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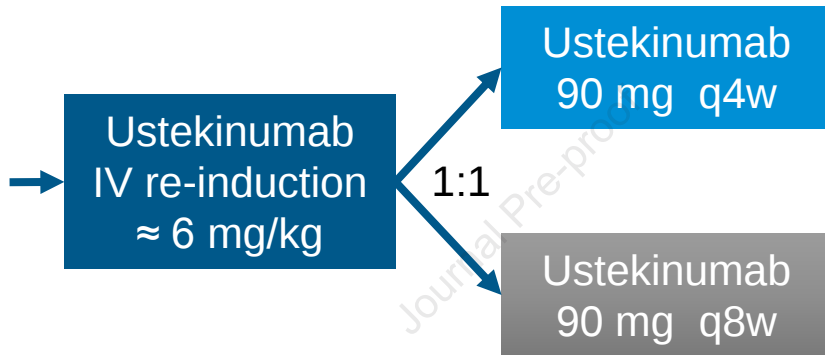
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The effect of dose-optimization after secondary loss of response to ustekinumab in Crohn's disease: Results of the REScUE study

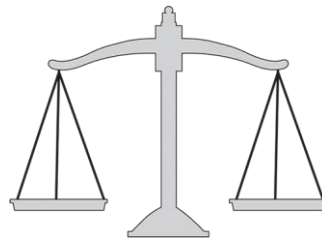
Loss of response in
Crohn's disease
treated with
ustekinumab 90 mg
q8w



Outcomes

- Steroid free clinical remission
- Endoscopic remission, response
- Biomarker remission

Week 48:
Low remission rate
No difference q4w vs q8w
No safety signal



Gastroenterology

Title: The effect of dose-intensification after secondary loss of response to ustekinumab in Crohn's disease: Results of the REScUE study

Short title: Dose-intensification with ustekinumab in Crohn's disease

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Abbreviations:

AP	Abdominal pain
CD	Crohn's disease
CI	confidence interval
CRP	C-reactive Protein
EU SmPC	European union Summary of Product Characteristics
FCP	Fecal Calprotectin
IBD	Inflammatory Bowel Disease
IQR	Interquartile ranges
IV	Intravenous
IWRS	Interactive Web Response System
MH-OR	Mantel-Haenszel common Odds Ratio
PRO	Patient Reported Outcome
Q4W	Every four weeks
Q8W	Every eight 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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Data availability:

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

ABSTRACT

Background and 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 two 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 q8 weeks and experiencing a secondary loss of response (PRO-2: abdominal pain (AP) score >1 and liquid or very soft stool frequency (SF) >3 and an objective documentation of disease). Patients were randomized 1:1 to receiving a single intravenous re-induction with ustekinumab $\approx$ 6mg/kg followed by either subcutaneous ustekinumab 90 mg q4 weeks or q8 weeks till week 48. 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 fecal calprotectin <250 μ g/g and no steroids in the 90 days prior to week 48.

Results: Between March 2020 and October 2023, 108 patients were randomized. Steroid free clinical remission at week 48 was reached in 15% versus 19% of patients in the Q4W versus the Q8W group (difference 4%; p=0.5). Serious adverse events occurred in 17% vs 13% of patients.

Conclusion: 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 one intravenous administration followed by 8 weekly SC dosing of ustekinumab. clinicaltrials.gov number: NCT04245215

Keywords: ustekinumab, dose-intensification, therapeutic drug monitoring, drug exposure, drug clearance

Introduction:

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 last 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 50-60% 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 two different dose-intensification regimens with ustekinumab in patients with CD experiencing secondary loss of response.

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 non-academic hospitals in Belgium all members of the Belgian IBD Research and Development (BIRD) group. This study evaluated the efficacy and safety of two dose-intensification regimens with in patients with documented primary response to ustekinumab but secondary loss of response . All

patients received an intravenous (IV) re-induction followed by two different subcutaneous (SC) maintenance regimens. Available data at the time of study design suggested that a single ustekinumab IV re-induction restored the response in a considerable proportion of patients, however we hypothesized that this single IV re-induction was insufficient to maintain clinical response and remission in the long term. The trial was conducted according to the Declaration of Helsinki, the 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 prior to 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 prior to 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 to a value maximum 3 or 6 months prior to 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 [two-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 to the lowest value obtained following induction with ustekinumab. (i.e. 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 one 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 prior to baseline. Concomitant treatment with another biological or small molecule therapy, steroids > 20 mg prednisolone or equivalent daily and ustekinumab 90mg SC administered at shortened intervals (<8 weeks) were exclusion criteria as well as intravenous (IV) re induction with ustekinumab in the six months prior to baseline. All patients were on 8 weekly dosing of ustekinumab prior to inclusion. Also, patients with an ileostomy were excluded. For full eligibility criteria see supplementary appendix page 3-4.

Procedures

Manual randomization used blocks of permutation. Randomization to one of the two 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 week 4, 12, 20, 28, 36 and 44 during study visits. Commercial ustekinumab (Stelara®) was given at week 0, 8, 16, 24, 32, 40 and 48.

All eligible subjects received a re-induction at baseline (week 0), with intravenous ustekinumab, in line with the EU SmPC, 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 four weeks (Q4W) arm received a blinded 90 mg SC injection of ustekinumab while subjects in the every eight 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 S1.

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. Prior to each infusion, serum was collected for ustekinumab concentrations. PRO-2 was calculated at each visit based upon patients' diaries excluding the day of the bowel preparation and day of endoscopy in case of an endoscopy. The PRO-2 includes two components.⁷ The stool frequency score is calculated based on the 7-day average of the number of liquid or very soft stools per day. The abdominal pain 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, week 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 eight subdomains grouped in two 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-CD¹¹. In case of discrepancy between the results of the local and central reading based on a sliding scale (Supplementary appendix page 4) 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 two central readers was used. The SES-CD ranges from 0 to 56, with higher scores indicating more severe endoscopic disease activity (Supplementary table S1).

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 $FCP < 250 \mu\text{g/g}$ and no steroids in the 90 days prior to the week 48 time point. Non-ranked secondary endpoints included complete endoscopic remission ($SES\text{-}CD < 3$), endoscopic remission ($SES\text{-}CD < 5$), endoscopic response ($\geq 50\%$ decrease in $SES\text{-}CD$ compared to screening) at week 48, clinical remission (PRO-2 remission: $AP \leq 1$ AND $SF \leq 3$) at week 8 and 48, biomarker remission ($CRP < 5 \text{ mg/L}$ and $FCP < 250 \mu\text{g/g}$) 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 Chi squared. 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 two study arms using a chi-square test with a two-sided alpha of 5%, between 64 to 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, Vienna, Austria).

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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, 37/54 (68%) patients in the Q4W arm and 35/54 (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 non-compliance (1 patient in the Q4W arm) and pregnancy (1 patient in the Q8W arm) (Figure 1). Patient characteristics were comparable between the two groups. Overall, the included patients had a median age of 41 years (IQR 32-54), were predominantly female (62%) and had a longstanding disease with a median disease duration of 14 years (IQR 7-22). The majority 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 $\mu\text{g/g}$ (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 [15%] of 54 patients) compared to the Q8W group (10 [19%] of 54 patients) ($p=0.5$; estimated effects (CI): 0.0502 (-0.09487-0.1953)). (Figure 2)

The endoscopic endpoints at week 48 showed numerically higher proportions of response and remission in the Q4W group compared to the Q8W group. However, none of the endoscopic endpoints achieved statistical significance. Complete endoscopic remission (SES-CD <3) was achieved in only 4 (8%) of 51 patients in the Q4W group and 3 (6%) of 50 patients in the Q8W group ($p=0.8$; MH-OR (95% CI): 0.787 (0.164-3.792)). Endoscopic remission (SES-CD <5) was achieved in 15 (29%) of 51 patients in the Q4W group and 8 (16%) of 50 patients in the Q8W group ($p=0.1$; MH-OR (95% CI) 0.467 (0.178-1.223)). Endoscopic response ($\geq 50\%$ decrease in SES-CD) was achieved in 12 (24%) of 51 patients in the Q4W group and 8 (16%) of 50 patients in the Q8W group ($p=0.7$; MH-OR (95% CI):

0.837 (0.320-2.187)). (Figure 3A) The majority of the 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 similar proportion of patients in the two treatment groups achieved clinical remission, with 19 (36%) of 53 patients in the Q4W group and 21 (39%) of 54 patients in the Q8W group ($p=0.7$; MH-OR (95% CI): 1.143 (0.526-2.484)). This clinical remission was relatively maintained till week 48, showing 16 (31%) of 52 patients in the Q4W group and 18 (36%) of 50 patients in the Q8W group ($p=0.6$; MH-OR (95% CI): 1.278 (0.562-2.904)) (Figure 3B). In the time to first clinical remission analysis, clinical remission in both treatment groups is achieved in the majority of patients prior to week 24 with no significant difference between the Q4W group and the Q8W group ($p=0.1$) (Supplementary figure S2).

Biomarker remission at week 48 was not significantly different between both treatment groups. In the Q4W group 18 (36%) of 50 patients compared to 13 (26%) of 50 patients in the Q8W group achieved biomarker remission ($p=0.3$; MH-OR (95% CI): 0.630 (0.268-1.483)) (Figure 3C). When analyzing only patients with elevated CRP ($n=52$) 6/29 (21%) achieved CRP normalization in the Q4W group and 4/23 (17%) in the Q8W group ($p>0.9$). Of patients with elevated FCP at baseline ($n=52$), 10/27 (37%) achieved FCP normalization in the Q4W group and 4/25 (16%) in the Q8W group ($p=0.09$) (Supplementary figure S3).

Exploratory analysis to identify predictors for short term effect (week 4) of an IV re-induction with ustekinumab showed no association with specific baseline characteristics (Supplementary tables S2). Additionally, we could not identify clinically relevant predictors for the primary endpoint based on the baseline characteristics (Supplementary tables S2).

Safety endpoints

Adverse events occurred in 91 (84.3%) of 108 patients 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 (32.4%) of 108 patients. A list of the major adverse events

and serious adverse events can be found in the supplementary appendix Table S3. Serious adverse events (SAE) occurred in 9 (17%) of 54 patients (n=11 SAEs) and 7 (13%) of 54 patients (n=16 SAEs) in the Q4W group and Q8W group respectively. Hospitalization occurred in 9 (17%) of 54 patients and 7 (13%) of 54 patients 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 week 0, 8 and 48 are trough concentration 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 re-induction 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 significant difference in the trough concentration of ustekinumab between the two 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 to the Q8W group respectively ($p = 0.002$). 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 to baseline. The ustekinumab serum levels at week 48 were 6.0 (4.8, 9.6) µg/mL and 2.1 (1.6, 2.9) µg/mL in the Q4W group compared to the Q8W group respectively ($p < 0.001$). (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 week 0, 8 and 48 with biomarker remission at week 48. (Supplementary table S4). 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 S4).

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 S5) Based on the SF-36 no clear difference in the impact was seen between the two treatment arms on the physical or mental domains through the study. (Supplementary table S5). There was an overall improvement of the quality of life in the 8 subdomains.

Discussion:

In this REScUE study in patients with Crohn's disease with secondary loss of response to ustekinumab, we demonstrated that dose-intensification with one IV re-induction of ≈ 6 mg/kg ustekinumab followed by 90 mg ustekinumab SC either Q4 weekly or Q8 weekly 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. The majority of the patients achieved clinical remission in the first 24 weeks after IV re-induction though, suggesting that the IV re-induction is the main driver of the effectiveness, rather than the subsequent SC dose-intensification. Our results are in contrast with several retrospective and observational non-randomized 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 re-induction with ustekinumab. We hypothesized that a direct increase in drug exposure based on an IV re-induction would be more favourable for recapturing the response/remission than a gradual increase based on 4 weekly dosing without IV re-induction. However, we also hypothesized that a single IV re-induction 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 to 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 Q4W 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 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 CD patients with secondary loss of response. This study compared one IV re-induction with ustekinumab ($\approx 6\text{mg/kg}$) versus placebo in patients on maintenance SC ustekinumab 90mg Q8W. The primary endpoint of clinical response (≥ 100 -point decrease from baseline/Crohn's disease activity index < 150) after 16 weeks was not met (49% in the IV re-induction versus 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 re-induction with ustekinumab. Since the treatment effect in RESCUE seems mainly to come from the IV re-induction, it can be questions if serial IV re-induction could be an option in repeated loss of response.

Previously, a target ustekinumab trough level of $1.4\text{ }\mu\text{g/ml}$ 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 $>2\text{ }\mu\text{g/ml}$ through week 48. These observations challenges the value of a general target trough concentration for ustekinumab. 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 the majority 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 previous 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

limitations. 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, the majority of 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 re-induction of ustekinumab followed by intensified maintenance dosing Q4W 90 mg SC was not superior in achieving steroid-free clinical remission over a single IV re-induction followed by Q8W 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 re-induction 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. Re-evaluation 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 Crohn's disease and enlarge the field of testing new strategies including serial IV re-induction.

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Figure 1: CONSORT flow diagram of the REScUE study

Figure 2: Steroid free clinical remission: PRO2 (AP ≤ 1 AND SF ≤ 3) and FCP $<250\mu\text{g/g}$ and no steroids for 90 days prior to week 48.

Figure 3: Secondary endpoints (A): Endoscopic outcomes at week 48: Complete endoscopic remission (SES-CD <3); Endoscopic remission (SES-CD <5); Endoscopic response ($\geq 50\%$ 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 $\mu\text{g/g}$) at week 48.

Table legends

Table 1: Baseline characteristics of the patients included in the REScUE study. (CD Crohn's disease, CRP C-reactive protein, FCP fecal calprotectin, IQR interquartile range, TNF tumor necrosis factor, UST ustekinumab)

Table 2: Evolution of the ustekinumab levels over time. * 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. † Wilcoxon rank sum test. (IQR interquartile range, n number).

Table 1

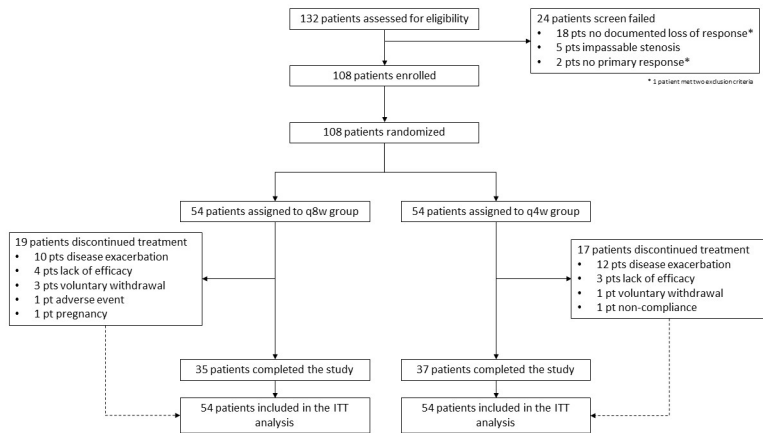
	Q4W UST group, N = 54	Q8W UST group, N = 54
Age (years; median (IQR))	40 (32, 57)	41 (32, 53)
Disease duration (years; median (IQR))	14 (8, 23)	12 (7, 21)
Sex (female)	35 (65%)	32 (59%)
Weight (kg; median (IQR))	69 (61, 81)	71 (61, 83)
Active smoking (n; %)	12 (22%)	13 (24%)
CD Montreal location		
L1 Ileal (n; %)	16 (30%)	10 (19%)
L2 Colonic (n; %)	9 (17%)	6 (11%)
L3 Ileocolonic (n; %)	29 (54%)	38 (70%)
L4 Proximal involvement (n; %)	4 (7%)	9 (17%)
Peri-anal involvement (n; %)	11 (20%)	14 (26%)

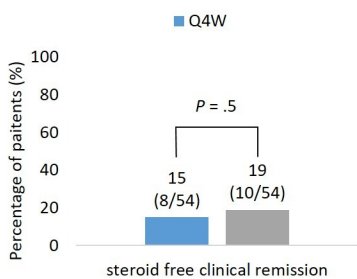
CD Montreal behaviour		
B1 Inflammatory	27 (50%)	25 (46%)
B2 Stricturing	20 (37%)	20 (37%)
B3 Penetrating	7 (13%)	9 (17%)
Previous resective surgery (n; %)	30 (56%)	28 (52%)
CRP (mg/L; median (IQR))	7 (3, 16)	4 (2, 7)
FCP (µg/g; median (IQR))	370 (164, 782)	520 (146, 931)
Steroids at baseline (n; %)	6 (11%)	6 (11%)
Previous anti-TNF exposure (n; %)	49 (91%)	50 (93%)

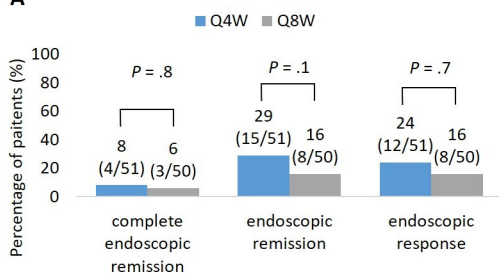
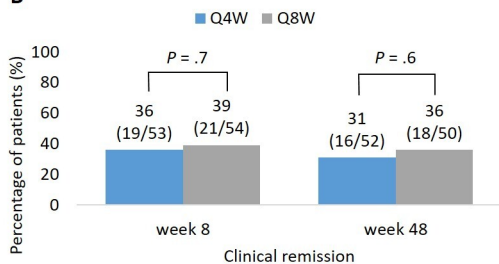
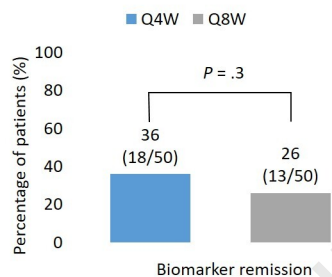
Table 2

Treatment group	Q4 N = 54	Q8* N = 54	p-value [‡]
Baseline (Week 0)			
Non-missing (n)	53	50	
Median (IQR) µg/mL	1.39 (0.84, 2.74)	1.31 (0.91, 2.34)	>0.9
Week 4			
Non-missing (n)	52	53	
Median (IQR) µg/mL	20 (16, 25)	20 (16, 30)	0.4
Week 8			
Non-missing (n)	53	50	
Median (IQR) µg/mL	10.8 (8.0, 15.9)	8.2 (4.9, 11.1)	0.002
Week 12			

Non-missing (n)	48	49	
Median (IQR) µg/mL	8.4 (5.3, 12.5)	7.5 (5.3, 9.6)	0.4
Week 20			
Non-missing (n)	44	44	
Median (IQR) µg/mL	6.9 (3.9, 9.7)	4.9 (3.5, 6.9)	0.049
Week 28			
Non-missing (n)	43	38	
Median (IQR) µg/mL	5.9 (4.0, 8.3)	4.6 (3.7, 5.6)	0.018
Week 36			
Non-missing (n)	37	34	
Median (IQR) µg/mL	5.74 (4.53, 8.61)	4.47 (3.28, 7.02)	0.031
Week 48			
Non-missing (n)	34	32	
Median (IQR) µg/mL	6.0 (4.8, 9.6)	2.1 (1.6, 2.9)	<0.001





A**B****C**

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.**

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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 Middelaes, 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 $\geq$ 1.7 mg/dL
 - d. AST and ALT > 3 times the ULN range
 - e. Direct (conjugated) bilirubin $\geq$ 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

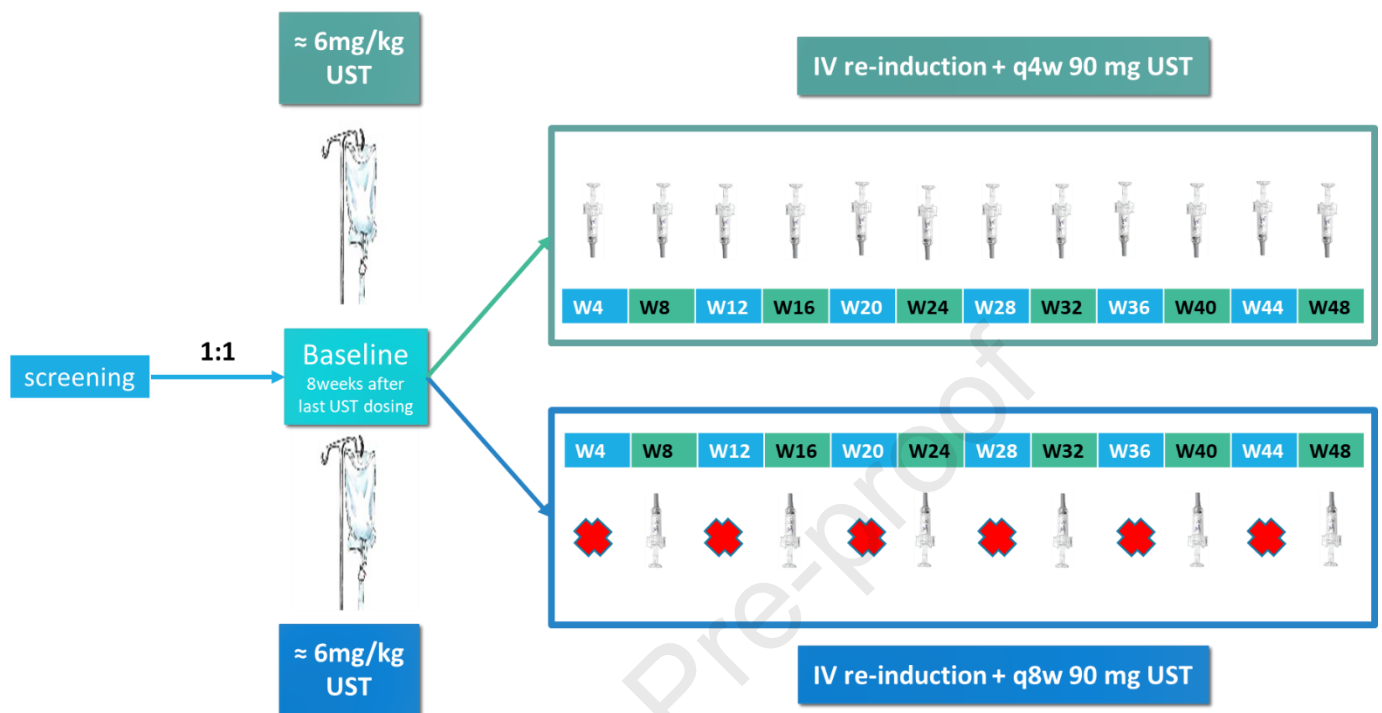


Figure S2: cumulative incidence of first clinical remission ($AP \leq 1$ and $SF \leq 3$) in the two treatment arms (non-parametric Fine-Gray test can test p-value = 0.1)

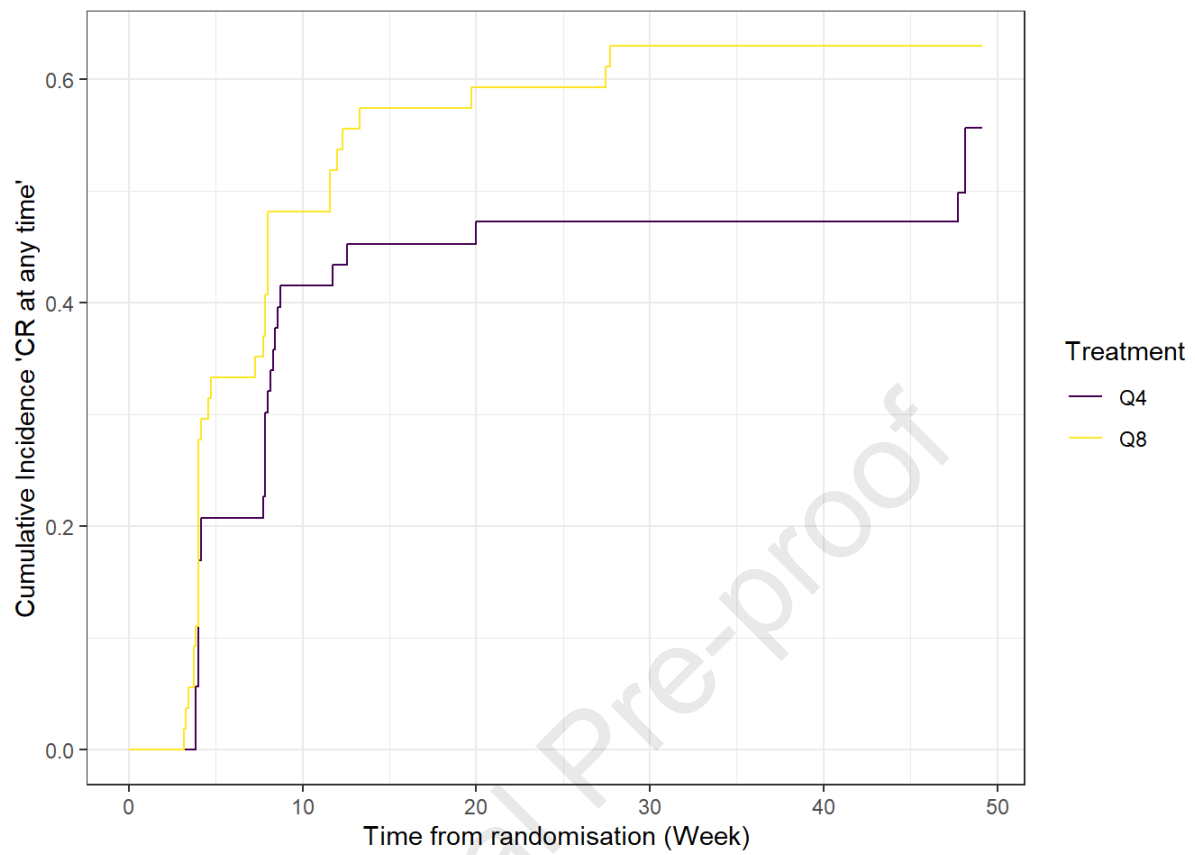


Figure S3: Biomarker remission in patients with elevated biomarker at baseline (CRP $\geq$ 5 mg/L; FCP $\geq$ 250 μ g/g) at week 48.

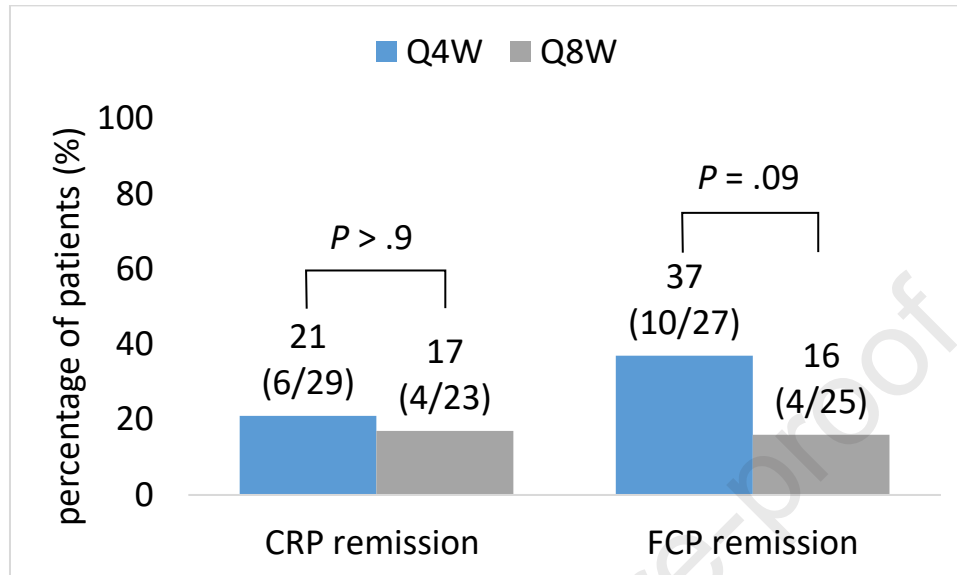


Figure S4: correlation between difference in ustekinumab levels at week 8 vs baseline and primary outcome

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)

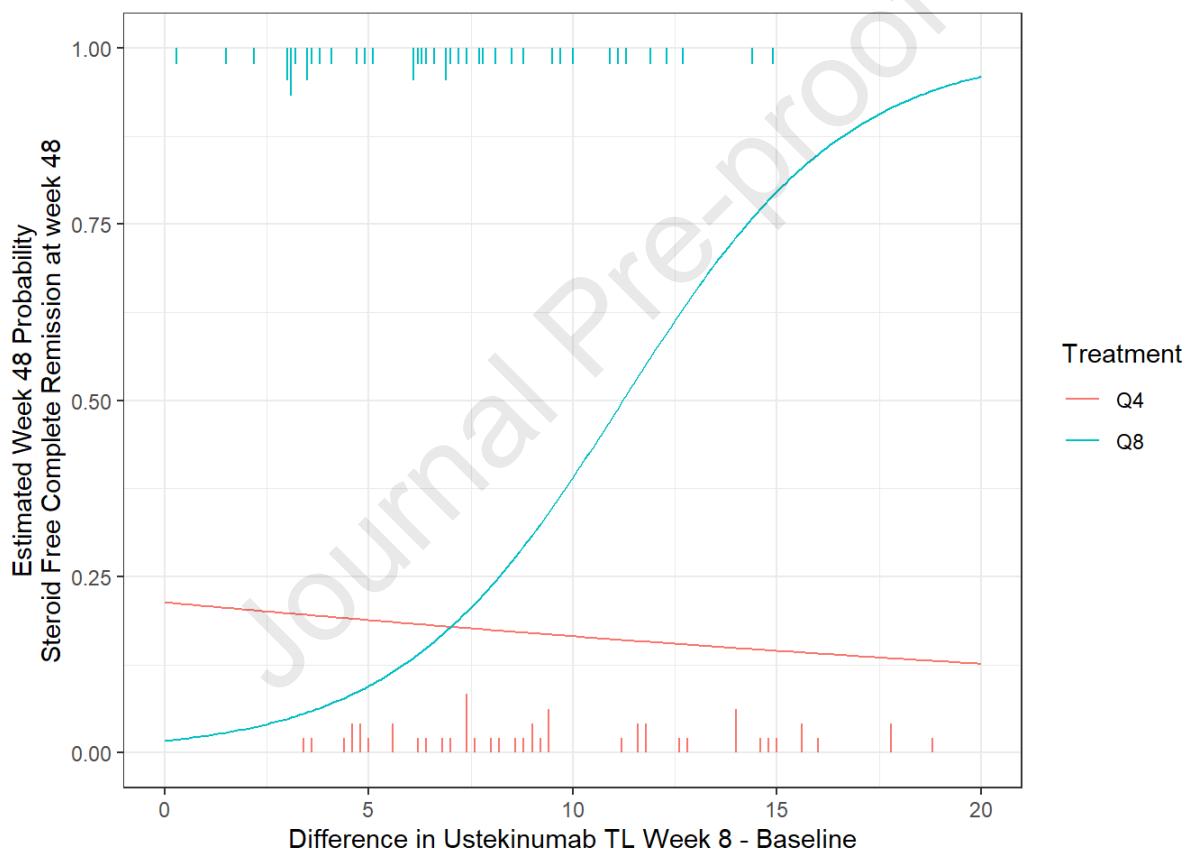
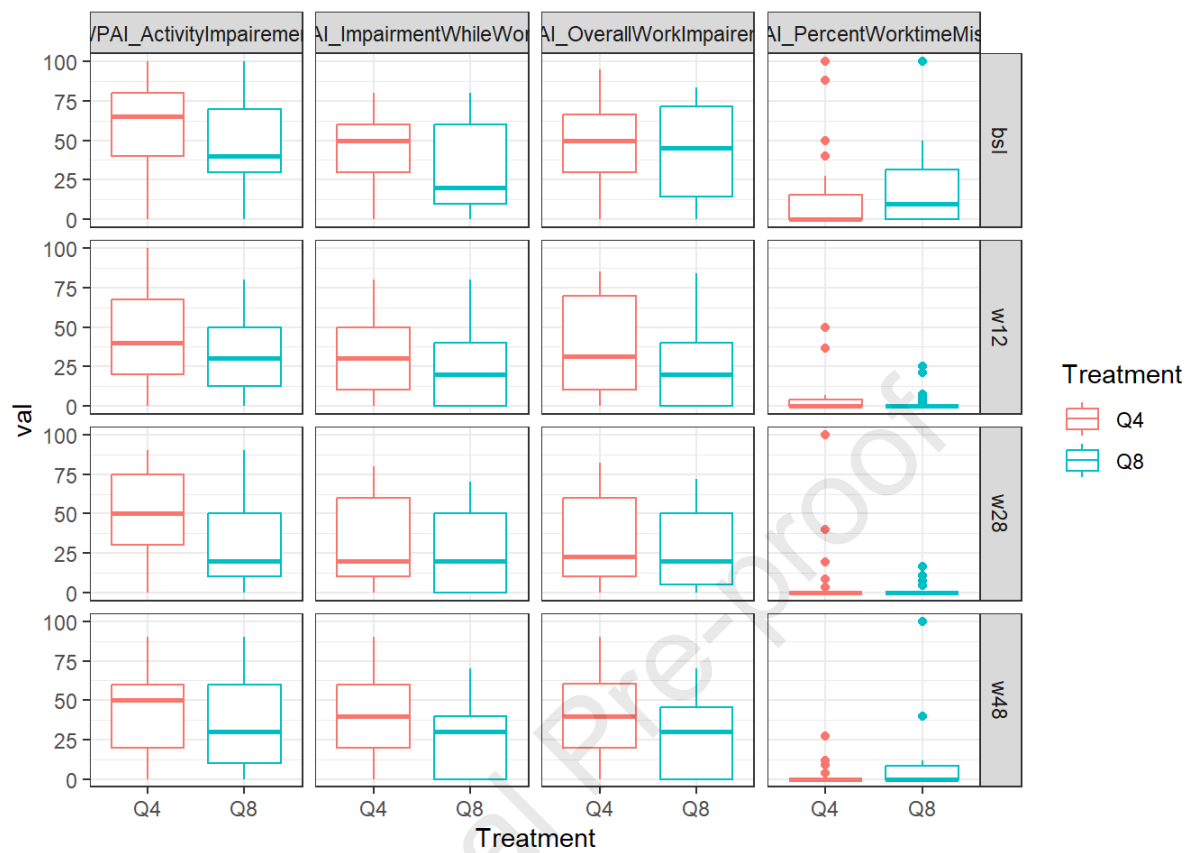


Figure S5: Work Productivity and Activity Impairment outcomes



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 μ g/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.

Characteristic	clinical remission			biomarker remission			PRO-2 response			biomarker response		
	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.

Characteristic	FCP remission (screening FCP >250 µg/g)			CRP remission (screening CRP >5 mg/L)		
	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
Stricture 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 disorders	1 (%)	2 (%)
	-	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 [†]	95% CI [†]	p-value	OR [†]	95% CI [†]	p-value	OR [†]	95% CI [†]	p-value	OR [†]	95% CI [†]	p-value
Baseline Trough Levels Ustekinumab	1.30	0.48, 2.00	0.2	1.40	0.49, 2.12	0.1	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, 1.22	0.049	1.08	1.00, 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, 1.30	0.13	0.95	0.82, 1.10	0.5	1.35	1.13, 1.61	0.002
No. Obs.	64			65			66			64		

[†] 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

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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.