A Phase 2b, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Oral Etrasimod as Induction Therapy in Subjects with Moderately to Severely Active Crohn*s Disease

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Main objective:*To evaluate the dose-response relationship of 2 doses of etrasimod versus placebo as induction therapy in subjects with moderately to severely active Crohn's disease (CD).*To select an oral etrasimod dose, based on efficacy and...

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

Summary

ID

NL-OMON49630

Source
ToetsingOnline

Brief title
Cultivate (APD334-202)

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Efficacy, Etrasimod, Placebo, Safety

Outcome measures

Primary outcome

Proportion of subjects who achieve endoscopic response at Week 14

Secondary outcome

* Proportion of subjects who achieve clinical remission APSF at Week 14

* Proportion of subjects who achieve CDAI < 150 by visit up to Week 14

* Proportion of subjects who achieve clinical response CDAI by visit up to Week

14

* Proportion of subjects who achieve clinical response APSF by visit up to Week

14

* Proportion of subjects who achieve clinical response CDAI-70 by visit up to

Week 14

* Proportion of subjects who achieve clinical response APSF-30 by visit up to

Week 14

* Change from baseline in CDAI score by visit up to Week 14

* Change from baseline in SES-CD at Week 14

* Proportion of subjects with clinical response by PRO2 at Week 14

* Proportion of subjects with endoscopic response and clinical remission by

PRO2 at Week 14

* Change and percentage change from baseline in absolute lymphocyte count by

visit up to Week 14

* Change and percentage change from baseline in FCP concentration at Weeks 2,

4, 6, 10, and 14

* Change and percentage change from baseline in CRP concentration at Weeks 2,

4, 6, 10, and 14

* Proportion of subjects who achieve endoscopic remission at Week 14 Extension

Period:

endpoints for the induction period will be assessed at scheduled visits up to

Week 66.

Study description

Background summary

CD is a chronic, relapsing and remitting, immune-mediated inflammatory condition that may affect the entire gastrointestinal tract and is associated with an increased risk for colon cancer. The transmural tissue damage observed with CD can result in intestinal infections and abscesses, intestinal perforation, strictures, and fistula formation.

Treatment for patients with CD is generally focused on symptomatic care and mucosal healing with overall goals of inducing and sustaining clinical remission, improving quality of life, and preventing more severe disease manifestations and complications that require hospitalization and surgical intervention. Treatment of CD includes several major classes of medications: corticosteroids, immunosuppressants (such as thiopurines [azathioprine and mercaptopurine] and methotrexate), biologics (anti-tumor necrosis factor alpha [TNF*] [infliximab, adalimumab, and certolizumab pegol], interleukin-12 and -23 antagonist [ustekinumab], integrin receptor antagonists [vedolizumab]), and antibiotics. Janus kinase (JAK) inhibitors are being explored for use in CD (tofacitinib and filgotinib). Though used in the treatment of IBD more broadly, the anti-inflammatory drug 5-aminosalicylic acid (5-ASA) demonstrates a low

efficacy preoperatively and at prevention of CD recurrence in the postoperative setting.

CD is considered neither medically nor surgically *curable,* with clinical, endoscopic, and surgical recurrence reported in 50%, 80%, and 30% of patients, respectively. The surgical burden in CD remains high. There remains a great unmet clinical need for new efficacious and safe treatments for CD, as current therapies often provide only transient or marginal symptomatic relief. The complex and heterogenous nature of the disease further underscores the need for a range of therapies for CD.

Given that immune system dysregulation is a pathophysiological feature of many immune-mediated inflammatory disorders, synthetic small molecule sphingosine 1-phosphate (S1P) modulators have the potential to act across a wide range of such diseases. S1P modulators have been shown to reduce inflammation and induce clinical remission in multiple sclerosis (fingolimod, ponesimod, siponimod, ozanimod), psoriasis (ponesimod), and ulcerative colitis (ozanimod, etrasimod). Therefore, S1P modulators may also reduce inflammation in CD and induce clinical remission.

Etrasimod (APD334) is an orally administered, selective, synthetic S1P receptor 1, 4, 5 modulator that is being developed to treat immune-mediated inflammatory disorders. A Phase 2 study with etrasimod in adult subjects with moderately to severely active UC demonstrated consistent and clinically meaningful improvements in endpoint measures reflecting cardinal symptoms of UC and objective endoscopic and histologic evidence of colorectal mucosal healing.

Study objective

Main objective:
*To evaluate the dose-response relationship of 2 doses of etrasimod versus placebo as induction therapy in subjects with moderately to severely active Crohn's disease (CD).
*To select an oral etrasimod dose, based on efficacy and safety, for continued development.

Secondary objective:
*To evaluate the long-term safety, tolerability, and efficacy of etrasimod in subjects with moderately to severely active Crohn's disease (CD).

Study design

This Phase 2b, multicentered, randomized, double-blind, placebo-controlled, parallel-group,
dose-ranging study will evaluate the efficacy, safety, and tolerability of 2 doses of etrasimod versus placebo as induction therapy in subjects with

moderately to severely active CD who are refractory or intolerant to at least 1 of the current therapies for CD (ie, corticosteroids, immunosuppressants, or biologics).
The study will start with a screening period of up to 28 days (28-Day Screening Period) to determine subject eligibility. Eligible subjects will be randomized in a double-blinded fashion to etrasimod 3 mg, etrasimod 2 mg, or matching placebo in a 14-week induction treatment period (Induction Period). All subjects who complete the Induction Period can enter a subsequent 52-week extension period (Extension Period), where they will be assigned to etrasimod 2mg or 3 mg. All subjects will have follow-up visits at 2 and 4 weeks after the last dose of study treatment during the 4-Week Follow-Up Period after Week 66 or the Early Termination (ET) Visit. This gives a total study duration of up to 74 weeks.

Intervention

Eligible subjects will be randomized in a double-blinded fashion (1:1:1 ratio) to etrasimod 3 mg, etrasimod 2 mg, or matching placebo in the Induction Period. In the Extension Period the subjects will be assigned to receive etrasimod 2 mg or 3 mg according to their Induction Period treatment and clinical response at Week 14.

Study burden and risks

To date, etrasimod has been found to be safe and well-tolerated in approximately 281 adult subjects treated at various doses. The safety and tolerability of etrasimod has been evaluated in Phase 1 studies with healthy adult subjects at single doses up to 5 mg and repeated doses up to 4 mg once daily (qd). In a Phase 2 dose-ranging study in UC patients (APD334-003), treatment with 2 mg etrasimod qd for 12 weeks led to clinically meaningful and statistically significant endoscopic and symptomatic improvements versus placebo. Sustained beneficial effects of etrasimod were observed for up to 46 weeks in the subsequent open-label extension study (APD334-005). Although UC and CD have different pathophysiology including extent and location of disease, they are both antigen- and immune-mediated inflammatory bowel diseases and there is evidence that drugs that are effective for the treatment of UC may also be efficacious for the management of CD. Therefore, it is reasonable to hypothesize that etrasimod may offer similar clinical benefits to CD patients with active disease as UC patients, and this clinical investigation is necessary to affirm or reject this hypothesis.

There have been no clinically significant safety concerns in clinical studies with etrasimod. In APD334-003, the most frequently reported treatment emergent adverse events (TEAEs), reported by > 2 subjects treated with 1 mg or 2 mg etrasimod were ulcerative colitis (worsening), upper respiratory tract infection, anemia, and headache. However, rare adverse events (AEs) such as

macular edema, liver enzyme elevations, and dyspnea have been reported with fingolimod, one of the currently licensed S1P receptor modulators. It is believed that the non-selectivity (ie, activity at all 5 S1P receptors) of this first-generation S1P receptor modulator contributes to many of these AEs. Etrasimod selectively modulates
S1P receptor subtypes 1, 4, and 5, which is expected to mitigate off-target effects for an improved safety profile.

Based on its mechanism of action, etrasimod is expected to dose-dependently reduce lymphocyte counts. This reduction is reversible, with lymphocyte counts returning to baseline levels within 7 days of study drug discontinuation.

Furthermore, S1P receptor modulators are associated with an expected, on-target dose-dependent effect of reducing heart rate (HR) upon first dosing with HR recovery to pre-dose baseline thereafter, but there have been no reported cases of symptomatic bradycardia on first dose and rare first- or second-degree atrioventricular (AV) block found on ECG has been asymptomatic and transient (ie, spontaneous resolution) with etrasimod.

Based on the preclinical and clinical data that have been generated from etrasimod studies and the precautions outlined above, the favorable benefit/risk assessment justifies the further clinical development of etrasimod in subjects with moderately to severely active CD in this current Phase 2, multicenter, randomized, double-blind induction, placebo-controlled study.

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

1. Men or women 18 to 80 years of age,
2. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
3. Diagnosed with CD * 3 months
4.Have moderately to severely active CD at Screening
5.Demonstrated inadequate response, loss of response to, or intolerance to * 1 of the following therapies for the treatment of CD:
a.Oral corticosteroids (eg, prednisone or its equivalent, budesonide)
b.Immunosuppressants (eg, azathioprine [AZA], 6 mercaptopurine [6 MP], or methotrexate [MTX])
c.Tumor necrosis factor alpha (TNF*) antagonists (eg, infliximab, adalimumab, certolizumab pegol, or biosimilars)
d.Integrin receptor antagonist (eg, vedolizumab)
e.Interleukin 12/ 23 antagonist (eg, ustekinumab)
6.Females of childbearing potential must be nonpregnant
7.Females of childbearing potential and males must use contraception

Exclusion criteria

- History of inadequate response (ie, primary non response) to agents from * 2 classes of biologics marketed for the treatment of CD (ie, TNF* antagonists, interleukin 12/ 23 antagonist, and integrin receptor antagonist).
- Have ulcerative colitis, indeterminate colitis, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease associated colitis, toxic megacolon, or active infectious colitis or test positive for Clostridium difficile toxin at Screening.
- Have functional or post operative short bowel syndrome or any associated complications that may require surgery or interfere with efficacy assessments
- Had surgical treatment for intra abdominal abscesses * 8 weeks prior to randomization or surgical treatment for perianal abscesses * 4 weeks prior to randomization.

- Had intestinal resection * 24 weeks prior to randomization or other intra abdominal surgeries * 12 weeks prior to randomization.
- Have an ileostomy or a colostomy.
- Have a serious infection requiring IV antibiotics/medication(s) * 4 weeks prior to randomization.
- Have primary or secondary immunodeficiency syndromes, opportunistic infection, or infection with HIV, HBV, HCV or tuberculosis (active or latent):.
- Have a clinically relevant cardiovascular condition or receiving treatments that may effect cardiovascular function
- Have active retinopathy or macular oedema.
- Have forced expiratory volume at 1 second or forced vital capacity < 70% of predicted values at Screening.
- Lactating female who is breastfeeding.
- Any acute illnesses or medical conditions including cognitive impairment and alcohol/drug abuse/dependence, or signs/symptoms suspicious for a serious disease that, in the Investigator's opinion, could put the subject at increased risk for safety event(s) or interfere with
protocol-specified procedures or adherence with study treatment.

Study design

Design

Study phase:	2
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):	05-08-2020
Enrollment:	1
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	23-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2020
Application type:	First submission
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	EUCTR2019-002895-14-NL
ClinicalTrials.gov	NCT04173273
CCMO	NL72428.056.20