A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by MLN0002 in Patients with Moderate to Severe Ulcerative Colitis

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Primary Objective for the Induction Phase* To determine the effect of MLN0002 induction treatment on clinical response at 6 weeksPrimary Objective for the Maintenance Phase* To determine the effect of MLN0002 maintenance treatment on clinical...

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

Summary

ID

NL-OMON33523

Source
ToetsingOnline

Brief title
C13006_MLN0002 for patients with Ulcerative Colitis

Condition

- Gastrointestinal inflammatory conditions

Synonym
Ulcerative Colitis - Inflammatory Bowel Disease

Research involving

Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: MLN0002, Ulcerative Colitis, Vedolizumab

Outcome measures

Primary outcome

Primary Endpoint for the Induction Phase

* Proportion of patients with clinical response at Week 6

Primary Endpoint for the Maintenance Phase

* Proportion of patients in clinical remission at Week 52

Secondary outcome

Secondary Endpoints for the Induction Phase

* Proportion of patients in clinical remission at Week 6

* Proportion of patients with mucosal healing at Week 6

Secondary Endpoints for the Maintenance Phase

* Proportion of patients with durable clinical response

* Proportion of patients with mucosal healing at Week 52

* Proportion of patients with durable clinical remission

* Proportion of patients using oral corticosteroids at baseline who have

discontinued corticosteroids and are in clinical remission at Week 52

Study description

Background summary

In this study, an investigational drug called MLN0002 will be tested to see if it is effective in treating UC. MLN0002 is a monoclonal antibody and works by attaching itself to a particular kind of white blood cell and reducing inflammation. The term "monoclonal"refers to the fact that is produced in a laboratory. MLN0002 is a new type of investigational drug that is being developed by scientists at Millennium, the sponsor of this study. Please see the protocol page 18 - 30 for a detailed background of this investigation.

Study objective

Primary Objective for the Induction Phase
* To determine the effect of MLN0002 induction treatment on clinical response at 6 weeks

Primary Objective for the Maintenance Phase
* To determine the effect of MLN0002 maintenance treatment on clinical remission at
52 weeks

Secondary Objectives for the Induction Phase
* To determine the effect of MLN0002 induction treatment on clinical remission at 6 weeks
* To determine the effect of MLN0002 induction treatment on mucosal healing at 6 weeks

Secondary Objectives for the Maintenance Phase
* To determine the effect of MLN0002 maintenance treatment on durability of clinical
response
* To determine the effect of MLN0002 maintenance treatment on mucosal healing at 52 weeks
* To determine the effect of MLN0002 maintenance treatment on durability of clinical
remission
* To determine the effect of MLN0002 maintenance treatment on corticosteroid-free
remission at 52 weeks

Study design

Overview of Study Design:

This phase 3, randomized, blinded, placebo-controlled study in patients with moderately to severely active UC comprises two phases:

* The Induction Phase, designed to establish the efficacy and safety of MLN0002 for the induction of clinical response and remission
* The Maintenance Phase, designed to establish the efficacy and safety of MLN0002 for the maintenance of clinical response and remission

The Induction Phase comprises patients who are enrolled in Cohorts 1 (randomized, blinded, placebo-controlled study drug assignment) and 2 (open label MLN0002 treatment). Patients enrolled in Cohort 1 will be randomized 3:2 to receive either MLN0002 or placebo at Week 0 (Day 1) and Week 2 (Day 15). Cohort 2 will be used to achieve the sample size of responders to MLN0002 induction treatment needed to power the efficacy endpoints for the Maintenance Phase.

All patients enrolled in Cohort 2 will receive MLN0002 at Week 0 (Day 1) and Week 2 (Day 15).

The analysis of the efficacy of MLN0002 for the induction of clinical response and remission will include data from Cohort 1 only.

After completing the Induction Phase, including the Week 6 pre-dose assessments, all patients will continue on to the Maintenance Phase. Those who received MLN0002 in the Induction Phase and achieved clinical response (as defined in the Study Definitions) at Week 6 will be randomized 1:1:1 to receive MLN0002 every 4 weeks, MLN0002 every 8 weeks, or placebo, for an additional 44 weeks. Patients who received MLN0002 in the Induction Phase but did not achieve clinical response at Week 6 will continue to receive MLN0002 every 4 weeks during the Maintenance Phase. Patients who received placebo in the Induction Phase will continue to receive placebo.

Infusions during the Maintenance Phase will occur at 4-week intervals for all patients.

The efficacy of MLN0002 for the maintenance of clinical response and remission will be analyzed based on data from patients who received MLN0002 in the Induction Phase and achieved clinical response (as defined in the Study Definitions) at Week 6. The analysis of the safety of MLN0002 in the Maintenance Phase will be based on data from all patients, including

those who received
MLN0002 in the Induction Phase and did not achieve clinical response at Week 6 and those who
received placebo in the Induction and Maintenance Phases.
After the Week 52 assessments, patients may be eligible to enroll in Study C13008 (Long-term
Safety) to receive active treatment with MLN0002. Patients withdrawn early due to sustained
non-response, disease worsening, or the need for rescue medications may also be eligible for
Study C13008. Patients who do not enroll into Study C13008 will complete the final on-study
safety assessment at Week 66 (or Final Safety Visit). In addition, after the end of the study, all
patients who do not enroll in Study C13008 will participate in a 2-year follow-up survey.

Intervention

MLN0002 or Placebo will be administered every four weeks per infusion.

Induction phase:
- Cohort 1, randomisation between Placebo and MLN0002 (2:3)
- Corhort 2, open label MLN0002

Maintenance phase:
If treated with Placebo during Induction phase --> Treatment with Placebo during maintenance phase (no randomisation)

If treated with MLN0002 during induction phase & clinical response after 6 weeks --> randomisation between placebo, MLN0002 every 4 weeks and MNL0002 every 8 weeks (1:1:1)

If treated with MLN0002 during induction phase AND no clinical response after 6 weeks --> MLN0002 every 4 weeks (no randomisation).

Study burden and risks

Common side effects from the study drug include headache, nausea, worsening of UC, stomach pain and tiredness and common cold, which occur in approximately 10-29% of the patients. There is also a risk in developing an allergic reaction towards MLN0002. Symptoms of an allergic reaction may include shortness of breath, wheezing, dizziness, fainting, skin rash, hives, itching, lip or face swelling, throat tightness and swallowing difficulties. Allergic reactions may require treatment with medications. If a very severe allergic reaction does not respond to treatment, it may result in death. In previous studies, three

patients who received MLN0002 developed allergic reactions during the infusion of the study drug: however these reactions were easily treated.

Contacts

Public
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Scientific
Millenium Pharmaceuticals

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria
Each patient must meet all of the following inclusion criteria to be enrolled in the study:
1. Age 18 to 80
2. Male or female patient who is voluntarily able to give informed consent
3. Female patients who:
* Are post-menopausal for at least 1 year before the screening visit, OR
* Are surgically sterile, OR
* If they are of childbearing potential, agree to practice 2 effective methods of

contraception, at the same time, from four weeks before the first dose of study drug through 6 months after the last dose of study drug, OR agree to completely abstain from heterosexual intercourse.
Male patients, even if surgically sterilized (ie, status post-vasectomy), who:
* Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
* Agree to completely abstain from heterosexual intercourse.
4. Diagnosis of ulcerative colitis established at least 6 months prior to enrollment by clinical and endoscopic evidence and corroborated by a histopathology report.
5. Moderately to severely active ulcerative colitis as determined by a Mayo score of 6 to 12 with an endoscopic subscore *2 within 7 days prior to the first dose of study drug (see Section 15.1)
6. Evidence of ulcerative colitis extending proximal to the rectum (*15 cm of involved colon)
7. Patients with extensive colitis or pancolitis of >8 years duration or left-sided colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (may be performed during screening).
8. Patients with a family history of colorectal cancer, personal history of

increased colorectal cancer risk, age >50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance (may be performed during screening)
9. Demonstrated, over the previous 5 year period, an inadequate response to, loss of response to, or intolerance of at least one of the following agents as defined below:
* Corticosteroids
o Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or intravenously for 1 week OR
o Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally OR
o History of intolerance of corticosteroids (including, but not limited to Cushing*s syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection)
* Immunomodulators
o Signs and symptoms of persistently active disease despite a history of at least one 8 week regimen of oral azathioprine (*1.5 mg/kg) or 6-mercaptopurine mg/kg (*0.75 mg/kg) OR
o History of intolerance of at least one immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, TPMT genetic mutation, infection)
* TNF* antagonists
o Signs and symptoms of persistently active disease despite a history of at

least one 4 week induction regimen of infliximab 5 mg/kg IV, 2 doses at least 2 weeks apart OR
o Recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) OR
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o History of intolerance of infliximab (including, but not limited to infusionrelated reaction, demyelination, congestive heart failure, infection)
10. May be receiving a therapeutic dose of the following drugs:
a. Oral 5-ASA compounds provided that the dose has been stable for the 2 weeks immediately prior to enrollment
b. Oral corticosteroid therapy (prednisone at a stable dose *30 mg/day, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately prior to enrollment if corticosteroids have just been initiated, or for the 2 weeks immediately prior to enrollment if corticosteroids are being tapered
c. Probiotics (eg, Culturelle, Saccharomyces boulardii) provided that the dose has been stable for the 2 weeks immediately prior to enrollment
d. Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
e. Azathioprine or 6-mercaptopurine provided that the dose has been stable for the 8 weeks immediately prior to enrollment

Exclusion criteria

Exclusion Criteria
The exclusion criteria are divided into 3 categories: gastrointestinal exclusion criteria, infectious disease exclusion criteria, and general exclusion criteria. Patients meeting any of the following exclusion criteria are not to be enrolled in the study.
5.2.1 Gastrointestinal Exclusion Criteria
1. Evidence of abdominal abscess or toxic megacolon at the initial screening visit
2. Extensive colonic resection, subtotal or total colectomy
3. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
4. Within 30 days prior to enrollment, have received any of the following for the treatment of underlying disease:
a. Non-biologic therapies (eg, cyclosporine, thalidomide) other than those permitted in Section 6.2
b. A non-biologic investigational therapy
c. An approved non-biologic therapy in an investigational protocol
5. Within 90 days prior to enrollment, have received any of the following:
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a. Infliximab
b. Other investigational or approved biologic agent
6. Any prior exposure to natalizumab or rituximab
7. Use of topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories within 2 weeks of the administration of the first dose of study drug
8. Evidence of or treatment for C. difficile infection within 60 days or other intestinal pathogen within 30 days prior to enrollment
9. Currently require or are anticipated to require surgical intervention for UC during the study
10. History or evidence of adenomatous colonic polyps that have not been removed
11. History or evidence of colonic mucosal dysplasia
12. Diagnosis of Crohn*s colitis or indeterminate colitis
5.2.2 Infectious Disease Exclusion Criteria
1. Chronic hepatitis B or C infection
2. Active or latent tuberculosis, regardless of treatment history, as evidenced by any of the following:
a. History of tuberculosis
b. A positive diagnostic tuberculosis (TB) test within one month of enrollment defined as:
i. a positive QuantiFERON® test or 2 successive indeterminate QuantiFERON® tests OR
ii. a tuberculin skin test reaction *10 mm (*5 mm in patients receiving the equivalent of > 15 mg/day prednisone).
c. Chest X-ray within 3 months of enrollment in which active or latent pulmonary tuberculosis cannot be excluded
3. Any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation)
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4. Any live vaccinations within 30 days prior to study drug administration except for the influenza vaccine
5. Clinically significant extra-intestinal infection (eg, pneumonia, pyelonephritis) within 30 days prior to enrollment
5.2.3 General Exclusion Criteria
1. Previous exposure to MLN0002
2. Female patients who are lactating or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 prior to study drug administration.
3. Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety
4. Had any surgical procedure requiring general anesthesia within 30 days prior

to enrollment or is planning to undergo major surgery during the study period
5. Any history of malignancy, except for the following: (a) adequately-treated non-metastatic basal cell skin cancer; (b) any other type of non-melanoma skin cancer that has been adequately treated and has not recurred for at least 1 year prior to enrollment; and (c) adequately treated in situ cervical cancer that has not recurred for at least 1 year prior to enrollment
6. History of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease
7. Positive PML subjective symptom checklist prior to the administration of the first dose of study drug
8. Any of the following laboratory abnormalities during the screening period:
a. Hemoglobin level <8 g/dL
b. WBC count <3 × 109/L
c. Lymphocyte count <0.5 × 109/L
d. Platelet count <100 × 109/L or >1200 × 109/L
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e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN)
f. Alkaline phosphatase >3 × ULN
g. Serum creatinine >2 × ULN
9. Current or recent history (within one year prior to enrollment) of alcohol dependence or illicit drug use
10. Active psychiatric problems that, in the investigator*s opinion, may interfere with compliance with the study procedures
11. Unable to attend all the study visits or comply with study procedures

Study design

Design

Study phase:	3
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):	07-12-2009
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not Applicable
Generic name:	Vedolizumab

Ethics review

Approved WMO Date:	11-02-2009
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	18-02-2009
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	10-06-2009
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	13-07-2009
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	20-07-2009
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO	

Date:	07-10-2009
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	20-11-2009
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	31-03-2010
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	17-05-2010
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	24-08-2010
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	19-05-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	22-06-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	16-08-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	EUCTR2008-002782-32-NL
CCMO	NL25207.096.08