Induction Study #2 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Oral Ozanimod as Induction Therapy for Moderately to Severely Active Crohn's Disease

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Primary objective:- Demonstrate the efficacy of ozanimod compared to placebo on the induction of clinical remissionSecondary objectives:- Demonstrate the efficacy of ozanimod compared to placebo on induction of clinical response, clinical remission...

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

Summary

ID

NL-OMON55896

Source
ToetsingOnline

Brief title
Study of Ozanimod as Induction Therapy in patients with Crohn's Disease

Condition

- Gastrointestinal inflammatory conditions

Synonym
bowel disease, immune-mediated inflammatory disease of the gastrointestinal tract

Research involving

Human

Sponsors and support

Primary sponsor: Celgene International II Sàrl
Source(s) of monetary or material Support: Celgene International II Sàrl

Intervention

Keyword: Crohn's disease, double-blind, induction therapy, placebo

Outcome measures

Primary outcome

Primary Endpoint:

- Proportion of subjects with a CDAI score < 150 at Week 12

Secondary outcome

Major Secondary Endpoints:

* Proportion of subjects with average daily abdominal pain score <= 1 point, and average daily stool frequency score <= 3 points and a stool frequency score no worse than baseline at Week 12

- Proportion of subjects with a Simple Endoscopic Score for Crohn*s Disease (SES-CD) score decrease from baseline of >= 50% at Week 12

- Proportion of subjects with CDAI reduction from baseline of >= 100 points or CDAI score < 150 at Week 12

- Proportion of subjects with CDAI reduction from baseline of >= 100 points or CDAI score < 150 and SES-CD decrease from baseline of >= 50% at Week 12

Other Secondary Endpoints:

- Proportion of subjects with CDAI score <150 at Week 12 and SES-CD decrease from baseline of >= 50% at Week 12

- Histologic Improvement: based on the significant differences between ozanimod and placebo in histologic disease activity scores (ie, Global Histologic Disease Activity Score changes (Geboes, 2000) at Week 12

- Proportion of subjects with CDAI reduction from baseline of >= 70 points at Week 12

- Proportion of subjects with absence of ulcers >= 0.5 cm with no segment with any ulcerated surface >= 10% at Week 12

- Proportion of subjects with a Crohn*s Disease Endoscopic Index of Severity (CDEIS) decrease from baseline of >= 50% at Week 12

Other Resource Utilization and Subject-Reported Outcome Endpoints:

- Improvement in Inflammatory Bowel Disease Questionnaire (IBDQ) scores

- Improvement in 36-Item Short Form-36 Survey (SF-36) scores

- Improvement in Work Productivity and Activity Impairment questionnaire for Crohn*s disease (WPAI-CD) scores

- Improvement in EuroQol 5 dimensions questionnaire (EQ-5D) scores

- Differences in CD-related hospitalizations and surgery

Exploratory Endpoints:

- Proportion of subjects with resolution of extraintestinal manifestations (EIM) of Inflammatory Bowel Disease (IBD) among those who had them at baseline

- Improvement in fecal calprotectin

- Improvement in C-reactive protein

- Proportion of subjects with SES-CD decrease from baseline of >= 25%

- Proportion of subjects with SES-CD <= 4 points and a SES-CD decrease >= 2

- Proportion of subjects with absence of ulcers (ulcerated surface score = 0

in all explored segments)

- Proportion of subjects with SES-CD = 0

- Change from baseline in SES-CD components

- Change from baseline in CDAI

- Improvement in Bristol Stool Scale

- Proportion of subjects with CDAI reduction from baseline of >= 100 points or CDAI score < 150 and SES-CD decrease from baseline of >= 50%

- Proportion of subjects with CDAI score < 150 and SES-CD <= 4 points and a SES-CD decrease >=2 points

- Proportion of subjects with average daily abdominal pain score <= 1 point and average daily stool frequency score <= 3 points and a stool frequency no worse than baseline and a SES-CD decrease from baseline of >= 50%

- Proportion of subjects with average daily abdominal pain score <= 1 point and average daily stool frequency score <= 3 points and a stool frequency score no worse than baseline and SES-CD <= 4 points and a SES-CD decrease >= 2 points

- Improvement in subject overall well-being based on the change in the visual analogue scale (VAS) from the EQ-5D

- Histologic improvement based on the significant differences between ozanimod and placebo in histologic disease activity score (Robarts Histologic Index)

- Proportion of subjects with CDAI score < 150 in subjects who had previously received biologic treatment

- Proportion of subjects with CDAI reduction from baseline of >= 100 points or CDAI score < 150 in subjects who had previously received biologic treatment

Biomarker Endpoints:

- Efficacy in subjects (clinical response, clinical remission, mucosal

improvement, and histologic improvement at Week 12) as a function of baseline

- Circulating lymphocyte concentration, such as plasmablasts

- Gene expression, such as interferon signature in blood and/or colon biopsy

- Protein biomarker concentration, such as high-density lipoprotein,

C-reactive protein, fecal calprotectin, immunoglobulin A (IgA)

- Pharmacogenetics, such as at the interferon regulatory factor (IRF) 5 locus

Study description

Background summary

Crohn*s disease (CD) is an immune-mediated inflammatory disease of the gastrointestinal (GI) tract. Annual incidence varies geographically, with estimates ranging from 3.1 to 14.6 per 100,000 people in the United States and from 0.1 to 16 per 100,000 worldwide (Lakatos, 2006). Subjects with CD suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever. Crohn*s disease is characterized by a lifelong chronic course of remissions and exacerbations. The pathology of this disease is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis. The transmural inflammatory process of CD predisposes subjects to the formation of fistulas and it has been estimated that approximately 35% of subjects will have at least 1 fistula during the course of their disease (Schwartz, 2002). In a recent study, within 10 years of diagnosis, 50% of adults with CD had undergone bowel surgery (Peyrin-Biroulet, 2010).
The current standard of medical care for patients with moderately to severely active CD consists of anti-inflammatory approaches, such as corticosteroids, azathioprine (AZA)/6-mercaptopurine (6-MP), methotrexate (MTX), and biologics such as anti-tumor necrosis factor (TNF)α, anti-IL-12/IL-23, or anti-integrins. Immunomodulators aid in corticosteroid withdrawal and in preventing relapse, but also are associated with considerable side effects. Infliximab, an anti-TNFα-therapy, is able to reduce signs and symptoms and induce and maintain remission in the majority of subjects for which it is indicated.
Therefore, there remains considerable unmet medical need for safe, effective, and oral treatments for adult subjects with CD, and the identification of biomarkers that predict response to therapy in a CD patient population with

significant genotypic and phenotypic diversity.

Study objective

Primary objective:
- Demonstrate the efficacy of ozanimod compared to placebo on the induction of clinical remission
Secondary objectives:
- Demonstrate the efficacy of ozanimod compared to placebo on induction of clinical response, clinical remission, endoscopic response, endoscopic remission, and histologic improvement
- Demonstrate the efficacy of ozanimod compared to placebo, in subjects who had previously received biologic therapy (eg, anti-IL-12, anti-IL-23, anti-TNF, or anti-integrin therapy)
- Characterize the population pharmacokinetics (PK) and PK/pharmacodynamics (PD) relationship of ozanimod
- Demonstrate the safety and tolerability of ozanimod as induction therapy

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled study to determine the effect of oral ozanimod as an induction treatment for subjects with moderately to severely active CD, defined as a CDAI score >= 220 to <= 450. Subjects who complete the Induction Study are anticipated to receive 12 weeks of treatment (12-week Induction Study). Subjects not entering the Maintenance Study or Open-label Extension Study will have a Safety Follow-Up Visit (30 to 45 days after the last dose of investigational product [IP]).
The end of study (Induction Study RPC01-3202) is defined as either the date of the last visit of the last subject to complete the safety follow-up, or the date of receipt of the last datapoint from the last subject that is required for primary or secondary analysis, as prespecified in the protocol, whichever is the later date.

Intervention

Subjects will receive a single 0.92 mg (equivalent to ozanimod HCl 1 mg) oral dose of ozanimod or matching placebo administered daily, starting with a 7-day dose escalation regimen of ozanimod 0.23 mg (equivalent to ozanimod HCl 0.25 mg) or matching placebo daily on Days 1 through 4 and ozanimod 0.46 mg daily (equivalent to ozanimod HCl 0.5 mg; administered as two 0.23 mg capsules) or two matching placebo capsules on Days 5 through 7, and reaching the final dose level, 0.92 mg, or matching placebo on Day 8. Subjects will then receive ozanimod 0.92 mg/day (or matched placebo) through Week 12.

Study burden and risks

Patients may experience drug-related side effects. For full list of side effects please refer to Appendix E of the main patient information sheet and infomed consent from. In addition to side effects patients may experience discomforts and risks associated with the study procedures such as blood drawing, endoscopies, colonic biopsies.

Contacts

Public
Celgene International II Sàrl

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Boudry 2017
CH
Scientific
Celgene International II Sàrl

Route de Perreux 1 1
Boudry 2017
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female subjects aged 18 to 75 years (at Screening).
2. Subject should not have any constraints under local regulations and, must provide written informed consent prior to any study-related procedures, and must have the ability to comply with the Table of Events.
3. Subject has signs and symptoms consistent with a diagnosis of CD for at

least 3 months (prior to first IP administration). The diagnosis should be confirmed by clinical and endoscopic evidence and corroborated by a histology report. (Note: endoscopy and histopathology confirmation may be obtained during Screening if no prior report is readily available).
4. Subject has met each of the following 2 criteria:
*- a CDAI score >= 220 and <= 450
*- an average daily stool frequency >= 4 points and/or an abdominal pain of >= 2 points
5. Subject has a SES-CD score of >= 6 (or SES-CD >= 4 in subjects with isolated ileal disease).
6. Subject has an inadequate response or loss of response to or is intolerant of at least 1 of the following systemic CD treatments (see Appendix B for additional details):
* - corticosteroids
* - immunomodulators
* - biologic therapies (eg, ustekinumab, TNFα antagonists, or vedolizumab)
7. If the subject is taking the following background therapies for CD, a stable dose must be maintained throughout the study beginning from the screening period as indicated below:
oral aminosalicylates (eg, mesalamine, sulfasalazine, olsalazine, balsalazide) with a stable dose for at least 3 weeks prior to Screening endoscopy prednisone (doses <= 20 mg per day) or equivalent with a stable dose for at least 2 weeks prior to Screening endoscopy budesonide therapy (doses <= 9 mg per day) or beclomethasone doses <= 5 mg/per day at a stable dose for at least 2 weeks prior to the Screening endoscopy.
8. Subject at high risk (ie, family history, CD duration) for colonic malignancy has documented evidence of having had a surveillance colonoscopy within the last 2 years or according to local and national medical guidelines to evaluate for polyps, dysplasia, or malignancy. If there is no recent history of surveillance colonoscopy, this can be done as part of the colonoscopy performed during Screening. Any visualized adenomatous polyps must be removed and any suspicious lesion confirmed free of cancer and/or dysplasia prior to randomization.
9. Female subjects of childbearing potential (FCPB):Note: For the purposes of this study, a female patient is considered to be of childbearing potential if she 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).
Must agree to practice a highly effective method of contraception throughout the study until completion of the 90-day Safety Follow-Up Visit. Highly effective methods of contraception are those that alone or in combination result in a failure rate of a Pearl Index of less than 1% per year when used consistently and correctly. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Counseling about pregnancy precautions and the potential risks of fetal

exposure must be conducted for FCBP. The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence at Screening and Day 1, as appropriate. The FCBP's chosen form of contraception must be effective by the time she is randomized into the study.
10. Subject must have documentation of positive varicella zoster virus (VZV) immunoglobulin G (IgG) antibody status or complete VZV vaccination at least 30 days prior to randomization.

Exclusion criteria

Exclusions Related to General Health:
1. Subject has any clinically relevant cardiovascular hepatic, neurological, pulmonary [severe respiratory disease (pulmonary fibrosis or chronic obstructive pulmonary disease)], ophthalmological, endocrine, psychiatric, or other major systemic disease making implementation of the protocol or interpretation of the study difficult or that would put the subject at risk by participating in the study.
2. Subject is likely to require, in the physician's judgment, bowel resection within 12 weeks of entry into the study.
3. Subject has a diagnosis of UC, indeterminate colitis, radiation colitis, or ischemic colitis, or has
strictures with prestenotic dilatation. Any other modality used in addition to the colonoscopy to assess this criterion must be discussed with the Medical Monitor.
4. Subject has current stoma, ileal-anal pouch anastomosis, symptomatic fistula, or need for ileostomy or colostomy.
5. Subject has extensive small bowel resection (> 100 cm) or known diagnosis of short bowel syndrome, or subject requires total parenteral nutrition.
6. Subject has suspected or diagnosed intra-abdominal or perianal abscess that has not been appropriately treated.
7. Subject has documentation of a positive test for toxin producing Clostridium difficile (C. difficile), or polymerase chain reaction (PCR) examination of the stool on their most recent test, which must have been done in the past 60 days. If positive, subjects may be treated and retested no earlier than 7 days after completion of treatment.
8. Subject has documentation of positive examination for pathogens (ova and parasites, and bacteria), which must have been done in the past 60 days. If positive, subjects may be treated and retested.
9. Subject is pregnant, lactating, or has a positive serum β-hCG test measured during Screening.
10. Subject has clinically relevant cardiovascular conditions, making implementation of the protocol or interpretation of the study difficult or that would put the subject at risk by participating in the study, including history or presence of the following:
- Recent (within the last 6 months) occurrence of myocardial infarction,

unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea
*- Second degree atrioventricular (AV) Block (eg, Mobitz II), third degree heart block unless subjects have a pacemaker in place
* - Prolonged QTcF interval (QTcF > 450 ms males, > 470 ms females)
* - Resting heart rate (HR) <55 bpm when taking vitals as part of a physical examination at Screening
11. Subject has a history of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c (HbA1c) > 9%, or is a diabetic subject with significant comorbid conditions such as retinopathy or nephropathy
12. Subject has a history of uveitis or macular edema.
13. Subject has a known active bacterial, viral, fungal (excluding fungal infection of nail beds, minor upper respiratory tract infections, and minor skin infections), mycobacterial infection (including tuberculosis [TB] or atypical mycobacterial disease) or any major episode of infection that either required hospitalization, treatment with intravenous (IV) antibiotics within 30 days of Screening, or treatment with oral antibiotics within 14 days of Screening. • Note: In the case of a known SARS-CoV-2 infection, symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician / Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving investigational treatment. SARS-CoV 2 testing may be conducted prior to randomization if required by and in accordance with national, local or institutional guidelines. See App C for more details.
14. History or known presence of recurrent or chronic infection (eg, hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]); recurrent urinary tract infections are allowed.
15. Subject has a history of active cancer within 5 years, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin or cervical dysplasia/cancer that have been excised and resolved) or colonic dysplasia that has not been completely removed.
16. Subject has a history of alcohol or drug abuse within 1 year prior to initiation of Screening. Please see the protocol for Exclusions Related to Laboratory Results and Exclusions related to Medications

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:	Completed
Start date (anticipated):	11-12-2019
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ozanimod
Generic name:	ozanimod

Ethics review

Approved WMO Date:	12-03-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-10-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-02-2019
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-07-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-03-2021
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Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-07-2021
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Approved WMO Date:	06-09-2021
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Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-10-2021
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-02-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-08-2023
Application type:	Amendment

Review commission: METC Brabant (Tilburg)

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	EUCTR2017-004293-33-NL
ClinicalTrials.gov	NCT03440385
CCMO	NL64984.028.18

Study results

Date completed: 25-08-2023

Results posted: 12-11-2024

Actual enrolment: 15

First publication
11-11-2024