Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

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Summary

Background TNF inhibitors have improved treatment of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis, but are expensive therapies. The aim of NOR-SWITCH was to examine switching from originator infliximab to the less expensive biosimilar CT-P13 regarding efficacy, safety, and immunogenicity.

Methods The study is a randomised, non-inferiority, double-blind, phase 4 trial with 52 weeks of follow-up. Adult patients on stable treatment with infliximab originator treated in a hospital setting for at least 6 months were eligible for participation. Patients with informed consent were randomised in a 1:1 ratio to either continued infliximab originator or to switch to CT-P13 treatment, with unchanged dosing regimen. Data were collected at infusion visits in 40 Norwegian study centres. Patients, assessors, and patient care providers were masked to treatment allocation. The primary endpoint was disease worsening during 52-week follow-up. 394 patients in the primary per-protocol set were needed to show a non-inferiority margin of 15%, assuming 30% disease worsening in each group. This trial is registered with ClinicalTrials.gov, number NCT02148640.

Findings Between Oct 24, 2014, and July 8, 2015, 482 patients were enrolled and randomised (241 to infliximab originator, 241 to CT-P13 group; one patient was excluded from the full analysis and safety set for CT-P13) and 408 were included in the per-protocol set (202 in the infliximab originator group and 206 in the CT-P13 group). 155 (32%) patients in the full analysis set had Crohn's disease, 93 (19%) had ulcerative colitis, 91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis. Disease worsening occurred in 53 (26%) patients in the infliximab originator group and 61 (30%) patients in the CT-P13 group (per-protocol set; adjusted treatment difference –4·4%, 95% CI –12·7 to 3·9). The frequency of adverse events was similar between groups (for serious adverse events, 24 [10%] for infliximab originator *vs* 21 [9%] for CT-P13; for overall adverse events, 168 [70%] *vs* 164 [68%]; and for adverse events leading to discontinuation, nine [4%] *vs* eight [3%], respectively).

Interpretation The NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a prespecified non-inferiority margin of 15%. The study was not powered to show non-inferiority in individual diseases.

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Introduction

Infliximab is a chimeric IgG1 antibody approved for treatment of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis. Across all these indications, infliximab and other tumour necrosis factor (TNF) inhibitors have substantially improved disease management.[1] However, access to TNF inhibitors varies and is inversely related to socioeconomic conditions in each country.[2] The patent for the infliximab originator (Remicade; Janssen Biologics, The Netherlands) expired in 2015 in Europe and in many other parts of the world.

The biosimilar infliximab CT-P13 was approved by the European Medicines Agency in 2013 and by the US Food and Drug Administration in 2016.

Randomised controlled trials in patients who have not previously received TNF inhibitors, comparing infliximab originator with CT-P13, have been done in ankylosing spondylitis (PLANETAS,[3] a phase 1 study) and rheumatoid arthritis (PLANETRA,[4] a phase 3 study). However, according to guidance for regulatory approval of biosimilars, CT-P13 has been approved for all six relevant indications.[5–7] This extrapolation of indication has been debated in clinical communities, especially gastroenterology,[8,9] because the mechanisms of action for infliximab might differ between indications.[10,11] Several other TNF inhibitor biosimilars have been approved or are under regulatory review and will be available for therapeutic use in the coming years.[6,12]

In Norway, an annual tender system for TNF inhibitors and related biological drugs was established in 2007.

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Research in context

Evidence before this study

Patients starting biological treatment can receive biosimilar CT-P13 in many countries. However, switching of stable patients who are doing well on originator infliximab is controversial. Follow-up data from the PLANETAS and PLANETRA studies, as well as observational data, suggest that switching from originator infliximab to CT-P13 is safe and does not reduce effectiveness of treatment, but independent and randomised studies have been lacking. We searched PubMed and the abstracts of major conferences using the terms "biosimilar", "infliximab", "switch", and either "IBD" or one of the individual diseases ("Crohns disease", psoriasis" etc) on Oct 23, 2016, with no constraints on the timeframe for the search and no language restrictions. We identified no published, randomised, switch studies on infliximab.

Added value of this study

NOR-SWITCH addresses the important issue of switching from originator to biosimilar infliximab in stable patients, and is the first government-funded randomised study to do so. The study examined patients in all six relevant disease groups, using disease worsening as the common primary outcome.

Implications of all the available evidence

The NOR-SWITCH trial showed that switching from originator infliximab to CT-P13 was not inferior to continued treatment with the originator drug according to a prespecified non-inferiority margin of 15%. Thus, the findings suggest that patients can be switched from originator infliximab to biosimilar infliximab CT-P13. The study findings could substantially affect the use of CT-P13 and health budgets in many countries. However, caution is recommended in generalising these findings to other biological agents.

Cost calculations and impact on health-care budgets are key factors for drug selection. In 2014, CT-P13 was recommended by Norwegian Health Authorities for patients starting treatment with infliximab. The cost saving for CT-P13 was 39% in 2014 compared with originator infliximab, and increased to 69% after the 2015 tender. Thus, the introduction of biosimilar drugs could reduce financial burdens on health-care budgets. Additionally, biosimilars could improve overall and earlier access to these drugs in many countries with prescription restrictions based on their high cost.

Cost savings are even more relevant if patients on stable treatment with an originator drug could safely be switched to the biosimilar. Concerns have been raised with regard to efficacy, safety, and formation of anti-drug antibodies (ADAbs) when switching to a biosimilar in patients who are doing well on a stable treatment with an originator drug.[13,14] To date, switch data from infliximab originator to infliximab biosimilar have been available only from open cohort studies[15–18] and from the second year extensions of the PLANETAS and PLANETRA studies.[19,20]

The Norwegian Government granted 20 million NOK (€2·2 million) in the 2014 governmental budget for a study to examine whether switching from the originator to the biosimilar is safe. The NOR-SWITCH study was designed as a randomised controlled trial encompassing all six relevant diagnoses for which infliximab is currently approved to assess if CT-P13 was non-inferior to infliximab originator regarding efficacy, safety, and immunogenicity in patients who had been on stable infliximab originator treatment for at least 6 months.

Methods

Study design and participants

The NOR-SWITCH study was designed as a 52-week randomised, double-blind, parallel-group, multicentre, non-inferiority comparative phase 4 study, in a hospital setting. 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. The study was conducted and analysed according to the protocol and the statistical analysis plan (appendix p 20). There were two protocol amendments during the trial, detailed in the appendix (p 3).

A project group (the main authors of this Article) including representatives from all four health regions, all three relevant specialties, and with patient representatives from all three relevant patient organisations planned and conducted the study.

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. Full inclusion and exclusion criteria are presented in the appendix (p 3). Participating centres were encouraged to identify patients on stable treatment with infliximab originator and ask about their willingness to be enrolled in the study when they met for their next infliximab infusion. The baseline visit would then usually be at the following infusion, because encouraged patients were given time to consider whether they were willing to participate.

All patients received verbal and written information about the study and signed an informed consent form. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study protocol and consent documents were approved by an independent ethics committee (Regional Committees for Medical and Health Research Ethics [REC] South East; reference number 2014/848), by appropriate institutional

review boards, and by the Norwegian Medicines Agency (reference number 14/07192-11).

Randomisation and masking

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 infusions. Confidentiality was obtained through eCRF user access restrictions. The allocation was not available until the patient had signed the informed consent form and was considered eligible to participate in the study.

After the patient had been included, the site person authorised for infusion preparation logged into the eCRF system to reveal the allocation, prepared allocated treatment in identical infusion bags, and applied labels with patient number and dose. Packaging identifying allocated treatment was dispatched. All treatment information was recorded in a restricted part of the eCRF.

The following personnel were not masked to treatment allocation: the statistician preparing the randomised allocation sequence; the data manager importing the allocation sequence into the eCRF system and providing access to the allocation sequence; and site personnel authorised to prepare study treatment. All individuals providing patient care were masked to treatment allocation, including investigators, nurses giving infusions, and personnel assessing outcomes. Monitors and patients were also masked to treatment allocation.

Unblinding of the treatment allocation was permissible only if the safety and wellbeing of the patient was compromised. The decision to reveal the treatment allocation during the study could only be done by the study principal investigator, and date and time of unblinding was documented in the eCRF and in the patient's hospital records.

Procedures

The dose and infusion intervals of patients' infliximab treatment regimens were kept unchanged from those before randomisation. Patients randomly assigned to continued treatment received infliximab originator, and the patients in the switch group received CT-P13.

Data were collected at infusion visits. The number of visits differed according to treatment regimen, ranging from 14 visits for patients with treatment every 4 weeks to five visits for patients with treatment every 12 weeks. Data collected included clinical assessments by a trained study nurse or physician according to variables needed to address the prespecified efficacy and safety information.

Blood sampling was done before the infusion for protocol-specified laboratory tests, including measurement of drug concentrations and ADAbs, and for storage in a biobank. Patients with inflammatory bowel disease were encouraged to deliver a faecal sample for calprotectin measurements after each visit (CalproLab, Calpro AS, Oslo, Norway, and Buhlmann Laboratories AG, Basel, Switzerland). Further details about the collected variables can be found in the appendix (p 4).

The main composite measures for the six diseases were the Harvey-Bradshaw Index for Crohn's disease, Partial Mayo Score for ulcerative colitis, Ankylosing Spondylitis Disease Activity Score for spondyloarthritis, Disease Activity Score in 28 joints for rheumatoid arthritis and psoriatic arthritis, and Psoriasis Area and Severity Index for chronic plaque psoriasis (appendix p 4).[21–25]

Outcomes

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).

Secondary endpoints included time to disease worsening, study drug discontinuation, overall remission status based on the main composite measures, changes (follow-up minus baseline) in investigator and patient global assessments, and changes in erythrocyte sedimentation rate and C-reactive protein (full details of secondary endpoints are provided in the appendix pp 4, 20). Prespecified secondary endpoints for Crohn's disease and ulcerative colitis were change and remission status of Harvey-Bradshaw Index and Partial Mayo Score, as well as changes in faecal calprotectin levels. In spondyloarthritis, change in Ankylosing Spondylitis Disease Activity Score and achievement of inactive disease according to this score were prespecified. Secondary endpoints for rheumatoid arthritis and psoriatic arthritis included achievement of remission according to Disease Activity Score in 28 joints, Clinical Disease Activity Index, and Simplified Disease Activity Index as well as American College of Rheumatology (ACR) and European League Against Rheumatism
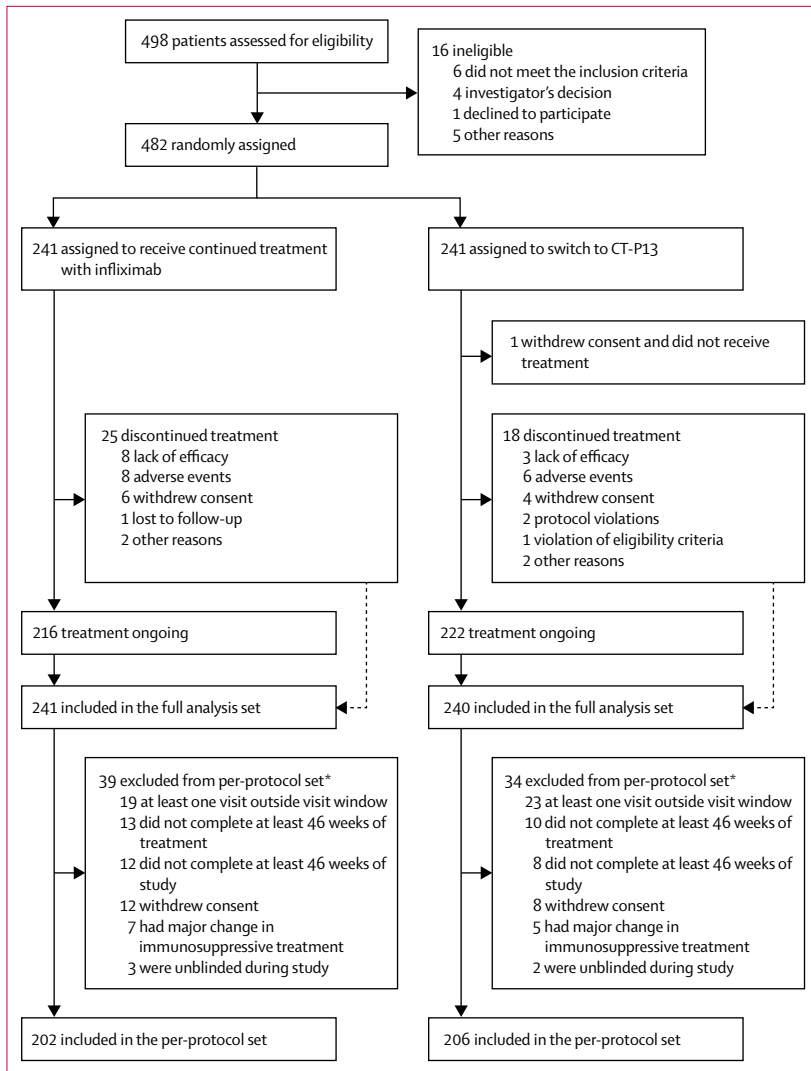
Figure 1: Trial profile
*Some patients had more than one reason for exclusion from the per-protocol set.

(EULAR) remission criteria. Other secondary endpoints were changes in Disease Activity Score in 28 joints, Clinical Disease Activity Index, and Simplified Disease Activity Index. In chronic plaque psoriasis, we prespecified complete clearance according to Psoriasis Area and Severity Index, mild to moderate disease, and remission as well as change in Psoriasis Area and Severity Index score as secondary endpoints.

Patient-reported outcome measures were secondary endpoints for all diseases included in the study: RAND 36-item Short Form Health Survey 1.0 (SF-36; change in each of the eight domains as well as the physical and mental component scores), change in EuroQol five dimensions questionnaire (EQ-5D) index score, and Work Productivity and Activity Impairment Questionnaire: general health version 2.0 (change in absenteeism, presenteeism, work productivity loss, and

activity impairment). Changes in disease-specific, patient-reported outcome measures were also secondary endpoints (for Crohn's disease and ulcerative colitis, the Inflammatory Bowel Disease Questionnaire; for spondyloarthritis, rheumatoid arthritis, and psoriatic arthritis, the Modified Health Assessment Questionnaire [MHAQ] score; for spondyloarthritis, the Bath Ankylosing Spondylitis Disease Activity Index; for rheumatoid arthritis, the Rheumatoid Arthritis Impact of Disease score; for psoriatic arthritis, the Psoriatic Arthritis Impact of Disease score; and for chronic plaque psoriasis, the Dermatology Life Quality Index; appendix p 4).

Measures of safety were planned to include clinical and laboratory adverse events. Coding of adverse events was done according to the Medical Dictionary for Regulatory Activities (MedDRA, version 13.0). Safety assessment also included vital signs, laboratory data, drug concentrations (trough measurements), infusion reactions, and ADAb measurements.

Trough drug concentrations and anti-drug antibodies

We analysed trough serum concentrations of infliximab originator and CT-P13 using an in-house, target-based assay in which human recombinant TNF is immobilised on the solid phase, infliximab in patient samples binds TNF, and a europium-labelled tracer binds the Fc-domain of infliximab. Serum drug concentrations were analysed within 2 working days after sample arrival in the laboratory.

ADAbs to infliximab originator and CT-P13 were analysed with in-house inhibition assays that only measure neutralising antibodies—ie, patient antibodies that block the TNF-binding capacity of infliximab originator or CT-P13. To minimise analytical variation, ADAbs were analysed with one batch of calibrators during a 6-day period after completion of the trial. Antibodies to infliximab originator and CT-P13 were assayed simultaneously in separate assays. ADAbs were not analysed in samples with concentrations of infliximab originator or CT-P13 above 5 mg/L, because high drug concentrations cause interference in the assays for ADAbs. Assays for drug serum concentrations and ADAbs are fully automated on the AutoDELFIA (PerkinElmer, Waltham, MA, USA) immunoassay platform.

Statistical analysis

Assuming no difference between the treatment groups in the proportion of patients with disease worsening during the 52 weeks of the study, we calculated that 394 patients (197 in each group) were required in the per-protocol set to ensure with 90% confidence that the upper limit of the two-sided 95% CI would exclude a difference in favour of infliximab originator of more than 15%. An additional assumption for this estimate was an expected 30% occurrence of disease worsening. Assuming 20% exclusions from the per-protocol set, we aimed to randomise 492 patients.

	Infliximab originator (n=241)	CT-P13 (n=240)
Demographics		
Age (years)	47·5 (14·8)	48·2 (14·9)
Female	99 (41%)	87 (36%)
Disease duration (years)	16·6 (10·9)	17·5 (10·5)
Duration of ongoing infliximab treatment (years)	6·7 (3·6)	6·9 (3·8)
Previous biological therapy		
TNFα inhibitors		
Not used	188 (78%)	188 (78%)
Used one	43 (18%)	40 (17%)
Used two	10 (4%)	9 (4%)
Used three or more	0	3 (1%)
Other biologicals	2 (1%)	1 (<1%)
Concomitant immunosuppressive therapy*	113 (47%)	129 (54%)
Concomitant use of prednisolone	13 (5%)	13 (5%)
Diagnoses		
Crohn's disease	78 (32%)	77 (32%)
Ulcerative colitis	47 (20%)	46 (19%)
Spondyloarthritis	45 (19%)	46 (19%)
Rheumatoid arthritis	39 (16%)	38 (16%)
Psoriatic arthritis	14 (6%)	16 (7%)
Psoriasis	18 (7%)	17 (7%)
General baseline characteristics		
Erythrocyte sedimentation rate (mm/h)	8 (4–14)	8 (5–16)
C-reactive protein (mg/L)	2·2 (1·0–5·0)	2·0 (1·0–5·0)
Patient's global assessment of disease activity (0–10)	2·0 (1·9)	2·2 (2·1)
Physician's global assessment of disease activity (0–10)	1·2 (1·2)	1·2 (1·3)
EQ-5D Index score	0·8 (0·2)	0·8 (0·2)
	(Table 1 continues in next column)	

	Infliximab originator (n=241)	CT-P13 (n=240)
(Continued from previous column)		
Disease-specific baseline characteristics		
Crohn's disease		
Harvey-Bradshaw Index	2 (1–4)	2 (0–4)
Ulcerative colitis		
Partial Mayo score	0 (0–1)	0 (0–1)
Crohn's disease and ulcerative colitis		
Faecal calprotectin (mg/kg)	56 (25–173)	53 (22–210)
Spondyloarthritis		
HLA-B27 positive†	31/33 (94%)	33/38 (87%)
Bath Ankylosing Spondylitis Disease Activity Index	2·6 (1·5)	3·6 (1·7)
Ankylosing Spondylitis Disease Activity Score	1·7 (0·7)	2·1 (0·8)
Rheumatoid arthritis		
Anti-citrullinated protein antibody positive†	25/30 (83%)	20/27 (74%)
Rheumatoid factor positive†	27/38 (71%)	25/33 (76%)
Psoriatic arthritis		
Disease Activity Score in 28 joints with CRP	2·7 (1·1)	2·2 (0·9)
Clinical Disease Activity Index	5·7 (4·1)	4·1 (3·2)
Simplified Disease Activity Index	5·9 (4·1)	4·5 (3·2)
Spondyloarthritis, rheumatoid arthritis, and psoriatic arthritis		
Modified Health Assessment Questionnaire	0·3 (0·3)	0·3 (0·4)
Chronic plaque psoriasis		
Psoriasis Area and Severity Index	2·3 (1·9)	3·0 (1·7)

Data are n (%), mean (SD), or median (IQR). TNF=tumour necrosis factor. HLA=human leucocyte antigen. EQ-5D=EuroQol questionnaire time trade-off (UK weighted). *Immunosuppressive concomitant medication includes methotrexate, leflunomide, sulfasalazine, azathioprine, and mercaptopurine.†Data were missing for some patients.

Table 1: Demographic and baseline characteristics (full analysis set)

The null hypothesis of this study was that CT-P13 would be inferior to infliximab originator with regard to the proportion of patients with disease worsening during 52 weeks of treatment by 15%. The alternative hypothesis was that CT-P13 would be non-inferior with regard to the proportion of patients with disease worsening by, at most, 15%. We regarded a non-inferiority margin of 15% as appropriate on the basis of clinical discussions within the study group, the PLANETRA study,[4] and discussions with the Norwegian Medicines Agency.

The primary efficacy analyses were done in the per-protocol set, consisting of eligible, randomised patients with no major protocol deviations affecting treatment efficacy (specifications are provided in the appendix p 7). Secondary efficacy analyses were performed in the full analysis set and safety parameters in the safety population, both consisting of eligible randomised patients who received at least one infusion after randomisation.

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. We checked the robustness of the primary results regarding centre effect using a multilevel mixed logistic model approach with centre as random variable, and by generalised estimating equations.

Continuous endpoints were examined by linear mixed models with patient-specific random intercept and treatment, time, treatment–time interaction, baseline value, diagnosis, and treatment duration of infliximab originator at baseline as fixed factors. C-reactive protein, erythrocyte sedimentation rate, and calprotectin were log-transformed before analyses because of anticipated skewed data distribution. Time to event endpoints were analysed with a Cox regression model adjusted for
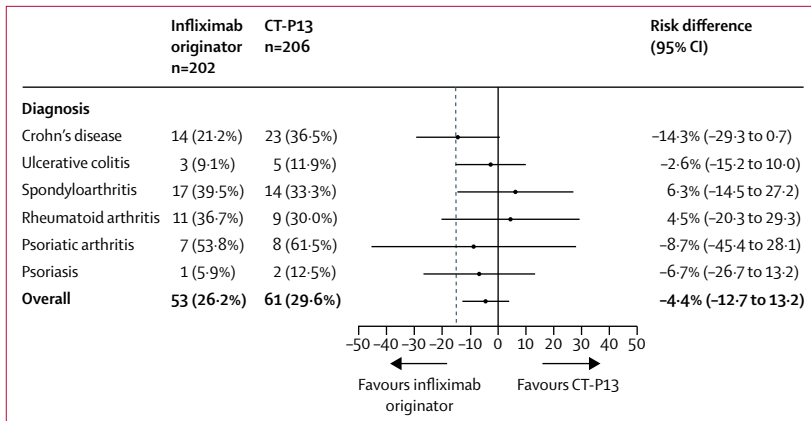
Figure 2: **Forest plot of risk difference according to disease**
Figure shows data for the per-protocol set. Risk difference is adjusted for treatment duration of infliximab originator at baseline.

diagnosis and treatment duration of infliximab originator at baseline. We included subgroup analyses by diagnosis for exploratory analyses. Missing data due to dropout for the primary endpoint were imputed with the worst outcome (disease worsening) in the full analysis set. Other handling of missing data is presented in the appendix (p 7). Statistical analyses were done with Stata version 14.1.

This trial is registered with ClinicalTrials.gov, number NCT02148640.

Role of the funding source

The funder of the study (Norwegian Ministry of Health and Care Services) had no role in the study design, data collection, data analysis, data interpretation, writing of this Article, or the decision to submit for publication. The corresponding author (TKK) together with the statistician (ICO) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 24, 2014, and July 8, 2015, 498 patients were recruited and 482 were randomised into the trial at 40 centres. 241 patients were assigned to receive continued treatment with infliximab originator and 241 to switch from infliximab originator to CT-P13. The patients were followed up for 52 weeks in each treatment group. The full analysis set included 481 patients (241 in the infliximab originator group and 240 in the CT-P13 group; one randomly assigned patient withdrew consent before treatment) and the per-protocol set included 408 patients (202 in the infliximab originator group and 206 in the CT-P13 group; figure 1).

In full analysis set, 186 (39%) patients were women, the mean age was 47·9 years (SD 14·8), and the mean duration of treatment with infliximab originator before randomisation was 6·8 years (SD 3·7). 155 (32%) patients had Crohn's disease, 93 (19%) had ulcerative colitis,

91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis (full analysis set; table 1). The two treatment groups were similar for major baseline demographic and disease characteristics in both the full analysis set (table 1) and in the per-protocol set (appendix p 10). Both the general and the disease-specific measures suggested low disease activity at baseline (table 1). The demographics and baseline characteristics for each of the six diagnoses in the full analysis set are shown in the appendix (pp 11–13).

Disease worsening occurred in 53 (26%) patients in the infliximab originator group and in 61 (30%) patients in the CT-P13 group (per-protocol set; figure 2). The 95% CI of the adjusted risk difference (–4·4%) was –12·7% to 3·9%, which was within the prespecified non-inferiority margin of 15%. Thus, our findings showed that CT-P13 is not inferior to infliximab originator (ie, that the null hypothesis was rejected). The adjusted relative risk of disease worsening in the CT-P13 group was 1·17 (95% CI 0·82–1·52) compared with the infliximab originator group. Robustness analyses adjusting for potential centre effect by mixed model and generalised estimating equations gave similar risk differences within the non-inferiority margin (appendix p 14). The risk of disease worsening in the full analysis set is shown in the appendix (p 16).

Remission occurred in 123 (61%) patients in the infliximab originator group and 126 (61%) patients in the CT-P13 group, with an adjusted rate difference of 0·6% (95% CI –7·5% to 8·8%; per-protocol set; appendix p 16). Remission rates in the full analysis set are provided in the appendix (p 17).

Disease state at baseline and changes in the generic disease variables and disease-specific composite measures from baseline to end of follow-up were generally similar in both groups, both in the per-protocol set (table 2) and in the full analysis set (appendix p 15). Figure 3 presents the disease-specific composite measures in each of the six diseases during follow-up; we noted no differences between the two treatment groups. Likewise, changes in patient-reported outcome measures were also similar in the per-protocol set (table 2) and full analysis set (appendix p 15). However, we noted statistically significant differences for two of the endpoints in the per-protocol set (MHAQ and SF-36 physical component summary score), both in favour of CT-P13 (table 2).

Time from randomisation to disease worsening (per-protocol set and full analysis set, appendix p 18), occurrence of drug discontinuation (per-protocol set, table 2; full analysis set, appendix p 15), and the time from randomisation to drug discontinuation (per-protocol set and full analysis set, appendix p 19) were similar in the two treatment groups.

Similar numbers of patients had at least one treatment-emergent adverse event in the two treatment groups (168 [70%] in infliximab originator group and 164 [68%]

in CT-P13 group; table 3). The most frequent treatment-emergent adverse events were related to infections (table 3). Ten (4%) patients in the infliximab originator group compared with four (2%) patients in the CT-P13 group had an infusion-related reaction (table 3). Similarly, the number of patients with a treatment-emergent serious adverse event did not differ between the two groups (24 [10%] in the infliximab originator group and 21 [9%] in the CT-P13 group; table 3). Nine (4%) patients in the infliximab originator group compared with eight (3%) patients in the CT-P13 group discontinued the study drug due to adverse events. No deaths occurred, and no suspected unexpected serious adverse reactions occurred. A summary of narratives for malignant diseases is presented in the appendix (p 9).

Trough drug concentrations were similar in the two groups during follow-up (appendix p 20). ADAbs were observed at any timepoint in 26 (11%) patients in the infliximab originator group and 30 (13%) patients in the CT-P13 group (full analysis set). The incidence of ADAbs detected during the study (excluding patients with detectable ADAb at baseline) was 17 (7%) for infliximab originator and 19 (8%) for CT-P13 (full analysis set).

As part of the exploratory analyses, we examined the primary endpoint within each diagnostic group. Non-inferiority was not shown for any of the diagnostic subgroups with the exception of spondyloarthritis (figure 2), whereas for Crohn's disease the confidence interval was close to inferiority for CT-P13. A sensitivity analysis was done in the full analysis set without any major changes in the results (appendix p 14).

Discussion

NOR-SWITCH is, to our knowledge, the first randomised study to show that switching from an originator to a biosimilar TNF inhibitor is not inferior to continued treatment with the originator drug, according to a prespecified non-inferiority margin of 15%.

	Baseline		52 weeks		Difference at 52 weeks (95% CI)
	Infliximab originator (n=202)	CT-P13 (n=206)	Infliximab originator (n=202)	CT-P13 (n=206)	
Change variables*					
Physician's global assessment of disease activity	1·2 (1·2)	1·2 (1·3)	0·1 (1·6)	0·1 (1·6)	−0·15 (−0·39 to 0·09)
Patient's global assessment of disease activity	2·0 (1·9)	2·2 (2·0)	0·4 (1·9)	0·3 (2·2)	−0·04 (−0·37 to 0·29)
Erythrocyte sedimentation rate (mm/h), log10	0·9 (0·4)	0·9 (0·4)	0 (0·3)	0 (0·3)	−0·02 (−0·06 to 0·03)
C-reactive protein (mg/L), log10	0·4 (0·4)	0·4 (0·4)	0 (0·3)	0 (0·4)	−0·02 (−0·09 to 0·04)
Calprotectin (mg/kg), log10	1·8 (0·6)	1·9 (0·7)	0 (0·5)	0·1 (0·5)	0·03 (−0·12 to 0·18)
Harvey-Bradshaw Index (Crohn's disease)	2·6 (2·4)	2·6 (2·4)	0·3 (2·3)	0·5 (3·1)	−0·41 (−1·14 to 0·33)
Partial Mayo score (ulcerative colitis)	0·6 (1·3)	0·6 (1·3)	0·1 (1·3)	−0·2 (1·7)	0·14 (−0·30 to 0·59)
ASDAS (spondyloarthritis)	1·7 (0·7)	2·1 (0·8)	0·1 (0·6)	−0·2 (0·7)	−0·01 (−0·27 to 0·24)
DAS28 (rheumatoid arthritis and psoriatic arthritis)	2·5 (1·0)	2·2 (0·9)	0·3 (1·0)	0·1 (0·9)	0·27 (−0·07 to 0·61)
CDAI (rheumatoid arthritis and psoriatic arthritis)	5·0 (3·5)	4·0 (3·1)	1·5 (5·5)	0·7 (3·9)	1·29 (−0·35 to 2·94)
SDAI (rheumatoid arthritis and psoriatic arthritis)	5·4 (3·5)	4·5 (3·1)	1·6 (5·7)	0·7 (4·4)	1·09 (−0·68 to 2·86)
PASI (chronic plaque psoriasis)	2·2 (1·9)	3·1 (1·7)	−0·5 (1·9)	−0·4 (1·9)	−0·28 (−1·10 to 0·55)
State variables†					
HBI remission (Crohn's disease)	41 (62%)	43 (68%)	46 (70%)	41 (65%)	6·1% (−9·6 to 21·9)
PMS remission (ulcerative colitis)	30 (91%)	38 (90%)	29 (88%)	39 (93%)	−5·0% (−18·6 to 8·6)
ASDAS inactive disease (spondyloarthritis)	16 (37%)	8 (19%)	10 (23%)	7 (17%)	6·6% (−10·3 to 23·5)
DAS28 remission status (rheumatoid arthritis and psoriatic arthritis)	26 (60%)	30 (70%)	23 (53%)	25 (58%)	−5·9% (−27·3 to 15·4)
CDAI remission status (rheumatoid arthritis and psoriatic arthritis)	11 (26%)	15 (35%)	11 (26%)	14 (33%)	−6·3% (−26·0 to 13·4)
SDAI remission status (rheumatoid arthritis and psoriatic arthritis)	17 (40%)	18 (42%)	15 (35%)	17 (40%)	−1·4% (−22·2 to 19·5)
ACR/EULAR remission status (rheumatoid arthritis and psoriatic arthritis)	14 (33%)	12 (28%)	9 (21%)	11 (26%)	−2·4% (−20·6 to 15·7)
PASI complete clearance (chronic plaque psoriasis)	1 (6%)	0	4 (24%)	2 (13%)	11·0% (−14·6 to 36·6)
PASI mild to moderate (chronic plaque psoriasis)	17 (100%)	16 (100%)	16 (94%)	15 (94%)	0·4% (−15·9 to 16·6)
PASI remission (chronic plaque psoriasis)	15 (88%)	12 (75%)	15 (88%)	14 (88%)	0·7% (−21·5 to 23·0)
Study drug discontinuation	··	··	9 (4%)	8 (4%)	0·4% (−3·4 to 4·3)

(Table 2 continues on next page)

	Baseline		52 weeks		Difference at 52 weeks (95% CI)
	Infliximab originator (n=202)	CT-P13 (n=206)	Infliximab originator (n=202)	CT-P13 (n=206)	
(Continued from previous page)					
Patient-reported outcome measures					
SF-36 physical functioning	50·6 (11·3)	50·5 (10·9)	–1·2 (7·0)	0 (6·3)	–0·91 (–2·08 to 0·27)
SF-36 role limitation physical	45·6 (11·6)	46·9 (11·3)	–1·1 (11·2)	–0·4 (9·4)	–1·31 (–2·99 to 0·37)
SF-36 pain	47·2 (8·5)	47·8 (9·5)	–0·7 (7·3)	–0·5 (7·7)	–0·46 (–1·69 to 0·78)
SF-36 general health	43·5 (10·2)	44·5 (10·2)	–1·1 (7·3)	–1·1 (7·1)	–0·76 (–2·02 to 0·49)
SF-36 emotional wellbeing	50·0 (9·8)	50·9 (8·9)	–1·3 (7·8)	–0·7 (7·8)	–0·47 (–1·85 to 0·90)
SF-36 role limitation emotional	48·8 (10·8)	50·0 (10·4)	–0·5 (12·2)	–2·4 (10·5)	1·42 (–0·36 to 3·20)
SF-36 social functioning	48·0 (10·5)	48·6 (9·5)	–0·2 (9·4)	–0·6 (10·4)	0·76 (–0·75 to 2·27)
SF-36 energy or fatigue	47·1 (10·4)	46·9 (10·2)	–1·9 (8·5)	0·5 (8·3)	–1·40 (–2·84 to 0·03)
SF-36 physical component summary score	46·4 (10·1)	46·8 (10·3)	–1·2 (6·9)	0·2 (6·6)	–1·60 (–2·74 to –0·46)
SF-36 mental component summary score	49·1 (10·7)	50·3 (9·3)	–0·7 (8·9)	–1·3 (8·9)	0·74 (–0·76 to 2·24)
EQ-5D index	0·8 (0·2)	0·8 (0·2)	0 (0·2)	0 (0·2)	–0·02 (–0·05 to 0·01)
WPAI percent work missed due to specified problem (absenteeism)	5·7 (15·6)	7·6 (22·5)	1·9 (19·5)	1·4 (19·2)	0·28 (–4·91 to 5·46)
WPAI percent impairment while working due to specified problem (presenteeism)	15·1 (19·2)	15·5 (20·4)	3·6 (21·6)	6·5 (21·3)	–3·68 (–8·22 to 0·86)
WPAI percent overall work impairment due to specified problem	19·0 (23·0)	18·6 (25·0)	3·5 (25·1)	6·1 (24·2)	–1·60 (–7·34 to 4·13)
WPAI percent activity impairment due to specified problem	24·2 (24·4)	24·3 (24·9)	0·9 (21·8)	1·6 (22·4)	–0·99 (–4·49 to 2·51)
IBDQ total score (Crohn's disease and ulcerative colitis)	189·5 (22·5)	187·0 (24·9)	–1·4 (19·4)	0·4 (18·2)	–0·72 (–5·00 to 3·56)
MHAQ (spondyloarthritis, rheumatoid arthritis, and psoriatic arthritis)	0·3 (0·3)	0·3 (0·3)	0·1 (0·2)	0·0 (0·3)	0·08 (0·01 to 0·15)
BASDAI (spondyloarthritis)	2·7 (1·4)	3·5 (1·7)	0·3 (1·0)	–0·2 (1·4)	–0·02 (–0·50 to 0·47)
RAID total score (rheumatoid arthritis)	2·2 (1·3)	2·0 (1·6)	0·6 (1·2)	0·2 (1·4)	0·47 (–0·14 to 1·08)
PsAID total score (psoriatic arthritis)	2·9 (1·6)	2·8 (1·5)	0·5 (1·2)	0·0 (1·1)	0·41 (–0·44 to 1·26)
DLQI total score (chronic plaque psoriasis)	2·5 (3·4)	3·2 (4·1)	–0·6 (2·0)	–0·5 (2·0)	–0·63 (–1·83 to 0·58)

MHAQ=Modified Health Assessment Questionnaire. BASDAI=Bath Ankylosing Spondylitis Disease Activity Index. ASDAS=Ankylosing Spondylitis Disease Activity Score. DAS28=Disease Activity Score in 28 joints with CRP. CDAI=Clinical Disease Activity Index. SDAI= Simplified Disease Activity Index. ACR/EULAR=American College of Rheumatology/European League Against Rheumatism. PASI=Psoriasis Area and Severity Index. SF-36=RAND Short Form Health Survey t-scores using Norwegian norms. EQ-5D=EuroQol questionnaire time trade-off UK weighted. WPAI=Work Productivity and Impairment Questionnaire. IBDQ=Inflammatory Bowel Disease Questionnaire. RAID=Rheumatoid Arthritis Impact of Disease. PsAID=Psoriatic Arthritis Impact of Disease. DLQI=Dermatology Life Quality Index. *Data are mean (SD) at baseline and mean (SD) change from baseline (follow-up minus baseline). Difference is adjusted treatment difference of change from baseline with 95% CI. †Data are N (%) of state at baseline and study end. Difference is adjusted treatment difference at study end.

Table 2: Secondary efficacy endpoints in the per-protocol set

Data from observational studies and from the extensions of the PLANETRA and PLANETAS studies have not raised any major concerns about the efficacy or safety of the infliximab biosimilar CT-P13.[15,16,19,20] However, treatment-emergent adverse events were reported in 71·4% of the patients who switched from infliximab originator to CT-P13 compared with 48·9% of those who maintained CT-P13 for the second-year extension of the PLANETAS study.[19] Further, about 6% of 647 patients in the DANBIO register[18] stopped treatment within about 3 months after switching from infliximab originator to CT-P13 because of adverse events or lack of efficacy. The patients had on average used infliximab originator for 6·7 years before the switch and the investigators

concluded that further investigations are needed before non-medical switch (ie, switching to reduce costs) can be recommended.[18] We believe that NOR-SWITCH has a better study design than these studies and our findings support the strategy of switching from originator to biosimilar infliximab.

The frequency of patients reporting adverse events or serious adverse events was similar between the two treatment groups, and no deaths or suspected unexpected serious adverse reactions occurred during the study. As expected, the most frequent adverse events reported were related to infections. More patients in the infliximab originator group had infusion-related reactions and discontinued the study
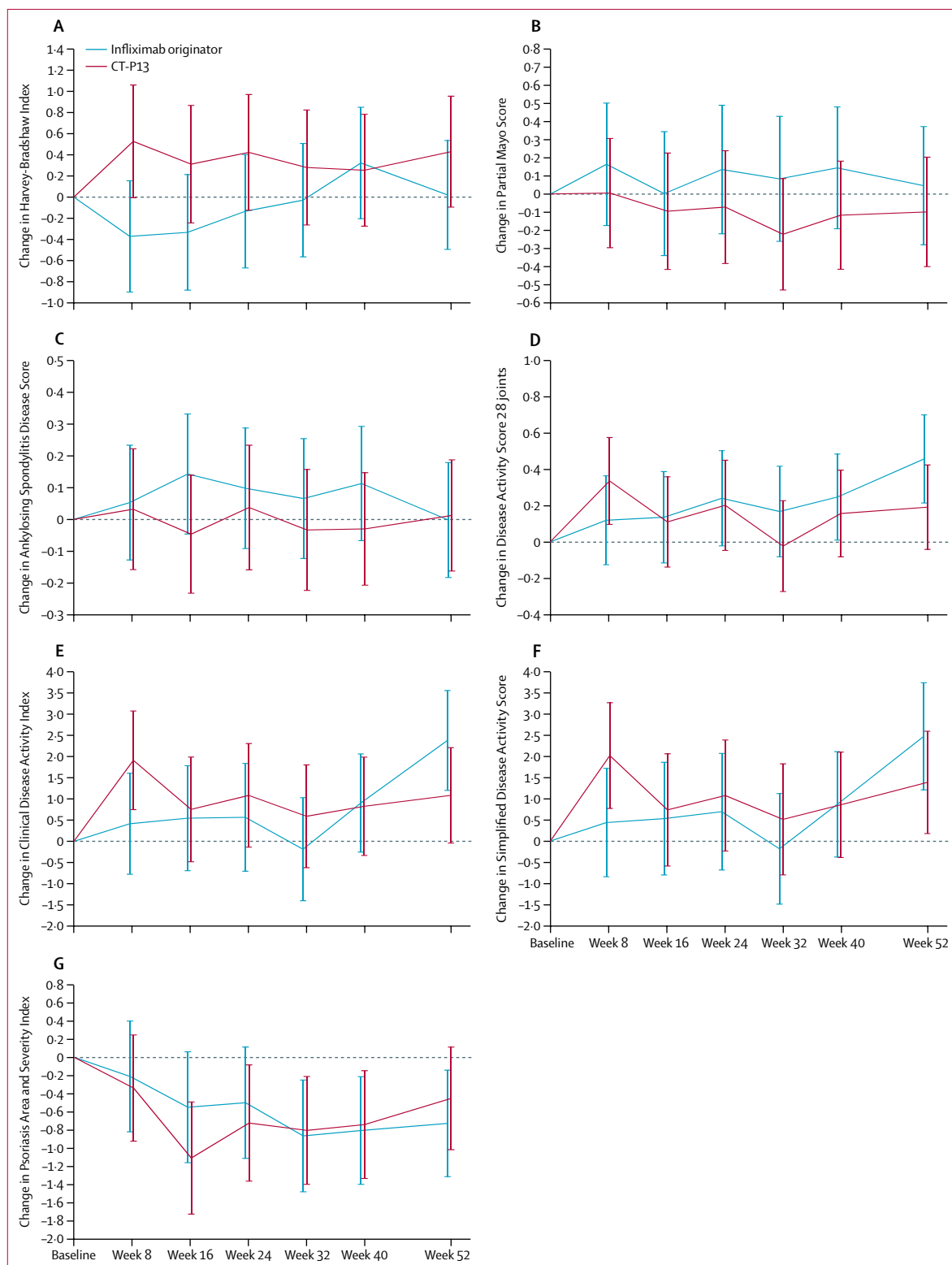
Figure 3: Change in disease-specific composite measures during 52 weeks of follow-up in the per-protocol set
(A) Harvey-Bradshaw index for Crohn's disease. (B) Partial Mayo Score for ulcerative colitis. (C) Ankylosing Spondylitis Disease Activity Score for spondyloarthritis.
(D) Disease Activity Score in 28 joints with C-reactive protein for rheumatoid arthritis and psoriatic arthritis. (E) Clinical Disease Activity Index for rheumatoid arthritis
and psoriatic arthritis. (F) Simplified Disease Activity Index for rheumatoid arthritis and psoriatic arthritis. (G) Psoriasis Area and Severity Index for psoriasis. Bars are
95% CIs from a mixed model adjusted for baseline value and infliximab treatment duration at baseline.

	Infliximab originator (n=241)	CT-P13 (n=240)
Overview		
SUSAR	0	0
Serious adverse events	32/24 (10%)	27/21 (9%)
Adverse events	422/168 (70%)	401/164 (68%)
Adverse events leading to study drug discontinuation*	18/9 (4%)	9/8 (3%)
Most frequent treatment-emergent adverse events		
Nasopharyngitis	29/23 (10%)	28/25 (10%)
Urinary tract infection	19/14 (6%)	9/7 (3%)
Skin rash	7/7 (3%)	14/13 (5%)
Headache	10/10 (4%)	8/7 (3%)
Arthralgia	12/11 (5%)	6/6 (3%)
Sinusitis	13/13 (5%)	4/3 (1%)
Infusion-related reaction	10/10 (4%)	5/4 (2%)
Influenza-like illness	7/7 (3%)	7/7 (3%)
Respiratory tract infection	4/4 (2%)	11/10 (4%)
Gastroenteritis	7/7 (3%)	6/6 (3%)
Treatment-emergent serious adverse events by system organ class		
Cardiac disorders	Acute myocardial infarction	Acute myocardial infarction, atrial fibrillation
Eye disorders	..	Retinal detachment
Gastrointestinal disorders	Melaena, pancreatitis	Abdominal pain
General disorders and administration site conditions	..	Chest pain
Hepatobiliary disorders	Cholecystitis, cholelithiasis	Two cholecystitis
Infections	Gingival abscess, peritonitis, sinusitis	Two anal abscess, two gastroenteritis, pyelonephritis, tonsillitis
Investigations	Kidney biopsy	..
Metabolism and nutrition disorders	Gout	..
Musculoskeletal and connective tissue disorders	Arthralgia	Arthritis
Neoplasms (benign, malignant, and unspecified)	Bladder cancer, breast cancer, prostate dysplasia	Bladder cancer
Nervous system disorders	Cerebrovascular incident, headache, syncope	..
Renal and urinary disorders	Two nephrolithiasis, renal cyst	Nephrolithiasis
Respiratory, thoracic, and mediastinal disorders	Rheumatoid lung	..
Surgical and medical procedures	Anorectal operation, aortic bypass, appendectomy, caesarean section, two colectomy	Cholecystectomy, pharyngeal operation, prostate photon radiation therapy, prostatic operation, shoulder operation
Vascular disorders	..	Femoral arterial embolus

Data are number of events/number of patients (%). SUSAR=suspected unexpected serious adverse reaction. *Patients could have other primary reason for study drug discontinuation.

Table 3: Treatment-emergent adverse events in the safety population

drug than in the CT-P13 group. These results support those from earlier observational studies and suggest that switching to CT-P13 is not associated with any safety concerns.[3,4,15–17,19,20]

We did not note immunogenicity to significantly differ in relation to CT-P13 compared with infliximab originator. Serum drug concentrations and occurrence of ADAbs were similar between the two groups throughout the study. This observation is in agreement with findings in the 2-year extensions of PLANETRA and PLANETAS, which showed similar serum concentrations of infliximab and occurrence of ADAbs in the maintenance and switch groups.[3,4,19,20]

The NOR-SWITCH trial has both strengths and weaknesses. The randomised design, inclusion of sufficient patients (according to the power calculations), and involvement of patient representatives in the planning and conduct of the study are obvious strengths. Further, the study was financed by the Norwegian Government and monitored within the health-care system. Pharmaceutical companies were not involved in any part of the planning or conduct of the study. Some companies were informed about the study through ClinicalTrials.gov and requested access to the study documents from the regional ethical committee. All drugs were provided to patients through the regular payment schedule for TNF inhibitors in the Norwegian health-care system.

Patients on stable, long-term infliximab treatment are probably not at high risk of developing immunogenicity to CT-P13.[26] However, the NOR-SWITCH study acquired an almost complete set of serum samples from all patients at all visits, enabling us to assess serum drug concentrations and ADAb status in study participants over the entire study period. By contrast, previous studies have generally assessed drug concentrations and ADAb status at a limited number of timepoints.[3,4,19,20]

One limitation is that this trial was not powered to demonstrate non-inferiority within each diagnostic group. However, we knew this would not be achievable based on the number of patients on stable treatment with infliximab originator who were eligible for inclusion in Norway and given the constraints on funds and the timeframe available. As such, the primary endpoint was designed to evaluate the occurrence of disease worsening in study participants across the disease groups. As expected, there were differences in treatment effects across diseases (figure 2). We caution against emphasising the treatment differences within each disease when interpreting these data. These analyses are prespecified as exploratory subgroup analyses and the study was not powered to show non-inferiority for each of the diagnoses separately. With six diagnosis-specific comparisons there is a substantial multiplicity issue, with a relatively high likelihood of at least one false-positive treatment difference. We did not reach this difference in our results, although the confidence interval for Crohn's disease was close to inferiority of CT-P13.

Our choice of a generic primary endpoint (disease worsening) might be perceived as controversial. Results across diagnoses were heterogeneous with occurrence of diseases worsening ranging from around 10% in psoriasis and ulcerative colitis, to almost 60% in

psoriatic arthritis. However, our definitions of disease worsening in each diagnosis were based on well established measures of disease activity with predefined cutoff points for disease state and change. The heterogeneity by diagnosis was adjusted for in the logistic regression.

The distribution of diagnoses in this study reflects the adult population of patients receiving infliximab in Norway. Competitive inclusion gave no room for preferential recruitment of patients with specific diagnoses. Although a diagnosis-specific trial might have given a definite conclusion for that particular diagnosis, extrapolation to the other diseases would have been problematic. We chose to do the trial in all diagnoses, with the aim of providing some—albeit not conclusive—evidence for all diagnoses.

Another issue was that the study could not be strictly blinded because local personnel had to prepare the infusions. However, we invested considerable effort in the planning of the procedures for preparation and administration of the infusions. Great care was taken to ensure that no patient had contact with anyone preparing study medication. The study coordinators and monitors had regular contact with the individual study centres to ensure adherence to blinding procedures.

Furthermore, we cannot rule out a possible skewed selection of patients that could affect the generalisability of the study. One might speculate that stable patients with low disease burden could be over-represented in the study cohort. Unfortunately, we do not have any demographic or disease characteristics about patients who declined participation.

The choice of a sensible non-inferiority margin is challenging in any non-inferiority trial. If the margin is too narrow the trial becomes infeasible, whereas a too wide margin could include clinically important differences. Our choice of 15% was based on the PLANETRA trial[4] as well as discussions with clinicians and the Norwegian Medicines Agency. Moreover, the European Medicines Agency viewed the 15% margin as sufficient in their assessment report of CT-P13.[27] There are limitations to this approach. The PLANETRA trial used a different primary endpoint and included only patients with rheumatoid arthritis, and we had no corresponding non-inferiority trials done in other disorders for validation of our chosen non-inferiority margin. Since the initiation of this study, three other phase 3 biosimilar studies with other TNF inhibitors (SB2, SB4, and GP2015) have been reported and used equivalence margins of at least 15%.[28–30] However, the US Food and Drug Administration suggested a margin of 12% as more appropriate when assessing the treatment difference with a 90% CI.[31] Our study showed non-inferiority both by the European Medicines Agency preference (95% CI and 15% margin) and the Food and Drug Administration preference (90% CI and 12% margin; data not shown). However, our trial would not have shown non-inferiority at the 95% CI and 12% margin, and it may be argued that the study was underpowered if a more stringent non-inferiority margin had been selected.

Currently, an open 6-month extension of the NOR-SWITCH study is ongoing (NCT02148640). Patients who received CT-P13 for 12 months in the randomised main study will be compared with patients switching to CT-P13 from infliximab originator. This extension will allow for further assessment of immunogenicity and disease activity over a longer time period than the original trial.

The medical community has only seen the beginning of the biosimilar era. In a few years, we will probably have access to several biosimilars used for patients with gastroenterological, rheumatic, and dermatological diseases. This situation will call for studies which examine multiple switches (eg, from one biosimilar to another and also back to the originator product). We initially considered a study design with multiple switches, but concluded with a single switch study for feasibility reasons and because no previous randomised switch study had been done for TNF inhibitors.

Findings from the NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to our prespecified non-inferiority margin. There was no suggestion of differences in safety or immunogenicity between the two treatment groups. Consequently, the study results support that patients can be switched from originator to biosimilar infliximab. However, the study was not powered to show non-inferiority in individual diseases and the 15% margin might be too wide to exclude all clinically important differences. Moreover, we recommend caution in generalising these findings to other biological agents. Further studies are needed to examine multiple-sequenced as well as back-and-forth switches.

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