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 Crohn*s Disease (CARMEN CD 305)

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Coprimary: The coprimary objectives of this study are to evaluate the efficacy of ontamalimab in subjects with moderate to severe Crohn*s disease (CD) in:* Inducing clinical remission based on 2 item patient reported outcome (PRO) (abdominal pain...

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

Summary

ID

NL-OMON50376

Source
ToetsingOnline

Brief title
SHP647-305

Condition

- Gastrointestinal inflammatory conditions

Synonym
a type of IBD that may affect any part of the gastrointestinal tract from mouth to anus, Crohn's Disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Anti-MAdCAM, Crohn's Disease, Induction Therapy, Ontamalimab

Outcome measures

Primary outcome

The coprimary objectives of this study are to evaluate the efficacy of

ontamalimab in subjects with moderate to severe Crohn*s disease (CD) in:

* Inducing clinical remission based on 2 item patient reported outcome (PRO)

(abdominal pain severity and very soft stool/liquid stool frequency)

* Inducing endoscopic response based on centrally read colonoscopy.

Secondary outcome

Key secondary:

* To evaluate the efficacy of ontamalimab in inducing clinical remission as

measured by CD Activity Index CDAI

* To evaluate the efficacy of ontamalimab in inducing enhanced endoscopic

response based on centrally read colonoscopy

* To evaluate the efficacy of ontamalimab in inducing clinical remission based

on abdominal pain severity and very soft stool/liquid stool frequency

(alternate thresholds)

* To evaluate the efficacy of ontamalimab in inducing clinical response based

on patient reported clinical signs and symptoms (as measured by 2-item PRO)

* To evaluate the efficacy of ontamalimab in inducing clinical remission based on patient reported clinical signs and symptoms (as measured by 2-item PRO) as well as inducing endoscopic response based on centrally read colonoscopy in the same subject

* To evaluate the efficacy of ontamalimab in inducing endoscopic healing based on centrally read colonoscopy.

Other secondary:

* To evaluate the safety and tolerability of ontamalimab

* To evaluate the effect of ontamalimab induction treatment on other clinical outcomes (clinical response defined by CDAI, or clinical remission over time, or change from baseline in frequency in CD related clinical parameters)

* To evaluate the effect of ontamalimab induction treatment on other endoscopic outcomes

* To evaluate the effect of ontamalimab on health related quality of life (HRQL) (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

* To evaluate the impact of ontamalimab on incidence of CD-related and other surgeries.

Study description

Background summary

Crohn*s disease (CD) is a chronic, relapsing disease marked by granulomatous inflammation of the gastrointestinal (GI) tract. Although the terminal ileum and right colon are the most commonly involved sites, CD can affect any part of the GI tract, from the mouth to the perianal region. Inflammation is typically transmural (full-thickness), segmental, and discontinuous, and symptoms are predominantly determined by the part of bowel or organ involved. Patients typically present with symptoms including abdominal pain, diarrhea, rectal bleeding, which may be persistent and lead to anemia, and weight loss due to pain on eating and malabsorption. As the disease progresses, extraintestinal manifestations and associated conditions can develop, including bowel obstruction, fistulas, and stenosis, as well as painful skin ulcerations, eye pain, and arthritis.

No clear difference in incidence has been observed between men and women. Although CD can occur at any age, peak incidence has been observed in the second to fourth decades of life, with a second modest rise in incidence in the latter decades of life (Molodecky et al., 2012).
Crohn*s disease is a lifelong condition with a serious effect on quality of life. The traditional approach to therapy of CD has been the step-up approach usually represented as a pyramid where, progressing from mild to severe disease, therapeutic choices proceed step by step from less potent drugs at the base of the pyramid to more potent but also more toxic drugs at the top. Despite recent advances, there is still an unmet need for a safe, effective, and durable pharmacological treatment that will induce and maintain clinical remission.

The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal sites of the 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

Coprimary: The coprimary objectives of this study are to evaluate the efficacy of ontamalimab in subjects with moderate to severe Crohn*s disease (CD) in:
* Inducing clinical remission based on 2 item patient reported outcome (PRO) (abdominal pain severity and very soft stool/liquid stool frequency)
* Inducing endoscopic response based on centrally read colonoscopy.

Key secondary:
* To evaluate the efficacy of ontamalimab in inducing clinical remission as measured by CD Activity Index CDAI
* To evaluate the efficacy of ontamalimab in inducing enhanced endoscopic response based on centrally read colonoscopy
* To evaluate the efficacy of ontamalimab in inducing clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
* To evaluate the efficacy of ontamalimab in inducing clinical response based on patient reported clinical signs and symptoms (as measured by 2-item PRO)
* To evaluate the efficacy of ontamalimab in inducing clinical remission based on patient reported clinical signs and symptoms (as measured by 2-item PRO) as well as inducing endoscopic response based on centrally read colonoscopy in the same subject
* To evaluate the efficacy of ontamalimab in inducing endoscopic healing based on centrally read colonoscopy.

Other secondary:
* To evaluate the safety and tolerability of ontamalimab
* To evaluate the effect of ontamalimab induction treatment on other clinical outcomes (clinical response defined by CDAI, or clinical remission over time, or change from baseline in frequency in CD related clinical parameters)
* To evaluate the effect of ontamalimab induction treatment on other endoscopic outcomes
* To evaluate the effect of ontamalimab on health related quality of life (HRQL) (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
* To evaluate the impact of ontamalimab on incidence of CD-related and other surgeries.

Study design

The study consists of a screening period up to 6 weeks and a 16 week treatment period. After the screening period, eligible subjects will be randomized to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo) in a 3:3:2 ratio. Randomization will be stratified based upon the subject*s status of prior antitumor necrosis factor (TNF) treatment (naïve or experienced), glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline), and Simple Endoscopic Score for CD (SES-CD) at baseline (SES-CD *17 or SES CD <17). Subjects will receive SC injections of SHP647 or placebo, using a PFS, on Week 0/Day 1 (Visit 2), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12 (Visit 6). Subjects will undergo efficacy, biomarker, pharmacokinetic (PK), safety, and health outcome assessments at these visits.

At the end of the 16 week treatment period, subjects will be offered the opportunity to participate in either a double blind maintenance study (SHP647-307; for subjects who fulfill the entry criteria) or a long-term safety extension (LTS) study (SHP647-304; for subjects who do not fulfill the entry criteria for Study SHP647 307). Subjects who withdraw early from the 16 week treatment period or who do not wish to enter the maintenance study (SHP647-307) 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 study (SHP647 305) 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

Ontamalimab may cause side effects. The most frequently reported side effects (in more than 1 out of every 10 subjects who received ontamalimab) across all studies and from any cause, including possibly ontamalimab, were joint pain, headache, pain in the belly, nausea, fever and inflammation or infection of the nasal passages and the throat. These side effects were generally mild to moderate.
Side effects reported less frequently (in more than 1 out of every 20 subjects but less than 1 out of every 10 subjects who received ontamalimab) across all studies and from any cause, including possibly ontamalimab, were vomiting, fatigue, back pain, diarrhea, influenza (the flu), urinary tract infections, inflammation or infection of the gastrointestinal tract, upper respiratory infection, inflammation of the bronchial tubes that carry air to the lungs, bodily rash, inflammation or infection of the throat, and anemia (reduced red blood cells). These side effects were also generally mild to moderate.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.
Crohn*s disease (CD) is a chronic, relapsing disease marked by granulomatous inflammation of the gastrointestinal (GI) tract. CD 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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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

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 *16.5 kg/m2.
4.Subjects must have active moderate to severe ileal (terminal ileum),

ileocolic, or colonic CD at baseline (Visit 2) as defined by:
a.CDAI score between 220 and 450 (inclusive) AND
b.Presence of ulcerations that are characteristic to CD, as determined by a colonoscopy performed during screening, and as defined by the SES-CD >6 (SES-CD *4 for isolated ileitis) AND
c.Meeting the following subscores in the 2-item PRO:
i.Abdominal pain subscore *5 (average worst daily pain on the 11-point NRS) AND abdominal pain subscore >2 (average daily pain on the 4-point abdominal pain variable of CDAI) over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous) AND/OR
ii.Average of the daily stool frequency subscore *4 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days out of the 10 days before colonoscopy preparation (may or may not be contiguous).
AND
c. Presence of ulcerations that are characteristic to CD, as determined by a colonoscopy performed during screening, and as defined by the SES-CD>6 (SES-CD *4 for isolated ileitis)
Note that the subject must be confirmed as meeting the CDAI score and PRO subscore requirements before a colonoscopy is done.
5.Subjects must have a documented diagnosis (endoscopic with histology) of CD for *3 months before screening. Documented diagnosisis defined as:
A biopsy report in which the description of the histological findings is consistent with the CD diagnosis AND
A report documenting disease duration based upon prior colonoscopy.
Note: If a biopsy report is not available in the source document at the time of screening, a biopsy must be performed during the screening colonoscopy and the histology report should be consistent with the CD diagnosis. If the histology diagnosis does not support the CD diagnosis at this time point, the subject should not be randomized
6.Subjects must be willing and able to undergo a colonoscopy during screening after all other inclusion criteria have been met.
7.Subjects must have had an inadequate response to, or lost response to, or had an intolerance to at least 1 conventional treatment such as sulfasalazine or mesalamine (5-ASA), glucocorticoids, immunosuppressants (AZA, 6-MP, or MTX), or anti-TNF. Subjects who have had an inadequate response to sulfasalazine or mesalamine should have also failed at least 1 other conventional treatment such as glucocorticoids.
8.Subjects receiving any treatment(s) for CD 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.
9. 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) 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 colitis, infectious colitis, or clinical/histologic findings suggestive of ulcerative colitis.
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 presence of enterovesical (ie, between the bowel and urinary bladder) or enterovaginal fistulae.
5. Subjects with current symptomatic diverticulitis or diverticulosis.
6. Subjects with clinically significant obstructive colonic stricture, or who have a history of bowel surgery within 6 months before screening, or who are likely to require surgery for CD during the treatment period. Subjects who have undergone previous colonic resection or ileocolectomy more than 6 months before screening must have at least 25 cm of colon remaining.
7. Subjects with past medical history of multiple small bowel resections resulting in clinically significant short bowel syndrome.
8. Subjects requiring total parenteral nutrition.
9. Subjects with past medical history of bowel surgery resulting in an existing or current stoma. Subjects who had a j-pouch are excluded as a j-pouch could result in a stoma.
10. Subjects have had prior treatment with ontamalimab (formerly PF-00547659; SHP647).
11. Subjects with known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
12. Subjects have received any nonbiologic treatment with immunomodulatory properties (other than AZA, 6 MP, or MTX) or continuous antibiotics (>2 weeks) for the treatment of CD within 30 days before baseline (Visit 2).
13. Subjects have received anti-TNF treatment within 60 days before baseline (Visit 2).
14. Subjects have received any biologic with immunomodulatory properties (other than anti TNFs) within 90 days before baseline (Visit 2).
15. Subjects have ever received anti-integrin/adhesion molecule treatment (eg, natalizumab, vedolizumab, efalizumab, etrolizumab, or any other investigational anti-integrin/adhesion molecule).
16. Subjects have received lymphocytes apheresis or selective monocyte granulocytes apheresis within 60 days before baseline (Visit 2).
17. Subjects have received enteral nutrition treatment within 30 days before

baseline (Visit 2).
18. Subjects have received parenteral or rectal glucocorticoids or rectal 5-ASA within 14 days before screening colonoscopy.
19. Subjects have taken >20 mg/day of prednisone, >9 mg/day of budesonide, or equivalent oral systemic corticosteroid dose within 14 days before baseline (Visit 2) or have taken *40 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 6 weeks before baseline (Visit 2).
20. 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 screening (Visit 1).
21. Subjects have received a live (attenuated) vaccine within 30 days before the baseline visit (Visit 2).
22. 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 retest 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).
23. Subjects with abnormal chest x-ray or other imaging findings at screening (Visit 1), such as presence of active tuberculosis (TB), general infections, heart failure, or malignancy. (A chest x ray, computed tomography scan, etc., 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.)
24. 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 baseline (Visit 2) 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 screening. If the IGRA 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 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 TB, a positive test on repeat will exclude

the subject. Subjects with a history of active or latent TBinfection must follow instructions for *Subjects with a prior diagnosis of active or latent TB 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 12 weeks 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 12 weeks before 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.
25. 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 s

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):	02-10-2019
Enrollment:	14
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	19-04-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-09-2018
Application type:	First submission
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:	25-10-2018

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-11-2018
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:	30-09-2019

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2020
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:	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)

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	EUCTR2017-000575-88-NL
Other	In process
CCMO	NL65340.028.18

Study results

Date completed:	07-07-2020
Results posted:	03-06-2021

First publication
16-04-2021