A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

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INDUCTION STUDY Primary Objectives:* To evaluate the efficacy of intravenous (IV) ustekinumab in inducing clinical remission in subjects with moderately to severely active UC.* To evaluate the safety of IV ustekinumab in subjects with moderately to...

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

Summary

ID

NL-OMON44076

Source
ToetsingOnline

Brief title
UNIFI

Condition

- Gastrointestinal inflammatory conditions

Synonym
Ulcerative Colitis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Phase 3 study, Placebo-controlled, Ulcerative Colitis, Ustekinumab (STELARA®)

Outcome measures

Primary outcome

Efficacy evaluations will include the following:

* Mayo score and partial Mayo score

* Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

* C-reactive protein

* Fecal lactoferrin and fecal calprotectin

* Inflammatory Bowel Disease Questionnaire (IBDQ)

* 36-item Short Form Health Survey (SF-36)

* EuroQoL-5D Health Questionnaire (EQ-5D)

The primary endpoint of the induction study is clinical remission at Week 8.

The primary endpoint of the maintenance study is clinical remission at Week 44.

Secondary outcome

The following are the major secondary endpoints in the induction study,

presented in the order in which they will be tested: endoscopic healing at

Week 8; clinical response at Week 8; the change from induction baseline in the

total score of the IBDQ at Week 8.

The following are the major secondary endpoints in the maintenance study, presented in the order in which they will be tested: maintenance of clinical response through Week 44; endoscopic healing at Week 44; maintenance of clinical remission through Week 44 among the subjects who had achieved clinical remission at maintenance baseline; clinical remission and not receiving concomitant corticosteroids at Week 44 of maintenance among the subjects receiving concomitant corticosteroids at maintenance baseline. Number of participants with clinical remission and not receiving concomittant corticosteroids at week 44. Number of participants with clinical remission among those who achieved clinical remission at maintenance study baseline.

Study description

Background summary

Ustekinumab (STELARA®) is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human interleukin (IL)-12/23p40 that binds with high affinity to human IL-12 and IL-23. Ustekinumab prevents IL-12 and IL-23 bioactivity by preventing their interaction with their cell surface IL-12R*1 receptor protein. Through this mechanism of action, ustekinumab effectively neutralizes 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 inflammatory bowel disease (IBD). Therefore, binding and inhibiting the IL-12/23p40 subunit may provide effective therapy in IBD, including Crohn's disease and ulcerative colitis (UC).
Ustekinumab has received marketing approval globally, including countries in North America, Europe, South America, and the Asia-Pacific region, for the treatment of adult patients with chronic moderate to severe plaque psoriasis or active psoriatic arthritis. Ustekinumab is currently being evaluated in a Phase 3 development program for Crohn*s disease.
Data from completed Phase 2 studies of ustekinumab in Crohn*s disease, along

with the shared biology and the similar response to current treatments between Crohn*s disease and UC, provide a substantial scientific and clinical rationale to justify a direct-to-Phase-3 approach to the study of ustekinumab in UC. Relative to approved therapies for UC (ie, tumor necrosis factor antagonists and the anti-*4*7 integrin antagonist, vedolizumab), ustekinumab offers the potential for a more convenient treatment regimen, with subcutaneous (SC) administration every 8 to 12 weeks during maintenance, as well as a novel mechanism of action in the treatment of UC, and a documented long-term safety profile.
The Phase 3 development program for ustekinumab in the treatment of UC will be conducted under a single protocol but will be designed and analyzed as 2 separate studies, an induction study and a maintenance study.

Study objective

INDUCTION STUDY
Primary Objectives:
* To evaluate the efficacy of intravenous (IV) ustekinumab in inducing clinical remission in subjects with moderately to severely active UC.
* To evaluate the safety of IV ustekinumab in subjects with moderately to severely active UC.

MAINTENANCE STUDY
Primary Objectives:
* To evaluate clinical remission for SC maintenance regimens of ustekinumab in subjects with moderately to severely active UC induced into clinical response with ustekinumab.
* To evaluate the safety of SC maintenance regimens of ustekinumab in subjects with moderately to severely active UC induced into clinical response with ustekinumab.

Exploratory Objective in Induction and Maintenance:
* To evaluate response using the Mayo score without the physician's global assessment (PGA) subscore.

Study design

The Phase 3 development program for ustekinumab in the treatment of UC will be conducted under a single protocol but will be designed and analyzed as 2 separate studies, an induction study and a maintenance study. Both will be Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies of ustekinumab in subjects with moderately to severely active UC. The induction study will target subjects with moderately to severely active UC who demonstrate an inadequate response or failure to tolerate conventional or biologic therapy. The maintenance study will be a randomized withdrawal study targeting subjects with moderately to severely active UC who

demonstrate a clinical response to induction treatment with IV ustekinumab.
Overall, the program will evaluate ustekinumab treatment in subjects with moderately to severely active UC through at least 1 year of induction and maintenance therapy. After completion of the maintenance study through Week 44, a long-term extension (LTE) will follow eligible subjects for an additional 3 years.
Throughout the induction and maintenance studies, efficacy, PK, biomarkers, and safety will be assessed at timepoints indicated in the appropriate Time and Events Schedules.
Blood samples for pharmacogenomic analyses will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.
An interim analysis to assess for futility is planned when the first 30% of subjects randomized in the induction study either complete the induction Week 8 visit or terminate study participation before Week 8.
An independent Data Monitoring Committee will be commissioned for this study.
The end of the CNTO1275UCO3001 study is defined as the date on which the last subject completes the last visit in the LTE.

Intervention

Induction: A target of 951 subjects will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups and will receive their assigned IV dose of study agent at Week 0:
* Placebo IV
* Ustekinumab 130 mg IV
* Weight-range-based ustekinumab doses approximating ustekinumab 6 mg/kg IV (ie, ustekinumab ~6 mg/kg IV):
*Ustekinumab 260 mg (weight *55 kg)
*Ustekinumab 390 mg (weight >55 kg but *85 kg)
*Ustekinumab 520 mg (weight >85 kg)
At Week 8, all subjects will be evaluated for the primary endpoint of clinical remission, and for clinical response. Further study agent administration will be determined by clinical response status (using the Mayo endoscopy subscore assigned by the local endoscopist) at Week 8, as follows:
* Subjects who are in clinical response at Week 8 are eligible to enter the maintenance study.
* Subjects who are not in clinical response at Week 8 will receive ustekinumab as follows:
*Subjects who were randomized to placebo at Week 0 will receive 1 dose of ustekinumab ~6 mg/kg IV plus placebo SC (to maintain the blind) at Week 8.
*Subjects who were randomized to ustekinumab at Week 0 will receive 1 dose of ustekinumab 90 mg SC plus placebo IV (to maintain the blind) at Week 8.
At Week 16, the subjects who were not in clinical response at Week 8 will be re-evaluated for clinical response (clinical response status will be based on the Mayo endoscopy subscore assigned by the local endoscopist):
*Subjects who achieve clinical response at Week 16 are eligible to enter the

maintenance study.
*Subjects who do not achieve clinical response at Week 16 will not enter the maintenance study and will have a safety follow-up visit approximately 20 weeks after their last (ie, Week 8) administration of study agent.
Maintenance: A target of 327 subjects who are in clinical response to IV ustekinumab induction will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups and will receive their assigned SC dose of study agent at maintenance Week 0:
* Placebo SC
* Ustekinumab 90 mg SC every 12 weeks (q12w)
* Ustekinumab 90 mg SC every 8 weeks (q8w)
Subjects who were in clinical response to IV ustekinumab during induction will comprise the primary population in the maintenance study:
* Subjects who were randomized to receive ustekinumab at Week 0 of the induction study and were in clinical response at induction Week 8.
* Subjects who were randomized to receive placebo at Week 0 of the induction study and were not in clinical response at induction Week 8, but were in clinical response at induction Week 16 after receiving a dose of IV ustekinumab at induction Week 8.
Additional subjects entering the maintenance study will include the following; these subjects will not be part of the primary population:
* Subjects who are in clinical response to placebo IV induction will receive placebo SC.
* Subjects who were delayed responders to ustekinumab induction (ie, were not in clinical response at induction Week 8 but were in clinical response at induction Week 16) will receive ustekinumab 90 mg SC q8w.

All subjects will receive their assigned dose of SC study agent at maintenance Week 0. Thereafter, to maintain the blind, all subjects will receive study agent at all scheduled study agent administration visits specified in the Time and Events Schedule for maintenance. Subjects will be assessed for clinical flare at every visit.

Study burden and risks

Number of blood draws: 58 x 7,07 ml per visit = 410 ml in total. Patient might experience discomfort from needle during blood draw.
Number of visits to the study doctor/hospital: 58 visits.
Intravenous injections: 2 x 250 ml. Patient might experience local discomfort from needle during IV injection.
Subcutaneous injections: 50 x 1 ml. Patient might experience local discomfort from needle during SC injection.
Physical examination: 6 times throughout the study. Patient might not experience any burden or risk from phys. examination.
Questionnaires: will be given to patient to fill out, in total 8 times during the study.
Mayo diary: will be given to patient to maintain throughout the study; patient

to return diary to study doctor 21 times during study.
Bristol Stool Form diary: will be given to patient during the induction part of the study to maintain throughout the study; patient to return diary to study doctor 5 times during study.
Physical discomfort of ECG: patient might experience local discomfort from the sticky padges (1 time during the study).
Physical discomfort of Chest X-ray: patient might not experience any discomfort from chest x-ray (1 time during the study).
Physical discomfort of endoscopy with biopsy: patient might experience discomfort from the tube when this is inserted in the rectum into the colon (5 times during the study).
Potential adverse effects of treatment: reported side effects of study medication.
Potential effect of use of placebo: possibly patient might not have a clinical benefit when receiving placebo.
Stool sample collection: 13 times throughout the study. Patient might experience this as a burden to collect his/her stool sample.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Has a clinical diagnosis of Ulcerative Colitis (UC) at least 3 months before Screening ;- Has moderately to severely active UC, defined as a Baseline (Week 0) Mayo score of 6 to 12, including a Screening endoscopy subscore of the Mayo score greater than or equal to (><=) 2 as determined by a central reading of the video endoscopy ;- Have failed biologic therapy, that is, have received treatment with 1 or more tumour necrosis factor (TNF) antagonists or vedolizumab at a dose approved for the treatment of UC, and have a documented history of failure to respond to or tolerate such treatment; OR Be naïve to biologic therapy (TNF antagonists or vedolizumab) or have received biologic therapy but have not demonstrated a history of failure to respond to, or tolerate, a biologic therapy and have a prior or current UC medication history that includes at least 1 of the following: ;a. Inadequate response to or failure to tolerate current treatment with oral corticosteroids or immunomodulators (6 mercaptopurine [6-MP] or azathioprine [AZA]) OR ;b. History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA) OR ;c. History of corticosteroid dependence (that is, an inability to successfully taper corticosteroids without a return of the symptoms of UC) ;- Before the first administration of study agent, the following conditions must be met: vedolizumab must have been discontinued for at least 4 months and antitumor necrosis factors (TNFs) [or approved biosimulars for these therapies) for at least 8 weeks

Exclusion criteria

- Has severe extensive colitis and is at imminent risk of colectomy ;- Has UC limited to the rectum only or to < 20 centimeters (cm) of the colon ;- Presence of a stoma or history of a fistula ;- Participants with history of extensive colonic resection (for example, less than 30 cm of colon remaining) that would prevent adequate evaluation of the effect of study agent on clinical disease activity ;- Participants with history of colonic mucosal dysplasia;- Participants will not be excluded from the study because of a pathology finding of *indefinite dysplasia with reactive atypia''

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:	Recruitment stopped
Start date (anticipated):	21-12-2015
Enrollment:	6
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	03-07-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-09-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-10-2015

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-06-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-10-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-11-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-07-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-08-2017

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-08-2018
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:	01-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-07-2020
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	EUCTR2014-005606-38-NL
ClinicalTrials.gov	NCT02407236
CCMO	NL53910.028.15

Study results

Date completed:	14-04-2020
Actual enrolment:	19