A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy

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

Summary

ID

NL-OMON38117

Source
ToetsingOnline

Brief title
UNITI-1

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's Disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Crohn's Disease, Ustekinumab

Outcome measures

Primary outcome

The primary endpoint is clinical response at Week 6, defined as a reduction

from baseline in the CDAI score of >= 100 points. Subjects with a baseline CDAI

score of >= 220 to <= 248 points are considered to be in clinical response if a

CDAI score of < 150 is attained.

Secondary outcome

The major secondary endpoints, in order of importance, are:

1. Clinical remission at Week 8, defined as a CDAI score of < 150 points.

2. Clinical response at Week 8.

3. 70-point response at Week 6, defined as a reduction from baseline in the

CDAI score of >= 70 points.

4. 70-point response at Week 3.

Study description

Background summary

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody (mAb) 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-12Rβ1 receptor protein. Through this mechanism of action, 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 inflammatory bowel disease, and binding the IL-12/23p40 subunit may provide effective therapy in Crohn*s disease.

Study objective

The primary objectives are:

- To evaluate the efficacy of IV induction regimens of ustekinumab in inducing clinical response in subjects with moderately to severely active Crohn*s disease who have failed or are intolerant to one or more tumor necrosis factor (TNF) antagonist therapies.
- To evaluate the safety of IV induction regimens of ustekinumab in subjects with moderately to severely active Crohn*s disease who have failed or are intolerant to one or more TNF antagonist therapies.

The secondary objectives are:

- To evaluate the efficacy of IV induction regimens of ustekinumab in inducing clinical remission.
- To evaluate the efficacy of IV induction regimens of ustekinumab in improving disease-specific health-related quality of life.
- To evaluate the pharmacokinetics and pharmacodynamics of ustekinumab therapy, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other pharmacodynamic biomarkers.
- To provide, along with induction study CNTO1275CRD3002, the target study population to be evaluated in the maintenance study CNTO1275CRD3003.

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of ustekinumab in subjects with moderately to severely active Crohn*s disease who have failed or are intolerant to TNF antagonist therapy. A target of 675 subjects (225 per treatment group) will be randomized in a 1:1:1 ratio (using permuted block randomization with study region, Crohn*s Disease Activity Index (CDAI) score
and initial response to TNF antagonist therapy as the stratification variables) to receive a single IV administration of placebo or 1 of 2 induction doses of ustekinumab at Week 0:
- Group 1 Placebo

- Group 2 Ustekinumab 130 mg
- Group 3 Weight-range based ustekinumab doses approximating ustekinumab 6 mg/kg:
- Ustekinumab 260 mg (weight <= 55 kg)
- Ustekinumab 390 mg (weight > 55 kg and <= 85 kg)
- Ustekinumab 520 mg (weight > 85 kg)

At Week 6, all subjects will be evaluated for the primary endpoint of clinical response. All subjects who received study agent at Week 0 and have completed the Week 8 visit will be eligible to enter maintenance study CNTO1275CRD3003; those who were randomized to ustekinumab induction therapy and have been induced into clinical response at Week 8 will enter as the primary efficacy population. Subjects not entering CNTO1275CRD3003 will have a final safety follow-up visit approximately 20 weeks after study agent administration at Week 0.

Intervention

Group 1: Placebo, administered at the visit in week 0. Group 2: Ustekinumab 130 mg, administered at the visit in week 0. Group 3: Weight-range based ustekinumab doses approximating ustekinumab 6 mg/kg, administered at the visit in week 0:
- Ustekinumab 260 mg (weight <= 55 kg)
- Ustekinumab 390 mg (weight > 55 kg and <= 85 kg)
- Ustekinumab 520 mg (weight > 85 kg)

Study burden and risks

Please refer to section E9.

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

Each potential subject must satisfy all of the following criteria to be enrolled in the study. Each
subject must:
1. Be a man or woman >= 18 years of age.;2. Have 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. Have active Crohn*s disease, defined as a baseline CDAI score of >= 220 and <= 450.;4. Have received infliximab, adalimumab, or certolizumab pegol at a dose approved for the
treatment of Crohn*s disease and
a. Did not respond initially (ie, primary nonresponders);
OR
b. Responded initially but then lost response with continued therapy (ie, secondary nonresponders);
OR
c. Were intolerant to the medication.;5. Adhere to the following requirements for concomitant medication for the treatment of
Crohn*s disease. The following medications are permitted provided doses meeting the requirements below are stable for or have been discontinued at least 3 weeks prior to baseline
(Week 0), unless otherwise specified.
a. Oral 5-ASA compounds.
b. Oral corticosteroids (eg, prednisone, budesonide) at a prednisone-equivalent dose of <= 40 mg/day or <= 9 mg/day of budesonide.
c. Antibiotics being used as a primary treatment of Crohn*s disease.
d. Subjects receiving conventional immunomodulators (ie, AZA, 6-MP, or MTX) must have been taking them for >= 12 weeks, and on a stable dose for a least 4 weeks prior to baseline.;6. Have screening laboratory test results within the following parameters:

a. Hemoglobin >= 8.5 g/dL
b. WBCs >= 3.5 x 103/uL
c. Neutrophils >= 1.5 x 103/uL
d. Platelets >= 100 x 103/uL
e. Serum creatinine < 1.7 mg/dL
f. AST and ALT concentrations must be within 2 times the ULN range for the laboratory conducting the test.
g. Direct (conjugated) bilirubin < 1.0 mg/dL.;7. Are considered eligible according to the following TB screening criteria:
a. Have no history of latent or active TB prior to screening. Exceptions are made for subjects currently receiving treatment for latent TB, if there is no evidence of active TB, or who have a history of latent TB and documentation of having completed adequate treatment for latent TB within 3 years prior to the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation.
Note: The exceptions outlined above exclude subjects in countries with high multidrugresistant
TB burden (eg, South Africa, Bulgaria, and the Russian Federation), due to potential concerns for multi-drug resistant TB.
b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study agent.
d. Within 2 months prior to the first administration of study agent, either have negative QuantiFERON-TB Gold test (Attachment 2), or have a newly identified positive QuantiFERON-TB Gold test in which active TB has been ruled out, and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of study agent (except in countries with high multidrugresistant TB burden [eg, South Africa, Bulgaria, and the Russian Federation]), where subjects with a newly identified positive QuantiFERON-TB Gold test result are excluded). Indeterminate results should be handled as outlined in Section 9.1.2. A negative tuberculin skin test (see Attachment 3) is additionally required if the QuantiFERON-TB gold test is not approved/registered in that country. The QuantiFERON-TB Gold In-Tube test is not required at screening for subjects with a history of latent TB and appropriate treatment as described in 7a.
e. Have a chest radiograph (at least a posterior-anterior view), taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.;8. If a woman, before entry she must be:
a. Postmenopausal, defined as
1) > 45 years of age with amenorrhea for at least 18 months,
OR
2) > 45 years of age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level > 40 IU/mL
OR
b. Menstrual

1) Surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
2) If heterosexually active, practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study and for 20 weeks after receiving study agent, or
3) Not heterosexually active.
Note: Women who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation
in the study.
1. If a woman of childbearing potential, she must have a negative serum *-human chorionic gonadotropin (*-hCG) pregnancy test at screening; and a negative urine pregnancy test at Week 0.
2. If a man and heterosexually active with a woman of childbearing potential, he must agree to
use a double barrier method of birth control and to not donate sperm during the study and for
20 weeks after receiving study agent.
3. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
4. Sign an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study, and intend to participate in the maintenance study if eligible.

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating
in the study. The subject will be excluded if he or she:
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 that 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 or any other intra-abdominal surgery
within 3 months prior to baseline.;4. Has a draining (ie, functioning) stoma or ostomy.;5. 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 (eg, 6-thioguanine [6-TG], cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil) < 6 weeks prior to baseline.
c. Non-biologic experimental or investigational agents < 4 weeks or within 5 half-lives of agent prior to baseline, whichever is longer.
d. Non-autologous stem cell therapy (eg, Prochymal), natalizumab, efalizumab, or biologic agents that deplete B or T cells (eg, rituximab, alemtuzumab, or visilizumab) < 12 months prior to baseline.
e. Anti-TNF biologic agents (eg, monoclonal antibody therapies) or other agents intended to suppress or eliminate TNF < 8 weeks prior to baseline.
f. Other immunomodulatory biologic agents < 12 weeks or within 5 half-lives of agent prior to baseline, whichever is longer.
g. Treatment with apheresis (eg, Adacolumn apheresis) or total parenteral nutrition (TPN) as a treatment for Crohn*s disease < 3 weeks prior to baseline.;6. 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.;7. Has previously received a biologic agent targeting IL-12 or IL-23, including but not limited to ustekinumab (CNTO 1275) or briakinumab (ABT-874).;8. Has received a Bacille Calmette-Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks of baseline.;9. 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 (eg, recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers.;10. Has current signs or symptoms of infection. Established nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.;11. Has a history of serious infection (eg, sepsis, pneumonia, or pyelonephritis), including any infection requiring hospitalization or IV antibiotics, for 8 weeks prior to baseline.;12. Has evidence of a herpes zoster infection * 8 weeks prior to baseline.;13. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Refer to inclusion criteria for information regarding eligibility with a history of latent TB.;14. 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.;15. Has or ever has had a nontuberculous mycobacterial infection or serious opportunistic infection (eg, cytomegalovirus colitis, Pneumocystis carinii, aspergillosis).;16. Is known to be infected with HIV, hepatitis B, or hepatitis C.;17. Has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.;18. Has a transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening).;19. Has a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy

and/or splenomegaly.;20. Has any known malignancy or has a history of malignancy (with the exception of basal cell
carcinoma; squamous cell carcinoma in situ of the skin; or cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening).;21. Has previously undergone allergy immunotherapy for prevention of anaphylactic reactions.;22. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.;23. Is known to have had a substance abuse (drug or alcohol) problem within the previous
12 months prior to baseline.;24. Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients (refer to
Investigator's Brochure).;25. Are currently or intending to participate in any other study using an investigational agent or
procedure during participation in this study.;26. Is a woman who is pregnant, or breast-feeding, or planning to become pregnant or is a man
who plans to father a child while enrolled in this study or within 20 weeks after the last dose of study agent.;27. Has any condition that, in the opinion of the investigator, would make participation not be in
the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or
confound the protocol-specified assessments.
NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes after screening but before first dose of study agent is given, such that they now meet an exclusion criterion, they should be excluded from participation in the study.

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):	20-08-2012
Enrollment:	48
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	04-05-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2013
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010□022758□18-NL
ClinicalTrials.gov	NCT01369329
CCMO	NL37072.078.11

Study results

Date completed:	03-07-2013
Actual enrolment:	32

Summary results
Trial is onging in other countries