A Multicenter, Randomized, Double-Blind, Parallel-Group Study to Assess the Efficacy and Safety of Oral Etrasimod as Induction and Maintenance Therapy for Moderately to Severely Active Crohn's Disease

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This study has been transitioned to CTIS with ID 2024-513569-38-00 check the CTIS register for the current data. Main objective: SSAThe safety, tolerability, and efficacy of 2 doses of etrasimod as induction therapy in subjects with moderately to...

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

Summary

ID

NL-OMON51883

Source
ToetsingOnline

Brief title
APD334-202EU (Cultivate)

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: Crohn□s Disease, Efficacy, Etrasimod, Safety

Outcome measures

Primary outcome

SS1-P2b

• Proportion of subjects with endoscopic response at Week 14

SS2-I

• Proportion of subjects with endoscopic response at Week 14

• Proportion of subjects with clinical remission CDAI at Week 14

SS3-M

• Proportion of subjects with clinical remission CDAI at Week 52

• Proportion of subjects with endoscopic response at Week 52

Secondary outcome

SA-P2:

• Proportion of subjects with endoscopic response

• Proportion of subjects with clinical remission CDAI

• Change from baseline in SES-CD score

• Change from baseline in CDAI score

SS1-P2b:

• Proportion of subjects with clinical remission CDAI at Week 14

SS2-I:

• Proportion of subjects with clinical remission PRO2 at Week 14

• Proportion of subjects with clinical response CDAI at Week 14

• Proportion of subjects with endoscopic response and clinical remission CDAI at Week 14

• Proportion of subjects with endoscopic remission at Week 14

SS3-M:

• Proportion of subjects with clinical remission CDAI at Week 52 among subjects in clinical remission CDAI at SS3-M baseline (defined as Week 14 or EI-Week 6 Visit)

• Proportion of subjects with endoscopic response at Week 52 among subjects in endoscopic response at SS3-M baseline

• Proportion of subjects with corticosteroid-free clinical remission CDAI at Week 52 among subjects receiving corticosteroids at SS3-M baseline

• Proportion of subjects with endoscopic remission at Week 52

• Proportion of subjects with clinical remission PRO2 at Week 52

SS4-E

• Proportion of subjects with clinical remission CDAI by visit up to the end of treatment

• Proportion of subjects with clinical remission PRO2 by visit up to the end of treatment

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 methotrexate [MTX] and the thiopurines azathioprine [AZA] and mercaptopurine), biologics (anti-tumor necrosis factor alpha [TNFα] antagonists [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) receptor modulators have the potential to act across a wide range of such diseases. S1P receptor 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 receptor 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

This study has been transitioned to CTIS with ID 2024-513569-38-00 check the CTIS register for the current data.

Main objective:
SSA
The safety, tolerability, and efficacy of 2 doses of etrasimod as induction therapy in subjects with moderately to severely active Crohn's disease (CD)
SS1 - Cohort 1
The dose-response relationship of 2 doses of etrasimod vs placebo as induction therapy
An oral etrasimod dose, based on efficacy and safety for continued development
SS1 Cohort 2
The dose-response relationship of 2 doses of etrasimod versus placebo as induction therapy in subjects with moderately to severely active CD
An oral etrasimod dose, based on efficacy and safety, for continued development along with data generated from SS1 Phase 2b Cohort 1
SS2
The efficacy of the selected etrasimod dose vs placebo as induction therapy in subjects with moderately to severely active CD
SS3
The efficacy of etrasimod vs placebo as maintenance therapy in subjects
SS4
The long-term safety and tolerability of etrasimod in subjects with moderately to severely active CD
To evaluate the long-term safety and tolerability of etrasimod in subjects with moderately to severely active CD

Secundaire doelstelling:
SSA
veiligheid, verdraagbaarheid en werkzaamheid op lange termijn van etrasimod bij personen met matig tot ernstig actieve coeliakie
PK-effecten van etrasimod als inductie- en onderhoudstherapie bij personen met matig tot ernstig actieve coeliakie
SS1
Veiligheid, verdraagbaarheid en werkzaamheid van etrasimod bij personen met matig tot ernstig actieve coeliakie
SS2
veiligheid en verdraagbaarheid van geselecteerde etrasimod Ph3-dosis versus placebo als inductietherapie bij proefpersonen met matig tot ernstig actieve coeliakie
SS3
werkzaamheid van etrasimod op aanhoudende klinische remissie en endoscopische respons, endoscopische remissie en corticosteroïdenvrije klinische remissie bij personen met matig tot ernstig actieve coeliakie karakteriseren de veiligheid en verdraagbaarheid van etrasimod als onderhoudstherapie bij personen met matig tot ernstig actieve coeliakie
SS4
Langetermijnwerkzaamheid van etrasimod bij personen met matig tot ernstig actieve coeliakie

Study design

This is a seamless Phase 2/3, multicenter, randomized, double-blind study that comprises 5 substudies designed to evaluate the efficacy, safety, and tolerability of etrasimod as 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).
Substudy A - Phase 2 (SSA-P2): A Phase 2, randomized, double-blind, substudy to assess the safety, tolerability, and efficacy of oral etrasimod therapy in subjects with moderate to severe CD that supports the selection of an induction and maintenance dose(s) for Phase 3.
Substudy 1 - Phase 2 (SS1-P2b): A Phase 2b randomized, double-blind, placebo-controlled, dose-ranging induction substudy to evaluate etrasimod as induction therapy and select an induction and maintenance dose(s) for continued evaluation in Phase 3.
Substudy 2 - Induction (SS2-I): A Phase 3 randomized, double-blind, placebo-controlled substudy to evaluate etrasimod as induction therapy.
Substudy 3 - Maintenance (SS3-M): A Phase 3 randomized, double-blind, placebo-controlled substudy to evaluate etrasimod as maintenance therapy.
Substudy 4 - Long-Term Extension (SS4-E): A long-term extension (LTE) substudy for subjects who complete at least 52 weeks of treatment.

Intervention

Depending on the substudy the subject will be taking etrasimod 3 mg, etrasimod 2 mg or matching placebo.

Study burden and risks

As of 30 August 2019, etrasimod has been found to be safe and well-tolerated in approximately 388 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. In APD334-005, the open-label extension of Study APD334-003, the most frequently reported events by > 5 subjects treated with 2 mg etrasimod were UC (worsening), gamma-glutamyl transferase increase, anemia, nasopharyngitis, and upper respiratory tract infection. 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 fingolimod, siponimod and ozanimod. 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 normal 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 2/3, 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. Subjects 18 to 80 years of age, inclusive, at the time of consent
2. Ability to provide written informed consent and to be compliant with the schedules of protocol assessments
3. Have CD for >= 3 months prior to randomization, involving the ileum and/or colon, at a minimum; diagnosis may be confirmed at any time in the past by endoscopy and/or histopathology. The screening endoscopy and histopathology reports may serve as source documents for subjects who do not have diagnostic endoscopy reports in their medical chart
4. Have moderately to severely active CD at Screening, defined as:
* Crohn's Disease Activity Index (CDAI) score >= 220 and <= 450, AND
* Unweighted average worst daily abdominal pain (AP) score >= 2 unweighted average daily loose/watery stool frequency (SF) score >= 4, AND
* Simple Endoscopic Score in Crohn's disease (SES-CD) of >= 6 or SES-CD >= 4 for subjects with isolated ileal disease
5. Demonstrated inadequate response, loss of response to, or intolerance to >= 1 of the following therapies for the treatment of CD
* Oral corticosteroids (eg, prednisone [or its equivalent] or budesonide)
* Immunosuppressants (eg, azathioprine, 6-mercaptopurine, or methotrexate)
* Tumor necrosis factor alpha (TNFα) antagonists (eg, infliximab, adalimumab, certolizumab pegol, or biosimilars)
* Integrin receptor antagonist (eg, vedolizumab)
* Interleukin-12/-23 antagonist (eg, ustekinumab)
6. Females of childbearing potential must be nonpregnant
7. 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 and confirmed by follicle-stimulating hormone (FSH) within

postmenopausal range according to local standards
* Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
b. A female who is of childbearing potential must agree to using a highly effective contraception method during treatment and for 4 weeks 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 (IUS)
* Bilateral tubal occlusion
* Vasectomized partner, provided that partner is the sole sexual partner of the FOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success
* Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug). 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 (calendar, symptothermal, post-ovulation methods) is not acceptable
c. A male must agree to using condoms during treatment and for 4 weeks following treatment
SS3-M, SS4-E: Females and males must continue to meet contraception criterion described above

Exclusion criteria

Key exclusion criteria:
- History of inadequate response (ie, primary non-response) to agents from >= 2 classes of biologics marketed for the treatment of CD (ie, TNFα 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 Clostridioides difficile toxin at Screening
- Have functional or post-operative short-bowel syndrome (ie, have > 3 small bowel resections) 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. Subjects who have undergone previous colonic resection or ileocolectomy must have > 25 cm of colon remaining
- Have an ileostomy or a colostomy
- Have a serious infection requiring intravenous antibiotic(s)/medication(s) <= 4 weeks prior to randomization
- Have primary or secondary immunodeficiency syndromes, history of organ transplant, history of an opportunistic infection, history of disseminated herpes simplex or herpes zoster, have or test positive for HIV, HBV, or active HCV
- Lactating female who is breastfeeding

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:	Recruiting
Start date (anticipated):	12-07-2021
Enrollment:	9
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Etrasimod

Generic name:	Etrasimod

Ethics review

Approved WMO Date:	02-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-04-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2024
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
EU-CTR	CTIS2024-513569-38-00
EudraCT	EUCTR2020-004775-40-NL
ClinicalTrials.gov	NCT04173273
CCMO	NL76169.056.21