A PHASE 2, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PARALLEL-GROUP STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF INDUCTION THERAPY WITH RPC1063 IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

Published: 27-05-2013
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The primary objective of the study is to compare the efficacy of RPC1063 vs placebo for induction of clinical remission at Week 8 in patients with moderately to severely active ulcerative colitis (UC)The secondary objectives are to:• Compare the...

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

Summary

ID

NL-OMON47857

Source
ToetsingOnline

Brief title
RPC01-202

Condition

- Gastrointestinal inflammatory conditions

Synonym
Ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Celgene International II Sarl (CIS II)
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: chronic gastrointestinal inflammatory disorder, RPC1063, Ulcerative colitis (UC)

Outcome measures

Primary outcome

The primary endpoint is the proportion of patients in clinical remission at

Week 8, defined as a Mayo score of <= 2 points and with no individual subscore

of > 1 point.

Secondary outcome

Secondary Efficacy Endpoints:

• Proportion of patients with a clinical response at Week 8, defined as a

reduction from baseline in Mayo score of >= 3 points and >= 30%, and a decrease

from baseline in the rectal bleeding subscore of >= 1 point or an absolute

rectal bleeding subscore of <= 1 point

• Change from baseline in Mayo score at Week 8

• Proportion of patients with mucosal healing at Week 8, defined by an

endoscopy subscore of <= 1 point

• Proportion of patients in clinical remission at Week 32 defined as Mayo score

of <= 2 points with no individual subscore of > 1 point

• Proportion of patients with a clinical response at Week 32, defined as a reduction from baseline in Mayo score of >= 3 points and >= 30%, and a decrease from baseline in the rectal bleeding subscore of >= 1 point or an absolute rectal bleeding subscore of <= 1 point

• Proportion of patients with mucosal healing at Week 32, defined as an endoscopy subscore of <= 1 point

Exploratory Efficacy Endpoints:

• Proportion of patients with clinical response, remission, or mucosal healing at Week 8 in the patients who had previously received anti-TNF therapy; who were refractory to anti-TNF therapy during initial anti-TNF therapy, or who lost response to anti-TNF therapy and were intolerant of anti-TNF therapy

• Proportion of patients with histologic remission at Week 8 as determined by a Geboes index score < 2.0

Safety Endpoints:

• The incidence and type of AEs, SAEs, AEs leading to discontinuation of study treatment, target AEs of special interest, laboratory abnormalities, vital signs, ECG, and physical exam abnormalities

Pharmacokinetic (PK) and Pharmacodynamic (PD) Endpoints:

• PK assessments will include PK sampling to determine plasma concentration of RPC1063 and active metabolites at scheduled assessments during the treatment period.

• Absolute lymphocyte count (ALC) derived from blinded hematology laboratory

results

• Plasma protein biomarkers (cytokines, chemokines, other inflammatory proteins)

• Stool culture for fecal biomarkers - fecal lactoferrin and calprotectin

• Total immunoglobulins (Igs) - IgA, IgG, IgM

Study description

Background summary

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder which involves the colon. UC is characterized by a life-long chronic course of remissions and exacerbations. Besides, patients with UC have an increased risk of carcinoma when compared with the general population. The overall goal of treatment for patients with active UC is to induce and maintain remission and to induce and maintain mucosal healing. For patients who do not respond to standard care treatment with 5-ASA or those with more severe disease, corticosteroids is generally the first-line treatment for inducing disease remission. However, treatment with corticosteroids is associated with multiple adverse effects. Therefore, there is an unmet need for a UC treatment that is highly effective, well-tolerated, and orally active.
RPC1063 is an orally available, potent, and selective S1P1R agonist that induces rapid, reversible lymphopenia in rodents, dogs, and nonhuman primates. A clinical development program for RPC1063 is being pursued in UC. The objective of the RPC1063 clinical development program in UC is to demonstrate that RPC1063 administered orally is safe and effective in inducing and maintaining remission in patients with moderately to severely active UC.

Study objective

The primary objective of the study is to compare the efficacy of RPC1063 vs placebo for induction of clinical remission at Week 8 in patients with moderately to severely active ulcerative colitis (UC)

The secondary objectives are to:
• Compare the efficacy of RPC1063 vs placebo at weeks 8 and 32 as measured by clinical response, clinical remission, and mucosal healing
• Compare the overall safety and tolerability of RPC1063 vs placebo for the duration of the study

The exploratory objectives are to:
• Examine the efficacy of RPC1063 vs placebo for induction of clinical response, remission, and mucosal healing in patients who had previously received anti-TNF therapy.
• Compare the efficacy of RPC1063 vs placebo for induction of histologic remission at Week 8
• Assess the pharmacokinetics (PK) and pharmacodynamics (PD) of RPC1063 in patients with UC

Study design

Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group

Intervention

Induction Period
On Day 1, patients will be randomly assigned 1:1:1 to 1 of 3 treatment regimens through Week 8:
• 0.5 mg RPC1063 oral capsule daily
• 1.0 mg RPC1063 oral capsule daily
• Matching placebo oral capsule daily
For patients randomized to one of the active treatment groups, there will be a 8-15 day dose titration regimen in the IP consisting of 4-7 days of treatment with 0.25 mg RPC1063, followed by 3-7 days treatment with 0.5 mg RPC1063, followed by the assigned treatment level.

Maintenance Period
Patients will continue to receive the same study treatment in the MP as received during the IP, and individual patient treatment will remain blinded until all patients have reached Week 32. Patient who complete the MP will be given the option to participate in the OLP.

Open label treatment Period
All patients in the OLP will receive daily oral study treatment with 1.0 mg RPC1063. There will be a 8-
15 day dose titration regimen consisting of 4-7 days of treatment with 0.25 mg RPC1063, followed by 3-7 days treatment with 0.5 mg RPC1063, followed by 1.0 mg RPC1063. The OLP will continue for up to 6 years or until marketing approval of RPC1063 for UC in the country of the clinical site (estimated to be in 2019), or until the Sponsor discontinues the development program.

Study burden and risks

Treatment with RPC1063 may lead to:
- a slowing of heart rate, and/or a blockage of electrical impulses that

normally travel through the heart.
- a decline in lung function tests or respiratory symptoms (trouble breathing, cough, wheezing).

RPC1063 works in a similar way to the approved drug, fingolimod (GilenyaTM). Therefore, risks associated with fingolimod could also be seen in patients who use RPC1063.
- Fingolimod is known to cause increases in liver enzymes in some patients, requiring them to stop taking the medication.
- Fingolimod has been known to cause a serious condition called macular oedema (swelling or thickening of the part of your eye responsible for detailed, central vision), which left untreated, can cause vision loss or blindness.
- Because fingolimod and RPC1063 work by changing your body*s immune system, RPC1063 could reduce the response to infections and should not be given to patients with infections or who are at risk for infections.
- Suppression of the immune system (reducing how well it works) may also increase the risk of skin cancer.

During the Phase 1 study in healthy volunteers, most side effects and discomforts were considered unrelated to the study drug by the doctor. The most common events considered probably or possibly related to RPC1063 were headache (6/68 subjects); sleepiness and nausea (5/68 subjects); dizziness, nausea and fatigue (3/68 subjects); decreased appetite, decline in lung function tests (tests that measure how well your lungs work) without symptoms, and dry mouth (2/68 subjects each). Most side effects (132) were considered mild in severity, with some (38) considered moderate. None were thought to be severe.
During the second Phase 1 study, the most common events considered probably or possibly related to RPC1063 were orthostatic hypotension (drop in blood pressure on standing, 5/62 subjects), headache (3/62 subjects), and dizziness (2/62 subjects).

Side effects due the study procedures
Blood sampling
During this study your blood will be taken to perform a variety of tests. The standard risks of drawing blood include temporary discomfort, bruising, swelling, in rare circumstances, infection.

Endoscopy
You might experience some discomfort from the Endoscopy examinations, but this is only during a short time during the examination and it is not harmful.

For a complete overview please refer to the schedule of events in the protocol. Patients must take one tablet of study medication one time a day. Patients are asked to complete a diary. There is a patient diary for holter monitoring, a diary to monitor the Mayo score, a diary for induction/ maintenance phase and a

diary for the open label phase.

Contacts

Public
Celgene International II Sarl (CIS II)

Rue du Pre-Jorat 14
Couvet 2108
CH
Scientific
Celgene International II Sarl (CIS II)

Rue du Pre-Jorat 14
Couvet 2108
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Males or female patients aged 18 to 75 years, inclusive
2. Have had UC diagnosed at least 2 months prior to screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence
3. Have active UC confirmed on endoscopy with >= 15 cm involvement
4. Have active UC defined as Mayo score of 6-12 inclusive with endoscopic subscore of >= 2
5. Have undergone colonoscopy or sigmoidoscopy within the past 2 years for extent of disease, and if the UC has been present for > 10 years, have had a colonoscopy with biopsy to rule out dysplasia

6. Female patients of childbearing potential:
Must agree to practice a highly effective method of contraception throughout the trial 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. Acceptable methods of birth control in the trial are the following:
- Combined hormonal (oestrogen and progestogen containing) contraception, which may be oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
- Placement of an intrauterine device (IUD)
- Placement of an intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence
- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.
7. Must be currently receiving treatment with at least 1 of the following therapies:
a. Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide) for at least 6 weeks with the dose stable for at least 3 weeks prior to screening endoscopy
b. Prednisone (doses <= 30 mg) or equivalent for at least 4 weeks and receiving a stable dose for at least 2 weeks
8. 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 baseline Mayo Score
9. All patients aged 45 years or over must have had a colonoscopy to screen for adenomatous polyps within 5 years of their first dose of investigational drug or must have had a colonoscopy at screening to assess for polyps. The adenomatous polyps must be removed prior to their first dose of investigational drug.
10. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
11. patients must have documentation of positive varicella zoster virus (VZV) IgG antibody status or complete vaccination at least 30 days prior to randomization.
12. Documentation of no evidence of chronic lung disease or tuberculosis (TB) on a chest X-ray completed within the 6 months prior to screening. If a chest x-ray was not done in the 6 months precreding the screening visit, it may be performed during the screening visit.

Exclusion criteria

1. Have severe extensive colitis evidenced by:
- Physician judgment that patient is likely to require colectomy or ileostomy within 12 weeks of baseline
- Current evidence of fulminant colitis, toxic megacolon or bowel perforation
- Previous total colectomy
- Have 4 or more of the following:
Temp > 38°C, Heart rate (HR) > 110 (bpm); Focal severe or rebound abdominal tenderness; Anemia (hemoglobin < 8.5 g/dL); Transverse colon diameter > 5cm on plain X-ray
2. Diagnosis of Crohn*s disease or indeterminate colitis or the presence or history of a fistula consistent with Crohn*s disease
3. Have positive stool culture for pathogens (O+P, bacteria) or positive test for C. difficile at screening. If C. difficile is positive, the patient may be treated and retested
4. Have had treatment with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 16 weeks of screening
5. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (hCG) measured during screening
6. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, psychiatric or other major systemic disease making implementation or interpretation of the study difficult or that would put the patient at risk
7. Clinically relevant cardiovascular conditions, including history or presence of
i. Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, sick sinus syndrome, decompensated heart failure requiring hospitalization, , Class III/IV heart failure or severe untreated sleep apnea
ii. Prolonged a QTcF interval (QTcF > 450 msec males, > 470 msec females), or at additional risk for QT prolongation (e.g. hypokalemia, hypomagnesemia, congenital long-QT syndrome)
iii. Patients with other pre-existing stable cardiac conditions who have not been cleared for the study by an appropriate cardiac evaluation by a cardiologist.
8. Resting HR less than 55 beats per minute (bpm) when taking vitals as part of a physical exam at screening.
9. History of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c > 7%, or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy.
10. History of uveitis
11. Known active bacterial, viral, fungal, mycobacterial infection or other infection (including TB or atypical mycobacterial disease [excluding fungal infection of nail beds]) or any major episode of infection that required hospitalization/treatment with intravenous (IV) antibiotics within 30 days or oral antibiotics within 14 days prior to screening

12. History or known presence of recurrent or chronic infection (e.g., hepatitis A, B, C or E, human immunodeficiency virus, syphilis, TB); recurring urinary tract infections are allowed
13. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved)
14. History of alcohol or drug abuse within 1 year prior to randomization
15. History of or currently active primary or secondary immunodeficiency
16. History of treatment with a biologic agent within 5 half-lives of that agent prior to randomization
17. History of treatment with an investigational agent within 5 half-lives of that agent prior to randomization
18. History of treatment with topical rectal steroids within 2 weeks of screening
19. Receipt of a live vaccine or attenuated live vaccine within 4 weeks prior to screening
20. Previous treatment with lymphocyte-depleting therapies (e.g., Campath, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
21. Previous treatment with D-penicillamine, leflunomide or thalidomide
22. Previous treatment with natalizumab or fingolimod
23. History of treatment with IVIg, plasmapheresis, within 3 months prior to randomization
24. Planned concurrent treatment with immunosuppressive agents (e.g., azathioprine, 6-MP, or methotrexate) after randomization. Subjects receiving azathioprine, 6-MP or methotrexate at screening must discontinue treatment with these agents prior to dosing with investigational drug.
25. Treatment with Class Ia or Class III anti-arrhythmic drugs or treatment with two or more agents in combination known to prolong PR interval.
26. Treatment with any of the following drugs or interventions within the corresponding
timeframe:
* At randomization: CYP2C8 inhibitors (eg, gemfibrozil or clopidogrel) or inducers (eg, rifampicin)
* Two weeks prior to randomization: Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
27. Serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men
28 Liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 times the upper limit of normal (ULN), or direct bilirubin > 1.5 times the ULN
29. Platelet count < 100,000 mircrolitres
30. Hgb <8.5 g/dL
31. Neutrophils <1500 microlitres
(Please refer to the protocol for the remaining criteria)

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):	02-07-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RPC1063

Ethics review

Approved WMO Date:	27-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-003123-38-NL
ClinicalTrials.gov	NCT01647516
CCMO	NL44266.018.13

Study results

Results posted: 23-09-2020

First publication
04-11-2015