A phase 3, Multi-Center, Randomized, Placebo-Controlled Study to Evaluate the Clinical Efficacy and Safety of Induction and Maintenance Therapy with Abatacept in Subjects with Active Crohn's Disease (CD) who have had an Inadequate Clinical Response and/or Intolerance to Medical Therapy

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Primary ObjectivesPlacebo-Controlled Induction Period: Primary Objective: Compare the proportion of subjects who have a clinical response (as defined by a reduction in Crohn*s Disease Activity Index [CDAI] >= 100 or an absolute CDAI score <...

Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON30746

Source
ToetsingOnline

Brief title
IM101-084

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's Disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Abatacept, Active Crohn's Disease (CD), Inadequate Clinical Response

Outcome measures

Primary outcome

Placebo-controlled Induction Period:

Compare the proportion of subjects who have a clinical response (as defined by a reduction in Crohn*s Disease Activity Index (CDAI) >= 100 or an absolute CDAI score < 150) at both Day IP-57 (Week 8) and Day IP-85 (Week 12) between the abatacept and placebo treatment regimens.

Maintenance Period:

Compare the proportion of subjects who are in clinical remission (as defined by a CDAI < 150) at Day MP-365 (12 months) between the abatacept and placebo treatment regimens.

Open-Label Extension Phase:

Assess the long-term clinical safety and tolerability of abatacept treatment during the Open-label Extension Phase.

Secondary outcome

Secondary Objectives: Placebo-controlled Induction Period

1) Compare the proportion of subjects who are in clinical remission (as defined by an absolute CDAI score < 150) at both Day IP-57 and Day IP-85 between the abatacept and placebo treatment regimens.

2) Evaluate the dose-response relationship by comparing the proportions of subjects who have a clinical response at both Day IP-57 and Day IP-85 induced by placebo and abatacept in increasing doses (3 mg/kg, ~10 mg/kg, 30/~10 mg/kg).

3) Assess improvements in quality of life at Day IP-85 and using the Inflammatory Bowel Disease Questionnaire (IBDQ) in abatacept vs. placebo treated subjects.

4) Assess the tolerability and safety of abatacept in subjects with CD.

5) Assess the immunogenicity of abatacept in subjects with CD.

6) Evaluate in subjects who have had an inadequate response and/or intolerance to anti-TNF therapy, the dose-response relationship by comparing the proportions of subjects in clinical response at Day IP-85 induced by placebo and abatacept in increasing doses (3 mg/kg, ~10 mg/kg, 30/~10 mg/kg).

7) Assess in abatacept vs placebo treated subjects who have had an inadequate response and/or intolerance to anti-TNF therapy, a) the proportion in clinical response, and b) the proportion in clinical remission, at both Day IP-57 and Day IP-85.

For the Secondary Objectives for the Maintenance Period and Open-Label

Extension Phase, please refer to pages 26-28 of the protocol.

Study description

Background summary

Crohn's Disease (CD) is a severe disorder with significant morbidity and impact on quality of life. Despite the availability of a range of medications, there still remains a need for therapeutic alternatives because patients may not respond to existing therapeutic choices, may not maintain a response, or may develop treatment limiting toxicities. Abatacept has the potential to be an effective and safe alternative to those therapies. The intended application of the results from this study is to prove that abatacept is effective and safe for the treatment of patients with active Crohn*s Disease with a view to obtaining a marketing license for this indication.

Study objective

Primary Objectives

Placebo-Controlled Induction Period: Primary Objective: Compare the proportion of subjects who have a clinical response (as defined by a reduction in Crohn*s Disease Activity Index [CDAI] >= 100 or an absolute CDAI score < 150) at both Day IP-57 (Week 8) and Day IP-85 (Week 12) between the abatacept and placebo treatment regimens.

Maintenance Period: Primary Objective: Compare the proportion of subjects who are in clinical remission (CDAI < 150) at Day MP-365 (12 months) between the abatacept and placebo treatment regimens.

Study design

The study consists of three periods (Screening, Induction, and Maintenance) and an Open-Label Extension phase. Following the Screening Period, eligible subjects will enter a 12-week Induction Period (IP). A first cohort of 469 subjects will be randomized to the IP in a 2:1:2:2 fashion to receive placebo or one of three doses of abatacept (3 mg/kg, ~10 mg/kg, or 30/~10 mg/kg) in a double-blind manner. Following the randomization of the initial cohort of 469 subjects, a second cohort of 120 subjects will be randomized to the IP to one of two dosing regimens of abatacept (~10 mg/kg or 30/~10 mg/kg) in a double-blind 1:1 manner. All subjects who meet protocol-defined response at the end of the IP will then enter a 12-month randomized double-blind

parallel-dosing, placebo-controlled Maintenance Period (MP) where they will be randomized to ~10 mg/kg abatacept or placebo. It is anticipated that approximately 334 subjects will enter the MP. Subjects who complete the IP but do not meet response criteria at Day IP-85 and subjects who complete the MP or who relapse during the MP may enter an Open-label Extension phase (OL).

Intervention

Abatacept will be administered IV. Induction Period: Days IP-1 and IP-15, subjects assigned to abatacept will receive 3 mg/kg (fixed dose), ~10 mg/kg dose (weight-tiered), or 30 mg/kg doses (fixed dose). On Days IP-29 and IP-57, subjects assigned to receive abatacept will receive 3 mg/kg or ~10 mg/kg dose. After entering the Maintenance Period, subjects assigned to abatacept, will receive ~10mg/kg every 28 days up to and including Day MP-337. In the Open-label Extension, all subjects receive open-label ~10mg/kg every 28 days.

Study burden and risks

The major identified risk of abatacept is an increased incidence of infection. Consistent with its mechanism of action, the abatacept RA program identified both non-serious and serious infections, mainly bacterial (urinary tract infections, pneumonia) and viral (herpes simplex) occurring more frequently in abatacept-treated subjects. Despite this identified risk, the majority of infections presented typically, responded appropriately to treatment, and there did not appear to be a major difference in outcome between abatacept and placebo. The risk for serious infections did not increase in the open-label periods with increasing exposure. Opportunistic infections and tuberculosis were uncommon, although all subjects were screened for latent TB. The overall risk of malignancy for abatacept-treated subjects was comparabale with placebo-treated subjects during the double-bllind periods. The incidence of malignancy did not appear to be greater with increased exposure. An important caution is that the clinical studies contain neither sufficient numbers of subjects nor follow up of sufficient duration to assess long term treatment or to rule out increases in the risk of adverse events with long latency, such as malignancy. Treatment with abatacept was associated with an excellent peri-infusional safety profile, and abatacept was associated with a low level of immunogenicity.

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) Subject is willing to participate in the study and has signed the informed consent
2) Subject must have had CD for at least 3 months from the time of initial diagnosis. Active CD must be confirmed by radiologic, endoscopic or histologic evidence within the previous 12 months. If previous confirmation of diagnosis is not available or if previous diagnosis is not deemed conclusive at time of screening, CD diagnosis should be confirmed by endoscopy, radiology or histology.
3) Subjects must satisfy at least one of the following criteria:
a) Having had an inadequate response to at least 1 of the following treatments (subjects may be currently receiving 1 of these medications or have received them previously):
i) oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalizide) at or above the approved label dose for at least 8 weeks and/or
ii) oral prednisone >= 30 mg/day (or equivalent) or budesonide >= 9 mg/day for at least 4 weeks and/or
iii) immunosuppressants (azathioprine >= 2 mg/kg/day or 6-mercaptopurine >= 1.0 mg/kg/day [or documentation of a therapeutic concentration of 6 thioguanine nucleotide] or methotrexate >= 15 mg/week) for at least 12 weeks and/or
iv) an approved anti-TNF agent at an approved labeled dose for at least 8 weeks
AND/OR
b) Have been intolerant to one of the above mentioned treatments (e.g., unable to achieve

doses or treatment durations because of dose limiting side effects [e.g., leukopenia]).
4) Moderate to severe CD as measured by a CDAI score >= 220 and <= 450
5) hsCRP > Upper Limit of Normal (ULN)
6)Men and women, ages >=18

Exclusion criteria

1) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 10 weeks after the study
2) WOCBP using a prohibited contraceptive method (there are no prohibited methods for this study)
3) Women who are pregnant or breastfeeding
4) Women with a positive pregnancy test on enrollment or prior to study drug administration
5) Diagnosis of Ulcerative or Indeterminate Colitis
6) CD isolated to the stomach, duodenum, jejunum, or perianal region, without colonic or ileal involvement
7) Suspected or diagnosed intra-abdominal or perianal abscess at screening
8) Known strictures or stenosis leading to symptoms or obstruction
9) Current evidence of fulminant colitis, toxic megacolon or bowel perforation
10) Subjects who are scheduled or anticipate the need for surgery, aside from dermatologic procedures
11) Subjects who have a history of clinically significant drug or alcohol abuse
12) Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, pulmonary, cardiac, neurological, ophthalmologic or cerebral disease. Concomitant medical conditions that in the opinion of the Investigator might place the subject at unacceptable risk for participation in this study
13) Subjects with a history of cancer within the last 5 years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to enrollment. Subjects with carcinoma in situ, treated with definitive surgical intervention, are allowed
14) Subjects at risk for tuberculosis (TB).
15) Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (such as chronic pyelonephritis, osteomyelitis and bronchiectasis)
16) Female subjects who have had a breast cancer screening that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations
17) A history of severe or anaphylactic infusion reaction after receiving a biologic agent, suspected to be associated with an immune response

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-03-2007
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Orencia
Generic name:	Abatacept

Ethics review

Approved WMO Date:	19-03-2007
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-08-2007
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-10-2007
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-12-2008
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-02-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-05-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2006-003371-13-NL
CCMO	NL15361.058.07