A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects with Moderate to Severe Ulcerative Colitis (FIGARO UC 301)

Published: 02-11-2017
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Primary: To evaluate the efficacy of ontamalimab in inducing remission, based on composite score of patient reported symptoms and centrally read endoscopy, in subjects with moderate to severe ulcerative colitis (UC).Key Secondary:* To evaluate the...

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

Summary

ID

NL-OMON50514

Source
ToetsingOnline

Brief title
SHP647-301

Condition

- Gastrointestinal inflammatory conditions

Synonym
chronic inflammationof the mucosa of the colon and rectum, Ulcerative Colitis

Research involving

Human

Sponsors and support

Primary sponsor: Shire
Source(s) of monetary or material Support: Shire

Intervention

Keyword: Induction Therapy, Ontamalimab, Phase 3, Ulcerative Colitis

Outcome measures

Primary outcome

To evaluate the efficacy of ontamalimab in inducing remission, based on composite score of patient reported symptoms and centrally read endoscopy, in subjects with moderate to severe ulcerative colitis (UC).

Secondary outcome

Key Secondary:

* To evaluate the efficacy of ontamalimab in achieving endoscopic remission, based on centrally read endoscopy.

* To evaluate the efficacy of ontamalimab in achieving clinical remission, based on composite score of patient reported symptoms.

* To evaluate the efficacy of ontamalimab in inducing clinical response, based on composite score of patient reported symptoms and centrally read endoscopy.

* To evaluate the efficacy of ontamalimab in achieving mucosal healing, based on endoscopic and histological assessment using the Geboes Score grading system.

Other Secondary:

* To evaluate the safety and tolerability of ontamalimab.

* To evaluate the effect of ontamalimab induction treatment on other clinical and endoscopic outcomes (including Mayo-based remission and clinical response, partial Mayo score over time, clinical remission over time, endoscopic remission, and deep remission).

* To evaluate the effect of ontamalimab on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores.

* To evaluate the effect of ontamalimab on health related quality of life (as measured by the Inflammatory Bowel Disease Questionnaire [IBDQ] and the Short Form-36 Health Survey [SF-36]).

* To evaluate the effect of ontamalimab on incidence of hospitalizations and total inpatient days.

Study description

Background summary

Ulcerative colitis (UC) is a chronic, relapsing disease marked by ulceration and inflammation of the colonic mucosa and submucosa. Initially it usually involves the rectum but may extend proximally to involve a portion of, or the entirety of, the colon. In the early stages, hemorrhagic and erythematous tissue is observed, progressing to mucosal ulceration with purulent exudates in severe cases. The ulceration pattern is continuous and may extend the entire length of the colon. Perforation of the bowel wall causing ileus and peritonitis can occur with transmural extension of the ulceration. Bloody diarrhea with or without mucus and lower abdominal pain with periods of remission and exacerbation are the most common symptoms.
Although UC can occur at any age, peak incidence has been observed in the second to fourth decades of life. UC is a lifelong condition with a serious effect on the quality of life. Current treatment primarily consists of symptomatic management with dietary modifications and opiates, as well as disease modifying agents, systemic glucocorticoids, immunosuppressive agents, and biologic therapy. Despite recent advances, there is still an unmet need for an effective pharmacological treatment that will induce and maintain remission. The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal

sites of the gastrointestinal (GI) tract is influenced by the endothelial expression of mucosal addressin cell adhesion molecule (MAdCAM). MAdCAM plays a role in gut immune surveillance, and also appears to facilitate excessive lymphocyte infiltration under conditions of chronic GI inflammation. Ontamalimab is a fully human immunoglobulin G2 kappa (IgG2k) monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation.

Study objective

Primary: To evaluate the efficacy of ontamalimab in inducing remission, based on composite score of patient reported symptoms and centrally read endoscopy, in subjects with moderate to severe ulcerative colitis (UC).

Key Secondary:
* To evaluate the efficacy of ontamalimab in achieving endoscopic remission, based on centrally read endoscopy.
* To evaluate the efficacy of ontamalimab in achieving clinical remission, based on composite score of patient reported symptoms.
* To evaluate the efficacy of ontamalimab in inducing clinical response, based on composite score of patient reported symptoms and centrally read endoscopy.
* To evaluate the efficacy of ontamalimab in achieving mucosal healing, based on endoscopic and histological assessment using the Geboes Score grading system.

Other Secondary:
* To evaluate the safety and tolerability of ontamalimab.
* To evaluate the effect of ontamalimab induction treatment on other clinical and endoscopic outcomes (including Mayo-based remission and clinical response, partial Mayo score over time, clinical remission over time, endoscopic remission, and deep remission).
* To evaluate the effect of ontamalimab on abdominal pain, urgency, diarrhea, and absolute stool frequency and bleeding scores.
* To evaluate the effect of ontamalimab on health related quality of life (as measured by the Inflammatory Bowel Disease Questionnaire [IBDQ] and the Short Form-36 Health Survey [SF-36].
* To evaluate the effect of ontamalimab on incidence of hospitalizations and total inpatient days.

Study design

The study consists of a screening period up to 6 weeks and a 12 week treatment period. After the screening period, eligible subjects will be randomly assigned to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo) in a 2:2:1 ratio. Randomization will be stratified based upon the subject*s status of prior anti TNF (tumor necrosis factor) treatment (naïve or experienced) and glucocorticoid use at baseline (on glucocorticoids at baseline

versus not on glucocorticoids at baseline). Subjects will receive SC injections of ontamalimab or placebo, using a PFS, on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), and Week 8 (Visit 5). Subjects will undergo efficacy, biomarker, pharmacokinetic, safety, and health outcome assessments at these visits. Patient-reported UC signs and symptom data (including stool frequency, rectal bleeding severity and frequency, diarrhea frequency, urgency frequency, and abdominal pain worst severity) will be collected using a daily electronic diary (e-diary) during the treatment period. The Mayo score is a measure of UC disease activity consisting of the following 4 subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician global assessment (PGA). The partial Mayo score consists of the Mayo score without the endoscopic subscores. The composite score is a recommended measure consisting of the Mayo score without the PGA subscore, and will be used for the primary efficacy endpoint. The Mayo scores and composite score will be based on subject daily e-diary entries.
At the end of the 12 week treatment period, eligible subjects will be offered the opportunity to participate in a double-blind maintenance study (SHP647-303; for subjects who achieve clinical response) or a long-term safety extension (LTS) study (SHP647-304; for subjects who do not achieve a clinical response). Subjects who withdraw early from the 12 week treatment period or who do not wish to enter the maintenance study (SHP647-303) or LTS study (SHP647-304) will continue into a 16 week safety follow-up period. Only those subjects who complete the full course of investigational product treatment in the induction studies (SHP647-301 or SHP647-302) will be eligible to continue in the maintenance study or LTS study.

Intervention

The participants receive a subcutaneous injection every 4 weeks; 1 group with 25 mg ontamalimab, 1 group with 75 mg ontamalimab, and 1 group with placebo.

Study burden and risks

Ontamlimab may cause side effects. The most frequently reported side effects (in more than 1 out of every 10 subjects) are: joint pain, headache, pain in the belly, nausea, fever and nasopharyngitis. If the patient receives placebo there is a possibility that symptoms of the disease may return or get worse. Also the study procedures may be accompanied by risks and discomforts. In addition the study drug, the study procedures and the combination of these may lead to risks that are as yet unknown.

Ulcerative colitis (UC) is a chronic, relapsing disease marked by ulceration and inflammation of the colonic mucosa and submucosa. Ulcerative colitis is a lifelong condition with a serious effect on the quality of life. Current treatment primarily consists of symptomatic management. Despite recent advances, there is still an unmet need for an effective pharmacological

treatment that will induce and maintain remission.

Considering the chronic and relapsing characteristics of this lifelong disease, we feel these side effects and the burden associated with participation, are in proportion considering the positive effects that participation in the study might have on the patients disease.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Subjects and/or their parent or legally authorized representative must have an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Subjects must be able to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent and/or assent, as applicable, to participate in the study.
3. Subjects must be between *16 and *80 years of age at the time of the signing of the informed consent/assent form.
NOTE: Subjects <18 years of age must weigh *40 kg and must have body mass index (BMI) *16.5 kg/m2.
4. Subjects must have a documented diagnosis (radiologic or endoscopic with histology) of UC for *3 months before screening. The following must be available in each subject*s source documentation:
* A biopsy report to confirm the histological diagnosis.
* A report documenting disease duration based upon prior colonoscopy.
NOTE: If this documentation is not available at the time of screening, a colonoscopy with biopsy to confirm the diagnosis is required during the screening period.
5. Subjects must be willing to undergo a flexible sigmoidoscopy or colonoscopy (if preferred), including biopsy sample collection, during screening after all other inclusion criteria have been met.
6. Subjects must have moderate to severe active UC, defined as a total Mayo score of *6, including a centrally read endoscopic subscore *2, rectal bleeding subscore *1, and stool frequency subscore *1 at baseline (Visit 2).
7. Subjects must have evidence of UC extending proximal to the rectum (ie, not limited to proctitis).
8. Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as mesalamine (5 aminosalicylic acid [5-ASA]), glucocorticoids, immunosuppressants (azathioprine [AZA], 6 mercaptopurine [6 MP], or methotrexate [MTX]), or anti-TNF.
9. Subjects receiving any treatment(s) for UC described in Section 5.2.1 of the protocol are eligible provided they have been, and are anticipated to be, on a stable dose for the designated period of time.
10. Subjects are males or nonpregnant, nonlactating females who, if sexually active, agree to comply with the contraceptive requirements of the protocol, or females of nonchildbearing potential. Males and females of reproductive potential who are sexually active must agree to use appropriate contraception (ie, highly effective methods for female and medically appropriate methods for male study subjects) (as described in Section 4.4 of the protocol) for the duration of the study.

Exclusion criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subjects with indeterminate colitis, microscopic colitis, non-steroidal anti-inflammatory drug-induced colitis, ischemic ischemic colitis, infectious colitis, or clinical/histologic findings suggestive of Crohn*s disease.
2. Subjects with colonic dysplasia or neoplasia. (Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed.)
3. Subjects with past medical history or presence of toxic megacolon.
4. Subjects with colonic stricture, past medical history of colonic resection, a history of bowel surgery within 6 months before screening, or who are likely to require surgery for UC during the treatment period.
5. Subjects at risk for colorectal cancer must have a colonoscopy performed during the screening period with results available within 10 days before the baseline visit (Visit 2), unless the subject has had a surveillance colonoscopy performed within 1 year prior to screening, and any adenomatous polyps found at that examination have been excised. Colonoscopy report and pathology report (if biopsies are obtained) from the colonoscopy performed during screening or in the prior year confirming no evidance of dysplasia and colon colon must be available in the source documents.
Subjects at risk for colorectal cancer include, but are not limited to:
* Subjects with extensive colitis for *8 years or disease limited to left side of colon (ie, distal to splenic flexure) for *10 years before screening, regardless of age.
* Subjects *50 years of age at the time of signing of the informed consent form.
6. Subjects have had prior treatment with ontamalimab (formerly PF-00547659; SHP647).
7. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
8. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
9. Subjects have received any biologic with immunomodulatory properties (other than anti TNFs) within 90 days before baseline (Visit 2).
10. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than their current background UC treatment) within 30 days before baseline (Visit 2).
11. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
12. Subjects have received parenteral or rectal glucocorticoids, or rectal 5-ASA, within 14 days before screening endoscopic procedure.
13. Subjects have received leukocyte apheresis or selective lymphocyte, monocyte, or granulocyte apheresis or plasma exchange within 30 days before baseline (Visit 2).
14. Subjects have participated in other investigational studies within either 30 days or 5 half lives of investigational product used in the study (whichever is longer) before baseline (Visit 2).
15. Subjects have received a live (attenuated) vaccine within 30 days before

the baseline visit (Visit 2).
16. Subjects with active enteric infections (positive stool culture and sensitivity), Clostridium difficile infection or pseudomembranous colitis [subjects with C. difficile infection at screening may be allowed re-test after treatment], evidence of active cytomegalovirus infection or Listeria monocytogenes, known active invasive fungal infections such as histoplasmosis or parasitic infections, clinically significant underlying disease that could predispose the subjects to infections, or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before the baseline visit (Visit 2).
17. Subjects with abnormal chest x-ray findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x ray performed up to 12 weeks before study entry [screening, Visit 1] may be used if available; documentation of the official reading must be located and available in the source documentation.)
18. Subjects with evidence of active or latent infection with Mycobacterium tuberculosis (TB) or subjects with this history who have not completed a generally accepted full course of treatment before randomization are excluded. All other subjects must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed. Subjects who have no history of previously diagnosed active or latent tuberculosis are excluded if they have a positive Mantoux (PPD) tuberculin skin test (ie *5 mm induration) or a positive IGRA (the latter to be tested at the site*s local laboratory) during screening or within 12 weeks before randomization. If IGRA test cannot be performed locally, a central laboratory may be used, with prior agreement from the sponsor.
* An IGRA is strongly recommended for subjects with a prior Bacillus Calmette-Guérin (BCG) vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation if performed locally. Acceptable IGRA products include QuantiFERON TB Gold Plus In-Tube Test.
* If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In subjects with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the subject. Subjects with a history of active or latent tuberculosis infection must follow instructions for *Subjects with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met* in this criterion.
* Subjects with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action). This consultation must be included in source documentation.
Results from a chest x-ray, taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.
Subjects with a prior diagnosis of active or latent tuberculosis are excluded

unless both of the following criteria are met:
* The subject has previously received an adequate course of treatment for either latent (eg, 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are <5%. Subjects from regions with higher rates of primary multidrug TB resistance are excluded) or active (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (ie, subject would be acceptable for immunosuppressant [eg, anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.
* A chest x-ray performed within 3 months prior to screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.
19. Subjects with a pre existing demyelinating disorder such as multiple sclerosis or new onset seizures, unexplained sensory motor, or cognitive behavioral, neurological deficits, or significant abnormalities noted during screening.
20. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period.

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):	19-09-2018

Enrollment:	29
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ontamalimab
Generic name:	-

Ethics review

Approved WMO Date:	02-11-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-03-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-09-2018
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:	20-12-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-01-2019
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:	27-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-06-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2019
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:	18-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-12-2020
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	EUCTR2017-000599-27-NL
ClinicalTrials.gov	NCT03259334

Register	ID
CCMO	NL62885.028.17

Study results

Date completed: 20-05-2020

Results posted: 02-06-2021

First publication
26-04-2021