A Phase 3, Open-label Study to Determine the Long-Term Safety and Efficacy of Vedolizumab (MLN0002) in Patients with Ulcerative Colitis and Crohn's Disease

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Study Objectives:Primary Objective* To determine the safety profile of long-term MLN0002 treatmentResource Utilization and Patient-Reported Outcome Objectives* To determine the effect of long-term MLN0002 treatment on time to major inflammatory...

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

Summary

ID

NL-OMON43573

Source
ToetsingOnline

Brief title
C13008_Vedolizumab (MLN0002) for patients with Inflammatory Bowel Disease

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's Disease/Inflammatory Bowel Disease, Ulcerative Colitis/ Inflammatory Bowel Disease

Research involving
Human

Sponsors and support

Primary sponsor: Takeda
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Crohn's Disease, MLN0002, Ulcerative Colitis, Vedolizumab

Outcome measures

Primary outcome

STUDY ENDPOINTS

Primary Endpoints

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

chemistry,

hematology, coagulation, urinalysis, and HAHA), and results of

electrocardiograms

(ECGs)

Secondary outcome

Resource Utilization and Patient Reported Outcome Endpoints

* Time to major IBD-related events (hospitalizations, surgeries, or procedures)

* Changes from baseline in IBDQ, SF-36, and EuroQual (EQ-5D) scores

Exploratory Endpoint

* Partial Mayo scores and HBI scores will be used to monitor changes in IBD

activity

during long-term MLN0002 treatment

Study description

Background summary

Ulcerative colitis (UC) is a relapsing, remitting inflammatory disease of the colonic mucosa and submucosa. The prevalence of UC is approximately 200/100,000 of population in the United States (US) and approximately 150/100,000 of population in Western Europe. A genetic contribution to the disease is indicated by the increased incidence of UC (of 30 to 100 times that of the general population) among first-degree relatives of patients with UC.
The characteristic pathology is one of chronic inflammation characterized by large numbers of lymphocytes and histiocytes in the diseased mucosa and submucosa with an acute inflammatory infiltrate composed of neutrophils variably present.
Crohn*s disease (CD) is a relapsing, remitting inflammatory disease that may involve any portion of the length of the gastrointestinal tract from mouth to anus in a transmural fashion from mucosa to serosa. The prevalence of CD is approximately 150/100,000 of population in the US and approximately 125/100,000 of population in Western Europe. The characteristic pathology involves a chronic inflammatory infiltrate consisting of neutrophils and macrophages. Hallmarks of CD include granulomatous inflammation and aphthous ulceration.
Clinical manifestations of both diseases include diarrhea (typically bloody in patients with UC), as well as abdominal pain, fecal urgency, and incontinence. Systemic features such as fever, weight loss, malaise, and fatigue are indicators of more extensive disease. Extraintestinal manifestations such as uveitis, arthritis, ankylosis spondylitis, or primary sclerosing cholangitis may also be seen in conjunction with inflammatory bowel disease (IBD). The diagnosis of UC or CD is usually made by histopathologic examination of endoscopic mucosal biopsy specimens obtained on ileocolonoscopy.
Current treatments have been effective for many patients with UC or CD but have numerous limitations for patients with moderate to severe disease.
5-Aminosalicylates (5-ASAs) are the mainstay of UC pharmacotherapy for induction and maintenance of remission for patients with mild to moderate disease, but are less effective in severe disease. The National Cooperative Crohn*s Disease Study demonstrated a role for sulfasalazine (a 5-ASA containing molecule) in moderate to severe Crohn*s disease , however, the efficacy of 5-ASAs in CD has been called into question by a recent meta analysis.
Corticosteroids are often required for the one-third of patients who fail to respond to 5-ASAs. While highly effective for induction of remission, corticosteroids are not useful in either disease for maintenance of remission and carry significant undesirable side effects, including osteoporosis, glucose intolerance, and increased risk of infection.
Immunomodulatory agents, including 6-mercaptopurine and azathioprine, have a

role in maintenance of remission in moderate to severe UC and moderate to severe CD. Their relatively slow onset of action precludes their use during flares of disease, and the use of these agents has been reported to potentially increase the risk of lymphoma in patients with IBD. Intravenous cyclosporine has a role in the management of severe UC; however, it is impractical in non-hospitalized patients, requires intense monitoring, and may cause irreversible nephrotoxicity, all of which limit its use to severe cases. Methotrexate, while ineffective in UC, has a role in the management of refractory CD; however, it also
demonstrates a number of dose-limiting toxicities. Antibiotics have marginal efficacy in maintenance of remission in CD and are not effective in UC.
Biologic agents, including monoclonal antibodies against tumor necrosis factor alpha (TNF*), such as infliximab (Remicade®) and adalimumab (Humira®), have been studied and have proven useful for both induction and maintenance of remission in CD. Infliximab is
also useful for induction and maintenance of remission in UC. However, only approximately one-third of patients have a sustained remission at one year following treatment with these agents. In addition, treatment with TNF* antagonists has been associated with a number of serious adverse events (SAEs) involving hypersensitivity and infection. Reactivations of latent tuberculosis (TB) and disseminated histoplasmosis have
been reported, and in some cases have been fatal. Induction of remission with infliximab occurs in only 31% to 39% of patients with UC and durable clinical remission (at 1 year) occurs in only 26% of patients with UC. Efficacy data for both infliximab and adalimumab
in CD are quite similar to the infliximab data in UC with only a minority of patients having a durable response at 1 year.
Failure of medical therapy leads to colectomy in 9% to 35% of patients with UC within 5 years. Colectomy is considered to be an important adjunct treatment for refractory UC;
however, colectomy with ileal pouch anal anastomosis (the standard surgical therapy) has many limitations and is associated with its own set of complications, including high stool frequency, female infertility, and a cumulative incidence of pouchitis of 50% at 10 years. Surgical removal of highly diseased, strictured, or stenotic segments of bowel in CD is not curative. Relapse occurs in a majority of patients with CD who undergo segmental resections, and the need for reoperation is the rule rather than the exception.
The limitations of current therapies for IBD indicate that there is a significant need for safer and more effective therapies. MLN0002 is being developed to fulfill this important unmet medical need.

Study objective

Study Objectives:
Primary Objective
* To determine the safety profile of long-term MLN0002 treatment

Resource Utilization and Patient-Reported Outcome Objectives
* To determine the effect of long-term MLN0002 treatment on time to major inflammatory bowel disease (IBD)-related events (hospitalizations, surgeries, and procedures)
* To examine the effect of long-term MLN0002 treatment on health-related quality of life (QOL) measurements

Study design

Overview of Study Design:
Following enrollment all patients will be administered 300 mg vedolizomab every 4 weeks for the duration of the study, followed by a 16-week posttreatment observation and safety assessment period. The total duration of MLN0002 treatment will vary by patient based on continued benefit until March 2016, or until vedolizumab is available in the country in which the patient resides, or until patient withdrawal, whichever is sooner.

Patients receiving oral corticosteroids will begin an oral corticosteroid tapering regimen once they achieve clinical response or if, in the opinion of the investigator, they demonstrate sufficient improvement in clinical signs and symptoms. After 6 months±
* patients still on oral corticosteroids should not exceed a daily oral corticosteriod dose of the equivalent of 5 mg/day of prednisone or 3 mg/day of budesonide. Attempts to taper and discontinue corticosteriods should continue, in clinically indicated.
* For patients who are otherwise doing well (in the opinion of the investigator) short-term oral corticosteriod courses (up to the equivalent of 30 mg/day of prednisone or 9 mg/day of budesonide) are permitted for documented disease exacerbations. In such instances, however, the dose must be tapered to the equivalent of 5mg/day of prednisone or 3 mg/day of budesonide within 3 months.

Patients who meet the criteria for treatment failure will be withdrawn from the study. In addition, patients who, in the opinion of the investigator or patient, are not benefiting from therapy will be withdrawn from the study; investigators should also consider withdrawing patients who require corticosteriod increases fot the control of their IBD more often than every 6 months.

Safety assessments and exploratory efficacy assessments (using the partial Mayo Score [for patients with UC] or the Harvey-Bradshaw Index (HBI) score [for patients with CD]) will be made throughout the treatment period, and at the Final Safety Visit/Early Termination visit. Serious adverse events (SAEs) and adverse events (AEs) will be collected throughout the study. Data pertaining to health care utilization and patient-reported outcomes will also be collected regularly throughout the study. In addition, safety data will be reviewed with reference to an external administrative database as part

of a separate observational study.

Intervention

see: study design above and the flowchart, protocol page: 5 - 8.

Study burden and risks

Potential Risks and Benefits (see: Protocol page 23-26)
Summary of Risks and Benefits
The integrated safety analysis for all completed and ongoing clinical studies (as of 10 March 2008) demonstrates that MLN0002 has an acceptable safety profile. Phase 2 studies have demonstrated efficacy in UC and CD. These data support a favorable benefit-to-risk profile
for MLN0002. In addition, based on its targeted mechanism of action, MLN0002 may prove to have a superior benefit-to-risk profile compared with conventional systemic immunosuppressive therapies for IBD, such as corticosteroids and TNF* antagonists. On this basis, as well as the risk management procedures implemented in this study, further investigation of this novel compound for the treatment of IBD is warranted.

Contacts

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Scientific
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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
Each patient must meet all of the following inclusion criteria to be enrolled in the study:
1. Voluntarily able to give informed consent.
2. Previous treatment in Study C13004, Study C13006, Study C13007 or Study C13011 that, in the
opinion of the investigator, was well tolerated. Patients who withdrew early from C13006 or C13007 must have withdrawn due to one of the following:
* Sustained Nonresponse for patients with UC in C13006: Failure to achieve a clinical response (2 point and 25% improvement in partial Mayo score) by Week 14 and a minimum partial Mayo score of *5 points
* Sustained Nonresponse for patients with CD in C13007: Failure to achieve a clinical response (70 point improvement in CDAI score) by Week 14 and a minimum CDAI score of 220 points
* Disease Worsening for patients with UC in C13006: An increase in partial Mayo score of *3 points on 2 consecutive visits from the Week 6 value (or an increase to 9 points on 2 consecutive visits if the Week 6 value >6) and a minimum partial Mayo score of *5 points
* Disease Worsening for patients with CD in C13007: A *100 point increase in CDAI score on 2 consecutive visits from the Week 6 value at any study visit and a minimum CDAI score of 220 points
* Required rescue medications for patients in C13006 and C13007 at week 14 or beyond. Requirement for rescue medication is defined as the receipt or need for any new medication or any increase in dose of a baseline medication required to treat new or unresolved UC or CD symptoms (other than antidiarrheals for control of chronic diarrhea). Patients who experienced treatment failure in Study C13006 or Study C13007 only as a result of receiving rescue medication (and without meeting the definition of Disease Worsening) before Week 14 are not eligible for Study C13008.
3. The first dose of MLN0002 in this study (ie, Week 0) must occur not more than 9 weeks after the last dose of study drug in the previous study; the preferable period is within 3 to 5 weeks after the last dose in the previous study.
4. Female patients who:
* are post-menopausal for at least 1 year before enrollment, 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 through 6 months after the last dose of MLN0002, 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 MLN0002, OR
* agree to completely abstain from heterosexual intercourse.
5. 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 of enrollment.
6. 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.
7. May be receiving a therapeutic dose of the following drugs:
a. Oral 5-ASA compounds
b. Oral corticosteroid therapy (prednisone at a stable dose *30 mg/day, budesonide at a stable dose *9 mg/day, or equivalent steroid)
c. Topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories
d. Probiotics (eg, Culturelle, Saccharomyces boulardii)
e. Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
f. Antibiotics used for the treatment of IBD (ie, ciprofloxacin, metronidazole).
g. Azathioprine, 6-mercaptopurine, or methotrexate (methotrexate for CD only).

Exclusion criteria

1. Female patients who are lactating or pregnant.
2. Had any surgical procedure requiring general anesthesia within 30 days prior to enrollment or is planning to undergo major surgery during the study period
3. Any live vaccinations within 30 days prior to MLN0002 administration except for the influenza vaccine.
4. Any new, unstable or uncontrolled major medical conditions that would confound study results or compromise patient safety
5. Withdrawal from a previous MLN0002 study due to a study-drug related AE.
6. Active psychiatric or substance abuse problems that, in the investigator's opinion, may interfere with compliance with the study procedures.
7. Unable to attend all the study visits or comply with study procedures

Study design

Design

Study phase: 3

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-02-2010
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
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:	19-06-2009
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:	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:	18-02-2011
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:	19-08-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO	

Date:	26-01-2012
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	15-05-2012
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	14-12-2015
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO	

Date:	25-04-2016
Application type:	Amendment
Review commission:	METC Atrium-Orbis-Zuyd
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	METC Atrium-Orbis-Zuyd

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	EUCTR2008-002784-14-NL
CCMO	NL25209.096.08