A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)

Published: 16-08-2016
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Primary Objective:To compare the efficacy of vedolizumab IV and placebo in terms of the percentage of subjects with chronic or recurrent pouchitis achieving clinically relevant remission.Secondary Objectives:To assess the efficacy of vedolizumab IV...

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

Summary

ID

NL-OMON47815

Source
ToetsingOnline

Brief title
Vedolizumab IV in the treatment of chronic pouchitis

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflamatory bowel disease, Ulcerative Colitis

Research involving
Human

Sponsors and support

Primary sponsor: Takeda Development Centre Europe, Ltd
Source(s) of monetary or material Support: Takeda Development Centre Europe Ltd.

Intervention

Keyword: Inflammatory Bowel Disease, Pouchitis, Ulcerative Colitis

Outcome measures

Primary outcome

The primary efficacy endpoint is the percentage of subjects with chronic or recurrent pouchitis achieving clinically relevant remission after 14 weeks of treatment. Clinically relevant remission will be defined as an mPDAI score <5 and a recution in overall score by >=2 points from Baseline.

Secondary outcome

- Percentage of subjects achieving mPDAI score <5 and a reduction of overall score by >=2 points from Baseline after 34 weeks of treatment (last dosing at week 30).
- Percentage of subjects achieving PDAI score <7 and a reduction of overall score by >=3 points from Baseline PDAI score after 14 weeks of treatment and after 34 weeks of treatment (last dosing at Week 30).
- Time to remission (defined as a PDAI score <7 and a decrease in PDAI score of >=3 points from Baseline).
- Percentage of subjects achieving a partial response (defined as a reduction in mPDAI score by >=2 points from Baseline) after 14 and after 34 weeks of treatment (last dosing at week 30).
- Change in PDAI endoscopic subscore at Weeks 14 and 34 compared to Baseline.

- Change in PDAI histologic subscore at Weeks 14 and 34 compared to Baseline.

- Change in total PDAI score at Weeks 14 and 34 compared to Baseline.

- Change in Inflammatory Bowel Disease Questionnaire (IBDQ), and Cleveland Global Quality of Life (CGQL, Fazio Score, 3 items) at Weeks 14, 22, and 34 compared to Baseline.

Study description

Background summary

The surgical treatment of choice for patients with ulcerative colitis (UC) is removal of the colon followed by construction of an ileal pouch anal anastomosis (IPAA). Inflammation of the *pouch,* commonly called pouchitis, is the most common long-term complication in these patients. Pouchitis is a poorly understood condition, with a reported cumulative frequency of 23% to 46% over 10 to 11 years in patients who underwent an ileoanal pouch procedure. Importantly, none of the experimental therapies have been shown to be effective in clinical trials. Furthermore, due to their nonspecific mechanism of action, use of some of these therapies may place patients at risk for infection complications. Chronic or recurrent pouchitis is often managed with long-term antibiotic administration, with metronidazole and ciprofloxacin being the antibiotics most often prescribed. There are presently no approved drugs for the treatment or prevention of pouchitis in the United States or Europe. Thus, a large unmet medical need exists in the management of refractory pouchitis. Therefore, well-designed prospective clinical trials specific for patients with chronic or recurrent pouchitis are needed.

Vedolizumab IV is approved for the treatment of adult patients with moderately to severely active UC and CD in several regions, including the United States and European Union. The current study will generate meaningful data with vedolizumab IV in the treatment of chronic or recurrent pouchitis.

Study objective

Primary Objective:
To compare the efficacy of vedolizumab IV and placebo in terms of the percentage of subjects with chronic or recurrent pouchitis achieving clinically relevant remission.

Secondary Objectives:

To assess the efficacy of vedolizumab IV by:
- Percentage of subjects achieving mPDAI <5 and a reduction of overall score by >=2 points from Baseline.
- Percentage of subjects achieving PDAI <7 and a reduction of overall score by >=3 points from Baseline.
- Time to remission (defined as a PDAI score <7 and a decrease in PDAI score of >=3 points from Baseline).
- Percentage of subjects achieving a partial response (defined as reduction of mPDAI score by >=2 points from
Baseline).
- Change in PDAI endoscopic subscore.
- Change in PDAI histologic subscore.
- Change in total PDAI.
- Change in Inflammatory Bowel Disease Questionnaire (IBDQ), and Cleveland Global Quality of Life (CGQL,
Fazio Score, 3 items).

Exploratory Objectives:
- To assess the change in Robarts Histopathology Index (RHI).
- To assess change in biomarkers (fecal calprotectin and C-reactive protein [CRP]).
- Time to relapse of pouchitis symptoms and number of relapses.

Safety Objective:
To assess the safety of vedolizumab IV in chronic or recurrent pouchitis.

Study design

Phase 4, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vedolizumab 300 mg intravenous (IV) infusion during a 34-week treatment period (with last dose at Week 30) using pouch endoscopy. Approximately 110 subjects with a proctocolectomy and ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC) who have developed chronic or recurrent pouchitis will be enrolled.

Chronic or recurrent pouchitis is defined as a modified Pouchitis Disease Activity Index (mPDAI) score >=5 assessed as the average from 3 days immediately prior to the Baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either:
(a) >=3 recurrent episodes within 1 year prior to the Screening visit, each treated with >=2 weeks of antibiotic or other prescription therapy, or
(b) requiring maintenance antibiotic therapy taken continuously for >=4 weeks immediately prior to the Baseline Endoscopy Visit.

Subjects will be randomized in a 1:1 ratio to either the approved UC vedolizumab dose regimen or placebo treatment at Day 1, Weeks 2, 6, 14, 22, and 30. All subjects will receive concomitant antibiotic treatment with

ciprofloxacin 500 mg twice daily from randomization through Week 4. Efficacy will be assessed at Week 14 and Week 34.

Intervention

Group 1: Vedolizumab Intravenously 300 mg at Day 1, Weeks 2, 6, 14, 22, and 30.
Group 2: Placebo Intravenously at Day 1, Weeks 2, 6, 14, 22, and 30.

All subjects will receive ciprofloxacin 500 mg twice daily through Week 4. Additional ciprofloxacin will be allowed, as needed, for flares after Week 14.

Study burden and risks

As of 19 November 2016, no side effects have been seen in more than 20% of subjects of 4200 subjects who received at least 1 dose of vedolizumab in the IV clinical trials.

Other side effects, reported in 2-9% of patients, include:
• nausea.
• fever.
• stomach pain.
• upper respiratory tract infection.
• tiredness.
• vomiting.
• low levels of red blood cells (anemia).
• cough.
• back pain.
• Bronchitis.
• flu.
• urinary tract infection.
• dizziness.
• diarrhea.
• sinus infection.
• flu-like illness.
• rash.
• sore throat.
• itching.
• swollen ankles.
• pains in arms or legs.
• stomach flu.
• an infected cavity filled with pus near the anus or rectum (anal abscess).
• small tunnel which connects an infected gland inside the anus to an opening on the skin around the anus (anal fistula).

Since many of these symptoms are commonly reported in patients with UC or CD, it is unclear which may be related to vedolizumab, which may be related to the

underlying illness, and which may have occurred by chance.

In addition to the risks listed above, vedolizumab and study procedures may have unknown risks. There is always the possibility that the patient will have a side effect that is currently unknown or not expected.

As with any drug, allergic reactions may occur. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction are:
• a rash (reddening or blistering of the skin).
• Difficulty breathing.
• wheezing when you breathe.
• sudden drop in blood pressure.
• swelling around the mouth, throat, or eyes.
• fast pulse.
• sweating.

There is a possibility of a greater chance of getting an infection, difficulty fighting off an infection, or reactivation of an old infection.

There is a possibility that treatment with vedolizumab could cause reactivation of an old infection such as tuberculosis (TB).

Patients with inflammatory bowel disease have an increased risk for colon cancer, and some of the drugs that are currently being used for treating CD and UC can increase the risk of certain cancers. Less than 1% of patients who received vedolizumab as part of the UC and CD studies were diagnosed with cancer, including colon cancer. It is also not known whether the events of cancer happened by chance or whether vedolizumab was a contributing factor.

No cases of Progressive Multifocal Leukoencephalopathy (PML), a serious and sometimes fatal brain infection, have been reported in people receiving vedolizumab. There is currently not enough information to know if vedolizumab will increase the risk of PML and a risk of PML cannot be ruled out.

Deaths have occurred in patients participating in vedolizumab clinical trials. The details of these cases were reviewed by an Independent Safety Monitoring Board that oversaw the safety of these patient studies. No changes in monitoring of the trials were recommended by the Board.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female subjects 18 to 80 years, inclusive.
- History of IPAA for UC completed at least 1 year prior to the Day 1 (Randomization) Visit.
Pouchitis that is chronic or recurrent, defined by an mPDAI score >=5 assessed as the average from 3 days immediately prior to the Baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either (a) >=3 recurrent episodes within 1 year prior to the Screening Period treated with >=2 weeks of antibiotic or other prescription therapy, or (b) requiring maintenance antibiotic therapy taken continuously for >=4 weeks immediately prior to the Baseline Endoscopy Visit.

Exclusion criteria

- Crohn*s disease (CD), CD of the pouch, irritable pouch syndrome (IPS), isolated or predominant cuffitis, diverting stoma, or mechanical complications

of the pouch.
- Previous treatment with vedolizumab, natalizumab, efalizumab, rituximab, etrolizumab, or anti-mucosal addressin cell adhesion molecule-1 (MAdCAM-1) therapy.
- Any investigational or approved biologic or biosimilar agent within 60 days of randomization.
- Nonbiologic investigational therapy within 30 days prior to randomization.
- Active or latent tuberculosis.
- Chronic hepatitis B virus (HBV) infection or chronic hepatitis C virus (HCV) infection or a known history of human immunodeficiency virus (HIV) infection (or is found to be seropositive at Screening) or subject is immunodeficient.
- Active, severe infection.
- Positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist at Screening.

Study design

Design

Study phase:	4
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):	07-12-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Entyvio

Generic name:	Vedolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-08-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-10-2020
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	EUCTR2015-003472-78-NL
CCMO	NL57329.018.16

Study results

Date completed: 01-11-2019

Actual enrolment: 10

Summary results
Trial is onging in other countries