Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SWITCHING FROM INNOVATOR INFLIXIMAB TO BIOSIMILAR INFLIXIMAB COMPARED WITH CONTINUED TREATMENT WITH INNOVATOR INFLIXIMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS, SPONDYLOARTHRITIS, PSORIATIC ARTHRITIS, ULCERATIVE COLITIS, CROHN'S DISEASE AND CHRONIC PLAQUE PSORIASIS

THE NOR-SWITCH STUDY

Summary

EudraCT number	2014-002056-40
Trial protocol	NO
Global end of trial date	16 June 2016

Results information

Result version number	v1 (current)
This version publication date	08 September 2018
First version publication date	08 September 2018
Summary attachment (see zip file)	NOR-SWITCH synopsis (NOR-SWITCH synopsis.docx)

Trial information

Trial identification

Sponsor protocol code	DIA2014-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02148640
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Diakonhjemmet Hospital AS
Sponsor organisation address	Diakonveien 12, Oslo, Norway,
Public contact	Principal Investigator, Diakonhjemmet Hospital AS, +47 22451500, t.k.kvien@medisin.uio.no
Scientific contact	Principal Investigator, Diakonhjemmet Hospital AS, +47 22451500, t.k.kvien@medisin.uio.no

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2016
Global end of trial reached?	Yes
Global end of trial date	16 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess if biosimilar infliximab (CT-P13) is non-inferior to innovator infliximab (INX) with regard to disease worsening in patients who have been on stable INX treatment for at least 6 months

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 498
Worldwide total number of subjects	498
EEA total number of subjects	498

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	425
From 65 to 84 years	73
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Each hospital department was considered a study centre, and 19 gastroenterology departments, 16 rheumatology departments, and five dermatology departments from 25 Norwegian hospitals recruited patients to the study.

Pre-assignment

Screening details:

Adult patients with a diagnosis of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, or chronic plaque psoriasis on stable treatment with infliximab originator for at least 6 months were eligible for participation.

Pre-assignment period milestones

Number of subjects started	498
Number of subjects completed	482

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 6
Reason: Number of subjects	Physician decision: 4
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Other reasons: 5

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P13

Arm description:

Biosimilar infliximab

Arm type	Experimental
Investigational medicinal product name	Infliximab CT-P13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose and infusion intervals of patients' infliximab treatment regimens were kept unchanged from those before randomisation.

Arm title	Originator infliximab

Arm description:

Originator infliximab

Arm type	Active comparator

Investigational medicinal product name	Infliximab Remicade
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose and infusion intervals of patients' infliximab treatment regimens were kept unchanged from those before randomisation.

Number of subjects in period 1[1]	CT-P13	Originator infliximab
Started	241	241
Completed	241	241

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There was some included patients who were not randomized, resulting in a difference in the numbers.

Period 2

Period 2 title	Intervention
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

Eligible patients with informed consent were randomised in a 1:1 ratio to either continued infliximab originator or switch to CT-P13 treatment, with a computer block randomisation procedure stratified by diagnosis and a fixed block size of six.
The computer-generated randomised allocation sequence was imported into the electronic case report form (eCRF) system (Viedoc; version 3.20) and made available exclusively to the study nurse authorised by the local principal investigator to prepare infus

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P13

Arm description:

Biosimilar infliimab

Arm type	Experimental
Investigational medicinal product name	Infliximab CT-P13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose and infusion intervals of patients' infliximab treatment regimens were kept unchanged from those before randomisation.

Arm title	Originator infliximab

Arm description:	
Originator infliximab	
Arm type	Active comparator
Investigational medicinal product name	Infliximab CT-P13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose and infusion intervals of patients' infliximab treatment regimens were kept unchanged from those before randomisation.

Number of subjects in period 2	CT-P13	Originator infliximab
Started	241	241
Completed	222	216
Not completed	19	25
Consent withdrawn by subject	5	6
Adverse event, non-fatal	6	8
Other reason	2	-
Other reasons	-	2
Lost to follow-up	-	1
Lack of efficacy	3	8
Protocol deviation	3	-

End points

End points reporting groups

Reporting group title	CT-P13
Reporting group description: Biosimilar infliximab	
Reporting group title	Originator infliximab
Reporting group description: Originator infliximab	
Reporting group title	CT-P13
Reporting group description: Biosimilar infliimab	
Reporting group title	Originator infliximab
Reporting group description: Originator infliximab	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description: Consisting of eligible, randomised patients with no major protocol deviations affecting treatment efficacy	

Primary: Disease worsening

End point title	Disease worsening
End point description: The primary endpoint was disease worsening during follow-up according to worsening in disease-specific composite measures or a consensus about disease worsening between investigator and patient leading to major change in treatment. Disease worsening according to disease-specific composite measures was defined as change from baseline in Harvey-Bradshaw Index of 4 points or more and a score of 7 points or greater points for Crohn's disease, change from baseline in Partial Mayo Score of more than 3 and a score of 5 or greater for ulcerative colitis, change from baseline in Ankylosing Spondylitis Disease Activity Score of 1·1 or more attaining a minimum score of 2·1 for spondyloarthritis, change from baseline in Disease Activity Score in 28 joints of 1·2 or more with a minimum score of 3·2 for rheumatoid arthritis and psoriatic arthritis, and change in Psoriasis Area and Severity Index of 3 or more and a score of 5 or greater for chronic plaque psoriasis (appendix p 4).	
End point type	Primary
End point timeframe: 12 months	

End point values	CT-P13	Originator infliximab	Per protocol set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	206	202	408	
Units: Subjects				
Disease worsening	61	53	114	
No disease worsening	145	149	294	

Attachments (see zip file)	Primary endpoint/Skjermbilde 2018-08-23 kl. 11.50.07.png

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

We analysed the primary outcome and secondary dichotomous endpoints using logistic regression with treatment as fixed effect, adjusted for diagnosis and the treatment duration of infliximab originator at baseline providing estimates (by the delta method) of adjusted risk difference and adjusted relative risk for the treatment difference.

Comparison groups	CT-P13 v Originator infliximab
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	3.9

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	CT-P13
Reporting group description: Biosimilar infliximab	
Reporting group title	Originator infliximab
Reporting group description: Originator infliximab	

Serious adverse events	CT-P13	Originator infliximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 240 (8.75%)	24 / 241 (9.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 240 (0.42%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysplasia			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Femoral artery embolism			

subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Anorectal operation			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic bypass			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicectomy			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Caesarean section			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colectomy			
subjects affected / exposed	0 / 240 (0.00%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal operation			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Photon radiation therapy to prostate			

subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic operation			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder operation			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Rheumatoid lung			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Biopsy kidney			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 240 (0.42%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 240 (0.83%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 240 (0.42%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gingival abscess			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 240 (0.83%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 240 (0.83%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	CT-P13	Originator infliximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 240 (68.33%)	168 / 241 (69.71%)	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	4 / 240 (1.67%)	10 / 241 (4.15%)	
occurrences (all)	5	10	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 240 (2.92%)	10 / 241 (4.15%)	
occurrences (all)	8	10	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	13 / 240 (5.42%)	7 / 241 (2.90%)	
occurrences (all)	14	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 240 (2.50%)	11 / 241 (4.56%)	
occurrences (all)	6	12	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	25 / 240 (10.42%)	23 / 241 (9.54%)	
occurrences (all)	28	29	
Urinary tract infection			
subjects affected / exposed	7 / 240 (2.92%)	14 / 241 (5.81%)	
occurrences (all)	9	19	
Sinusitis			
subjects affected / exposed	2 / 240 (0.83%)	13 / 241 (5.39%)	
occurrences (all)	4	13	
Influenza			
subjects affected / exposed	7 / 240 (2.92%)	7 / 241 (2.90%)	
occurrences (all)	7	7	
Respiratory tract infection			
subjects affected / exposed	10 / 240 (4.17%)	4 / 241 (1.66%)	
occurrences (all)	11	4	
Gastroenteritis			

subjects affected / exposed occurrences (all)	6 / 240 (2.50%) 6	7 / 241 (2.90%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2015	This amendment added exclusion criteria 6: "For patients with UC and CD: Functional colostomy or ileostomy. Extensive colonic resection with less than 25 cm of the colon left in situ." In addition, the protocol was amended to enable further recording of background demographic information for each patient.
21 July 2015	This amendment added details of a 26-week open-label extension with CT-P13 to the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28502609