A Phase 2b, Extension Study to Determine the Long-term Safety of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn*s Disease.;(Long-term Safety With Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn*s Disease)

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Primary Objective: • To determine the safety profile of long-term vedolizumab IV treatment in pediatric subjects with UC or CD.Secondary Objectives:• To determine the effect of long-term vedolizumab IV treatment on time to major inflammatory bowel...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON48714

Source
ToetsingOnline

Brief title
Hubble Zoom

Condition

- Gastrointestinal inflammatory conditions

Synonym
Ulcerative Colitis (UC); Crohn's Disease (CD)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Crohn's Disease (CD), Ulcerative Colitis (UC)

Outcome measures

Primary outcome

The primary endpoint for this study is percentage of subjects with

treatment-emergent adverse events (TEAEs).

Secondary outcome

The secondary endpoints for this study are:

• Percentage of UC subjects who, at Week 32, achieve and maintain clinical

response based on complete Mayo score, as defined by a continued reduction in

complete Mayo score of >=3 points from the baseline (at initiation of

MLN0002-2003) and continued decrease in rectal bleeding subscore of >=1 point

from baseline, or absolute rectal bleeding subscore of <=1 point at Week 32.

• Percentage of CD subjects who, at Week 32, achieve and maintain clinical

response as defined by a 50% reduction in SES-CD score on endoscopy compared to

the baseline endoscopy (at initiation of MLN0002-2003); and continued reduction

in CDAI that is a >=70 point decrease from the baseline CDAI score at the

initiation of MLN0002-2003.

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

• Changes from Baseline in IMPACT-III (where translations are available) total

and subscale scores at Week 24 and every 24 weeks, thereafter.

• Height velocity at Week 48 and every 48 weeks, thereafter.

• Change from Baseline in height, weight, and body mass index (BMI) at Week 24

and every 24 weeks, thereafter.

• Percentage of subjects achieving Tanner stage V at or before age 16 years

(females) or 17 years (males).

Study description

Background summary

Takeda Development Centre Europe Ltd., the study Sponsor, is paying the study hospital and the study doctor to carry out this research study. Approximately 80 children from 2-17 years old from about 72 study centers from around the world will take part in the research study. Approximately half will have CD and the other half will have UC.

Vedolizumab, the study drug, has been approved in several regions, including the United States (US) and European Union (EU) for the treatment of adult patients with moderately to severely active CD or UC who have had an inadequate response to, loss of response to, or intolerance to conventional treatments.

The use of vedolizumab in children has not been approved by regulatory agencies and therefore when used during research it is considered an investigational drug. Vedolizumab has not yet been tested in children in a research study. Vedolizumab may be referred to as *the study drug*.

Ulcerative colitis (UC) is a condition that affects the large bowel and the rectum which is the end of the bowel where the stools are stored. The condition causes the inflammation of the lining of the large bowel and rectum, which can result in small ulcers developing. Symptoms of UC can include recurring diarrhoea that may include blood, pain in the stomach, loss of appetite, weight loss and tiredness.

Crohn*s disease (CD) is a condition that can affect any part of the digestive

system, anywhere from the mouth to the back passage. It commonly affects the end of the small bowel and start of the large bowel. The condition causes inflammation of these areas that result in symptoms such as diarrhoea which may include blood, pain in the stomach, loss of appetite, weight loss, fever and tiredness. Other problems may also occur as a result of CD such as mouth ulcers, skin rashes, red and sore eyes and swelling and joint pain.

Study objective

Primary Objective:
• To determine the safety profile of long-term vedolizumab IV treatment in pediatric subjects with UC or CD.

Secondary Objectives:
• To determine the effect of long-term vedolizumab IV treatment on time to major inflammatory bowel disease (IBD)-related events (hospitalizations, surgeries, and procedures) in pediatric subjects with UC or CD.
• To examine the effect of long-term vedolizumab IV treatment on health-related quality-of- life measurements in pediatric subjects with UC or CD.
• To determine the effect of long-term vedolizumab IV treatment on patterns of growth and development in pediatric subjects with UC or CD.

Study design

This is a phase 2b, open-label, long-term extension study enrolling male and female pediatric subjects with ulcerative colitis (UC) or Crohn*s disease (CD) who initiated vedolizumab intravenous (IV) treatment in the phase 2 Study MLN0002-2003 between the ages of 2 and 17 years, inclusive. To enter the open-label extension (OLE) study, subjects will have completed Study MLN0002-2003 and in the opinion of the investigator are expected to benefit from continued vedolizumab treatment. The study will evaluate the long-term safety of vedolizumab administered by IV infusion. The study will also evaluate the effect of long-term vedolizumab IV treatment on the time to major IBD-related events (hospitalizations, surgeries, or procedures), health-related quality-of-life measurements, patterns of growth and development, and exploratory efficacy measures.

Eligibility will be determined and informed consent/pediatric assent will be obtained on or after Week 14 of Study MLN0002-2003; relevant assessments from the Week 22 Visits (and endoscopy at Week 14) of Study MLN0002-2003 will be used as the predose assessments for this OLE study. Subjects will be administered vedolizumab IV once every 8 weeks (Q8W) at the dose administered at Week 14 in Study MLN0002-2003. Subjects who experience disease worsening while receiving the low dose may be escalated to the high dose at the investigator*s discretion. After completion of the MLN0002-2003 study, subjects who have their dose increased based on nonresponse should be dosed based on

weight at the time of nonresponse. Blood samples will be collected every 8 weeks to assess pharmacokinetics (PK); the presence of antivedolizumab antibodies (AVA) will be assessed every 16 weeks. The study will include an 18-week Follow-up Period (Final Safety Visit) and a long-term follow-up safety survey by telephone, 6 months after the subject*s last dose of study drug, for all subjects including those who discontinue the study.

Intervention

Subjects who weigh >=30 kg will receive vedolizumab IV 300 mg (high dose) or 150 mg (low dose) Q8W.
Subjects who weigh <30 kg will receive vedolizumab IV 200 mg (high dose) or 100 mg (low dose) Q8W.

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; therefore it is important to read the section on pregnancy carefully, even if the patient is a male.

Vedolizumab side effects
The patient will receive vedolizumab, the study drug. During the study the patient should not take any other medications without talking to the study doctor/staff. This includes over the counter medications, herbal preparations (tablets, capsules, etc.) or vitamins. As of 19 November 2016, more than 4200 adult subjects have received at least 1 dose of vedolizumab in clinical trials and 1832 subjects have received at least 12 months of vedolizumab exposure. In intravenous studies to date, vedolizumab has been well tolerated.

The most common side effects from controlled clinical trials, reported in 10% -20% of adult patients, include:
• worsening of CD in patients with CD
• worsening of UC in patients with UC
• 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.

Risks associated with an endoscopy (flexible sigmoidoscopy or colonoscopy)
An ileocolonoscopy (also called a colonoscopy) or flexible sigmoidoscopy is an examination that looks at the inside of the colon (large intestine), rectum, and if an ileocolonoscopy is performed the exam may include the first part of

the small intestine as well as the large intestine and rectum. The examination uses a tool called a colonoscope or flexible sigmoidoscope. In preparation the patient will need to completely cleanse your intestines.

The patient will be provided with detailed instructions about the cleansing preparation, but in general it consists of drinking a large volume of a special cleansing solution or several days of a clear liquid diet and laxatives or enemas (fluid injection given through the rectum) prior to the examination. These instructions should be followed exactly as prescribed or the examination may be unsatisfactory.

On the day of the examination the patient may be given medicine prior to the examination to help the patient relax, or given a general anaesthetic; the patient could have some discomfort during the examination. The patient will lie on his left side with his knees drawn up toward his chest. The colonoscope or flexible sigmoidoscope is inserted into the anus and, under visual control, is gently moved into the rectum and through the colon. Air will be inserted through the scope to provide a better view and suction may be used to remove fluid or stool.

The patient may feel pressure as the scope moves inside. Following the examination, the patient will be kept in an observation area until the effects of the medications that have been given adequately wear off. Passing gas is necessary and should be expected. Feeling bloated and swollen are also common due to the air inflated into the bowel; this usually lasts only 30 to 60 minutes.

The following are possible discomforts or risks associated with a colonoscopy:
• Heavy or ongoing bleeding from biopsy or removal of polyp
• Cramping, pain, abdominal bloating
• Peritonitis (inflammation of the lining of the abdominal cavity)
• Perforation (a hole) of the intestinal wall. Surgery may be needed if a perforation occurs
• Nausea, vomiting, bloating, or rectal irritation caused by the bowel cleanse preparation
• Side effects, like drowsiness following sedative or pain medication

Risks associated with infusion site reactions (IV administration)
An infusion site reaction is a localized reaction that may occur along the vein or surrounding area where the medication is injected. 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. The patient should tell the study doctor/staff right away if the patient experiences any problems at the infusion site.

Risks associated with Electrocardiograms (ECGs)
An electrocardiogram (ECG) is a test that tells how the heart is working. The patient will have small, soft pads, placed temporarily on different parts of your body. 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
During the collection of blood samples, the patient may experience pain and/or bruising at the needle injection site. 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.

Vedolizumab side effects
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. It is not known if the side effects seen in adults will be similar to those seen in children.

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. It is important that the patient will report any and all symptoms/health problems to the study doctor/staff, whether or not they think these problems are related to the study drug. The patient will be monitored for side effects and the study doctor may decide that the patient should be withdrawn from the study for the patient's safety.

As with any drug, allergic reactions may occur. If the patient has a very bad allergic reaction, the patient 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

The study doctor/staff should be notified immediately if the patient has these or any other side effects during the study. The study doctor and team will be prepared to treat the patient if the patient has an allergic reaction.

There is possibility of a greater chance of getting an infection, difficulty fighting off an infection, or reactivation of an old infection. Serious infections have occurred. The patient will be monitored for infections and treated as needed. Please tell the patient's study doctor if the patient currently has, or has recently had, any of the following signs and/or symptoms which could be due to a serious infection:
• A sudden change in level of consciousness
• High or low temperature (>38.5 or <36°C)
• Fast heart beat
• Difficult or fast breathing
• Passing out or feeling faint
• Drowsiness or are difficult to wake up
• Unusual irritability
• Poor eating or drinking
• Seizure (fits)
• Sudden or dramatic increase in pain

There is a possibility that treatment with vedolizumab could cause reactivation of an old infection such as TB. The study doctor must be told if the patient has ever had or been treated for TB. Patients with long standing inflammation of the colon due to UC or CD 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.

As mentioned above, no cases of Progressive Multifocal Leukoencephalopathy (PML) 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. PML is caused by a virus called JCV (John Cunningham virus) that can infect the brain. Many people carry the virus but do not get sick from PML. When PML does occur, it is usually in people who have a weakened immune system and a decreased ability to fight off infection. PML usually causes death or severe disability. There is no proven treatment, prevention or cure for PML. During this study the patient will be monitored to see if you have any symptoms of PML. The patient will be instructed about the symptoms of PML. If the patient has any one of these symptoms, they must be reported to the study doctor immediately. The study doctor will be prepared to test the patient and send the patient to a specialist for further tests if needed. The specialist may order a brain scan called an MRI and may perform a spinal tap.

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 and were not felt to be due to vedolizumab. 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
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- The subject is male or female with UC or CD and was between 2 to 17 years, inclusive, at the time of their randomization in Study MLN0002-2003. (Note: A subject remains eligible to participate in this study after they reach 18 years of age if they continue to meet the inclusion criteria and do not meet any exclusion criteria.)
- The subject completed Study MLN0002-2003 and at Week 22, achieved clinical response as defined by a reduction of partial Mayo score of >=2 points and >=25% from Baseline, or a reduction of the PUCAI of >=20 points from baseline for subjects with UC; or a reduction of the CDAI as defined by a >=70-point decrease from Baseline or a decrease of PCDAI of >=15 points for subjects with CD.
- The subject may be receiving a therapeutic dose of the following drugs:
- Oral 5-aminosalicylic (5-ASA) compounds.
- Oral corticosteroid therapy (prednisone or equivalent steroid at a dose <=50 mg/day).
- Topical (rectal) treatment with 5-ASA or corticosteroids.
- Probiotics (eg, Saccharomyces boulardii).
- Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
- Antibiotics used for treatment of CD (eg, ciprofloxacin, metronidazole).
- Azathioprine, 6-mercaptopurine, or methotrexate provided the subject was receiving this medication during prior participation in Study MLN0002-2003.

Exclusion criteria

- The subject is female and is lactating or pregnant.
- The subject has hypersensitivity or allergies to vedolizumab or any of its excipients.
- The subject has withdrawn from Study MLN0002-2003.
- The subject has developed any new unstable or uncontrolled cardiovascular, heart failure moderate to severe (New York Class Association III or IV), pulmonary, hepatic, renal,

gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurological, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.
- The subject has a positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist prior to the administration of the first dose of study drug.
- The subject currently requires major surgical intervention for UC or CD (eg, bowel resection), or is anticipated to require major surgical intervention for UC or CD during the study.
- The subject has other serious comorbidities that will limit their ability to complete the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Entyvio
Generic name:	Vedolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	28-09-2017

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-03-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-002182-21-NL
ClinicalTrials.gov	NCT03196427
CCMO	NL62092.091.17