PHASE III, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF THE EFFICACY AND SAFETY OF ETROLIZUMAB DURING INDUCTION AND MAINTENANCE IN PATIENTS WITH MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS WHO HAVE BEEN PREVIOUSLY EXPOSED TO TNF INHIBITORS.

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The primary efficacy objectives for this study are as follows:* To evaluate the efficacy of etrolizumab (105 mg SC every 4 weeks [Q4W]) compared with placebo for the induction of remission as determined by the MCS at W14* To evaluate the efficacy of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal ulceration and perforation
Study type	Interventional

Summary

ID

NL-OMON47040

Source
ToetsingOnline

Brief title
ETRO UC5 (GA28950)

Condition

- Gastrointestinal ulceration and perforation

Synonym
inflammatory bowel disease, Ulcerative colitis (UC)

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: efficacy, etrolizumab, safety, ulcerative colitis

Outcome measures

Primary outcome

Co-Primary Efficacy Outcome Measures

* Remission at Week 14, as determined by the Mayo Clinic Score (MCS)

* Remission at Week 66 among patients with a clinical response at W14 as

determined by MCS

Secondary outcome

Percentage of participants in/with

1. Clinical remission at W14 and W66, as determined by MCS

2. Clinical response at W14, as determined by MCS

3. Improvement in endoscopic appearance of the mucosa at W14 and W66, as

determined by Mayo Endoscopic Subscore

4. Endoscopic and histologic remission at W14 and W66, as determined by Mayo

Endoscopic Subscore and Nany Histological Score (NHI) respectively

5. Change from baseline in rectal bleed and stool frequency subscore at W6, as determinedby Mayo rectal bleeding and stool frequency Subscores respectively

6. Change from baseline in UC bowel movement signs and symptoms and abdominal symptoms at W14 and W66, as assessed by UC-PRO/SS

7. Change from baseline in health-related Quality of Life at W14 and W66, as assessed by IBDQ

8. Clinical remission at W66 among patients in clinical remission at W14, as determined by MCS

9. Remission at W66 among patients in remission at W14, as determined by MCS

10. Corticosteroid (CS)-free clinical remission and remissoin at W66 in patients who were receiving CSs at baseline, as determined by MSC

11. Etrolizumab Serum Concentration

12. Adverse Events

13. Anti-Therapeutic Antibodies to Etrolizumab

Study description

Background summary

Although there are therapeutic options including anti-TNF agents, a significant proportion of patients with UC will not experience a durable clinical benefit with those treatment options. Furthermore, adverse events associated with anti-TNFs include elevated rates of serious bacterial infection, including TB, and (more rarely) lymphoma and demyelination. No currently available therapy achieves sustained remission in more than 10% to 30% of patients with IBD who have chronic disease. As noted above, etrolizumab distinguishes itself from other anti-integrins on the basis of gut selectivity combined with a potential dual mechanism of action.

A global Phase II multicenter study (Study ABS4986g; EUCALYPTUS) designed to determine the exposure-response relationship and to further characterize the

safety and tolerability of etrolizumab in treatment of adult patients with moderate to severely active UC patients has been completed.

In EUCALYPTUS, etrolizumab showed clinically meaningful efficacy for both doses relative to placebo for the primary endpoint. The present study is powered to detect a 10% difference in induction of remission rates between etrolizumab and placebo-treated patients. Given that patients failing TNF inhibitor therapy have very limited treatment options available to them, the TNF-IR patient population represent an unmet medical need population. Consequently, the potential benefits of etrolizumab in this population warrant further investigation.

Study objective

The primary efficacy objectives for this study are as follows:
* To evaluate the efficacy of etrolizumab (105 mg SC every 4 weeks [Q4W]) compared with placebo for the induction of remission as determined by the MCS at W14
* To evaluate the efficacy of etrolizumab (105 mg SC Q4W) compared with placebo for remission at W66 among patients with a clinical response at W14, as determied by the MCS.

The secondary efficacy objectives for this study are as follows:
* Clinical remission at W14 and W66
* Clinical response at W14
* Improvement in endoscopic appearance of the mucosa at W14 and W66
* Endoscopic and histologic remission at W14 and W66
* Change from baseline (BL) in rectal bleed and stool frequency subscore at W6
* Change from BL in UC bowel movement signs and symptoms and abdominal symptoms at W14 and W66, as assessed by Ulcerative Colitis Patient Reported Outcome Signs and Symptoms (UC-PRO/SS)
* Change from BL in Patients Reported health related Quality of Life at W14 and W66, as assessed by Inflammatory Bowel Disease Questionnaire (IBDQ)
* Clinical remission at W66 in patients in clinical remission at W14
* Remission at W66 among patients in remission at W14
* Corticosteroid (CS)-free clinical remission and remission at W66 in patients receiving CSs at BL
* Etrolizumab Serum Concentration
* Percentage of participants with Adverse Events
* Percentage of participants with Anti-Therapeutic Antibodies to Etrolizumab

Study design

This is a multicenter, Phase III, double-blind, placebo-controlled study evaluating the safety, efficacy, and tolerability of etrolizumab during induction and maintenance of remission compared with placebo in the treatment

of moderately to severely active UC.
The study will be divided into:
* Screening period of up to 28 days during which patient eligibility will be determined
* Induction Phase of 14 weeks (Cohort 1: open-label etrolizumab treatment; Cohort 2: randomized to etrolizumab or placebo)
* Randomization of etrolizumab responders prior to a double-blind Maintenance Phase of 52 weeks or continued blinded treatment with placebo Q4W for 52 weeks for placebo induction responders
* Safety follow-up period of 12 weeks

The total length of the treatment period will be 66 weeks. Patients who do not achieve a clinical response at Week 14, patients who have clinical relapse during the Maintenance Phase, patients who receive defined rescue treatment (see Section 4.3.2.2), and patients who complete 66 weeks of the study may be given the option of enrolling into the OLE (Part 1) of the OLE-SM study, where they will receive open-label etrolizumab
treatment. Those who do not enroll in Part 1 of the OLE-SM study will continue to 12 weeks of safety follow-up in this study and then be requested to enroll in Part 2 (SM) of the OLE-SM study for 92 weeks of monitoring for PML.

The total length of the study is expected to last from the first patient screened to either the last patient in last follow-up visit in this protocol or last patient enrolled into the OLE-SM study, whichever is the later.

Intervention

Etrolizumab
Etrolizumab will be supplied by the Sponsor as a liquid formulation in PFSs and is administered as an SC injection. Each 1-mL PFS will contain 150 mg/mL of etrolizumab (0.7 mL nominal volume). Etrolizumab is formulated as 150 mg/mL in 20 mM histidine, 0.2 M arginine succinate, and 0.04% polysorbate 20, pH 5.8. Each syringe is for single-dose parenteral administration and contains no preservatives.

Placebo
Drug product composition for the placebo is exactly the same as that of active drug product without the presence of etrolizumab.

The first 2 doses of study medication will be administered via a prefilled syringe (PFS) by a health care professional (HCP) in the clinic. The subsequent two doses will be self-administered by the patient or his or her caregiver in the clinic; if deemed appropriate by the HCP, the remaining doses of study drug, starting at Week 16, will be self-administered by the patient or administered by his or her caregiver at home Q4W. The administration of the study medication at home by the patients or their caregivers will occur after their study assessments in the clinic setting. If necessary, patients or their

HCPs may choose to continue administration of study medication in the clinic. The details of study medication administration are provided in the protocol.

Study burden and risks

During the participation in this study, the subject is at risk for the side effects described below. Subject should discuss these with the study doctor. There may also be other side effects that cannot be predicted.
- As etrolizumab is designed to block the movement of white blood cells involved in inflammation of the gut lining, there is a chance that the subject is more likely to get an infection after taking etrolizumab.
- The use of some medicines that suppress the immune system has been associated with PML, a rare but serious viral infection of the brain. The present understanding is that etrolizumab does not affect entry of immune cells into your brain and thus far no cases of PML have been observed in subjects treated with etrolizumab. Nonetheless, subjects in this study will be closely monitored for potential development of PML.
- There is a chance the vaccination may not work correctly if given with etrolizumab.
- Risk of developing cancer with etrolizumab is currently unknown.
- Remote chance that subject might experience an allergic reaction to etrolizumab.
- Risks of study procedures (Tapering Current Steroid Therapy, Taking Biopsies, Drawing blood , Colonscopy, Sigmoidoscopy, X-ray, MRI, ECG, lumbar puncture).
- Reproductive risks or risks for the unborn child are unknown.

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

* Treatment within 5 years prior to screening with one or two induction regimens that contain TNF inhibitors (including TNF inhibitor biosimilars)
* 18-80 years of age inclusive, and able and willing to provide written informed consent.
* Diagnosis of UC established at least 3 months prior to Day 1.
* Moderately to severely active ulcerative colitis (UC) as determined by the Mayo Clinic Score assessment (MCS).
* Washout of TNF inhibitor therapy for at least 8 weeks preceding Day 1
* Background regimen for UC may include oral 5-aminosalicylic acid (5-ASA), oral corticosteroids, budenoside therapy, probiotics, AZA, 6-MP, or MTX if doses have been stable during the screening period.
* Use of highly effective contraception as defined by the protocol.
* Have received a colonoscopy within the past year or be wiling to undergo a colonoscopy in lieu of a flexible sigmoidoscopy at screening.

Exclusion criteria

* A history of or current conditions and diseases affecting the digestive tract, such as indeterminate colitis, Crohn's disease, fistulas or abdominal abscesses, colonic mucosal dysplasia, intestinal obstruction, toxic megacolon, or unremoved adenomatous colonic polyps.
* Prior or planned surgery for UC.
* Past or present ileostomy or colostomy.
* Have received non-permitted inflammatory bowel disease (IBD) therapies (including natalizumab, vedolizumab, and efalizumab) as stated in the protocol.
* Any prior treatment with anti-adhesion molecules (e.g., anti-MAdCAM-1)
* Any treatment with tofacitinib during screening
* Congenital or acquired immuno deficiency, chronic hepatitis B or C infection, Human

Immonudeficiency Virus (HIV) positive, or history of tuberculosis (active or latent).
* Evidence of or treatment for Clostridium difficile within 60 days prior to Day 1 or other intestinal pathogens within 30 days prior to Day 1
* History of recurrent opportunisctic infections, severe disseminated viral infections and organ transplant
* Any major episode of infection requiring treatment with intravenous (IV) antibiotics within 8 weeks prior to screening or oral antibiotics within 4 weeks prior to screening.
* Received a live attenuated vaccine within 4 weeks prior to Day 1

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):	27-01-2015
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	etrolizumab

Ethics review

Approved WMO Date:	23-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	02-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-10-2018
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	EUCTR2013-004278-88-NL
ClinicalTrials.gov	NCT02100696
CCMO	NL48052.018.14