Etrasimod Versus Placebo as Induction Therapy in Moderately to Severely Active Ulcerative Colitis

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Main Information

Primary registry identifying number
LBCTR2020043427

Protocol number
APD334-302

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
04/05/2015

Primary sponsor
Arena Pharmaceuticals Inc.

Primary sponsor: Country of origin
United States of America

Date of registration in primary registry
07/12/2020

Date of registration in national regulatory agency
04/05/2015

Public title
Etrasimod Versus Placebo as Induction Therapy in Moderately to Severely Active Ulcerative Colitis

Acronym

Scientific title
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

Acronym

Brief summary of the study: English
The purpose of this study is to assess the efficacy and safety of Etrasimod on clinical remission in participants with moderately to severely active ulcerative colitis (UC)

Brief summary of the study: Arabic
الغرض من هذه الدراسة هو تقييم سلامة و فعالية etrasimod على تخفيف الاعراض والالأم عند المرضى المشاركين في الدراسة و الذين يعانون من التهاب القولون التقرحي المعتدل إلى الشديد

Health conditions/problem studied: Specify
Ulcerative Colitis (UC)

Interventions: Specify
Drug: Etrasimod (APD334) 2mg tablet by mouth, once daily up to 12-Week Induction Treatment Period
Drug: Placebo tablet by mouth, once daily up to 12-Week Induction Treatment Period

Key inclusion and exclusion criteria: Inclusion criteria
Subjects must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:
1. Men or women 16 to 80 years of age, inclusive, at the time of assent/consent
2. Ability to provide written informed consent or assent (parent or legal guardian must provide consent for a subject < 18 years of age who has assented to participate in the study or as required per local regulations) and to be compliant with the schedule of protocol assessments
Disease-specific inclusion criteria:
3. Diagnosed with UC ≥ 3 months prior to screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence. The

endoscopy and histology report should be present in the source documents; however, if not available, the screening endoscopy and histology may serve as such
4. Active UC confirmed by endoscopy with ≥ 10 cm rectal involvement. Inclusion of subjects with proctitis only at baseline 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 (performed according to local standard) 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.
Prior 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. Oral 5-aminosalicylic acid (5-ASA) compounds
b. Corticosteroids
c. Thiopurines
Biologic therapy or JAK inhibitor therapy
a. Antitumor necrosis factor alpha (TNFα) antibodies (eg, infliximab, adalimumab, golimumab, or biosimilars)
b. Anti-integrin antibodies (eg, vedolizumab)
c. JAK inhibitors (eg, tofacitinib)
Note: The medication used to qualify the subject for entry into this category must be approved for the treatment of UC in the country of use.
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
• Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
If oral aminosalicylates 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.
Other general inclusion criteria:
9. Vital signs at screening and prerandomization taken in the sitting position: heart rate ≥ 50 bpm, systolic blood pressure (BP) ≥ 90 mm Hg, and diastolic BP ≥ 55 mm Hg
10.Screening and pre-randomization 12-lead electrocardiogram (ECG) showing no clinically significant abnormalities with a PR interval ≤ 200 ms, Fridericia's corrected QT interval (QTcF) < 450 ms (men) or QTcF < 470 ms (women)
11.Adequate hematological function defined by white blood cell count ≥ 3.5 × 109/L with absolute neutrophil count ≥ 1.5 × 109/L, lymphocyte count ≥ 0.8 × 109/L, platelet count ≥ 100 × 109/L, and hemoglobin ≥ 8 g/dL
12.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 ≤ 3.0 × ULN. Subjects with an isolated total bilirubin and normal AST and ALT diagnosed with Gilbert's syndrome may participate
13.Adequate renal function defined by an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m2 by the CKD-EPI equation at screening
14.Eligible women of childbearing potential must be:
a. Nonpregnant, evidenced by a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening and a urine dipstick pregnancy test at Day 1
b. Not breastfeeding
15.Both men and women subjects agree to use a highly effective method of birth control throughout the entire study period, from informed consent through the adverse event reporting period (30 days after the last dose of study treatment), if the possibility of conception exists. Eligible men and women subjects must also agree not to participate in a conception process (ie, actively attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization) during the study and for 30 days after the last dose of study treatment. Highly effective birth control methods include the following:
• Oral, implantable, or injectable contraceptives (starting ≥ 60 days before dosing) in combination with a diaphragm with vaginal spermicide, cervical cap with vaginal spermicide, or male condom; hormonal contraceptives (subjects should be consistently taking the hormonal contraceptive for at least 3 months [90 days] prior to screening)
• Standard intrauterine device (IUD; eg, Copper T 380A IUD), intrauterine system (IUS; eg, LNg 20 IUS - progesterone IUD), progesterone implant, or tubal sterilization (≥ 180 days after surgery)
• Vasectomized male subjects using a condom, partner using diaphragm with spermicide, cervical cap with spermicide, estrogen and progesterone oral contraceptives ("the pill"), estrogen and progesterone transdermal patch, vaginal ring, or progesterone injection
• Complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments. 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, sympto-thermal, post-ovulation methods) is not acceptable
Note: Women who are surgically sterile or postmenopausal (defined as: 12 consecutive months with no menses without an alternative medical cause) are not considered to be of childbearing potential. If of childbearing potential, female partners of participating male subjects should agree to utilize a highly effective method of contraception for the duration of study participation.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

16

Key inclusion and exclusion criteria: Age maximum

80

Key inclusion and exclusion criteria: Exclusion criteria

Exclusions related to general health:
1. Severe extensive colitis as evidenced by:
• Physician judgment that the subject is likely to require hospitalization for medical care or surgical intervention of any kind for UC (eg, colectomy) within 12 weeks of baseline
• 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 or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease
3. Diagnosis of microscopic colitis, ischemic colitis, or infectious colitis
4. Hospitalization for exacerbation of UC requiring intravenous (IV) steroids within 12 weeks of screening (a single dose of IV steroids given is acceptable)
5. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or positive test for Clostridium difficile toxin at screening (If C. difficile is positive, the subject may be treated and retested ≥ 4 weeks after completing treatment)
6. Pregnancy, lactation, or a positive serum β-hCG measured during screening
7. Clinically relevant hematologic, hepatic, neurological, pulmonary, ophthalmological, endocrine, metabolic (including, but not limited to, hypo- and hyperkalemia), psychiatric or other major systemic disease making implementation of the protocol or interpretation of the study difficult or would put the subject at risk
8. Recent history (within 2 months of the Screening Visit) of cardiovascular disease, including myocardial infarction or unstable angina
9. Any history of the following, unless treated with an implanted pacemaker or an implanted cardioverter-defibrillator with pacing:
• History or presence of symptomatic bradycardia
• History of sick sinus syndrome or neurocardiogenic syncope
• Second or third-degree atrioventricular (AV) block
• Periods of asystole > 3 seconds
10.Forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values and FEV1/FVC ratio < 0.70 at screening
11.Uncontrolled diabetes as determined by hemoglobin A1c (HbA1c) > 9% at screening, or subjects with diabetes with significant comorbid conditions such as retinopathy
12.History of macular edema or retinopathy
13.Current or past history of active tuberculosis (TB), history of untreated latent TB infection, or test positive for latent TB infection at screening. The following are EXCEPTIONS to this exclusion criteria:
• Subjects with latent TB, who have been ruled out for active TB, have completed an appropriate course of TB prophylaxis treatment per national/local medical guidelines or WHO guidelines, and have not had recent close contact with a person with active TB are eligible to enroll in the study. It is the responsibility of the Investigator to verify the adequacy of previous TB treatment and provide appropriate documentation
• Subjects diagnosed with latent TB at screening, ruled out for active TB and received at least 4 weeks of an appropriate TB prophylaxis regimen may be rescreened for enrollment
Note: The 2 exceptions to this exclusion criterion outlined above do NOT apply to subjects in countries identified by WHO as a high multi-drug resistant TB burden country due to the high risk of latent infection with multi-drug resistance.
14.Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including TB or atypical mycobacterial disease) or any major episode of infection that required hospitalization or treatment with IV antibiotics within 30 days of screening or during screening or oral antibiotics within 14 days prior to screening. Fungal infection of nail beds is allowed
15.Have human immunodeficiency virus (HIV)/acquired immune deficiency syndrome or test positive for HIV antibodies at screening
16.Have acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at screening (positive for hepatitis B surface antigen [HBsAg], or negative for HBsAg and

positive for antihepatitis B core antibody in conjunction with detectable HBV DNA, or detectable HBV DNA)
17.Have current hepatitis C infection or test positive for hepatitis C virus (HCV) at screening as defined by positive for hepatitis C antibody and detectable HCV RNA
18.History of an opportunistic infection (eg, pneumocystis carinii, cryptococcal meningitis, progressive multifocal leukoencephalopathy) or serious bacterial, viral, or fungal infections (eg, disseminated herpes simplex, disseminated herpes zoster) and requiring IV medication(s) ≤ 3 weeks prior to randomization
19.History of or currently active primary or secondary immunodeficiency
20.History of cancer within the last 5 years, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) or colonic mucosal dysplasia
21.History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma
22.History of alcohol or drug abuse within 1 year prior to randomization
Exclusions related to medications:
23.Prior treatment with sphingosine 1-phosphate receptor modulators
24.Treatment with a biologic agent within 8 weeks or 5 elimination half-lives, whichever is shorter, prior to randomization
25.Treatment with an investigational therapy within 3 months prior to randomization
26.Treatment failure with ≥ 3 biologic agents or ≥ 2 biologics plus a JAK inhibitor approved for treatment of UC
27.Treatment with topical rectal 5-ASA, short-chain fatty acid enemas, or steroids within 2 weeks of screening or during screening
28.Treatment with cyclosporine, tacrolimus, sirolimus, methotrexate, or mycophenolate mofetil within 16 weeks of screening
29.Receipt of a live vaccine within 4 weeks prior to randomization
30.Previous treatment with natalizumab
31.Previous treatment with lymphocyte-depleting therapies (eg, alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
32.Previous treatment with D-penicillamine, leflunomide, or thalidomide
33.Treatment with IV immune globulin or plasmapheresis within 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 within 4 weeks prior to randomization

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

APD334 (Etrasimod)

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

Highly Selective Sphingosine-1 Phosphate (S1P) Receptor Modulator

Therapeutic indication

Ulcerative Colitis

Therapeutic benefit

Clinical remission of patients with moderately to severely active ulcerative colitis

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples with DNA**

Biospecimen description

Both Samples with DNA and Samples without DNA will be processed

Target sample size

16

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

01/08/2020

Date of study closure: Type

Anticipated

Date of study closure: Date

06/01/2022

Recruitment status

Pending

Recruitment status: Specify

Date of completion

07/07/2021

IPD sharing statement plan

IPD sharing statement description

No	N/A

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
clinicaltrials.gov	NCT03996369
European Clinical Trials Database	EudraCT Number: 2018-003986-33

Sources of Monetary or Material Support

Name
Arena Pharmaceuticals Inc. USA

Secondary Sponsors

Name
N/A

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Hasan Dakkak	Wahat Al Arab Building 3rd floor - Al Arab Street – Barbir – Beirut	Lebanon	009617002 7779	hasan.dakkak@iqvia.com	IQVIA
Scientific	Chris Cabell	6154 Nancy Ridge Dr. ▪ San Diego, CA 92121	United States of America	+1858453 7200	ccabell@arenapharm.com	Arena Pharmaceuticals

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
American University of Beirut Medical Center	Dr. Alaa Sharara	Gastroenterology	Approved
Hotel Dieu de France Hospital	Dr. Cesar Yaghi	Gastroenterology	Approved
Saint George University Medical Center	Dr. Said Farhar	Gastroenterology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Hotel Dieu de France	26/09/2019	Pr. Sami Richa	cue@usj.edu.lb	9611421229
American University of Beirut Medical Center	10/09/2020	Pr. Ali Abou Alfa	N/A	9611350000
Saint George Hospital University Medical Center	24/09/2020	Dr. Michel Daher	NA	9611441000

Countries of Recruitment

Name
Australia
Austria
Belgium
Brazil
Bulgaria
Canada
Chile
China
Croatia
Czech Republic
Denmark
Estonia

France
Germany
Hungary
India
Italy
Republic of Korea
Republic of Moldova
Netherlands
Poland
Portugal
Russian Federation
Republic of Serbia
Slovakia
South Africa
Spain
Taiwan
Thailand
Turkey
Ukraine
United Kingdom
United States of America
Belarus
Latvia
Lithuania
Georgia

Health Conditions or Problems Studied

Condition	Code	Keyword
Ulcerative Colitis	Ulcerative colitis (K51)	Colitis Colitis, Ulcerative Ulcer Gastroenteritis Gastrointestinal Diseases Digestive System Diseases Colonic Diseases Intestinal Diseases Pathologic Processes Inflammatory Bowel Diseases

Interventions

Intervention	Description	Keyword
Drug	APD334 (Etrasimod) 2mg tablet	Etrasimod
Drug	Matching Placebo tablet	Placebo

Primary Outcomes

Name	Time Points	Measure
Proportion of Participants With Clinical Remission	Week 12	Mayo Component Sub-scores

Key Secondary Outcomes

Name	Time Points	Measure
Proportion of Participants Achieving Endoscopic Improvement	Week 12	Mayo Component Sub-scores
Proportion of participants With Mucosal Healing	Week 12	Geboes Index Scores

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files