Study of Treat to Target Versus Routine Care Maintenance Strategies in Crohn*s Disease Patients Treated with Ustekinumab

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A *treat to target* strategy has been advocated as an optimized management approach for various diseases, by which strictly defined treatment targets facilitate decision making in clinical practice. Key to the success of this treatment strategy is...

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

Summary

ID

NL-OMON47710

Source
ToetsingOnline

Brief title
Stardust

Condition

- Gastrointestinal inflammatory conditions

Synonym
chronic inflammation of the intestinal wall, enteritis regionalis

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag

Source(s) of monetary or material Support: Janssen B.V.

Intervention

Keyword: Crohn, Routine Care, treat-to-target, Ustekinumab

Outcome measures

Primary outcome

To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving endoscopic response.

Secondary outcome

-To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted.

-To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving endoscopic remission.

-To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving mucosal healing.

-To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving clinical remission.

-To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving clinical response.

-To evaluate the efficacy of a treat to target strategy coupled with early

endoscopic assessment versus a clinically driven (routine care) approach in eliminating the need for corticosteroids while maintaining disease control.

-To evaluate the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on serum CRP and FC levels.

-To evaluate the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on health-related quality of life (QoL), patient-reported outcomes and pharmacoeconomics.

Study description

Background summary

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human IL-12/23p40 that binds with high affinity to the p40 subunit of human IL-12 and IL-23. By inhibiting interaction with the cell surface IL-12R*1 receptor protein, ustekinumab effectively neutralizes all IL-12 (Th1) and IL-23 (Th17) mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune- mediated diseases including Crohn*s disease.

Ustekinumab (STELARA®) has been approved by the EMA for the treatment of moderate to severe plaque psoriasis in adults or adolescent patients, and for the treatment of active psoriatic arthritis. At the time of protocol writing, ustekinumab has positive opinion from the CHMP at
the EMA, and approval from the United States Food and Drug Administration for the treatment of adult patients with moderately to severely active Crohn*s disease who have had an inadequate response with, lost response to, were intolerant to, or have medical contraindications to either:
conventional therapy, or TNF* antagonist therapy.

Inflammatory bowel diseases (IBD) are chronic, progressive, and disabling conditions. Most current strategies, which target control of symptoms, do not appear to significantly alter the natural course of the disease. Recent studies in Crohn*s disease underscore the need to look beyond symptoms and to treat

endoscopic/macroscopic lesions, ultimately with the aim of preventing structural damage and disability. Due to the invasive nature and/or cost of endoscopies or cross-sectional imaging, frequent repetition of these procedures is not feasible; STELARA (ustekinumab) therefore, surrogate biomarkers of inflammation, including CRP and fecal calprotectin (FC) have been increasingly studied in IBD.

Study objective

A *treat to target* strategy has been advocated as an optimized management approach for various diseases, by which strictly defined treatment targets facilitate decision making in clinical practice. Key to the success of this treatment strategy is the definition of appropriate treatment targets and adoption of algorithms that drive therapeutic changes within distinct time frames. This approach has been shown to be successful in chronic, immune-mediated inflammatory disorders such as rheumatoid arthritis and psoriatic arthritis. Recently, the value of such an approach in patients* management has been suggested for IBD.

The goal of this study of adult Crohn*s disease subjects treated with ustekinumab is to demonstrate that a maintenance strategy based on early endoscopy followed by regular assessment of biomarkers (FC and CRP) and clinical symptoms (CDAI) with subsequent adjustment of treatment in case of persistent inflammatory disease activity (failure to achieve the target) is more successful in achieving endoscopic improvement than a pragmatic maintenance strategy based on guidance provided in the EU SmPC for the use of ustekinumab in Crohn*s disease.

Study design

This is a randomized, open-label, parallel-group, multicenter, multinational, Phase 3b interventional study of ustekinumab in adult subjects with active moderate to severe Crohn*s disease. The benefit of a treat to target maintenance treatment strategy versus routine care will be investigated. For the treat to target strategy, ustekinumab treatment will be adjusted based on the regular assessment of disease activity by objective clinical and biological outcome measures and clinical symptoms. Maintenance treatment in the routine care arm will be pragmatic, in compliance with the EU SmPC for ustekinumab in Crohn*s disease.

A target of 650 adult male and female subjects with endoscopic evidence of active disease will be enrolled. Subjects enrolled will have previously had an inadequate response with, lost response to, been intolerant to, or had medical contraindications to either conventional therapy, or one previous biologic therapy approved for the treatment of Crohn*s disease in the countries in which the study is conducted. Study subjects may be biologic-naïve or

biologic-experienced, having received no more than one prior biologic approved for the treatment of Crohn*s disease.

During a screening period of up to 5 weeks, eligibility of subjects will be evaluated, and centrally-read endoscopic assessments at screening will be used for baseline evaluation. At Week 0, all eligible subjects will initiate intravenous (IV) induction treatment with ustekinumab, in line with the EU SmPC, on a weight-tiered basis at a dose of approximately 6 mg/kg IV. At Week 8, all subjects will receive a 90 mg SC injection of ustekinumab.

At Week 16, subjects who do not achieve a CDAI improvement of 70 points versus Week 0 (CDAI-70) will leave the study. Subjects who remain in the study will be randomized in a 1:1 ratio to either one of two arms for open-label maintenance treatment up to Week 48: the treat to target arm or the routine care arm. Randomized subjects will be stratified according to whether biologic-naïve at baseline versus prior exposure to 1 biologic for the treatment of Crohn*s disease, and according to baseline SES-CD score *16 or SES-CD >16.

In the routine care arm, assessment visits will be scheduled according to the timing of maintenance treatment injections, which will be in compliance with the EU SmPC for ustekinumab for the treatment of Crohn*s disease, in which dosing every 12 weeks is recommended. At Week 16, (ie, 8 weeks after the first SC dose), subjects who have not shown adequate response based on the investigator*s judgment may
receive a second SC dose at that time. During the routine care maintenance treatment period, clinical assessments in case of disease flare will be at the investigator*s discretion. Consistent with the EU SmPC for ustekinumab, subjects who lose response during 12-weekly dosing may benefit from an adjustment to 8-weekly maintenance treatment. Subjects may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. In contrast, those subjects previously receiving 8-weekly treatment will not be able to adjust the ustekinumab dose following disease flare and will leave the study if they would not benefit from continuing study treatment in the investigator*s judgment.

In the treat to target arm, initial ustekinumab maintenance treatment assignment will be based on centrally-read ileocolonoscopy findings. Subjects with <25% improvement in SES-CD score at Week 16 versus baseline will be assigned to 8-weekly maintenance treatment. Subjects with *25% improvement in SES-CD score at Week 16 versus baseline will be assigned to 12-weekly treatment. Subsequently, at assessment visits (from Week 24 for subjects assigned to the 8-weekly regimen or from Week 20 for the 12-weekly group) ustekinumab maintenance treatment will be directed by treat to target assessments. The treatment target will be the achievement of either:
- CDAI <220 and a CDAI-70 response (defined as a 70-point improvement in CDAI score from baseline)
AND:

- CRP *10 mg/L or FC *250 *g/g.

For subjects who do not have elevated CRP at baseline (ie, CRP *2.87 mg/L at Week 0) in the presence of active disease, CRP would not be considered a biomarker target for dose adjustment

Subjects meeting the treatment target will continue on the same ustekinumab dosing frequency. Maintenance dosing frequency will be optimized for subjects failing to meet the treatment targets: those subjects previously on 12-weekly regimens will be adjusted to 8-weekly dosing; those previously on 8-weekly regimens will be adjusted to 4-weekly dosing. Subjects subsequently failing to meet treatment targets at the next assessment visit 4 weeks after dosing will not be able to optimize dosing further and will leave the study. In case of disease flare between scheduled assessment visits for the treat to target arm, subjects will undergo CDAI and biomarker (CRP and FC) assessments. Dosing frequency will be adjusted for subjects failing to meet the treatment target.

All subjects will have study visits at Weeks 0, 8 and 16, at each assessment visit at the times scheduled for study drug administration, and at Week 48. In cases of disease flare arising between scheduled study visits, subjects in both arms will also be assessed at the time of disease flare. A final ileocolonoscopic assessment will be performed at the Week 48 study visit. Subjects discontinuing treatment before Week 48 will have an early termination visit at the time of discontinuation, unless consent is withdrawn.
Early termination assessments should include an ileocolonoscopic assessment.

Subjects will be allowed to enter the study on oral corticosteroids at a prednisone-equivalent dose of *40 mg/day or *9 mg/day of budesonide. For subjects receiving corticosteroids who are randomized at Week 16 (CDAI-70 responders) corticosteroid tapering is mandatory. A recommended corticosteroid tapering schedule is specified in the protocol. Corticosteroid tapering can be initiated from Week 8 in subjects already demonstrating response (CDAI-70) to ustekinumab treatment.

From Week 48, subjects will continue ustekinumab treatment in the study extension period, up to Week 104. The frequency of dosing will be based on endoscopic and/or clinical remission at Week 48, and subsequently on clinical remission and biomarker findings.

For all subjects, final safety follow-up assessments will be performed 16 weeks after the last administration of ustekinumab within the study. For subjects completing the 104-week study and moving to commercially-available ustekinumab, final safety follow-up assessments should be performed before the first dose of commercially-available drug. The study will be considered completed with the last visit for the last subject participating in the study.

Intervention

At Week 0, all eligible subjects will initiate intravenous (IV) induction treatment with ustekinumab, on a weight-tiered basis at a dose of approximately 6 mg/kg IV. At Week 8, all subjects will receive a 90 mg SC injection of ustekinumab.

At Week 16, subjects who do not achieve a CDAI improvement of 70 points versus Week 0 (CDAI-70) will leave the study. Subjects who remain in the study will be randomized in a 1:1 ratio to either one of two arms for open-label maintenance treatment up to Week 48: the treat to target arm or the routine care arm.

In the routine care arm, assessment visits will be scheduled according to the timing of maintenance
treatment injections (every 8 or 12 weeks) based on the investigator*s judgment. Subjects previously receiving 8-weekly treatment will not be able to adjust the ustekinumab dose following disease flare and will leave the study if they would not benefit from continuing study treatment in the investigator*s judgment.

In the treat to target arm, initial ustekinumab maintenance treatment assignment will be based on centrally-read ileocolonoscopy findings (every 8 or 12 weeks).Subsequently, at assessment visits (from Week 24 for subjects assigned to the 8-weekly regimen or from Week 20 for the 12-weekly group) ustekinumab maintenance treatment will be directed by treat to target assessments. The treatment target will be the achievement of either:
- CDAI <220 and a CDAI-70 response (defined as a 70-point improvement in CDAI score from baseline)
AND:
- CRP *10 mg/L or FC *250 *g/g.
For subjects who do not have elevated CRP at baseline (ie, CRP *2.87 mg/L at Week 0) in the presence of active disease, CRP would not be considered a biomarker target for dose adjustment
subjects previously on 12-weekly regimens will be adjusted to 8-weekly dosing; those previously on 8-weekly regimens will be adjusted to 4-weekly dosing. Subjects subsequently failing to meet treatment targets at the next assessment visit 4 weeks after dosing will not be able to optimize dosing further and will leave the study.

From Week 48, subjects will continue ustekinumab treatment in the study extension period, up to Week 104. The frequency of dosing will be based on endoscopic and/or clinical remission at Week 48, and subsequently on clinical remission and biomarker findings.

Study burden and risks

For side effects of Ustekinumab, I refer to the Informed consent form.
Side effects related to procedures:

Blood draw: Taking blood may cause bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur.

X-Ray Risks: The radiation dose that is in the x-ray(s) taken for this study is small. There is no significant risk from this amount of radiation.

ECG Risk: There is generally no risk with having an ECG. The sticky patches may pull your skin or cause redness or itching.

Ileocolonoscopy: A long, flexible, tube is inserted through the rectum into the colon up to the last part of the ileum. The doctor will explain this in more detail before the procedure is performed and will also explain possible risks and discomforts for these in more detail.

Abdominal ultrasound:An ultrasound scanning device consists of computer and a transducer that is used to scan the body. A transducer is a small hand-held device about the size of a bar of soap that is attached to the scanner by a cord. A lubricating gel is spread on the skin over the area being examined, and then the transducer is pressed firmly against the skin to obtain images.The doctor will explain this in more detail before the procedure is performed and will also explain possible risks and discomforts for these in more detail.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Male or female *18 years of age;2) Have active moderate to severe Crohn*s disease;3) Has had an inadequate response with, lost response to, was intolerant to, or had medical contraindications to either:;*conventional therapy, or;*one previous biologic therapy approved for the treatment of Crohn*s disease in the countries in which the study is conducted.;4) Adhere to the following requirements for concomitant medication for the treatment of Crohn*s disease.;5) Are eligible according to tuberculosis (TB) infection screening criteria;6) Must sign an informed consent form (ICF) (or their legally acceptable representative if applicable must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study ;7) A woman of childbearing potential must have a negative highly sensitive serum pregnancy test at screening, and a negative urine pregnancy test at Week 0.;8) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.;9) A woman must agree not to donate eggs for the purposes of assisted reproduction during the study and for 15 weeks after the last study drug administration.;10) During the study and for 15 weeks after receiving the last dose of study drug, in addition to a highly effective method of contraception, a man;- who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception ;- must agree not to donate sperm.;11) Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

Exclusion criteria

1)Has 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 prior to baseline, or 8 weeks prior to baseline for intra-abdominal abscesses, provided there is no anticipated need for any further surgery. ;Subjects with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses identified.;3) Has had any kind of bowel resection within

6 months prior to baseline.;4) Has a draining stoma or ostomy.;5) Has received more than one previous biologic therapy approved for the treatment of Crohn*s disease in the countries in which the study is conducted.;6) Has previously received a biologic agent targeting IL-12 and/or IL-23, including but not limited to ustekinumab.;7) Has received any of the following prescribed medications or therapies within the specified period:;a. IV corticosteroids <3 weeks prior to baseline.;b. Other oral immunomodulatory agents <6 weeks prior to baseline.;c. Non-autologous stem cell therapy or biologic agents that deplete B or T cells;d. Vedolizumab <12 weeks prior to baseline.;e. Anti-TNF biologic agents or other agents intended to suppress or eliminate TNF <8 weeks prior to baseline.;f. Any investigational drug within 4 weeks before first administration of study drug or within 5 half-lives of the investigational drug, whichever is longer.;g. Treatment with apheresis or total parenteral nutrition as a treatment for;Crohn*s disease <3 weeks prior to baseline.;8) Has received a Bacille Calmette-Guérin vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks of baseline.;9) Have a stool culture or other examination positive for an enteric pathogen, including Clostridium difficile toxin, in the last 4 months unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.;10) Has 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, or open, draining, or infected skin wounds or ulcers.;11) Has current signs or symptoms of infection. Established nonserious infections need not be considered exclusionary at the discretion of the investigator.;12) Has a history of serious infection, including any infection requiring hospitalization or IV antibiotics, for 8 weeks prior to baseline.;13) Has evidence of a herpes zoster infection *8 weeks prior to baseline.;14) Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. ;15) Has 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.;16) Has or ever has had a nontuberculous mycobacterial infection or serious opportunistic infection;17) Is known to be infected with HIV, hepatitis B, or hepatitis C.;18) Has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.;19) Has a transplanted organ >12 weeks prior to screening.;20) Has a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.;21) Has any known malignancy or has a history of malignancy;22) Has previously undergone allergy immunotherapy for prevention of anaphylactic reactions.;23) Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients or an allergy to latex;24) is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 15 weeks after the last dose of study drug;25) is a man who plans to father a child while enrolled in this study or within 15 weeks after the last dose of study drug.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-08-2017
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Stelara
Generic name:	Ustekinumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	02-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	14-06-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	08-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-002918-43-NL

Register	ID
CCMO	NL60565.056.17

Study results

Date completed: 25-05-2021

Results posted: 15-07-2022

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

Internal documents
File