A Randomized DoubleBlind Phase 4 Study to Evaluate the Safety and Proportion of Subjects With Fistula Healing in 2 Dose Regimens of Entyvio (Vedolizumab IV) in the Treatment of Fistulizing Crohn*s Disease (ENTERPRISE)

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Primary Objectives:To evaluate the proportion of subjects with fistula healing at Week 30 with 2 different dose regimens of vedolizumab IV 300 mg in subjects with perianal fistulizing CD.Secondary Objective:To evaluate fistula healing over a 30-week...

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

Summary

ID

NL-OMON45760

Source
ToetsingOnline

Brief title
Vedolizumab IV 300 mg in the Treatment of Fistulizing Crohn's Disease

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn Disease, inflamatory bowel disease

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: Crohn Disease, Fistulas, Inflammatory Bowel Diseases

Outcome measures

Primary outcome

The primary endpoint for this study is the proportion of subjects with a reduction of at least 50% from Day 1 in number of draining perianal fistulae at Week 30 (where closed fistulae are no longer draining despite gentle finger compression).

Secondary outcome

- The proportion of subjects with a reduction of at least 50% from Day 1 in the number of draining perianal fistulae at both Week 22 and Week 30 (where closed fistulae are no longer draining despite gentle finger compression).

-The proportion of subjects with 100% perianal fistulae closure at Week 30 (where all fistulae are no longer draining despite gentle finger compression).

-Time to first perianal fistula closure.

-Time to last (100%) perianal fistulae closure.

-Duration of perianal fistula response (eg, number of days with drainage).

Study description

Background summary

Crohn Disease (CD) is focal, may be transmural, and can involve any segment of the gastrointestinal tract from mouth to anus. CD is neither medically or surgically curable at the current time. Fistulizing disease complicates CD in up to 40% of patients. Patients with fistulizing CD experience symptoms of anal pain, purulent discharge, and incontinence, which result in high morbidity and impaired quality of life.

Fistulae rarely heal spontaneously and usually require medical therapy or surgery. Although a range of medical and surgical options is available for CD, the management of perianal CD is challenging and often requires a comprehensive approach including medical and surgical interventions. Well-designed prospective clinical trials specific to the fistulizing CD patient population are needed. The current study will generate meaningful data with vedolizumab IV in the treatment of perianal fistula(e) and is expected to provide guidance on an optimal dose regimen for this complex patient population.

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.

Study objective

Primary Objectives:
To evaluate the proportion of subjects with fistula healing at Week 30 with 2 different dose regimens of vedolizumab IV 300 mg in subjects with perianal fistulizing CD.

Secondary Objective:
To evaluate fistula healing over a 30-week evaluation period.

Study design

This is a phase 4 randomized double-blind multicenter study to evaluate the safety and the proportion of subjects with fistula healing in 2 dose regimens of Entyvio (vedolizumab IV) over a 30-week treatment period (with the last dose at Week 22). Approximately 100 subjects with moderately to severely active Crohn*s disease (CD) with 1 to 3 draining perianal fistula(e) will be enrolled. Subjects must have historically had an inadequate response with, lost response to, or been intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNF-α) antagonist for their underlying CD to be eligible. Subjects will be followed for a total of 48 weeks.

Intervention

Group 1: Vedolizumab IV 300 mg dose at Weeks 0, 2, 6, 14 and 22, and a placebo infusion at Week 10.
Group 2: Vedolizumab IV 300 mg dose at Weeks 0, 2, 6, 10, 14 and 22.

Participants will be required to take oral antibiotic medication from Day 1 till Week 6.

Study burden and risks

All drugs have the possibility of complications and undesirable side effects that are unknown at this time and could possibly occur. There may be risks from the study medication to an unborn child or breast-feeding infant that are not currently known.

As of 19 november 2016 approximately 4200 subjects have received at least 1 dose of , vedolizumab in clinical trials and approximately 1832 subjects have received 12 months of vedolizumab in clinical trials. In IV studies to date, vedolizumab has been well tolerated.
The most common side effects from controlled clinical trials, reported in 10% - 20% of patients, include:

• worsening of Crohn*s disease in patients with Crohn*s disease.
• worsening of ulcerative colitis in patients with ulcerative colitis
• common cold
• headache
• joint pains

No side effects have been seen in more than 20% of subjects who received at least 1 dose of vedolizumab.
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.
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. Serious infections have occurred. 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.

Risks associated with infusion site reactions (IV administration)
Symptoms associated with an infusion site reaction may include redness, tenderness, warmth, itching, or discomfort. An additional risk could occur as a result of the medication leaking out from the blood vessel where it was infused which would cause pain, blistering, and severe skin damage.

Risks associated with Electrocardiograms (ECGs)
There is no pain or discomfort during an ECG; however the patches may cause a skin reaction such as redness or itching. Taking the pads off may cause localized irritation to the skin and/or hair loss, similar to having a bandage taken off.

Risks associated with blood draws
Although rare, excess bleeding, clots and infections at the injection site may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood is taken.

Risks associated with an MRI
The risks and discomforts associated with the MRI test are:
• Nausea, vomiting, bloating, or rectal irritation caused by the bowel cleanse prep (common).
• Abdominal bloating (common) from drinking fluid prior to scan.
• Discomfort from lying on the scanner table or the noise during the scan.
• Feeling of being closed in while in the large tube of the scanner (claustrophobic). If you feel too claustrophobic, the test can be stopped.
• Allergic reaction to medication used to slow bowel motion (rare).
• Potential side effects of injected MRI contrast agent.
• Irritation, bruising or infection (rare) at the injection site for the bowel medication or MRI contrast.

Risks associated with a brain MRI
• Discomfort from lying on the scanner table or the noise during the scan.
• Feeling of being closed in while in the large tube of the scanner (claustrophobic). If you feel too claustrophobic, the test can be stopped.
• Potential side effects of injected MRI contrast agent.
• Irritation, bruising or infection (rare) at the injection site for the MRI contrast.

Risks associated with spinal tap
• Bleeding into the spinal canal.
• Discomfort during the test.

• Headache after the test.
• Hypersensitivity to the anesthetic.
• Infection introduced by the needle.
• Increased risk of bleeding for people that take blood thinners.
• Nerve damage

Pregnancy, contraception and breastfeeding
There may be risks from the study medication to an unborn child or breast-feeding infant that are not currently known. Rarely, there have been reports of birth defects in children born to women who were exposed to vedolizumab. We do not know whether the birth defects are related to the use of vedolizumab. Due to unknown risks and potential harm to the unborn child/ infant, patients should not become pregnant, nurse a baby, or father a child while participating in this study and for 18 weeks after their last dose.

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

Adult subjects, aged 18 to 80 years, inclusive, with moderately to severely active CD and 1 to 3 draining perianal fistula(e) of at least 2 weeks duration.
Subjects who have historically had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist for their underlying CD (does not require treatment failure for currently active draining fistula); for subjects from France only: subjects who have historically failed (ie, had an inadequate response with, lost response to, or was intolerant to) infliximab for treatment of their underlying CD or fistulizing CD.

Exclusion criteria

Subjects who have perianal abscesses greater than 2 cm or an abscess that the investigator feels requires drainage based on either clinical assessment or MRI.
Subjects who have a CDAI score greater than 400.
Subjects who have ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.
Subjects who have significant anal or rectal stenosis.
Subjects who have any evidence of an active infection (eg, sepsis, cytomegalovirus, or listeriosis) during screening, other than related to the fistula(e).
Subjects who have a positive progressive multifocal leukoencephalopathy (PML) subjective checklist.
Subjects who have received any investigational or approved biologic or biosimilar agent within 60 days of randomization.
Subjects who have had prior exposure to vedolizumab, natalizumab, efalizumab, rituximab, etrolizumab, or antimucosal addressin cell adhesion molecule-1 (MAdCAM-1) therapy.
Subjects who have active or latent tuberculosis.
Subjects who have a known history of hepatitis B virus (HBV), hepatitis C virus (HCV), acquired human immunodeficiency virus (HIV), or are found to be seropositive 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):	14-12-2016
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:	30-05-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2016
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:	17-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2018
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	EUCTR201500085212-NL
ClinicalTrials.gov	NCT02630966
CCMO	NL57591.018.16