A Phase 3b, Randomized, Double-blind, Multicenter Study to Evaluate the Safety and Efficacy of Intravenous Re-induction Therapy With Ustekinumab in Patients With Moderately to Severely Active Crohn*s Disease

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

Summary

ID

NL-OMON52420

Source
ToetsingOnline

Brief title
POWER-Study

Condition

- Gastrointestinal inflammatory conditions

Synonym
Chronic Inflammatory Bowel Disease; Enteritis regionalis

Research involving

Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen Cilag

Intervention

Keyword: Crohn, Re-induction Therapy, secondary loss of response, ustekinumab

Outcome measures

Primary outcome

The primary objective is to evaluate the achievement of clinical response at

Week 16 following a single IV re-induction dose of *6 mg/kg ustekinumab,

compared with continuing regular SC q8w 90 mg ustekinumab administration, in

participants with secondary loss of response (LoR) to SC q8w 90 mg ustekinumab

maintenance therapy.

Secondary outcome

The secondary objectives are to:

* Evaluate the achievement of clinical response and clinical remission, as well

as the reduction in inflammatory biomarkers (serum C-reactive protein [CRP]

and fecal calprotectin [FCal] levels), after IV ustekinumab re-induction.

* Assess the overall safety of IV ustekinumab re-induction.

Study description

Background summary

The study hypothesis is that in patients with secondary LoR to SC q8w 90 mg ustekinumab maintenance treatment, a single weight-tiered based IV ustekinumab re-induction dose of *6 mg/kg (ie, IV

ustekinumab/SC placebo at Week 0) followed by q8w 90 mg ustekinumab maintenance will result in a higher clinical response rate (defined as a >=100-point reduction from the baseline CDAI score, or a CDAI score <150) compared with continuous SC q8w 90 mg ustekinumab maintenance treatment (ie, IV placebo/SC ustekinumab at Week 0) after 16 weeks.

Study objective

The primary objective is to evaluate the achievement of clinical response at Week 16 following a single IV re-induction dose of *6 mg/kg ustekinumab, compared with continuing regular SC q8w 90 mg ustekinumab administration, in participants with secondary loss of response (LoR) to SC q8w 90 mg ustekinumab maintenance therapy.
The secondary objectives are to:
* Evaluate the achievement of clinical response and clinical remission, as well as the reduction in inflammatory biomarkers (serum C-reactive protein [CRP] and fecal calprotectin [FCal] levels), after IV ustekinumab re-induction.
* Assess the overall safety of IV ustekinumab re-induction.
The exploratory objectives are to assess endoscopy and patient-reported assessment of bowel inflammation following IV ustekinumab re-induction, and to assess the steroid-sparing effect and pharmacokinetics following a single IV re-induction dose of *6 mg/kg ustekinumab.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter, 24-week, Phase 3b study in adult patients with active moderate to severe Crohn*s disease who initially responded (as defined in Section 10.2, Appendix 2 of the protocol) to ustekinumab induction therapy per label followed, at any time, by secondary LoR to SC q8w ustekinumab maintenance therapy. The benefit of a single weight- tiered based IV re-induction dose of *6 mg/kg body weight ustekinumab versus continuous SC q8w maintenance treatment will be evaluated. Secondary LoR is defined as a CDAI score of >=220 and <=450 plus at least one of the following:
* Elevated CRP (>3.0 mg/L); and/or
* Elevated FCal (>250 mg/kg); and/or
* Endoscopy (ileocolonoscopy) with evidence of active Crohn*s disease during the current disease flare (ie, ulcerations in the ileum and/or colon).
Eligible participants will be randomly assigned to 1 of the following 2 re-induction groups in a 1:1 ratio, using permuted block randomization stratified at the study level by participant*s baseline CDAI score (<=300 or >300) and prior biologic failure (yes or no) at baseline.
* Ustekinumab re-induction: IV ustekinumab and SC placebo at Week 0.
* Continuous maintenance: IV placebo and SC ustekinumab at Week 0.
At baseline (Week 0), approximately 8 weeks (±2 weeks) after the previous per label dose of SC 90 mg ustekinumab maintenance, participants will undergo

clinical assessments. Following randomization, participants will receive IV ustekinumab *6 mg/kg and SC placebo or IV placebo and SC ustekinumab 90 mg in a double-blind manner.
At study visits at Weeks 8 and 16, all participants will receive SC ustekinumab 90 mg and will undergo clinical assessments, including ileocolonoscopy at Week 16.
At Week 24, all participants will undergo study assessments before resuming their standard of care at the discretion of the treating physician. All participants will also have a follow-up for evaluation of safety at Week 36, which may be conducted at a site visit or by telephone.
Key efficacy assessments will include clinical response (CDAI reduction >=100), clinical remission (CDAI value <150) and biomarker normalization. Safety assessments will include the monitoring of adverse events, vital signs, and clinical laboratory tests.

Intervention

Study intervention will start at baseline (Week 0), approximately 8 weeks (±2 weeks) after the previous dose of per label SC 90 mg ustekinumab maintenance treatment. The date of the previous dose of ustekinumab will be recorded in the case report form (CRF).
To maintain the double-blind, all participants will receive one IV injection of study intervention (ustekinumab *6 mg/kg or placebo) plus one SC administration of study intervention (ustekinumab 90 mg or placebo) at Week 0.
At Weeks 8 and 16, all participants will receive SC maintenance injections of 90 mg ustekinumab. Following study assessments at Week 24, all participants will resume their standard-of-care therapy with either ustekinumab maintenance therapy per label (SC 90 mg ustekinumab at this visit and q8w thereafter) or another treatment modality at the discretion of their physician.

Study burden and risks

The expected therapeutic effect justifies the burden and risks for the participants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Each potential participant must satisfy all the following criteria to be enrolled in the study:, 1. Male or female aged >=18 years (or the legal age of consent in the jurisdiction in which the study is taking place if older than 18 years)., 2. A history of Crohn*s disease or fistulizing Crohn*s disease of at least 3 months* duration, with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography, histology, and/or endoscopy., 3. Initially responded to ustekinumab induction therapy (a), administered according to the local label, followed by secondary LoR to ustekinumab (b)., a) Initial response to ustekinumab as defined in Section 10.2., b) Secondary LoR to ustekinumab is defined as active disease at study baseline, proven by a crohn*s disease activity index (CDAI) score of >=220 and <=450 with at least one of the following:, - Elevated CRP (>3.0 milligram per litre [mg/L]); and/or, - Elevated fCal (>250 mg/kg); and/or, - Endoscopy (performed within the 3 months before baseline) with evidence of active Crohn*s disease during the current disease flare (ie, ulcerations in the ileum and/or colon). Participants must currently be on a SC 90mg ustekinumab q8w maintenance dose regimen and have received at least 2 doses of SC 90mg ustekinumab treatment 8 weeks apart prior to enrollment., 4. The following medications for the treatment of Crohn*s disease are permitted providing the doses indicated are stable for at least 3 weeks before baseline or have been discontinued at least 3 weeks before baseline:, * Oral 5-aminosalicylic acid (5-ASA) compounds., * Oral corticosteroids (eg, prednisone, budesonide) at a prednisone-equivalent dose of <=40 mg/day or <=9 mg/day of budesonide., * Antibiotics used as the primary

treatment of Crohn*s disease., * Any participants receiving conventional immunomodulators (ie, azathioprine, [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) must have been taking them for >=12 weeks and must have been on a stable dose for a least 4 weeks before baseline., 5. The following laboratory test results are within the specified limits at screening:, * Hemoglobin >=8.5 g/dL (>=85 g/L)., * White blood cell (WBC) count >=3.5 x 10^3/µL (>=3.5 GI/L)., * Neutrophils >=1.5 x 10^3/µL (>=1.5 GI/L)., * Platelets >=100 x 10^3/µL (>=100 GI/L)., * Serum creatinine < 1.7 mg/dL (<=150 µmol/L)., * Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels <=2 times the upper limit of normal for the laboratory conducting the test., * Direct (conjugated) bilirubin <1.0 mg/dL (<0.01 g/L)., 6. Meet the following TB screening criteria:, * No history of latent or active TB before screening. An exception is made for participants who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB prior to first administration of study intervention, or have documentation of having completed appropriate treatment for latent TB within 5 years prior to the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation., * No signs or symptoms suggestive of active TB upon medical history and/or physical examination., * No recent close contact with a person with active TB. If there has been such contact, the participant will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, will receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study intervention., * Meets all other protocol-specified TB inclusion criteria, 8. All female participants of childbearing potential must have a negative highly sensitive serum (-human chorionic gonadotropin [-hCG]) pregnancy test at screening and a negative urine pregnancy test at baseline and prior to each administration of study intervention., 9. A male participant who is heterosexually active with a woman of childbearing potential and is not surgically sterile must agree to use a double-barrier method of birth control and not donate sperm during the study and for 15 weeks after receiving study intervention., 11. Sign an informed consent document indicating that he/she understands the purpose of and procedures required for the study and is willing to participate in the study., Please see protocol for an overview of all inclusion criteria

Exclusion criteria

1.Complications of Crohn*s disease, such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation that might be anticipated to require surgery, could preclude the use of the CDAI to assess response to therapy, or would possibly confound the ability to assess the effect of treatment with ustekinumab., 2.Currently has or is suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if

drained and adequately treated at least 3 weeks before baseline, or 8 weeks before baseline for intra-abdominal abscesses, provided there is no anticipated need for any further surgery. Participants with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses identified., 3.Any kind of bowel resection within 6 months or any other intra-abdominal surgery within 3 months before baseline., 4.A draining (ie, functioning) stoma or ostomy., 5.Received any of the following prescribed medications or therapies within the specified period:, *Any known history of shortened frequency of SC dose administration (response where the participant did not, in the opinion of treating physician,
benefit from the dose interval shortening *Use of IV ustekinumab re-induction after the initial weight-tiered based IV induction dose of ustekinumab., *Intravenous corticosteroids as a treatment for Crohn*s disease within 3 weeks before baseline., *Oral immunomodulatory agents other than AZA, 6-MP, or MTX (eg, Janus kinase [JAK] inhibitors, 6-thioguanine [6-TG], cyclosporine, tacrolimus, sirolimus, tofacitinib, or mycophenolate mofetil) within 4 weeks before baseline., *Any other investigational agent for Crohn*s disease (eg other biologics, small molecules or anti-sense RNA such as mongersen), unless at least 3 months or 5 half-lives (whichever is longer) have elapsed since the last dose., *Treatment with apheresis (eg, Adacolumn apheresis) or total parenteral nutrition as a treatment for Crohn*s disease within 3 weeks before baseline., 6.A stool culture or other examination in the last 4 months that is positive for an enteric pathogen, including Clostridium difficile toxin, unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen., 7.Received a Bacille Calmette-Guérin (BCG) vaccination within 12 months before baseline or any other live bacterial or live viral vaccination within 2 weeks before baseline., 8.A history of, or ongoing, chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection, recurrent urinary tract infection (eg, recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers., 9.Any current signs or symptoms of infection. Established non-serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator., 10.A history of serious infection (eg, sepsis, pneumonia, or pyelonephritis), including any infection requiring hospitalization or IV antibiotics, for 8 weeks before baseline., 11.Evidence of a herpes zoster infection <=8 weeks before baseline., 12.A history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening; refer to Inclusion Criterion 6 for information regarding eligibility with a history of latent TB., 13.Evidence of current active infection, including TB, or a nodule suspicious for lung malignancy on screening or any other available chest radiograph, unless definitively resolved surgically or by additional imaging and with source document confirmation., 14.A current or (lifetime) history of a nontuberculous mycobacterial infection or serious opportunistic infection (eg, Cytomegalovirus colitis, Pneumocystis carinii, aspergillosis)., 15.Known to be infected with human immunodeficiency virus, hepatitis B, or hepatitis C., 16.Severe,

progressive, or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or any signs or symptoms thereof., 17.A transplanted organ, with the exception of a corneal transplant performed >12 weeks before screening., 18.A known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly., 19.Any known malignancy or a history of malignancy, with the exception of: basal cell carcinoma; squamous cell carcinoma in situ of the skin; cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that was treated with no evidence of recurrence within 5 years before screening., 20.Previous allergy immunotherapy for prevention of anaphylactic reactions., 21.Unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins., Please see protocol for an overview of all exclusion criteria

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):	13-08-2019
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ustekinumab

Generic name:	Stelara
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-11-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-07-2019
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-04-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-07-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-06-2021
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2018-002629-51-NL
CCMO	NL67051.091.18

Study results

Date completed:	21-07-2022
Results posted:	08-01-2024

URL result

URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File