A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis

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

Summary

ID

NL-OMON55010

Source
ToetsingOnline

Brief title
ELEVATE UC 12 (APD334-302)

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: 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

Secondary outcome

The key secondary efficacy endpoints are:

* The proportion of subjects achieving endoscopic improvement at Week 12

* The proportion of subjects achieving symptomatic remission at Week 12

* The proportion of subjects with mucosal healing at Week 12

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 when administered for 12 weeks on clinical remission in subjects with moderately to severely active ulcerative colitis (UC). The secondary objective is to assess the efficacy of etrasimod when administered for 12 weeks on clinical response, symptomatic response and remission, endoscopic changes, corticosteroid free remission, and mucosal healing in subjects with moderately to severely active UC. The safety objective is to assess the long-term safety of etrasimod after daily doses of 2 mg for up to 12 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 Induction Treatment Period, and a 4 Week Follow Up Period. At the end of the Induction Treatment Period, subjects will undergo the Week 12 study assessments. All subjects will then have the option to enter an open label extension (OLE) study (APD334 303) following completion of Week 12 study procedures and providing they meet all inclusion criteria for the OLE.

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 habe been evaluated in Phase 2 studies in

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.
8 visits will take place in 20 weeks (4 weeks of screening, 12 weeks of treatment, 4 weeks follow-up). If the subject completes all visits, a total amount of 217 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, women and adolescents 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 laws 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 enrolled
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 to rule out dysplasia in subjects with pancolitis > 8 years duration or subjects with left-sided colitis > 12 years duration. Subjects without a surveillance colonoscopy within the prior 12 months will have a colonoscopy at screening (ie, in place of screening proctosigmoidoscopy). Any adenomatous polyps must be removed prior to their first dose of study treatment
7. Demonstrated an inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies as defined below:
Conventional therapy
a. Corticosteroids
b. Thiopurines
Biologic therapy or JAK inhibitor therapy
a. Antitumor necrosis factor alpha (TNF*) antibodies (eg, infliximab, adalimumab, golimumab, or biosimilars)
b. Anti-integrin antibodies (eg, vedolizumab)
c. Anti-Interleukin 12/23 antibodies (eg, ustekinumab)
d. JAK inhibitors (eg, tofacitinib)
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
If oral 5-ASA or corticosteroids have been recently discontinued, they must have been stopped for at least 2 weeks prior to the endoscopy used for the baseline MMS.
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
For other criteria see the protocol.

Exclusion criteria

1. Severe extensive colitis as evidenced by:
Physician judgement that the subject is likely to require hospitalization for medical care or surgical intervention of any kind for UC (eg, colectomy) within 12 weeks following randomization
Current evidence of fulminant colitis, toxic megacolon or recent history (within last 6 months) of toxic megacolon, or bowel perforation
Previous total or partial colectomy
2. Diagnosis of Crohn's disease (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
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 & during the Screening Period
History or presence of second-degree or third-degree atrioventricular block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker

History or presence of recurrent symptomatic bradycardia or recurrent cardiogenic syncope
Screening and W0/D1 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/D1 prerandomization ECG with PR interval > 200 ms or Fridericia's corrected QT interval QTcF * 450 ms in men or * 470 ms in women
Start, stop, change or planned in dosage of any anti-arrhythmic drugs (Class I to IV) *1 week before screening or 1w before or after randomization
9. Forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values and 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
For other criteria see the protocol.

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):	18-08-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Etrasimod

Generic name:	Etrasimod

Ethics review

Approved WMO Date:	22-08-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-06-2021
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2021
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	EUCTR2018-003986-33-NL
Other	IND 125154
CCMO	NL70301.056.19