A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Maintenance Therapy in Subjects With Moderate to Severe Crohn*s Disease (CARMEN CD 307)

Published: 17-04-2018
Last updated: 10-01-2025

Coprimary: The coprimary objectives of the study are to evaluate the efficacy of ontamalimab as maintenance treatment in subjects with moderate to severe Crohn*s disease (CD) based on:* Clinical remission based on 2 item patient-reported outcome (...

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

Summary

ID

NL-OMON50298

Source
ToetsingOnline

Brief title
SHP647-307

Condition

- Gastrointestinal inflammatory conditions

Synonym
a type of IBD that may affect any part of the gastroinestinal 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, Maintenance Therapy, Ontamalimab

Outcome measures

Primary outcome

Coprimary: The coprimary objectives of the study are to evaluate the efficacy of ontamalimab as maintenance treatment in subjects with moderate to severe Crohn*s disease (CD) based on:

* Clinical remission based on 2 item patient-reported outcome (PRO) (abdominal pain severity and very soft stool/liquid stool frequency)

* Enhanced endoscopic response based on centrally read colonoscopy.

Secondary outcome

Key secondary:

* To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission as measured by Crohn's Disease Activity Index (CDAI)

* To evaluate the efficacy of ontamalimab as maintenance treatment on glucocorticoid free clinical remission based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)

* To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)

* To evaluate the efficacy of ontamalimab on maintenance of clinical remission among subjects in clinical remission at baseline of the SHP647-307 study based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
* To evaluate the efficacy of ontamalimab on maintenance of enhanced endoscopic response among subjects with enhanced endoscopic response at baseline of the SHP647-307 study based on centrally read colonoscopy
* To evaluate the efficacy of ontamalimab as maintenance treatment based on achieving clinical remission as well as achieving enhanced endoscopic response in the same subject
* To evaluate the effect of ontamalimab as maintenance treatment on complete endoscopic healing.

Other secondary:
* To evaluate the safety and tolerability of ontamalimab as maintenance treatment
* To evaluate the effect of ontamalimab as maintenance treatment on other clinical outcomes (2 item PRO based clinical response over time, 2-item PRO based and CDAI based clinical remission over time, and 2 item PRO based and CDAI based sustained clinical remission over time)
* To evaluate the effect of ontamalimab on abdominal pain, very soft stool/liquid stool frequency (as shown by type 6/7 on Bristol Stool Form Scale [BSFS]), total stool frequency, rectal urgency, rectal bleeding, nausea, vomiting, and rectal incontinence
* To evaluate the efficacy of ontamalimab as maintenance treatment on different

grades of clinical responses to treatment as measured by CDAI

* To evaluate the effect of ontamalimab as maintenance treatment on endpoints related to endoscopic healing and histological changes

* To evaluate the effect of ontamalimab as maintenance treatment 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 impact of ontamalimab as maintenance treatment on incidence of hospitalizations and total inpatient days

* To evaluate the impact of ontamalimab as maintenance treatment 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 the study are to evaluate the efficacy of ontamalimab as maintenance treatment in subjects with moderate to severe Crohn*s disease (CD) based on:
* Clinical remission based on 2 item patient-reported outcome (PRO) (abdominal pain severity and very soft stool/liquid stool frequency)
* Enhanced endoscopic response based on centrally read colonoscopy.

Key secondary:
* To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission as measured by Crohn's Disease Activity Index (CDAI)
* To evaluate the efficacy of ontamalimab as maintenance treatment on glucocorticoid free clinical remission based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
* To evaluate the efficacy of ontamalimab as maintenance treatment on clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)
* To evaluate the efficacy of ontamalimab on maintenance of clinical remission among subjects in clinical remission at baseline of the SHP647-307 study based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)
* To evaluate the efficacy of ontamalimab on maintenance of enhanced endoscopic response among subjects with enhanced endoscopic response at baseline of the SHP647-307 study based on centrally read colonoscopy
* To evaluate the efficacy of ontamalimab as maintenance treatment based on achieving clinical remission as well as achieving enhanced endoscopic response in the same subject
* To evaluate the effect of ontamalimab as maintenance treatment on complete endoscopic healing.

Other secondary:

* To evaluate the safety and tolerability of ontamalimab as maintenance treatment
* To evaluate the effect of ontamalimab as maintenance treatment on other clinical outcomes (2 item PRO based clinical response over time, 2-item PRO based and CDAI based clinical remission over time, and 2 item PRO based and CDAI based sustained clinical remission over time)
* To evaluate the effect of ontamalimab on abdominal pain, very soft stool/liquid stool frequency (as shown by type 6/7 on Bristol Stool Form Scale [BSFS]), total stool frequency, rectal urgency, rectal bleeding, nausea, vomiting, and rectal incontinence
* To evaluate the efficacy of ontamalimab as maintenance treatment on different grades of clinical responses to treatment as measured by CDAI
* To evaluate the effect of ontamalimab as maintenance treatment on endpoints related to endoscopic healing and histological changes
* To evaluate the effect of ontamalimab as maintenance treatment 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 impact of ontamalimab as maintenance treatment on incidence of hospitalizations and total inpatient days
* To evaluate the impact of ontamalimab as maintenance treatment on incidence of CD related and other surgeries.

Study design

This study consists of a 52 week, double-blind treatment period, followed by a 16 week safety follow-up period for subjects who either discontinue treatment early or who complete the treatment period and do not enter the long-term safety extension (LTS) study (SHP647-304).

Eligible subjects who received active treatment in one of the induction studies and fulfilled the efficacy entry criteria of this study, including achieving endoscopic and/or clinical response, will be randomized as follows: subjects who received 25 mg ontamalimab in one of the induction studies will be randomized (1:1) to receive either 25 mg ontamalimab or placebo, and subjects who received 75 mg ontamalimab in one of the induction studies will be randomized (1:1) to receive either 75 mg ontamalimab or placebo.

Eligible subjects who received placebo in one of the induction studies and fulfilled the efficacy entry criteria of this study including achieving endoscopic and/or clinical response will be randomized in a 2:2:1 ratio to receive 1 of 3 treatments (25 mg ontamalimab, 75 mg ontamalimab, or placebo, respectively) during this maintenance study.

Subjects will be stratified according to glucocorticoid use at Study SHP647-307 baseline, the subject*s status of prior anti tumor necrosis factor (TNF) treatment (naïve or experienced), and whether or not the subject achieved clinical remission by 2-item PRO or enhanced endoscopic response in the

induction study.
Subjects enrolled in this study (SHP647-307) will receive double-blind maintenance treatment in the form of SC injections, using a PFS, every 4 weeks for 52 weeks. Subjects will undergo efficacy, biomarker, pharmacokinetic (PK), safety, and health outcome assessments.

Subjects who complete the double-blind treatment period in this maintenance study may be eligible to enter the LTS study (SHP647-304). Subjects who are withdrawn from the study prior to completing the double-blind treatment period due to fulfilling the criteria for treatment failure also may be eligible to enter the LTS study. The intent of providing rescue treatment in the LTS study rather than in this maintenance study following *treatment failure* is to maintain study integrity. Offering treatment in the LTS study after exiting this maintenance study allows non-responder subjects on placebo, as well as subjects on active study drug, to potentially benefit from a prolonged or different dose of active treatment. Subjects will enter a 16 week safety follow up period if they withdraw early from the treatment period, are treatment failures and do not enter the LTS study (SHP647-304), or complete the study and do not wish to enter the 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 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, gastroenteritis (inflammation or infection of the gastrointestinal tract), upper respiratory infection (inflammation of the bronchial tubes that carry air to the lungs), bodily rash, pharyngitis (inflammation or infection of the throat), and anemia (reduced red blood cells). These side effects were also generally mild to moderate. 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.

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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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 have completed the 16 week induction treatment period from study SHP647 305 or SHP647 306 and met the following criteria at baseline in maintenance Study SHP647 307:
a) Meet endoscopic response criteria of a reduction in the Simple Endoscopic Score for CD (SES-CD) from induction study (SHP647 305 or SHP647 306) baseline by *25% at Week 16 of induction study (SHP647 305 or SHP647 306)
OR
b) Meet at least 1 of the following 4 criteria at baseline in maintenance Study SHP647-307, in addition to no worsening of endoscopic score as measured by SES-CD relative to induction study (SHP647 305 or SHP647 306) baseline:
i. Achieving clinical remission as determined by meeting the criteria for clinical remission using the 2 item PRO, ie, 2-item PRO subscores of average worst daily abdominal pain *3 (based on 11 point numerical rating scale [NRS]) over the 7 most recent days* and average daily stool type frequency *2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days*.
ii. A decrease of at least 100 points in CDAI score (CDAI-100) from induction study (SHP647 305 or SHP647 306) baseline.
iii. A decrease of *30% and at least 2 points from induction study (SHP647 305 or SHP647 306) baseline in the average daily worst abdominal pain over the 7 most recent days*, with the average daily stool frequency of type 6/7 (very soft stools/liquid stools) either: (i) not worsening from induction study (SHP647 305 or SHP647 306) baseline and/or (ii) meeting the criteria for clinical remission, ie, 2 item PRO subscore of average daily stool frequency *2 of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days*.
iv. A decrease of *30% from induction study (SHP647 305 or SHP647 306) baseline in the average daily stool frequency of type 6/7 (very soft stools/liquid stools) as shown in the BSFS over the 7 most recent days*, with the average daily worst abdominal pain either: (i) not worsening from induction study (SHP647 305 or SHP647 306) baseline and/or (ii) meeting the criteria for clinical remission, ie, 2 item PRO subscore of average worst daily abdominal pain *3 (based on 11 point NRS) over the 7 most recent days*.
*Note: The 7 days may or may not be contiguous during the 10 days of data collection before colonoscopy preparation, depending on days to be excluded because of missing data. If fewer than 7 days are available, the criterion will

be calculated on all available most recent 6 or 5 days. If fewer than 5 days are available, the criterion will be treated as missing.
4. 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.

Exclusion criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:
1. Subjects who had major protocol deviation(s) (as determined by the sponsor) in induction study SHP647 305 or SHP647 306.
2. Subjects who permanently discontinued investigational product because of an adverse event (AE), regardless of relatedness to investigational product, in induction study SHP647 305 or SHP647 306.
3. Subjects who are likely to require surgery for CD during the study period, except minor interventions (eg, seton placement for anal fistulas).
4. Subjects are females who became pregnant during induction study SHP647-305 or SHP647 306, females who are lactating, females who are planning to become pregnant during the study period, and males or females of childbearing potential not agreeing to continue using appropriate contraception methods (ie, highly effective methods for female subjects and medically appropriate methods for males, as described in Section 4.4 of the protocol) through the conclusion of study participation.
5. Subjects who do not agree to postpone donation of any organ or tissue, including male subjects who are planning to bank or donate sperm, and female subjects who are planning to harvest or donate eggs, for the duration of the study and through 16 weeks after last dose of investigational product.
6. Subjects who, in the opinion of the investigator or the sponsor, will be uncooperative or unable to comply with study procedures.
7. Subjects who have developed obstructive colonic stricture, or enterovesical or enterovaginal fistulae during the induction study (SHP647 305 or SHP647-306).
8. Subjects who have a newly diagnosed malignancy or recurrence of malignancy (other than resected cutaneous basal cell carcinoma, squamous cell carcinoma, or carcinoma in situ of the uterine cervix that has been treated with no evidence of recurrence).
9. Subjects who have developed any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal [except disease under study], endocrine, cardiovascular, pulmonary, immunologic [eg, Felty*s syndrome], or local active infection/infectious illness) that, in the investigator*s judgment, will substantially increase the risk to the subject if he or she participates in the study.
10. Subjects with any other severe acute or chronic medical or psychiatric condition or laboratory or electrocardiogram (ECG) abnormality that may increase the risk associated with study participation or investigational

product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
11. Subjects with known exposure to Mycobacterium tuberculosis since testing at screening in induction study SHP647-305 or SHP647-306 and who have been advised to require treatment for latent or active disease, but who are without a generally accepted course of treatment.
12. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during the evaluation of the last visit in the SHP647 305 or SHP647 306 studies. If the results are considered by the investigator to be transient and inconsistent with the subject*s clinical condition, may be repeated once prior to enrolment in Study SHP647-307.
* Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels *3.0 x the upper limit of normal (ULN)
* Total bilirubin level *1.5 times the ULN or >2.0 x ULN if the subject has a known documented history of Gilbert's syndrome
* Hemoglobin level *80 g/L (8.0 g/dL)
* Platelet count *100 × 109/L (100,000 cells/mm3) or *1000 × 109/L (1,000,000 cells/mm3)*
* White blood cell count *3.5 × 109/L (3500 cells/mm3)
* Absolute neutrophil count <2 ×109/L (<2000 cells/mm3)
* Serum creatinine level >1.5 x the ULN or estimated glomerular filtration rate <30 mL/min/1.73 m2 based on the abbreviated Modification of Diet in Renal Disease Study Equation.
*Note: If platelet count is <150,000 cells/mm3, a further evaluation should be performed to rule out cirrhosis, unless another etiology has already been identified.
13. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are sponsor employees directly involved in the conduct of the study.
14. Subjects who are participating in other investigational studies (other than induction study SHP647 305 or SHP647 306) or plan to participate in other investigational studies during Study SHP647 307.

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):	18-02-2020
Enrollment:	7
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	17-04-2018
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	EUCTR2017-000617-23-NL
Other	in process

Register	ID
CCMO	NL65341.028.18

Study results

Date completed: 07-12-2020

Results posted: 14-03-2022

First publication
31-01-2022