Phase IIB, Randomized, Multi-Center, Double-Blind, Dose-Ranging, Placebo/Active Controlled Study to Evaluate the Efficacy and Safety of BMS-945429 Subcutaneous Injection With or Without Methotrexate in Subjects with Moderate to Severe Rheumatoid Arthritis with Inadequate Response to Methotrexate.

Published: 27-05-2011
Last updated: 28-04-2024

Primary Objective During Double-Blind Period:To compare the efficacy of BMS-945429 SC versus placebo on a background of methotrexate as assessed by ACR20 response rates at 12 weeks.Secondary Objectives During Double-Blind Period:1) To assess...

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

Summary

ID

NL-OMON38282

Source
ToetsingOnline

Brief title
IM133-001

Condition

- Autoimmune disorders

Synonym
"Chronic inflammation of the joints", "Rheumatoid arthritis"

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: BMS-945429, Inadequate clinical response, Rheumatoid arthritis

Outcome measures

Primary outcome

Primary Objective During Double-Blind Period:

To compare the efficacy of BMS-945429 SC versus placebo on a background of methotrexate as assessed by ACR20 response rates at 12 weeks.

Long-term Extension Period Primary Objective:

Assess the long-term clinical safety and tolerability of BMS-945429 treatment during the Long-term Extension Period.

Secondary outcome

Secondary Objectives During Double-Blind Period:

1) To assess additional efficacy outcomes of BMS-945429 SC at 12 weeks as measured by ACR50 and 70 response rates, DAS28-CRP, CDAI, SDAI, remission, physical function and health-related quality of life outcomes.

2) To assess efficacy of BMS-945429 SC at 24 weeks as measured by ACR 20, 50 and 70 response rates, DAS28-CRP, CDAI, SDAI, remission, physical function and health-related quality of life outcomes.

3) To assess radiographic progression of joint damage by imaging studies: MRI at 12 weeks and x-ray at 24 weeks.

4) To assess safety and tolerability including immunogenicity rates.

Exploratory Objectives During Double-Blind Period:

1) To assess the efficacy of BMS-945429 as measured by ACR20, 50 and 70 response rates, DAS28-CRP, CDAI, SDAI, remission, physical function and health-related quality of life, x-ray changes at 48 weeks.

2) To assess the clinical profile of BMS-945429 relative to adalimumab.

3) To evaluate potential biomarkers (including soluble, intracellular and genomic) which can be used as pharmacodynamic markers to inform dose selection and as markers to potentially predict treatment responses/safety.

4) To obtain BMS-945429 serum concentrations versus time data for future population pharmacokinetic analysis.

5) To assess consistency of efficacy between Japanese subjects and subjects from the rest of the world.

Long-term Extension Period Secondary Objectives:

Assess durability of efficacy and immunogenicity.

Study description

Background summary

To date, BMS-945429 for injection has been administered intravenously to healthy subjects, subjects with advanced cancer, subjects with rheumatoid arthritis, and subjects with non-small cell lung cancer. It has been administered subcutaneously to healthy subjects in one clinical trial.

IM133-001 is the second study of BMS-945429 in subjects with moderate to severe rheumatoid arthritis. The BMS-945429 doses chosen for this study are based on results of the prior Phase 2a study ((ALD518-CLIN-003) of BMS-945429 plus methotrexate in subjects with moderate to severe with an inadequate response to methotrexate treatment. BMS-945429 was administered intravenously in this Phase 2a study and the primary aim of the study was to assess the clinical efficacy of BMS-945429 in this patient population.
The study met the primary with 81.3%, 70.6%, and 82.1% subjects in the BMS-945429 80, 160, and 320 mg groups achieving ACR20 at 12 weeks respectively, compared with 27.3% in the placebo group. BMS-945429 was well-tolerated in this study.

In the phase 2a study, three IV doses were studied, 80 mg, 160 mg, and 320 mg. A distinct dose response profile between the doses was not apparent, although the data seemed to indicate that the 320 mg dose resulted in the best efficacy responses. Given this, and the fact that a sub-cutaneous formulation of BMS-945429 will be utilized in this study, dose range selection was based on the following factors: targeting exposures that would encompass exposures observed in the Phase 2a study, exposure-response modeling and simulation, and safety considerations.

For this planned Phase 2b study, a 25 mg sub-cutaneous dose (administered 4-weekly) has been chosen to provide a response level at the lower end of the dose response relationship that may still result in some efficacy. A 100 mg sub-cutaneous dose (administered 4-weekly) has been chosen to provide a response level in the mid area of the dose response relationship. A 200 mg sub-cutaneous dose (administered 4-weekly) has been chosen to provide a response at the upper range of the dose response relationship. Unlike the IV doses in the Phase 2a study, the responses predicted for these SC doses differ by enough to be clearly distinguishable.

While the Phase 2a study provided the initial proof of concept that the IV administration of BMS-945429 was effective and safe in a short term clinical trial in RA, the currently proposed Phase 2b study will evaluate the subcutaneous (SC) formulation to: a) Assess the efficacy and safety of different doses of the SC formulation of BMS-945429 in combination with MTX and as monotherapy. b) Determine the effect of BMS-945429 on reducing radiographic

progression of joint damage following both short and longer term treatment. c) Assess the efficacy and safety of BMS-945429 relative to an anti-TNF active comparator. Collectively, the results from this study will better characterize the clinical profile of BMS-945429 and inform on dose selection for future studies.

Study objective

Primary Objective During Double-Blind Period:
To compare the efficacy of BMS-945429 SC versus placebo on a background of methotrexate as assessed by ACR20 response rates at 12 weeks.

Secondary Objectives During Double-Blind Period:
1) To assess additional efficacy outcomes of BMS-945429 SC at 12 weeks as measured by ACR50 and 70 response rates, DAS28-CRP, CDAI, SDAI, remission, physical function and health-related quality of life outcomes.
2) To assess efficacy of BMS-945429 SC at 24 weeks as measured by ACR 20, 50 and 70 response rates, DAS28-CRP, CDAI, SDAI, remission, physical function and health-related quality of life outcomes.
3) To assess radiographic progression of joint damage by imaging studies: MRI at 12 weeks and x-ray at 24 weeks.
4) To assess safety and tolerability including immunogenicity rates.

Exploratory Objectives During Double-Blind Period:
1) To assess the efficacy of BMS-945429 as measured by ACR20, 50 and 70 response rates, DAS28-CRP, CDAI, SDAI, remission, physical function and health-related quality of life, x-ray changes at 48 weeks.
2) To assess the clinical profile of BMS-945429 relative to adalimumab.
3) To evaluate potential biomarkers (including soluble, intracellular and genomic) which can be used as pharmacodynamic markers to inform dose selection and as markers to potentially predict treatment responses/safety.
4) To obtain BMS-945429 serum concentrations versus time data for future population pharmacokinetic analysis.
5) To assess consistency of efficacy between Japanese subjects and subjects from the rest of the world.

Long-term Extension Period Primary Objective:
Assess the long-term clinical safety and tolerability of BMS-945429 treatment during the Long-term Extension Period.

Long-term Extension Period Secondary Objectives:
Assess durability of efficacy and immunogenicity.

Study design

This is a Phase 2b, multi-center, randomized, double-blind, dose ranging,

placebo/active-controlled study in subjects with moderate to severe active rheumatoid arthritis with inadequate response to methotrexate. This study is designed to compare the efficacy and safety of BMS-945429 with methotrexate or BMS-945429 monotherapy to placebo on background methotrexate over 24 weeks.

Subjects who completed the first 24 weeks will be evaluated over a 24 week extension period (total of 48 weeks). For ethical reasons, subjects in the placebo with methotrexate arm will begin to receive BMS-945429 with methotrexate after 24 weeks. An active comparator arm with adalimumab (Humira®) is also included.
For effective blinding, a double-dummy approach is used (see Section 4.3.1 in Protocol). A long term extension is planned for subjects who have completed the 48 week study.
Approximately 406 subjects (~58 per arm) will be randomized to 1 of 7 arms. Three doses of BMS-945429 in combination with MTX and 2 doses of BMS-945429 without methotrexate will be evaluated against placebo with MTX and adalimumab with methotrexate. The primary endpoint is ACR20 response rate at 12 weeks.
It is anticipated that the enrollment period will be approximately 12 months. When the global recruitment of subjects approaches the target number of subjects randomized, screening may be closed to leflunomide treated subjects with an expected screening period of more than 10 weeks (eg, due to washout requirements; screening procedures scheduled at other offices) to allow close control over the final number of randomized subjects. For subjects not treated with leflunomide, this period may be 2 weeks.

See Figure 3.1 on Page 34 of the Protocol for schematic diagram of the study design.

Intervention

In this protocol, investigational product(s) is/are:
• BMS-945429 sub-cutaneous injection, 1.2 ml/vial (100 mg/ml)
• Adalimumab (Humira®) SC injection, 40 mg/pre-filled syringe (40 mg/0.8 ml)
• Adalimumab Placebo, SC injection pre-filled syringe 0.8 ml
• Methotrexate, 2.5 mg, tablet or over encapsulated capsule
• Methotrexate Placebo, tablet or capsule.

See Figure 3.1 on Page 34 of the Protocol for schematic diagram of the study design.

Study burden and risks

There is a possibility that BMS-945429 may be an effective treatment for rheumatoid arthritis. However, it is not known if individual patients entering this trial will benefit directly. The information gained from this study may help future patients with rheumatoid arthritis.

Patients will have the inconvenience of more frequent interventions/procedures and longer visits to the hospital than would be usual for routine clinical care. They will have to undergo additional procedures. Potential side effects are known from research studies in a small number of subjects. Additional unforeseen side effects could occur and some side effects could be life threatening or fatal. Safety monitoring is included throughout the protocol. At all times throughout the study, the patient has the right to withdraw consent without their usual standard of care being affected.

Contacts

Public
Bristol-Myers Squibb

Vijzelmolenlaan 9
3447 GX Woerden
NL
Scientific
Bristol-Myers Squibb

Vijzelmolenlaan 9
3447 GX Woerden
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

a) Men and Women, ages >= 18 years
b) Subjects have a documented diagnosis of active RA by standard criteria (ARA [1987] or

ACR/EULAR [2010]) at least 16 weeks prior to screening.
c) Subjects have an ACR global functional status class of 1 to 3.
(d) Subjects must be methotrexate inadequate responders. Subjects must have been taking methotrexate for at least 3 months at a minimal weekly dose of >=15 mg, and at a stable dose for 4 weeks prior to randomization (Day 1). A methotrexate weekly dose as low as 10 mg is only permitted if there is verifiable documentation in the medical record prior to entry into the study that the subject did not respond to at least 15 mg or higher dose and the dose is reduced for toxicity/intolerability.
e) Subjects have a minimum of 6 swollen and 6 tender joints on a 66/68 joint count on screening visit #1 for those not requiring washout and on screening visit #2 for those requiring washout.
f) Evidence of synovitis in at least 1 hand or wrist by clinical examination on screening visit #1 for those not requiring washout and on screening visit #2 for those requiring washout.
g) Subjects have a hsCRP of >= 0.8 mg/dL (8mg/L) [by central laboratory values] on screening visit #1 for those not requiring washout and on screening visit #2 for those requiring washout.

Exclusion criteria

a) Subjects with documented juvenile rheumatoid arthritis.
b) Subjects who have previously received or are currently receiving an approved biologic therapy for RA (the eligibility of other Biologic therapies including experimental therapies should be discussed with the BMS Medical Monitor)
c) Subjects who treated with leflunomide based on the following conditions:
i) currently treated with leflunomide prior to screening:
(1) Subjects will be allowed to enroll only if they are willing to undergo the drug elimination procedure found in section 3.1.1 after stopping treatment with leflunomide and wait for an additional 10 weeks (5 half-lives)
ii) no longer treated with leflunomide prior to screening:
(2) Leflunomide plasma levels will be obtained at Screening; if the levels are non-detectable [less than 0.02 mg/L or 0.02 mcg/mL], the subject is eligible to enroll immediately if they have not been treated with leflunomide within 10 weeks prior to Screening. If there are still detectable leflunomide plasma levels, the subject may enroll only if they follow the drug elimination procedure found in section 3.1.
d) Subjects who are currently receiving calcineurin inhibitors.
e) Subjects who are currently receiving nimesulide.
f) Subjects using parenteral MTX for administration of their weekly dose.
g) Subjects who have been treated with IM or IA glucocorticosteroids within 4 weeks of randomization (Day 1).

Study design

Design

Study phase:	2
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):	10-08-2011
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-945429
Generic name:	BMS-945429
Product type:	Medicine
Brand name:	Humira
Generic name:	adalimumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rheumatrex
Generic name:	methotrexate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	27-05-2011
Application type:	First submission

Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	28-07-2011
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	03-10-2011
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	11-10-2011
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	17-01-2012
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	09-02-2012
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	EUCTR2010-023956-99-NL
CCMO	NL36137.048.11