A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction of Clinical Response and Remission by Vedolizumab in Patients With Moderate to Severe Crohn's Disease

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Primary Objective• To determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in the subgroup of patients defined as having failed tumor necrosis factor alpha (TNFa) antagonist therapy (TNFa subpopulation)Secondary...

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

Summary

ID

NL-OMON36532

Source
ToetsingOnline

Brief title
C13011_MLN0002 for patients with Crohn's Disease

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's Disease- Inflammatory Bowel Disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Crohn's Disease, MLN0002, Phase 3, Vedolizumab

Outcome measures

Primary outcome

Primary Endpoint

* Proportion of patients in clinical remission at Week 6 in the TNF*

subpopulation

Secondary outcome

Secondary Endpoints

* Proportion of patients in clinical remission at Week 6 in the entire study

population

* Proportions of patients in clinical remission at Week 10 in the TNF*

subpopulation

and in the entire study population

* Proportions of patients with sustained clinical remission (ie, clinical

remission at

both Week 6 and Week 10) in the TNF* subpopulation and in the entire study

population

Vedolizumab (MLN0002)

Clinical Study Protocol C13011

Confidential 26

* Proportion of patients with enhanced clinical response at Week 6 in the TNF*

subpopulation

3.3 Safety Endpoints

AEs, SAEs, vital signs, results of standard laboratory tests (clinical

chemistry,

hematology, coagulation, urinalysis, and HAHA), and results of 12-lead

electrocardiograms (ECGs)

Study description

Background summary

Vedolizumab (research name MLN0002); formerly known as LeukoSite development project
2 [LDP-02] and MLN02) is a humanized monoclonal antibody that is being investigated as a
potential treatment for inflammatory bowel disease (Crohn*s disease and ulcerative colitis).

There is currently an ongoing induction and maintenance study in patients with moderate to severe CD (C13007). Study C13007 is approved in 41 countries, including The Netherlands, and has actively recruited approximately 1000 patients globally.

Study C13011 will be conducted to support registration of MLN0002 in the induction of clinical response and remission in patients with moderately to severely active CD, who have had an inadequate response to 1 or more therapies, including but not limited to TNFα antagonists. Following patient completion of the study, the patient may be eligible to receive open-label MLN0002 by enrolling in a long-term safety study (protocol C13008, Amendment 5). This study is also approved in 41 countries and actively recruiting subjects globally. Protocol C13008, Amendment 5, is pending submission in the Netherlands for review and approval.

Study objective

Primary Objective
• To determine the effect of vedolizumab induction treatment on clinical

remission at Week 6 in the subgroup of patients defined as having failed tumor necrosis factor alpha (TNFa) antagonist therapy (TNFa subpopulation)

Secondary Objectives
• To determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in the entire study population
• To determine the effect of vedolizumab induction treatment on clinical remission at Week 10 in the TNF* subpopulation and in the entire study population
• To determine the effect of vedolizumab induction treatment on sustained clinical remission (ie, clinical remission at both Week 6 and Week 10) in the TNF* subpopulation and in the entire study population
• To determine the effect of vedolizumab induction treatment on enhanced clinical response at Week 6 in the TNF* subpopulation

Study design

This phase 3, randomized, blinded, placebo-controlled study in patients with moderately to severely active CD is designed to establish the efficacy and safety of vedolizumab for the induction of clinical response and remission.
Patients will be randomized 1:1 to receive either 300 mg vedolizumab or placebo intravenously (IV) at Weeks 0, 2, and 6. The randomization to treatment assignment will be stratified by:
• Previous failure of TNF* antagonist therapy
• Concomitant use of oral corticosteroids
• Concomitant use of immunomodulator (6-mercaptopurine, azathioprine, or methotrexate)
After completing the Week-10 assessments, patients will be eligible to enroll in Study C13008 (open-label, long-term safety study) if study drug was well tolerated (eg, if there was no study drug-related adverse event leading to discontinuation) and no major surgical intervention for CD occurred or is required (see Section 5.2.1 of the full protocol for details).
Patients who do not enroll in Study C13008, whether they complete Week 10 or withdraw early from the study, must complete the Final Safety visit (Week 22, or 16 weeks after the last dose of study drug). 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

see: study design above and the flowchart, protocol page: 5 - 9.

Study burden and risks

Potential Risks and Benefits (see: Protocol page 20-22) Summary of Risks and Benefits; CD. An integrated

safety analysis of healthy subjects and patients with UC or CD has demonstrated an acceptable safety profile for MLN0002. Phase 2 studies have demonstrated efficacy in CD. These data support a favorable benefit-to-risk profile for MLN0002.

Contacts

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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
1. Age 18 to 80.
2. Male or female patient who is voluntarily able to give informed consent.
3. Female patients who:
• Are postmenopausal for at least 1 year before screening, OR
• Are surgically sterile, OR

• If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form (ICF) 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 postvasectomy), 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 CD established at least 3 months before enrollment by clinical and endoscopic evidence and corroborated by a histopathology report. Cases of CD established at least 6 months before enrollment for which a histopathology report is not available will be considered based on the weight of the evidence supporting the diagnosis and excluding other potential diagnoses, and must be discussed with the sponsor*s (or designee*s) medical monitor on a case-by-case basis before enrollment.
5. Moderately to severely active CD as determined by a CDAI score of 220 to 400 within 7 days before enrollment and 1 of the following:
a. CRP level > 2.87 mg/L during the Screening period, OR
b. Ileocolonoscopy with 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) consistent with CD, within 4 months before enrollment, OR
c. Fecal calprotectin > 250 ug/g stool during the Screening period in conjunction with computed tomography (CT) enterography, magnetic resonance (MR) enterography, contrast-enhanced small bowel radiography, or wireless capsule endoscopy revealing Crohn*s ulcerations (aphthae not sufficient), within 4 months before screening. (Patients with evidence of fixed stenosis or small bowel stenosis with prestenotic dilation should not be included.)
6. CD involvement of the ileum and/or colon, at a minimum.
7. Patients with extensive colitis or pancolitis of > 8 years duration or limited colitis of > 12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months before enrollment (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 1of the following agents as defined below:
• 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 MP (>= 0.75 mg/kg), OR
o Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of methotrexate (>= 12.5 mg/week), OR
o History of intolerance of at least 1 immunomodulator (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, TPMT genetic mutation, infection).
• TNFa antagonists
o Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of 1 of the following agents:
* Infliximab: 5 mg/kg IV, 2 doses at least 2 weeks apart

* Adalimumab: one 80-mg subcutaneous (SC) dose, followed by one 40-mg dose, at least 2 weeks apart
* Certolizumab pegol: 400 mg SC, 2 doses at least 2 weeks apart, OR
o Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), OR
o History of intolerance of at least 1 TNFa antagonist (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, infection).;ONLY APPLICABLE TO PATIENTS OUTSIDE THE US (who may be enrolled on the basis of corticosteroid treatment history):
• 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 on 2 separate occasions, OR
o History of intolerance of corticosteroids (including, but not limited to, Cushing*s syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and 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 before enrollment
b. Oral corticosteroid therapy (prednisone at a stable dose <30 mg/day, budesonide at a stable dose < 9 mg/day, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately before enrollment if corticosteroids have just been initiated, or for the 2 weeks immediately before enrollment if corticosteroids are being tapered
c. Probiotics (eg, Culturelle, Saccharomyces boulardii) provided that the dose has been stable for the 2 weeks immediately before enrollment
d. Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
e. Azathioprine or 6-MP provided that the dose has been stable for the 8 weeks immediately before enrollment
f. Methotrexate provided that the dose has been stable for the 8 weeks immediately before enrollment
g. Antibiotics used for the treatment of CD (ie, ciprofloxacin, metronidazole) provided that the dose has been stable for the 2 weeks immediately before enrollment

Exclusion criteria

Exclusion Criteria
Gastrointestinal Exclusion Criteria
1. Evidence of abdominal abscess during screening
2. Extensive colonic resection or subtotal or total colectomy
3. History of > 3 small bowel resections or diagnosis of short bowel syndrome
4. Have received tube feeding, defined formula diets, or parenteral alimentation within 21 days before enrollment
5. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
6. Within 30 days before enrollment, have received any of the following for the treatment of

underlying disease:
a. Nonbiologic therapies (eg, cyclosporine, thalidomide) other than those specifically listed in Section 6.2.1 of the full protocol
b. A nonbiologic investigational therapy
c. An approved nonbiologic therapy in an investigational protocol
d. Adalimumab
7. Within 60 days before enrollment, have received any of the following:
a. Infliximab
b. Certolizumab pegol
c. Any other investigational or approved biological agent, other than local administration for non-IBD conditions (eg, intra-ocular injections)
8. Any prior exposure to natalizumab, efalizumab, or rituximab
9. Use of topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories within 2 weeks before enrollment
10. Evidence of or treatment for C. difficile infection or other intestinal pathogen within 28 days before enrollment
11. Currently require or are anticipated to require major surgical intervention for CD (eg, bowel resection) during the study. (Minor surgical procedures to treat complications of CD [eg, fistulotomy] are acceptable.)
12. History or evidence of adenomatous colonic polyps that have not been removed
13. History or evidence of colonic mucosal dysplasia
14. Diagnosis of ulcerative colitis or indeterminate colitis
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 TB test defined as:
i. A positive QuantiFERON* test or 2 successive indeterminate QuantiFERON* tests within 1 month before enrollment, OR
ii. A tuberculin skin test reaction > 10 mm (> 5 mm in patients receiving the equivalent of > 15 mg/day prednisone) within 3 months before enrollment
c. Chest X-ray within 3 months before enrollment in which active or latent pulmonary TB cannot be excluded
3. Any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation)
4. Any live vaccinations within 30 days before enrollment except for the influenza vaccine
5. Clinically significant extra-intestinal infection (eg, pneumonia, pyelonephritis) within 30 days before screening or during screening
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 before enrollment.
3. Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, 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 (eg, endotracheal) anesthesia within 30 days before enrollment or is planning to undergo major surgery during the study period.
5. Any history of malignancy, except for the following: (a) adequately treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year before enrollment; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years before enrollment. Patients with remote history of malignancy (eg, > 10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor*s (or designee*s) medical monitor on a case-by-case basis before enrollment.
6. History of any major neurological disorders including, but not limited to, stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
7. Positive PML subjective symptom checklist before enrollment.
8. Any of the following laboratory abnormalities during the Screening period:
a. Hemoglobin level < 8 g/dL (80 g/L)
b. White blood cell (WBC) count < 3 x 10 3/uL (3 x 10 9/L)
c. Lymphocyte count < 0.5 x 10 3/uL (0.5 x 10 9/L)
d. Platelet count < 100 x 103/uL (100 x 10 9/L) or > 1200 x 10 3/uL (1200 x 10 9/L)
e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN)
f. Alkaline phosphatase > 3 x ULN
g. Serum creatinine > 2 x ULN
h. Albumin < 2.0 g/dL (< 20 g/L)
9. Current or recent history (within 1 year before 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):	31-12-2010
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	Vedolizumab

Ethics review

Approved WMO Date:	05-11-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2011

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2009-016488-12-NL
ClinicalTrials.gov	NCT01224171
CCMO	NL34356.078.10