A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis

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The primary objective is to assess the efficacy of etrasimod on clinical remission in subjects with moderately to severely active ulcerative colitis (UC) after 12 and 52 weeks of treatment. The secondary objective is to assess the efficacy of...

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

Summary

ID

NL-OMON55828

Source
ToetsingOnline

Brief title
ELEVATE UC 52 (APD334-301)

Condition

- Gastrointestinal inflammatory conditions

Synonym
ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Arena Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Ulcerative Colitis

Outcome measures

Primary outcome

The primary efficacy endpoints will evaluate etrasimod versus placebo in:

* The proportion of subjects achieving clinical remission at Week 12

* The proportion of subjects achieving clinical remission at Week 52

Secondary outcome

The key secondary efficacy endpoints are:

* The proportion of subjects achieving endoscopic improvement at Week 52

* The proportion of subjects achieving endoscopic improvement at Week 12

* The proportion of subjects achieving symptomatic remission at Week 52

* The proportion of subjects achieving symptomatic remission at Week 12

* Proportion of subjects in clinical remission at Week 52 and who had not been

receiving corticosteroids for * 12 weeks prior to Week 52

* Proportion of subjects with mucosal healing at Week 52

* Proportion of subjects with mucosal healing at Week 12

* Proportion of subjects achieving clinical remission at both Weeks 12 and 52

Study description

Background summary

Crohn*s disease (CD) and ulcerative colitis (UC) are chronic recurrent, remittent, or progressive inflammatory conditions that may affect the entire gastrointestinal tract (CD) and the colonic mucosa (UC), and are associated with an increased risk for colon cancer. Treatment for subjects with UC is generally for symptomatic care (relief of symptoms) and mucosal healing and includes 5 major classes of medications: 5 aminosalicylic acid (5 ASA), antibiotics, corticosteroids, immunomodulators, biologic therapies (eg, tumor necrosis factor [TNF] inhibitors and anti integrins) and most recently Janus kinase (JAK) inhibitor therapy.
An unmet medical need exists for the development of targeted therapies for the treatment of UC with easily administered and stable oral drugs, particularly as most patients treated with biologics experience inadequate responses or lose responsiveness over time, even though their initial response may have been positive.
Etrasimod (APD334) is an orally administered, selective, synthetic sphingosine 1 phosphate (S1P) receptor 1, 4, 5 modulator that is being developed to treat immune-mediated inflammatory disorders, including UC. A Phase 2 study with etrasimod in subjects with moderately to severely active UC demonstrated consistent and clinically meaningful improvements in endpoint measures reflecting cardinal symptoms of UC and objective findings of endoscopic improvement.

Study objective

The primary objective is to assess the efficacy of etrasimod on clinical remission in subjects with moderately to severely active ulcerative colitis (UC) after 12 and 52 weeks of treatment. The secondary objective is to assess the efficacy of etrasimod on clinical response, symptomatic response and remission, endoscopic changes, corticosteroid free remission, and mucosal healing in subjects with moderately to severely active UC at timepoints up to 52 weeks of treatment. The safety objective is to assess the long-term safety of etrasimod after daily doses of 2 mg for up to 52 weeks in subjects with moderately to severely active UC.

Study design

This is a multicenter, randomized, double blind, placebo controlled study to evaluate the efficacy and safety of etrasimod 2 mg in subjects with moderately to severely active UC. The study consists of a 28 Day Screening Period, a 12 Week Treatment Period, a 40 Week Treatment Period, and a 2 Week and 4-Week Follow Up Period. Subjects whose disease is stable or improving after the 12 Week Treatment Period will continue with their double-blind treatment and move into the 40 Week Treatment Period. Subjects whose active UC worsens according to protocol defined criteria, who have and who meet other eligibility criteria will have the option to enroll in the open label extension (OLE) study APD334 303. At the end of the 40 Week Treatment Period (ie, Week 52) and following

completion of all study procedures, subjects will have the option to enter into the OLE study (APD334 303) providing they meet all inclusion criteria. Subjects who do not participate in the OLE study will have 2 Week and 4 Week Follow Up visits after their last on treatment visit/Early Termination visit.

Intervention

Eligible subjects will be randomized (2:1 ratio) to receive either etrasimod (2 mg once daily) or matching placebo (once daily) in a double-blind fashion.

Study burden and risks

Common adverse events that have been reported with S1P receptor modulators include bradycardia at the first dose or atrioventricular (AV) block, macular edema, hypertension, headache, cough, dyspnea, back pain, influenza, and diarrhea.
Safety and tolerability of etrasimod have been evaluated in Phase 1 studies with healthy adult subjects at single doses up to 5 mg and repeat doses up to 4 mg once daily. Repeated doses of 2 mg have been evaluated in Phase 2 studies of subjects with moderately to severely active UC (refer to the current edition of the IB). Etrasimod was found to be safe and well tolerated in these studies, with no clinically significant safety concerns with respect to vital signs, electrocardiograms (ECGs), pulmonary function tests (PFTs), ophthalmoscopy, or clinical laboratory tests. Etrasimod produced a dose dependent sustained decrease in total lymphocyte count, which is expected given etrasimod*s mechanism of action. Lymphocyte counts returned to approximately baseline levels within 7 days after the last dose.
15 visits will take place in 56 weeks (4 weeks of screening and 52 weeks of treatment). If the subject completes all visites, a total amount of 389 ml of blood will be drawn. Participant might need to undergo an X-ray at screening. Participant will have at least one proctosigmoidoscopy/colonoscopy, biopsy, eye examination (ophthalmoscopy) and optical coherence tomography (OCT) performed throughout the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Men or women 16 to 80 years of age, inclusive, at the time of assent/consent. Enrollment of subjects < 18 years should be conducted only if acceptable according to local law and regulations
2. Ability to provide written informed consent or assent and to be compliant with the schedule of protocol assessments
3. Diagnosed with UC * 3 months prior to screening confirmed by endoscopic and histologic evidence
4. Active UC confirmed by endoscopy with * 10 cm rectal involvement. Subjects with proctitis only at baseline who meet the other eligibility criteria for inclusion, including the endoscopic and rectal bleeding criteria for moderate to severe disease, will be capped at 15% of the total subjects
5. Moderately to severely active UC defined as MMS of 4 to 9, including an ES of * 2 and RB score * 1
6. Received a surveillance colonoscopy within 12 months before baseline. Subjects without a surveillance colonoscopy within the prior 12 months will have a colonoscopy at screening (ie, in place of screening proctosigmoidoscopy).
7. Demonstrated an inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies:
a. Corticosteroids
b. Thiopurines
Biologic therapy or JAK inhibitor therapy
a. Antitumor necrosis factor alpha (TNF*) antibodies

b. Anti-integrin antibodies
c. Anti-Interleukin 12/23 antibodies (eg, ustekinumab)
d. JAK inhibitors
Concomitant treatments:
8. Subjects are permitted to be receiving a therapeutic dose of the following drugs:
- Oral 5-ASA compounds provided the dose has been stable for * 2 weeks immediately prior to randomization
- Oral corticosteroid therapy (prednisone at a stable dose * 20 mg/day, budesonide at a stable dose * 9 mg/day, or equivalent steroid provided the dose has been stable for the 4 weeks immediately prior to the screening endoscopy assessment
- Immunosuppressive agents such as oral azathioprine or 6- mercaptopurine must be discontinued * 2 weeks prior to randomization
- Probiotics (eg, Culturelle®, Saccharomyces boulardii) provided the dose has been stable for the 2 weeks immediately prior to randomization
9.Adequate hematological function defined by white blood cell count * 3.5 × 109/L with absolute neutrophil count (ANC) * 1.5 × 109/L, lymphocyte count * 0.8 × 109/L, platelet count * 100 × 109/L, and hemoglobin * 8 g/dL
10.Adequate hepatic function defined by a total bilirubin level * 1.5 × the upper limit of normal (ULN) range and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels * 2.0 × ULN. Subjects with an isolated total bilirubin and normal AST and ALT diagnosed with Gilbert's syndrome may participate
11. Adequate renal function defined by an estimated glomerular filtration rate * 30 mL/min/1.73 m2 by the CKD-epidemiology collaboration equation at screening
12. Females must meet either a or b of the following criteria and males must meet criterion c to qualify for the study:
a. A female who is not of childbearing potential must meet 1 of the following:
* Postmenopausal, defined as no menses for 12 months without an alternative medical cause;
* Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
b. Non-pregnant female of childbearing potential must agree to using a highly effective contraception method during treatment and for 30 days following treatment that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following are considered highly effective birth control methods:
* Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
* Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
* Intrauterine device (IUD)
* Intrauterine hormone-releasing system
* Bilateral tubal occlusion
* Vasectomized partner, provided that partner is the sole sexual partner of the

WOCBP trial subject and that the vasectomized partner has received medical assessment of the surgical success.
* Sexual abstinence. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence is not acceptable.
c. A male subject with a pregnant or non-pregnant female of childbearing potential partner must agree to using condoms during treatment and for 30 days following treatment

Exclusion criteria

1. Severe extensive colitis as evidenced by
Physician judgment that subject is likely to require hospitalization for medical care or surgical intervention for UC within 12 weeks following randomization
Current evidence of fulminant colitis, toxic megacolon or recent history (last 6 months) of toxic megacolon, or bowel perforation
Previous total or partial colectomy
2. Diagnosis of CD or indeterminate colitis or the presence or history of a fistula consistent with CD
3. Diagnosis of microscopic colitis, ischemic colitis, or infectious colitis
4. Hospitalization for exacerbation of UC requiring IV steroids within 12 weeks of screening
5. Positive assay or stool culture for pathogens or positive test for Clostridioides difficile toxin at screening
6. Pregnancy, lactation, or a positive serum *-hCG measured during screening
7. Clinically relevant neurological, endocrine, metabolic, psychiatric, cognitive impairment, alcohol/drug abuse/dependence or other major systemic disease making implementation of the protocol or interpretation of the study difficult or would put the subject at risk interpretation of the study difficult or would put the subject at risk
8. Have any of the following conditions or receiving treatments that may affect cardiovascular function:
Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure *6 months prior to or during Screening period
History or presence of:
Second-degree or third-degree atrioventricular block, sick sinus syndrome or periods of asystole >3 seconds without a functional pacemaker
History or presence of recurrent symptomatic bradycardia or recurrent cardiogenic syncope
Screening or W0/Day 1 prerandomization vital signs with a heart rate < 50 bpm OR systolic blood pressure < 90 mm Hg OR diastolic BP < 55 mm Hg
Screening or W0/Day 1 prerandomization ECG with PR interval > 200 ms or Fridericia's corrected QT interval * 450 ms in men or * 470 ms in women

Start, stop, change or planned change in dosage of any anti-arrhythmic drugs (Class I to IV) *1 week before screening or within 1 week before or after randomization
9. Forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values & FEV1/FVC ratio < 0.70 at screening
10. Uncontrolled diabetes as determined by hemoglobin A1c (HbA1c) > 9% at screening, or subjects with diabetes with significant comorbid conditions such as retinopathy
11. History of macular edema or retinopathy
12. History of active tuberculosis (TB), history of untreated or inadequately treated latent TB infection, active or latent TB infection at screening
13. clinically significant active infection * 28 days prior to randomization, required IV medication * 14 days prior to randomization or that may worsen
14. Have HIV/acquired immune deficiency syndrome or test positive for HIV antibodies
15. Have acute or chronic hep B infection or test positive for hepatitis B virus at screening (detectable HBV DNA or positive for hep B surface antigenor negative for HBsAg and positive for antihepatitis B core antibody in conjunction with detectable HBV DNA, or detectable HBV DNA)
16. Have current hep C infection or test positive for hep C virus (HCV)
17. History of an opportunistic infection or history of disseminated herpes simplex or disseminated herpes zoster
18. History of or currently active primary or secondary immunodeficiency
19. History of cancer within the last 5 years, including solid tumors and haematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) or colonic mucosal dysplasia
20. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma
21. Hypersensitivity to etrasimod or any of the excipients or placebo compounds
22. Prior treatment with S1P receptor modulators
23. Treatment with a biologic agent *8 weeks or a small molecule agent *5 elimination half-lives and detectable drug level prior to randomization
24. Treatment with an investigational therapy *3 months prior to randomization
25. Treatment with * 3 biologic agents or * 2 biologics plus a JAK inhibitor approved for treatment of UC
26. Treatment with topical rectal 5-ASA, short-chain fatty acid enemas, or steroids *2 weeks prior to and during screening
27. Treatment with topical rectal traditional medicine (e.g. Chinese medicine), herb enemas, or suppositories *2 weeks prior to randomization
28. Treatment with methotrexate *8 weeks prior to and during screening or cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil *16 weeks prior to and during screening
29. Receipt of a live vaccine *4 weeks prior to randomization
30. Previous treatment with natalizumab
31. Previous treatment with lymphocyte-depleting therapies
32. Previous treatment with D-penicillamine, thalidomide, dimethyl fumarate, or

pyrimidine synthesis inhibitors
33. Treatment with IV immune globulin or plasmapheresis, *3 months prior to randomization
34. Chronic use of therapies that moderately/strongly inhibit/induce cytochrome P450 (CYP) 2C8 and 2C9 metabolism and inhibitors of UGT1A7 *4 weeks prior to randomization

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):	15-05-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Etrasimod
Generic name:	Etrasimod

Ethics review

Approved WMO

Date:	09-07-2019

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2021
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	EUCTR2018-003985-15-NL
ClinicalTrials.gov	NCT03945188
CCMO	NL69098.056.19