease Modifying Anti-rheumatic Drugs (csDMARDs)

or biologic Disease Modifying Anti-rheumatic Drugs (bDMARDs) or both, duration

of adalimumab therapy, remission duration, disease activity, c-reactive protein (CRP) and Health Assessment Questionnaire (HAQ) score

* Proportion of subjects who regain clinical remission (defined as DAS28 [ESR] < 2.6 and defined as DAS28 (ESR) decrease > 1.2 if DAS28 [ESR] was less than 2.6 at flare) in the Open-Label Rescue Arm over time

* Time to regain clinical remission in the Open-Label Rescue Arm

* Proportion of subjects with low disease activity (defined as DAS28 [ESR] < 3.2) in the Open-Label Rescue Arm over time

* Change from Baseline in DAS28 (ESR), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI)

* Proportion of subjects maintaining clinical remission (defined by DAS, SDAI and CDAI: DAS28 [ESR] < 2.6; SDAI * 3.3; CDAI * 2.8) throughout the study

* Change from dbBaseline to Week 40 or final Visit in MRI synovitis, BME and erosions RAMRIS scores

* Change from Baseline in Health Assessment Questionnaire * Disability Index (HAQ-DI) over time

* Proportion of subjects with HAQ-DI normal (HAQ-DI * 0.5) at dbBaseline and at Week 40

* Change from dbBaseline in RAPID 3 scores assessed during Visits

* Change from Flare Week 0 in RAPID 3 at home assessments

* Change from dbBaseline in Swollen Joint Count (both 28 and 66 joints)

* Change from dbBaseline in Tender joint Count (both 28 and 68 joints)

* Change from dbBaseline in Patient's Global Assessment of Disease activity

* Change from dbBaseline in Patient's Global Assessment of RA pain

* Change from dbBaseline in Physician's Global Assessment of Disease activity

* Change from dbBaseline in morning stiffness assessment

* Change from dbBaseline in Sleep disturbance assessment

* Change from dbBaseline in Treatment Satisfaction Questionnaire for Medication (TSQM)

* Change from dbBaseline in Work Productivity and Activity Impairment (WPAI)

* Change from dbBaseline in Short Form-36 (SF-36)

* Change from dbBaseline in Functional Assessment of Chronic Illness Therapy * fatigue (FACIT fatigue)

* Change from dbBaseline in CRP

* Change from dbBaseline in ESR

Exploratory Variables

* dbBaseline and change from dbBaseline to the time of flare in PDUS and GSUS individual and composite scores of synovitis, synovial hypertrophy and tenosynovitis

* dbBaseline and change from dbBaseline on biomarker values (MMP3, SAA, C1M, C3M, CRPM, VICM, IL-6, CXCL10, CXCL13)

Pharmacokinetics:

* Adalimumab concentrations measurement dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4 and 16 (if applicable)

* AAA measurement at dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4, 10 and 16 (if applicable)

Safety:

Screening assessments will include medical history, vital signs, physical examination, and clinical and laboratory tests. The following safety evaluations will be performed during the study: concomitant medication review, adverse event (AE) monitoring, vital signs, physical examination (if required) and laboratory tests.

Study description

Background summary

The treatment interventions in this study, dose tapering and withdrawal, are treatment algorithms used in clinical practice.

Study objective

The primary objective is to investigate the association between residual disease activity at Baseline as detected by magnetic resonance imaging (MRI) and the occurrence of flares in RA subjects randomized to an adalimumab dose tapering regimen controlled by adalimumab withdrawal.
The Secondary Objectives are:
* To assess the occurrence and severity of flares and the time to flare in both taper and withdrawal arms.
* To investigate the association between Double-Blind Baseline (dbBaseline) subject demographic and disease characteristics and the occurrence of flares.
* To investigate the association between dbBaseline adalimumab trough concentrations and the occurrence of flares.
* To evaluate the effectiveness of rescue therapy with open-label adalimumab 40 mg every other week (eow) over 16 weeks in subjects experiencing a flare.
* To assess the change in rheumatoid arthritis MRI scoring system (RAMRIS) scores from Baseline to Final visit in the taper, withdrawal and Open-Label Rescue Arms.
* To investigate the MRI-flare associations in sub-groups of subjects who meet additional clinical remission criteria at dbBaseline including simplified disease activity index (SDAI) * 3.3, clinical diseases activity index (CDAI) * 2.8 and ACR/EULAR 2011 boolean-based remission, as well as to describe the course of disease and patient reported outcome (PRO) measures in the taper, withdrawal and Open-Label Rescue Arms overall and per dbBaseline subgroup.
* To assess the rate of anti-adalimumab antibodies (AAA) positive subjects in the taper and withdrawal arms.
The study also has the following exploratory objectives:

* In the subgroup of subjects with a Baseline Ultrasound (US) assessment:
o To investigate the association between Baseline ultrasound scores and the occurrence of flares.
o To investigate the association between the Baseline ultrasound scores and Baseline MRI RAMRIS scores.
o To describe the change in the ultrasound scores from Baseline to the time of the occurrence of a flare in the taper and withdrawal arms.
* To investigate the association between biomarker values at dbBaseline (and their change over time) and the occurrence of flares.

Study design

This is a Phase 4, multicenter, randomized, double-blind, parallel-group study in subjects with RA who are in stable clinical remission defined as DAS28 (ESR) or DAS28 (CRP) < 2.6 for at least 6 months prior to the Screening Visit.
Though the cut-off for clinical remission of DAS28 (CRP) may not be equivalent to the DAS (ESR), in clinical practice both are frequently used to define remission as < 2.6. Both ESR or CRP and 4 or 3 (when Patient Global Assessment [PGA] is not available) variables DAS28 will be allowed for the purposes of identifying subjects for Screening; however, throughout the study clinical remission will be defined by the more stringent 4 variables DAS28 (ESR) < 2.6 criteria. At Screening, only subjects with confirmed 4 variables DAS28 (ESR) < 2.6 will be considered for inclusion in the study.
The study activities will start with a Screening Period of up to 28 days to confirm inclusion/exclusion criteria including a DAS28 (ESR) assessment of < 2.6.
Subjects who have signed the Informed Consent and who fulfill all Screening criteria will enter the study. The study starts with a 4-week Lead-In Open Label (OL) Period during which stable DAS28 (ESR) clinical remission in 2 assessments 4 weeks apart will be confirmed. Subjects will receive adalimumab 40 mg sc eow starting at the Week 0 Visit of the Lead-In Period; this will be approximately 2 weeks after their last commercial Humira®. If needed for study procedures completion or injection scheduling adjustment, the lead-in period can be extended for up to 2 more weeks in which case the Week 4 Visit study procedures will occur up to 6 weeks after the Week 0 Visit.
At Week 4, the end of the Lead-In Period, subjects will have a dbBaseline visit. Subjects must have a confirmed DAS28 (ESR) remission at two time points in order to be randomized:
1. DAS28 (ESR) < 2.6 at the Lead-In Period Week 0
2. DAS28 (ESR) < 2.6 at the dbBaseline visit Week 4
Subjects who meet the remission criteria will be randomized (5:1) to one of two double-blind arms and followed for additional 36 weeks in the Double-Blind Period:
1. A reduced frequency of adalimumab 40 mg sc every 3 weeks (q3wks): taper arm, or
2. Adalimumab placebo sc q3wks: withdrawal arm.
All subjects who are taking concomitant MTX (any dose oral, subcutaneous [sc]

or intramuscular [im]) and/or other csDMARDs at a stable dose for at least 12 weeks prior to Week 0 Visit will maintain the regimen throughout the Lead-In and Double-Blind Periods of study. Subjects who have not been taking any csDMARDs for at least 12 weeks prior to the Week 0 Visit, will also maintain this regimen throughout the Lead-In and Double-Blind Periods of study.
Any other allowed RA concomitant medications should also be kept stable throughout the Lead-In and Double-Blind Periods of the study; these medications and MTX will be received by local prescriptions.
During the Double-Blind Period, subjects will be evaluated every 6 weeks for efficacy, including detection of flares, PROs, safety and laboratory assessments at scheduled visits on: Weeks 4, 10, 16, 22, 28, 34 and 40 (Final visit).
Other unscheduled visits will occur in the suspected event of a flare. During the interval between scheduled visits, subjects will be asked to contact their physicians in case of feeling their disease is worsening: an unscheduled visit will be performed within 2 weeks of contact with the site to assess if subjects are experiencing a flare.
Subjects with a confirmed flare (defined as an increase from dbBaseline in DAS28 [ESR] of > 0.6 AND a DAS28 [ESR] > 2.6, OR an increase in DAS28 (ESR) of * 1.2 irrespective of the resulting DAS28 [ESR]) at any time point (at a scheduled or unscheduled visit) will undergo Flare Week 0 visit procedures and will be immediately switched to an Open-label rescue arm initiating adalimumab 40 mg eow rescue therapy.
In the Open-Label Rescue Arm, subjects will be further evaluated at Flare Weeks 4, 10 and 16 for efficacy, PROs, safety and laboratory assessments.
During this period, further treatment escalation/change will be allowed based on the Investigator's medical judgment. Any treatments escalation/change will be documented. At Flare Week 0, all subjects will be requested to initiate weekly at home self-assessment of their RA disease activity by using Routine Assessment of Patient Index Data (RAPID)-3 questionnaires until Week 16.
A high-field contrast MRI of the most affected hand (2nd to 5th MCP) and wrist will be performed on all subjects during the Lead-In Period (prior to the dbBaseline visit) and at Final/Early Termination Visit. If both sides are considered equally affected, the MRI of the dominant hand (2nd to 5th MCP) and wrist will be performed.
The acquired MRI images will be centrally read and Investigators will be blinded to the results. Subjects should be randomized only when the MRI has been confirmed to be received and complete by Central Imaging.
In sites that meet pre-specified ultrasound requirements and who wish to participate in the ultrasound portion of the study, subjects will undergo US assessment using Gray Scale Ultrasonography (GSUS) and Power Doppler Ultrasonography (PDUS) consisting of a systematic longitudinal and transverse multiplanar examination of 46 joints and 18 tendon/tendon compartment during Lead In or at dbBaseline Visit prior to randomization and at the Flare Week 0 Visit (if applicable). US will be performed and assessed by local Ultrasonographer independent of the clinical assessor who will be blinded to the US scores.

Pharmacokinetics (PK) and immunogenicity will be assessed based on serum adalimumab trough concentrations and serum anti-adalimumab antibodies (AAA), respectively. Blood samples for adalimumab concentrations and measurements of AAA will be taken prior to dosing at dbBaseline (Week 4), at Weeks 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4 and 16 (if applicable).
A panel of inflammatory biomarkers: matrix metalloproteinase 3 (MMP3), Collagen neo-epitope (C1M), Type III collagen neo-epitope (C3M), Matrix metalloproteinase-mediated c-reactive protein (CRPM), Matrix metalloproteinase-degraded citrullinated vimentin (VICM), Serum amyloid-associated protein (SAA), Interleucin-6 (IL-6), Chemokine (C-X-C motif) ligand 10 CXCL10 and CXCL13 will be assessed at dbBaseline (Week 4), Weeks 10, 16, 28, 40 or at Early Termination, Flare Weeks 0, 4 and 16 (if applicable) on blood samples taken prior to dosing. At the time of analysis, other potential biomarkers identified as adding value to predict flare in this patient population may be included.
Additional optional samples for future biomarker research will be collected.

Intervention

Lead-In Period: Adalimumab 40 mg OL eow for 4 weeks
Double-Blind Period: Adalimumab 40 mg q3wks for 36 weeks
Open-Label Rescue Arm: Adalimumab 40 mg OL eow for a minimum of 16 weeks

Study burden and risks

Adalimumab Risks:
More than 28,000 subjects participating in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, pediatric Enthesitis Related Arthritis, Crohn's disease, pediatric Crohn's disease, psoriasis, pediatric psoriasis, hidradenitis suppurativa, ankylosing spondylitis, non-radiographic axial spondyloarthritis, peripheral spondyloarthritis, psoriatic arthritis, intestinal Behçet's disease, uveitis and ulcerative colitis clinical studies have been treated with adalimumab. The majority of side effects experienced following administration of adalimumab were mild to moderate in severity.
Other Adalimumab Risks:
Formation of auto-antibodies, antibodies that develop against one's own cells or proteins, have been identified during adalimumab administration. In rare cases auto-antibody production, joint pain and rash can develop that appear similar to that seen in a disease called systemic lupus erythematosus (SLE) that is referred to as lupus-like syndrome. In most people these symptoms go away when adalimumab is stopped. SLE may affect internal organs. The role of treatment with adalimumab on the development of autoimmune diseases is unknown.
Cases of worsening or new onset of psoriasis (including palmoplantar pustular psoriasis) have been reported in subjects treated with adalimumab.
There have been cases of hair loss (alopecia) reported in both clinical trials as well as outside of clinical trials for adalimumab.

Other side effect that have been reported include fever, cutaneous vasculitis (inflammation of the blood vessels in the skin), sarcoidosis (an inflammatory disease of unknown cause that affects multiple organs in the body), and pancreatitis (an inflammation of the pancreas, a gland located behind the stomach that produces insulin).
The most common reasons that patients stop taking adalimumab are infections.
Abnormal laboratory test values seen in patients taking adalimumab include: high cholesterol, elevated fats (lipids) in the blood, blood in the urine, and increased liver enzymes. Liver problems like inflammation of the liver (hepatitis) may happen in people who use TNF-blocker medicine like adalimumab. These problems can lead to liver failure and death.
Deaths have occurred during treatment with adalimumab. The overall rate of death is not increased compared to normal death rates.
Certain medicines should not be used together because an interaction may occur. The use of adalimumab and other immune drugs such as anakinra (Kineret) or abatacept (Orencia) or other TNF-blockers is not recommended because patients taking the combination of adalimumab and either of these drugs may have an increased risk of infection and other potential interactions. Tell your health care professional if you are taking any other prescription or nonprescription (over-the-counter [OTC]) medicine.
Risks Associated with Placebo:
Some people in the study will get placebo instead of adalimumab. Receiving placebo is the same as not receiving anything for your rheumatoid arthritis. If you use placebo during the study, it is possible that your rheumatoid arthritis may get worse. Please ask the study doctor or study staff if you have any questions about placebo.
Allergic Reaction Risk
Allergic reactions such as allergic rash and itching have been observed in approximately 2.9% of subjects taking adalimumab. In addition, there have been cases of erythema multiforme reported outside of the clinical trials. This is an allergic reaction caused by medication, illness or infection that presents as a red, splotchy rash on the body. Serious allergic reactions (e.g., Stevens-Johnson syndrome, anaphylaxis, angioedema) that can be life-threatening were observed rarely in people taking adalimumab. Before starting the study drug, you must tell your study doctor about any drug allergies. You should notify the study doctor right away if you have any allergy symptoms such as rash, hives, swelling, itching, shortness of breath, or trouble breathing.
The needle cover of the prefilled syringe contains dry rubber (latex). If you are sensitive to dry rubber (latex), please tell your study doctor before you start participating in this clinical study.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Main Inclusion:
* Male or female subjects * 18 years of age.
* Subject has a diagnosis of RA as defined by the 1987 revised ACR classification criteria and/or the ACR/EULAR 2010 classification criteria (any duration since diagnosis).
* Subject must meet the following criteria:
o Must be treated with adalimumab 40 mg sc eow for at least 12 months prior to Week 0 Visit;
o Must be treated with concomitant MTX at a stable dose (oral, sc or im at any dose) for at least 12 weeks prior to Week 0 Visit or if not on MTX, must be treated with other allowed csDMARDs at stable dose for at least 12 weeks prior to Week 0 Visit or if not treated with csDMARDs must maintain this regimen for at least 12 weeks prior to Week 0 Visit.
* Subject must be in sustained clinical remission based on the following:
o At least one documented 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) < 2.6 (or calculated based on documented components of the DAS28) in the patient chart 6 months or longer prior to the Screening Visit;
o 4 variables DAS28 (ESR) assessed at Screening < 2.6, with all components including ESR

assessed at Screening.
Main Inclusion (Continued):
* If subjects are receiving concomitant allowed csDMARDs (in addition or not to MTX) the dose must be stable for at least 12 weeks prior to the Week 0 Visit (e.g., chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and/or leflunomide).
* If subjects are receiving concomitant oral corticosteroids, prednisone or equivalent must be < 10 mg/day and the dose must be stable for at least 4 weeks prior to the Week 0 Visit.
* If subjects are receiving concomitant non-steroidal anti-inflammatory drugs (NSAIDs), tramadol or other equivalent opioids and/or non-opioid analgesics, the dose and/or therapeutic scheme must be stable for at least 4 weeks prior to the Week 0 Visit.
* Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

Exclusion criteria

* Any 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) (or calculated based on documented components of the DAS28) assessed within 6 months prior to the Screening Visit * 2.6.
* Subject is on an additional concomitant biological disease-modifying anti-rheumatic drug (bDMARD) (including but not limited to abatacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab or tocilizumab).
* Subject has been treated with intra-articular or parenteral corticosteroids within the last 4 weeks before Screening.
* Subject has undergone joint surgery within 12 weeks of Screening (at joints to be assessed by MRI and/or ultrasound).
* Subject has a medical condition precluding an MRI (e.g., magnetic activated implanted devices * cardiac pace-maker, insulin pump, neurostimulators, etc. and metallic devices or fragments or clips in the eye, brain or spinal canal and in the hand/wrist undergoing MRI).
* Subject has a medical condition precluding a contrast MRI with gadolinium (e.g., nephrogenic systemic fibrosis, previous anaphylactic/anaphylactoid reaction to gadolinium containing contrast agent, pregnancy or breastfeeding, severe renal insufficiency with an estimated Glomerular Filtration Rate [eGFR] below 30 mL/min/1.73 m2 at Screening, hepato-renal syndrome, severe chronic liver function impairment).
* Subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Screening Visit.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-10-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	24-09-2014
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	13-02-2015
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	14-04-2015

Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	28-09-2015
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	01-02-2016
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	06-05-2016
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	14-08-2017
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	26-09-2017

Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	16-05-2018
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	02-07-2018
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	EUCTR2014-001114-26-NL
CCMO	NL49533.048.14