A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ETROLIZUMAB AS AN INDUCTION AND MAINTENANCE TREATMENT FOR PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN*S DISEASE

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Induction Phase (IP)* To independently evaluate the efficacy of etrolizumab dose regimens compared with placebo in inducing clinical remission and endoscopic improvement at the end of the Induction Phase (Week 14)Maintenance Phase (MP)* To...

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

Summary

ID

NL-OMON47704

Source
ToetsingOnline

Brief title
ETRO-GA29144

Condition

- Gastrointestinal inflammatory conditions

Synonym
chronic bowel inflamation, inflammatory bowel disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Crohn□s disease, Etrolizumab, inflammatory bowel disease

Outcome measures

Primary outcome

The primary efficacy objectives for ex-U.S. are:

Induction Phase

* Clinical remission at Week 14

* Endoscopic improvement at Week 14

Maintenance Phase, among patients who achieve CDAI-70 response at Week 14

* Clinical remission at Week 66

* Endoscopic improvement at Week 66

Secondary outcome

The secondary efficacy outcome measures

Induction Phase

a, Clinical remission at Week 6

b, SES CD *4 (*2 for ileal patients), with no segment having a

subcategory score that is >1, at Week 14

c, Change in CD signs and symptoms from baseline to Week 14 as

assessed by the CD-PRO/SS measure

Maintenance Phase

a, Clinical remission at Week 66 among patients who achieved clinical

remission at Week 14

b, Corticosteroid-free clinical remission at Week 66 among patients who were

receiving corticosteroids at baseline

c, Endoscopic improvement at Week 66 among patients who achieved

endoscopic improvement at Week 14

d, SES CD *4 (*2 for ileal patients), with no segment having a

subcategory score that is >1, at Week 66

e, Durable clinical remission

f, Corticosteroid-free clinical remission for 24 weeks at Week 66 among

patients who were receiving corticosteroids at baseline

g, Change in CD signs and symptoms from baseline to Week 66 as

assessed by the CD-PRO/SS measure

Study description

Background summary

So far, there is no cure for CD. The treatment goals for CD are to induce and maintain

symptom improvement, induce mucosal healing, avoid surgery, and improve quality of
life. Etrolizumab, a subcutaneously administered mAb, is a novel anti-integrin which unlike
vedolizumab, targets both the *4*7 and *E*7 receptors that regulate trafficking, and
retention of T-cell subsets in the intestinal mucosa, respectively. Thus, etrolizumab
offers the potential of an additive therapeutic effect in CD via a dual mechanism of action
(MOA), without generalized immunosuppression.

Study objective

Induction Phase (IP)
* To independently evaluate the efficacy of etrolizumab dose regimens compared with placebo in inducing clinical remission and endoscopic improvement at the end of the Induction Phase (Week 14)
Maintenance Phase (MP)
* To independently evaluate the efficacy of etrolizumab compared with placebo in achieving clinical remission and endoscopic improvement at 1 year of maintenance treatment (Week 66), for patients who achieved a Crohn's Disease Activity Index (CDAI) 70 response (defined as a decrease of at least 70 points from baseline CDAI) at Week 14 Safety Objectives
* To evaluate the overall safety and tolerability of etrolizumab compared with placebo during Induction and Maintenance Phases of therapy
*in achieving clinical remission at Week 6
*in achieving an SES-CD *4, with no segment having a subcategory score that is >1, at Week 14
* in achieving a reduction of CD signs and symptoms Evaluate in MP the efficacy of etrolizumab compared with placebo:
*in maintaining clinical remission at Week 66 for patients who achieved clinical remission at Week 14
*in achieving corticosteroid-free clinical remission at Week 66
*in maintaining endoscopic improvement at Week 66 for patients who achieved endoscopic improvement at Week 14
*in achieving a SES CD *4, with no segment having a subcategory score that is >1, at Week 66
*in achieving durable clinical remission during 1 year of maintenance therapy
*in change of CD signs and symptoms from baseline to Week 66
*corticosteroid-free clinical remission at Week 66 in patients who were receiving corticosteroids at baseline

Study design

The study design will comprise 1) a Screening Phase (up to 28 days) to

determine patients*
eligibility for the study, 2) an Induction Phase (14 weeks), followed by 3) a Maintenance Phase
(60 weeks) in patients demonstrating a CDAI-70 response at the end of the Induction Phase,
and 4) a Safety Follow-Up Phase (12 weeks) after administration of the last dose of study drug
in the Maintenance Phase for those patients who are not participating in Part 1 of open-label
extension Study GA29145 to receive etrolizumab treatment. At the completion of the Safety
Follow-Up Phase, patients will be asked to enter an extended PML-monitoring phase
(open-label extension Study GA29145, Part 2) for 92 weeks. An independent Data Monitoring
Committee (iDMC) will monitor safety and study conduct on an ongoing basis.
Patients will have an option to consent and participate in a PK/PD substudy. The objective of
the substudy is to determine the relationship between etrolizumab exposure and receptor
occupancy in peripheral blood in patients with CD. To achieve this objective, it is planned to
enroll approximately 150 patients in the substudy. Blood sampling for the PK/PD substudy will
continue in the Maintenance Phase. Patients in all cohorts will provide blood samples for
population PK analysis and PD characterization.

Intervention

Depending on the dose assignment in the Induction Phase,
patients receive either study drug in a 1-mL PFS containing 0.7 mL of etrolizumab (105-mg
dose) or a 2.25-mL PFS containing 1.4 mL of etrolizumab (210-mg dose) according to the
treatment schedule. To preserve the blind to study drug assignment in the Induction Phase, at
Weeks 0, 4, 8, and 12 all patients receive two injections: one 0.7-mL dose and a second
1.4-mL dose, and either one (if in one of the study drug arms) or both (if in placebo arm) will
contain placebo.
At Week 2, all patients will receive one 1.4-mL dose injection, which will contain placebo for patients in the low-dose etrolizumab and placebo arms and study drug for
the high-dose etrolizumab arm. In the Maintenance Phase, patients receive a single 0.7-mL

dose (105-mg dose) that will either contain etrolizumab or placebo, according to the treatment
schedule.

Study burden and risks

Given the significant clinical and non-clinical data generated to date for etrolizumab,
there is a strong rationale and a positive benefit-risk assessment for studying etrolizumab in a Phase III clinical trial in CD, supported by:
- An anti-*4*7 mAb, vedolizumab, approved for the treatment of patients with moderate to severe CD.
- Completed studies with etrolizumab in UC demonstrating clinically meaningful benefit, as well as a full characterization of the PK/PD profile in UC, and importantly,
an acceptable safety profile in previous etrolizumab studies.
- Data that implicate *4*7 receptors in the pathobiology of CD with the possibility that
inhibition of the *E*7/E-cadherin interaction by etrolizumab could bring enhanced
efficacy.
- An acceptable safety profile in the ongoing clinical development program, and a
carefully designed Phase III CD program with robust safety monitoring.

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet the following criteria for study entry:
- 18-80 years of age (inclusive)
- Moderately to severely active Crohn's disease as determined by the Crohn's Disease Activity Index (CDAI), patient reported outcomes and endoscopically defined disease activity in the ileum and/or colon
- Intolerance, loss of response or failure to respond to corticosteroids (CS) or, immunosuppressants (IS), or TNF inhibitors within the previous 5 years
- Use of effective contraception as defined by the protocol, A complete list of inclusion criteria can be found in the protocol

Exclusion criteria

- A history of, or current conditions affecting the digestive tract, such as ulcerative colitis, indeterminant colitis, abdominal or perianal abscess, adenomatous colonic polyps, colonic mucosal dysplasia, and short bowel syndrome
- Sinus tract with evidence for infection (e.g., Fistula with purulent discharge) in the clinical judgment of the investigator. Fistulas related to Crohn's disease are not exclusionary
- Planned surgery for CD
- Ileostomy or colostomy
- Has received non-permitted inflammatory bowel disease (IBD) therapies (including natalizumab, vedolizumab, and efalizumab, as stated in the protocol)
- Chronic hepatitis B or C infection, HIV, active or latent tuberculosis (patients with prior history of BCG vaccination must pass protocoldefined screening criteria)

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):	02-12-2015
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RO5490261
Generic name:	Etrolizumab

Ethics review

Approved WMO

Date:	02-04-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	03-09-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date: 30-05-2018

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: 24-07-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 16-04-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 10-05-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 02-10-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 10-10-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 10-11-2020

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 27-01-2021

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date:	26-03-2021
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	EUCTR2014-003824-36-NL
ClinicalTrials.gov	NCT02394028
CCMO	NL52291.018.15