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ORIGINAL RESEARCH ARTICLE

Subcutaneous Infliximab Monotherapy Versus Combination Therapy with Immunosuppressants in Inflammatory Bowel Disease: A Post Hoc Analysis of a Randomised Clinical Trial

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Abstract

Background and Objective Whether benefits and risks of intravenous (IV) infliximab combotherapy with immunosuppressants versus infliximab monotherapy apply to subcutaneous (SC) infliximab is unknown. This post hoc analysis of a pivotal randomised CT-P13 SC 1.6 trial aimed to compare SC infliximab monotherapy with combotherapy in inflammatory bowel disease (IBD).

Methods Biologic-naïve patients with active Crohn's disease or ulcerative colitis received CT-P13 IV 5 mg/kg at Week (W) 0 and 2 (dose-loading phase). At W6, patients were randomised (1:1) to receive CT-P13 SC 120 or 240 mg (patients < 80 or ≥ 80 kg) every 2 weeks until W54 (maintenance phase), or to continue CT-P13 IV every 8 weeks until switching to CT-P13 SC from W30. The primary endpoint—non-inferiority of trough serum concentrations—was assessed at W22. We report a post hoc analysis comparing pharmacokinetic, efficacy, safety and immunogenicity outcomes up to W54 for patients randomised to CT-P13 SC, stratified by concomitant immunosuppressant use.

Results Sixty-six patients were randomised to CT-P13 SC (37 monotherapy, 29 combotherapy). At W54, there were no significant differences in the proportions of patients achieving target exposure (5 µg/mL; 96.6% monotherapy vs 95.8% combotherapy; $p > 0.999$) or meeting efficacy or biomarker outcomes including clinical remission (62.9% vs 74.1%; $p = 0.418$). Monotherapy and combotherapy groups had comparable immunogenicity (anti-drug antibodies [ADAs]: 65.5% vs 48.0% [$p = 0.271$], neutralising antibodies [in ADA-positive patients]: 10.5% vs 16.7% [$p = 0.630$], respectively).

Conclusions Pharmacokinetics, efficacy and immunogenicity were potentially comparable between SC infliximab monotherapy and combotherapy in biologic-naïve IBD patients.

Trial Registration ClinicalTrials.gov: NCT02883452.

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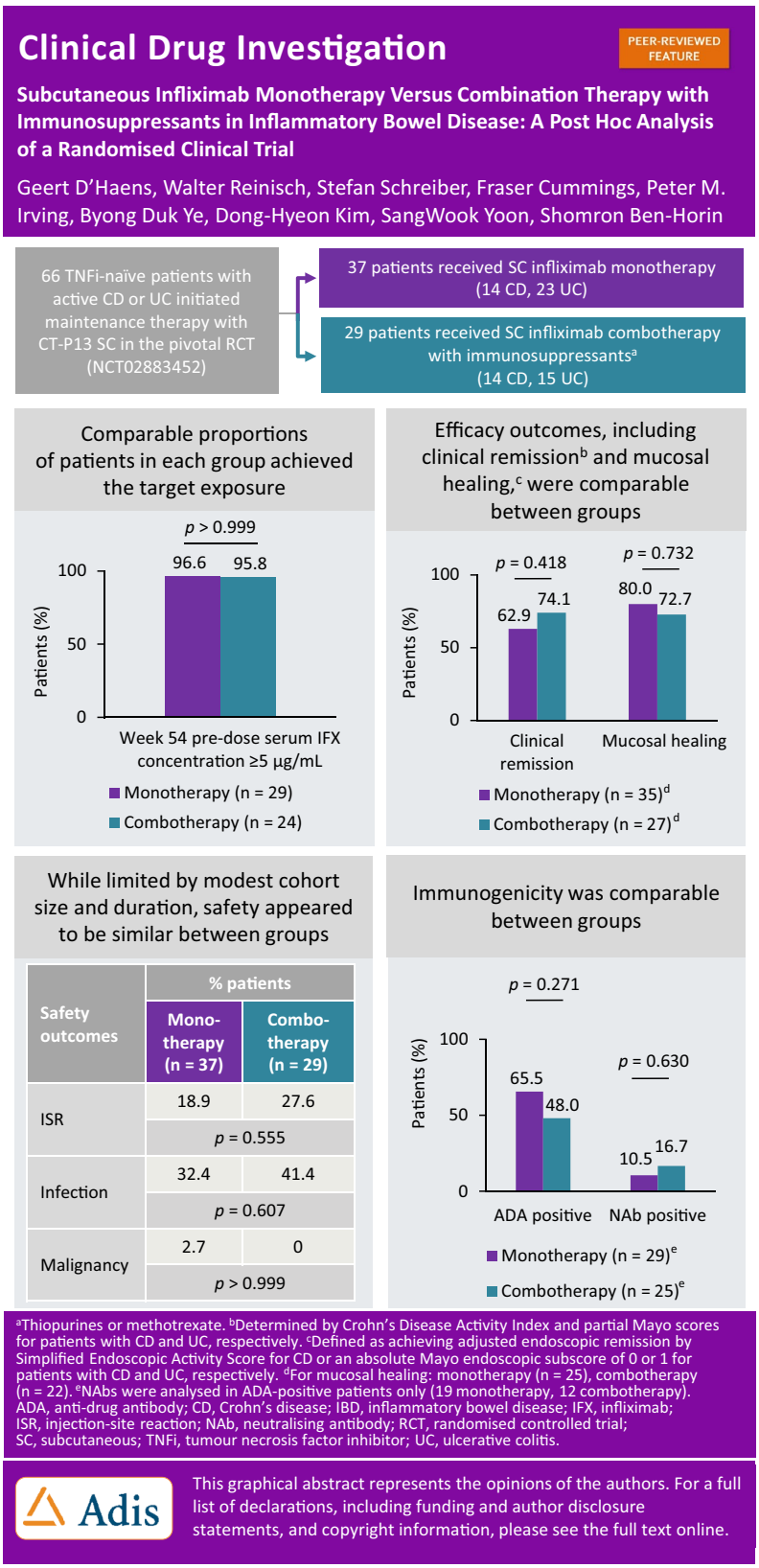
Graphical Abstract



Key Points

Intravenous infliximab combination with immunosuppressants (combotherapy) is more efficacious than monotherapy for biologic-naïve inflammatory bowel disease patients, but it is not known whether this applies to subcutaneous (SC) infliximab treatment.

Clinical outcomes—comprising pharmacokinetics, efficacy and immunogenicity—were comparable with SC infliximab monotherapy and combotherapy in tumour necrosis factor inhibitor-naïve patients with inflammatory bowel disease.

If corroborated by larger studies, this analysis could be regarded as initial evidence that SC infliximab combotherapy is not superior to SC infliximab monotherapy, paving the way to use potentially safer monotherapy treatment options for patients with inflammatory bowel disease.

1 Introduction

The tumour necrosis factor inhibitor (TNFi) infliximab is recommended in guidelines for first- or second-line biologic therapy for inflammatory bowel disease (IBD), which comprises Crohn's disease (CD) and ulcerative colitis (UC) [1–4]. Although the prescribing information for reference infliximab does not contain specific recommendations on the concomitant use of immunosuppressants when treating patients with CD or UC [5, 6], infliximab may be used in combination with immunosuppressants such as azathioprine, 6-mercaptopurine, or methotrexate [7, 8], in line with treatment guidelines [1–4]. Meta-analyses of clinical trial data and studies of real-life cohorts of patients with IBD have yielded conflicting results as to whether combotherapy with intravenous (IV) infliximab and an immunosuppressant offers clinical benefits in terms of efficacy compared with IV infliximab monotherapy [9–13]. However, in immunosuppressant- and biologic-/TNFi-naïve patients with moderate to severe CD or UC, randomised controlled trials and cohort studies have shown that initiating combotherapy is associated with improved outcomes, when compared with IV infliximab monotherapy [14–17], with the benefits of combotherapy related to increased serum infliximab levels [18]. In addition, combotherapy is associated with protection from developing immunogenicity to IV infliximab [17].

Subcutaneous (SC) CT-P13 (CT-P13 SC) is the first SC infliximab product to receive regulatory approval in Europe, which was initially obtained for the treatment of rheumatoid arthritis [19, 20]. Regulatory approval was later extended to other rheumatic diseases and IBD indications on the basis of the pivotal randomised controlled CT-P13 SC 1.6 study (NCT02883452), which compared CT-P13 SC and CT-P13 IV treatment in patients with active CD or UC [21, 22]. Part 2 of this study demonstrated pharmacokinetic non-inferiority of CT-P13 SC to CT-P13 IV, and suggested comparability of efficacy, safety, and immunogenicity profiles between treatment arms [22]. CT-P13 SC also offered potential pharmacokinetic benefits compared with CT-P13 IV, with trough serum concentrations (C_{trough}) relatively stable and consistently maintained above the generally accepted target exposure [22]. Consequently, SC infliximab has been perceived by an expert panel as a biobetter based on the potential clinical benefits over IV infliximab, particularly in terms of pharmacokinetics [23]. Subcutaneous infliximab was also shown to elicit similar, if not potentially slightly diminished, immunogenicity compared with IV infliximab [24, 25].

Whether the advantages of combining an immunosuppressant with IV infliximab are also true for combotherapy with SC infliximab and immunosuppressants has not hitherto been addressed. Therefore, we conducted a post hoc analysis to compare the efficacy of SC infliximab monotherapy versus combotherapy with immunosuppressants, using data from the pivotal trial.

2 Methods

The primary study was conducted according to International Council for Harmonisation guidelines and following the principles of the Declaration of Helsinki and all applicable national, state, and local laws [22]. The protocol and written study materials were approved by institutional review boards/independent ethics committees prior to study initiation [22]. All patients provided written informed consent [22]. Individual participant data are not available to be shared. The original study was pre-registered (ClinicalTrials.gov: NCT02883452) but this post hoc analysis was not.

Patients were enrolled in this open-label, randomised, multicentre, parallel-group Phase 1 study at 50 sites in 15 countries, as previously reported [22]. Full eligibility criteria have been reported; briefly, biologic-naïve patients (aged 18–75 years) with active CD or UC, who had a disease duration of ≥ 3 months and had not responded to an adequate course of conventional therapy, were enrolled in the study [22]. Patients received CT-P13 IV 5 mg/kg at Weeks 0 and 2 (dose-loading phase), and were then randomised (1:1) at Week 6 (maintenance phase) to continue therapy with CT-P13 IV every 8 weeks (until Week 30 when patients switched to receive CT-P13 SC) or CT-P13 SC 120 mg

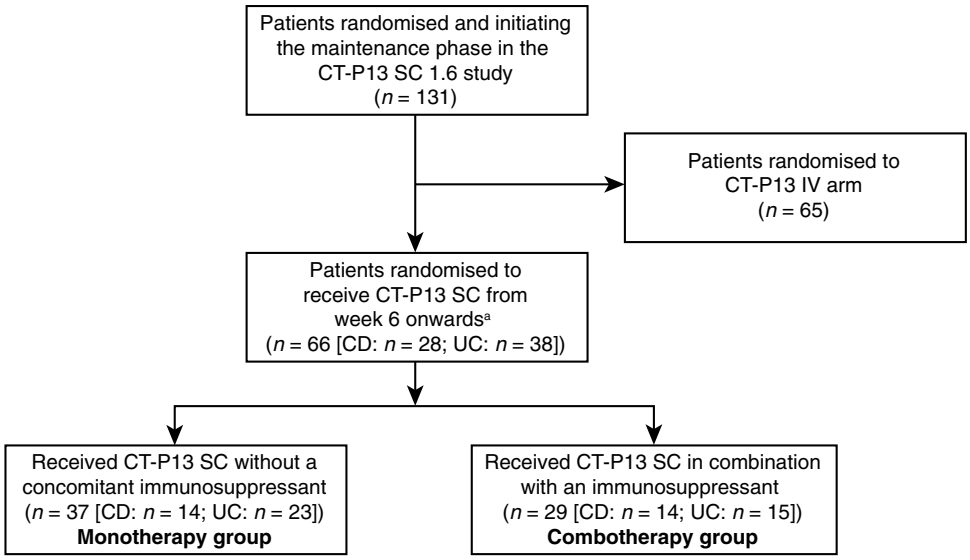


Fig. 1 Patient disposition, updated from Schreiber et al [22]. [a]Based on body weight at Week 6, patients received CT-P13 SC 120 mg Q2W (for patients weighing < 80 kg) or CT-P13 SC 240 mg Q2W (for patients weighing ≥ 80 kg). *CD* Crohn's disease, *IV* intravenous, *SC* subcutaneous, *Q2W* every 2 weeks, *UC* ulcerative colitis

(patients weighing < 80 kg) or 240 mg (patients weighing ≥ 80 kg) every 2 weeks from Weeks 6 to 54 (Fig. 1) [22]. Randomisation was stratified by use of immunosuppressant treatment (yes vs no), disease type (UC vs CD), clinical response at Week 6 (yes vs no), and body weight at Week 6 (< 80 kg vs ≥ 80 kg) [22]. Patients could receive concomitant immunosuppressants provided the dose remained unchanged throughout the study and had been stable for ≥ 8 weeks (thiopurines) or ≥ 6 weeks (methotrexate) prior to first infliximab administration [22].

The primary endpoint of the original study was non-inferiority of C_{trough} of CT-P13 at Week 22 for CT-P13 SC versus CT-P13 IV; this has been previously reported [22]. The present post hoc analysis included only patients who received CT-P13 SC from Week 6 onwards and compared pharmacokinetic, efficacy, safety, and immunogenicity endpoints up to Week 54 for patients who received CT-P13 SC alone (monotherapy group) versus patients who received CT-P13 SC in combination with immunosuppressants (combotherapy group). For pharmacokinetic assessment, infliximab pre-dose concentration at all study visits was measured using Meso Scale Discovery electrochemiluminescence (Meso Scale Diagnostics, LLC, Rockville, MD, USA) [22, 26]. Bioanalytical methods were validated according to European Medicines Agency guidelines and assay performance for the measurement of infliximab was appropriately demonstrated [19]. The therapeutic target exposure of 5 µg/mL (as suggested by the American Gastroenterological Association) [27] was defined as an exploratory endpoint [22]. Efficacy assessments were performed prior to infliximab treatment at all study visits (other than the pharmacokinetic monitoring visit) and included Crohn's Disease Activity Index (CDAI) score for patients with CD and partial Mayo score for patients with UC [22]. Colonoscopy or sigmoidoscopy were performed at screening, Week 22, and Week 54 (or the end-of-study visit), and scored for Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) in patients with CD or for Mayo endoscopic sub-score in patients with UC [22]. For patients with CD, CDAI-100 response was defined as a decrease in CDAI score of ≥ 100 points from baseline [22]. For patients with UC, partial Mayo response was defined as a decrease in partial Mayo score of ≥ 2 points compared with baseline, plus a decrease in the sub-score for rectal bleeding of ≥ 1 point, or an absolute sub-score for rectal bleeding of 0 or 1 [22]. In this analysis, mucosal healing in patients with CD was defined as achieving adjusted endoscopic remission by SES-CD, with an absolute overall SES-CD score of ≤ 2 points in patients who had confirmed mucosal abnormalities (overall SES-CD score > 0) at baseline. For patients with UC, mucosal healing was defined as an absolute Mayo endoscopic sub-score of 0 or 1 [22]. C-reactive protein (CRP) and faecal calprotectin (FC) levels were evaluated at all study visits (apart from the pharmacokinetic monitoring visit) [22]. Safety outcomes evaluated were the number of patients experiencing an injection-site reaction, infection, or malignancy, which may have occurred during either CT-P13 IV induction or CT-P13 SC maintenance therapy. Serum samples that were obtained pre-dose at each treatment visit (except at Week 2) were also analysed for immunogenicity (anti-drug antibodies [ADAs] and neutralising antibodies [NAbs]) using drug-tolerant electrochemiluminescence assays with affinity capture elution steps (Celltrion, Inc., Incheon, Republic of Korea) [22]. Anti-drug antibody concentrations ≥ 25 ng/mL were detectable in the presence of 120 µg/mL serum infliximab; NAb concentrations ≥ 1000 ng/mL were detectable with 40 µg/mL serum infliximab [22].

The sample size for the primary study endpoint has been previously described [22]. For this post hoc analysis, patients with available data at relevant time points were included in each analysis. For Week 54 clinical response and remission analyses (determined by CDAI and partial Mayo scores) and pharmacodynamic outcomes (FC and CRP), missing values for patients who had discontinued the study due to lack of/or insufficient efficacy or due to disease progression were imputed as non-responders. Statistical comparisons between monotherapy and combotherapy groups used the Fisher exact test for categorical variables or the Mann-Whitney *U* test for continuous variables. Differences are reported in a descriptive manner. Statistical analyses were conducted using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

3 Results

3.1 Patients

Overall, 136 patients were enrolled in the study after screening between 27 March 2018 and 8 August 2018, with follow-up concluding on 17 January 2020 [22]. Sixty-six of these patients were randomised to receive CT-P13 SC from Week 6 onwards and were included in the current analysis, comprising 37 patients in the monotherapy group and 29 patients in the combotherapy group (Fig. 1). Other than concomitant immunosuppressant use, demographics and baseline disease characteristics were comparable between the monotherapy and combotherapy groups (Table 1). Most patients (96.6%) in the combotherapy group were receiving concomitant

Table 1 Baseline characteristics for patients who received CT-P13 SC without a concomitant immunosuppressant (monotherapy group) or in combination with immunosuppressants (combotherapy group)

Characteristic	Monotherapy ($n = 37$)	Combotherapy ($n = 29$)	*P* value
Sex, *n* (%)			> 0.999[a]
Male	20 (54.1)	16 (55.2)	
Female	17 (45.9)	13 (44.8)	
Age, years, mean (SD)	37.9 (15.3)	37.7 (15.1)	0.992[b]
Race, *n* (%)			> 0.999[c]
White	35 (94.6)	27 (93.1)	
Asian	2 (5.4)	1 (3.45)	
Other	0	1 (3.45)[d]	
Body weight, kg, mean (SD)	67.9 (14.0)	71.4 (15.1)	0.358[b]
Disease duration, years, mean (SD)	5.28 (5.11)	6.24 (7.06)	0.603[b]
Serum albumin, g/L, mean (SD)	42.6 (4.38)	43.5 (5.55)	0.194[b]
Disease activity, mean (SD)			
CDAI score[e]	310.8 (60.6)	282.0 (56.2)	0.208[b]
SES-CD[f]	11.5 (8.31)	12.4 (10.6)	0.984[b]
Partial Mayo score[g]	5.43 (1.24)	5.47 (1.46)	0.826[b]
Total Mayo score[g]	7.91 (1.38)	7.87 (1.51)	0.920[b]
C-reactive protein, mg/dL, median (IQR)	0.35 (0.18–0.56)	0.30 (0.08–0.69)	0.379[b]
Faecal calprotectin, µg/g, median (IQR)	1074 (470–1842)	856 (204–1525)	0.418[b]
Concomitant immunosuppressant, n (%)			N/A
Azathioprine	0	27 (93.1)	
6-mercaptopurine	0	1 (3.45)	
Methotrexate	0	1 (3.45)	

CD Crohn's disease, *CDAI* Crohn's Disease Activity Index, *IQR* interquartile range, *N/A* not applicable, *SC* subcutaneous, *SD* standard deviation, *SES-CD* Simplified Endoscopic Activity Score for Crohn's Disease, *UC* ulcerative colitis

[a]Fisher exact test

[b]Mann-Whitney U test

[c]Fisher exact test between White and Asian/Other

[d]Patient was Moroccan

[e]Patients with CD: monotherapy, $n = 14$; combotherapy, $n = 14$

[f]Patients with CD: monotherapy, $n = 13$; combotherapy, $n = 14$

[g]Patients with UC: monotherapy, $n = 23$; combotherapy, $n = 15$

thiopurines at Week 6 (the inception of the current post hoc analysis); only one patient was receiving methotrexate.

3.2 Pharmacokinetics

In both groups, mean pre-dose serum infliximab concentrations at or approaching peak values were reached at Week 2, with a slight decrease in concentrations observed at Week 6 (Fig. 2). For the remainder of the study period (from Week 14 to Week 54), mean pre-dose concentrations remained relatively consistent in both groups, within the bounds of 18.8 µg/mL to 23.7 µg/mL. Mean pre-dose concentrations exceeded the target exposure (5 µg/mL) throughout the study period (from Week 2 onwards), regardless of whether or not patients were receiving concomitant immunosuppressant therapy. Moreover, there was no significant difference between the monotherapy and combotherapy groups in terms of the proportion of patients with pre-dose concentration exceeding the target exposure at Week 54 (28/29 [96.6%] vs 23/24 [95.8%]; $p > 0.999$; Table 2).

3.3 Efficacy

There was no significant difference between the monotherapy and combotherapy groups in terms of clinical response rates at Week 54, assessed by CDAI-100 response and partial Mayo score for patients with CD and UC, respectively ($p = 0.673$ and $p = 0.628$, respectively; Table 2; Fig. S1a, b in the Electronic Supplementary Material [ESM]). There were no significant differences between groups in the proportions of patients achieving clinical remission (monotherapy: 22/35 [62.9%] vs 20/27 [74.1%]; $p = 0.418$; Table 2; Fig S1c in the ESM), mucosal healing (20/25 [80.0%] vs 16/22 [72.7%]; $p = 0.732$; Table 2; Fig. S1d), normal CRP levels (26/35 [74.3%] vs 22/27 [81.5%]; $p = 0.555$; Table 2; Fig. S1e), and normal FC levels (10/33 [30.3%] vs 5/24 [20.8%]; $p = 0.547$; Table 2; Fig. S1f) at Week 54.

Mean absolute values and changes from baseline in CDAI and partial Mayo scores were also comparable between monotherapy and combotherapy groups throughout the study (Fig. 3).

3.4 Safety

There were no significant differences between the monotherapy and combotherapy groups in terms of the incidence of injection-site reactions ($p = 0.555$), infections ($p = 0.607$), or malignancy ($p > 0.999$) (Table 2). However, there were numerical differences between groups in the proportion of patients experiencing injection-site reactions (monotherapy: 7/37 [18.9%] vs combotherapy: 8/29 [27.6%]) and infection (12/37 [32.4%] vs 12/29 [41.4%]).

3.5 Immunogenicity

Despite the use of concomitant immunosuppressants in the combotherapy group, the incidence of immunogenicity did not differ between groups when assessed using a drug-tolerant assay (Table 2; Fig. S2 in the ESM). Specifically, the proportion of ADA-positive patients was 65.5% (19/29) in the monotherapy group and 48.0% (12/25) in the combotherapy group ($p = 0.271$). The proportion of NAb positivity among ADA-positive patients was 10.5% (2/19) in the monotherapy group and 16.7% (2/12) in the combotherapy group ($p = 0.630$).

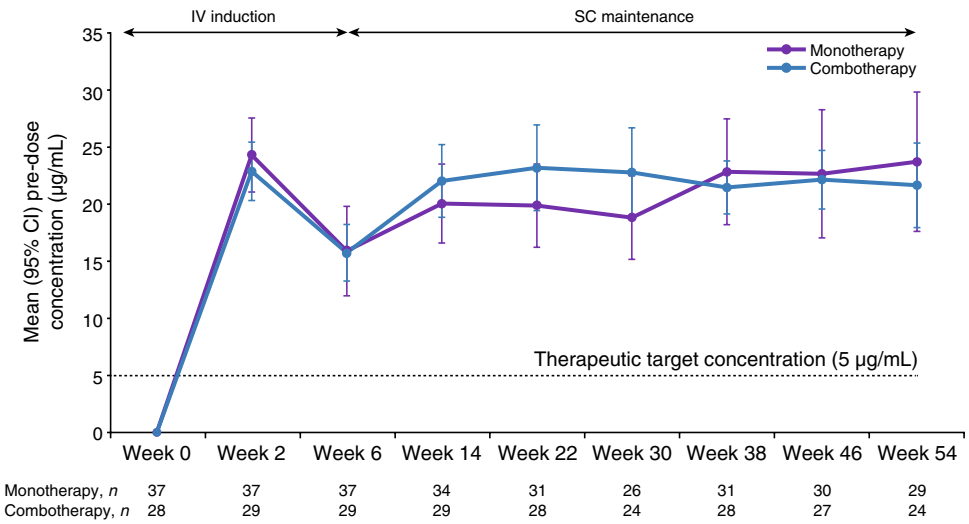


Fig. 2 Mean (95% CI) pre-dose concentration for CT-P13 SC up to Week 54. Patients with available data at the respective week were analysed. Concentrations below the lower limit of quantification before Week 0 were set to zero; other concentrations below the lower limit of quantification were set to the lower limit of quantification. *CI* confidence interval, *IV* intravenous, *SC* subcutaneous

Table 2 Pharmacokinetic, efficacy, safety, and immunogenicity outcomes at Week 54 for patients who received CT-P13 SC without a concomitant immunosuppressant (monotherapy group) or in combination with immunosuppressants (combotherapy group)

Outcome, *n/N* (%)	Indication	Monotherapy	Combotherapy	Difference, % (95% CI)	*P* value
Pharmacokinetics[a,b]					
Pre-dose serum infliximab concentration ≥ target exposure	CD + UC	28/29 (96.6)	23/24 (95.8)	0.7 (− 9.7, 11.1)	> 0.999
Pre-dose serum infliximab concentration < target exposure		1/29 (3.4)	1/24 (4.2)		
Efficacy[c]					
CDAI-100 response	CD	8/13 (61.5)	10/13 (76.9)	− 15.4 (− 50.4, 19.6)	0.673
CDAI-100 non-response		5/13 (38.5)	3/13 (23.1)		
Partial Mayo response	UC	18/22 (81.8)	13/14 (92.9)	− 11.0 (− 32.1, 10.0)	0.628
Partial Mayo non-response		4/22 (18.2)	1/14 (7.1)		
Clinical remission achieved	CD + UC	22/35 (62.9)	20/27 (74.1)	− 11.2 (− 34.2, 11.8)	0.418
Clinical remission not achieved		13/35 (37.1)	7/27 (25.9)		
Mucosal healing achieved	CD + UC	20/25 (80.0)	16/22 (72.7)	7.3 (− 17.1, 31.6)	0.732
Mucosal healing not achieved		5/25 (20.0)	6/22 (27.3)		
CRP normal (≤ 0.50 mg/dL)	CD + UC	26/35 (74.3)	22/27 (81.5)	− 7.2 (− 27.8, 13.4)	0.555
CRP high (> 0.50 mg/dL)		9/35 (25.7)	5/27 (18.5)		
FC normal (≤ 50 µg/g)	CD + UC	10/33 (30.3)	5/24 (20.8)	9.5 (− 13.1, 32.0)	0.547
FC high (> 50 µg/g)		23/33 (69.7)	19/24 (79.2)		
Safety[d]					
Injection-site reaction	CD + UC	7/37 (18.9)	8/29 (27.6)	− 8.7 (− 29.3, 11.9)	0.555
No injection-site reaction		30/37 (81.1)	21/29 (72.4)		
Infection	CD + UC	12/37 (32.4)	12/29 (41.4)	− 8.9 (− 32.4, 14.5)	0.607
No infection		25/37 (67.6)	17/29 (58.6)		
Malignancy	CD + UC	1/37 (2.7)[e]	0/29 (0.0)	2.7 (− 2.5, 7.9)	> 0.999
No malignancy		36/37 (97.3)	29/29 (100.0)		
Immunogenicity[a]					
ADA positive	CD + UC	19/29 (65.5)	12/25 (48.0)	17.5 (− 8.6, 43.6)	0.271
ADA negative		10/29 (34.5)	13/25 (52.0)		
NAb positive[f]	CD + UC	2/19 (10.5)	2/12 (16.7)	− 6.1 (− 31.3, 19.1)	0.630
NAb negative[f]		17/19 (89.5)	10/12 (83.3)		

ADA anti-drug antibody, *CD* Crohn's disease, *CDAI* Crohn's Disease Activity Index, *CI* confidence interval, *CRP* C-reactive protein, *FC* faecal calprotectin, *NAb* neutralising antibody, *SC* subcutaneous, *UC* ulcerative colitis

[a]Patients with available data at Week 54 were analysed

[b]Target serum infliximab exposure was 5 µg/mL

[c]Patients who ended the study early due to a lack of efficacy, or insufficient efficacy, were considered to be non-responders and to have high CRP and FC levels; mucosal healing was assessed as observed

[d]Safety outcomes were observed from Week 0 to 54

[e]One patient experienced a treatment-emergent serious adverse event of non-small cell lung cancer after Week 50, which led to discontinuation of study treatment

[f]NAbs were analysed among ADA-positive patients only

4 Discussion

In this post hoc analysis of patients in the CT-P13 SC arm of Part 2 of the pivotal CT-P13 SC 1.6 study, pharmacokinetic, efficacy, and immunogenicity outcomes were comparable between patients with CD or UC who received either CT-P13 SC monotherapy or CT-P13 SC in combination with an immunosuppressant. To our knowledge, the present analysis provides the first insights into the potential clinical comparability of SC infliximab monotherapy and combotherapy with immunosuppressants.

Previous research has demonstrated that combotherapy with IV infliximab and an immunosuppressant can improve outcomes for immunosuppressant- and biologic-/TNFi-naïve

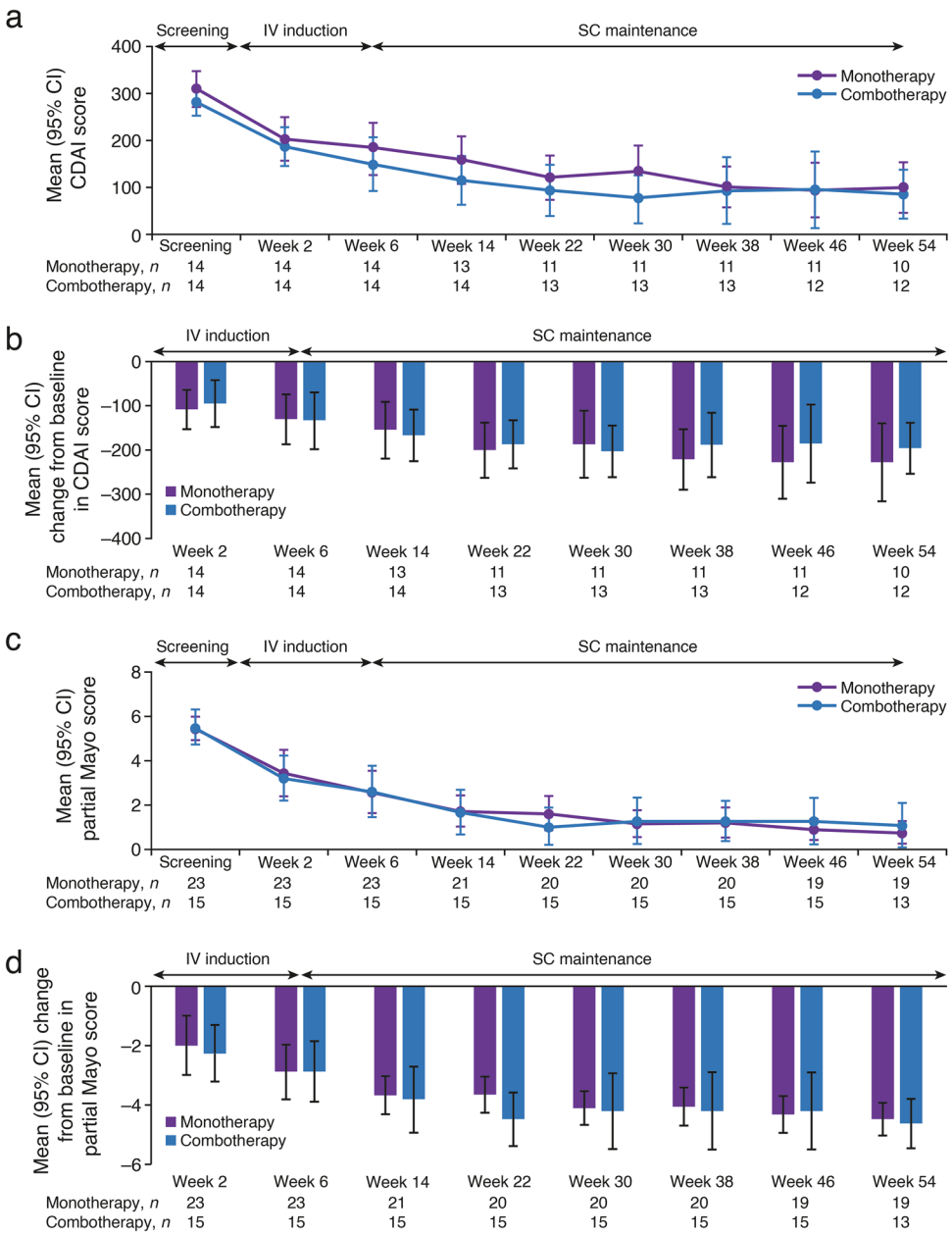


Fig. 3 Efficacy outcomes up to Week 54. **a** Mean CDAI score, **b** CDAI change from baseline, **c** mean partial Mayo score, **d** partial Mayo score change from baseline. Patients with available data at the respective week were analysed. *CDAI* Crohn's Disease Activity Index, *CI* confidence interval, *IV* intravenous, *SC* subcutaneous

patients with IBD, relative to infliximab monotherapy [12, 14–17]. However, some studies have reported that combotherapy may not improve clinical effectiveness compared with monotherapy [9–11], including specifically for patients who have had an inadequate response to immunosuppressant treatment [9, 10]. The association between higher infliximab C_{trough} and combotherapy (vs IV infliximab monotherapy) is well established [17, 18, 28–30], although not all analyses have found differences in C_{trough} values between patients receiving combotherapy and those receiving monotherapy [31]. There is also strong evidence, including from the PANTS study, for a link between combotherapy and reduced immunogenicity of IV infliximab [17, 18, 28, 30]. In turn, this is associated with an improved pharmacokinetic profile and efficacy outcomes [13, 18]. A post hoc analysis of the SONIC study showed that, among patients who achieved high trough drug levels with IV infliximab, there were no significant differences in efficacy outcomes between those who did and did not receive concomitant immunosuppressants [18]. Our current results are in line with and extend these observations by showing that the pharmacokinetic profile and higher pre-dose concentrations achieved with SC infliximab therapy (compared with IV infliximab [22, 23]) may potentially translate into comparable efficacy for SC infliximab-treated patients, regardless of whether they receive concomitant immunosuppressants [22, 23].

In our analysis, overall immunogenicity was comparable between groups. Specifically, rates of total ADAs were

numerically higher in the monotherapy group versus the combotherapy group but were not significantly different. Moreover, the rate of NAb positivity, which is more instrumental in mediating clinically relevant immunogenicity [32] and can impact efficacy more directly [33, 34], was similar or even numerically lower in the monotherapy compared with the combotherapy group (6.9% vs 8.0% of the overall group, respectively). It may be hypothesised that the high and stable serum infliximab (antigen) concentrations mediated by SC infliximab administration inhibit the induction of ADAs through high-zone tolerance, or a favourable infliximab-to-TNF ratio may reduce the formation of immune complexes and, consequently, ADAs [22]. This may reduce immune activation towards the drug, thereby dampening production of high-affinity ADAs or NAbs [22, 34], resulting in the observed comparability of immunogenicity between groups, even when assessed using a drug-tolerant assay.

Although the modest cohort size and limited exposure time preclude firm conclusions about safety, SC infliximab monotherapy may conceivably be associated with reduced risks of infection and malignancy relative to combotherapy with immunosuppressants as was previously reported in studies considering the IV infliximab formulation [9, 35, 36]. While it is debatable whether TNFi monotherapy is associated with an increased risk of lymphoproliferative disease in patients with IBD [37], it will be important to collect further data on this topic in patients with IBD receiving infliximab SC monotherapy. In addition, monotherapy may offer additional advantages by reducing the pill burden that has been associated with non-adherence to treatments for IBD [38, 39]. Avoiding combotherapy with thiopurines may also lead to a reduced risk of developing severe COVID-19 [40], further incentivising to explore ways to optimise monotherapy strategies.

The current findings are limited by the exploratory nature of the post hoc analyses conducted and the modest sample size that may render it underpowered to detect small differences; as such, the findings should be interpreted with caution. In addition, since all but one patient included in the combotherapy group received a thiopurine, results may not be representative for patients receiving other immunosuppressants, such as methotrexate; while this is well aligned with immunosuppressant usage in routine clinical practice, future studies should aim to enrol more patients receiving methotrexate as a component of combotherapy. The generalisability of our findings to clinical practice could be impacted by the TNFi-naïve study population [22], as prior biologic exposure may be associated with reduced efficacy due to the development of immunogenicity [33]. Finally, while no histological outcomes were included in the present post hoc analysis, the endpoint definitions employed were consistent with those used in the primary analysis of the study [22]. Acknowledging these limitations, our study provides valuable initial insights into the pharmacokinetics, efficacy, safety, and immunogenicity of CT-P13 SC monotherapy versus immunosuppressant combotherapy, opening up avenues for further investigation. However, larger comparative studies are warranted.

5 Conclusion

Subcutaneous infliximab monotherapy may provide comparable clinical efficacy, pharmacokinetics, and immunogenicity to combotherapy with immunosuppressants in TNFi-naïve patients with active CD or UC. Larger comparative studies are needed to confirm these observations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-023-01252-z.

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Declarations

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Conflicts of interest Geert D'Haens has served as a speaker for AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Celltrion, Eli Lilly, Galapagos, Immunic, Johnson and Johnson, and Pfizer; served on a Data Safety Monitoring Board for AbbVie, Ablynx, Allergan, AstraZeneca, Galapagos, GlaxoSmithKline, and Seres Health; served as a consultant for AbbVie, Agomab, AM Pharma, AMT, Arena Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Exeliom Biosciences, Exo Biologics, Galapagos, Gilead, GlaxoSmithKline, Gossamerbio, Immunic, Index Pharmaceuticals, Johnson and Johnson, Kaleido, Origo, Pfizer, Polpharma, Procise Diagnostics, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist, and Roche; and received grants or contracts from AbbVie, Bristol Myers Squibb, Helmsley Foundation, Pfizer, and Takeda. Walter Reinisch has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, Celltrion, Falk Pharma, Ferring, Janssen, Medice, Mitsubishi Tanabe Pharma Corporation, MSD, Pfizer, Pharmacosmos, PLS Education, Roche, Shire, Takeda, Therakos, and Vifor; served as a consultant for AbbVie, Algernon, Amgen, Arena Pharmaceuticals, Astellas, AstraZeneca, Bioclinica, Boehringer Ingelheim, Bristol Myers Squibb, Calyx, Celgene, Celltrion, Eli Lilly, Ernst & Young, Falk Pharma, Ferring, Fresenius, Galapagos, Gatehouse Bio, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Intrinsic Imaging, Janssen, Johnson & Johnson, Landos Biopharma, LivaNova, Mallinckrodt, Medahead, MedImmune, Mitsubishi Tanabe Pharma Corporation, MSD, Nash Pharmaceuticals, Nestle, Novartis, OMass, Otsuka, Parexel, Periconsulting, Pfizer, Pharmacosmos, Prometheus, Protagonist, Provention, Quell Therapeutics, Robarts Clinical Trial, Roche, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics,

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Data Availability The data underlying this article are available in the article and in its online supplementary material. The individual participant data cannot be shared publicly for the privacy of individuals.

Code Availability Not applicable.

Ethics Approval This post hoc analysis is based on the primary study (NCT02883452) that was conducted according to International Council for Harmonisation guidelines and following the principles of the Declaration of Helsinki and all applicable national, state, and local laws. The protocol and written study materials were approved by institutional review boards/independent ethics committees prior to study initiation.

Consent to Participate All patients provided written informed consent.

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Authors' Contributions GD'H: Conceptualisation (lead), methodology (lead), supervision (lead), visualisation (equal), writing—original draft (equal), and writing—reviewing and editing (equal). WR: conceptualisation (equal), methodology (equal), writing—original draft (equal), and writing—reviewing and editing (equal). SS: conceptualisation (equal), methodology (equal), writing—original draft (equal), and writing—reviewing and editing (equal). FC: conceptualisation (equal), methodology (equal), writing—original draft (equal), and writing—reviewing and editing (equal). PMI: conceptualisation (equal), methodology (equal), writing—original draft (equal), and writing—reviewing and editing (equal). BDY: conceptualisation (equal), methodology (equal), writing—original draft (equal), and writing—reviewing and editing (equal). D-HK: conceptualisation (equal), formal analysis (lead), methodology (equal), validation (lead), writing—original draft (equal), and writing—reviewing and editing (equal). SWY: conceptualisation (equal), formal analysis (lead), methodology (equal), validation (lead), writing—original draft (equal), and writing—reviewing and editing (equal). SB-H: conceptualisation (lead), methodology (lead), supervision (lead), visualisation (equal), writing—original draft (equal), and writing—reviewing and editing (equal). All authors had access to the post hoc analysis data and contributed to manuscript drafting, critical review, and revision. All authors approved the final manuscript for submission.

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