# VERDICT: In actiVE ulcerative colitis, a RanDomIzed Controlled Trial for determination of the optimal treatment target

Published: 02-04-2021
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This study has been transitioned to CTIS with ID 2024-514183-21-00 check the CTIS register for the current data. The primary objective of this trial is to determine whether, in subjects with moderately to severely active UC, treating to achieve a...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Gastrointestinal inflammatory conditions |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON51131

**Source**
ToetsingOnline

**Brief title**
VERDICT

### Condition

- Gastrointestinal inflammatory conditions

**Synonym**
Chronic inflammatory bowl disease, Ulcerative colitis

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Alimentiv B.V.

**Source(s) of monetary or material Support:** Takeda Development Center Americas Inc

## Intervention

**Keyword:** Optimal treatment target, Ulcerative Colitis

## Outcome measures

### Primary outcome

The primary efficacy evaluation is time to UC-related complication according to the achieved-target population, defined by the subset who met their assigned treatment targets. Time to UC-related complication starts from the point the subjects reach their assigned targets. The primary comparison is between subjects randomized to the treatment target of corticosteroid-free symptomatic + endoscopic + histological remission (Group 3) and subjects randomized to the treatment target of corticosteroid-free symptomatic remission (Group 1). UC-related complication is defined as any of the following: 1) hospitalization for treatment of a UC flare; 2) a colectomy for UC (defined as a colectomy for chronic active or acute severe colitis, but not primarily for dysplasia); 3) rescue therapy (such as new initiation or dose intensification of a corticosteroid, TNF antagonist, vedolizumab, tofacitinib, or ustekinumab) for a documented UC flare 4) UC treatment-related complication; or 5) other UC disease-related complication. Time will be censored for subjects lost to follow-up or for subjects who do not experience a UC-related complication at the end of the study.

### Secondary outcome

The secondary outcome evaluations of the study will compare the treatment groups with regards to:

1. Time to UC-related complication in the full analysis set, including subgroups on and off corticosteroids at the time of achieving other relevant components of the treatment target

2. Whether treatment to the target of symptomatic + endoscopic remission (Group 2) is superior to a treatment target of symptomatic remission (Group 1) in terms of the primary endpoint (both in the full and the achieved target populations)

3. Whether treatment to the target of corticosteroid-free symptomatic + endoscopic + histological remission (Group 3) is superior to a treatment target of corticosteroid-free symptomatic + endoscopic remission (Group 2) in terms of the primary endpoint (both in the full and the achieved-target populations)

4. Time to UC-related complication (as in the primary outcome and secondary outcomes 2 and 3) in the subgroup of subjects who exclusively reach their assigned target and not a higher target by Week 48

5. Time taken to achieve the respective targets in each group.

6. Across the 3 randomized groups, time to each type of UC-related complication separately that comprises the primary endpoint 7. The effect of treatment(s) on UC-related complications that is mediated through treatment targets

8. Change in fecal calprotectin levels from baseline to Weeks 8, 16, 32, 48, and 96 (both in the full and the achieved-target populations)

9. Change in C-reactive protein (CRP) concentration from baseline to Weeks 8, 16, 32, 48, 64, 80, and 96 (both in the full and the achieved-target populations)

10. Change in the UC-100 score from baseline to Weeks 16, 32, 48, and 96 (both

in the full and the achieved target populations)

11. Change in health-related quality of life (HRQoL) using the Inflammatory Bowel Disease Questionnaire (IBDQ) from baseline to Weeks 16, 32, 48, 64, 80, and 96 (both in the full and the achieved-target populations)

12. Change in the Work Productivity and Activity Impairment-UC (WPAI-UC) questionnaire from baseline to Weeks 16, 32, 48, 64, 80, and 96 (both in the full and the achieved-target populations)

13. Change in Mayo Clinic Score (MCS; and subcomponents including the MES) from baseline to Weeks 16, 32, 48, and 96 (both in the full and the achieved-target populations)

14. Change in Geboes scores from baseline to Weeks 16, 32, 48, and 96 (both in the full and the achieved-target populations)

15. Change in Robarts Histopathology Index (RHI) scores from baseline to Weeks 16, 32, 48, and 96 (both in the full and the achieved-target populations)

16. Change in Nancy Histological Index scores from baseline to Weeks 16, 32, 48, and 96 (both in the full and the achieved-target populations)

17. The numbers of adverse events (AEs) and serious AEs among the 3 randomized groups

18. Evaluation of urine, stool, colonic mucosa, and serum samples for biomarkers and drug concentrations that are associated with clinically important outcomes

19. Validation of the Symptom and Impacts Questionnaire for Ulcerative Colitis (SIQ-UC) tool in English-fluent subjects

# Study description

**Background summary**

Disease activity and response to therapy in ulcerative colitis (UC) can be assessed by a range of endpoints including symptoms, endoscopic mucosal activity, histological disease activity, and biomarkers. Within the same subject, however, considerable discordance exists between these endpoints. Symptoms inherently have a degree of subjectivity and, if used alone for therapeutic decision making, are likely to lead to under or overtreatment of disease. Accordingly, consensus recommendations that define treatment targets in UC acknowledge that resolution of symptoms is not a sufficient treatment target and that objective evaluation of inflammation of the mucosa by endoscopy is necessary. It should be recognized that this recommendation is based on expert opinion in the absence of any controlled data to confirm that a treatment target of endoscopy is superior to one based on resolution of symptoms. Nevertheless, achievement of endoscopic mucosal healing is associated with lower rates of relapse, hospitalization, colectomy, and cancer.2-4 Furthermore, the combination of achieving clinical (symptomatic) and endoscopic remission in newly diagnosed subjects with UC has been shown to reduce rates of relapse, hospitalization, and colectomy compared to subjects achieving resolution of symptoms alone in up to 5 years of follow-up. While endoscopic mucosal healing is accepted as the treatment goal in UC, this treatment target is not *curative* and relapses are still observed in subjects who reach this objective, despite continuation of therapy. Importantly, histological disease activity persists in approximately one-quarter of subjects with normal appearing mucosa. Several studies now indicate strong associations between the achievement of histological disease remission and lower risk of corticosteroid use, hospitalization, and development of colorectal cancer, compared with endoscopic remission alone, suggesting that the concept of histological remission may be a distinct treatment target in UC. These observations have led clinicians to challenge existing concepts of deep remission and explore whether histological healing can confer additional prognostic benefit.

Attainment of histological improvement and/or remission in UC has been reported with several therapeutic classes of drugs including aminosalicylates, corticosteroids, biologics, and small molecules. In a small, open-label study of subjects with moderately to severely active UC, 35% of subjects achieved histological remission, defined as a Geboes score of <= 3.0, after 52 weeks of treatment with infliximab. Given the gut-selective mechanism of action, efficacy, and highly attractive safety profile, there is considerable interest in whether vedolizumab can improve these rates. In a post hoc analysis of 41 subjects from the GEMINI 1 and GEMINI long-term safety (LTS) studies, 55% of subjects who achieved endoscopic mucosal healing were also in histological

remission at Week 52, notwithstanding that remission was defined more stringently as a Geboes score of <= 1.

**Study objective**

This study has been transitioned to CTIS with ID 2024-514183-21-00 check the CTIS register for the current data.

The primary objective of this trial is to determine whether, in subjects with moderately to severely active UC, treating to achieve a target of corticosteroid-free symptomatic + endoscopic + histological remission is superior to a treatment target of corticosteroid-free symptomatic remission, with regards to a primary endpoint of time to UC-related complication within up to 80 weeks of follow-up after achieving target.

**Study design**

In this multicenter, controlled trial, subjects with active UC will be randomized to 1 of 3 groups, each with a different treatment target.
Group 1 will be treated to a target of corticosteroid-free symptomatic remission
Group 2 will be treated to a target of corticosteroid-free endoscopic + symptomatic remission
Group 3 will be treated to a target of corticosteroid-free histological + endoscopic + symptomatic remission.
Randomization will be stratified by the following factors: current corticosteroid use (yes; no), current immunosuppressive use (yes; no), and tumor necrosis factor (TNF) antagonist use (current; past; never).
Subjects will be followed up every 16 weeks of treatment to determine whether their assigned remission target has been achieved.
At Week 16, Week 32, and Week 48, there will be an assessment of symptoms, endoscopic disease, histological disease,
corticosteroid use and collection of urine, stool, mucosa, and blood samples for biomarkers and drug concentrations.
Treatment Algorithm
Treatment algorithms will feature the use of vedolizumab. A key premise is that vedolizumab has a favorable safety profile and can be safely and effectively used to treat subjects who are in symptomatic remission but who have not attained endoscopic or histopathologic remission.
Investigators will be trained on the algorithms and the 3 target groups. Study subjects will be blinded to target group assignment, whereas investigators will be unblinded. Investigators and site personnel must not share subject target group assignments or influence subject-reported symptom scores. Endoscopic and histopathologic assessments will be completed by central readers who are blinded to target group assignment. All endoscopy and histopathology images will be provided to an unblinded offsite assessor, along with details of corticosteroid use and visit; these will be used to inform the site

investigator regarding the need to escalate the algorithm. For the treat to symptom group, decisions will be based upon the subject*s self-reported symptoms of bleeding, as well as corticosteroid use.
If the subject has reached their remission target corticosteroid-free, no further treatment escalation will be required. If the remission target is reached but the subject is taking corticosteroids, the subject must taper steroids and continue therapy (if Week 16). If the remission target is not achieved, the subject will escalate therapy (if Week 32). If the remission target has not been reached, treatment will be escalated as per the algorithm and another assessment will take place 16 weeks later. There will be 3 opportunities, approximately 16 weeks apart, to escalate treatment according to the study algorithms. Once the remission target has been reached (corticosteroid-free) for a subject at a scheduled visit, he/she will continue therapy for the remainder of the follow-up visits. After Week 48, if the subject has not reached their remission target, subsequent therapies will be prescribed according to investigator judgement. Otherwise, subjects are expected to continue the same therapy from the time of achieving corticosteroid free remission target.

## Intervention

Group 1 will be treated to a target of corticosteroid-free symptomatic remission
Group 2 will be treated to a target of corticosteroid-free endoscopic + symptomatic remission
Group 3 will be treated to a target of corticosteroid-free histological + endoscopic + symptomatic remission.

## Study burden and risks

Participation in a trial involves some risk.
During the trial, depending on what (if any) UC treatments de patient is currently receiving and on how he responds to treatment he might receive vedolizumab. During the trial de patient should not take any other medications without talking to the investigator or trial staff. This includes over the counter medications, herbal preparations (tablets, capsules, etc.,) or vitamins. As of 19 May 2019 approximately 6376 subjects have received at least 1 dose of vedolizumab in clinical trials and approximately 2553 subjects have received 12 months of vedolizumab. In IV studies to date, vedolizumab has been well tolerated. No side effects have been seen in more than 20% of subjects who received at least 1 dose of vedolizumab.
Even if previous studies have shown that vedolizumab was normally well tolerated, patients might still experience the following side effects:
Very Common (10-20% of patients)
• worsening of ulcerative colitis in patients with UC • common cold • headache
• joint pains Common (2-9% of patients)

• 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, 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 a patient will have a side effect that is currently unknown or not expected. It is important that patients 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.
Patients will be monitored for side effects and the study doctor may decide that the patient should be withdrawn from the study for their safety. If any new information becomes available during the course of the study that may affect the patients willingness to participate, they will be informed.

As with any drug, allergic reactions may occur. If patients have a very bad allergic reaction, they 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 patient should notify the study doctor/staff immediately if they have these or any other side effects during the study. The study doctor and team will be prepared to treat the patient if he 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. The patient should notify their study doctor if they currently have, or have recently had, any infections or symptoms of an infection.
There is a possibility that treatment with vedolizumab could cause reactivation of an old infection such as tuberculosis (TB). Patients will be tested to see if they have ever been exposed to 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 UC can increase the risk of certain cancers.
Less than 1 % of patients who received vedolizumab as part of the UC 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. Progressive Multifocal Leukoencephalopathy (PML) is a serious and sometimes fatal brain infection. 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 they have any symptoms of PML. The patient will be instructed about the symptoms of PML. If they have any one of these symptoms, they must report them to the study doctor immediately. The study doctor will be prepared to test the patient and send him to a specialist for further tests if needed.
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.
The possible risks or discomforts of the examinations during the trial:
Below is described the study tests/procedures and their possible risks and/or discomforts: The patient is asked to ask the doctor if there is something they do not understand.
Blood samples: Pain. bruising and/or bleeding where the needle enters your vein. Some people feel light-headed or faint. Rarely blood taking can lead to swelling and/or infection of the vein.

Flexible Sigmoidoscopy: Cramping, pain, abdominal bloating (common).Peritonitis Onflammation of the lining of the abdominal cavity) (rare).
Perforation (a hole) of the intestinal wall (rare). Surgery may be needed if a perforation occurs (rare).
Intestinal biopsy: Persistent bleeding after biopsy or polyp removal (if taken) can occur. Biopsy results can identify a cancer of the intestine (bowel) you did not know about.

Stool sample: No discomfort/risk expected. Some may find stool collection unpleasant.
Video capture sigmoidoscopy: No discomfort/risk is expected from the video capture. Video images are identified by study identification number. There is the chance that the video images may accidentally identify you however that is not planned or expected.

Risks associated with infusion site reactions OV 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 need to tell the study

doctor/staff right away if he experiences any problems at the infusion site.

Risks associated with injection site reactions (Subcutaneous administration): An injection site reaction is a localized reaction that may occur at the site where the medication is injected. Symptoms associated with an injection site reaction may include redness, tenderness, warmth, itching, discomfort, bleeding, or a nodule or hardening of the skin in the area surrounding where the medication was administered or severe skin or tissue damage. The patient needs to tell the study doctor/staff rig

## 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

Subjects must meet each of the following criteria for enrollment into the study:

1. Age >= 18 years
2. Diagnosis of UC confirmed by clinical, endoscopic, and histological evidence prior to screening as per standard criteria
3. Moderately to severely active UC with a Mayo rectal bleeding subscore >= 1 and a MES >= 2, with minimum disease extent of 15 cm and objective evidence of inflammation that can be visualized using central endoscopic imaging system
4. Ability of subject to participate fully in all aspects of this clinical trial
5. Written informed consent must be obtained and documented
6. Agree not to participate in an investigational trial for the duration of the trial (observation or other noninterventional trials may be permitted at the discretion of the investigator)
7. Negative standard of care tuberculosis (TB) test and hepatitis B and C test prior to randomization, unless negative results available from within 12 months prior
8. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose
9. A female subject of childbearing potential* who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study and for 18 weeks after last dose
10. Up to date with colorectal carcinoma surveillance according to local standards and guidelines. If a subject is not up to date at screening, a standard of care surveillance assessment may be performed during the screening period.
11. Subjects who are not responding to their existing treatment for UC (Netherlands-specific criterion).

## Exclusion criteria

Subjects who exhibit any of the following conditions are ineligible for the study:
1. Subjects who have historically failed (i.e., had an inadequate response with, lost response to, or were intolerant to) 2 or more compounds or classes of advanced therapeutic options (biologics or small molecules; e.g., anti-TNFs, ustekinumab, or tofacitinib) for the treatment of their UC
2. Current or previous treatment with vedolizumab, etrolizumab, or natalizumab
3. Topical therapy (corticosteroid or 5-aminosalicylate [5-ASA]) use within 2 weeks prior to screening endoscopy
4. Change to oral corticosteroid dosing within 2 weeks prior to randomization or a corticosteroid dose of > 30 mg of prednisone or equivalent at randomization
5. Known diagnosis of CD, indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or microscopic colitis

6. Short gut syndrome
7. Positive stool culture for or active Clostridiodes difficile infection
8. Pregnant women
9. Known hepatitis B or C infection. If a negative test result is available in the 12 months prior to randomization, retesting is not required
10. Known active or latent TB. If a negative test results is available in the 12 months prior to randomization, confirmatory testing (per standard of care) is not required before randomization.
11. Received any investigational drug within 30 days prior to enrollment/target assignment
12. Serious underlying disease other than UC that in the opinion of the investigator may interfere with the subject*s ability to participate fully in the study or would compromise subject safety (such as history of malignancies, major neurological disorders, or any unstable or uncontrolled medical disorder)
13. History of alcohol or drug abuse that in the opinion of the investigator may interfere with the subject*s ability to comply with the study procedures
14. The subject has active cerebral/meningeal disease, signs, symptoms, or any history of progressive multifocal leukoencephalopathy (PML) prior to randomization
15. Hypersensitivity to any excipient of vedolizumab
16. History of HIV or positive test at screening (Italy-specific criterion).
17. Any other contraindication(s)to vedolizumab (Italy-specific criterion).
18. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after the last dose; or intending to donate ova during such time period.
19. If male, the subject intends to donate sperm during the course of this study or for 18 weeks after the last dose.
20. Vaccination with a live or live-attenuated vaccine within 4 weeks prior to randomization, or planned vaccination during conduct of the study, except vaccination for coronavirus disease of 2019 (COVID-19)

# Study design

## Design

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| Study phase: | 4 |
| Study type: | Interventional |
| Masking: | Single blinded (masking used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 13-07-2021 |
| Enrollment: | 38 |
| Type: | Actual |

## Medical products/devices used

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

# Ethics review

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| Approved WMO Date: | 02-04-2021 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 23-04-2021 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 09-07-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 20-07-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

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|---|---|
| Date: | 07-05-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-09-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 29-01-2024 |
| 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 |
|---|---|
| EU-CTR | CTIS2024-514183-21-00 |
| EudraCT | EUCTR2019-002485-12-NL |
| ClinicalTrials.gov | NCT04259138 |
| CCMO | NL76268.056.20 |