A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of AMG 181 in Subjects with Moderate to Severe Crohn*s Disease

Published: 16-10-2012
Last updated: 26-04-2024

To evaluate the efficacy of AMG 181 as measured by the proportion of subjects achieving Crohn*s Disease Activity Index (CDAI) remission (CDAI < 150) at week 8.

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

Summary

ID

NL-OMON39826

Source
ToetsingOnline

Brief title
20110232-AMG 181 in Moderate to Severe Crohn*s Disease

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's Disease, inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: AMG 181, M. Crohn, Phase 2

Outcome measures

Primary outcome

To evaluate the efficacy of AMG 181 as measured by the proportion of subjects achieving Crohn*s Disease Activity Index (CDAI) remission (CDAI < 150) at week 8.

Secondary outcome

Key Secondary

* To evaluate the efficacy of AMG 181 as measured by the proportion of subjects with a CDAI response (defined as either remission or CDAI reduction from baseline of * 100) at week 8

Other Secondary

* To evaluate the efficacy of AMG 181 as measured by the proportion of subjects achieving sustained remission at both week 8 and week 24

* To evaluate change from baseline in CDAI at week 8

-To evaluate the efficacy of AMG 181 as measured by the proportion of subjects achieving sustained remission at both week 12 and week 24

-To evaluate change from baseline in CDAI score at week 12

Safety

* To evaluate the safety profile of AMG 181 in subjects with Crohn*s disease

* To evaluate anti-AMG 181 antibodies

Exploratory

* To evaluate the onset of treatment response, as measured by time to CDAI response and remission

* To evaluate the efficacy of AMG 181, as measured by the proportion of subjects with a CDAI response and remission at all measured time points other than week 8

* To evaluate the efficacy of AMG 181 as measured by the proportion of subjects achieving sustained response, defined as achieving the criteria for response at both week 8 and week 24

* To evaluate the efficacy of AMG 181 as measured by the proportion of subjects achieving response or remission at week 24 in subjects achieving response or remission at week 8

* To evaluate change from baseline in CDAI at all measured time points other than week 8

* To evaluate disease worsening in subjects who achieved response at week 8

* To evaluate the impact of AMG 181 on corticosteroid withdrawal

* To evaluate the effect of treatment on inflammatory markers in blood and stool

* To investigate potential biomarker development by biochemical analysis of blood and stool samples (optional substudy)

* To characterize the effects of AMG 181 on memory CD4 *4*7 hi cell numbers, and *4*7 receptor occupancy in peripheral blood (optional substudy)

* To investigate the effects of genes, and drug target genes on inflammatory bowel diseases and/or subject response to AMG 181 (optional substudy)

* To characterize the pharmacokinetics (PK) of AMG 181

* To quantify the dose or exposure-response relationships for efficacy

* To evaluate the effect of AMG 181 on Patient Reported Outcomes (PRO)

-To evaluate the efficacy of AMG 181 as measured by the proportion of subjects

achieving CDAI remission (CDAI < 150) at week 12

* To evaluate the efficacy of AMG 181 as measured by the proportion of subjects

with a CDAI response (defined as either remission or a CDAI reduction from

baseline of * 100) at week 12

Study description

Background summary

Inflammatory bowel disease (IBD) affects approximately 1.4 million people in the US and 2.2 million people in Europe. The peak onset is between 15 and 30 years of age (Loftus and Sandborn, 2002). IBD comprises 2 types of chronic intestinal disorders: CD and ulcerative colitis (UC). Accumulating evidence suggests that IBD results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host (Abraham and Cho, 2009). Treatment of IBD includes lifestyle alterations, medical management, and surgical interventions. The overarching goals of medical management are: first, to induce disease remission and, second, to ensure that this remission is sustained over long periods of time. Medical management of IBD patients typically uses a step-up approach (Devlin and Panaccione, 2010). The standard therapies available for CD include 5-aminosalicylates, antimicrobial therapy, corticosteroids, immunosuppressive agents, and monoclonal antibodies. In the US there are currently 4 biologic agents marketed for use in Crohn*s disease. Three are in the anti-TNF (Tumor Necrosis Factor) class: infliximab (Remicade®, administered intravenously [IV]), adalimumab (Humira®, administered SC), and certolizumab pegol (Cimzia®, administered SC). The fourth one, natalizumab (Tysabri®, administered IV), is an anti-trafficking agent targeting the *4 integrin chain and thereby binding to both the *4*1 and *4*7 heterodimeric receptors. In the EU, infliximab and adalimumab are the only biological agents commercialized for use in Crohn*s disease. Induction therapy for patients with mild-to-moderate CD typically uses 5-aminosalicylates or antimicrobial agents. The immunosuppressive agents azathioprine (AZA), 6-mercaptopurine (6-MP), and methotrexate (MTX) can also be used to induce remission, yet are typically

slow-acting and require concomitant administration of corticosteroids. Failure to induce remission with the aforementioned agents, or more severe forms of the disease, will lead to the use of high dose corticosteroids or monoclonal antibodies as induction therapy. Only the immunosuppressive agents (AZA, 6-MP, and MTX) and biologic agents have documented efficacy in the maintenance of response and remission in CD. Because of therapeutic failures and serious side effects of present therapies, additional treatment alternatives are needed.

AMG 181 is a fully human monoclonal immunoglobulin IgG2 antibody that specifically recognizes the human *4*7integrin heterodimer. AMG 181 binds *4*7 with high affinity and blocks its interaction with MAdCAM 1. Refer to the AMG 181 investigator*s brochure for additional information.
No serious adverse events considered by the investigator to be related to AMG 181 have been reported through 3 January 2012. No anti AMG 181 antibodies have been detected from serum samples collected thus far from healthy subjects. Refer to the AMG 181 investigator*s brochure for additional information.

Study objective

To evaluate the efficacy of AMG 181 as measured by the proportion of subjects achieving Crohn*s Disease Activity Index (CDAI) remission (CDAI < 150) at week 8.

Study design

This is a randomized, double-blind, placebo-controlled, parallel group, multiple dose study to evaluate the efficacy of AMG 181 compared with placebo as measured by the proportion of subjects in remission (CDAI score < 150) at week 8. After completing all screening assessments and meeting all eligibility criteria, subjects will be randomized in a 2:1:2:1 ratio to receive placebo or AMG 181 21 mg, 70 mg or 210 m (randomization will be stratified by prior anti-TNF use and participation in the pharmacokinetics [PK] substudy). At the end of the double-blind period (week 24), subjects will enter a 108-week open-label period during which all subjects will receive open-label 210 mg AMG 181 every 3 months. Subjects who fail to achieve minimal improvement, or experience disease worsening after initial response (criteria defined in Section 3.1.2.1), are eligible to enter the open-label period early beginning at week 12 or after. All subjects must withdraw immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) at week 8. Corticosteroid tapering will be mandated for patients in remission as described in Section 6.3. Subjects will enter a 2-year safety follow-up period starting from the last dose of double-blind investigational product or last dose of open-label AMG 181 (whichever comes later). Disease remission (defined as a CDAI score < 150) and disease response (defined as either remission or a reduction of the CDAI score with * 100 points) will be assessed at all visits.
Prior to entry into the open-label period, subjects will complete the

procedures of the week 24/end of double-blind visit and the open-label baseline visit as described in Section 3.1.2.1 of the protocol. Subjects who have achieved response at week 8 and subsequently experience disease worsening are eligible to enter the open-label period early beginning at week 12 or after as described in Section 3.1.2.1 of the protocol. At the open-label week 12 visit, withdrawal of open-label AMG 181 and completion of an early termination (ET) visit is recommended for subjects with a CDAI score > 250, unless they have a decrease of * 70 points from either the baseline CDAI score or the week 24/End of Double-Blind CDAI score, whichever was higher. In addition, for subjects experiencing recurrence of significant CD symptoms as per investigator judgment at any time during the open-label period, withdrawal of open-label AMG 181 and completion of an early termination (ET) visit is recommended.
A safety follow-up interview (in person or by phone) to assess for symptoms of PML will be conducted at approximately 3, 6, 12, 18, and 24 months after the last dose of open-label AMG 181 (ie, open-label week 96 visit). For subjects that early terminate from the study and agree to the safety follow-up period, phone calls will be conducted at the same frequency, but scheduled based on the subject*s last dose of double-blind investigational product or last dose of open-label AMG 181, whichever comes later. Any new, clinically significant, unexplained neurological symptom will mandate evaluation by a neurologist consultant. An independent committee with expertise in neurological manifestations of PML will review clinical data and may apply a pre-specified diagnostic algorithm for PML (see Sections 2.4.2 and 7.1.6 in the protocol).
Subjects with abnormal hepatic laboratory values (eg, ALP, AST, ALT, total bilirubin) or signs/symptoms of hepatitis may meet the criteria for withholding of investigational product. Withholding is either permanent or conditional depending upon the clinical circumstances. Criteria for permanent or conditional withholding investigational product in the event that a subject develops signs or symptoms of hepatitis during a clinical trial is provided in Appendix C.
In the event that a subject receives a treatment listed in Section 6.4 of the protocol, investigational product must be withdrawn and the subject must complete an early termination visit.
A maximum of approximately 80% of subjects with any prior anti-TNF agent use will be allowed in the study. If approximately 80 % of the aimed number of randomized patients who haved used an anti-TNF drug has been randomized, only subjects who are anti-TNF naif and have used an immunomodulator will be allowed in the study.

Intervention

-Completion of Patient Reported Outcomes and a patient diary
-SC injections with the asigned study medication (AMG 181 or placebo)
-Blood en urine collections
-ECGs
-Physical examination
-Chest X-ray (if applicable)

-Brain MRI (if applicable)
-Lumbar punction (if applicable)
-Brain biopsy (if applicable)
-Tuberculosis test (PPD or quantiferon; if applicable)
-Collection stool samples

Patients may not use specific treatments during the study (from screening until the end of the open label period). See protocol page 41, section 6.4 ("Excluded Treatments During the Study Period").

Study burden and risks

Risks: side effects from the study drug.

Burden:
-Additional visit as described in question E2
-Physical examination
-Blood collections
-Urine collectoions
-ECG's
-Patiënten Reported Outcomes
-Completing patient diary
-SC injections with AMG 181 and/or placebo
-Optional PK study (additional blood collections)
-Chest X-ray (if applicable)
-Brain MRI (if applicable)
-Lumbar punction (if applicable)
-Brain biopsy (if applicable)
-Tuberculosis test (PPD or quantiferon; if applicable)
-Collection stool samples
-Optional Biomarker blood- and stool samples sub study (additional blood samples)
-Optional White Blood Cell Type Testing (additional blood samples)

Patients may not use specific treatments during the study (from screening until the end of the open label period). See protocol page 41, section 6.4 ("Excluded Treatments During the Study Period").

Risks:
See answer question E9.

Contacts

Public

Amgen

Minervum 7061
Breda 4817 ZK
NL
Scientific
Amgen

Minervum 7061
Breda 4817 ZK
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Subject has provided informed consent
- Subject is * 18 and * 65 years of age at screening
- Subject has diagnosis of ileal, ileo-colonic, or colonic Crohn*s disease for a minimum of 6 months prior to baseline
- Subject has moderately to severely active Crohn*s disease, as defined by a CDAI score * 220 and * 450 at baseline
- Subject has evidence of active inflammation, as demonstrated by at least one of the following:
* Elevated C-Reactive Protein (CRP) at screening (* 5 mg/L)
* Elevated fecal calprotectin at screening (* 200 *g/g)
* Endoscopic evidence of inflammation within 12 weeks prior to baseline as demonstrated by photographic documentation of a minimum of 3 nonanastomotic ulcerations (each > 0.5 cm in diameter) or 10 aphthous ulcerations (involving a minimum of 10 contiguous cm of intestine)
- Subject has demonstrated an inadequate response to, loss of response to, or intolerance to at least one of the following agents: Immunomodulators, Anti-TNF agents or corticosteroids

(coricosteroids in non-US countries only)
- Subject can be receiving the following treatments:
* 5-aminosalicylates, oral prednisone or equivalent * 20 mg/day, budesonide (* 9 mg/day), oral antibiotics for treatment of Crohn*s disease (ie, ciprofloxacin, metronidazole) if stable dosage for * 2 weeks prior to baseline
* Methotrexate (* 25 mg/week), azathioprine, 6-mercaptopurine if stable dosage for * 8 weeks prior to baseline
* Probiotics (eg, Culturelle, Saccharomyces boulardii) provided that the dose has been stable for the 2 weeks prior to baseline
* Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
- Subject has neurological exam free of clinically significant, unexplained signs or symptoms in the opinion of the investigator during screening and no clinically significant change prior to randomization;-Subject has no known history of active tuberculosis
-Subject has a negative test for tuberculosis during screening
For a full list of inclusion criteria, please refer to section 4.1 of the protocol

Exclusion criteria

Disease Specific
- Subject has clinical manifestations of short bowel syndrome (defined as requiring oral or parenteral supplemental or total nutrition in order to maintain stable body weight)
- Subject had stricture with obstructive symptoms within 3 months prior to baseline
- Subject has ileostomy and/or colostomy, or gastric or intestinal pouch
- Subject has evidence of an infected abscess
- Subject had bowel perforation or evidence of noninflammatory obstruction during the 6 months prior to baseline
- Subject has stool positive for C. difficile toxin at screening ;Excluded Medications
- Subject received an anti-TNF agent within 8 weeks or 5 times the respective elimination half-life, whichever is longer (eg, 8 weeks for infliximab, 10 weeks for adalimumab or certolizumab pegol), prior to baseline
- Subject received cyclosporine, mycophenolate mofetil, sirolimus (rapamycin), thalidomide, or tacrolimus within 1 month prior to baseline
- Subject received topical (rectal) aminosalicylic acid (eg, mesalamine) or topical (rectal) steroids within 2 weeks prior to baseline
- Subject received intravenous or intramuscular corticosteroids within 2 weeks prior to screening and during screening
- Subject had any prior exposure to antagonists of integrins or integrin ligands (eg, natalizumab, efalizumab, or vedolizumab), rituximab, or TNF kinoid immunotherapies
- Subject had any prior exposure to AMG 181;Laboratory Abnormalities
- Subject has abnormal laboratory results at screening:
* Liver tests: either aspartate aminotransferase (AST), alanine transaminase (ALT), or alkaline phosphatase (ALP) > 2.0 Upper Limit of Normal (ULN) or total bilirubin (TBL) > 1.5 ULN (except for subjects with Gilbert Syndrome)
* White blood cell count < 3,000 cells/mm3 (< 3 x 109/L in SI units)
* Hemoglobin < 10 g/dL;General

- Female subject is not willing to use two highly effective methods of birth control during treatment and for * 7 months after the last dose of investigational product (except if 2 years postmenopausal or surgically sterile).
Highly effective methods of birth control include not having intercourse or using birth control methods that work at least 99% of the time when used correctly and include hormonal birth control methods (pills, shots, implants or patches), intrauterine devices, sexual activity with a male partner who has had a vasectomy, condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide.
- Subject is pregnant, breast feeding, or might become pregnant within 7 months after the last dose of investigational product;For a full list of exclusion criteria, please refer to section 4.2 of the protocol

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):	20-03-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	16-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-000529-31-NL
CCMO	NL41390.018.12