A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) FOR TREATMENT OF SUBJECTS WITH ACTIVE ULCERATIVE COLITIS

Published: 19-05-2015
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Primary ObjectiveTo evaluate the clinical efficacy of apremilast (30 mg twice daily [BID] and 40 mg BID), compared with placebo, in subjects with active UC.Secondary Objective To evaluate the safety and tolerability of apremilast (30 mg BID and 40...

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

Summary

ID

NL-OMON45076

Source
ToetsingOnline

Brief title
Celgene CC-10004-UC-001

Condition

- Gastrointestinal inflammatory conditions

Synonym
Chronic colon inflammation, Ulcerative colitis

Research involving

Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Apremilast, Ulcerative Colitis

Outcome measures

Primary outcome

Details of the statistical analysis are outlined in Section 10 of the Protocol.

Key elements of the analysis are described below.

The ITT population will be the primary population for efficacy analyses. A supportive analysis using the PP population will also be performed for the primary efficacy endpoint.

The comparisons for the primary efficacy endpoint will be based on two-sided statistical tests at a significance level of 0.1. A hierarchical approach will be used to adjust for multiplicity. For the primary endpoint, the first test in the hierarchy will be the apremilast 40 mg BID treatment group compared to placebo, followed by the apremilast 30 mg BID treatment group compared to placebo. If any of the active treatment groups (apremilast 30 mg or 40 mg BID) is discontinued prior to the end of the study, the treatment comparison will be conducted for the retained treatment group vs. placebo based on a two-sided statistical test at the 0.1 level. Additional endpoints subsequent to the primary endpoint comparisons may be added to the hierarchy and specified in the

SAP.

Summary of all efficacy endpoints over time will be provided using frequency and percent for categorical endpoints and descriptive statistics for continuous endpoints.

The primary efficacy endpoint is clinical remission, as defined as a TMS of * 2 with no individual subscore > 1 at Week 12. The proportion of subjects who achieve a clinical remission at Week 12 between any apremilast (30 mg BID or 40 mg BID) group and the placebo group will be compared using the Cochran-Mantel-Haenszel (CMH) test controlling for the randomization stratification factors specified. Subjects who prematurely discontinue the study before Week 12 will be considered.

Secondary outcome

The secondary efficacy endpoints defined in Section 3.2.1 will be analyzed using the CMH test controlling for the randomization stratification factors as will be done for the primary efficacy endpoint.

Study description

Background summary

The main objectives of treatment in patients with UC are to induce and maintain the remission of symptoms and mucosal inflammation in order to improve patients* quality of life. Treatment of UC currently involves pharmacological treatment and surgery, which is indicated when pharmacological treatment fails or when a surgical emergency (eg, perforation of the colon) occurs. Treatment takes into consideration the level of clinical activity combined with the

extent of disease (proctitis, left-sided disease, extensive disease, or pancolitis). Pharmacological treatment usually involves aminosalicylates and glucocorticoids as an initial approach. Various immunosuppressants, as well as biologic tumor necrosis factor (TNF) blockers, are used in refractory or severe disease. Although these drugs can provide clinical benefit, they have important limitations. Aminosalicylates are only modestly effective. Glucocorticoids can cause unacceptable adverse events (AEs) and do not provide a benefit as maintenance therapy.
Additionally, immunosuppressant use has been restricted to maintenance therapy and is also
associated with significant potential toxicities. The TNF blockers, although efficacious,
predispose patients to serious infections (including opportunistic infections) and possibly
malignancies. Because apremilast specifically inhibits PDE4,
which increases intracellular cyclic adenosine monophosphate (cAMP) and this modulates
multiple pro-inflammatory and anti-inflammatory mediators, such as TNF-*, IL-12, and IL-23, it is believed there may be a role for this drug in the treatment of UC.
The additional burden caused by comorbidities induced by adverse effects of some of these drugs indicates that an unmet medical need exists for effective and well-tolerated orally active agents for inducing and maintaining remission in patients with active UC.

Study objective

Primary Objective
To evaluate the clinical efficacy of apremilast (30 mg twice daily [BID] and 40 mg BID), compared with placebo, in subjects with active UC.
Secondary Objective To evaluate the safety and tolerability of apremilast (30 mg BID and 40 mg BID), compared with placebo, in subjects with active UC.
Exploratory Objectives
**To evaluate the onset of clinical effect of apremilast (30 mg BID and 40 mg BID),
compared with placebo, in subjects with active UC
**To evaluate the benefit of apremilast (30 mg BID and 40 mg BID) on health-related
quality of life (HRQoL) outcome measures, compared with placebo, in subjects with
active UC
** To evaluate the long-term safety in subjects with active UC, receiving apremilast (20 mg BID or 40 mg BID)
**To evaluate the durability of response in subjects with active UC, receiving apremilast (30 mg BID or 40 mg BID) Pharmacokinetic (PK) Objectives, Pharmacodynamic (PD) Objectives, and Pharmacogenetic (PG) Objective
**To characterize the PK of apremilast (30 mg BID and 40 mg BID) in subjects

with
active UC
**To explore the relationship between apremilast exposure and the efficacy of apremilast (30 mg BID and 40 mg BID) in subjects with active UC
**To evaluate the change in biomarkers such as high sensitivity C-reactive protein
(hsCRP) and fecal calprotectin (FCP) in response to apremilast (30 mg BID and 40 mg BID) compared with placebo in subjects with active UC
**To explore the PD effects of apremilast (30 mg BID and 40 mg BID) such as inflammatory cell infiltration, tissue destruction and gene expression in colonic
mucosal biopsies from subjects with active UC
**To explore the association of the PD parameters with the efficacy of apremilast (30
mg BID and 40 mg BID) in subjects with active UC
**To explore the association of PG markers with the efficacy of apremilast (30 mg BID and 40 mg BID) in subjects with active UC

Study design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of 2 doses of apremilast in subjects with active UC (defined as a total Mayo score [TMS] of * 6 to * 11, with an endoscopic subscore * 2). Approximately 165 subjects (55 subjects per arm) will be randomized in a 1:1:1 ratio to receive oral apremilast (30 mg BID or 40 mg BID), or identically appearing placebo BID for up to 20 weeks. Treatment assignment will be stratified via an Interactive Voice Response System (IVRS)/or an Interactive Web Response System (IWRS) based on (1) concomitant use of oral aminosalicylates and (2) previous exposure to immunosuppressants (eg, 6-mercaptopurine [6-MP], azathioprine [AZA], or methotrexate [MTX]).The number of subjects with previous exposure to immunosuppressants is targeted to comprise no more than 50% of the subjects enrolled, and no less than 30%.

The study will consist of 3 phases:
**Screening Phase * up to 4 weeks
**Double-blind Placebo-controlled Phase * Weeks 0 to 12
** Blinded Active-treatment Phase * Weeks 12 to 52
**Extension Phase * Weeks 52 to 104
**Post-treatment Observational Follow-up Phase * Weeks 52 to 56 or weeks 104 to 108, or for subjects who are discontinued early, the 4-week period after the last dose of investigational product (IP).

Double-blind Placebo-controlled Phase
Eligible subjects will enter the Double-blind, Placebo-controlled Phase at the Baseline Visit (Week 0/Visit 2). Subjects will be randomly assigned to study treatment as described above. With the aim to mitigate potential dose-related

side effects associated with apremilast, such as headache and gastrointestinal (GI) disturbances, apremilast-treated subjects will be dose titrated in 10-mg/day increments over the first 8 days of treatment. All subjects will receive blister cards of identical appearance to maintain blinding. Subjects will continue to receive the treatment assigned at baseline for 12 weeks.

Blinded Active-treatment Phase
Following 12 weeks of treatment, subjects will enter the Blinded Active-treatment Phase. At the Week 12 visit, subjects will be evaluated for clinical improvement based on the TMS. The endoscopy subscore assessed by the investigator will be used for the calculation of the Week 12 TMS.
Subjects who achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive
the following IP between the Week 12 Visit and the Week 52 Visit:
* Subjects who were randomized to apremilast (30 mg BID or 40 mg BID) at baseline will continue to receive the treatment assigned at baseline.
* Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments
over the first 8 days of treatment (Table 5).
Subjects who do not achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP until the Week 52 Visit:
* Subjects who were randomized to apremilast 30 mg BID at baseline will be re-assigned apremilast 40 mg BID, with no dose titration.
* Subjects who were randomized to apremilast 40 mg BID at baseline will continue to receive apremilast 40 mg BID.
* Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment (Table 5). In order to maintain the blind for the treatment assigned at baseline, all subjects will receive blister cards of identical appearance during the titration period beginning at Week 12. However, for subjects continuing on the dosage of apremilast assigned at baseline, and for subjects who are not undergoing dose titration (as noted above), the IP included in the *titration* portion of the blister card will include the total daily dose of apremilast (30 or 40 mg BID) and will not include the dose titration.

Extension Phase
At the end of the Blinded Active-treatment Phase (Week 52), subjects who have a Mayo endoscopy score * 1 will have the opportunity to participate in the Extension Phase. Subjects participating in the Extension Phase will continue to receive the same treatment assigned during the Blinded Active-treatment Phase for an additional 52 weeks (Weeks 52 to 104).

Post-treatment Observational Follow-up Phase
Subjects who complete the Double-blind Placebo-controlled Phase, as well as subjects who prematurely discontinue from study, for any reason, will enter the

Post-treatment Observational Follow-up Phase, the 4-week period after the last dose of IP.

Intervention

Subjects will receive one of two dose regimens of apremilast in the Double-blind Placebocontrolled Phase (30 mg BID or 40 mg BID), or placebo BID. Apremilast will be provided in blister cards as 10-mg, 20-mg, or 30-mg tablets in the clinical image. Matched placebo tablets will also be provided. Tablets will be taken by mouth twice daily, morning and evening, approximately 12 hours apart, with no food restrictions.

Study burden and risks

RISKS DUE TO THE STUDY PROCEDURES
Blood sampling. Blood sampling and the use of needles are associated with a certain risk. Possible side effects may be: fainting, bleeding, bruising, discomfort, dizziness, infection and/or pain at the site of the injection.
Electrocardiogram (ECG) * Sometimes, an ECG may cause irritation where the adhesive pads have been applied or if the study staff has to shave the area where the pads are applied.
Blood Pressure * Although it is very rare, blood pressure measurements might bruise. Also, the blood pressure cuff will be very tight and might pinch a little for a short time.
X-ray examinations. Exposure to radiation.
Rectosigmoidoscopy or colonoscopy: This procedure may involve some discomfort. Rare complications include tearing of the colon, intestinal perforation (poking a hole in the gut), and/or bleeding that may require surgical repair. When a biopsy (removal of a small piece of tissue) is performed during the procedure, bleeding from the biopsy site may occur. Other complications that may occur include infection at the biopsy site and bacteria in the blood.

RISKS DUE TO THE STUDY MEDICINE
The following list of side effects is the ones that may be associated with the use of apremilast:
* Very common: Diarrhea, Nausea (stomach upset), Vomiting
* Common: Upper abdominal (stomach) pain, Indigestion, Frequent bowel movement, Heartburn, Fatigue, Bronchitis (infection of the tubes to the lungs), Redness/swelling/pain in the sinuses, Inflammation or infections of the nose and throat Weight loss, Decreased appetite, Back pain, Headache (including tension and migraine), Difficulty sleeping, Cough, Rash, Dizziness, Weakness, Flu, Muscle pain, Numbness, Itchiness
* Uncommon: Allergic reaction.
Reports of various types of cancers, heart problems, and serious infections have been found from apremilast studies. However, these events in patients being treated with apremilast happened as often as those being treated with

placebo (sugar pill).

Severe diarrhea, nausea, and vomiting has been reported with the use of apremilast. Some patients were hospitalized. If you are 65 years of age or older, and/or become dehydrated or experience low blood pressure, you may be at a higher risk of complications. If you experience severe diarrhea, nausea, or vomiting please notify your study doctor immediately.

Contacts

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Scientific
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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. Male or female aged 18 and over at the time of signing the informed consent.
2. Must understand and voluntarily sign an informed consent document

prior to any study related assessments/procedures being conducted.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Diagnosis of UC with duration of at least 3 months prior to the Screening Visit
5. TMS * 6 to * 11 (range: 0-12) prior to randomization in the study.
6. Endoscopic subscore * 2 (range: 0-3) on the Mayo score prior to randomization in the study.
7. Subjects are required to have a colonoscopy if not performed within 12 months of the Screening Visit
8. Subjects must have had a therapeutic failure, been intolerant to, or have a contraindication to, at least one of the following: oral aminosalicylates (ie, 5-aminosalicylic acid [5-ASA] compounds or sulfasalazine [SSZ]), budesonide, systemic corticosteroids, or immunosuppressants (eg, 6-mercaptopurine [6-MP], azathioprine [AZA], or methotrexate [MTX]).
9. Subjects receiving oral corticosteroids may continue their use during the study, provided that the dose (prednisone * 20 mg/day or equivalent, budesonide * 9 mg/day) has been stable for 3 weeks prior to the Screening Visit. If oral corticosteroids were recently discontinued, discontinuation must have been completed at least 3 weeks prior to the Screening Visit. Corticosteroid doses should remain stable until the subject is eligible to start corticosteroids tapering, beginning at the Week 12 Visit.
10. Oral aminosalicylates are permitted during the study, provided that treatment started at least 6 weeks prior to randomization with a stable dose of at least 14 days prior to the Screening Visit. The dose of oral aminosalicylates must remain stable through Week 52 or until Week 104 for subjects who participate in the Extension Phase.
11. Must meet the following laboratory criteria:
- White blood cell count * 3000/mm3 (* 3.0 X 10E9/L) and < 14,000/mm3 (< 14 X 10E9/L)
- Platelet count * 100,000/mm3 (* 100 X 10E9/L)
- Serum creatinine * 1.5 mg/dL (* 132.6 *mol/L)
- AST (SGOT) and ALT (SGPT) *2 X upper limit of normal (ULN). If initial test shows ALT or AST > 2 times the ULN, one repeat test is allowed during the screening period
- Total bilirubin * 2 mg/dL (* 34 *mol/L) or albumin > lower limit of normal (LLN). If initial test result is > 2 g/dL, one repeat test is allowed during the screening period
- Hemoglobin * 9 g/dL (* 5.6 mmol/L)
12. Females of childbearing potential (FCBP) must have a negative pregnancy test at Screening and the Baseline Visit. While on IP and for at least 28 days after taking the last dose of IP, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options2 described below:
Option 1: Any one of the following highly effective methods: hormonal

contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy
OR
Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide
13. Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on investigational product and for at least 28 days after the last dose of investigational product.

Exclusion criteria

1. Diagnosis of Crohn's disease, indeterminate colitis, ischemic colitis, microscopic colitis, radiation colitis or diverticular disease-associated colitis.
2. Ulcerative colitis restricted to the distal 15 cm or less (eg, ulcerative proctitis).
3. Subjects who have had surgery as a treatment for UC or who, in the opinion of the Investigator, are likely to require surgery for UC during the study.
4. Clinical signs suggestive of fulminant colitis or toxic megacolon.
5. Evidence of pathogenic enteric infection.
6. History of colorectal cancer or colorectal dysplasia (with the exception of adenomatous colonic polyps that have been completely resected).
7. Prior use of any TNF inhibitor (or any biologic agent).
8. Prior use of mycophenolic acid, tacrolimus, sirolimus, cyclosporine or thalidomide.
9. Use of IV corticosteroids within 2 weeks of the Screening Visit
10. Use of immunosuppressants (AZA, 6-MP or MTX) within 8 weeks of the Screening Visit.
11. Use of topical treatment with 5-ASA or corticosteroid enemas or suppositories within 2
weeks of the Screening Visit
12. History of any clinically significant neurological, renal, hepatic, gastrointestinal,
pulmonary, metabolic, cardiovascular, psychiatric, endocrine, hematological disorder or
disease, or any other medical condition that, in the investigator's opinion, would preclude
participation in the study.

13. Prior history of suicide attempt at any time in the subject's lifetime prior to
randomization in the study or major psychiatric illness requiring hospitalization within 3
years of study randomization.
14. Any condition, including the presence of laboratory abnormalities, which places the
subject at unacceptable risk if he/she was to participate in the study or confounds the
ability to interpret data from the study.
15. Pregnant or breast feeding.
16. History of any of the following cardiac conditions within 6 months of screening:
myocardial infarction, acute coronary syndrome, unstable angina, new onset atrial
fibrillation, new onset atrial flutter, second- or third-degree atrioventricular block,
ventricular fibrillation, ventricular tachycardia, heart failure, cardiac surgery,
interventional cardiac catheterization (with or without a stent placement), interventional
electrophysiology procedure, or presence of implanted defibrillator.
17. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or
other infections (including but not limited to tuberculosis and atypical mycobacterial
disease and herpes zoster), human immunodeficiency virus (HIV), or any major episode
of infection requiring hospitalization or treatment with intravenous (IV) or oral
antibiotics within 4 weeks of screening.
18. Subjects with active hepatitis B infection as described in Appendix E are ineligible for
the study. Subjects without current hepatitis B infection, as described in Appendix F, may
participate in the study.
19. Subjects who are confirmed positive for hepatitis C antibody not eligible for the study.
20. History of congenital or acquired immunodeficiency (eg, Common Variable Immunodeficiency Disease).
21. History of malignancy, except for:
a. Treated (ie, cured) basal cell or squamous cell in situ skin carcinomas
b. Treated (ie, cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years
22. Any condition that could affect oral drug absorption, including gastric resections,

gastroparesis or bariatric surgery, such as gastric bypass.
23. Subjects has received any investigational drug or device within
1 months or 5 elimination half-lives, whichever is longer, prior to the Screening Visit.
24. History of alcohol, drug, or chemical abuse within the 6 months prior
to screening.
25. Known hypersensitivity to apremilast or any excipients in the
formulation.

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):	06-09-2016
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Apremilast
Generic name:	Apremilast

Ethics review

Approved WMO

Date:	19-05-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-10-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-11-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	23-11-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-03-2019
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	EUCTR2014-002981-64-NL
ClinicalTrials.gov	NCT02289417

Register	ID
CCMO	NL51337.028.15

Study results

Results posted: 28-01-2020

First publication
04-12-2019