A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study, with a Vedolizumab IV Reference Arm, to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

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Primary:* To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active UC who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0...

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

Summary

ID

NL-OMON43689

Source
ToetsingOnline

Brief title
vedolizumab SC maintenance in Ulcerative Colitis [MLN0002SC-3027]

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammatory bowel disease, ulcerative colitis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Maintenance Therapy, Ulcerative Colitis, Vedolizumab SC

Outcome measures

Primary outcome

The primary endpoint for the study is the proportion of subjects with clinical remission, defined as a complete Mayo score of *2 points and no individual subscore >1 point, at Week 52.

Secondary outcome

Secondary endpoints for this study are:

* Proportion of subjects with mucosal healing, defined as Mayo endoscopic subscore of *1 point, at Week 52.

* Proportion of subjects with durable clinical response, defined as clinical response at Weeks 6 and 52, where clinical response is defined as a reduction in complete Mayo score of *3 points and *30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of *1 point or absolute rectal bleeding subscore of *1 point.

* Proportion of subjects with durable clinical remission, defined as clinical

remission at Weeks 6 and 52.

Study description

Background summary

Current treatments have been effective for many patients with UC but have numerous limitations for patients with moderately to severely active disease. These limitations indicate that there is a significant need for safer and more effective therapies. Vedolizumab (also called MLN0002) is a humanized immunoglobulin (Ig) G1 mAb developed as a treatment for UC and CD that acts as a gut-selective immunomodulator. The aim of the current study is to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in subjects with moderately to severely active UC who achieved a clinical response following open-label therapy with vedolizumab IV. The study includes a vedolizumab IV reference arm to allow for within study descriptive comparisons on efficacy, safety, and immunogenicity between the two vedolizumab presentations.

Study objective

Primary:
* To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active UC who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

Secondary:
* To determine the effect of vedolizumab SC maintenance treatment on mucosal healing at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To determine the effect of vedolizumab SC maintenance treatment on durable clinical response at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To determine the effect of vedolizumab SC maintenance treatment on durable clinical remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To determine the effect of vedolizumab SC maintenance treatment on corticosteroid free remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

Exploratory objectives:

* To assess the PK of multiple doses of vedolizumab SC maintenance treatment in subjects with moderately to severely active UC.
* To assess the immunogenicity of multiple doses of vedolizumab SC maintenance treatment in subjects with moderately to severely active UC who achieve clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To determine the effect of vedolizumab SC maintenance treatment on patient-reported outcomes (PRO) from Baseline to Week 52 and from Week 6 to Week 52 in subjects with moderately to severely active UC who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To determine the effect of vedolizumab SC maintenance treatment on time to major UC-related events (hospitalizations, colectomies, and procedures) at Week 52 in subjects with moderately to severely active UC who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To determine the effect of vedolizumab SC maintenance treatment on Work Productivity and Activity Impairment (WPAI-UC) from Baseline (Week 0) to Week 52 and from Week 6 to Week 52 in subjects with moderately to severely active UC who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To descriptively compare the efficacy, safety, and immunogenicity of the vedolizumab IV and vedolizumab SC presentations.
* To correlate UC-associated genetic polymorphisms and inflammation biomarkers with therapeutic response to vedolizumab SC maintenance treatment, if indicated.
* To determine the effect of vedolizumab SC maintenance treatment on histological remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To determine the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2 using an alternate definition on clinical remission.
* To determine the effect of vedolizumab SC maintenance treatment on achieving corticosteroid free status for 90 days and 180 days, respectively, at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
* To determine the effect of vedolizumab SC maintenance treatment on durable clinical remission at Week 52, where durable clinical remission is defined as clinical remission at Weeks 6 and 52 in subjects who achieved remission at Week 6.

Study design

This is a pivotal, phase 3, multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled trial, including a vedolizumab IV reference arm, designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in adult subjects with moderately to severely active UC who achieved a clinical response at Week 6 following open-label therapy with 300 mg vedolizumab IV administered at Weeks 0 and 2. The study

includes a vedolizumab IV reference arm to allow for within study descriptive comparisons on efficacy, safety, and immunogenicity between the two vedolizumab presentations.
Moderately to severely active UC is defined as a complete Mayo score of 6 to 12 points with endoscopic subscore of *2. Subjects that are tumor necrosis factor-alpha (TNF-*) antagonist naïve or with TNF-* antagonist failure will be included, ensuring that no more than 50% of subjects with TNF-* antagonist failure are enrolled.

Intervention

Following screening, all subjects that meet the entry criteria for the study will enter a 6-week induction phase during which they will receive 300 mg open label vedolizumab IV at weeks 0 and 2.

If at week 6 a clinical response is achieved, subjects will be randomized over 3 groups for the maintenance phase. 50% will receive vedolizumab SC injections and placebo infusions (group 1). 25% will receive placebo injections and vedolizumab IV infusions (group 2). 25% will receive placebo injections and placebo infusions (group 3).

During maintenance, subjects will receive 300 mg vedolizumab IV/placebo infusions at weeks 6, 14, 22, 30, 38 and 46. Including the induction phase, in total 8 infusions will be given during the course of the study.

During maintenance, subjects will receive 108 mg vedolizumab SC/placebo injections every 2 weeks from week 6 till week 50. In total, 23 injections will be given during the course of the study. Subjects will be trained to administer these injections themselves.

Study burden and risks

Including screening and follow-up the study will consist of 30 visits over a period of 68 weeks. These visits will partly be in the hospital and partly take place at home. The hospital will need to be visited at least 15 times. During the treatment period subjects will receive 8 infusions and 23 injections over a period of 50 weeks. The injections will largely be administered by subjects themselves. Subjects will need to maintain a daily electronic diary throughout the study up until week 52 and complete 3 questionnaires at 5 study visits. Procedures will among others include 3 flexible sigmoidoscopies, 2 ECGs and collection of blood (15x), stool (4x) and urine (4x) samples. As part of the study screening subjects will be tested for HIV and Hepatitis B/C and be informed of any positive result.
The most common side effects of the study drug, reported in more than 10% of patients, include common cold, headache, joint pains and worsening of Crohn*s disease in patients with Crohn*s disease. To address the theoretical risk of

the development of PML in subjects treated with vedolizumab, a Risk Minimization Action Plan for PML will be implemented.

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

1. The subject has a diagnosis of UC established at least 6 months prior to screening, by clinical and endoscopic evidence and corroborated by a histopathology report.;2. The subject has moderately to severely active UC as determined by a complete Mayo score of 6-12 with an endoscopic subscore *2 within 10 days prior to the first dose of study drug.;3. The subject has evidence of UC extending proximal to the rectum (*15 cm of involved colon).;4. The subject has demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents: immunomodulators, corticosteroids, or TNF-alpha antagonist.

Exclusion criteria

1. The subject has evidence of abdominal abscess or toxic megacolon at the initial Screening Visit.;2. The subject has had extensive colonic resection, subtotal or total colectomy.;3. The subject has had ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.;4. The subject has received any of the investigational or approved non-biologic therapies (eg, cyclosporine, tacrolimus, thalidomide, methotrexate or tofacitinib, except for those specifically listed in the protocol) for the treatment of underlying disease within 30 days or 5 half-lives of screening (whichever is longer).;5. The subject has received any investigational or approved biologic or biosimilar agent within 60 days or 5 half-lives of screening (which ever is longer). ;6. The subject currently requires or is anticipated to require surgical intervention for UC during the study.;7. The subject has a history or evidence of adenomatous colonic polyps that have not been removed, or has a history or evidence of colonic mucosal dysplasia.;8. The subject has a suspected or confirmed diagnosis of Crohn*s entercolitis, indeterminate colitis, ischaemic colitis, radiation colitis, diverticular disease associated with colitis, or microscopic colitis.;9. The subject has evidence of an active infection during the Screening Period.;10. The subject has evidence of, or treatment for, C. difficile infection or other intestinal pathogen with 28 days prior to first dose of study drug. ;11. The subject has chronic hepatitis B virus (HBV) infection or chronic hepatitis C virus (HCV) infection. HBV immune subjects (ie, being hepatitis B surface antigen [HBsAg] negative and hepatitis B antibody positive) may, however, be included.;12. The subject has active or latent TB as evidenced by the following:
i. A positive diagnostic TB test within 30 days prior to screening or during the Screening Period, defined as:
1. A positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests, (or, A positive T-SPOT TB test [Japan only]), OR,
2. A tuberculin skin test reaction *5 mm.
Note: if subjects have received BCG vaccine then a QuantiFERON TB Gold test should be performed instead of the tuberculin skin test.
OR
ii. Chest X-ray within 3 months prior to Week 0 which is suspicious for pulmonary TB, and a positive or 2 successive indeterminate QuantiFERON tests (or, A positive T-SPOT TB test [Japan only]) within 30 days prior to Screening or during the Screening Period.
Note: subjects with documented previously treated TB with a negative QuantiFERON test can be included in the study.;13. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).;14. The subject has received any live vaccinations within 30 days prior to screening.;15. The subject had a clinically significant infection (eg, pneumonia, pyelonephritis) within 30 days prior to screening, or ongoing chronic infection.;16. The subject has used a topical (rectal) treatment with 5-aminosalicylic acid (5-ASA) or corticosteroid enemas/suppositories within 2 weeks of the administration of the first dose of study drug.

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):	27-09-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	29-12-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	21-03-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2015-000480-14-NL
ClinicalTrials.gov	NCT02611830
CCMO	NL55501.056.15