An open-label, multicentre, phase IV study to investigate the infliximab serum concentration of Remsima* (infliximab biosimilar) after switching from Remicade (infliximab) in subjects with Crohn*s Disease (CD), Ulcerative Colitis (UC) or Rheumatoid Arthritis (RA) in stable remission.

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To demonstrate that the infliximab serum concentration of Remsima* is non-inferior to the infliximab serum concentration of Remicade , 16 weeks after switch from Remicade to Remsima* in subjects with CD, UC or RA in stable remission for > 30…

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

Summary

ID

NL-OMON43846

Source
ToetsingOnline

Brief title
Infliximab serum concentration of Remsima* after switch from Remicade

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
Reumatoid Arthritis/Rheumatism; Crohn's Disease/Inflammatory Bowel Disease (IBD); Colitis Ulcerosa/IBD

Research involving
Human

Sponsors and support

Primary sponsor: Mundipharma
Source(s) of monetary or material Support: Mundipharma Pharmaceuticals B.V.

Intervention

Keyword: Phase IV, Remsima, Serum inliximab concentration

Outcome measures

Primary outcome

• Infliximab serum concentration of Remsima* 16 weeks after switch from

Remicade by ELISA compared to baseline.

Secondary outcome

• Infliximab serum concentration of Remsima* 8 weeks after switch from Remicade

by bridging ELISA.

• Anti-drug infliximab (ADI) levels at 8 and 16 weeks after switch from

Remicade by radio-immune assay (RIA).

• Disease activity:

For CD: Harvey-Bradshaw Index (HBI), and serum C-reactive protein (CRP) at week

8 and 16 and faecal calprotectin at week 16.

For UC: Simple Clinical Colitis Activity Index (SCCAI), and serum CRP at week 8

and 16 and faecal calprotectin at week 16.

For RA: Disease Activity Score (DAS)-28 score and serum CRP at week 8 and 16.

• Serial measurements in EQ-5D score, overall and per disease group at week

16.

• Incidence and type of AEs, SAEs and infusion reactions at week 8 and 16

(Remsima*).

Study description

Background summary

Inflammatory autoimmune diseases like RA, CD, and UC are generally chronic and life-long. Their impact on patients* quality of life and on healthcare budgets is considerable.

Treatment with tumor necrosis factor alpha (TNF-α) inhibitors like infliximab is an important treatment option for the above mentioned inflammatory autoimmune disease. The introduction of biologic therapeutics (biologicals) for treatment of inflammatory bowel disease (IBD) and for the treatment of RA has significantly improved patient outcomes. TNF-α inhibitors and other biologicals are costly compared with conventional DMARDs and have led to increased costs to healthcare systems. For this reason, much interest in biosimilar products has developed. A biosimilar is a biotherapeutic product similar in quality, safety, and efficacy to an already licensed reference biotherapeutic product. Unlike generics, which are identical copies of traditional small molecules, biosimilars are not the same as the original biologic medicine. This is an inevitable because biologicals are made of living cells as opposed to the chemical composition of traditional drugs. Because of unavoidable differences in the manufacturing processes, a biosimilar and its respective reference product will not be entirely identical.

Remsima* (CT-P13) is one of the world*s first biosimilar infliximab approved by the European Medicines Agency (EMA). It is produced in the same type of cell line and has an identical amino acid sequence to the originator infliximab (Remicade). Remsima* is approved for the management of inflammatory autoimmune disorders for all indications as the reference infliximab (Remicade). The approval is based on the fact that Remsima* demonstrated similarity to reference infliximab in an extensive comparability exercise, including bioanalytical, preclinical and clinical analyses. Remsima* demonstrated an equivalent pharmacokinetic profile, efficacy and safety to that of reference infliximab in ankylosing spondylitis patients and also equivalent efficacy and safety to that of reference infliximab in RA patients. Remsima* is generally well tolerated, with a similar tolerability profile to that of the reference infliximab.

Despite the establishment of a specific approval pathway, the issuance of detailed scientific guidelines for the development of biosimilars and the approval of several biosimilars in the European Union (EU), acceptance of biosimilars in the medical community continues to be low. This is especially true in therapeutic indications for which no specific clinical trials with the biosimilar have been performed, like CD and UC, and which have been licensed based on pharmacokinetics and extrapolation of efficacy and safety data from other indications.

This is also shown in a recently performed web based survey at ECCO, most IBD specialists have the opinion that biosimilar infliximab is not interchangeable with the originator, unless strong evidence is shown about similarity for each indication. Most of the 272 clinicians regarded cost-sparing (89%) as the main advantage of biosimilars, immunogenicity (serum drug levels and antibodies to the drug) (69%) as their main concern. Most clinicians thought that medical societies should promote information about biosimilars (66%), collaborate with health institutions to develop rules (78%) and guidelines (57%) on the use of biosimilars, and create multispecialty safety registries (80%).

Limited clinical data in CD and UC are available. Case series in Korea indicated the clinical efficacy, safety, and interchangeability of CT-P13 in the treatment of IBD compared with its originator. Furthermore, antibodies-to-Remicade in sera of Remicade-treated IBD patients recognized Remsima* to a similar extent, suggesting shared immuno-dominant epitopes on these two infliximab agents.

Study objective

To demonstrate that the infliximab serum concentration of Remsima* is non-inferior to the infliximab serum concentration of Remicade , 16 weeks after switch from Remicade to Remsima* in subjects with CD, UC or RA in stable remission for > 30 weeks measured by a bridging enzyme-linked immunosorbent assay (ELISA).

Study design

Study IFX4501 is an open-label, multicentre, phase IV study. All study subjects exposed to Remsima* treatment serve as their own controls, using the data collected before the first infusion with Remsima* (Day 0, V1), as baseline data.

All subjects treated with Remsima* will be followed up until 16 weeks after switch from Remicade.

Assessments will be performed as follows:
V1 (day 0) before infusion with Remsima*:
- Demography

- Pregnancy test (if applicable)
- Medical history, including details of treatment regimen for Remicade
- Remicade infliximab serum concentration (bridging ELISA)
- Antibody-to-Infliximab (RIA test)
- Prior medication use (previous year)
- Disease activity:
o For CD: HBI, faecal calprotectin and serum CRP
o For UC: SCCAI, faecal calprotectin and serum CRP
o For RA: DAS-28 and serum CRP
- Quality of Life; EQ-5D
- ADRs of Remicade
- Infliximab dose

V1 (day 0) after infusion with Remsima*:
- Concomitant medication
- (S)AEs
- Remsima* dose

V2 (week 8±1) and V3 (week 16±2)
- Concomitant medication
- Remsima* infliximab serum concentration by ELISA
- ATI Remsima* by RIA test
- Disease activity:
o For CD: HBI and serum CRP. Faecal calprotectin only at V3.
o For UC: SCCAI and serum CRP. Faecal calprotectin only at V3.
o For RA: DAS-28 score and serum CRP
- Quality of Life: EQ-5D (only at V3)
- (S)AEs
- Remsima* dose
In case of early discontinuation (i.e. before V3), the same data will be collected as described for V3. In addition, the reason for early discontinuation as well as the discontinuation date will be recorded.

Intervention

The IMP in this study is the by EMA approved infliximab biosimilar, Remsima. Eligible subjects will have been treated for more than 30 weeks with Remicade before they are enrolled in this study. Eligible subjects are switched from Remicade, which will be used in this study as a reference drug. During the study, subjects will be treated with two intravenous infusions of Remsima at Day 0 (visit 1), Week 8 (visit 2). Subjects will be treated in the hospital.
The starting dose of Remsima will be identical to the dose of Remicade before and remains stable over the study period.

Study burden and risks

The biosimilar infliximab (Remsima*) has been approved by EMA for the management of inflammatory autoimmune disorders rheumatoid arthritis, ankylosing spondylitis, CD, UC, psoriatic arthritis and psoriasis, based on quality, safety and efficacy profiles comparable to those of infliximab (Remicade).

Since Remsima* is biosimilar to the originator, it is estimated that risk of treatment is limited. The benefit for the patient in the clinical trial is the monitoring of the switch for this individual patient in the trial. The overall benefit for the health care is the collection of more clinical data in the switch to the biosimilar for controlled patients. This will contribute to more confidence in the biosimilar and herewith to a reduction in costs in the Health Care.

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, age >=18 years.
2. Subject will have a confirmed diagnosis of RA, UC, or CD.
3. Stable remission defined as HBI<=4, SCCAI<3, DAS 28<3.2 at screening.
4. Stable and continuous treatment with Remicade during the last 30 weeks, and no foreseen dose adjustment for the coming 2 months for infliximab.
5. Stable concomitant treatment; if concomitant drugs than stable for 4 months and no foreseen changes in drugs. For RA: stable and continuous treatment with MTX.
6. Non-pregnant, non-nursing female.
7. Subject capable of understanding and signing an informed consent form.

Exclusion criteria

1. Subjects with evidence of the following major comorbidities such as: severe diabetic mellitus, tuberculosis, severe infections,
uncontrollable hypertension, severe cardiovascular disease (New York Heart Association [NYHA] class 3 or 4) and/or severe respiratory diseases.
2. Any other condition/disease, which in the opinion of the investigator makes the subject ineligible for the study.
3. Any clinically relevant hypersensitivity to (anaphylaxis or infusion related reactions) infliximab or to other murine proteins
4. Change of major co-medication during the last 4 months prior to screening and foreseen dose adjustments during the next 2 months:
RA: Initiation of systemic corticosteroids or synthetic DMARDs or other medication, which according to the investigator would interfere with the stability of the disease.
UC and CD: Initiation of systemic corticosteroids or an immunosuppressant or other medication, which according to the investigator would interfere with the stability of the disease.
5. Change in treatment with Remicade during the last 30 weeks due to disease related factors, not including dose/frequency adjustments due to drug concentration measurements.
6. Simultaneous treatment with another biological or a not registered New Chemical Entity.
7. Psychiatric or mental disorders, alcohol abuse or other substance abuse (and/or history of opioid abuse), language barriers or other factors which makes adherence to the study protocol impossible.
8. Inadequate birth control, pregnancy, and/or breastfeeding.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-06-2015
Enrollment:	129
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Remicade
Generic name:	infliximab innovator
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remsima
Generic name:	infliximab biosimilar
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	12-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-004904-31-NL

Register	ID
CCMO	NL42505.018.15