Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study

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Summary

Background The infliximab biosimilar CT-P13 was approved for use in Crohn's disease after clinical comparison with originator infliximab in ankylosing spondylitis and rheumatoid arthritis; however, concerns about such indication extrapolation have been expressed. This study investigated whether CT-P13 is non-inferior to infliximab in patients with Crohn's disease who were naive to biological therapy.

Methods In this randomised, multicentre, double-blind, phase 3 non-inferiority study, we enrolled patients with active Crohn's disease who had not responded to, or were intolerant to, non-biological treatments. Patients were randomly assigned (1:1:1:1) to receive CT-P13 then CT-P13, CT-P13 then infliximab, infliximab then infliximab, or infliximab then CT-P13, with switching occurring at week 30. Patients received 5 mg/kg CT-P13 or infliximab at weeks 0, 2, 6, and then every 8 weeks up to week 54. The primary endpoint was the proportion of patients with a decrease of 70 points or more in Crohn's Disease Activity Index (CDAI) from baseline to week 6. A non-inferiority margin of –20% was set (CT-P13 was non-inferior to infliximab if the lower limit of the two-sided 95% CI for the treatment difference was greater than –20). This trial is registered with ClinicalTrials.gov, number NCT02096861, and is completed.

Findings Between Aug 20, 2014, and Feb 15, 2017, 308 patients were assessed for eligibility, and 220 patients were enrolled: 111 were randomly assigned to initiate CT-P13 (56 to the CT-P13–CT-P13 group and 55 to the CT-P13–infliximab group) and 109 to initiate infliximab (54 to the infliximab–infliximab group and 55 to the infliximab–CT-P13 group). CDAI-70 response rates at week 6 were similar for CT-P13 (77 [69·4%, 95% CI 59·9 to 77·8] of 111) and infliximab (81 [74·3%, 95% CI 65·1 to 82·2] of 109; difference –4·9% [95% CI –16·9 to 7·3]), thereby establishing non-inferiority. Over the total study period, 147 (67%) patients experienced at least one treatment-emergent adverse event (36 [64%] in the CT-P13–CT-P13 group, 34 [62%] in the CT-P13–infliximab group, 37 [69%] in the infliximab–infliximab group, and 40 [73%] in the infliximab–CT-P13 group).

Interpretation This study showed non-inferiority of CT-P13 to infliximab in patients with active Crohn's disease. Biosimilar CT-P13 could be a new option for the treatment of active Crohn's disease.

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Introduction

Crohn's disease is a chronic, relapsing inflammatory disorder that predominantly affects the gastrointestinal tract.[1] Although the disease is heterogeneous in its severity and prognosis, it often progresses to complications such as stricture, fistula, or abscess.[2] Biological therapies targeting tumour necrosis factor (TNF), a pro-inflammatory cytokine with an important role in disease pathophysiology, are an important treatment.[3] Step-up to anti-TNF-based therapy is recommended in patients with moderate-to-severe disease if immunosuppressive therapies have failed or are poorly tolerated.[4] The costs of anti-TNF and other biological drugs are often high, placing a financial burden on health-care systems and sometimes limiting access to these drugs.[5,6] For this reason, biosimilar drugs with high likeness to already licensed biological therapies (originator drugs), have been developed. Biosimilars are subject to strict approval criteria by regulatory authorities[7,8] such that an approved biosimilar should show "no clinically meaningful differences [versus the originator] in terms of safety, purity, and potency".[7]

CT-P13 is a biosimilar version of the anti-TNF monoclonal antibody infliximab (Janssen Biotech, Horsham, PA, USA). CT-P13 has been approved by the European Medicines Agency (EMA) and licensed by the US Food and Drug Administration (FDA) for adult and paediatric Crohn's disease, adult ulcerative colitis, and all other indications of infliximab.[9,10] CT-P13 is currently licensed

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Research in context

Evidence before this study

The infliximab biosimilar CT-P13 was approved for use in Crohn's disease based on the concept of indication extrapolation. Searches of PubMed performed on Feb 19, 2018, using the terms "CT-P13", "biosimilar", "infliximab", and "Crohn's disease" identified low-level clinical evidence for the efficacy and safety of CT-P13 versus innovator infliximab in patients with Crohn's disease. This evidence took the form of real-world evidence collected after approval of CT-P13 and the primary report of a randomised controlled trial (RCT), NOR-SWITCH. The NOR-SWITCH RCT, which was performed across several immune-mediated diseases, supported the equivalence between CT-P13 and infliximab in patients with low disease activity. However, inflammatory bowel disease represented only a small subset of the trial population, with efficacy assessed in a secondary analysis.

Added value of this study

This study provides the first high-level evidence of the non-inferior efficacy of CT-P13 to infliximab in anti-tumour necrosis factor (TNF) agent-naive patients with active Crohn's disease. The study demonstrated no notable differences in the efficacy, pharmacokinetics, pharmacodynamics, safety, or immunogenicity of CT-P13 and infliximab in the recruited population. Additionally, the study confirmed the validity of extrapolation for this biosimilar monoclonal antibody.

Implications of all the available evidence

The findings should assist clinicians in their decision making when starting a patient on anti-TNF treatment. Indication extrapolation based on scientific evidence should be justified during development of biosimilars.

in 86 countries, including Australia, Canada, Japan, and South Korea, as well as Europe and the USA. The efficacy of infliximab in patients with Crohn's disease was first established in clinical studies reported by Targan and colleagues[11] and Hanauer and colleagues (ACCENT I).[12] Per regulatory guidelines, approval of CT-P13 was based on proof of biosimilarity versus infliximab in physicochemical, in-vitro, and clinical studies—including randomised controlled trials (RCTs) in patients with ankylosing spondylitis or rheumatoid arthritis—that established equivalence of the drugs in terms of pharmacokinetics and efficacy, as well as similarity in terms of safety and immunogenicity.[13–15] Approval of CT-P13 in inflammatory bowel disease (IBD) and other non-rheumatological indications was based on extrapolation—a process that allows approval of a biosimilar in a non-studied indication based on the totality of evidence from the development programme, including comparative analytical (structural and functional), non-clinical, and clinical studies in non-studied indications to enhance the rational of extrapolation. Such extrapolation is awarded by regulatory authorities if biosimilarity has been proven and is scientifically justified.[7,8] However, concerns about extrapolation have been expressed[16] and, to date, no RCT has compared the efficacy and safety of a biosimilar with infliximab in patients with IBD.

The aims of this study were to establish non-inferior efficacy of CT-P13 compared with infliximab in patients with active Crohn's disease who were naive to biological therapy, at week 6 using the Crohn's Disease Activity Index (CDAI),[17] as well as to assess endoscopy findings, inflammation biomarkers, pharmacokinetics, safety, and immunogenicity up to week 54 after switching or continued treatment at week 30. Our study was conducted to support market access and designed to validate the extrapolation process on which the approval of CT-P13 for the treatment of IBD was based.

See Online for appendix

Methods

Study design and participants

In this randomised, multicentre, double-blind, phase 3 non-inferiority study, we enrolled patients with active Crohn's disease who had not previously received any biological drug for Crohn's disease treatment, or any anti-TNF agent for treatment of any comorbidities, from 58 centres in 16 countries (Belgium, Brazil, Denmark, France, Germany, Hungary, Italy, Israel, Mexico, the Netherlands, Poland, Republic of Korea, Romania, Russia, Ukraine, USA; study centres listed in the appendix). Briefly, patients were aged 18–75 years; had a disease duration of 12 weeks or more before randomisation and a CDAI of 220–450 points; and had not responded to, were intolerant of, or had contraindications for, non-biological treatments for active Crohn's disease. Full patient inclusion and exclusion criteria are listed in the appendix.

The study protocol was reviewed and approved by independent ethics committees for each centre. All patients provided written informed consent. Protocol amendments are detailed in the appendix. The study was conducted in line with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable regulatory requirements.

Randomisation and masking

Patients were randomly assigned (1:1:1:1) to receive CT-P13 followed by CT-P13 at week 30 (CT-P13–CT-P13 group); CT-P13 followed by infliximab at week 30 (CT-P13–infliximab group); infliximab followed by infliximab at week 30 (infliximab–infliximab group); and infliximab followed by CT-P13 at week 30 (infliximab–CT-P13 group). Randomisation was stratified by region (European or non-European); history of treatment with immunomodulators (eg, azathioprine, 6-mercaptopurine, or methotrexate); and disease duration (<3 years or ≥3 years). An interactive

web response system was used to assign patients to treatment groups per a predefined randomisation code. PPD Bioanalytical Laboratory Services (Bellshill, Scotland, UK) generated the randomisation schedule for the interactive web response system, which linked sequential patient randomisation numbers to treatment codes. Randomisation numbers were aggregated in eight blocks, and within each block the same number of patients was allocated to each treatment group. Block size was not revealed. CT-P13 and infliximab were supplied in identical vials in prepacked supply kits for each patient and administered via the same procedure. The study was double-blinded throughout. Randomisation codes were not revealed to patients, investigators, or centre personnel, except for predefined unblinded personnel from Celltrion and PPD, until all final clinical data were entered into the database and the database was locked and released for analysis.

Procedures

The study comprised a 6-week screening period followed by a two-phase treatment period (dose-loading phase and maintenance phase) up to week 54. The dose-loading phase consisted of three doses of study drug (weeks 0, 2, and 6). The maintenance phase consisted of a further six doses of study drug administered every eight weeks (starting on week 14, with the last dose administered no later than week 54), followed by an eight-week interval before an end-of-study visit. At week 14, responders (defined by a ≥70-point decrease in CDAI [CDAI-70]) continued in the study up to week 54; non-responders at week 14 discontinued study treatment. Study drug was administered as 2-h intravenous infusions of 5 mg/kg CT-P13 or infliximab. Infusions followed site-specific protocols, in line with local guidelines and product information for infliximab.

To assess treatment response, CDAI was calculated at screening and on weeks 0, 6, 14, 30, and 54. The Short Inflammatory Bowel Disease Questionnaire (SIBDQ), which measures physical, social, and emotional status in patients with IBD, was completed at screening and before study drug infusion on weeks 0, 6, 14, 30, and 54. Stool samples for calprotectin testing were collected on weeks 0, 6, 14, 30, and 54 and were analysed by PPD using an enzyme-linked immunosorbent assay (ELISA) kit (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland). The presence, and level of healing, of mucosal abnormalities were assessed by colonoscopy at baseline and at week 54 at a designated independent reading centre (with one video read by one blinded reviewer). The extent of endoscopic disease activity was assessed with the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD).[18]

Serum samples for anti-infliximab antibody testing were collected before dose administration on weeks 0, 14, 30, and 54, and when a patient experienced any infusion-related reaction that resulted in a change to the dose or rate of infusion or a temporary or permanent halt to infusion.

Pharmacokinetic variables for CT-P13 and infliximab were determined in the pharmacokinetic population at weeks 0, 2, 6, and 14. Blood samples for pharmacokinetic analysis were collected on dosing days before dose administration up to week 22 and within 15 min after the end of infusion up to week 14. Pharmacodynamics were assessed via measurement of CRP levels. Blood samples for assessment of C-reactive protein (CRP) were collected before study drug administration at baseline, week 6, week 14, week 30, and week 54. CRP levels were measured with a Roche COBAS 8000 C module analyser (Roche Diagnostics, Indianapolis, USA) at the central laboratory.

Observed trough serum study drug concentration immediately before the next infusion (C_{trough}) and maximum study drug concentration at each dose (C_{max}) were determined.

Immunogenicity was defined as the incidence of anti-drug antibodies (ADAs; determined via ELISA), and neutralising antibodies (NAbs; determined using an electrogenerated chemiluminescence bead method). Reagents and procedures for both antibody-detecting methods were developed and validated at PPD and are proprietary to Celltrion.

Outcomes

The primary efficacy endpoint was CDAI-70 response at week 6. Secondary efficacy endpoints were CDAI-70 response at week 14, clinical remission (defined as an absolute CDAI <150 points) at weeks 6 and 14, and SIBDQ scores at weeks 0, 6, and 14. Secondary endpoints were assessed again at weeks 30 and 54 in patients who continued the study. Tertiary efficacy endpoints were CDAI-100 response at weeks 6, 14, 30, and 54, steroid-free remission (defined as a CDAI <150 points at week 30 without the use of corticosteroids in the 3 months before week 30), sustained steroid-free remission (CDAI <150 at weeks 30 and 54 without the use of corticosteroids in the 3 months before week 54), faecal calprotectin levels, and the proportion of patients with mucosal healing (absence of mucosal abnormality [ie, SES-CD score ≤2] at week 54 in patients with confirmed mucosal abnormality at baseline). In a post-hoc analysis, CDAI was used to derive the two-item patient reported outcome (PRO-2) endpoint.[19]

Safety endpoints were incidence, causality, and severity of adverse events, including serious adverse events. Safety was assessed throughout the study via monitoring of adverse events, adverse events of special interest (infections and infusion-related reactions), and clinical laboratory results. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 19.1) and graded for severity with the Common Terminology Criteria for Adverse Events (CTCAE; version 4.03).

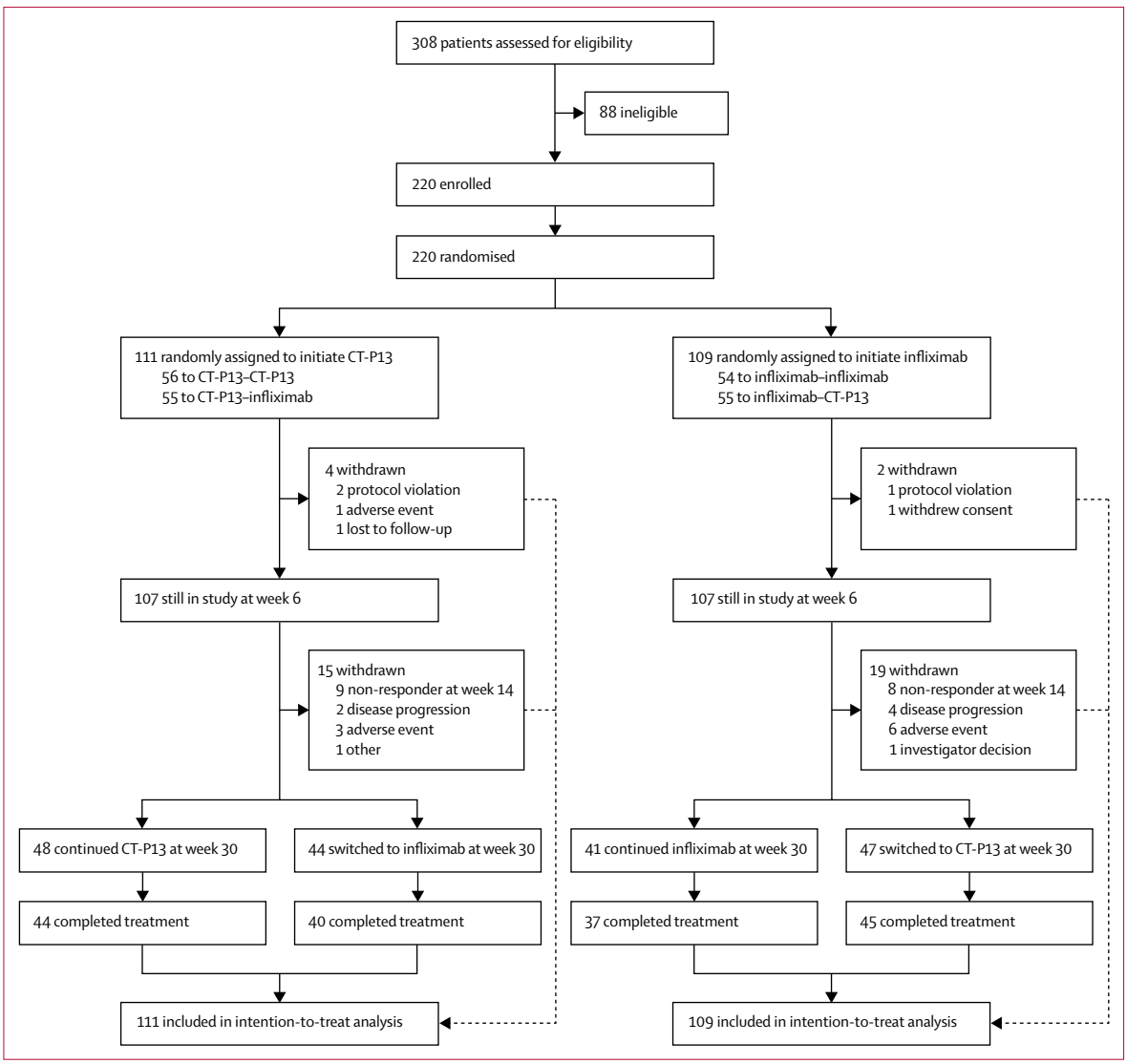

Figure: **Trial profile**

Statistical analysis

In total, 214 randomly assigned patients (107 patients initiating each drug) were required to achieve at least 85% power for a non-inferiority margin of –20% with a one-sided α level of 0·025. In the sample size calculation, the therapeutic non-inferiority of CT-P13 to infliximab was based on a response rate of 64·5%, as defined by CDAI-70 at week 6.[20] The non-inferiority margin was defined as –20% to preserve 50% effectiveness of infliximab, and was selected based on data from previous RCTs.[11,12,20] Non-inferiority of CT-P13 to infliximab with respect to response rates would be met for the primary endpoint if the lower limit of the two-sided 95% CI for the difference between CT-P13 and infliximab was greater than the non-inferiority margin of –20%.

CDAI-70 and CDAI-100 response rates at weeks 6, 14, and 30 were analysed in the intention-to-treat population and the per-protocol population using the exact binomial approach, calculating a point estimate and 95% CI for the difference in proportion between the two treatment groups (infliximab *vs* CT-P13). The intention-to-treat population included all patients who were enrolled and randomly assigned to receive a dose of study drug (regardless of whether any study drug dosing was completed). The per-protocol population included all randomly assigned patients, except for those with major protocol deviations (as defined in the statistical analysis plan). Patients with missing or incomplete data for assessment of CDAI-70 response at week 6 were considered non-responders. CDAI-70 and CDAI-100 response rates, mucosal healing at week 54, steroid-free remission, and sustained steroid-free remission were analysed using the χ^2 test to analyse the difference in proportion between the four treatment groups. CRP

levels, calprotectin levels, change from baseline in SIBDQ score, and PRO-2 scores were analysed using a *t* test for two-group analysis (up to week 30) and analysis of variance for four-group analysis at week 54. All analyses were performed based on a significance level of 0·05.

For pharmacokinetic analyses, serum drug concentrations and pharmacokinetic variables were summarised using quantitative descriptive statistics by treatment group at each scheduled collection time. The pharmacokinetic population included patients who received at least one full dose of study drug and had at least one post-treatment pharmacokinetic data value. For pharmacodynamic analysis, CRP level was summarised by treatment group at each scheduled collection time. The safety population included all patients who received at least one partial or full dose of study drug. The primary endpoint was analysed using StatXact PROCs 11.0 for SAS 9.2–9.3, and all other analyses were performed using SAS software version 9.2 and Enterprise guide 7.1. All data, including safety and efficacy data, were monitored by an independent data monitoring committee throughout the study period. This trial is registered with ClinicalTrials.gov, number NCT02096861, and is completed.

Role of the funding source

The sponsor was involved in study conception and design, and data collection, analysis, and interpretation. All authors, including employees of the sponsor, provided intellectual contribution to manuscript development, as detailed in the Contributors section. All authors had full access to all study data and final responsibility for the decision to submit for publication.

Results

Between Aug 20, 2014, and Feb 15, 2017, 308 patients were screened, of whom 220 were randomly assigned to receive CT-P13 (n=111; 56 in the CT-P13–CT-P13 group and 55 in the CT-P13–infliximab group) or infliximab (n=109; 54 in the infliximab–infliximab group and 55 in the infliximab–CT-P13 group) at week 0. The week 6 visit, when the primary endpoint was assessed, was completed by 214 patients (107 in each of the two pre-switch groups [CT-P13 and infliximab]). 166 patients completed the study. The most common reason for discontinuation was lack of response at week 14, as assessed by CDAI (figure). 14 patients with major protocol deviations were excluded from the per-protocol analysis (appendix). Overall, patient demographics and disease characteristics at baseline were similar between the CT-P13 and infliximab groups (table 1). Patient demographics and disease characteristics in the four switch or continued-treatment groups are shown in the appendix.

77 (69·4%, 95% CI 59·9 to 77·8) of 111 patients assigned to receive CT-P13 and 81 (74·3%, 65·1 to 82·2) of 109 patients assigned to receive infliximab achieved a CDAI-70 response at week 6 (difference –4·9% [95% CI –16·9 to 7·3]; table 2). Similar results were observed for the per-protocol population at week 6, with 75 (71·4%, 61·8 to 79·8) of 105 in the CT-P13 groups and 76 (75·2%, 65·7 to 83·3) of 101 in the infliximab groups achieving a CDAI-70 response (–3·8%, 95% CI –15·9 to 9·0). Overall, prespecified non-inferiority criteria were met for both populations, and CT-P13 was considered non-inferior to infliximab.

The proportion of patients with a CDAI-70 response at weeks 14 and 30 was similar in the CT-P13 and infliximab groups (table 2). Both CDAI-100 response rate and the proportion of patients achieving clinical remission were similar in the CT-P13 and infliximab groups at weeks 6, 14, and 30 (table 2). Efficacy was well maintained and similar between groups after switching (appendix). Overall, CDAI-70 or CDAI-100 response rates and clinical remission rates between groups were similar at weeks 6, 14, 30, or 54.

Mean baseline PRO-2 score was 18·5 (SD 5·47) in patients assigned to receive CT-P13 and 18·3 (SD 5·13) in those assigned to infliximab (appendix), in line with the inclusion criteria (with a CDAI of 220–450 equivalent to a PRO-2 score of 14–34[19]). PRO-2 scores improved after study drug infusion. At week 54, mean PRO-2 scores in all four switch or continued-treatment groups were

	CT-P13 (n=111)	Infliximab (n=109)
Median age, years	35·0 (26·0–46·0)	32·0 (24·0–45·0)
Sex		
Male	63 (57%)	60 (55%)
Female	48 (43%)	49 (45%)
Race		
White	86 (77%)	79 (72%)
Asian	25 (23%)	29 (27%)
Other	0	1 (1%)*
Smoking status		
Current or former tobacco user	35 (32%)	39 (36%)
Non-tobacco user	76 (68%)	70 (64%)
Disease duration,† years	4·2 (4·59)	5·3 (7·27)
CDAI	296·3 (54·30)	295·7 (55·46)
SIBDQ score	34·3 (10·92)	33·9 (9·27)
SES-CD score	9·6 (7·92)	9·8 (7·83)
Median calprotectin, µg/g	516·5 (184·0–1570·0)	459·0 (197·0–1694·0)
Median CRP (range), mg/dL	0·4 (0·1–1·2)	0·6 (0·2–2·1)
Corticosteroid use	37 (33%)	33 (30%)
History of treatment with immunomodulators‡	84 (76%)	80 (73%)

Data are n (%), mean (SD), or median (IQR) in the intention-to-treat population. CDAI=Crohn's Disease Activity Index. SIBDQ=Short Inflammatory Bowel Disease Questionnaire. SES-CD=Simplified Endoscopic Activity Score for Crohn's Disease. CRP=C-reactive protein. *One patient in the infliximab group was North African. †Crohn's disease duration (years)=[(date of informed consent–date of initial CD)+1]/365·25. ‡Immunomodulators include 6-mercaptopurine, azathioprine, and methotrexate.

***Table 1*: Baseline patient and disease characteristics**

	CT-P13 (n=111)	Infliximab (n=109)	Difference
Week 6			
CDAI-70	77 (69·4%; 95% CI 59·9 to 77·8)	81 (74·3%; 95% CI 65·1 to 82·2)	−4·9% (−16·9 to 7·3)
CDAI-100	67 (60·4%; 50·6 to 69·5)	70 (64·2%; 54·5 to 73·2)	−3·9% (−16·7 to 9·6)
Clinical remission	47 (42·3%; 33·0 to 52·1)	49 (45·0%; 35·4 to 54·8)	−2·6% (−16·2 to 10·6)
Week 14			
CDAI-70	96 (86·5%; 78·7 to 92·2)	96 (88·1%; 80·5 to 93·5)	−1·6% (−10·7 to 7·7)
CDAI-100	78 (70·3%; 60·9 to 78·6)	83 (76·1%; 67·0 to 83·8)	−5·9% (−17·7 to 6·3)
Clinical remission	59 (53·2%; 43·4 to 62·7)	60 (55·0%; 45·2 to 64·6)	−1·9% (−15·2 to 11·8)
Week 30			
CDAI-70	85 (76·6%; 67·6 to 84·1)	82 (75·2%; 66·0 to 83·0)	1·3% (−10·3 to 12·9)
CDAI-100	80 (72·1%; 62·8 to 80·2)	80 (73·4%; 64·1 to 81·4)	−1·3% (−13·3 to 10·6)
Clinical remission	61 (55·0%; 45·2 to 64·4)	62 (56·9%; 47·0 to 66·3)	−1·9% (−15·2 to 11·7)

Data are n (%; 95% CI). CDAI=Crohn's Disease Activity Index.

***Table 2*: CDAI-70 response, CDAI-100 response, and clinical remission at weeks 6, 14, and 30**

	CT-P13 to week 30 (n=111)	Infliximab to week 30 (n=109)
Steroid-free remission		
Week 30	51 (45·9%; 95%CI 36·5–55·7)	55 (50·5%; 95% CI 40·7–60·2)
SIBDQ score		
Baseline	34·3 (10·92)	33·9 (9·27)
Change from baseline		
Week 6	12·2 (11·54)	12·1 (11·47)
Week 14	14·4 (13·21)	16·9 (10·47)
Week 30	16·7 (13·32)	18·6 (11·70)
Calprotectin, µg/g		
Baseline	1072·5 (1476·41)	1544·2 (2479·96)
Week 6	485·5 (715·51)	479·8 (882·42)
Week 14	801·6 (2104·47)	598·2 (1015·84)
Week 30	746·3 (1483·19)	684·4 (1250·55)

Data are n (%) or mean (SD) in the intention-to-treat population. SIBDQ=Short Inflammatory Bowel Disease Questionnaire.

***Table 3*: Secondary and tertiary efficacy endpoints**

less than 8 (ie, equivalent to CDAI-defined remission[19]). There was no notable difference in PRO-2 scores between groups at any timepoint during the study.

51 (45·9%; 95% CI 36·5–55·7) of 111 in the CT-P13 groups and 55 (50·5%; 40·7–60·2) of 109 in the infliximab groups achieved steroid-free remission at week 30 (table 3). Sustained steroid-free remission rates were well maintained and similar between groups after switching (appendix). 16 (33%) of 48 in the CT-P13–CT-P13 group, 12 (26%) of 46 in the CT-P13–infliximab group, 12 (27%) of 44 in the infliximab–infliximab group, and eight (21%) of 38 in the infliximab–CT-P13 group had mucosal healing at week 54 (appendix). There were no notable differences between CT-P13 and infliximab groups in change from baseline in SIBDQ score at weeks 6, 14, or 30 (table 3). SIBDQ scores were well maintained and similar between groups after switching (appendix). Mean calprotectin levels decreased from baseline to week 6 and then remained stable, with no notable differences between groups at any visit (table 3, appendix).

Pharmacokinetic and pharmacodynamic findings were similar between treatment groups. C_{max} and C_{trough} values in CT-P13 and infliximab groups were similar at weeks 0, 2, 6, and 14 (appendix). Mean CRP levels decreased from baseline to week 6 and then remained stable, with no notable differences between groups (appendix).

Over the total 1-year study period, 147 (67%) patients experienced at least one treatment-emergent adverse event (36 [64%] in the CT-P13–CT-P13 group, 34 [62%] in the CT-P13–infliximab group, 37 [69%] in the infliximab–infliximab group, and 40 [73%] in the infliximab–CT-P13 group; table 4). No treatment-related adverse events of grade 4 or higher, malignancies, or deaths were reported in any group. The proportion of patients with at least one treatment-emergent adverse event was similar between groups before and after drug switching at week 30 (table 4). No new or unexpected treatment-emergent serious adverse events were identified after switching and the proportion of patients with at least one treatment-emergent serious adverse event was similar between groups before and after drug switching at week 30 (table 4). The proportion of patients with an infusion-related reaction event was similar between the two groups before switching and between the four groups on or after switching at week 30 (appendix). Two patients had infusion-related reactions at week 30 before switching and both were ADA-positive (one in the CT-P13–infliximab group, and one in the infliximab–infliximab group). The proportion of treatment-emergent adverse events due to infection was similar between the two groups before switching and between the four groups after switching (appendix).

The proportion of patients with a positive ADA result was similar between the CT-P13 and infliximab treatment groups at week 14 (15 [14%] *vs* 19 [17%]) and week 30 (43 [39%] *vs* 49 [45%]). The proportion who were positive for NAbs was also similar between groups at week 14 (10 [9%] *vs* 13 [12%]) and week 30 (22 [20%] *vs* 21 [19%]). At week 54, ADAs were detected in 22 [39%] in the CT-P13–CT-P13 group, 18 [33%] in the CT-P13–infliximab group, 21 [39%] in the infliximab–infliximab group, and 30 [55%] in the infliximab–CT-P13 group. Two [4%] patients in the CT-P13–CT-P13 group, three [5%] in the CT-P13–infliximab group, and seven [13%] in the infliximab–CT-P13 group (none in the infliximab–infliximab group) were ADA positive at week 54 but not at week 14 or 30. All newly ADA-positive patients had a very low ADA titre (dilution factor ≤8), none had infusion-related reactions, and there were no clinically meaningful changes in efficacy in these patients. Two patients were newly positive for NAbs at week 54 (one [2%] each in the CT-P13–CT-P13 and CT-P13–infliximab groups).

	CT-P13–CT-P13 (n=56)	CT-P13–infliximab (n=55)	CT-P13 up to week 30 (n=111)	Infliximab–infliximab (n=54)	Infliximab–CT-P13 (n=55)	Infliximab up to week 30 (n=109)
TEAEs*						
Total number of TEAEs	132	90	..	107	150	..
Patients with ≥1 TEAE	36 (64%)	34 (62%)	..	37 (69%)	40 (73%)	..
Treatment-related	17 (30%)	12 (22%)	..	17 (31%)	17 (31%)	..
Before switching	..	..	63 (57%)	..	..	70 (64%)
After switching	18 (32%)	15 (27%)	..	14 (26%)	21 (38%)	..
Patients with ≥1 TEAE leading to discontinuation	3 (5%)	3 (5%)	..	3 (6%)	3 (5%)	..
TESAEs						
Total number of TESAEs	5	4	..	5	8	..
Patients with ≥1 TESAE	4 (7%)	4 (7%)	..	4 (7%)	7 (13%)	..
Treatment-related	1 (2%)	1 (2%)	..	2 (4%)	1 (2%)	..
Before switching	..	..	6 (5%)	..	..	9 (8%)
After switching	1 (2%)	1 (2%)	..	0	2 (4%)	..

Data are n (%) in the safety population. TEAE=treatment-emergent adverse event. TESAE=treatment-emergent serious adverse event. There were no grade 4 events or deaths in any treatment group.

***Table 4*: Adverse events**

Discussion

This phase 3 RCT is, to our knowledge, the first investigation of the therapeutic efficacy of an infliximab biosimilar powered to show non-inferiority to infliximab in IBD and is the first to provide scientific evidence of extrapolation of a biosimilar monoclonal antibody. Non-inferiority was established because the 95% CI for the treatment difference in the primary endpoint (CDAI-70 response at week 6) fell within the prespecified margins, with a week-6 CDAI-70 response observed in 69·4% of CT-P13-treated patients and 74·3% of infliximab-treated patients. Performing analyses in the intention-to-treat population in non-inferiority trials could bias the results in favour of non-inferiority due to the inclusion of patients who might have discontinued or not adhered to treatment. Therefore, week 6 CDAI-70 response was also evaluated in the per-protocol population as a prespecified supportive analysis, as recommended in FDA guidance on non-inferiority trials.[21] Results in the per-protocol population at week 6 (response rates of 71·4% in the CT-P13 group and 75·2% in the infliximab group) were similar to those in the intention-to-treat population. Week 6 CDAI-70 responses in our study were also similar to those in the pivotal RCTs of infliximab in patients with Crohn's disease, including the study by Targan and colleagues[11] (81% at week 4) and ACCENT I (58·5% at week 2).[12] As with the primary endpoint, there were no notable differences between patients treated with CT-P13 or infliximab in CDAI-100 response and remission rates (CDAI <150) at weeks 6, 14, and 30 or CDAI-70 response at weeks 14 and 30.

Efficacy findings beyond week 30 (ie, after patients had switched or continued treatment) were broadly similar among the four groups, although this study was not powered to show statistical differences beyond week 30. These findings add to growing real-world evidence collected in patients with IBD,[22–24] and data from the phase 4 SECURE[25] and NOR-SWITCH trials.[26] SECURE, an open-label trial, demonstrated that serum concentrations with CT-P13 were non-inferior to serum concentrations with infliximab in patients with IBD 16 weeks after switching from infliximab to CT-P13.[25] Additionally, CT-P13 was considered to be well tolerated.[25] The NOR-SWITCH RCT demonstrated non-inferior efficacy of switching from infliximab to CT-P13 versus continued treatment with infliximab in patients with long-term immune-mediated diseases, including Crohn's disease, who were stably treated with infliximab on study entry.[26] However, NOR-SWITCH had some limitations, including that this study a disease worsening endpoint not previously used in similar studies; that switching between CT-P13 and infliximab was not controlled by an arm in which patients continued treatment with CT-P13; and that investigation of efficacy in IBD was only performed via post-hoc analysis. Additionally, NOR-SWITCH enrolled patients who had received infliximab for nearly 7 years and had low disease activity, whereas this study recruited patients with active disease who had not previously received biological drugs.

Mucosal healing is an important goal in IBD treatment, and is associated with reduced hospital admissions and surgery.[4] High CRP levels correlate with active disease, and persistently elevated levels suggest reduced or lost efficacy, and calprotectin is increasingly regarded as a surrogate biomarker for mucosal healing; both predict clinical relapse.[4] Therefore, it is reassuring that mean CRP and mean calprotectin levels decreased from baseline to week 6 and then remained stable in both CT-P13 and infliximab groups.

Treatments were well tolerated throughout our study. Across groups, broadly similar proportions of patients experienced at least one treatment-emergent adverse event (62–73%); rates of discontinuation due to treatment-emergent adverse events and treatment-emergent serious adverse events were also similar between groups. In patients who switched from CT-P13 to infliximab or vice versa at week 30, the incidence and severity of treatment-emergent adverse events were similar before and after switching. These results should assist clinicians in their decision making when considering switching stable patients to CT-P13 from infliximab.

At week 54, a substantial proportion of patients were ADA-positive, ranging from 33% to 55% across groups. The rate of ADA detection was higher than in previous studies such as ACCENT I, although this could be explained by the greater sensitivity of the ADA assay used in our study (0·533 ng/mL versus 630 ng/mL).[12] Although the proportion of ADA-positive patients seemed slightly higher in the infliximab–CT-P13 group, the similar safety and efficacy data among the groups suggest that any differences in immunogenicity did not impact treatment outcomes. There was no clinically meaningful difference in newly ADA-positive patients at week 54 between groups, and the proportion of patients positive for NAbs was also similar, and generally low, across groups.

A limitation of the study is that it was not powered to show statistically significant differences between groups for any secondary or tertiary endpoints, including those after week 30, limiting the extent to which data obtained at week 54 can be interpreted. Additionally, the duration of follow-up (22 weeks) after continuation or switch at week 30 might not be sufficient for differences to be observed.

Approval of CT-P13 by the EMA and FDA, including for Crohn's disease, was based on extrapolation of data, including comparative RCTs in patients with rheumatoid arthritis and ankylosing spondylitis.[14,15] Thus, CT-P13 was not specifically tested in patients with IBD before approval. Extrapolation of approval to non-studied indications has led to considerable debate, not least because it assumes that the mechanisms of action for infliximab are similar between indications. Although previous real-world and clinical study data have suggested that CT-P13 was non-inferior to infliximab for the treatment of Crohn's disease,[22–26] our study is, to our knowledge, the first phase 3 RCT to provide confirmatory evidence on the validity of the extrapolation process for an infliximab biosimilar in IBD.

CDAI is recognised as the gold standard for evaluation of treatment activity in Crohn's disease due to its rigorous development and wide use in clinical trials that have led to the regulatory approval of several novel treatments.[27] Despite this, concerns have been raised about the subjective nature of some CDAI items and the potential interobserver variation in interpretation of symptoms, although these limitations can be addressed by terminology education.[27,28] However, direct comparison with other clinical trials is often confounded by the wide variation in efficacy endpoints used. For example, CDAI-based clinical response may be defined as a decrease in CDAI of 70 or 100 points, and some trials use clinical remission (CDAI <150 points) as an endpoint.

To delineate the CDAI, which amalgamates PRO, laboratory changes, and physicians' assessments, recent trials in Crohn's disease have separated patient symptomatology (eg, by using the PRO-2 outcome measure, adapted from the CDAI)[19] and objective assessments of inflammation (eg, endoscopy). PROs are increasingly used as endpoints in clinical trials, but they have not been thoroughly evaluated in IBD.[29] Ideally, future trials will include PROs and objective measures of disease activity as coprimary endpoints. In our trial, the wide congruence between key endpoints, including a post-hoc analysis of PRO-2, supports similarity between CT-P13 and infliximab. More recent trials of biological drugs have used additional objective measures of disease activity, such as biomarkers (eg, CRP and calprotectin), endoscopy, and radiological evaluation of intestinal inflammation.[30]

Although TNF-targeted biological therapies have led to a paradigm shift in the clinical management of Crohn's disease, their high cost might be a barrier to treatment in some settings. Whether total cost savings can be achieved with the introduction of biosimilars such as CT-P13 will depend on market price and local price negotiations, as well as administration and monitoring costs. However, savings are expected; a budget impact model of CT-P13 in five European countries based on a discount of 10–30% predicted cumulative annual cost savings of £25·79–77·37 million for treatment of six inflammatory autoimmune diseases, including Crohn's disease.[31]

In conclusion, this phase 3 RCT showed the therapeutic non-inferiority of CT-P13 to infliximab in patients with active Crohn's disease. The results show that CT-P13 was well tolerated, with a similar safety profile to infliximab, and no clinically meaningful differences in immunogenicity.

Contributors

BDY, SYL, SS, and Y-HK were involved in conception and design of the study and analysis and interpretation of the data. JHC was involved in conception and design of the study. HUK was involved in design of the study and interpretation of the data. BDY, MP, OA, MO, AL, AD, SF, OL, JHC, MLS, R-BM, K-ML, SS, and Y-HK were involved in acquisition of data. SJL was involved in statistical modelling and analysis and statistical inference of study data. OA, CSE, HF, and RC were involved in interpretation of data. All authors reviewed drafts of the manuscript and approved the final version.

Declaration of interests

BDY reports personal fees and non-financial support from Celltrion during the conduct of the study and personal fees from Abbvie Korea, Cornerstones Health, Ferring Korea, IQVIA, Janssen Korea, Kangstem Biotech, Kuhnil Pharm, Robarts Clinical Trials, Shire Korea, and Takeda Korea outside the submitted work. AL reports consultancy and lecture fees from Takeda and lecture fees from Abbvie, Celltrion, and Janssen outside the submitted work. MLS reports advisory board fees from

Janssen, Mundipharma, and Pfizer and advisory board and speaker fees from Abbvie and Takeda outside the submitted work. R-BM reports personal fees from Amgen outside the submitted work; personal fees and non-financial support from Abbvie, Alfa Sigma, Alvogen, Dr Reddys, Egis Pharmaceutical, MSD, and Takeda outside the submitted work; and grants from Abbvie outside the submitted work. K-ML reports consultancy and lecture fees from Takeda and consultancy fees from Celltrion outside the submitted work. CSE reports consultancy and lecture fees from Celltrion outside the submitted work. SJL is an employee of, and has stock options for, Celltrion. SYL and HUK are employees of Celltrion. SS reports consulting (advisory board) fees from AbbVie, Biogen/Samsung, Boehringer Ingelheim, Celltrion, Merck, Pfizer, Sandoz, Shire, and UCB outside the submitted work. HF reports consultancy fees from Pfizer UK Limited during the conduct of the study and consultancy fees from Pfizer UK Limited outside the submitted work. RC is an employee of Pfizer. Y-HK reports personal fees from Celltrion during the conduct of the study and personal fees from Chong Kun Dang Pharm, Eisai Korea, Ferring Korea, Janssen Korea, Shire Korea, and Takeda Korea outside the submitted work. MP, OA, MO, AD, SF, OL, and JHC declare no competing interests.

Data sharing

De-identified participant data from the study are freely available through ClinicalTrials.gov, number NCT02096861, and the EU Clinical Trials Register, EudraCT number 2013-004497-10. Data were made available on the EU Clinical Trials Register in March, 2018, and on ClinicalTrials.gov in April, 2018. Additional documents related to the study (eg, study protocol, statistical analysis plan, and informed consent form) will not be available.

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