A Randomized, Double-blind, Multiple Dose Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of AMG 181 in Subjects with Moderate to Severe Ulcerative Colitis

Published: 23-07-2012
Last updated: 26-04-2024

Evaluation the effect of AMG 181 on induction of remission in subjects with moderate to severe UC at week 8 as assessed by a total Mayo Score >= 2 points, with no individual subscore > 1 point.

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

Summary

ID

NL-OMON39233

Source
ToetsingOnline

Brief title
20110166-AMG 181 in Ulcerative Colitis

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammatory bowel disease, Ulcerative Colitis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AMG 181, Phase 2, Ulcerative Colitis

Outcome measures

Primary outcome

Remission at week 8 defined by a total Mayo Score <= 2 points, with no

individual subscore > 1 point

Secondary outcome

-Response at week 8 as defined by a decrease from baseline in the total Mayo

Score of >= 3 points and >= 30%, with an accompanying decrease in the subscore

for rectal bleeding of >= 1 point or an absolute subscore for rectal bleeding of

0 or 1

-Mucosal healing at week 8 as defined by an absolute subscore for

rectosigmoidoscopy of 0 or 1

-Sustained remission at both week 8 and week 24

Safety Endpoints:

-Adverse events

-Serious adverse events

-Significant changes in laboratory values and vital signs

-Anti AMG 181 antibodies

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 in persons 15 to 30 years of age. IBD comprises 2 types of chronic intestinal disorders: Crohn*s disease (CD) and UC. Accumulating evidence suggests that IBD results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host.
Treatment of UC includes lifestyle alterations, medical management, and surgical interventions. The overarching goals of treatment of UC are induction and maintenance of remission of symptoms to provide an improved quality of life, reduction in need for long term corticosteroids, and minimization of cancer risk. Medical management of IBD patients typically uses a step up approach.
Induction therapy for mild to moderate UC generally consists of orally administered aminosalicylate derivatives (mesalamine or sulfasalazine) often combined with rectal administration of aminosalicylates. This approach is often an effective strategy and approximately 40% to 80% of patients will respond within 4 weeks. For those UC patients who do not respond to aminosalicylates or who have more severe forms of the disease, corticosteroids are an effective induction therapy but are not ideal for maintenance of remission due to side effects. The only biologic agent approved by the Food and Drug Administration and European Medicines Agency for use in patients with moderate to severe active UC who have had an inadequate response to conventional therapy is the anti TNF antibody, infliximab (Remicade®). Infliximab has well documented efficacy in inducing remission in UC. However, clinical trials showed that disease remission after 1 year of treatment was sustained in less than 50% of UC patients in whom it had been induced at week 8. In UC patients, anti TNF therapy has been associated with some rare, but fatal cases of lymphoma (Remicade® label).
The current treatment options for patients with moderate to severe disease are limited. Approximately 9 to 35% of UC patients require a colectomy within 5 years of initial diagnosis. Therefore, novel alternative therapies are needed for patients with moderate to severe UC to induce and maintain remission and to reduce the requirement for surgery.

AMG 181 is a fully human monoclonal immunoglobulin IgG2 antibody that specifically recognizes the human α4β7integrin heterodimer. AMG 181 binds α4β7 with high affinity and blocks its interaction with MAdCAM 1. Based on blinded clinical data available to date, the safety profile of AMG 181 is acceptable. Refer to the investigator*s brochure for additional information.

Study objective

Evaluation the effect of AMG 181 on induction of remission in subjects with moderate to severe UC at week 8 as assessed by a total Mayo Score >= 2 points, with no individual subscore > 1 point.

Study design

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 (total Mayo Score >= 2 points with no individual subscore > 1 point) at week 8. After completing all screening assessments and meeting all eligibility criteria, subjects will be randomized in a 2:1:2:2:2 ratio to receive placebo or 7 mg, 21 mg, 70 mg or 210 mg of AMG 181 (randomization will be stratified by any prior anti tumor necrosis factor (TNF) use and participation in the pharmacokinetics (PK) substudy). At the end of the double blind period (week 24) subjects will enter an open label period during which all subjects will receive open label 210 mg AMG 181 every 3 months until week 132. Subjects who failed to achieve a response at week 8 and also have an inadequate response at week 12 or after are eligible to enter the open label period of the study early. Subjects who achieved response and/or remission at week 8 and subsequently experience disease worsening are eligible to enter the open label period early ONLY if a confirmatory rectosigmoidoscopy, performed to characterize disease severity, is scored >= 2 as outlined in Section 3.1.2.1. Subjects that complete the open label period or early terminate from the study will enter the 2 years safety follow up period.
Withdrawal of open-label AMG 181 and completion of an early termination visit is recommended for subjects who entered the open label period early (ie, experienced inadequate response) and who by the week 12 open-label visit continue to have an inadequate response defined by failure to achieve a 2 point reduction and 25% improvement in partial Mayo Score (and having a minimum partial Mayo Score of >= 5 points) compared to the open label baseline visit.
Withdrawal of open-label AMG 181 and completion of an early termination visit is recommended for subjects who experience recurrence of significant UC symptoms during the open-label period as per investigator judgment.
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. See appendix C of the protocol for the criteria.
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 50% of subjects with any prior anti-TNF agent use will be allowed in the study. If approximately 50 % of the aimed number of randomized patients who have 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
-Rectosigmoïdoscopy

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
-Rectosigmoïdoscopy
-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

-Age 18 to 65 at screening (inclusive)
-Diagnosis of UC established >= 3 months before baseline by clinical and endoscopic evidence and corroborated by a histopathology report
-Moderate to severe active UC as defined by a total Mayo score of 6 to 12 with a centrally read rectosigmoidoscopy score >= 2 prior to baseline
-Demonstrated an inadequate response to, loss of response to, or intolerance to

immunomodulators, anti-TNF agents or to corticosteroids (corticosteroids: non-US sites only)
-Subjects can be receiving the following treatments:
• Azathioprine or 6 mercaptopurine if treatment initiated at least 12 weeks prior to baseline and if stable dosage for >= 8 weeks prior to baseline
• Methotrexate up to 25 mg/week if stable dosage for >= 8 weeks prior to baseline
• 5 aminosalicylates and/or oral prednisone or equivalent up to 20 mg/day, if stable dosage for >= 2 weeks prior to baseline
-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

Exclusion criteria

Disease Specific
-Disease limited to the rectum (ie, within 10 cm of the anal verge)
-Toxic megacolon
-Crohn*s Disease
-History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for UC
-Planned bowel surgery within 24 weeks from baseline
-Stool positive for C. Difficile toxin at screening
-History of gastrointestinal surgery within 8 weeks of baseline
-Primary Sclerosing Cholangitis ;Excluded Medications:
-Immunosuppressive therapy with either cyclosporine A, tacrolimus, or mycophenolate mofetil, within 1 month prior to baseline
-Prior exposure to anti TNF agents, within 2 months, or 5 times the respective elimination half life (whichever is longer) prior to baseline
-Any prior exposure to vedolizumab, rituximab, efalizumab, natalizumab
-Use of topical (rectal) aminosalicylic acid (eg, mesalamine) or topical (rectal) steroids within 2 weeks prior to baseline
-Use of intravenous corticosteroids within 2 weeks prior to screening and during screening
-Subject previously treated with AMG 181
-Subject who has received any type of live attenuated vaccine < 1 month prior to baseline or is planning to receive any such live attenuated vaccine over the course of the study
-Treatment of infection with intravenous (within 30 days of baseline) or oral (within 14 days prior to baseline) antibiotics, antivirals, or antifungals

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):	26-02-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	23-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2013
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2013
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	EUCTR2011-005251-13-NL
ClinicalTrials.gov	NCT01694485
CCMO	NL40584.018.12