A study of the Efficacy and Safety of SHP647 as Induction Therapy in Subjects With Moderate to Severe Crohn's Disease (CARMEN CD 306)

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Main Information

Primary registry identifying number
LBCTR2019090248

Protocol number
SHP647-306

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency

Primary sponsor
Shire Human Genetic Therapies, Inc. ("Shire")

Primary sponsor: Country of origin
USA

Date of registration in primary registry
23/10/2019

Date of registration in national regulatory agency

Public title
A study of the Efficacy and Safety of SHP647 as Induction Therapy in Subjects With Moderate to Severe Crohn's Disease (CARMEN CD 306)

Acronym
CARMEN CD 306

Scientific title
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 306)

Acronym
CARMEN CD 306

Brief summary of the study: English
This study is designed to evaluate the efficacy and safety of SHP647 in inducing clinical remission and endoscopic response in subjects with moderate to severe Crohn Disease.

Brief summary of the study: Arabic
تم تصميم هذه الدراسة لتقييم فعالية وسلامة دواء الدراسةفي تحفيز التحسن السريري والاستجابة بالمنظار لدى المشاركين المصابين بمرض كرون بدرجة متوسطة الى شديدة

Health conditions/problem studied: Specify
Crohn Disease

Interventions: Specify
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 SHP647, 75 mg SHP647, or placebo) in a 3:3:2 ratio. Randomization will be stratified based upon the subject's status of prior anti-TNF treatment (naïve or experienced), glucocorticoid use at baseline (on glucocorticoids at baseline versus not on glucocorticoids at baseline), and SES-CD at baseline (SES-CD ≥17 or SES-CD <17). Subjects will receive SC injections of SHP647 or placebo, using a prefilled syringe (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 and at the time points specified in Table 1.

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) as shown in Figure 1. 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 (SHP647-306) will be eligible to continue in the maintenance study or LTS study.

Key inclusion and exclusion criteria: 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 assent as applicable to participate in the study.
3. Subjects must be between ≥18 and ≤80 years of age at the time of the signing of the informed consent/assent form.
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).

5. Subjects must have a documented diagnosis (endoscopic with histology) of CD for ≥3 months before screening. Documented diagnosis is defined as:
   - A biopsy report to confirm the histological 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 is not clear 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 (refer to Appendix 4 for guidance). 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 (as described in Section 4.4) for the duration of the study.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

80

Key inclusion and exclusion criteria: Exclusion criteria

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 diverticulos is.
6. Subjects with obstructive 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 CD during the treatment period.
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 SHP647 (formerly PF-00547659).
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 immunomodulator y 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/adhes ion 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 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 baseline (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 cytomegalovir us infection or Listeria monocytogenes, known active invasive fungal infections such as histoplasmos is 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 baseline (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 ha ve no history of previously diagnosed active or latent TB 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 baseline (Visit 2). 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 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 TB are excluded unless both of the following criteria are met:
• The subject has previously received an adequate course of treatment for either late nt (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 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 screening.
26. Subjects with any unexplained symptoms suggestive of progressive multifocal leukoencephalopathy (PML) based on the targeted neurological assessment during the screening period (Section 7.2.3.3).
27. Subjects with a transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.
28. Subjects with a significant concurrent medical condition at the time of screening (Visit 1) or baseline (Visit 2), including, but not limited to, the following:
• Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, GI [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.
• Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (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).
• Presence of acute coronary syndrome (eg, acute myocardial infarction, unstable angina pectoris) within 24 weeks before screening (Visit 1).
• History of significant cerebrovascular disease within 24 weeks before screening (Visit 1).
29. Subjects who have had significant trauma or major surgery within 4 weeks before screening (Visit 1), or with any major elective surgery scheduled to occur during the study.
30. Subjects with evidence of cirrhosis with or without decompensation (ie, esophageal varices, hepatic encephalopathy, portal hypertension, ascites).
31. Subjects with primary sclerosing cholangitis.
32. Subjects with evidence of positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Note: If a subject tests negative for HBsAg, but positive for HBcAb, the subject would be considered eligible if no presence of HBV DNA is confirmed by HBV DNA PCR reflex testing performed in the central laboratory.
33. Subjects with chronic hepatitis C (HCV) (positive HCVAb and hepatitis C ribonucleic acid [HCVRNA]). Note: Subjects who are HCVAb positive without evidence of HCVRNA may be considered eligible (spontaneous viral clearance or previously treated and cured [defined as no evidence of HCVRNA at least 12 weeks prior to baseline]).
34. Subjects with any of the following abnormalities in hematology and/or serum chemistry profiles during screening (Visit 1). Note: Screening laboratory tests, if the results are considered by the investigator to be transient and inconsistent with the subject's clinical condition, may be repeated once during the screening period for confirmation. Results must be reviewed for eligibility prior to the screening colonoscopy

procedure.
- Alanine aminotransferase and aspartate aminotransferase levels ≥3 × the upper limit of normal (ULN)
- Total bilirubin level ≥1.5 × ULN or >2.0 × 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 × ULN or estimated glomerular filtration rate <30 mL/min/1.73m2 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.
35. Subjects with known HIV infection based on documented history with positive serological test or positive HIV serologic test at screening, tested at the site's local laboratory in accordance with country requirements, or tested at the central laboratory. Note: A documented negative HIV test within 6 months of screening is acceptable and does not need to be repeated.
36. Subjects who have, or who have a history of (within 2 years before screening [Visit 1]), serious psychiatric disease, alcohol dependency, or substance/drug abuse of any kind including abuse of medicinal marijuana (cannabis).
37. 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.
38. Female subjects who are planning to become pregnant during the study period.
39. 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.
40. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Shire employees directly involved in the conduct of the study.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

3

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

Ontamalimab

Year of authorization

Month of authorization

Type of IMP

Immunological

Pharmaceutical class

IgG2 monoclonal antibody

Therapeutic indication

Crohn Disease

Therapeutic benefit

This study is designed to evaluate the efficacy and safety of SHP647 in inducing clinical remission and endoscopic response in subjects with moderate to severe CD.
SHP647, a fully human IgG2κ antihuman MAdCAM monoclonal antibody, is under development for the treatment of CD. SHP647 prevents the binding of α4β7 lymphocytes to MAdCAM-expressing sites with high affinity and selectivity. Principal sites of MAdCAM expression on normal tissue include intestine, pancreas, stomach, esophagus, spleen, and to a lesser extent lung, liver, and bladder but not the CNS (Steffen et al., 1996).
Although selective targeting of the MAdCAM receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these α4β + lymphocytes to the MAdCAM receptor and the resultant efficacy in CD is well established.
SHP647, in doses of 7.5 mg, 22.5 mg, and 75 mg, appears to increase the rate of remission in subjects with UC, and may have an effect in patients with CD who have greater evidence of inflammation based on biomarker or endoscopic data.

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective

N/A

Time perspective: Explain time perspective

N/A

Time perspective: Specify perspective

N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention

Samples without DNA

Biospecimen description

N/A

Target sample size

6

Actual enrollment target size

Date of first enrollment: Type

Actual

Date of first enrollment: Date

30/11/2019

Date of study closure: Type

Actual

Date of study closure: Date

01/11/2022

Recruitment status

Other

Recruitment status: Specify

Study not initiated yet

Date of completion

27/08/2021

IPD sharing statement plan

No

IPD sharing statement description

Not decided yet

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
No numbers	No Numbers

Sources of Monetary or Material Support

Name
Shire Human Genetic Therapies, Inc. ("Shire")

Secondary Sponsors

Name
None

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Aziz Zoghbi	MCT Lebanon s.a.r.l.	Lebanon	01--612500 ext2040	Zog_Az@Mctcro.com	CRO
Scientific	Shire Human Genetic Therapies, Inc. US US	300 Shire Way Lexington Post code MA 02421	United States of America	+1 781 482 0852	chantal.letourneau@shire.com	sponsor "Clinical Trial Information Desk"

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Al Zahraa University Hospital	Dr. Mahmoud Hallal	Gastroenterologist	NA
Hammoud Hospital University Medical Center	Dr. Majed Bahlawan	Gastroenterologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Hammoud Hospital University Medical Center	15/07/2019	ghada aoun	medical@hammoudhospital.org	+9617721021

Countries of Recruitment

Name
Lebanon
Belgium
Bulgaria
Estonia
Hungary
Ireland
Portugal
Slovakia
Spain
Bosnia and Herzegovina
Canada
Colombia
Japan
Mexico
Democratic People Republic of Korea
Ukraine
United States of America

Health Conditions or Problems Studied

Condition	Code	Keyword
Crohn Disease	Crohn s disease, unspecified (K50.9)	CD

Interventions

Intervention	Description	Keyword
SHP647 25mg	SHP647 will be administered subcutaneously in a PFS 1ml	randomization ratio of 3:3:2 to receive SC injections of 25 mg SHP647, 75 mg SHP647, or placebo
SHP647 75mg	SHP647 will be administered subcutaneously in a PFS 1ml	randomization ratio of 3:3:2 to receive SC injections of 25 mg SHP647, 75 mg SHP647, or placebo
Placebo	The placebo solution will contain the same sterile aqueous buffered solution as the test product but will not contain SHP647	randomization ratio of 3:3:2 to receive SC injections of 25 mg SHP647, 75 mg SHP647, or placebo

Primary Outcomes

Name	Time Points	Measure
Clinical remission based on 2-item patient-reported outcome (PRO) (abdominal pain severity and very soft stool/liquid stool frequency)	week 16	Clinical remission at week 16
Inducing endoscopic response based on centrally read colonoscopy.	Week 16	Endoscopic response at week 16

Key Secondary Outcomes

Name	Time Points	Measure
Clinical remission as measured by CDAI	week 16	Clinical remission at week 16
Enhanced endoscopic response based on centrally read colonoscopy	Week 16	Enhanced endoscopic response at week 16
Clinical remission based on abdominal pain severity and very soft stool/liquid stool frequency (alternate thresholds)	Week 16	Clinical response at week 16
Clinical response based on patient-reported clinical signs and symptoms (as measured by 2-item PRO)	Week 16	Clinical response at week 16
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	week 16	Clinical remission at week 16
Endoscopic healing based on centrally read colonoscopy.	Week 16	Endoscopic healing at Week 16

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files