A phase IIb, Double Blind, Randomized, placebo- controlled, Double-Dummy, Dose Ranging Study To Evaluate the Clinical Efficacy and Safety of Induction and Maintenance therapy with BMS-945429 in subjects with Moderate to Severe Crohn's Disease.

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Objectives1.3.1 Primary ObjectiveCompare the efficacy of BMS-945429 versus placebo for induction of clinical remission (defined by an absolute Crohn*s Disease Activity Index [CDAI] score < 150) at Week 8 (IP-57).1.3.2 Secondary Objectives•...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON37627

Source
ToetsingOnline

Brief title
IM133-005

Condition

- Gastrointestinal inflammatory conditions
- Immune disorders NEC

Synonym

Crohns Disease, inflamation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Clinical efficacy, Crohn's Disease, Safety, Therapy

Outcome measures

Primary outcome

The primary efficacy assessment is clinical remission as defined by CDAI score <= 150 at week 8.

CDAI stands for: Crohn*s Disease Activity Index (CDAI)

The response measure (CDAI) will be reviewed and discussed with the investigational staff at the Investigators* Meeting or other forum as a method of standardizing the grading between the investigational staff. Training and instruction on the CDAI assessment will be provided and discussed at the Investigators* Meeting or at workshops.

Subjects will record CDAI data on a paper diary. In the event electronic diaries are used to obtain study assessment(s), these data will be captured electronically rather than on paper.

CDAI diary entries completed by the subject from the 7 days preceding the visit

will be used to calculate the CDAI score. A phone call should be placed 8 (induction period only) days prior to each subject visit/CDAI assessment to remind the subject to complete the CDAI diary. In addition to the diary, CDAI assessments also include weight, hematocrit, assessment of extraintestinal disease and abdominal mass. Physician*s assessments (assessment of extraintestinal manifestations and abdominal mass) used to determine the CDAI score must be performed by the Investigator or Sub-Investigator.

The Sub-Investigator may be a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physicians Assistant (PA) or Nurse Practitioner (NP). See Appendix 1 of the protocol for details and calculation of the CDAI score.

Secondary outcome

The secondary efficacy assessments clinical response as defined by a reduction in CDAI score >= 100 or an absolute CDAI score < 150 at week 8

Study description

Background summary

Crohn*s Disease (CD) is a relapsing and remitting inflammatory disorder of the gastrointestinal (GI) tract and extra-intestinal tissues. While its exact cause remains unknown, genetic and environmental factors have a role. The incidence and prevalence of CD vary by geographic region but are higher in industrialized countries. The prevalence of Crohn*s disease is approximately 1 million, with 0.6 million in the US alone. The
onset is typically between the ages of 20 and 40 years, although both children and the elderly can be affected.

Clinically, CD can be defined by location (ileum, colonic, ileo-colonic, or upper GI tract) and/or by clinical behavior (fistulizing, fibrostenosing, or inflammatory). The clinical features are largely dependent on the extent of GI

tract involvement and by the severity of inflammation. Colonic CD may be associated with bloody diarrhea whereas small bowel CD may be associated with abdominal pain, and other more insidious symptoms such as weight loss, nutritional deficiencies, and fever. Severe clinical features of CD include intestinal strictures, fistulas (including perianal fistulas), and intra-abdominal abscesses. The clinical course of gastrointestinal symptoms is characterized by periods of
exacerbation (acute flares) and remission, although some patients have a more continuously active course.

Conventional medications used in the treatment of CD include oral aminosalicylates, corticosteroids, thiopurines (6-mercaptopurine, azathioprine), methotrexate, and antibiotics. Combination therapy is common; the choice and sequence of drugs is based on a number of factors including severity of disease, location of disease, and the goal of therapy, i.e. treatment of an acute flare, maintenance of remission, treatment of fistulas, steroid sparing. While the efficacy of sulfasalazine and 5-aminosalicylate (5 - ASA) products in CD are controversial, they are often used in patients with mild disease. Corticosteroids are used to treat more severe disease. While quite effective in treating acute flares they are not efficacious in maintaining remission. They are not suitable for long term use due to their well known toxicity profile.

Thus, despite the availability of a range of medications, there still remains a need for developing therapeutic alternatives with different modes of action to overcome the needs of patients that may not respond to existing therapies, may develop treatment limiting toxicities or may not maintain response to therapy
.
BMS-945429 (also known as ALD518) is a fully humanized monoclonal antibody discovered by Alder Pharmaceuticals and manufactured in the yeast Pichia pastoris that targets the IL-6 cytokine. BMS-945429 has been previously studied in improving the signs and symptoms of joint disease in rheumatoid arthritis (RA), but has not been studied, so far, in patients with CD. Interleukin 6 (IL-6) plays an important role in the
pathology in CD. A blocker of IL-6 may be effective in reducing the signs and symptoms of CD. The current study is designed to be a phase IIb dose ranging induction and exploratory maintenance study to evaluate the efficacy, safety, and PK profile of
BMS-945429 in subjects with moderate to severely active CD.

Study objective

Objectives
1.3.1 Primary Objective
Compare the efficacy of BMS-945429 versus placebo for induction of clinical remission (defined by an absolute Crohn*s Disease Activity Index [CDAI] score < 150) at Week 8 (IP-57).

1.3.2 Secondary Objectives
• Compare the efficacy of BMS-945429 versus placebo for induction of clinical response (defined by a reduction in CDAI >= 100 or an absolute CDAI score < 150) at Week 8 (IP-57)
• Assess health-related quality of life outcomes (IBDQ and SF-36) of BMS-945429 in the induction period
• Assess the safety, tolerability and immunogenicity of BMS-945429 in the induction period
• Characterize the pharmacokinetics of BMS-945429 during the induction period

Study design

This study consists of five (5) periods: Screening, Induction, Maintenance, Open Label Extension, and a Post-Dose Follow-up Period. After a brief Screening Period, eligible subjects will enter a 12-week, double-blind, placebo-controlled, double-dummy, Induction Period.
It will be followed by a 48-week double-blind, placebo-controlled, Maintenance Period. At specified intervals (see section 3.1.3), subjects will roll into an Open-Label period.

Intervention

BMS-945429 will be supplied as 100 mg/ml in 1.2 mL single use vials (saline will be used as placebos - not provided by BMS).

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 the individual patients entering this trial will benefit directly the information gained from this study may help future patients with Chrons disease.

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 smaller number of subjects. Additional unforeseen side effects could occur and some side effects could be life threatining or fatal. Safety Monitoring is included throughout the protocol. At all times throughout the study, the patient has the right to withdraw consent with their usual standard of care being affected.

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

Inclusion Criteria
1) Signed Written Informed Consent
a) Subject is willing to participate in the study, able to provide written informed consent, and has signed the informed consent.;2) Target Population
a) Subject must have had Crohn*s Disease for at least 3 months from the time of initial diagnosis. Diagnosis of Crohn*s Disease must have been confirmed by radiologic, endoscopic or histologic evidence within the past 12 months.
b) Moderate to severe CD as measured by a CDAI score >= 220 and <= 450
c) hsCRP >= 5 mg/L or fecal calprotectin > 250 µg/g or evidence of active disease on screening MRE
d) Subjects must satisfy at least one of the following criteria:;i) INADEQUATE RESPONDERS:;In the past, had an inadequate response to one or more of the following treatments:
• Oral prednisone >= 40 mg/day (or equivalent) or budesonide >= 9 mg/day for at least 2 weeks and/or
• 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
• An approved anti-TNF agent at an approved labeled dose for at least 8 weeks. The study will include a maximum of approximately 50% subjects who have had prior anti-TNF experience. Upon reaching the maximum number of allowed anti-TNF-experienced subjects, subjects who have had prior anti-TNF experience will no longer be allowed to enter the study.;AND/OR;ii) INTOLERANCE:
In the past, experienced intolerance to one or more of the above mentioned treatments (e.g., unable to achieve doses or treatment durations because of dose limiting side effects [e.g. leucopenia, psychosis, uncontrolled diabetes, elevated liver enzymes]).;AND/OR;iii) DEPENDENCE;Currently receiving one or more of the following treatments:
• Oral Prednisone >= 20 mg/day (or equivalent) or budesonide >= 3 mg/day for at least 4 weeks
• Immunosuppressants [azathioprine >= 2 mg/kg/day or 6-mercaptopurine >= 1.0 mg/kg/day, (or documentation of a therapeutic concentration of 6-thioguanine nucleotide)] for at least 12 weeks.
Subjects currently receiving and tolerating the above mentioned treatments (with the exception of anti-TNF agents and methotrexate; see section 3.3.2; Item #4) should continue their treatment.
e) Drug stabilization requirements (for subjects entering the study on one or more of these medications)
i. Oral corticosteroid treatment must have been the equivalent of <= 30 mg prednisone or <= 9 mg budesonide daily at a stable dose for at least 2 weeks prior to entry into the Induction Period (IP-1)
ii. Oral aminosalicylates should be at a stable dose for at least 2 weeks prior to entry into the Induction Period (IP-1)
iii. Azathioprine, and 6-mercaptopurine should be at a stable dose for at least 8 weeks prior to entry into the Induction Period (IP-1)
3) Age and Reproductive Status
a) Men and women, >= 18 years of age
b) Women of childbearing potential (WOCBP) must use highly effective methods of birth control for up to 24 weeks after the last dose of investigational product to minimize the risk of pregnancy. WOCBP must follow instructions for birth control for the entire duration of the study including a minimum of 24 weeks after dosing has been completed. Acceptable methods of highly effective birth control include:
• Condom with spermicide
• Diaphragm and spermicide
• Cervical cap and spermicide
The use of intrauterine devices, (IUDs) shall be at the discretion of the Investigator.
Hormonal contraceptives may not be used for contraception unless a drug-drug interaction study has demonstrated that the pharmacokinetics of the hormone based contraceptive has not been adversely affected. The use of hormone based contraceptives is not otherwise restricted.
c) Women must have a negative serum or urine pregnancy test (minimum sensitivity

25 IU/L or equivalent units of HCG) within 48 hours prior to the start of investigational product.
d) Women must not be breastfeeding
e) Sexually active fertile men must use highly effective birth control if their partners are WOCBP. Men that are sexually active with WOCBP must follow instructions for birth control for the entire duration.

Exclusion criteria

Exclusion Criteria
1) Target Disease Exceptions
a) Current diagnosis of Ulcerative Colitis or Indeterminate Colitis or clinical findings suggestive of Ulcerative Colitis;b) CD isolated to the stomach, duodenum, jejunum, or perianal region, without colonic or ileal involvement
c) Subjects with history of diverticulitis or intestinal and/or upper GI perforation
d) Active intra-abdominal/perianal abscesses or subclinical diverticulitis and intraabdominal or perianal abscesses diagnosed at screening with MRE.
e) Known strictures or stenosis (without inflammatory component) leading to symptoms of obstruction
f) Current stoma or current need for colostomy or ileostomy.
g) Previous total proctocolectomy or subtotal colectomy with ileorectal anastomosis
h) Surgical bowel resection within 6 months before screening
i) Extensive small bowel resection (> 100 cm) or known short bowel syndrome
j) History of primary sclerosing cholangitis (PSC) or diagnosed at screening
k) Currently receiving total parenteral nutrition;2) Medical History and Concurrent Diseases
a) 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
b) Current evidence of colonic dysplasia or past evidence colonic dysplasia that has not been definitively treated
c) Have present or previous malignancies, except history of cured squamous or basal skin cell carcinoma or cured breast or cervical cancer for >= 5 years without evidence of recurrence
d) Subjects who are scheduled or anticipate the need for surgery, aside from dermatologic procedures
e) Subjects with a history of (within 12 months of signing the consent), or known current problems with drug or alcohol abuse or known cirrhosis including alcoholic cirrhosis.
f) Concomitant illness that in the opinion of the Investigator, is likely to require parenteral glucocorticosteroid therapy during the study (e.g. moderate to severe asthma)
g) Subjects with a clinically significant abnormal chest x-ray at screening;h) Subjects at risk for tuberculosis (TB).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	13-06-2012
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-945429
Generic name:	BMS-945429

Ethics review

Approved WMO Date:	30-05-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-10-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	16-01-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-06-2013
Application type:	Amendment
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	EUCTR2011-004763-72-NL
CCMO	NL39906.091.12
Other	www.ukcrn.org.uk