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INFLAMMATORY BOWEL DISEASE

Early Ultrasound Response and Progressive Transmural Remission After Treatment With Ustekinumab in Crohn's Disease

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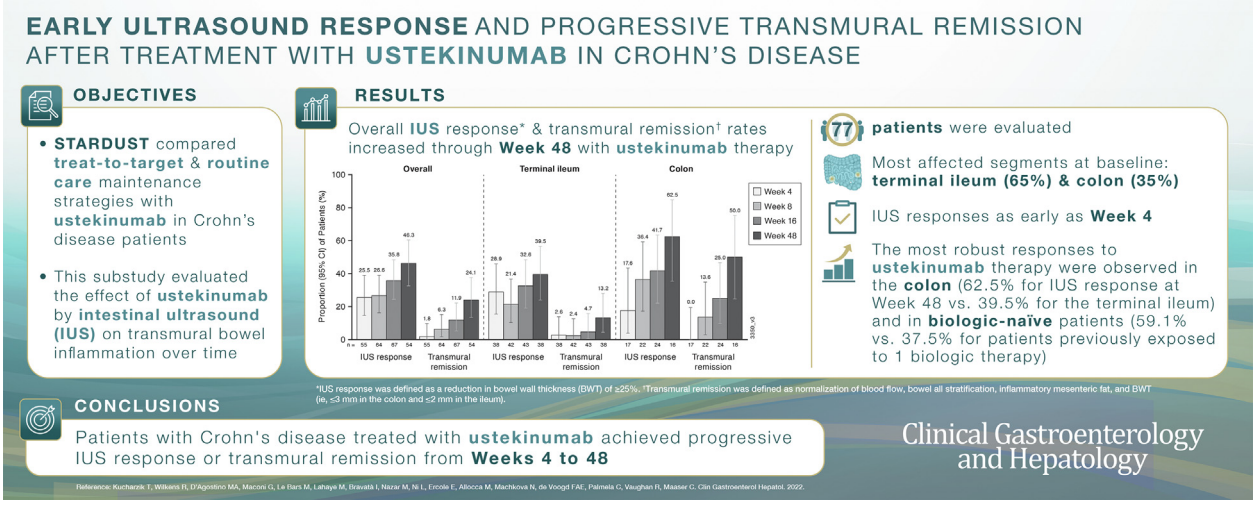

BACKGROUND & AIMS: **In this STARDUST substudy, the effect of ustekinumab on transmural bowel inflammation was assessed in adults with moderate-to-severe Crohn's disease (CD) by using intestinal ultrasound (IUS), a noninvasive imaging procedure.**

Abbreviations used in this paper: **BWS, bowel wall stratification; BWT, bowel wall thickness; CD, Crohn's disease; CDS, color Doppler signal; CI, confidence interval; ECCO, European Crohn's and Colitis Organisation; ESGAR, European Society of Gastrointestinal and Abdominal Radiology; IBD, inflammatory bowel disease; IUS, intestinal ultrasound; NPV, negative predictive value; NRI, nonresponder imputation; SES-CD, Simple Endoscopic Score for Crohn's Disease; STARDUST, Study of Treat to Target Versus Routine Care Maintenance Strategies in CD Patients treated with Ustekinumab; T2T, treat-to-target.**

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METHODS: **STARDUST was an international, multicenter, phase 3b, interventional, randomized controlled trial specifically designed to compare treat-to-target and standard-of-care treatment strategies in ustekinumab-treated CD patients. In this substudy, the most affected bowel segment at baseline by IUS was used for all analyses. Key IUS endpoints (centrally read, parameter-blinded) were IUS response, transmural remission, bowel wall thickness (BWT), blood flow, bowel wall stratification, and inflammatory fat.**

RESULTS: **Seventy-seven patients were evaluated. IUS response could be determined 4 weeks after treatment initiation, with progressive improvement through week 48. IUS response and transmural remission rates at week 48 were 46.3% and 24.1%, respectively. IUS response, transmural remission, BWT, and blood flow normalization rates were more pronounced in the colon and biologic-naive patients. Fair/moderate reliability (κ = 0.21–0.51) was observed between week 4 IUS response and week 48 overall endoscopic response and fecal calprotectin/complete biomarker outcomes. Endoscopy and IUS baseline agreement was >90% in determining the terminal ileum as the most affected bowel segment. IUS response absence at week 4 was associated with no endoscopic response (based on the simplified endoscopic score for Crohn's disease terminal ileum subscore) at week 48 (negative predictive value = 73%).**

CONCLUSIONS: **In this first international, multicenter, interventional study, IUS showed that ustekinumab-treated CD patients achieved progressive IUS response (46.3%) and transmural remission (24.1%) through week 48, with a more robust response in the colon and biologic-naive patients. ClinicalTrials.gov number: NCT03107793**

Keywords: STARDUST; Crohn's Disease; Intestinal Ultrasound; Transmural Remission.

Disease activity defined solely by clinical endpoints is inadequate,[1] and frequent repetition of invasive procedures like endoscopy is not feasible. Intestinal ultrasonography (IUS) is a noninvasive, quick and accurate, radiation-free, cost-effective, patient-preferred imaging technique used as a standard procedure for Crohn's disease (CD) in many European inflammatory bowel disease (IBD) centers.[2] Meta-analyses have demonstrated high and equivalent sensitivity and specificity compared with magnetic resonance enterography and computed tomography in primary diagnosis, detection of complications, and follow-up of intestinal involvement in CD patients.[3,4] The joint European Crohn's and Colitis Organisation (ECCO) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) recommend IUS as a first-line diagnostic tool.[5]

IUS permits visualization of bowel wall thickness (BWT), blood flow (ie, vascularization), and the occurrence of mesenteric fat proliferation,[6,7] all considered key imaging features of intestinal inflammatory activity in CD.[6,8,9] Increased vascularization visualized by increased color Doppler signal (CDS) correlates with endoscopy, histology, and the CD Activity Index.[10] Disturbance of the typical bowel wall stratification (BWS) can be an indicator of active inflammation/ulcers.[11] Mesenteric fat proliferation occurs rapidly during an acute disease flare.[6,11]

Therefore, transmural activity and remission can be assessed and monitored by IUS in CD.[6,12] The updated Selecting Therapeutic Targets in Inflammatory Bowel Disease-II recommendations for CD now recognize transmural healing as an important adjunctive treatment measure.[1] This IUS substudy of STARDUST (Study of Treat to Target Versus Routine Care Maintenance Strategies in CD Patients Treated with Ustekinumab)[13] was conducted to evaluate the effect of ustekinumab on transmural bowel inflammation over time.

Methods

Patients

STARDUST is a European, multicenter, phase 3b randomized interventional study of ustekinumab in adults with moderate-to-severe CD to investigate the benefit of a treat-to-target (T2T) versus standard-of-care maintenance treatment strategy.[13] The protocol was approved by relevant ethics committees or institutional review boards and conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations.

For all patients participating in this substudy, IUS assessments were performed at weeks 0, 4, 8, 16, and 48 or upon early termination. Patients who were obese or exhibiting other characteristics precluding IUS visualization of the affected bowel segment, or with normal BWT (ie, $\leq$2.0 mm for the terminal ileum; $\leq$3.0 mm for the colon) in all segments at week 0 were excluded. Before any substudy-specific assessment was performed, an additional informed consent form was signed by participating patients. All authors had access to the study data and reviewed and approved the final manuscript.

Intestinal Ultrasound

This substudy was performed in selected centers with IUS expertise that also participated in the STARDUST

main study. Study-specific IUS preparatory training was undertaken to ensure uniformity of investigation and documentation standards. Neither patients nor treating physicians were blinded to treatment assignment in the main study; however, the gastroenterologist or radiologist performing IUS and the IUS central reader were blinded to the endoscopy results and treatment decisions; treating physicians were blinded to the IUS findings.

For visits requiring IUS and endoscopy per the main protocol, a minimum 2-day interval was mandatory because ileocolonoscopic bowel cleansing may cause bowel wall edema and affect measurement of BWT.

At each substudy visit, IUS assessed the terminal ileum, cecum, ascending, transverse, descending, and sigmoid colon. If deemed pathologic, all parameters of the pathologic segment(s) were then evaluated. Cineloops were annotated and recorded in cross-sectional and longitudinal scan planes for each pathologic bowel segment. Rectal involvement was not an exclusion criterion for the substudy. However, because the rectum was not routinely examined because of general poor imaging quality, it was not deemed the most severe segment in any case. The fasting status of patients (fasting period $\leq$4 hours versus $>$4 hours) was noted. Another cineloop recorded color Doppler imaging optimized for slow flow.[8]

All IUS cineloops and still images underwent central reading, blinded to clinical, endoscopic findings, and treatment arm. Only centrally read results were used for analysis.

Intestinal Ultrasound Parameters and Endpoints

Key IUS parameters (Supplementary Table 1) were segmental BWT, increased blood flow, BWS, and inflammatory mesenteric fat.[8]

IUS defined the most affected bowel segment at baseline as the segment with the largest BWT. This segment was followed through the study and used for all analyses.

Segmental IUS response and transmural remission were prospectively defined as a reduction in BWT of $\geq$25% and normalization of all IUS parameters, respectively, in the target bowel segment.

For patients discontinuing from the study before week 48 an early termination assessment was performed as closely as possible to the time of discontinuation unless consent was withdrawn.

IUS central reading procedures are described in detail in the Supplementary Material. All data collected by local IUS investigators were entered in the electronic case report form. Central readers could accept the imputations by the local IUS investigator, update entered data based on consensus reading, or decline the IUS examination in total. Central reading results were used as endpoints for statistical analyses.

What You Need to Know

Background

Intestinal ultrasound (IUS) has many advantages as a noninvasive, accurate, radiation-free, cost-effective imaging technique, which is well-accepted and used as a standard procedure for patients with Crohn's disease (CD).

Findings

IUS response and transmural remission rates progressively increased through week 48 with ustekinumab therapy; they were most pronounced in the colon and biologic-naive patients. Fair-moderate reliability between early IUS response and week 48 endoscopic and biomarker responses was observed.

Implications for patient care

Noninvasive IUS is complementary to endoscopy for assessing CD activity, particularly in patients with terminal ileum strictures, and could be used early for potential therapy modification with improved outcomes.

Statistical Analysis

This substudy was exploratory and designed to collect IUS parameters in CD patients treated with ustekinumab.

The intent-to-treat population of the IUS substudy was defined as all patients who signed informed consent, were not screening failures, were randomized, and provided data for at least 1 IUS parameter. This analysis was performed when all patients enrolled in the substudy had completed the week 48 IUS assessments or discontinued earlier.

No formal hypotheses were prespecified (it was estimated that the IUS response at week 16 would vary between 60% and 80% (80% after 3 months with tumor necrosis factor alpha antagonists[14] and 55%–60% with ustekinumab).[15]

On the basis of feasibility assessments, it was anticipated that 60–90 patients could be enrolled. A sample size of 62 would produce a 2-sided 95% confidence interval (CI) with a width equal to 20% when the sample proportion of IUS response at week 16 was 80%. A sample size of 93 would produce a 2-sided 95% CI with a width equal to 20% when the sample proportion of IUS response at week 16 was 60%.

Descriptive statistics summarized data of each IUS endpoint as observed.

No comparison between T2T and standard-of-care was planned because of the exploratory nature of the substudy.

The Spearman correlation coefficient was used to explore the association between continuous IUS and clinical, biomarker, and endoscopic response variables.

Reliability between IUS response at different time points and overall endoscopic response, clinical and biomarker outcomes at week 48 was assessed using kappa statistics (Cohen's kappa statistic and in some cases positive predictive value and negative predictive value [NPV]) and interpreted as suggested by Cohen.[16]

For dichotomous endoscopic, clinical, and biomarker outcomes used to assess reliability with IUS response, patients with missing data (defined as those who terminated the study before the designated visit) or patients who have a missing value at the designated visit were considered not to have achieved their efficacy endpoint (non-responder imputation [NRI]). For continuous endoscopic, clinical, and biomarker variables used to analyze correlations, the last available non-missing value was carried forward for patients with missing data. A post hoc sensitivity analysis using $\leq$3 mm both in the colon and terminal ileum was performed to assess transmural remission and BWT normalization overall and by biologic treatment history following a recently published study.[17,18]

Results

Patient Characteristics and Disposition

Eighty-eight patients at 18 sites in Europe were enrolled and randomized at week 16 (January 2018 to March 2020). Seventy-seven patients had a baseline IUS assessment, and 71 had baseline and at least 1 post-baseline IUS assessment (Supplementary Figure 1).

Baseline characteristics of this IUS patient subgroup were similar to those of the overall STARDUST population (Table 1).

Intestinal Ultrasound Results by Most Affected Bowel Segment

At baseline, IUS determined terminal ileum as the most affected segment in 50 patients (65.0%) and colon in 27 of 77 patients (35.0%).

Statistically significant relative and absolute reductions from baseline in BWT were observed as early as week 4 (Figure 1, Supplementary Figure 2).

Overall IUS response and transmural remission rates increased progressively through week 48 to 46.3% and 24.1%, respectively. Rates were numerically greater in the colon (62.5% and 50.0%, respectively) than the terminal ileum (39.5% and 13.2%, respectively) (Figure 2). An NRI sensitivity analysis showed a similar progressive increase in IUS response and transmural remission (Supplementary Figure 3).

The proportion of patients with normalized IUS parameters increased progressively from weeks 0 through 48. At week 48, normalization of IUS parameters was numerically more pronounced in the colon than terminal ileum, mainly for BWT (50.0% versus 15.8%) and blood flow (85.7% versus 67.6%). Differences were less pronounced for BWS (66.7% versus 63.2%) and mesenteric inflammatory fat (68.8% versus 50.0%) (Figure 3).

A post hoc sensitivity analysis using a less stringent definition of normalized BWT as $\leq$3 mm for both the terminal ileum and colon showed the rate of patients with BWT normalization and transmural remission nearly doubled at week 48 for the terminal ileum (28.9% from 15.8%) and increased overall (31.5% from 24.1%). Meaningful differences were observed between the colon and terminal ileum (50.0% versus 28.9%, respectively) (Supplementary Figure 4).

The IUS subgroup's endoscopic, clinical, and inflammatory biomarker results were consistent with the STARDUST main study (Table 2).[14] At week 48, the endoscopic response was higher in colonic segments than the terminal ileum. In contrast, C-reactive protein concentration improvement and normalization were comparatively more pronounced when the terminal ileum was deemed most affected by IUS.

Intestinal Ultrasound Results by Biological Treatment History

Statistically significant relative and absolute reductions from baseline in BWT for biologic-naive patients were observed as early as week 4 (Supplementary Figure 5). IUS response and transmural remission rates at week 48 (Supplementary Figure 6) were numerically higher for biologic-naive (59.1% and 31.8%, respectively) than for patients with prior exposure to one biologic therapy (37.5% and 18.8%, respectively). The proportion of patients with normalized IUS parameters increased progressively from weeks 0 through 48. At week 48, normalization of transmural remission components (Supplementary Figure 7) was numerically more pronounced for biologic-naive patients than for patients with prior exposure to one biologic therapy for BWT (31.8% versus 21.9%), BWS (76.2% versus 56.3%), and mesenteric inflammatory fat (63.6% versus 50.0%), but not blood flow (70.0% versus 74.2%).

Independent of the cutoff used for BWT normalization, transmural remission rates increased progressively through week 48, and normalization of BWT at week 48 was numerically higher for biologic-naive patients than for patients with prior exposure to one biologic therapy (Supplementary Figure 8).

Reliability Between Intestinal Ultrasound Assessment and Week 48 Endoscopic and Biomarker Response

Fair to moderate reliability (κ range, 0.21–0.51) was observed between IUS response at different time points (weeks 4, 8, 16, and 48) and endoscopic and biomarker responses at week 48. In particular, the reliability between IUS response and $\geq$50% improvement in fecal

Table 1. Demographic and Disease Characteristics of the IUS Substudy and Overall Patient Populations

Characteristics	IUS substudy (N = 77)	All randomized (N = 440)
Age, *y*, mean (SD)	37.5 (11.9)	37.3 (13.0)
Female, n (%)	34 (44.2)	225 (51.1)
Body mass index, kg/m^2, mean (SD)	23.0 (4.0)	23.8 (4.7)
Time from diagnosis to first study drug administration, *mo*	105.2 (86.9)	113.6 (105.6)
CDAI, N mean (SD)	77 294.8 (64.0)	439 287.2 (60.1)
CRP, *mg/L*, N median (IQR)	77 8.8 (4.0–17.0)	437 7.4 (2.4–21.0)
FC, *μg/g*, N median (IQR)	77 798.0 (322–1747)	385 866.0 (304–1780)
Prior exposure to biologics, n (%)		
Biologic-naive	31 (40.3)	169 (38.4)
Prior exposure to 1 biologic	46 (59.7)	271 (61.6)
Loss of or inadequate response	32 (69.6)	212 (78.2)
Intolerance	4 (8.7)	28 (10.3)
All other reasons	10 (21.7)	31 (11.4)
SES-CD score, mean (SD)	13.8 (7.4)	13.1 (8.2)
Location of disease by endoscopy, n (%)		
N	77	415
Terminal ileum	20 (26.0)	108 (26.0)
Colonic	30 (39.0)	155 (37.3)
Ileocolonic	27 (35.1)	152 (36.6)
Most affected bowel segment by IUS		
Overall, n (%)	77 (100.0)	N/A
Terminal ileum, n (%)	50 (65.0)	N/A
Colon, n (%)	27 (35.0)	N/A
Bowel wall thickness, *mm*		
Overall, n	71	N/A
mean (95% CI)	5.60 (5.26–5.94)	N/A
Terminal ileum, n	46	N/A
mean (95% CI)	5.42 (5.02–5.83)	N/A
Colon, n	25	N/A
mean (95% CI)	5.93 (5.30–6.56)	N/A
Biologic-naive, n	29	N/A
mean (95% CI)	5.72 (5.07–6.37)	N/A
Prior exposure to 1 biologic, n	42	N/A
mean (95% CI)	5.52 (5.14–5.90)	N/A

NOTE. Values are mean (±SD) unless otherwise indicated.
CDAI, Crohn's disease activity index; CI, confidence interval; CRP, C-reactive protein; FC, fecal calprotectin; IQR, interquartile range; IUS, intestinal ultrasound; N/A, not applicable; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease.

calprotectin at week 48 was moderate (κ = 0.51 [0.25–0.78]) (Supplementary Figures 9 and 10).

Agreement Between Intestinal Ultrasound and Endoscopic Crohn's Disease Inflammation

Agreement between IUS and endoscopy at baseline was >90% in defining the most affected bowel segment, particularly for the terminal ileum (36/39, 92.3%), and good for specific overall bowel segment and specific colon segment (53/66, 80.3% and 17/27, 63.0%, respectively).

Association between BWT and Simple Endoscopic Score for Crohn's Disease (SES-CD) was tested only in the terminal ileum, where agreement between IUS and endoscopy was the highest in identifying the most affected bowel segment. A moderate and statistically significant correlation was found between BWT and SES-CD terminal ileum subscore and SES-CD total score at week 48 (Supplementary Figure 11). The NPV between IUS response at weeks 4, 8, 16, and 48 and endoscopic response based on SES-CD terminal ileum subscore at week 48 ranged from 73.3 to 80.0 (Table 3).

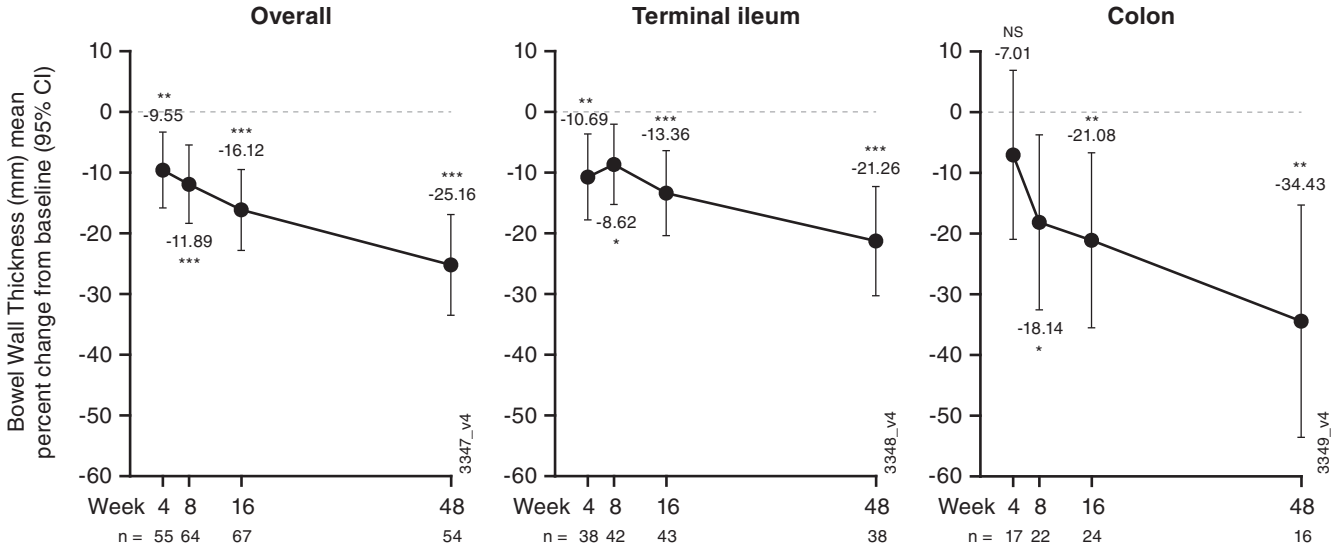

Figure 1. As observed analysis of mean percent change from baseline in bowel wall thickness over time for all patients in the IUS substudy and by bowel segment. Only patients with non-missing baseline value and at least one non-missing post-baseline value during the main treatment period are included in the analysis. CI, confidence interval; IUS, intestinal ultrasound. *$P < .05$, **$P < .01$, ***$P < .001$ (Wilcoxon signed-rank test, change from baseline).

Discussion

In this first international, multicenter, interventional substudy, centrally read IUS was used to assess response in ustekinumab-treated CD patients. We further explored the association of IUS response with endoscopic, clinical, and biomarker outcomes during 48 weeks of treatment.

Here we used a stringent definition of transmural remission measured by IUS based on 4 ultrasound components reflecting active inflammation or ulcers in CD patients: abnormally increased BWT, blood flow, loss

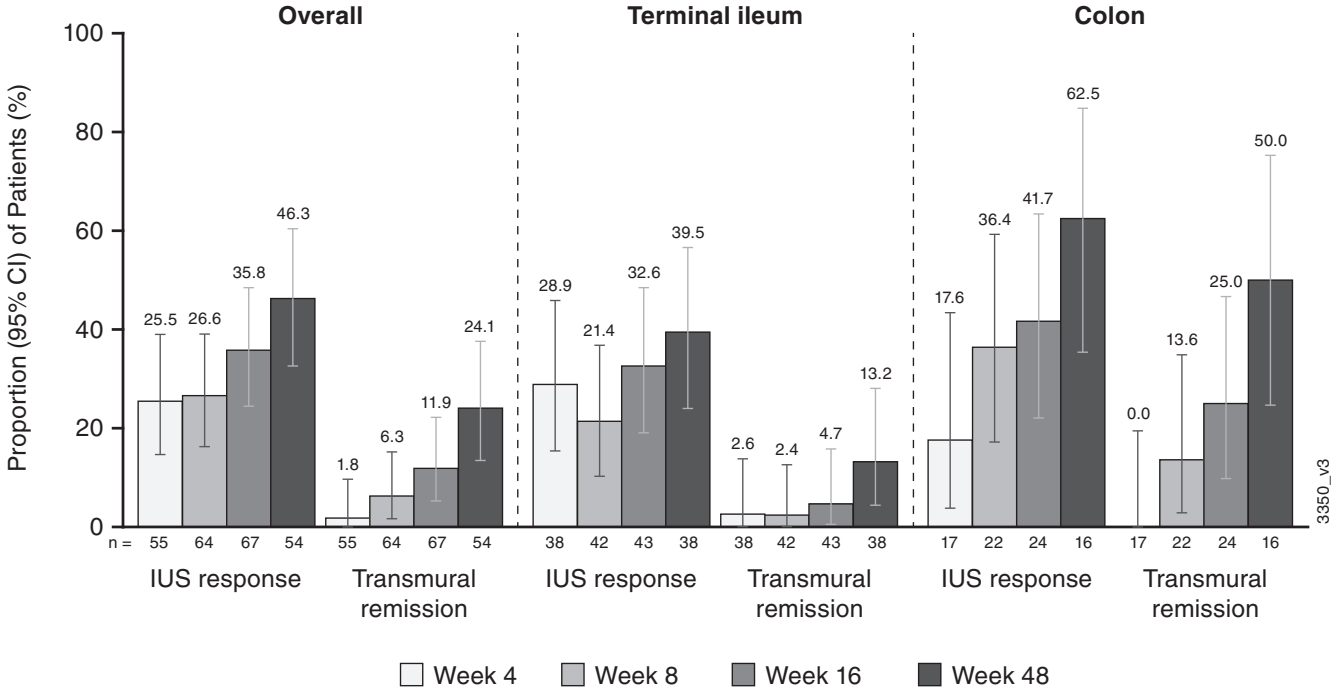

Figure 2. As observed analyses over time at week 48 of IUS response and transmural remission for all patients in the IUS substudy overall and by most affected bowel segment. NOTE. Only patients with non-missing baseline value and at least one non-missing post-baseline value during the main treatment period are included in the analysis. N at baseline and through week 48. IUS response was defined as reduction of ≥25% from baseline in BWT. Transmural remission was defined as normalization of BWT, blood flow (color Doppler signal), bowel wall stratification, and inflammatory mesenteric fat. The most affected (most thickened) bowel segment at baseline was used for IUS response/remission evaluation in the follow-up scans. If 3 of the 4 IUS parameters were normalized and the fourth is 'Not assessed/Not assessable', transmural remission is considered 'Yes'. BWT, bowel wall thickness; CI, confidence interval; IUS, intestinal ultrasound.

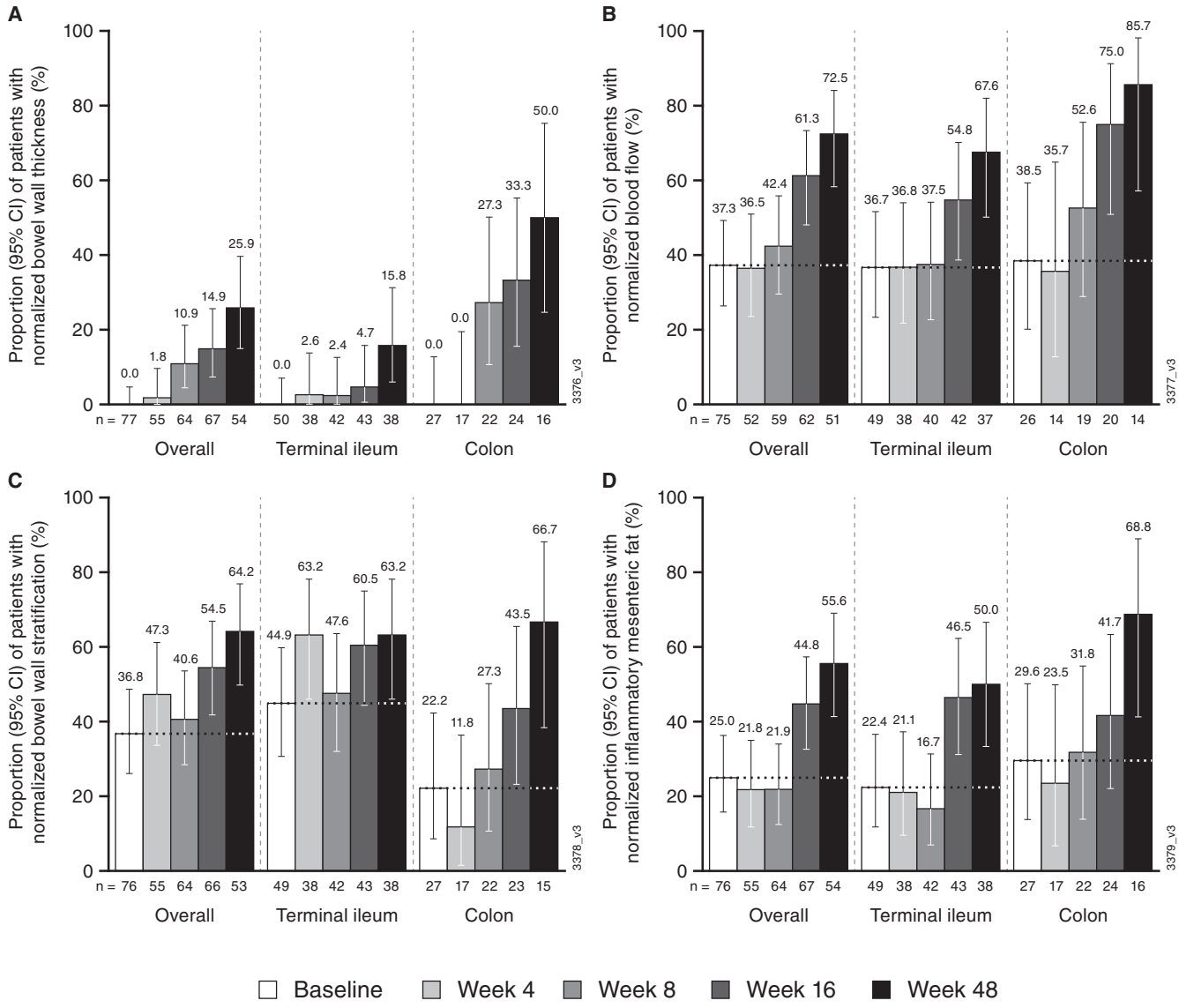

Figure 3. As observed analyses over time of normalized pathologic bowel wall thickness (*A*), blood flow (*B*), bowel wall stratification (*C*), and inflammatory mesenteric fat (*D*) at week 48 for all patients in the IUS substudy overall and by bowel segment. NOTE. Normalization of bowel wall thickness was defined as terminal ileum ≤2 mm and colon ≤3 mm. Normalization of blood flow (color Doppler signal 0 or 1). Normalization of bowel wall stratification was defined as normal/preserved bowel wall stratification. Normalization of inflammatory mesenteric fat was defined as absence of inflammatory fat. CI, confidence interval; IUS, intestinal ultrasound.

of BWS, and mesenteric inflammatory fat. These parameters were used to define IUS response and transmural remission.[19,20] By using this strict definition, transmural remission rates with ustekinumab increased progressively through week 48 up to 24.1%.

IUS response was observed as early as week 4, improving over time through week 48, suggesting that IUS could be a valuable objective tool to detect early response to treatment, potentially allowing for early treatment optimization. In addition, there was a fair-moderate reliability between IUS assessment over time and week 48 endoscopic and biomarker response, confirming that transmural remission is an important parameter to consider in CD, and transmural remission, measured by IUS, is an important endpoint in clinical practice and studies.[20,21]

Independent of the cutoff used in defining normalization for the terminal ileum, numerically higher IUS response and transmural remission rates with ustekinumab were noted in the colon versus terminal ileum. Differences between the terminal ileum and colon have been previously shown for other biologics and immunosuppressants.[14,22,23]

Because differences in cutoff values do not appear to affect the observed different response rates measured by IUS between colon and terminal ileum, it can only be speculated that separate pathophysiological mechanisms may account for these variations. Differences in inflammatory mesenteric fat and T-cell composition underscore the novel concept of colonic and ileal CD as distinct IBD entities.[24] Fibrosis with the potential to develop fibrostenosis is more likely to occur in the terminal ileum than

Table 2. Analyses of IUS (AO), Endoscopic, Clinical, and Inflammatory Biomarker Outcomes (NRI) at Week 48 by Most Affected Bowel Segment Defined by IUS

	Overall	Terminal ileum	Colon
IUS response	25/54 (46.3)	15/38 (39.5)	10/16 (62.5)
Transmural remission	13/54 (24.1)	5/38 (13.2)	8/16 (50.0)
Endoscopic response	29/77 (37.7)	17/50 (34.0)	12/27 (44.4)
Endoscopic remission	7/77 (9.1)	4/50 (8.0)	3/27 (11.1)
Clinical response	58/77 (75.3)	39/50 (78.0)	19/27 (70.4)
Clinical remission	50/77 (64.9)	33/50 (66.0)	17/27 (63.0)
CRP normalization	24/61 (39.3)	18/40 (45.0)	6/21 (28.6)
CRP ≥50% improvement	32/61 (52.5)	24/40 (60.0)	8/21 (38.1)
FC normalization	18/52 (34.6)	11/32 (34.4)	7/20 (35.0)
FC ≥50% improvement	22/52 (42.3)	13/32 (40.6)	9/20 (45.0)
Complete biomarker response	23/73 (31.5)	16/47 (34.0)	7/26 (26.9)

NOTE. Results are presented as n/N (%). The most affected (most thickened) part of the bowel wall was used for IUS response/transmural remission evaluation. As observed (AO) analysis: patients with data available at week 48 were included in the analysis. IUS response was defined as reduction of ≥25% from baseline in BWT. Transmural remission was defined as normalization of BWT, blood flow (color Doppler signal), bowel wall stratification, and inflammatory mesenteric fat. The most affected (most thickened) part of the bowel wall was used for response/remission evaluation. If 3 of the 4 IUS parameters are normalized and the fourth is 'Not assessed/Not assessable', transmural remission is considered 'Yes.' Non-responder imputation analysis (NRI): patients with a missing value at week 48 were considered not to have achieved their dichotomous efficacy endpoint. Endoscopic response was defined as reduction from baseline in SES-CD of ≥50%. Endoscopic remission was defined as SES-CD ≤2. Patients with missing data were analyzed as non-responders or non-remitters. Clinical response was defined as ≥100-point reduction from baseline CDAI score or CDAI score <150. Clinical remission was defined as CDAI score ≤150 points. Patients with missing data were analyzed as non-responders or non-remitters. Normalized CRP was defined as ≤3 mg/L. Normalized FC was defined as ≤250 μg/g. Patients with normalized CRP or FC at baseline are excluded. Patients with missing data are considered not normalized. Patients with normalized CRP at baseline (CRP ≤3 mg/L) or FC at baseline (FC ≤250 μg/g) are excluded. Patients with missing values are considered to have no improvement. Complete biomarker response was defined as both CRP and FC normalized. Patients with normalized CRP and FC at baseline are excluded, and patients with both missing CRP and FC at baseline are excluded. AO, as observed analysis; BWT, bowel wall thickness; CDAI, Crohn's disease activity index; CRP, C-reactive protein; FC, fecal calprotectin; IUS, intestinal ultrasound SES-CD, Simple Endoscopic Score for Crohn's Disease.

the colon, which may partially explain differences in treatment response to biological therapy.[25,26]

Here, IUS response and transmural remission rates were more pronounced in biologic-naive than in biologic-experienced patients, which is similar to clinical observations made previously.[27]

The STARDUST IUS substudy allowed for comparing invasive endoscopy and noninvasive IUS procedures in

Table 3. Agreement Over Time in Patients With Terminal Ileum Identified as the Most Affected Bowel Segment Having IUS Response (As Observed Analysis) and Endoscopic Response (Non-Responder Imputation)

	Endoscopic response at week 48					
IUS response	Yes	No	Overall agreement %	Kappa coefficient (95% CI)	PPV	NPV
Week 4						
Yes	2	7	54.2	–0.05 (–0.42 to 0.33)	22.2	73.3
No	4	11				
Week 8						
Yes	3	3	73.1	0.28 (–0.13 to 0.69)	50.0	80.0
No	4	16				
Week 16						
Yes	3	8	55.6	0.02 (–0.33 to 0.38)	27.3	75.0
No	4	12				
Week 48						
Yes	5	7	58.3	0.17 (–0.21 to 0.54)	41.7	75.0
No	3	9				

NOTE. Analyses used the ileum subscore for the SES-CD.
CI, confidence interval; IUS, intestinal ultrasound; NPV, negative predictive value; PPV, positive predictive value; SES-CD, Simple Endoscopic Score for Crohn's Disease.

identifying the most affected bowel segment. The high agreement between IUS and endoscopy observed at baseline in defining the terminal ileum as the most affected bowel segment suggests that IUS could be useful to objectively measure bowel inflammation in clinical studies along with endoscopy. The lower endoscopic remission rate observed, as compared with a higher IUS transmural remission rate, is probably due to the difference in segments included for remission and response; endoscopic remission considers normalization of all segments examined, whereas here the most affected segment was monitored by IUS over time. Because of the current lack of a validated activity score for IUS response, the study team decided to focus the analysis on the most affected segment because this usually leads to CD clinical symptoms. Also, less involved segments commonly respond in parallel to the most affected segment in clinical practice. Endoscopic response is defined as an improvement of $\geq$50% in SES-CD, whereas IUS response is defined as BWT reduction of $\geq$25% and not measuring the same pathophysiological improvement (mucosa vs transmural). Definitions for endoscopic and transmural remission vary, and direct comparison is rarely performed.[20] The reliability between biomarkers and IUS response was fair-moderate, thus, we believe that IUS is complementary to biomarkers. The lack of response on IUS at weeks 4, 8, and 16 is highly predictive of lack of endoscopic response and therefore serves as a helpful tool to direct clinicians for the need to either escalate therapy or change therapeutic agent in the maintenance phase.

Some limitations should be mentioned; the definition of IUS response and transmural remission is still debated,[19,20] and our study design was exploratory. Future large, prospective, and randomized controlled studies are needed to confirm whether early IUS response can predict long-term therapeutic outcomes for CD patients and whether IUS parameters such as transmural remission can be used as treatment targets in a T2T concept. This exploratory substudy was designed to estimate IUS response over time. The sample size was based on IUS response at week 16 of 60%–80% from real-world studies, producing 95% CI width of 20%. With 67 patients in our substudy, we obtained an IUS response of 36%; the width of the 95% CI was 22%. Note that we used a different definition of the objective IUS measure. Finally, at the time this study was performed, no validated score with demonstrable responsiveness was available. Here, IUS response based on decreases in BWT of $>$2 mm or $>$1 mm in BWT and 1-point CDS based on the Limberg score could not be calculated because no absolute values were recorded in patients who reached normal values for BWT below the defined cutoff. Thus, different individual IUS parameters were assessed. Using IUS parameters in a highly standardized manner and with central reading, we demonstrated very good objective response in ustekinumab-treated patients. Establishment of a validated score may lead to increased acceptance of IUS transmural remission as a future relevant target in CD patients.

This study also helped scientific societies such as ECCO and ESGAR reach a consensus on the standardized use of parameters for reporting cross-sectional imaging studies including IUS in IBD.[9]

Overall, our study demonstrated a progressive resolution of transmural disease activity predominantly in the colon starting 4 weeks after ustekinumab treatment initiation and biologic-naive patients presented a more robust response than patients with prior exposure to one biologic therapy. IUS could complement biomarker and symptomatic assessments to provide a complete clinical depiction of the impact of novel therapies in CD patients. IUS could be of value and complementary to endoscopy in assessing CD activity particularly in patients with conditions such as terminal ileal strictures and replace more invasive techniques (endoscopy) in monitoring CD patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2022.05.055.

References

1. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD)—Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology 2021;160:1570–1583.
2. de Voogd FAE, Verstockt B, Maaser C, et al. Point-of-care intestinal ultrasonography in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2021;18:209–210.
3. Horsthuis K, Bipat S, Bennink RJ, et al. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. Radiology 2008;247:64–79.
4. Panés J, Bouzas R, Chaparro M, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther 2011;34:125–145.
5. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis 2019;137:144–164.
6. Wilkens R, Dolinger M, Burisch J, et al. Point-of-care testing and home testing: pragmatic considerations for widespread incorporation: stool tests, serum tests, intestinal ultrasound. Gastroenterology 2022;162:1476–1492.
7. Maconi G, Nylund K, Ripolles T, et al. EFSUMB recommendations and clinical guidelines for intestinal ultrasound (GIUS) in inflammatory bowel diseases. Ultraschall Med 2018;39:304–317.

8. Novak KL, Nylund K, Maaser C, et al. Expert consensus on optimal acquisition and development of the international bowel ultrasound segmental activity score [IBUS-SAS]: a reliability and inter-rater variability study on intestinal ultrasonography in Crohn's disease. J Crohns Colitis 2021;15:609–616.
9. Kucharzik T, Tielbeek J, Carter D, et al. ECCO-ESGAR topical review on optimising reporting for cross-sectional imaging in IBD. J Crohns Colitis 2022;16:523–543.
10. Sasaki T, Kunisaki R, Kinoshita H, et al. Use of color Doppler ultrasonography for evaluating vascularity of small intestinal lesions in Crohn's disease: correlation with endoscopic and surgical macroscopic findings. Scand J Gastroenterol 2014; 49:295–301.
11. Wilkens R, Hagemann-Madsen RH, Peters DA, et al. Validity of contrast-enhanced ultrasonography and dynamic contrast-enhanced MR enterography in the assessment of transmural activity and fibrosis in Crohn's disease. J Crohns Colitis 2018; 12:48–56.
12. Bryant RV, Friedman AB, Wright EK, et al. Gastrointestinal ultrasound in inflammatory bowel disease: an underused resource with potential paradigm-changing application. Gut 2018; 67:973–985.
13. Danese S, Vermeire S, D'Haens G, et al. Treat to target versus standard of care for patients with Crohn's disease treated with ustekinumab (STARDUST): an open-label, multicentre, randomised phase 3b trial. Lancet Gastroenterol Hepatol 2022; 7:294–306.
14. Kucharzik T, Wittig BM, Helwig U, et al. TRUST study group: use of intestinal ultrasound to monitor Crohn's disease activity. Clin Gastroenterol Hepatol 2017;15:535–542.
15. Ma C, Fedorak RN, Kaplan GG, et al. Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort. Aliment Pharmacol Ther 2017; 45:1232–1243.
16. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.
17. Moreno N, Ripollés T, Paredes JM, et al. Usefulness of abdominal ultrasonography in the analysis of endoscopic activity in patients with Crohn's disease: changes following treatment with immunomodulators and/or anti-TNF antibodies. J Crohns Colitis 2014;8:1079–1087.
18. Ilvemark JFKF, Hansen T, Goodsall TM, et al. Defining transabdominal intestinal ultrasound treatment response and remission in inflammatory bowel disease: systematic review and expert consensus statement. J Crohns Colitis 2022; 16:554–580.
19. Helwig U, Fischer I, Hammer L, et al. Transmural response and transmural healing defined by intestinal ultrasound: new potential therapeutic targets? J Crohns Colitis 2022; 16:57–67.
20. Wilkens R, Novak KL, Maaser C, et al. Relevance of monitoring transmural disease activity in patients with Crohn's disease: current status and future perspectives. Ther Adv Gastroenterol 2021;14:1–18.
21. Goodsall TM, Jairath V, Feagan BG, et al. Standardisation of intestinal ultrasound scoring in clinical trials for luminal Crohn's disease. Aliment Pharmacol Ther 2021;53:873–886.
22. Zorzi F, Ghosh S, Chiaramonte C, et al. Response assessed by ultrasonography as target of biological treatment for Crohn's disease. Clin Gastroenterol Hepatol 2020; 18:2030–2037.
23. Calabrese E, Rispo A, Zorzi F, et al. Ultrasonography tight control and monitoring in Crohn's disease during different biological therapies: a multicenter study. Clin Gastroenterol Hepatol 2022;20:e711–e722.
24. Kredel LI, Jödicke LJ, Scheffold A, et al. T-cell composition in ileal and colonic creeping fat–separating ileal from colonic Crohn's disease. J Crohns Colitis 2019;13:79–91.
25. Lichtenstein GR, Olson A, Travers S, et al. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. Am J Gastroenterol 2006; 101:1030–1038.
26. Bettenworth D, Bokemeyer A, Baker M, et al. Assessment of Crohn's disease-associated small bowel strictures and fibrosis on cross-sectional imaging: a systematic review. Gut 2019; 68:1115–1126.
27. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clin Gastroenterol Hepatol 2017;15:229–239.

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Conflicts of interest

These authors disclose the following: T Kucharzik reports consulting fees/speaker's honoraria from AbbVie, Amgen, Boehringer Ingelheim, Biogen, Celltrion, Celgene, Bristol-Myers Squibb, Hospira, Mundipharma, Dr. Falk Pharma GmbH, Ferring Arzneimittel GmbH, Galapagos, Gilead, Janssen, MSD Sharp & Dome GmbH, Novartis, Pfizer, Roche, Takeda Pharma GmbH, and Vivor Pharma. R Wilkens reports consulting fees/speaker's honoraria from AbbVie, Takeda, Janssen, and Pfizer. MA D'Agostino reports consultancy fees from Janssen, Novartis, BMS, Galapagos, Eli Lilly, AbbVie, and Pfizer. G Maconi reports consulting fees/speaker's honoraria from Alfa Sigma, Arena Pharmaceuticals, Gilead, Janssen, and Roche. M Le Bars is an employee of Janssen-Cilag and has restricted stocks. M Lahaye is an employee of Janssen-Cilag B.V. and has restricted stocks. I Bravatà is an employee of Janssen-Cilag S.p.A. and has restricted stocks. M Nazar is an employee of Janssen-Cilag Polska Sp. Z. o.o and has restricted stocks. L Ni is an employee of Janssen-Cilag Russia and has restricted stocks. M Allocca has received consulting fees from Nikkiso Europe, Mundipharma, Janssen, AbbVie, Ferring, and Pfizer. N Machkova has received lecture fees from Janssen-Cilag, LLC, AbbVie Inc, and Takeda Pharmaceutical Ltd. FAE de Voogd reports honoraria and/or speaker fees from AbbVie and Janssen. C Palmela reports consulting fees/speaker's honoraria from Vitorias Laboratory and Janssen and travel support from Merck Sharp & Dohme and AbbVie. R Vaughan reports education expenses from Janssen. C Maaser reports honorary fees from AbbVie, Biogen, Celgene, Ferring, Falk Foundation, Janssen, MSD Sharp & Dome, Takeda Pharma, and Vifor Pharma. UH received lecture and consulting fees from AbbVie, Celltrion, MSD, Ferring, Falk Foundation, Takeda, Mundipharma, Hospira, Pfizer, Amgen, Biogen, Shield, Janssen, and Vifor Pharma. The remaining authors disclose no conflicts.

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Supplementary Material

Intestinal Ultrasound Central Reading

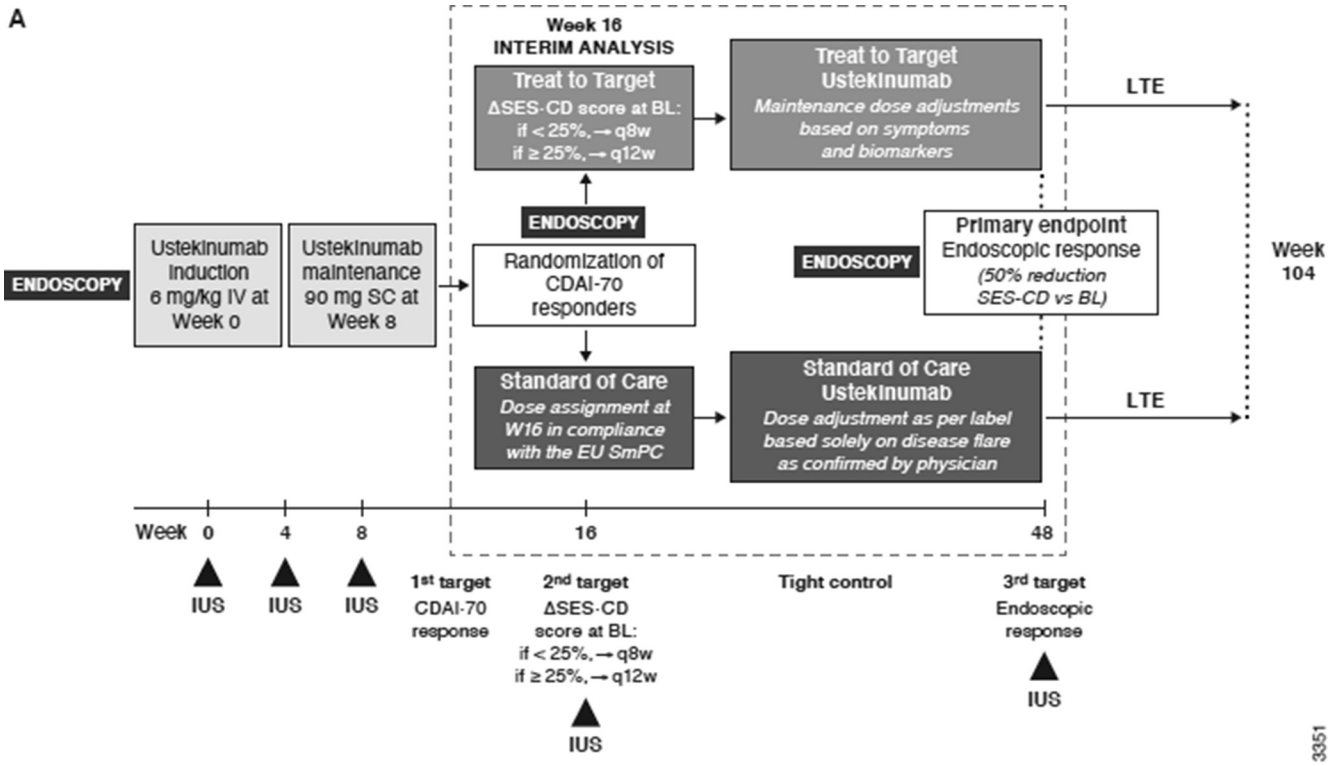
IUS sites exported all relevant IUS examination documentation (cine loops and still images) from the ultrasound machine in pseudonymized DICOM format that was uploaded to a dedicated and secure server. All sites initially uploaded a test file for quality check before recruitment was allowed. All scans and the first baseline scan per site underwent immediate quality check by 1 of 2 central readers (RW or CP). Scans were assessed for correct acquisition (scan planes, number of cine loops, image quality, annotation, Doppler settings, identified pathology, and accurate placement of calipers for measurement of bowel wall thickness. A report was automatically generated to the responsible site/investigator with acceptance of the performed scan or requests for additional images/improvement.

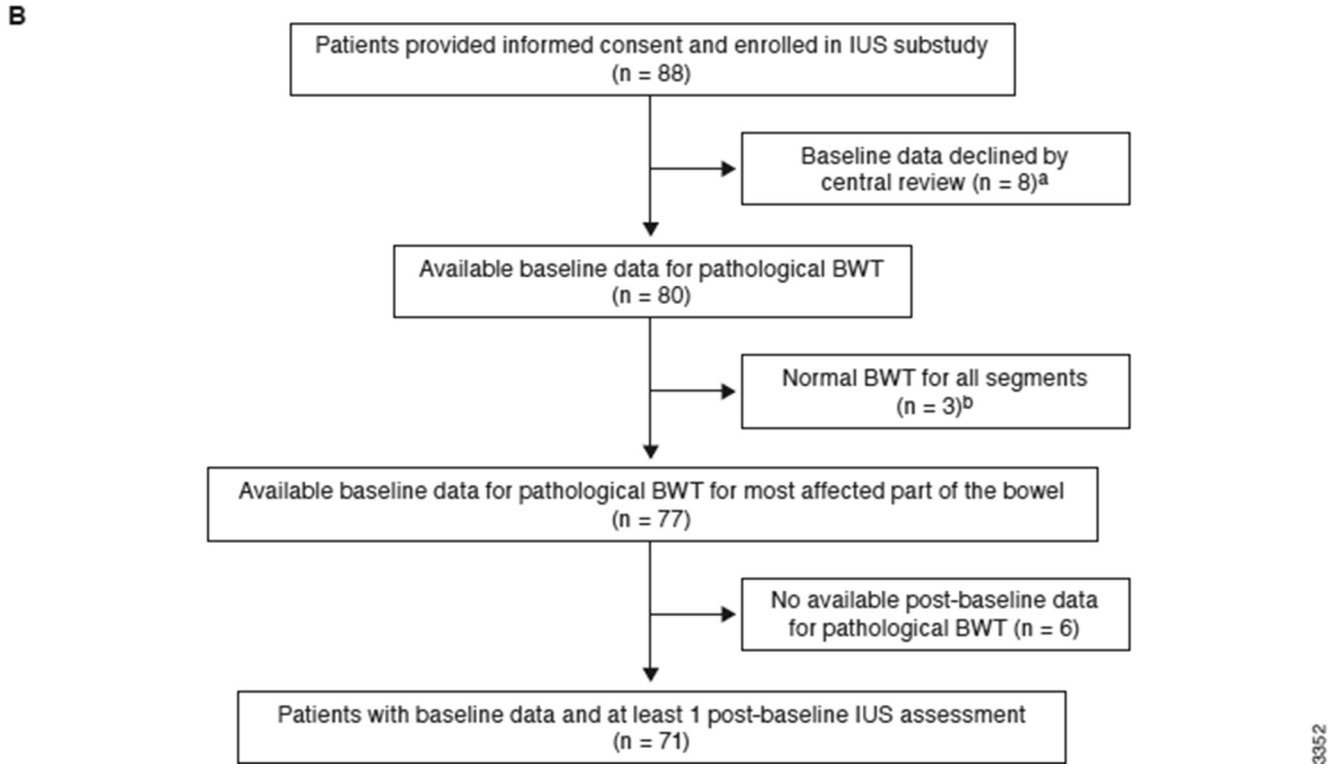
In some cases, files were uploaded in PC format rather than DICOM format. Those files were converted to DICOM format using Sante DICOM Editor [Windows], Version 7.8.1. Pseudonymized DICOM files were securely shared among the 3 pairs of central readers (CM & TK, RW & FdV, CP & RV) and assessed using either RadiAnt for Windows, version 5.5 (Meixant, Poznan, Poland) or Horos for Mac 4.0. All uploaded files were rated in consensus by the central reader pair. Study scans acquired by a central reader, participating as an IUS investigator, also underwent central reading by a different central reader. Scans were batch analyzed for baseline and weeks 4, 8, and 16 by the same pair of central readers for the interim analysis. Week 48 data were assessed by the same pair of central readers who evaluated the first scans. All data were entered into iMedidata Rave (Medidata, New York, NY) electronic case report form.

Central reading was performed in pairs without a prior individualized assessment. Whenever there was disagreement between the 2 readers, consensus was reached by agreement after intensive discussion of individual parameters or by using the mean between 2 assessments. Data for the individual reader are not available. Therefore, variability data cannot be provided for this study. However, in a recent Delphi consensus, 11 experts representing 7 countries where most of the authors of the current article have been involved, key activity measurements on IUS have been defined and generalized intraclass correlation coefficients have been determined.[1] In this study, intraclass correlation coefficient for BWT was almost perfect at 0.96. In addition, vascularization, echo stratification, and inflammatory mesenteric fat have been identified as additional key parameters demonstrating moderate to good reliability.

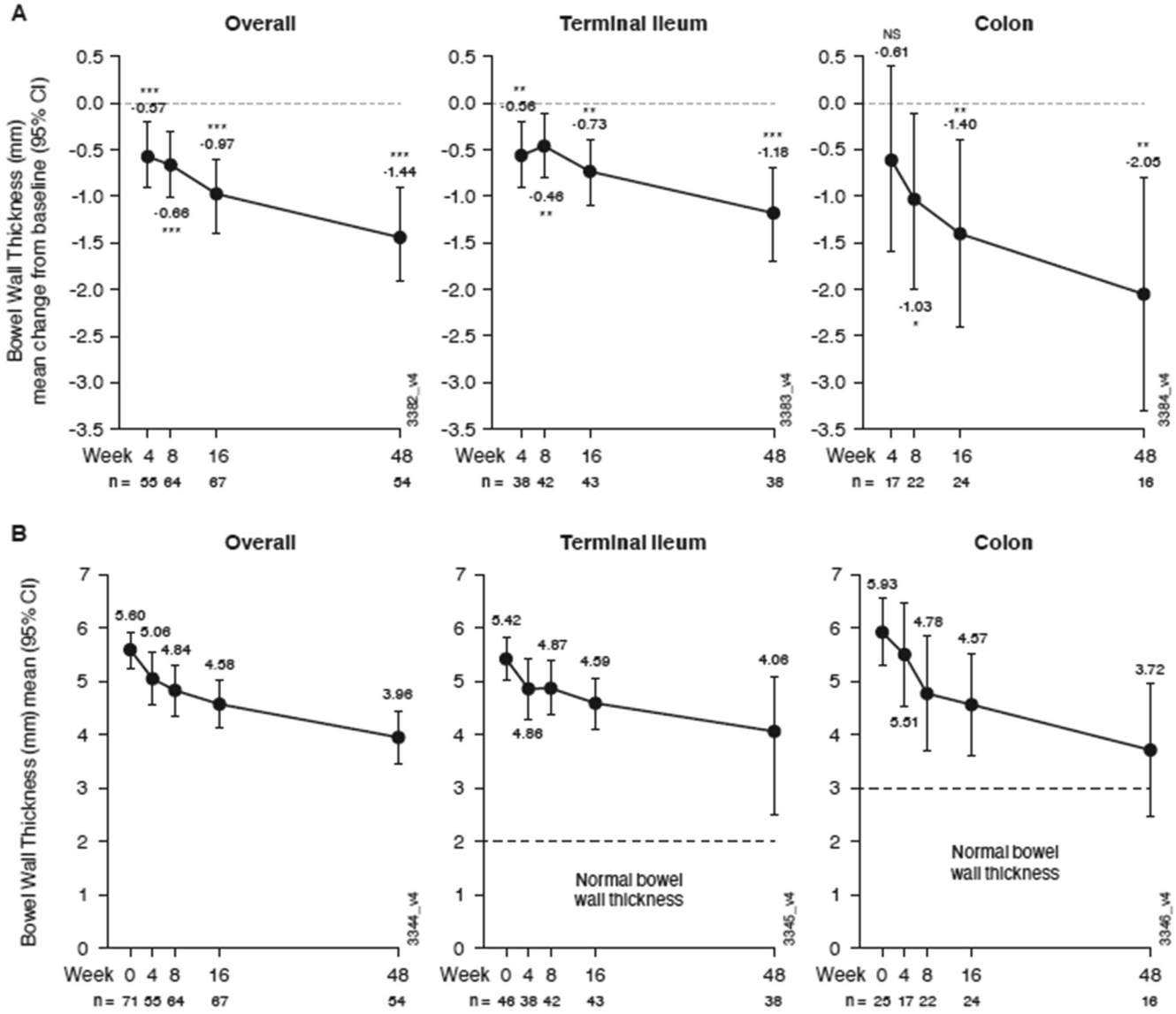
Reference

1. Novak KL, Nylund K, Maaser C, et al. Expert consensus on optimal acquisition and development of the International Bowel Ultrasound Segmental Activity Score [IBUSSAS]: a reliability and inter-rater variability study on intestinal ultrasonography in Crohn's disease. J Crohns Colitis 2021;15:609–616.

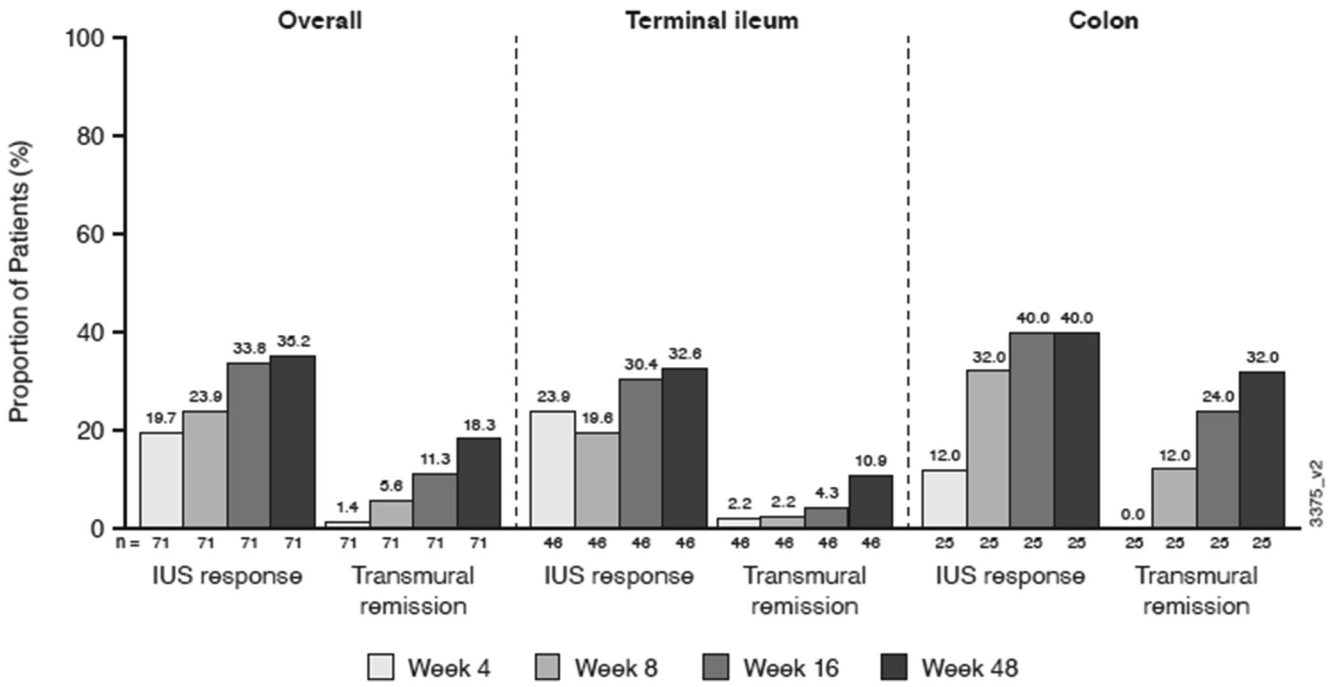




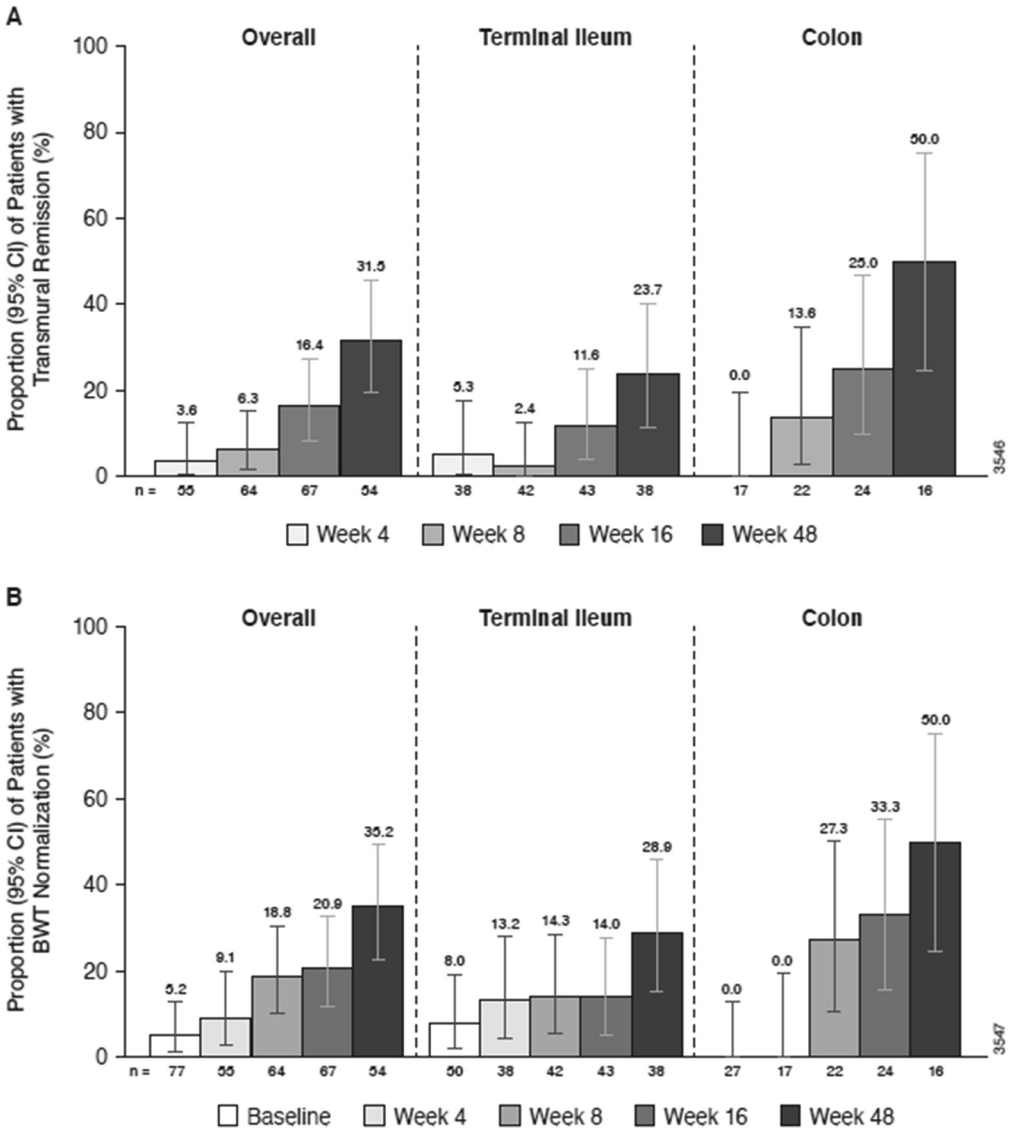
Supplementary Figure 1. IUS study flow and patient disposition. BL, baseline; BWT, bowel wall thickness; CDAI-70, 70-point decrease from baseline in Crohn's disease activity index score; EU-SmPC, European Union summary of product characteristics; IUS, intestinal ultrasound; IV, intravenous; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; W16, week16. [a]The most affected bowel segment could not be identified at baseline. [b]Patients were excluded from analysis if bowel wall thickness was normal (ie, $\leq$2.0 mm for the terminal ileum; $\leq$3.0 mm for the colon) for all bowel segments at baseline (week 0). The most affected bowel segment could not be identified.



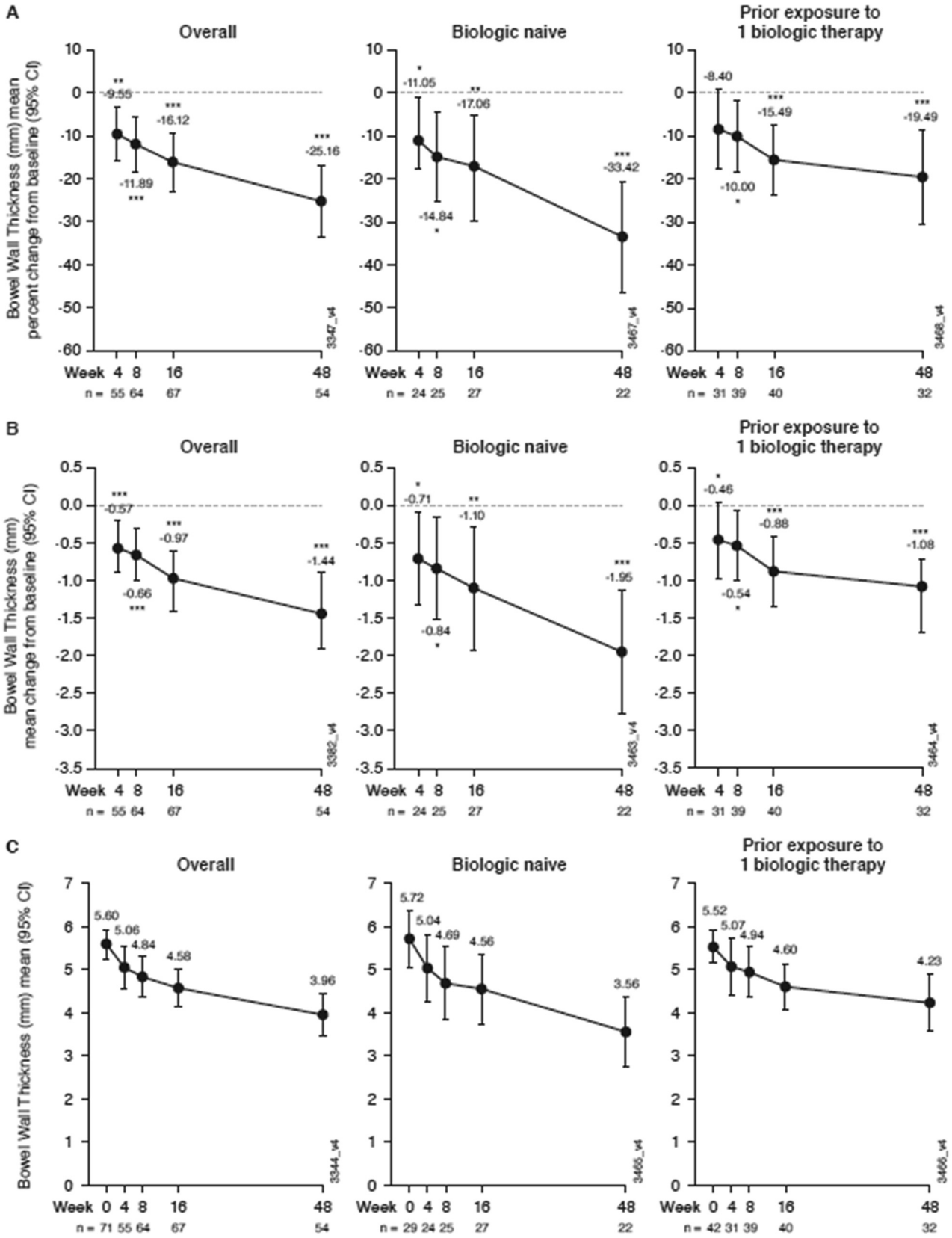
Supplementary Figure 2. As observed analyses of mean change from baseline (95% confidence intervals) (*A*) and mean values (95% confidence intervals) (*B*) in bowel wall thickness (mm) over time for all patients in the IUS substudy overall and by most affected bowel segment. Only patients with non-missing baseline value and at least one non-missing post-baseline value during the main treatment period are included in the analysis. N at baseline and through week 48. N for change from baseline is the number of patients with non-missing values at both baseline and the post-baseline time point. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ (Wilcoxon signed-rank test, change from baseline). CI, confidence interval; IUS, intestinal ultrasound.



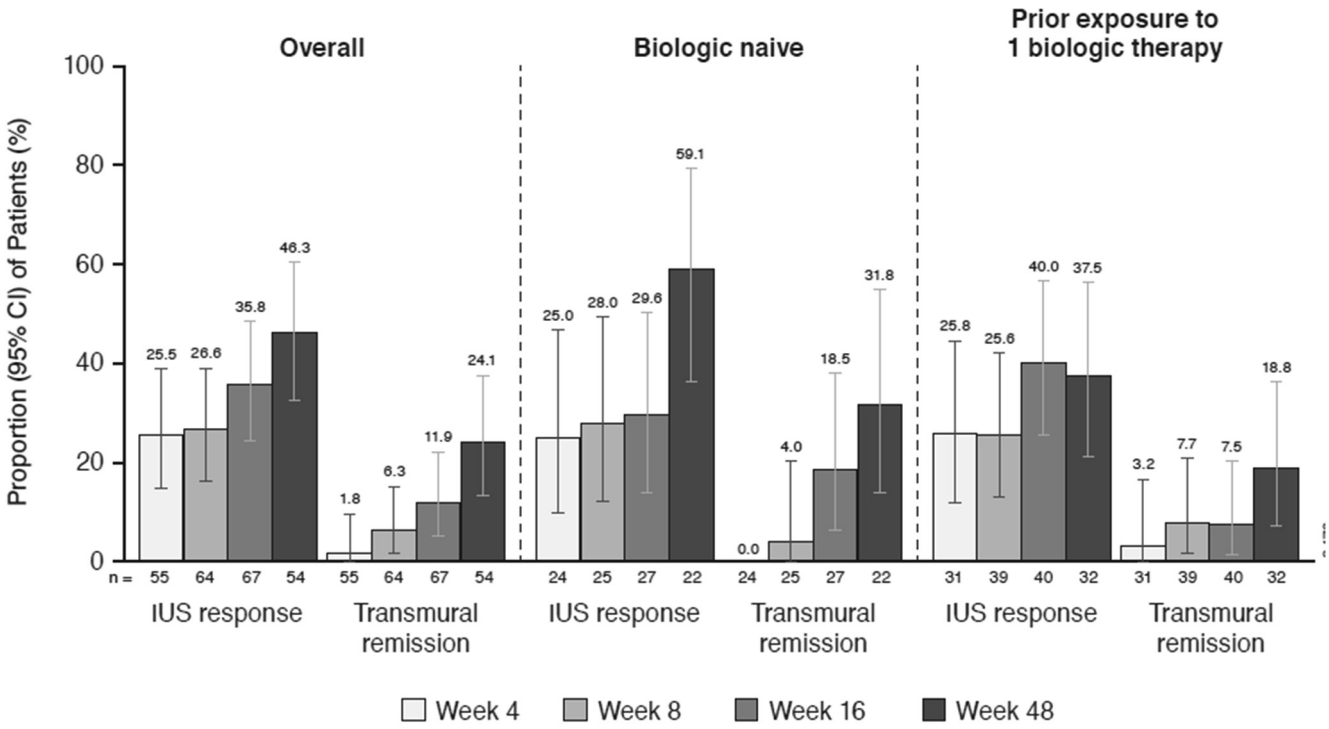
Supplementary Figure 3. Non-responder imputation analyses of IUS response and transmural remission over time for all patients in the IUS substudy overall and by most affected bowel segment. Patients with a missing value at the designated visit were considered not to have achieved their dichotomous efficacy endpoint. IUS response was defined as reduction of $\geq$25% from baseline in BWT. Transmural remission was defined as normalization of BWT, blood flow (color Doppler signal), bowel wall stratification, and inflammatory mesenteric fat. The most affected (most thickened) part of the bowel wall was used for response/remission evaluation in the follow-up scans. If 3 of the 4 IUS parameters were normalized and the fourth is 'Not assessed/Not assessable', transmural remission is considered 'Yes'. BWT, bowel wall thickness; IUS, intestinal ultrasound.



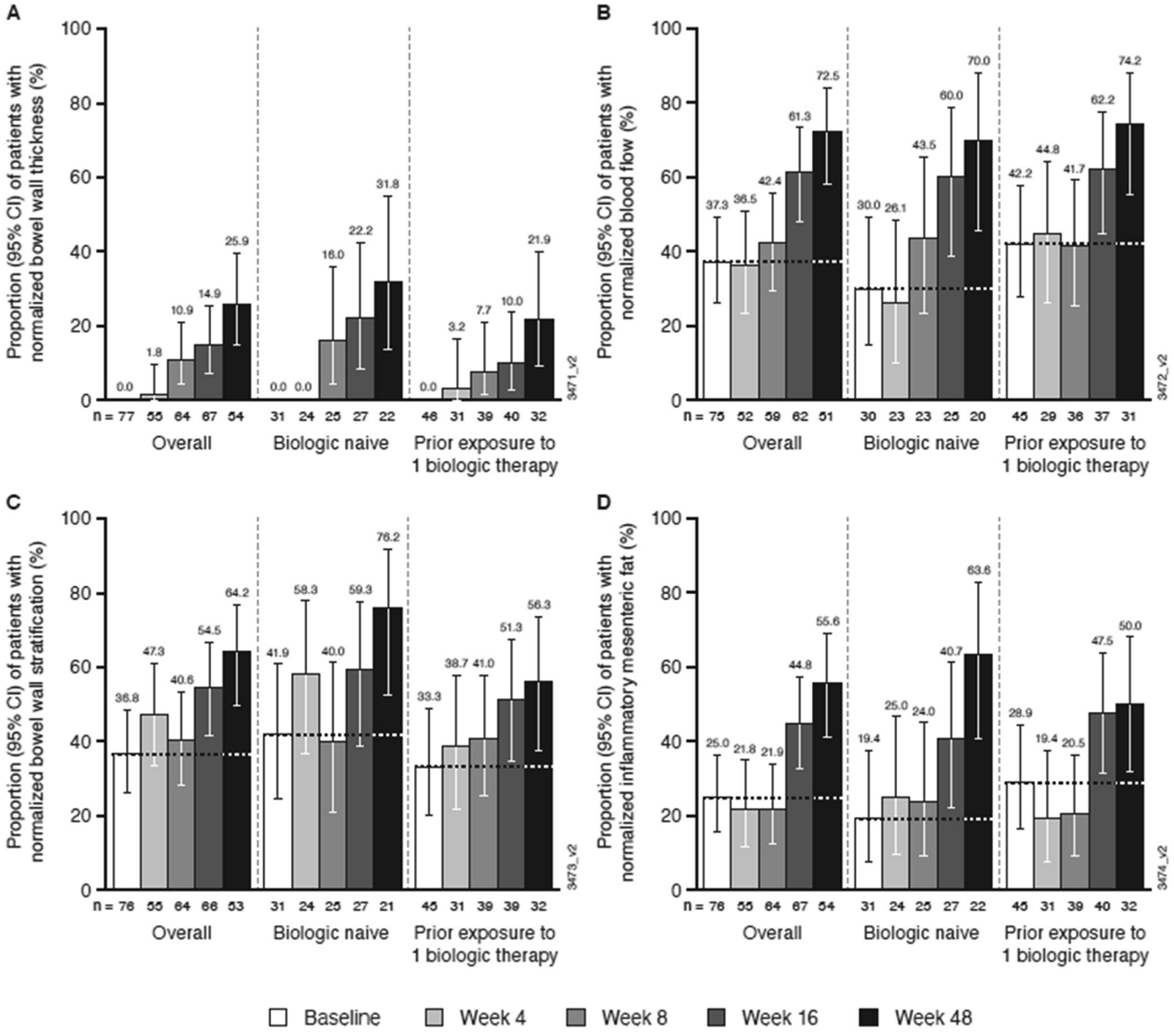
Supplementary Figure 4. Post hoc as observed sensitivity analyses of transmural remission (*A*) and BWT normalization (*B*) over time for all patients in the IUS substudy overall and by most affected bowel segment. Transmural remission was defined as normalization of BWT, blood flow (color Doppler signal), bowel wall stratification, and inflammatory mesenteric fat. The most affected (most thickened) bowel segment at baseline was used for response/remission evaluation in the follow-up scans. If 3 of the 4 IUS parameters were normalized and the fourth is 'Not assessed/Not assessable', transmural remission is considered 'Yes'. Normalization of bowel wall thickness was defined as $\leq$3 mm in the colon and ileum. BWT, bowel wall thickness; CI, confidence interval; IUS, intestinal ultrasound.



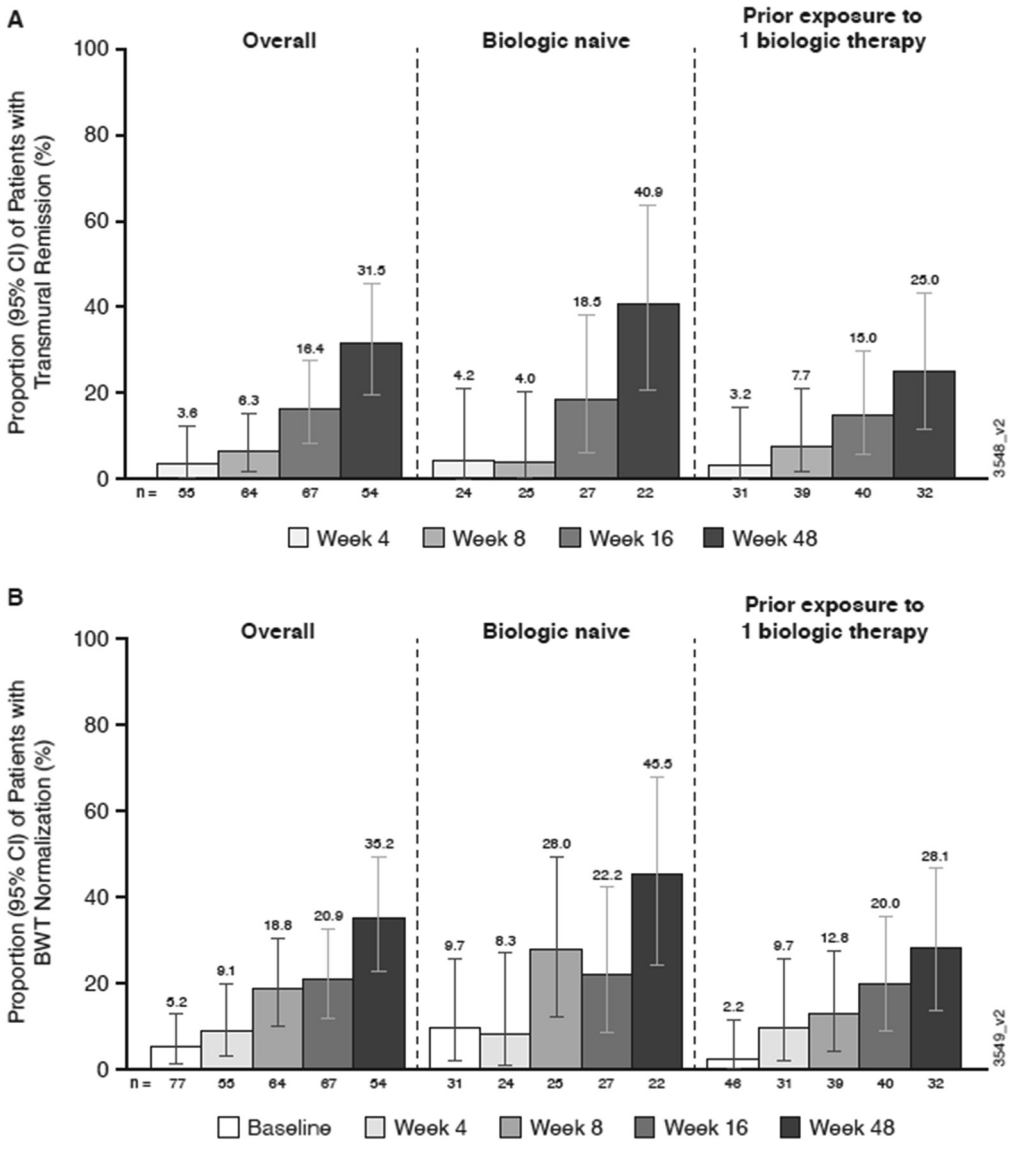
Supplementary Figure 5. As observed analyses of mean percent change from baseline (*A*), mean change from baseline (*B*), and mean values (*C*) in bowel wall thickness (mm) over time for all patients in the IUS substudy overall and by biologic treatment history. Only patients with non-missing baseline value and at least one non-missing post-baseline value during the main treatment period are included in the analysis. N for change from baseline is the number of patients with non-missing values at both baseline and the post-baseline time point. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ (Wilcoxon signed-rank test, change from baseline). CI, confidence interval; IUS, intestinal ultrasound.



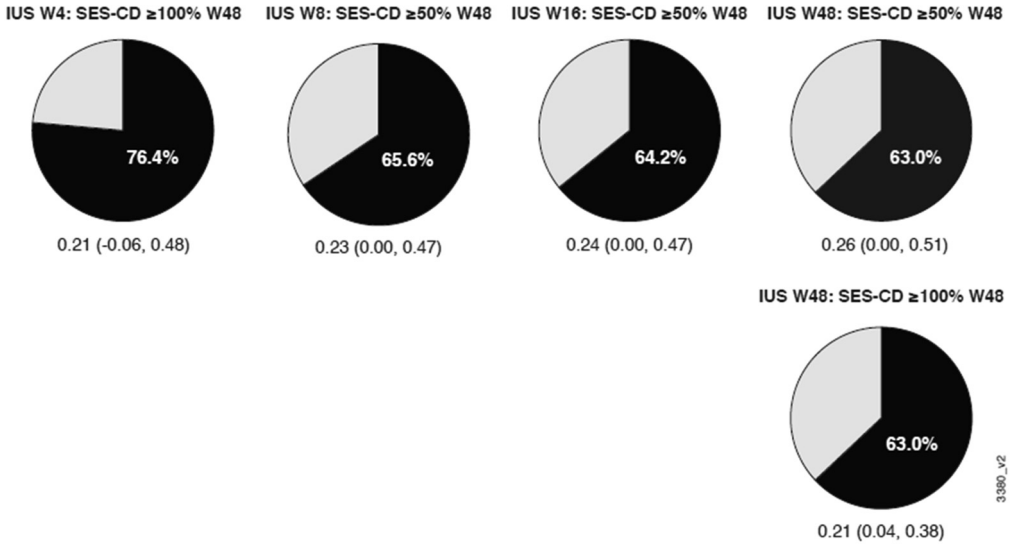
Supplementary Figure 6. As observed analyses of IUS response and transmural remission over time for all patients in the IUS substudy overall and by biologic treatment history. IUS response was defined as a reduction of $\geq$25% from baseline in BWT. Transmural remission was defined as normalization of BWT, blood flow (color Doppler signal), bowel wall stratification, and inflammatory mesenteric fat. The most affected (most thickened) bowel segment at baseline was used for response/remission evaluation in the follow-up scans. If 3 of the 4 IUS parameters were normalized and the fourth is 'Not assessed/Not assessable', transmural remission is considered 'Yes'. BWT, bowel wall thickness; CI, confidence interval; IUS, intestinal ultrasound.



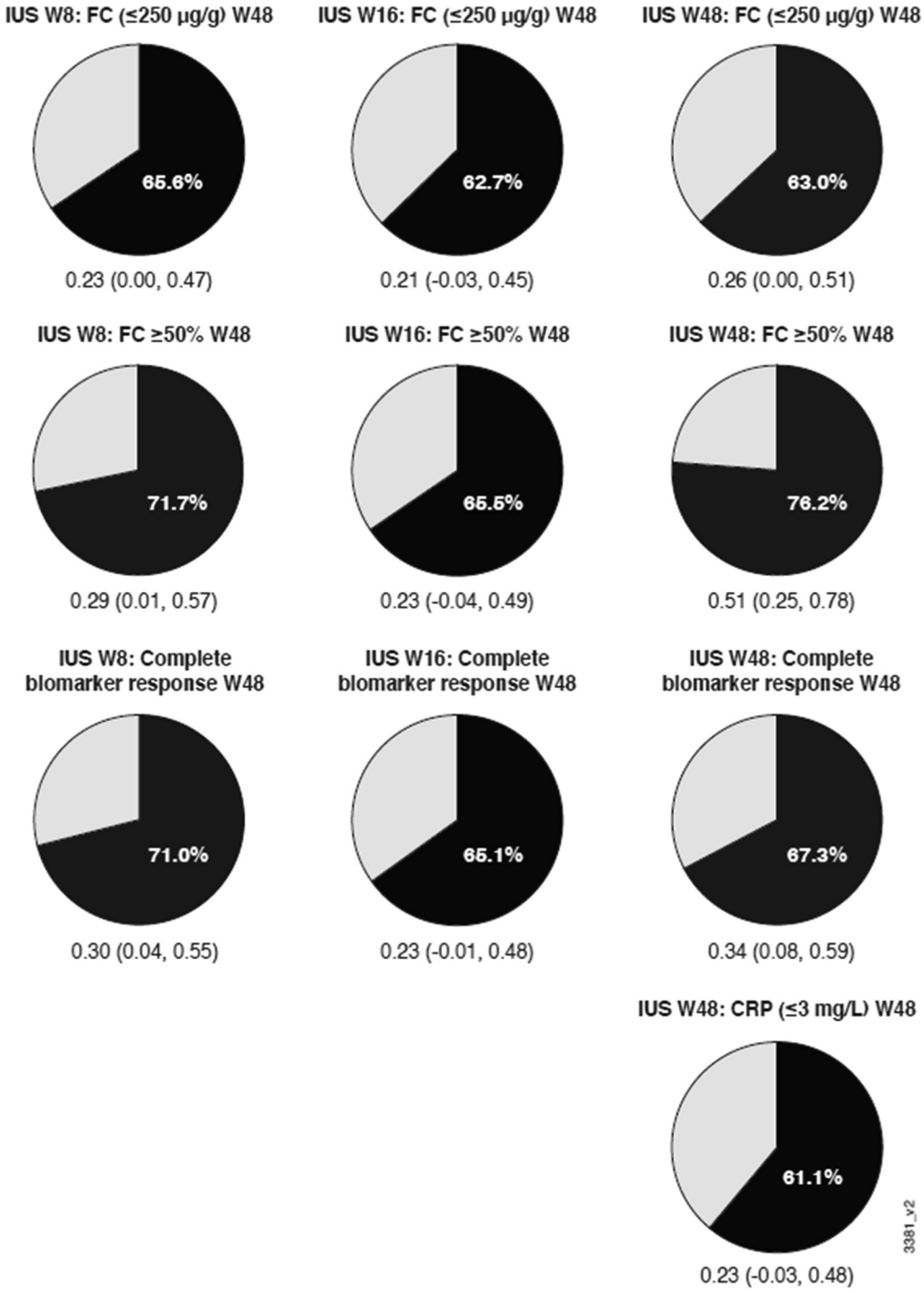
Supplementary Figure 7. As observed analyses of normalized pathologic bowel wall thickness (*A*), blood flow (*B*), bowel wall stratification (*C*), and inflammatory mesenteric fat (*D*) over time for all patients in the IUS substudy overall and by biologic treatment history. Normalization of bowel wall thickness was defined as terminal ileum $\leq$2 mm and colon $\leq$3 mm. Normalization of blood flow (color Doppler signal 0 or 1). Normalization of bowel wall stratification was defined as normal/preserved echo stratification. Normalization of inflammatory mesenteric fat defined as absence of inflammatory mesenteric fat. CI, confidence interval; IUS, intestinal ultrasound.



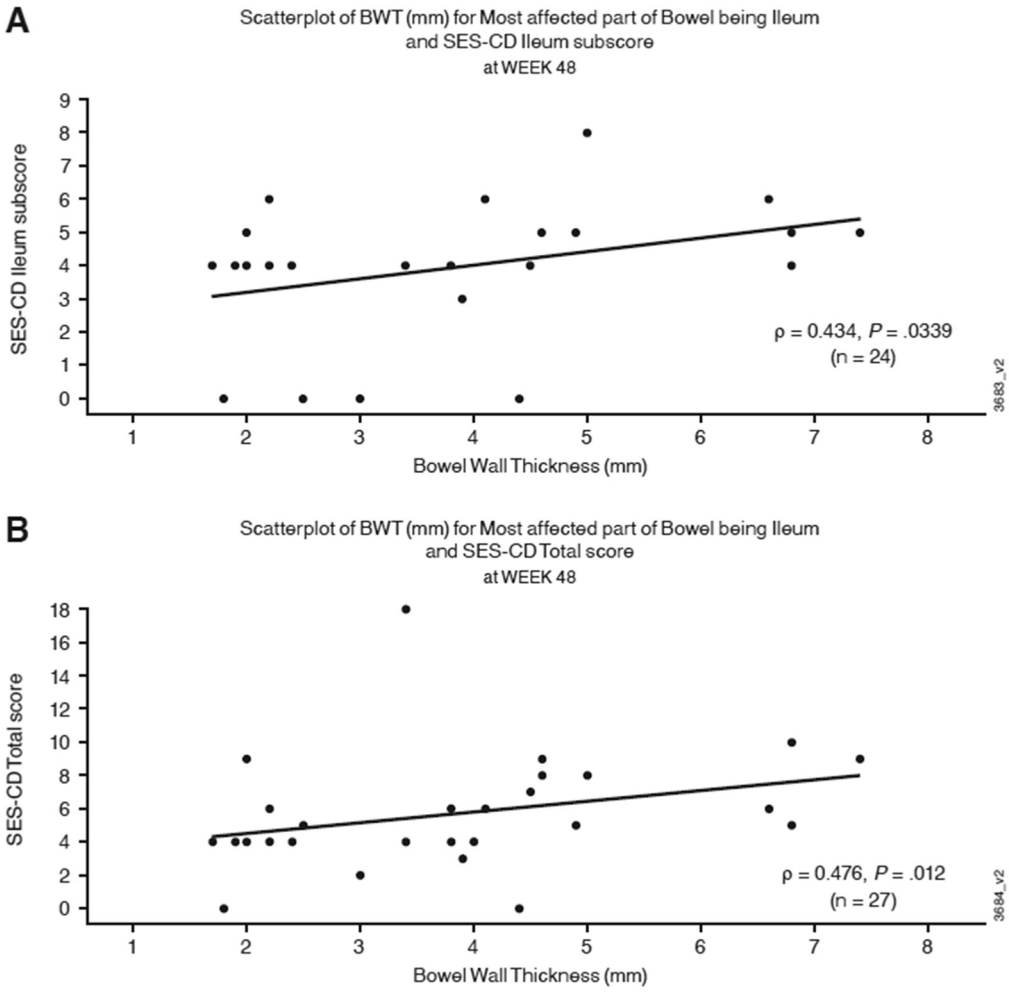
Supplementary Figure 8. Post hoc as observed sensitivity analyses of transmural remission (*A*) and BWT normalization (*B*) over time for all patients in the IUS substudy overall and by biologic treatment history. Transmural remission was defined as normalization of BWT, blood flow (color Doppler signal), bowel wall stratification, and inflammatory mesenteric fat. The most affected (most thickened) bowel segment at baseline was used for response/remission evaluation in the follow-up scans. If 3 of the 4 IUS parameters were normalized and the fourth is 'Not assessed/Not assessable', transmural remission is considered 'Yes'. Normalization of bowel wall thickness was defined as $\leq$3 mm in the colon and ileum. BWT, bowel wall thickness; CI, confidence interval; IUS, intestinal ultrasound.



Supplementary Figure 9. Reliability between IUS response of most affected bowel segment at weeks 4, 8, 16, and 48 (as observed analysis) and endoscopic response at week 48 (non-responder imputation analysis). Pie charts show percentage of patients with 'Yes' (*black*) for both IUS response and the tested outcome or 'No' (*white*) for both. Kappa (95% confidence interval) results are presented. Only patients with non-missing baseline value and at least one non-missing post-baseline value during the main treatment period are included in the analysis. Patients with a missing value at the designated visit were considered not to have achieved their dichotomous efficacy endpoint. For continuous endpoints, the last available value was carried forward for patients with missing data. IUS, intestinal ultrasound; SES-CD, Simple Endoscopic Score for Crohn's Disease; W, week.



Supplementary Figure 10. Reliability between IUS response of most affected bowel segment at weeks 8, 16, and 48 (as observed analyses) and biomarkers at week 48 (non-responder imputation analyses). Pie charts show percentage of patients with 'Yes' (*black*) for both IUS response and the tested outcome or 'No' (*white*) for both. Kappa (95% confidence interval) results are presented. Only patients with non-missing baseline value and at least one non-missing post-baseline value during the main treatment period are included in the analysis. Patients with a missing value at the designated visit were considered not to have achieved their dichotomous efficacy endpoint. For continuous endpoints, the last available value was carried forward for patients with missing data. CRP, C-reactive protein; FC, fecal calprotectin; IUS, intestinal ultrasound; W, week.



Supplementary Figure 11. Correlation between BWT and SES-CD terminal ileum subscore (*A*) and SES-CD total score (*B*) at week 48 for patients with terminal ileum being the most affected bowel segment by IUS and endoscopy. BWT, bowel wall thickness; IUS, intestinal ultrasound; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Supplementary Table 1. Key Intestinal Ultrasound Parameters

Parameters	Definition
Segmental bowel wall thickness	The mean of 4 measurements (2 in cross-section and 2 in longitudinal) of the most affected (ie, most inflamed) part of each segment. Bowel wall thickness was considered pathologic if >2.0 mm in the terminal ileum and >3.0 mm in the colon.
Blood flow	Color Doppler signal: 0, no signal; 1, minimal pixels, scant; 2, increased signal limited to the wall; 3, signal is significant in the wall and mesentery. Normalization of color Doppler signal was defined as ≤1.
Bowel wall stratification	0, normal/preserved echo stratification; 1, uncertain presence of echo stratification; 2, focal disruption (<3 cm); 3, extensive disruption (≥3 cm). Normalization of bowel wall stratification was defined as normal/preserved echo stratification.
Inflammatory mesenteric fat	0, absent, no evidence of proliferative, mesenteric inflammatory fat; 1, uncertain (increased fat is possible, either the quality or the views are insufficient to determine the contribution); 2, present. Normalization of inflammatory mesenteric fat was defined as absence of inflammatory mesenteric fat.