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The Effect of Dose Intensification After Secondary Loss of Response to Ustekinumab in Crohn's Disease: Results of the REScUE Study

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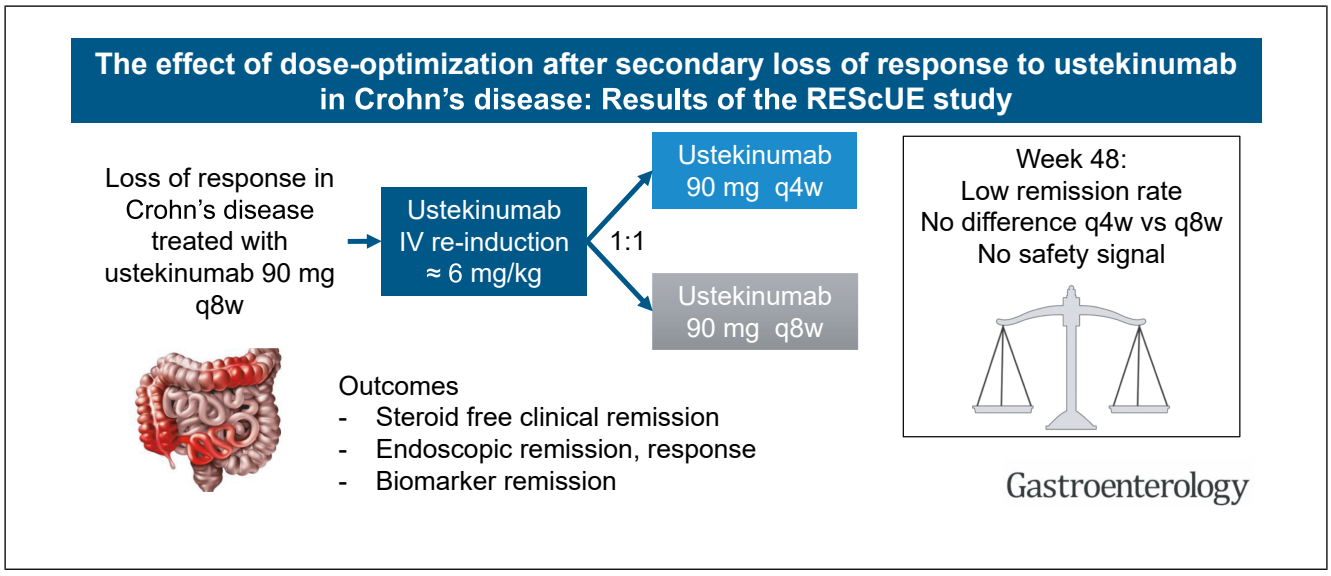

BACKGROUND & AIMS: Secondary loss of response to ustekinumab is observed in patients with Crohn's disease (CD). Multiple dose-intensification regimens have been proposed. We aimed to test prospectively 2 different dose-intensification regimens with ustekinumab in patients with CD experiencing secondary loss of response. **METHODS:** This was an investigator-initiated, multicenter, randomized, placebo-controlled trial conducted at 15 hospitals in Belgium. Eligible patients were adults with CD treated with ustekinumab on maintenance dosing of 90 mg subcutaneous every 8 weeks and experiencing a secondary loss of response (Patient-Reported Outcomes 2: abdominal pain score >1 and liquid or very soft stool frequency >3 and an objective documentation of disease). Patients were randomized 1:1 to receiving a single intravenous reinduction with ustekinumab ≈6 mg/kg followed by either subcutaneous ustekinumab 90 mg every 4 weeks or every 8 weeks until week 48. The primary endpoint was the proportion of patients with steroid-free clinical remission at week 48, defined as Patient-Reported Outcomes 2 remission: (abdominal pain ≤ 1 and stool frequency ≤3) and fecal calprotectin <250 μg/g and no steroids in the 90 days before week 48. **RESULTS:** Between March 2020 and October 2023, 108 patients were randomized. Steroid-free clinical remission at week 48 was reached in 15% vs 19% of patients in the every 4 weeks vs the every 8 weeks group (difference 4%; $P = 0.5$). Serious adverse events occurred in 17% vs 13% of patients. **CONCLUSIONS:** In patients with CD and secondary loss of response to ustekinumab, dose intensification with a

single intravenous administration and followed by 4 weekly subcutaneous dosing of ustekinumab was not more effective than 1 intravenous administration followed by 8 weekly subcutaneous dosing of ustekinumab. (ClinicalTrials.gov, Number: NCT04245215)

Keywords: Ustekinumab; Dose-Intensification; Therapeutic Drug Monitoring; Drug Exposure; Drug Clearance.

Crohn's disease (CD) is a debilitating condition affecting predominantly the terminal ileum and the colon. Although the exact cause is unknown, it is assumed that CD results from an inappropriate inflammatory immune reaction to the gut microbiome in genetically predisposed patients.[1] Current treatments aim to reduce the inflammatory burden and by this restore the integrity of the bowel wall leading to clinical and endoscopic remission. The therapeutic armamentarium has expanded over the past decades, but in clinical practice a therapeutic ceiling is perceived.[2] Moreover, patients having an initial adequate control of inflammation may experience a loss of response over time. Previous experiences with anti–tumor necrosis factor (TNF) in inflammatory bowel disease (IBD) have led to the concept of a drug exposure response relationship. In case of loss of response, therapeutic drug monitoring and subsequent dose intensification in case of underexposure demonstrated benefit in regaining disease control.[3]

In patients with CD treated with ustekinumab, secondary loss of response was seen in 26% of the patients in a large real-world cohort.[4] A meta-analysis of 13 studies in CD showed annual risk of loss of response to ustekinumab and dose escalation among primary responders of 21%.[5] Although prospective evidence is lacking, multiple real-world uncontrolled and retrospective studies demonstrate a clinical effect of dose intensification in patients with CD experiencing secondary loss of response. Two meta-analyses showed that in 50% to 60% of patients, a recapture of response or remission can be achieved after dose intensification.[5,6] Several options for dose intensification with ustekinumab have been proposed and applied in daily practice. For this, the aim of this study was to test prospectively the effect of 2 different dose-intensification regimens with ustekinumab in patients with CD experiencing secondary loss of response.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The annual risk for loss of response to ustekinumab in Crohn's disease is about 20% in primary responders. Clinical response after dose intensification with ustekinumab is >50% in observational and retrospective studies. No prospective data are available.

NEW FINDINGS

This prospective randomized controlled study demonstrated the effect of intravenous reinduction with ustekinumab followed by 2 different maintenance dosing regimens. The rate of recapture of remission was low in both groups and not significantly different between the 2 regimens. Most of the patients achieved the endpoint within the first 24 weeks after intravenous reinduction.

LIMITATIONS

Remission rate was low potentially because a strict primary endpoint was used. Data cannot be extrapolated to a bionaive population as most of the patients were anti–tumor necrosis factor exposed.

CLINICAL RESEARCH RELEVANCE

Our results show that dose intensification with ustekinumab might be a valuable option in case of secondary loss of response. For this, one intravenous reinduction is sufficient and the treatment effect can be expected in the first 24 weeks after intravenous reinduction. Strict monitoring of response based on clinical and objective markers of disease activity is required. Switch to another advanced treatment is suggested if no response is seen at week 24.

BASIC RESEARCH RELEVANCE

Although drug exposure was higher in the intensified q4w group, this was not associated with significant differences in the clinical outcomes. These findings challenge the principle of target trough levels for ustekinumab in Crohn's disease.

Methods

Study Design

The REScUE (Loss of RESponse to Ustekinumab treated by dose Escalation) study was an investigator-initiated, multicenter, randomized, placebo-controlled trial conducted at 15 academic and nonacademic hospitals in Belgium, all members of the Belgian IBD Research and Development (BIRD) group. This study evaluated the efficacy and safety of 2 dose-intensification regimens in patients with documented primary response to ustekinumab but secondary loss of response. All patients received an intravenous (IV) reinduction follow by 2 different subcutaneous (SC) maintenance regimens. Available data at the time of study design suggested that a single ustekinumab IV reinduction restored the response in a considerable proportion of patients; however, we hypothesized that this single IV reinduction was insufficient to maintain clinical response and remission in the long term. The trial was conducted according to the Declaration of Helsinki, the

Abbreviations used in this paper: **AP, abdominal pain; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; FCP, fecal calprotectin; IBD, inflammatory bowel disease; IQR, interquartile range; IV, intravenous; MH-OR, Mantel-Haenszel common odds ratio; PRO, patient-reported outcome; Q4W, every 4 weeks; Q8W, every 8 weeks; REScUE, Loss of RESponse to Ustekinumab treated by dose Escalation; SAE, serious adverse event; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; SF-36, Short Form Survey Instrument 36; TNF, tumor necrosis factor; WPAI, Work Productivity and Activity Impairment.**

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International Council for Harmonization Tripartite Guidelines for Good Clinical Practice, and applicable local regulatory requirements. The study was approved by the central ethical committee of the University Hospitals of Leuven (S62931) and the local ethical committees of the participating centers. Written informed consent was provided by all participants before any study-related interventions. The trial has been registered with the EU Clinical Trial Register (EudraCT; 2018-004269-14) and ClinicalTrials.gov (NCT04245215). All authors had access to the study data and reviewed and approved the final manuscript.

Participants

Eligible patients were at least 18 years old and were diagnosed with CD at least 3 months before baseline. All patients were treated with ustekinumab at a standard maintenance dose of 90 mg every 8 weeks SC. Eligible patients needed to have a documented primary response to standard IV induction with ustekinumab at an approximate dose of 6 mg/kg. Primary response was defined as clinical improvement as per treating physician discretion AND either a decrease in biomarker (C-reactive protein [CRP] or fecal calprotectin [FCP]) OR a documented endoscopic improvement during induction compared with a value maximum 3 or 6 months before ustekinumab induction, respectively. A strict definition of secondary loss of response was applied in the study. Patients with a secondary loss of response had a patient-reported outcome (PRO)-based moderate to severely active CD (2 items Patient-Reported Outcome 2 [PRO-2]: abdominal pain score [AP] >1 and liquid or very soft stool frequency [SF] >3) AND an objective documentation of disease activity. This was defined as either (1) a documentation of endoscopic lesions AND a documented increase in biomarker based on an increased value compared with the lowest value obtained following induction with ustekinumab (ie, an increase in CRP to an absolute value above 5 mg/L OR an increase in FCP to an absolute value above 250 μg/mg) OR (2) a documented relapse on endoscopy defined as the presence of ulcers in at least 1 segment of the ileum or colon and a Simple Endoscopic score for Crohn's disease (SES-CD) ≥ 6 (or SES-CD ≥ 4 for patients with isolated ileitis). All CD treatments needed to be stable at least 2 weeks before baseline. Concomitant treatment with another biological or small molecule therapy, steroids >20 mg prednisolone or equivalent daily and ustekinumab 90 mg SC administered at shortened intervals (<8 weeks) were exclusion criteria as well as IV reinduction with ustekinumab in the 6 months before baseline. All patients were on 8-weekly dosing of ustekinumab before inclusion. Also, patients with an ileostomy were excluded. For full eligibility criteria, see the Supplementary Methods.

Procedures

Manual randomization used blocks of permutation. Randomization to 1 of the 2 treatment groups was stratified according to previous exposure to anti-TNF and steroids at baseline. Patients, investigators, and study-related personnel remained blinded to the treatment group allocation. Study medication was prepared by an un-blinded study hospital pharmacist. Placebo syringes matched the syringes with active drug (ustekinumab) and was given at weeks 4, 12, 20, 28, 36, and 44 during study visits. Commercial ustekinumab (Stelara) was given at weeks 0, 8, 16, 24, 32, 40, and 48.

All eligible subjects received a reinduction at baseline (week 0), with IV ustekinumab, in line with the European Union Summary of Product Characteristics, on a weight-tiered basis at a dose of approximately 6 mg/kg IV. Subjects with a body weight ≤ 55 kg received 260 mg IV ustekinumab, >55 kg and ≤ 85 kg received 390 mg IV ustekinumab, and >85 kg received 520 mg IV ustekinumab, respectively. At week 4, the subjects in the every 4 weeks (Q4W) arm received a blinded 90-mg SC injection of ustekinumab and subjects in the every 8 weeks (Q8W) arm received blinded placebo. Subsequently, subjects in the Q4W arm continued to receive 90 mg ustekinumab SC at designated 4-weekly injection times. The subjects in the Q8W arm received a 90-mg SC injection of ustekinumab every 8 weeks and placebo every 4 weeks in-between. For study design, see Supplementary Figure 1.

At the screening visit, a physical examination was performed and disease characteristics were captured. Gender was assessed by self-reporting (male or female). Patient demographics and medical and surgical history were recorded. At the baseline visit and at weeks 4, 8, 12, 20, 28, 36, 44, and 48, vital signs, hematology, serum chemistry, and fecal calprotectin were evaluated, and physical examination was performed, concomitant medications were recorded, and adverse events were assessed. Before each infusion, serum was collected for ustekinumab concentrations. PRO-2 was calculated at each visit based on patients' diaries excluding the day of the bowel preparation and day of endoscopy in case of an endoscopy. The PRO-2 includes 2 components.[7] The SF score is calculated based on the 7-day average of the number of liquid of very soft stools per day. The AP score is based on the 7-day average of the daily abdominal pain score (none $=0$, mild $=1$, moderate $=2$, severe $=3$). The 36-Item Short Form Survey Instrument (SF-36)[8] questionnaire and Work Productivity and Activity Impairment for Crohn's disease (WPAI-CD) questionnaire[9,10] were recorded at baseline and weeks 12, 28, and 48. The SF-36 ranges from 36 to 180 with higher scores indicating more impact of the disease on physical and mental health. There are 8 subdomains grouped in 2 major domains of physical (Physical functioning, Role limitations due to physical health, Pain, General health) and mental health (Role limitations due to emotional problems, Energy/fatigue, Emotional well-being, Social functioning). The overall WPAI scores range from 0% to 100%, with lower scores indicating better work productivity. The WPAI has 4 subdomains (absenteeism, presentism, overall work performance, and activity impairment).

Colonoscopies were recorded at screening and week 48 or at early termination. Video recordings were scored by the local and a central independent reader for the SES-CD.[11] In case of discrepancy between the results of the local and central reading based on a sliding scale (Supplementary Methods), a second central reader score was obtained. In case of agreement, the average score of the agreeing scores was used as final score. If no 2 scores were in agreement (within respective predefined confines), the average of the 2 central readers was used. The SES-CD ranges from 0 to 56, with higher scores indicating more severe endoscopic disease activity (Supplementary Table 1).

Outcomes

The primary endpoint was the proportion of patients with *steroid-free clinical remission* at week 48, defined as PRO-2

remission: (AP $\leq$1 AND SF $\leq$3) and FCP $<$250 μg/g and no steroids in the 90 days before the week 48 time point. Non-ranked secondary endpoints included complete endoscopic remission (SES-CD $<$3), endoscopic remission (SES-CD $<$5), endoscopic response ($\geq$50% decrease in SES-CD compared with screening) at week 48, clinical remission (PRO-2 remission: AP $\leq$1 AND SF $\leq$3) at weeks 8 and 48, biomarker remission (CRP $<$5 mg/L and FCP $<$250 μg/g) at week 48, and adverse events. Major exploratory endpoints were pharmacokinetic and pharmacodynamic evaluations, time to clinical remission, and quality of life improvement. Safety assessments were based on adverse events that occurred during the study. Reasons for an eventual treatment discontinuation were recorded.

Statistical Analysis

Descriptive statistics were reported as percentages for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables. For the primary endpoint, treatment discontinuation and forbidden medication were captured in a composite endpoint, by setting these to "failure." The primary analysis estimated the marginal difference in proportions through a standardized estimator using a logistic regression model with treatment, the stratification factors, and their interactions with treatment.[12] Sensitivity analyses implement the same analysis to a multiply imputed dataset including the same variables plus the clinical remission status at weeks 4, 8, 12, 20, 28, 36, and 44 plus a Cochran-Mantel-Haensel (CMH) test with missing set to failure. Secondary response and remission outcomes were analyzed with CMH on observed data, without sensitivity analyses. Variability of the primary endpoint is described using estimated effects and confidence interval (CI) and standardized/marginal mean difference, and for the secondary endpoints using Mantel-Haenszel common odds ratio (MH-OR) and CI. Time to clinical remission is analyzed using Fine-Gray, with "forbidden medication use" and "end of treatment due to lack of efficacy" as competing risks. Quality of life scales were compared using Wilcoxon's rank sum test, other binary variables with Pearson's χ^2. For the association between serum levels and outcomes, a logistic regression was used. A P value $<$0.05 was considered significant. No adjustments were made for multiple testing. To achieve 80% power to detect an expected 30% difference in proportions of treatment response between the 2 study arms using a χ^2 test with a 2-sided alpha of 5%, between 64 and 86 patients in total were assumed to be necessary depending on the rate in the reference group ranging from 10% to 60%. The maximum sample size of 86 patients corresponds with about a 35% vs 65% response rate and has 90% power for a reference rate of 10% or 60%. To account further for an expected attrition rate of 20%, the study therefore requires 108 patients (54 patients in each treatment arm) to achieve at least 80% power regardless of the response rate in the reference group. Analyses were performed using R version 4.3.1 (The R Foundation for Statistical Computing).

Role of the Funding Source

The study was supported by an investigator-initiated study research grant by Johnson & Johnson Innovative Medicine NV, Belgium (grant number: CNTO1275CRD4021). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patient Characteristics and Disease Characteristics

Between March 11, 2020, and October 17, 2023, a total of 132 patients were screened and 108 patients were randomized (screen failure rate of 18%). Overall, after 48 weeks, 37 of 54 (68%) patients in the Q4W arm and 35 of 54 (65%) patients in the Q8W arm completed the trial. The reasons for discontinuation were disease exacerbation (12 patients in the Q4W arm and 10 patients in the Q8W arm), lack of efficacy (3 patients in the Q4W arm and 4 patients in the Q8W arm), patient decision (1 patient in the Q4W arm and 3 patients in the Q8W arm), adverse events (1 patient in the Q8W arm), investigator decision for noncompliance (1 patient in the Q4W arm), and pregnancy (1 patient in the Q8W arm) (Figure 1). Patient characteristics were comparable between the 2 groups. Overall, the included patients had a median age of 41 years (IQR 32–54), were predominantly female (62%) and had a long-standing disease with a median disease duration of 14 years (IQR 7–22). Most of the included patients were previously exposed to anti-TNF (92%) and 11% were treated with steroids at baseline. All patients had active disease at baseline with a median SES-CD of 8.5 (IQR 6–12.5), median FCP of 383 μg/g (IQR 159–848) and a median CRP of 6 mg/L (IQR 2–12) (Table 1).

Primary and Secondary Efficacy Endpoints

The primary endpoint of *steroid-free clinical remission* at week 48 was attained in similar proportion in the Q4W group (8 of 54 patients [15%]) compared with the Q8W group (10 of 54 patients [19%]) (P = .5; estimated effects, 0.0502; CI, −0.09487 to 0.1953) (Figure 2).

The endoscopic endpoints at week 48 showed numerically higher proportions of response and remission in the Q4W group compared with the Q8W group; however, none of the endoscopic endpoints achieved statistical significance. Complete endoscopic remission (SES-CD $<$3) was achieved in only 4 of 51 patients (8%) in the Q4W group and 3 of 50 patients (6%) in the Q8W group (P = .8; MH-OR, 0.787; 95% CI, 0.164–3.792). Endoscopic remission (SES-CD $<$5) was achieved in 15 of 51 patients (29%) in the Q4W group and 8 of 50 patients (16%) in the Q8W group (P = .1; MH-OR, 0.467; 95% CI, 0.178–1.223). Endoscopic response ($\geq$50% decrease in SES-CD) was achieved in 12 of 51 patients (24%) in the Q4W group and 8 of 50 patients (16%) in the Q8W group (P = .7; MH-OR, 0.837; 95% CI, 0.320–2.187) (Figure 3*A*) Most patients (62% in each arm) reaching week 48 had an improvement in endoscopic disease activity.

Clinical remission was achieved early after dose intensification. At week 8 a similar proportion of patients in the 2 treatment groups achieved clinical remission, with 19 of 53 patients (36%) in the Q4W group and 21 of 54 patients (39%) in the Q8W group (P = .7; MH-OR, 1.143; 95% CI,

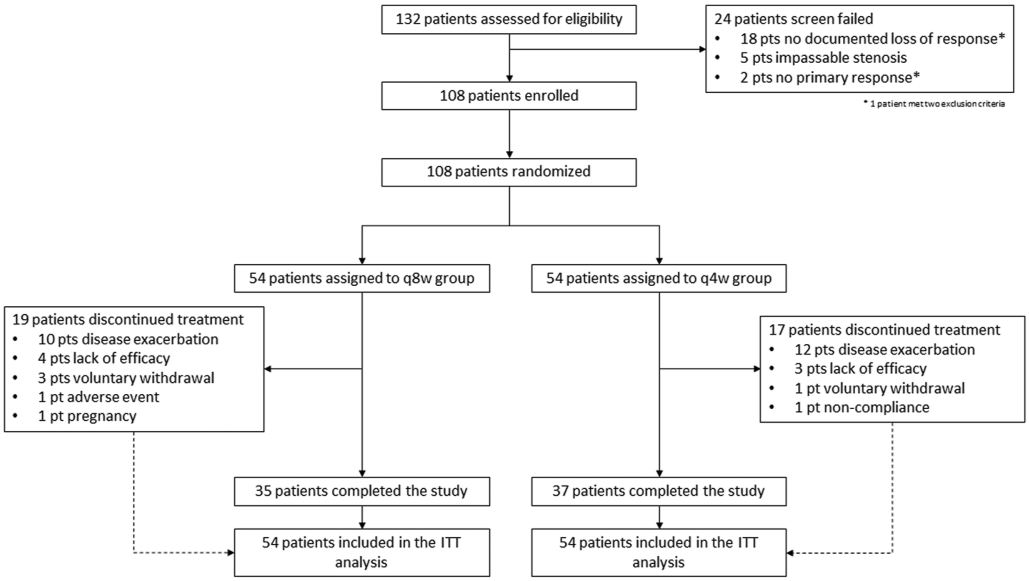

Figure 1. CONSORT flow diagram of the REScUE study. ITT, intention to treat; pt, patient.

0.526–2.484). This clinical remission was relatively maintained until week 48, showing 16 of 52 patients (31%) in the Q4W group and 18 of 50 patients (36%) in the Q8W group ($P = .6$; MH-OR, 1.278; 95% CI, 0.562–2.904) (Figure 3*B*). In the time to first clinical remission analysis, clinical remission in both treatment groups is achieved in most patients before week 24 with no significant difference between the Q4W group and the Q8W group ($P = .1$) (Supplementary Figure 2).

Biomarker remission at week 48 was not significantly different between both treatment groups. In the Q4W group 18 of 50 patients (36%) compared with 13 of 50 patients (26%) in the Q8W group achieved biomarker remission ($P = .3$; MH-OR, 0.630; 95% CI, 0.268–1.483) (Figure 3*C*). When analyzing only patients with elevated CRP (n = 52) 6 of 29 (21%) achieved CRP normalization in the Q4W group and 4 of 23 (17%) in the Q8W group ($P > .9$). Of patients with elevated FCP at baseline (n = 52), 10 of

Table 1. Baseline Characteristics of the Patients Included in the REScUE Study

	Q4W UST group, n = 54	Q8W UST group, n = 54
Age, *y*, median (IQR)	40 (32, 57)	41 (32, 53)
Disease duration, *y*, median (IQR)	14 (8, 23)	12 (7, 21)
Sex, female (%)	35 (65)	32 (59)
Weight, *kg*, median (IQR)	69 (61, 81)	71 (61, 83)
Active smoking, n (%)	12 (22)	13 (24)
CD Montreal location, n (%)		
L1 Ileal	16 (30)	10 (19)
L2 Colonic	9 (17)	6 (11)
L3 Ileocolonic	29 (54)	38 (70)
L4 Proximal involvement	4 (7)	9 (17)
Peri-anal involvement	11 (20)	14 (26)
CD Montreal behavior, n (%)		
B1 Inflammatory	27 (50)	25 (46)
B2 Stricturing	20 (37)	20 (37)
B3 Penetrating	7 (13)	9 (17)
Previous resective surgery, n (%)	30 (56)	28 (52)
CRP, *mg/L*, median (IQR)	7 (3, 16)	4 (2, 7)
FCP, *μg/g*, median (IQR)	370 (164, 782)	520 (146, 931)
Steroids at baseline, n (%)	6 (11)	6 (11)
Previous anti-TNF exposure, n (%)	49 (91)	50 (93)

UST, ustekinumab.

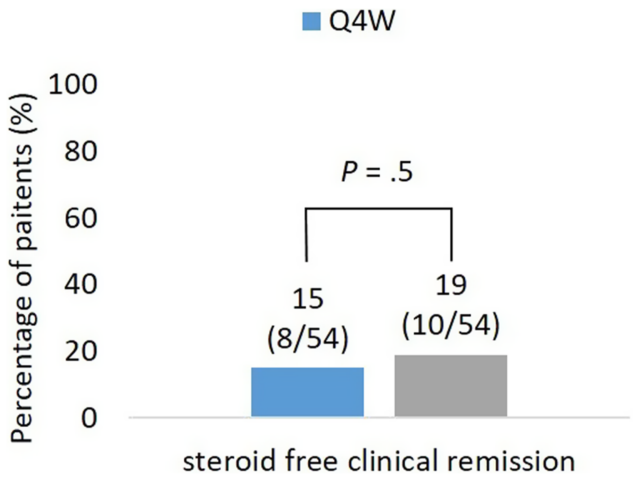

Figure 2. Steroid-free clinical remission: PRO2 (AP ≤1 AND SF ≤3) and FCP <250 μg/g and no steroids for 90 days before week 48.

27 (37%) achieved FCP normalization in the Q4W group and 4 of 25 (16%) in the Q8W group ($P = .09$) (Supplementary Figure 3).

Exploratory analysis to identify predictors for short-term effect (week 4) of an IV reinduction with ustekinuab showed no association with specific baseline characteristics (Supplementary Table 2). In addition, we could not identify clinically relevant predictors for the primary endpoint based on the baseline characteristics (Supplementary Table 2).

Safety Endpoints

Adverse events occurred in 91 of 108 patients (84.3%) with a total of reported adverse events of 183 in the Q4W group and 228 in the Q8W group, respectively. Adverse events probably or possibly related to the study drug occurred in 35 of 108 patients (32.4%). A list of the major adverse events and serious adverse events (SAEs) can be found in Supplementary Table 3. SAEs occurred in 9 of 54 patients (17%) (n = 11 SAEs) and 7 of 54 patients (13%) (n = 16 SAEs) in the Q4W group and Q8W group, respectively. Hospitalization occurred in 9 of 54 patients (17%) and 7 of 54 patients (13%) in the Q4W group and Q8W group, respectively. There were no deaths during the study.

Pharmacodynamic Endpoints

Serum levels of ustekinumab were obtained at each in-hospital visit (except screening and week 44) during the study. This provided a total of 748 measurements in this cohort. For the Q4W group, all measurements are trough levels. For the Q8W group, only measurements at weeks 0, 8, and 48 are trough concentrations of ustekinumab, and all other measurements for the Q8W group are considered as intermediate ustekinumab levels. At baseline, the median ustekinumab level was below 2 μg/mL in both groups. After IV reinduction, a significant increase was seen in the levels with an intermediate level at week 4 of approximately 20 μg/mL in both groups. At week 8, there was a

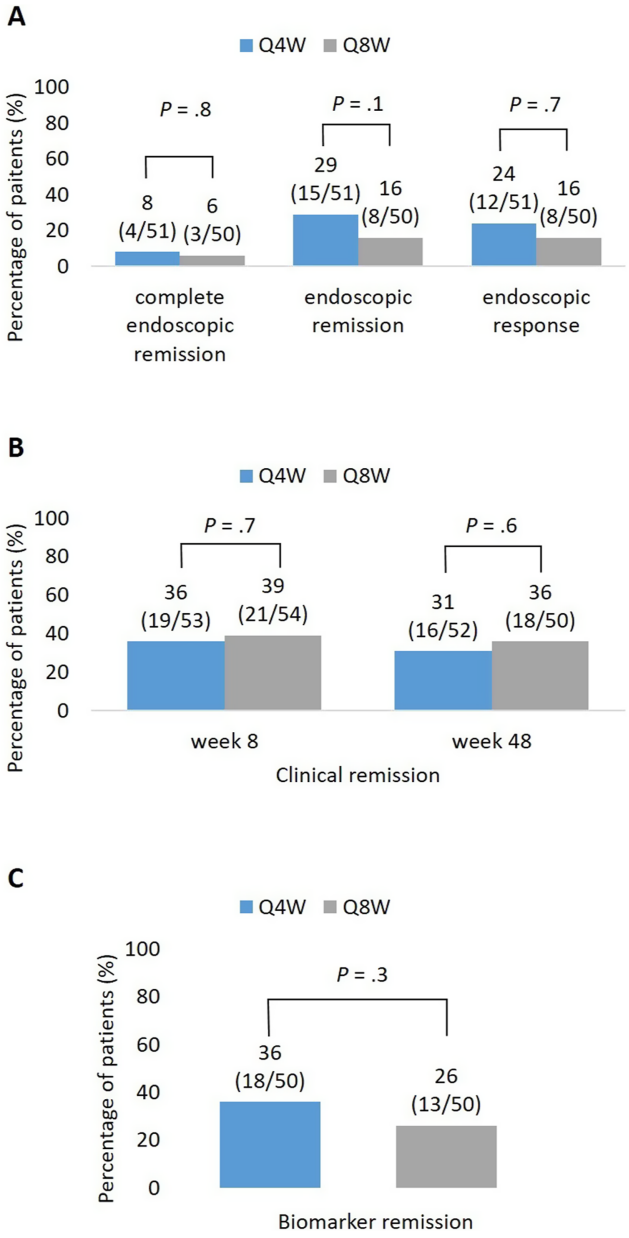

Figure 3. Secondary endpoints. (*A*) Endoscopic outcomes at week 48: complete endoscopic remission (SES-CD <3); endoscopic remission (SES-CD <5); endoscopic response (≥50% decrease in SES-CD). (*B*) Clinical outcomes: clinical remission (PRO-2 remission: AP ≤1 AND SF ≤3) at week 8 and week 48. (*C*) Biomarker outcomes: biomarker remission (CRP <5 mg/L and FCP <250 μg/g) at week 48.

significant difference in the trough concentration of ustekinumab between the 2 treatment arms. At week 8, the median serum level of ustekinumab was 10.8 (IQR 8–15.9) μg/mL and 8.2 (IQR 4.9–11.1) μg/mL in the Q4W group compared with the Q8W group, respectively ($P = .002$). At the end of the study (week 48) the serum levels remained significantly higher in the Q4W group. However, in the Q8W group, the median serum level of ustekinumab remained >50% higher compared with baseline. The ustekinumab serum levels at week 48 were 6.0 (4.8, 9.6)

Table 2. Evolution of the Ustekinumab Levels Over Time

Treatment group	Q4W, n = 54	Q8W[a], n = 54	*P* value[b]
Baseline (Week 0)			
Non-missing, n	53	50	
Median (IQR) *μg/mL*	1.39 (0.84, 2.74)	1.31 (0.91, 2.34)	>.9
Week 4			
Non-missing, n	52	53	
Median (IQR) *μg/mL*	20 (16, 25)	20 (16, 30)	.4
Week 8			
Non-missing, n	53	50	
Median (IQR) *μg/mL*	10.8 (8.0, 15.9)	8.2 (4.9, 11.1)	.002
Week 12			
Non-missing, n	48	49	
Median (IQR) *μg/mL*	8.4 (5.3, 12.5)	7.5 (5.3, 9.6)	.4
Week 20			
Non-missing, n	44	44	
Median (IQR) *μg/mL*	6.9 (3.9, 9.7)	4.9 (3.5, 6.9)	.049
Week 28			
Non-missing, n	43	38	
Median (IQR) *μg/mL*	5.9 (4.0, 8.3)	4.6 (3.7, 5.6)	.018
Week 36			
Non-missing, n	37	34	
Median (IQR) *μg/mL*	5.74 (4.53, 8.61)	4.47 (3.28, 7.02)	.031
Week 48			
Non-missing, n	34	32	
Median (IQR) *μg/mL*	6.0 (4.8, 9.6)	2.1 (1.6, 2.9)	<.001

NOTE. [a]For the Q4W group, all measurements are trough concentrations, for the Q8W group only measurements at week 0, 8, and 48 are trough concentrations of ustekinumab, and all other measurements for the Q8W group are considered as intermediate ustekinumab levels.
[b]Wilcoxon rank sum test.

μg/mL and 2.1 (1.6, 2.9) μg/mL in the Q4W group compared with the Q8W group respectively ($P < .001$) (Table 2).

There was no significant correlation between the serum ustekinumab levels and steroid-free clinical remission, endoscopic remission, or clinical remission at week 48. However, a significant correlation was found between the serum ustekinumab levels at weeks 0, 8, and 48 with biomarker remission at week 48 (Supplementary Table 4). The delta in the serum levels between baseline and week 8 was correlated with the primary outcome of steroid-free clinical remission in the Q8W group but not in the Q4W group. In the Q8W group, a delta in ustekinumab serum levels between baseline vs week 8 of 11 μg/mL or higher was linked to an increased probability of >50% of steroid-free clinical remission at week 48 (Supplementary Figure 4).

Quality of Life Endpoints

Overall work productivity based on the WPAI improved during the study in both groups. There was an imbalance in the subdomain of activity impairment at baseline with higher impairment in the Q8W group. The imbalance persisted over time but was no longer significant at week 48 (Supplementary Figure 5). Based on the SF-36, no clear difference in the impact was seen between the 2 treatment arms on the physical or mental domains through the study (Supplementary Table 5). There was an overall improvement of the quality of life in the 8 subdomains.

Discussion

In this REScUE study in patients with CD with secondary loss of response to ustekinumab, we demonstrated that dose intensification with 1 IV reinduction of ≈6 mg/kg ustekinumab followed by 90 mg ustekinumab SC either every 4 weeks or every 8 weeks is equally effective to inducing clinical remission. Remarkably, the overall steroid-free clinical remission rates at week 48 were low in both arms: 15% and 19% for ustekinumab Q4W and Q8W, respectively. Most of the patients achieved clinical remission in the first 24 weeks after IV reinduction though, suggesting that the IV reinduction is the main driver of the effectiveness, rather than the subsequent SC dose intensification. Our results are in contrast with several retrospective and observational nonrandomized and open-label cohort studies suggesting a clinical response rate after dose

intensification up to 60% and clinical remission rates up to 50% after 1 year of treatment.[4,13–17]

Dose intensification with ustekinumab is applied frequently in daily practice even in the absence of prospective evidence supporting the efficacy and safety. This practice is mainly based on an extrapolation of data coming from cohorts of patients with CD treated with anti-TNF. For anti-TNF, the use of dose intensification driven by therapeutic drug monitoring has shown to be effective.[18–21] These observations were the base for the study design of the REScUE study in which all patients received an IV reinduction with ustekinumab. We hypothesized that a direct increase in drug exposure based on an IV reinduction would be more favorable for recapturing the response/remission than a gradual increase based on 4 weekly dosing without IV reinduction. However, we also hypothesized that a single IV reinduction was insufficient to maintain clinical response and remission in the long term. For ustekinumab, a positive exposure response relationship was documented in the initial registration trials and subsequent independent cohorts, although target levels associated with specific outcomes could not be confirmed.[22–24] In this context, it is still difficult to differentiate whether the association between drug exposure and response is reflecting any causality.

All major objective secondary endpoints were numerically higher in the Q4W group compared with the Q8W group, although this did not meet statistical significance. The degree of endoscopic remission and response was overall low in the REScUE study, but comparable with the outcomes of other prospective studies with a similar population. In the STARDUST study 23.5% of the patients were dose-escalated and only 11% of the total population achieved endoscopic remission (SES-CD <3) after 104 weeks of treatment with ustekinumab.[25] In the SEQUENCE trial, no dose escalation was allowed with ustekinumab, after 48 weeks of treatment with ustekinumab, 16% of patients achieved endoscopic remission (SES-CD <5).[26] The trend in favor of 4 weekly dosing in our cohort was most pronounced for the endpoint of FCP normalization, showing a difference of 21% (37% vs 16%) at week 48. Biomarker remission was positively associated with serum trough levels of ustekinumab at baseline, week 8, and week 48 but not with clinical or endoscopic outcomes. The inverse correlation between ustekinumab serum levels and the biomarkers (CRP and FCP) could be explained by a clearance effect that was previously suggested as a better predictor of response rather than serum levels as such.[27]

In our study, the effect of dose intensification was mainly observed in the first 6 months with no cumulative benefit in the subsequent 6 months, despite persistent differences in ustekinumab serum levels until 48 weeks. The POWER study is the only prospective study testing a dose-intensification strategy with ustekinumab in patients with CD with secondary loss of response. This study compared 1 IV reinduction with ustekinumab ($\approx$ 6 mg/kg) vs placebo in patients on maintenance SC ustekinumab 90 mg every 8 weeks. The primary endpoint of clinical response ($\geq$100-point decrease from baseline/CD activity index <150) after 16 weeks was not met (49% in the IV reinduction vs 37% in the SC group).[28] Taking the results from POWER and REScUE together, we propose to switch to another advanced treatment when no clinical effect is documented within 24 weeks after IV reinduction with ustekinumab. Because the treatment effect in REScUE seems mainly to come from the IV reinduction, it can be questioned if serial IV reinduction could be an option in repeated loss of response.

Previously, a target ustekinumab trough level of 1.4 μg/mL was associated with clinical remission over time.[23] In our study, the median baseline ustekinumab level was around this target level and during the study the median levels in both treatment groups were above >2 μg/mL through week 48. These observations challenge the value of a general target trough concentration for ustekinumab. A more personalized model-based dosing might eventually be more informative.[29]

Our study has several strengths. First, we used a strict definition of primary response and applied an objective definition of loss of response to ustekinumab either by endoscopic and/or biomarker documentation. In most of the available data, this has not been strictly applied. Second, patients and study personnel were blinded for the allocated dose-intensification regimen. This in contrast to previously published data that had a retrospective or observational study design. Third, all endoscopies were centrally read through a strict central reading method including a sliding scale and adjudication. Finally, in line with the STRIDE 2.0 recommendations, we used robust endpoints of clinical, biomarker, and endoscopic outcomes.[30] We recognize that our study also had some . First, sample size and power calculation was based on the available data from retrospective and observational studies at the moment of study conception. Based on our results, the used assumptions might have been inflated. Second, we used a very strict primary endpoint of clinical remission combined with a biomarker and absence of steroids. This is a high bar to reach certainly in a population of patients with refractory CD. However, after 1 year of continued treatment this endpoint is aligned with the STRIDE 2.0 recommendations. Third, most patients ($>$90%) were anti-TNF exposed, for this the current data cannot be directly extrapolated to a bio-naïve population of patients with CD.

In conclusion, in patients with CD experiencing secondary loss of response to ustekinumab, dose intensification with a single IV reinduction of ustekinumab followed by intensified maintenance dosing every 4 weeks of 90 mg SC was not superior in achieving steroid-free clinical remission over a single IV reinduction followed by every 8 weeks of 90 mg SC. Overall, the rates of successful recapture of response and remission were low. Therefore, based on our study results, we advise that in case of secondary loss of response to ustekinumab, a single IV reinduction of ustekinumab can be administered. The number needed to treat is 5.8 to achieve the stringent endpoint of steroid-free clinical remission as defined in the REScUE study. Reevaluation should be done after maximum 24 weeks based on clinical and objective markers of disease activity. These

results question the current strategy of dose intensification with ustekinumab in CD and enlarge the field of testing new strategies including serial IV reinduction.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2026.01.042.

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CRediT Authorship Contributions
Peter Bossuyt, MD, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Resources: Lead; Supervision: Lead; Validation: Lead; Visualization: Lead; Writing original draft: Lead; Writing – review & editing: Lead)

Jean-Francois Rahier, MD, PhD (Conceptualization: Supporting; Investigation: Supporting; Methodology: Supporting; Supervision: Supporting; Writing – review & editing: Supporting)

Filip Baert, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)

Edouard Louis, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)

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Conflicts of interest
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Data Availability

Data will made available to other researchers based on reasonable request.

Gastroenterology, Volume ■

Supplemental information

The Effect of Dose Intensification After Secondary Loss of Response to Ustekinumab in Crohn's Disease: Results of the REScUE Study

Peter Bossuyt, Jean-Francois Rahier, Filip Baert, Edouard Louis, Elisabeth Macken, Triana Lobaton, Julie Busschaert, Harald Peeters, Pieter Dewint, Denis Franchimont, Barbara Willandt, Christophe Claessens, Laura Vansteenkiste, Olivier Dewit, Marc Ferrante, on behalf of the Belgian IBD Research and Development (BIRD) group, and Séverine Vermeire

Supplementary Appendix

This appendix has been provided by the authors to give the readers additional information about their work.

Supplement to: Bossuyt P, Rahier JF, Filip Baert et al. **The effect of dose-optimization after secondary loss of response to ustekinumab in Crohn's disease: Results of the REScUE study**.

Table of content

List of Study Investigators

Site	Principal Investigator	Patients recruited
University Hospital Leuven, Leuven, Belgium	Séverine Vermeire, MD, PhD	39
AZ Delta, Roeselare, Belgium	Filip Baert, MD, PhD	12
CHU University Hospital, Liège, Belgium	Edouard Louis, MD, PhD	10
University Hospital Antwerp, Antwerp, Belgium	Elisabeth Macken, MD, PhD	6
Imelda General Hospital, Bonheiden, Belgium	Peter Bossuyt, MD, PhD	5
Ghent University Hospital, Ghent, Belgium	Triana Lobaton, MD, PhD	5
AZ Sint-Lucas, Brugge, Belgium	Julie Busschaert, MD	5
AZ St-Lucas, Ghent, Belgium	Harald Peeters, MD, PhD	5
CHU Namur, Yvoir, Belgium	Jean-Francois Rahier, MD, PhD	4
AZ Maria Middelares, Ghent, Belgium	Pieter Dewint, MD, PhD	4
Erasme University Hospital, Brussels, Belgium	Denis Franchimont, MD, PhD	4
ZNA Jan Palfijn, Merksem, Belgium	Joris Dutré, MD	4
AZ Sint Jan, Brugge, Belgium	Barbara Willandt, MD	2
AZ Turnhout, Turnhout, Belgium	Christophe Claessens, MD	2
St. Luc University Hospital, Brussels, Belgium	Olivier Dewit, MD, PhD	1

Supplementary methods

Inclusion criteria

1. ≥18 years
2. Diagnosis of Crohn's disease for at least 3 months prior to visit 1 by endoscopic and/or radiologic examination.
3. Patient currently treated with UST, independent of previous biological exposure.
DocuSign Envelope ID: 1E501846-7F99-4A90-8348-5FD5A2EF5CD2
4. Patients treated with maintenance UST SC 90 mg Q8W (meaning after a minimum of 2 SC injections)
5. Documented primary response at any time point during induction (up to week 20) defined as a clinical response (physician discretion)
AND confirmed by either any of the following:
    1. A documented decrease in biomarkers based on a value during induction period compared to a value prior to UST induction (max. 3 months prior to start of UST induction)
        a. A decrease in CRP
    OR
        b. A decrease in FCP
    2. A documented endoscopic improvement (evaluation during the induction period compared to an evaluation prior to UST induction (max. 6 months prior to start of UST induction)
6. Documented loss of response after induction (at any timepoint after week 16) assessed by the physician as moderate to severe active Crohn's disease. The increase in symptoms reported by the patient is defined as: PRO-2 (AP > 1 AND SF > 3)
AND confirmed by either any of the following*:
    1. Documentation of endoscopic lesions in at least one segment of the ileum or colon as assessed by ileocolonoscopy AND a documented increase in biomarkers based on an increased value compared to the lowest value obtained during induction or after week 16 UST induction.
        a. An increase in CRP and >5 mg/L
    OR
        b. An increase in FCP and > 250µg/mg
    2. A documented relapse on endoscopy: Presence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD ≥ 6 (for patients with isolated ileitis ≥4), as assessed by ileocolonoscopy.
7. Adequate contraception in female of reproductive age (oral contraception, intra uterine device, sterilisation or barrier method).
8. Have the capacity to understand and sign an informed consent form.
9. Be able to adhere to the study visit schedule and other protocol requirements.
10. All Crohn's Disease treatments stable for at least 2 weeks prior to baseline.

* the criterion used to proof loss of response does not have to be identical to the one used to proof primary response: e.g. one can use an increase in biomarkers to proof primary response and a relapse on endoscopy to proof loss of response

Exclusion criteria

1. Ongoing treatment with
    a. other concomitant biological (vedolizumab, anti-TNF)
    b. Steroids >20 mg prednisolone or equivalent at baseline (budesonide >6 mg); >5 mg beclomethasone dipropionate at baseline

c. Q4w ustekinumab

2. Women that are pregnant, nursing, or planning pregnancy
3. Have screening laboratory test results within the following parameters:
    a. Haemoglobin < 8.5 g/dL
    b. Platelets < 100,000 /mm3
    c. Serum creatinine ≥ 1.7 mg/dL
    d. AST and ALT > 3 times the ULN range
    e. Direct (conjugated) bilirubin ≥ 3.0 mg/dL.
4. Have current signs or symptoms of infection confirmed by positive stool or blood testing (including gastrointestinal pathogens, TB, HIV, Hep B, Hep C).
5. Patients with a positive stool sample for gastrointestinal pathogen including Clostridium difficile.
6. Evidence of current or previous clinically significant disease, medical condition other than CD, finding of the medical examination, or laboratory value at the screening visit outside the reference range that is of clinical relevance, that in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data.
7. Patients with an ileostomy
8. Patients that received an IV re-induction with UST within the 6 months prior to baseline.
9. Patients with an impassable stenosis even after attempt of endoscopic balloon dilation.
10. Patients with an abscess.

Central reading method [1]

All endoscopic videos will be scored locally with the SES-CD. After the study all endoscopic videos will be re-read by a blinded central reader. In case of discrepancy based on a sliding scale. In case of disagreement between the local and central reader a second central reader will perform an adjudication reading. In case of agreement the average score of the agreeing scores will be used as final score. If no 2 scores were in agreement (within respective predefined confines), the average of CR 1 and CR 2 will be used.

Sliding scale

SES-CD range	Allowed difference
0-3	1 point
4-7	2 points
8-15	3 points
≥ 16	4 points

Supplementary figures

Figure S1: schematic study design of the REScUE study

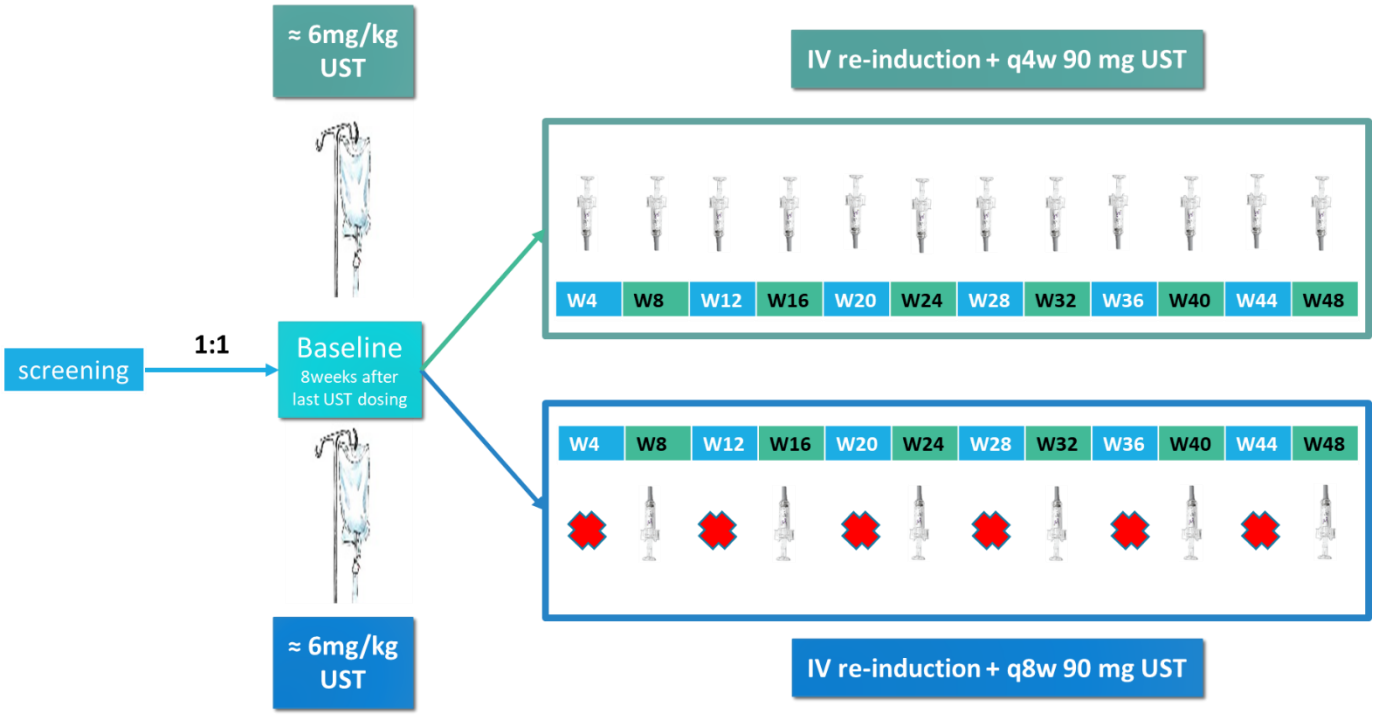


Figure S2: cumulative incidence of first clinical remission (AP ≤ 1 and SF ≤ 3) in the two treatment arms (non-parametric Fine-Gray test can test p-value = 0.1)

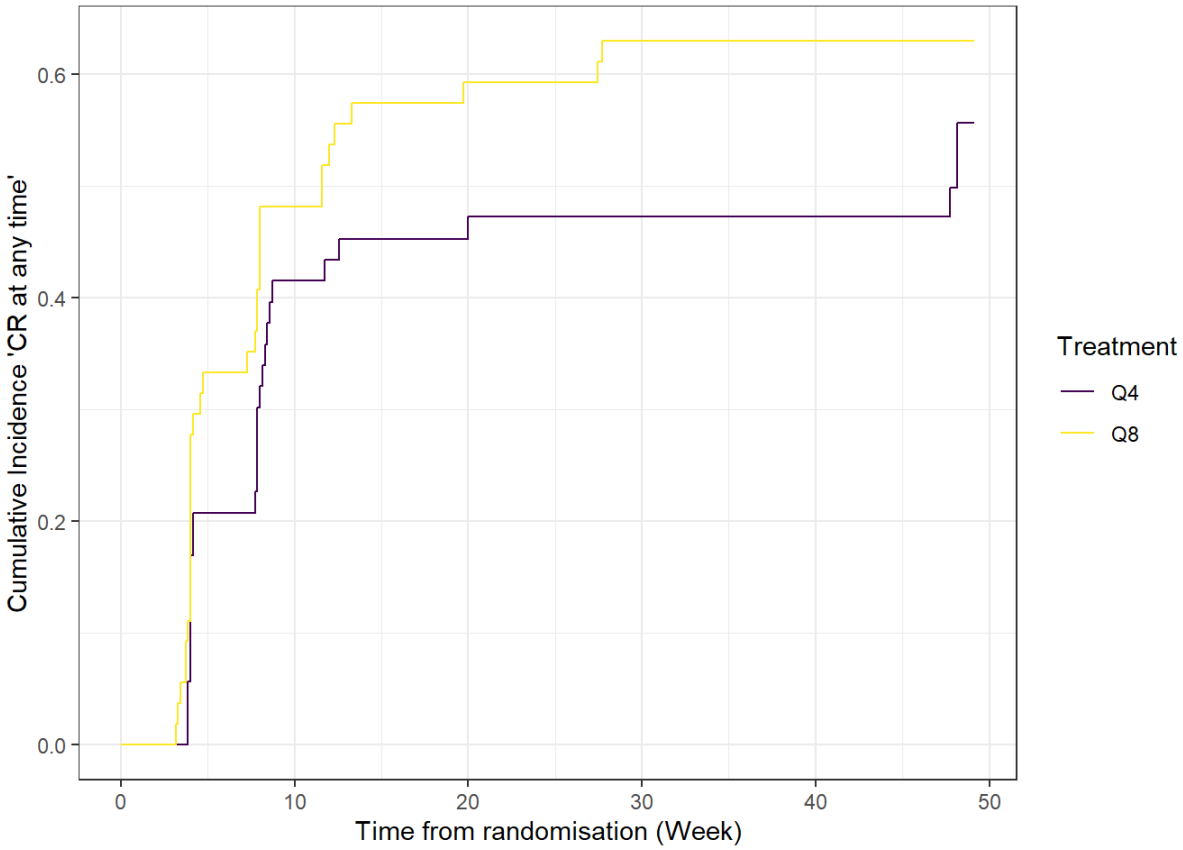


Figure S3: Biomarker remission in patients with elevated biomarker at baseline (CRP≥5 mg/L; FCP ≥ 250 µg/g) at week 48.

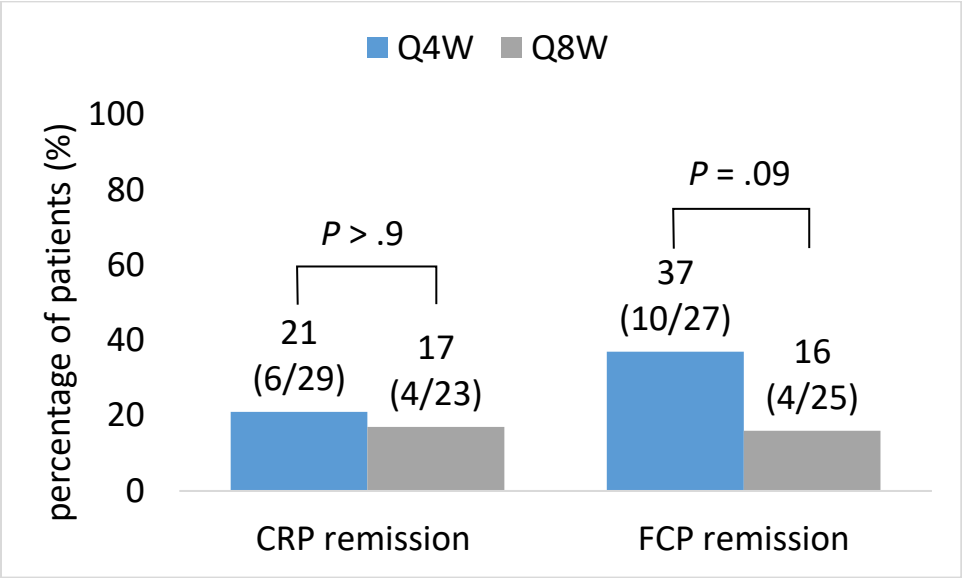


Figure S4: correlation between difference in ustekinumab levels at week 8 vs baseline and primary outcome

Within Q4W group (red line), the slope for difference in ustekinumab levels (for change of log odds for Steroid Free Clinical Remission) is -0.0315 [-0.22;0.16], indicating no evidence that among those with Week 8 ustekinumab levels measured, the difference in ustekinumab levels is prognostic for the primary outcome.

Within Q8W, the slope is 0.36 [0.10;0.62] indicating that among those with Week 8 ustekinumab levels measured, the difference in ustekinumab levels is prognostic for the primary outcome (higher Delta TL results in a higher probability of Steroid Free Clinical Remission)

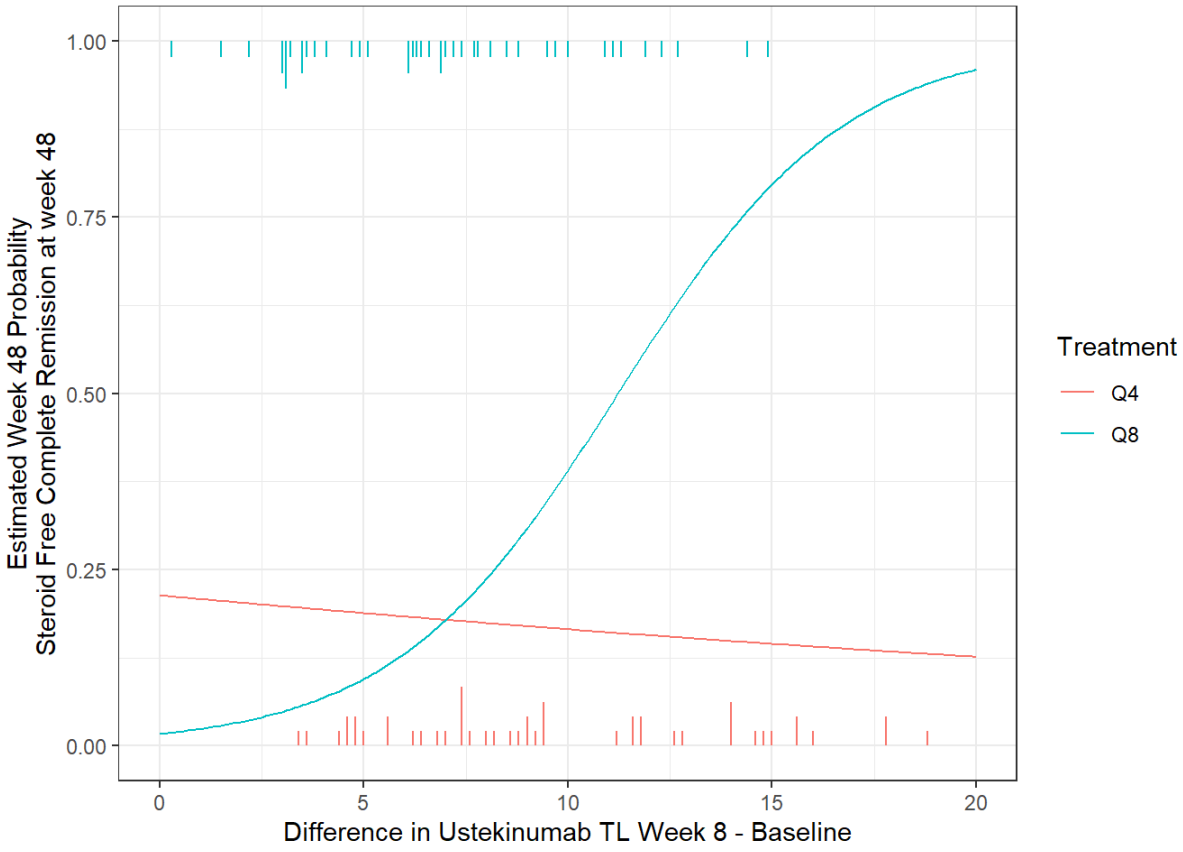
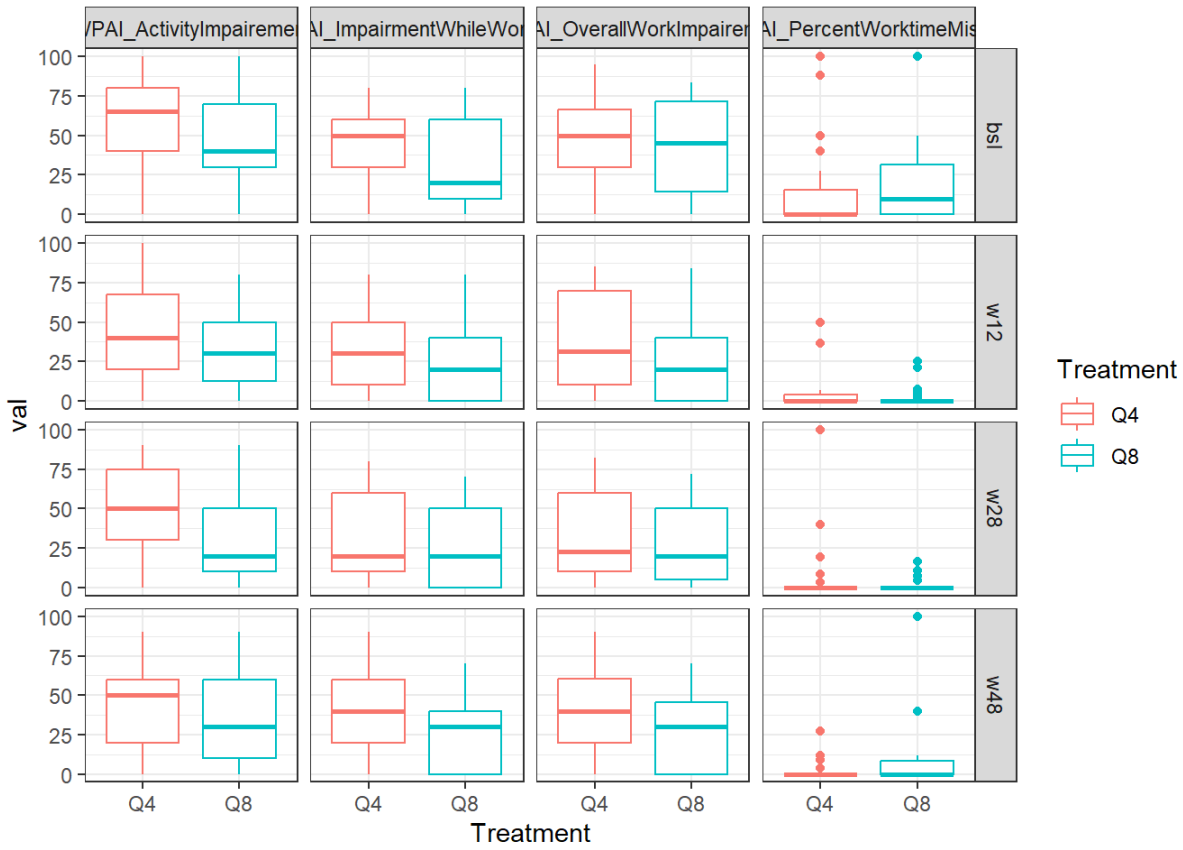


Figure S5: Work Productivity and Activity Impairment outcomes



Supplementary tables

Table S1. Simple Endoscopic Score for Crohn's Disease [2]

Score the rectum, Sigmoid and descending Colon, Transverse Colon, Ascending Colon, and Ileum accordingly:

Size of Ulcers	0	If none
	1	If aphthous ulcers (diameter 0·1 to <0·5 cm)
	2	If large ulcers (diameter 0·5 to <2 cm)
	3	If very large ulcers (diameter >2 cm)
Ulcerated Surfaces	0	If none
	1	If <10%
	2	If 10-30%
	3	If >30%
Affected Surfaces	0	If unaffected segments
	1	If <50%
	2	If 50-75%
	3	If >75%
Presence of narrowing	0	If none
	1	If single, can be passed
	2	If multiple, can be passed
	3	If cannot be passed

Table S2. Predictors of remission

We evaluated the short term response and remission rates independent of the treatment arm. As patients in the Q4W group received their first SC ustekinumab at week 4 we used the response and remission rates at week 4 to analyse the predictors of short term treatment effect.

The definitions used in this analysis were: *Clinical remission*: PRO-2 remission: AP ≤ 1 AND SF ≤ 3 [SF: average number of liquid stools for 1 week, AP: average scoring for abdominal pain for 1 week (0=none; 1=mild, 2=moderate; 3= severe)]; *PRO-2 Response*: Decrease in SF and/or AP score; *Biomarker remission*: CRP <5 mg/L and FCP <250 µg/g; *Biomarker response*: decrease in CRP and/or FCP score.

Rates of response and remission at week 4 after IV reinduction with ustekinumab are represented in the table below.

Characteristic	**N = 108**[1]
Clinical Remission	29 (27%)
Unknown	1
Biomarker Remission	28 (28%)
Unknown	7
PRO-2 Response	95 (90%)
Unknown	2
Biomarker Response	87 (90%)
Unknown	11
[1] n (%)	

A univariate analysis was performed for the association between the different baseline characteristics and the specific outcome. As shown in the table below no clear signal could be identified. The lack of predictors can be associated to the high response rates at week 4 (90%) on the one hand and the low remission rates at week 4 (27-28%) on the other hand. Based on these findings a multivariate analysis was not performed as it deemed not contributing any additional information.

	clinical remisson			biomarker remisson			PRO-2 response			biomarker response		
Characteristic	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**
Baseline Trough Level	0.94	0.62, 1.39	0.8	**2.28**	**1.47, 3.77**	**<0.001**	1.10	0.64, 2.21	0.7	**0.58**	**0.34, 0.99**	**0.040**
Age	0.99	0.96, 1.02	0.6	**1.06**	**1.03, 1.10**	**0.001**	1.01	0.97, 1.07	0.6	1.00	0.95, 1.06	>0.9
Disease duration	0.97	0.93, 1.01	0.2	**1.04**	**1.01, 1.08**	**0.026**	0.98	0.93, 1.04	0.5	0.99	0.94, 1.05	0.7
Sex												
Female	—	—		—	—		—	—		—	—	
Male	1.26	0.52, 3.01	0.6	0.95	0.37, 2.32	>0.9	1.07	0.30, 4.31	>0.9	1.36	0.35, 6.64	0.7
Weight	0.99	0.96, 1.02	0.7	0.98	0.94, 1.01	0.14	0.98	0.94, 1.02	0.3	1.02	0.98, 1.07	0.4
Smoking status												
Smoker (> 1 cigarette/day)	—	—		—	—		—	—		—	—	
Non smoker	2.79	0.89, 10.7	0.10	0.36	0.11, 1.15	0.082	0.80	0.16, 3.19	0.8	1.34	0.17, 7.61	0.7
Former smoker	1.68	0.46, 7.03	0.4	1.05	0.34, 3.31	>0.9	4.36	0.52, 91.4	0.2	0.88	0.11, 5.02	0.9
CD Montreal location												
L1 Ileal	—	—		—	—		—	—		—	—	
L2 Colonic	1.50	0.39, 5.72	0.5	0.28	0.05, 1.17	0.10	1.17	0.10, 26.5	>0.9	0.00		>0.9
L3 Ileocolonic	0.66	0.24, 1.88	0.4	**0.33**	**0.12, 0.93**	**0.035**	0.59	0.09, 2.59	0.5	0.00		>0.9
Previous lower intestinal resection(s) ?												
0	—	—		—	—		—	—		—	—	
1	**0.23**	**0.08, 0.56**	**0.002**	2.29	0.94, 5.95	0.076	0.61	0.15, 2.15	0.5	1.17	0.31, 4.51	0.8
CRP at screening	1.00	0.96, 1.03	>0.9	0.97	0.91, 1.01	0.3	0.99	0.96, 1.04	0.5	1.10	0.99, 1.31	0.2
Baseline anti-TNF												
0	—	—		—	—		—	—		—	—	
1	**0.15**	**0.03, 0.63**	**0.012**	0.96	0.19, 6.96	>0.9	0.00		>0.9	1.50	0.08, 10.3	0.7
FCP at Screening	1.00	1.00, 1.00	0.2	**1.00**	**1.00, 1.00**	**0.044**	1.00	1.00, 1.00	0.6	1.00	1.00, 1.00	0.5
SES at Screening	**1.10**	**1.02, 1.18**	**0.016**	0.97	0.88, 1.04	0.4	0.96	0.87, 1.08	0.5	1.00	0.90, 1.14	>0.9
Steroids at baseline ?												
0	—	—		—	—		—	—		—	—	
1	0.88	0.19, 3.23	0.9	0.21	0.01, 1.16	0.14	0.53	0.11, 3.79	0.5	1.17	0.19, 22.7	0.9

[1] OR = Odds Ratio, CI = Confidence Interval

We repeated the exercise for biomarker remission in patients with elevated FCP and CRP at screening respectively and could not find a clear signal for predictive factors. See table below.

	FCP remission (screenig FCP >250 µg/g)			CRP remission (screening CRP >5 mg/L)		
Characteristic	**OR[1]**	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**
Baseline Trough Level	1.52	0.62, 3.60	0.3	2.32	0.84, 6.96	0.10
Age	**1.06**	**1.00, 1.12**	**0.047**	1.05	0.99, 1.14	0.13
Disease duration	1.06	0.99, 1.14	0.10	1.04	0.95, 1.12	0.4
Sex						
Female	—	—		—	—	
Male	1.25	0.28, 5.04	0.8	2.81	0.42, 23.1	0.3
Weight	0.97	0.91, 1.02	0.2	0.99	0.93, 1.04	0.7
Smoking status						
Smoker (> 1 cigarette/day)	—	—		—	—	
Non smoker	1.00	0.13, 21.0	>0.9	0.72	0.06, 16.6	0.8
Former smoker	2.40	0.27, 53.1	0.5	1.50	0.12, 35.3	0.8
CD Montreal location						
L1 Ileal	—	—		—	—	
L2 Colonic	0.30	0.03, 2.46	0.3	38,549,598	0.00,	>0.9
L3 Ileocolonic	0.20	0.03, 1.27	0.076	10,842,074	0.00,	>0.9
Previous lower intestinal resection(s) ?						
0	—	—		—	—	
1	2.07	0.50, 8.53	0.3	0.33	0.02, 2.41	0.3
CRP at screening	**0.68**	**0.46, 0.89**	**0.022**	1.03	0.99, 1.10	0.12
Baseline anti-TNF						
0	—	—		—	—	
1	0.86	0.11, 17.8	0.9	4,947,071	0.00,	>0.9
FCP at Screening	1.00	1.00, 1.00	0.3	1.00	1.00, 1.00	0.4
SES at Screening	1.00	0.87, 1.12	>0.9	1.03	0.88, 1.19	0.7
Steroids at baseline ?						
0	—	—		—	—	
1	0.62	0.03, 4.15	0.7	2.05	0.09, 17.9	0.6

[1] OR = Odds Ratio, CI = Confidence Interval

We performed an additional analysis for predictors of treatment success at week 48. This analysis used a generalized linear model comparing the two treatment regimens. In this analysis, for each variable, a model was fitted with a main effect of treatment, a main effect of that variable and an interaction between these two. For categorical variables, an estimated treatment-effect was derived from that model for each level. For continuous variables, an estimated treatment-effect was derived for quartile 1, 2 (median) and 3. No adjustment for multiple testing was made. The Results are shown in the table below. We could not find a significant predictor for treatment success at week 48. Only for smoking status there was a signal but this needs to be evaluated with caution as this finding seems very difficult to be explained clinically. The extremely high OR for L4 phenotype is linked to the fact that there was one steroid free clinical remission in the Q8 group and none in the Q4 group.

Variable	Values	OR	CI_Low	CI_Hi	p	p_int
Baseline Trough Levels	0.895	1.282	0.327	5.029	0.722	0.754
	1.315	1.358	0.423	4.355	0.607	
	2.402	1.578	0.513	4.852	0.426	
Age	32.5	2.236	0.507	9.866	0.288	0.321
	41	1.599	0.519	4.927	0.414	
	55	0.921	0.253	3.351	0.900	
Disease duration	8	1.109	0.335	3.667	0.865	0.512
	14	1.371	0.478	3.932	0.558	
	23.5	1.916	0.422	8.712	0.400	
Sex	Female	1.812	0.458	7.175	0.397	0.450
	Male	0.812	0.169	3.895	0.795	
Weight	60.55	1.342	0.320	5.624	0.687	0.953
	70.3	1.314	0.447	3.864	0.619	
	81.9	1.282	0.407	4.040	0.671	
Smoking status	Smoker (> 1 cigarette/day)	0.267	0.023	3.080	0.290	**0.008**
	Non smoker	0.409	0.067	2.495	0.333	
	Former smoker	14.000	1.460	134.247	0.022	
CD Montreal location	L1 Ileal	0.524	0.045	6.092	0.605	0.667
	L2 Colonic	2.333	0.216	25.245	0.486	
	L3 Ileocolonic	1.739	0.384	7.872	0.473	
	L4 Upper GI tract involvement	2.235.908.685	0.000	Inf	0.990	
Previous lower intestinal resection(s) ?	0	1.250	0.288	5.427	0.766	0.934
	1	1.364	0.324	5.735	0.672	
CRP at screening	2.2	1.553	0.464	5.205	0.475	0.387
	5.9	1.249	0.417	3.741	0.691	
	11.6	0.892	0.219	3.636	0.874	
Previous anti-TNF exposure ?	0	0.333	0.017	6.654	0.472	0.278
	1	1.895	0.582	6.166	0.288	

(OR: odd's ratio, CI: confidence interval, Hi: high, p int: integrated p value; CD: Crohn's disease; CRP: C-reactive protein, TNF: Tumour necrosis factor).

Table S3. Adverse Outcomes (Safety Analysis Set)*

	Q4W (n=54)	**Q8W (n=54)**
Adverse events reported in >5% of patients in either group, no. (%)	# of patients	# of patients
Fatigue	8	5
Headache	5	7
Respiratory infection	21	25
Flu	7	8
Worsening of Crohn's Disease	7	5
Gastroenteritis	4	5
Lab abnormalities/deficiencies	10	15
Skin abnormalities	6	9
Psychiatric symptoms	5	3
Abdominal pain	10	15
Musculoskeletal and connective tissue disorders	19	22
Serious adverse events, no. (%)	# of patients (%) - # of SAEs	# of patients (%) - # of SAEs
Any serious adverse event	9 (17%) – 11	7 (13%) – 16
Gastrointestinal disorders	7(13%)	4 (7%)
Extensive colitis	1 - 1	-
Gastro-enteritis	-	1 - 1
Abdominal pain	-	2 - 2
Small bowel ileus	-	1 - 1
(sub) obstruction	3 - 3	1 - 1

Bowel obstruction terminal ileitis	1 - 1	-
Flare of Crohn's disease	2 - 2	-
Presacral abscess	-	1 - 2
Stricturing Crohn's Disease	1 - 1	-
Hepatobiliary disorders	-	1 (%)
Cholangitis	-	1 – 2
Stenosis hepaticojejunostomia	-	1 - 1
Infections and infestations	1 (%)	1 (%)
Infection Giardia Lamblia	1 - 1	-
E. Coli urosepsis	-	1 - 1
Surgery and medical procedures	1 (%)	1 (%)
Cardiac ablation	1 - 1	-
Laparoscopic right hemicolectomy	-	1 - 1
Nutritional and metabolic disorders	-	1 (%)
Electrolyte abnormalities	-	1 - 1
Musculoskeletal and connective tissue	1 (%)	2 (%)
disorders	-	1 - 1
Stress fracture femoral neck left	1 – 1	-
Arthralgia due to Infliximab	-	1 - 1
Recurrent abdominal wall hernia		
Injury, poisoning or procedural complications	(%)	1 (%)
Abdominal pain after right hemicolectomy	-	1 - 1
Pregnancy	-	1 (%)
Hospitalisation	9 (17%)	7 (13%)

Table S4. Correlation between serum levels of ustekinumab and outcomes at week 48.

Characteristic	Steroid Free Clinical Remission			Complete Endoscopic Remission			Clinical Remission			Biomarker Remission		
	OR[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**
Baseline Trough Levels Ustekinumab	1.30	0.84, 2.00	0.2	1.40	0.94, 2.12	0.10	1.11	0.76, 1.61	0.6	2.98	1.85, 5.23	**<0.001**
No. Obs.	95			96			97			95		
Week 8 Trough Levels Ustekinumab	1.09	0.98, 1.21	0.12	1.10	1.00, 1.21	**0.049**	1.08	1.0, 1.18	0.069	1.18	1.07, 1.31	**<0.001**
No. Obs.	96			97			98			96		
Week 48 Trough Levels Ustekinumab	0.99	0.83, 1.17	>0.9	1.12	0.97, 1.32	0.13	0.95	0.82, 1.09	0.5	1.35	1.13, 1.66	**0.002**
No. Obs.	64			65			66			64		

[1] OR = Odds Ratio, CI = Confidence Interval

Table S5. Short Form Survey Instrument 36 outcomes

	Q4W				**Q8W**			
	bsl	w12	w28	w48	bsl	w12	w28	w48
	N = 54	N = 54	N = 54	N = 54	N = 54	N = 54	N = 54	N = 54
Physical health								
Physical functioning								
Median (Q1, Q3)	70 (50, 85)	78 (55, 90)	80 (50, 90)	75 (65, 85)	75 (60, 85)	83 (63, 95)	75 (55, 95)	85 (60, 90)
Missing data	8	12	19	25	13	18	27	29
Role limitations due to physical health								
Median (Q1, Q3)	0 (0, 25)	25 (0, 100)	50 (0, 100)	50 (0, 100)	25 (0, 100)	75 (25, 100)	75 (25, 100)	50 (25, 100)
Missing data		4	11	17		5	15	19
Bodily pain								
Median (Q1, Q3)	41 (41, 62)	62 (41, 74)	62 (41, 80)	62 (62, 72)	52 (41, 72)	67 (52, 84)	74 (41, 84)	74 (52, 100)
Missing data	8	12	19	25	13	18	27	29
General health								
Median (Q1, Q3)	35 (25, 42)	35 (30, 57)	40 (32, 57)	45 (32, 52)	30 (20, 45)	42 (32, 52)	47 (35, 57)	47 (30, 57)
Missing data		4	11	17		5	15	19
Mental health								

, Energy and fatigue								
Median (Q1, Q3)	35 (25, 50)	50 (30, 65)	45 (30, 60)	50 (30, 60)	45 (25, 60)	55 (38, 65)	55 (40, 65)	60 (40, 65)
Missing data	8	12	19	25	13	18	27	29
Social functioning								
Median (Q1, Q3)	50 (38, 63)	63 (38, 88)	63 (38, 88)	63 (50, 88)	63 (50, 88)	75 (56, 100)	88 (50, 100)	88 (63, 100)
Missing data	8	12	19	25	13	18	27	29
Role limitations due to emotional problems								
Median (Q1, Q3)	67 (0, 100)	100 (33, 100)	100 (0, 100)	100 (0, 100)	83 (33, 100)	100 (33, 100)	100 (33, 100)	100 (33, 100)
Missing data		4	11	17		5	15	19
Emotional well-being								
Median (Q1, Q3)	66 (48, 76)	72 (60, 84)	68 (56, 76)	76 (52, 88)	72 (56, 80)	80 (70, 86)	76 (60, 84)	76 (60, 84)
Missing data	8	12	19	25	13	18	27	29

References

1. Reinisch W, Mishkin DS, Oh YS, et al. Impact of various central endoscopy reading models on treatment outcome in Crohn's disease using data from the randomized, controlled, exploratory cohort arm of the BERGAMOT trial. *Gastrointest Endosc*. Jan 2021;93(1):174-182.e2. doi:10.1016/j.gie.2020.05.020

2. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. Oct 2004;60(4):505-12.