A Randomized, Double-Blind, Parallel-Group, Phase 3 Study to Demonstrate Noninferiority in Efficacy and to Assess the Safety of CT-P13 Compared to Remicade in Patients With Active Crohn*s Disease

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Primary objective:- To demonstrate that CT-P13 is noninferior to Remicade at Week 6 (Dose 3), in terms of efficacy, asdetermined by the Crohn*s Disease Activity Index (CDAI)-70 response rate.Secondary objectives:-To evaluate long-term secondary...

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

Summary

ID

NL-OMON41931

Source
ToetsingOnline

Brief title
Celltrion CT-P13 3.4 CD

Condition

- Gastrointestinal inflammatory conditions

Synonym
active Crohn's disease, inflammatory bowel disease

Research involving

Human

Sponsors and support

Primary sponsor: CELLTRION, Inc.
Source(s) of monetary or material Support: Sponsor/Farmaceut

Intervention

Keyword: Crohn□s Disease, CT-P13 3.4, Infliximab

Outcome measures

Primary outcome

Primary Endpoint: The CDAI-70 response will be assessed at Week 6 to determine whether a patient is a responder. A responder is defined as a patient with a decrease in CDAI score of 70 points or more from the baseline value.

Secondary outcome

Secondary Endpoints: Secondary efficacy endpoints will be assessed at Screening, Day 0 (Week 0), Day 42 (Week 6), Day 98 (Week 14), Day 210 (Week 30), Day 378 (Week 54), and the End-of-Study Visit, if not obtained at Week 54. The following efficacy parameters for CT-P13 and Remicade will be determined as secondary endpoints:

- CDAI-70 response
- CDAI-100 response
- Clinical remission

- Steroid-free remission

- Sustained steroid-free remission

- Time to loss of response up to and including Week 54 in the Week 14 responders

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Tertiary Endpoints: Tertiary efficacy endpoints will be assessed at Screening,

Day 0 (Week 0), Day 42

(Week 6), Day 98 (Week 14), Day 210 (Week 30), Day 378 (Week 54), and the

End-of-Study Visit, if not

obtained at Week 54. The following efficacy parameters for CT-P13 and Remicade

will be determined as

tertiary endpoints:

- Closure of fistulas

- Calprotectin

- Mucosal healing at Week 54 in patients with confirmed mucosal ulceration at

Baseline

Pharmacokinetic Assessments: The secondary PK analyses will be performed on the

PK population, with

approximately 214 patients, up to Week 54.

Secondary PK Endpoints:

The following PK parameters for CT-P13 and Remicade will be determined for the

PK population as

secondary endpoints:

- Cav Average concentration, estimated as (Cmax + Ctrough)/2

- Ctrough Trough concentration (immediately before the next application)

- Cmax Observed maximum serum concentration

- Swing (Cmax - Ctrough)/Ctrough

- Degree of fluctuation (Cmax - Ctrough)/Cav

Biomarker Assessments (Optional): For patients who sign a separate informed consent form for the biomarker assessments, a blood sample for evaluation genotype (NOD2, and/or any necessary genotypes) will be collected after randomization and before study drug administration on Day 0, Week 0. Additional genotyping tests could be conducted if it is required from a regulatory or medical perspective.

Safety Assessments: Safety analysis will be performed on the safety population by presenting data on immunogenicity testing, immunoglobulin E testing, hypersensitivity monitoring via vital sign measurements (including weight, blood pressure, heart and respiratory rates, and temperature), ECGs, signs and symptoms of TB monitored throughout the study, interferon-γ release assay, diabetes mellitus assessment, congestive heart failure assessment, hepatitis B and C and HIV-1 and -2 status, physical examination findings, AEs (including

serious AEs), infections, infusion-related reactions, clinical laboratory

analyses (including erythrocyte

sedimentation rate and C-reactive protein), pregnancy testing,

anti-double-stranded DNA testing, concomitant

medications, and colonoscopy results.

Study description

Background summary

CT-P13 (Remsima) has been developped as biosimilar of Remicade (infliximab). In earlier phase 3 studies in patients with with rheumatoid arthritis and ankylosing spondylitis it has been shown that CT-P13 (Remsima)was comparable to the treatment with Remicade. The EMA has granted marketing authorization for CT-P13 (Remsima) for these indications and also for Crohn*s disease. The conditions for the authorization were that the sponsor provides missing clinical data for patients with Crohn*s disease. This study is conducted to provide these missing data, and has been designed to demonstrate that CT-P13 is noninferior in efficacy to Remicade at Week 6 (Dose 3), and to evaluate long-term secondary efficacy of CT-P13 in comparison with Remicade up to Week 54.Furthermore, the overall safety and pharmacokinetics of CT-P13 will be evaluated in comparison with Remicade. The results of this study will determine if CT-P13 is an affordable alternative for Remicade in the treatment of Crohn*s disease patients.

Study objective

Primary objective:
- To demonstrate that CT-P13 is noninferior to Remicade at Week 6 (Dose 3), in terms of efficacy, as
determined by the Crohn*s Disease Activity Index (CDAI)-70 response rate.
Secondary objectives:
-To evaluate long-term secondary efficacy of CT-P13 in comparison with Remicade up to Week 54.
- To evaluate pharmacokinetics of CT-P13 in comparison with Remicade up to Week 54.
- To evaluate overall safety of CT-P13 in comparison with Remicade up to Week 54.
Tertiary objectives:
- To evaluate long-term tertiary efficacy of CT-P13 in comparison with Remicade

up to Week 54.

Study design

Approximately 214 male or female patients with active Crohn*s disease will be randomly assigned in a
1:1:1:1 ratio to one of two CT-P13 or one of two Remicade treatment groups in this study. Approximately 107
patients will be randomly assigned to one of two CT-P13 treatment groups, consisting of 1 treatment group of
approximately 53 patients randomly assigned to continue on CT-P13 at Week 30 and another treatment group
of approximately 54 patients randomly assigned to switch to Remicade at Week 30. Approximately
107 patients will be randomly assigned to one of two Remicade treatment groups, consisting of 1 treatment
group of approximately 53 patients randomly assigned to continue on Remicade at Week 30 and another
treatment group of approximately 54 patients randomly assigned to switch to CT-P13 at Week 30. Patients will
receive CT-P13 or Remicade as a single dose of study drug on the first day of each dosing period during the
Dose Loading Phase and Maintenance Phase.

Intervention

Patient will receive CT-P13 or Remicade, in a dose-loading phase, at the start of the study, after 2 weeks and after 6 weeks. From week 14 there is a maintenance phase, patients will receive CT-P13 or Remicade at week 14,22,30,38,46 and 54.

Study burden and risks

11 visits; 1 screening visit, 9 visits with administration of study medication, 1 end-of-study visit. For visits where study medication is administered, it is required for the patient to be confined in the hospital for 5-6 hours.
6x a 7-day questionnaire of 3 short questions

1x medical history
11x physical examination
11x vital signs
11x blood sample collection, in total 260ml per patient (196 ml for safety analysis; 10 ml for immunogenicity testing, 54 ml for pharmacokinetics).
11x urinalysis
6x faecal samples
11x pregnancy test (2x serum, 9x urine)

4x ECG
1x thorax x-ray (posterior-anterior and lateral)
6x Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
1-2x colonoscopy
9x study drug administration

The above procedures are applicable when the subject has completed the study without early withdrawal.

Both male and female patients, the patient and his or her partner of childbearing potential need to use protocol specific methods of contraception during the course of the study and for 6 months following discontinuation of study drug.

The most frequent side-effects (affects more than 1 subject in 10) are, stomach pain, upper respiratory infections, infusion related reactions, viral infections such as herpes or flu, headache and pain. Other side effects are described in addendum VI, as well side effects that are related to procedures and tests.

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.Patient is a male or female aged 18 to 75 years old, inclusive.
2.Patient has Crohn's disease of at least 12 weeks* duration with a score on the CDAI between 220 and 450 points and of at least 12 weeks' disease duration prior to randomization.
3.Patient has been treated for active Crohn's disease but has not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who is intolerant to or has medical contraindications for such therapies. Patients receiving the following treatments are eligible:
•5-aminosalicylates or antibiotics (if the dose remained constant for at least 4 weeks prior to randomization)
•Corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 30 mg per day of prednisone or less (stable dose for 2 weeks prior to randomization)
•Azathioprine (stable dose for 8 weeks prior to randomization)
•6-mercaptopurine (6-MP) (stable dose for 8 weeks prior to randomization)
•Methotrexate (MTX) (stable for 6 weeks prior to randomization)
4.Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
•Serum creatinine <1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula)
•Serum alanine aminotransferase <2.5 × ULN
•Serum aspartate aminotransferase <2.5 × ULN
•Serum total bilirubin <2 × ULN
5.Patient has the following hematology laboratory test results at Screening:
•Hemoglobin >=8.5 g/dL
•White blood cell count >=3.5 × 10ex3 cells/µL (SI [Système International d'Unités] units: >=3.5 × 10ex9 cells/L)
•Neutrophil count >=1.5 × 10ex3 cells/µL (SI units: >=1.5 × 10ex9 cells/L)
•Platelet count >=100 × 10ex3 cells/µL (SI units: >=100 × 10ex9 cells/L)
6.Patient has the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.
7.Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, is given ample time and opportunity to read and understand this information, and has signed and dated the written informed consent before inclusion in the study.
8.For both male and female patients, the patient and his or her partner of childbearing potential agree to use 2 of the following medically acceptable methods of contraception

during the course of the study and for 6 months following discontinuation of study drug (excluding women who are not of childbearing potential and men who have been sterilized):
•Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel)
•Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
•Intrauterine device
•Male and female patients and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use 2 medically acceptable methods of contraception.
•Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

Exclusion criteria

1.Patient who has previously received a biological agent for the treatment of Crohn's disease and/or a TNFa inhibitor for the treatment of other disease.
2.Patient who has allergies to any of the excipients of infliximab, any other murine and/or human proteins, or patient with a hypersensitivity to immunoglobulin product.
3.Patient who has a current or past history of chronic infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus (HIV)-1 or -2 or who has a positive result to the screening test for those infections.
4.Patient who has an infection requiring oral antibiotics within 2 weeks before randomization, other serious infection within 6 months before randomization, or a history of recurrent herpes zoster or other chronic or recurrent infection within 6 weeks before randomization.
5.Patient who has a history of TB or a current diagnosis of TB or other granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infection, or invasive fungal infection such as histoplasmosis) or a past diagnosis without sufficient documentation of complete resolution following treatment.
6.Patient who has had recent exposure to persons with active TB, or patient who has a positive result to the screening test for latent TB (defined as a positive result for interferon-γ release assay [IGRA] with a negative examination of chest x-ray). A patient with sufficient documentation of prophylaxis or complete resolution following TB treatment based on local guidelines can be enrolled.
•If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the screening period. If the repeated IGRA result is again indeterminate, the patient must be excluded from the study. If the repeated IGRA result is negative, the patient may be included in the study.
•Patients who have a positive result to the IGRA at initial or repeated test with negative examination of chest x-ray during Screening. During Screening, a patient with a positive result for IGRA and a negative examination of chest x-ray who has received at least the first 30 days of country-specific TB therapy and intends to complete the entire course of that therapy can be enrolled.
7.Patient who is taking any of the following concomitant medications or treatment:
<Please see Protocol Section 3.3.2 for detailed listing> updated and extended in V2.2
8.Patient who has a medical condition including one or more of the following:

•Classified as obese (body mass index >=30 kg/m2)
•Diabetes mellitus unless on a stable dosing regimen for at least 4 weeks prior to randomisation.
•Uncontrolled hypertension (as defined by systolic blood pressure >=160 mmHg or diastolic blood pressure >=100 mmHg)
•Active entero-vesical, entero-retroperitoneal, entero-cutaneous, and entero-vaginal fistulae for within 6 months prior to Screening. Entero-enteral fistulae without clinical significant symptoms upon investigator*s opinion and anal fistulae without draining problems are allowed
•History of short bowel syndrome
- Stoma (e.g. ileostomy or colostomy) within 6 months prior to randomization.
•History of any malignancy within the 5 years prior to randomization except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
•History of lymphoma or lymphoproliferative disease or bone marrow hyperplasia
•New York Heart Association (NYHA) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, arrhythmias, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the 6 months prior to randomization
•History of organ transplantation, including corneal graft/transplantation
•Any uncontrolled, clinically significant respiratory disease (in the opinion of the investigator), including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion
•Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain Barré syndrome
•Any conditions significantly affecting the nervous system (ie, neuropathic conditions or nervous system damage)
•Any other serious acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results
9.Patient who has a current or past history of drug or alcohol abuse.
10.Patient who has had treatment with any other investigational device or medical product within 4 weeks of randomization or 5 half-lives, whichever is longer.
11.Female patient who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed within 6 months of the last dose of study drug.
12.Patient who, in the opinion of his or her general practitioner or the investigator, should not participate in the study.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-06-2015
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CT-P13
Generic name:	Infliximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remicade
Generic name:	Infliximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-06-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-08-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2014

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-05-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2016
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	EUCTR2013-004497-10-NL
ClinicalTrials.gov	NCT02096861
CCMO	NL49297.028.14