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The Effects of Ustekinumab on Health-related Quality of Life in Patients With Moderate to Severe Crohn's Disease

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Abstract

Background and Aims: We assessed the effect of ustekinumab on health-related quality of life [HRQOL] in adults with Crohn's disease [CD].

Methods: Patients with moderately to severely active CD and inadequate response or intolerance to tumour necrosis factor antagonists [UNITI-1, $n = 741$], or conventional therapy [UNITI-2, $n = 627$] were randomised to placebo, ustekinumab 130 mg, or 6 mg/kg intravenous induction therapy. At Week 8, ustekinumab-treated responders (Crohn's Disease Activity Index [CDAI] reduction ≥100 or CDAI <150 points) were re-randomised to subcutaneous maintenance therapy [IM-UNITI, $n = 388$] with placebo, ustekinumab 90 mg every 12 weeks [q12w], or ustekinumab 90 mg every 8 weeks [q8w], for 44 additional weeks. Inflammatory Bowel Disease Questionnaire [IBDQ] and 36-item Short Form Health Survey [SF-36] physical component summary [PCS] and mental component summary [MCS] scores were completed at induction baseline and Week 8, and at maintenance Weeks 20 and 44. Clinically meaningful improvement in IBDQ and PCS and MCS scores were evaluated. For all HRQOL outcomes, each ustekinumab dose and placebo were compared.

Results: Induction baseline mean values of IBDQ, PCS, and MCS were similar across groups, but impaired relative to general population norms. At Week 8, ustekinumab induced greater improvement than placebo in both HRQOL scores. Significantly greater proportions of patients receiving ustekinumab 6 mg/kg or 130 mg had clinically meaningful IBDQ improvement [UNITI-1: 54.8%, 46.9% versus 36.5%, respectively; UNITI-2: 68.1%, 58.7% versus 41.1%, respectively; $p < 0.05$, all comparisons]. Similarly, greater proportions of ustekinumab-treated patients in both studies had clinically meaningful improvements in PCS and MCS as compared with placebo. At Week 44, improvements in IBDQ, PCS, and MCS scores were maintained with ustekinumab.

Conclusions: Ustekinumab improved HRQOL in patients with moderately to severely active CD.

Key Words: Patient-reported outcomes; inflammatory bowel disease questionnaire; medical outcome survey short form-36

1. Introduction

Crohn's disease [CD] often has important negative effects on patients' health-related quality of life [HRQOL], because of the impacts of disease on both physical and mental well-being. HRQOL is usually assessed by either the 36-item Short-Form Health Survey [SF-36], a generic multi-item scale that evaluates both physical [PCS] and mental component summary scores [MCS],[1] or a disease-specific instrument: the Inflammatory Bowel Disease Questionnaire [IBDQ].[2] Previous studies have shown that SF-36 is a reliable and valid instrument to measure general health status in patients with CD.[3] Importantly, as can only be determined using a generic instrument, patients with CD have substantially impaired HRQOL compared with the general population.[4] Furthermore, the effects of the disease on SF-36 MCS scores is relatively more profound than observed in other chronic inflammatory diseases such as rheumatoid arthritis.

The IBDQ, a 32-item questionnaire comprising four domains [bowel symptoms, systemic symptoms, emotional function, and social function] is the most commonly used disease-specific measure for evaluation of HRQOL in CD. The IBDQ is more sensitive than the SF-36 to clinically meaningful changes in health status, and therefore can be used to detect relatively small differences in treatment effects in specific disease subgroups or drug treatment regimens.

Ustekinumab, a monoclonal antibody to the p40 subunit of interleukins [IL]-12 and -23, is approved for the treatment of active CD based on the results of three Phase 3 studies.[5] Herein we report the effects of ustekinumab on HRQOL in patients with moderate to severe CD.

2. Methods

The UNITI and IM-UNITI studies were multicentre, randomised, double-blind, placebo-controlled Phase 3 studies designed to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in patients with moderately to severely active CD.

Briefly, patients with moderately to severely active CD (defined by a CD Activity Index [CDAI] score of 220–450) and with inadequate response or intolerance to tumour necrosis factor [TNF] antagonists [UNITI-1] or conventional therapy [UNITI-2], were randomised in a 1:1:1 ratio to receive a single intravenous [IV] infusion of placebo, ustekinumab 130 mg, or weight-range based dosing of approximately 6 mg/kg ustekinumab (260 mg [weight ≤55 kg], 390 mg [weight >55 kg and ≤85 kg], or 520 mg [weight >85 kg], hereafter referred to as 6 mg/kg). Patients with a clinical response [defined as a CDAI reduction ≥100 points or CDAI <150] to ustekinumab at Week 8 were re-randomised into the primary maintenance population in IM-UNITI to receive subcutaneous [SC] placebo, or ustekinumab 90 mg every 12 weeks [q12w], or ustekinumab 90 mg every 8 weeks [q8w], through Week 44 [52 weeks after induction baseline].

Table 1. Mean [SD] and mean change [SD] from baseline in the IBDQ and SF-36 scores at Week 8 of induction therapy.

	UNITI-1				UNITI-2			
		Ustekinumab				Ustekinumab		
Patient- reported Outcome	Placebo	130 mg	6 mg/kg[a]	Combined	Placebo	130 mg	6 mg/kg[a]	Combined
IBDQ score, *n* =	247	245	249	494	209	209	209	418
Baseline, *n*	244	243	248	491	207	208	207	415
Mean [SD]	120.0 [29.27]	119.5 [29.47]	118.2 [26.64]	118.8 [28.06]	122.7 [31.32]	118.2 [30.99]	122.8 [31.62]	120.5 [31.35]
Week 8, *n*	244	243	248	491	207	208	207	415
Mean [SD]	131.9 [34.61]	137.5 [37.95]	140.3 [34.39]	138.9 [36.19]	137.3 [37.33]	147.3 [36.74]	158.0 [34.54]	152.6 [36.02]
Change from baseline								
Week 8[b,c], *n*	244	243	248	491	207	208	207	415
Mean [SD]	11.9 [26.51]	18.1* [28.02]	22.1*** [28.59]	20.1*** [28.35]	14.7 [26.96]	29.1*** [33.82]	35.3*** [36.05]	32.2*** [35.04]
SF-36 score, n	225	231	235	466	190	194	196	390
Physical component summary								
Baseline, *n*	223	231	232	463	189	193	195	388
Mean [SD]	37.8 [7.12]	37.8 [7.12]	37.2 [7.09]	37.5 [7.11]	39.7 [7.19]	38.9 [7.62]	38.9 [7.05]	38.9 [7.33]
Week 8, *n*	223	231	232	463	189	193	195	388
Mean [SD]	40.4 [7.56]	41.0 [8.32]	40.7 [8.48]	40.9 [8.39]	42.3 [7.79]	44.0 [8.39]	44.9 [8.75]	44.4 [8.57]
Change from baseline								
Week 8[b,c], *n*	223	231	232	463	189	193	195	388
Mean [SD]	2.6 [6.50]	3.2 [6.43]	3.6 [6.75]	3.4 [6.60]	2.6 [5.88]	5.1** [7.24]	6.0*** [7.70]	5.5*** [7.48]
Mental component summary								
Baseline, *n*	223	231	232	463	189	193	195	388
Mean [SD]	37.8 [10.64]	37.3 [9.98]	36.4 [9.89]	36.9 [9.93]	37.1 [10.75]	37.2 [10.81]	37.9 [11.15]	37.6 [10.98]
Week 8, *n*	223	231	232	463	189	193	195	388
Mean [SD]	40.0 [11.38]	40.6 [11.79]	41.3 [10.45]	41.0 [11.13]	40.4 [11.79]	43.1 [11.36]	44.7 [10.72]	43.9 [11.06]
Change from baseline								
Week 8[b,c], *n*	223	231	232	463	189	193	195	388
Mean [SD]	2.2 [8.47]	3.3 [9.41]	4.9** [9.28]	4.1* [9.37]	3.3 [9.47]	5.9** [10.55]	6.8*** [11.34]	6.4*** [10.95]

IBDQ, Inflammatory Bowel Disease Questionnaire; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

[a]Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg [weight ≤55 kg], 390 mg [weight >55 kg and ≤85 kg], 520 mg [weight >85 kg].

[b]Patients who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes before Week 8 had their baseline value carried forward.

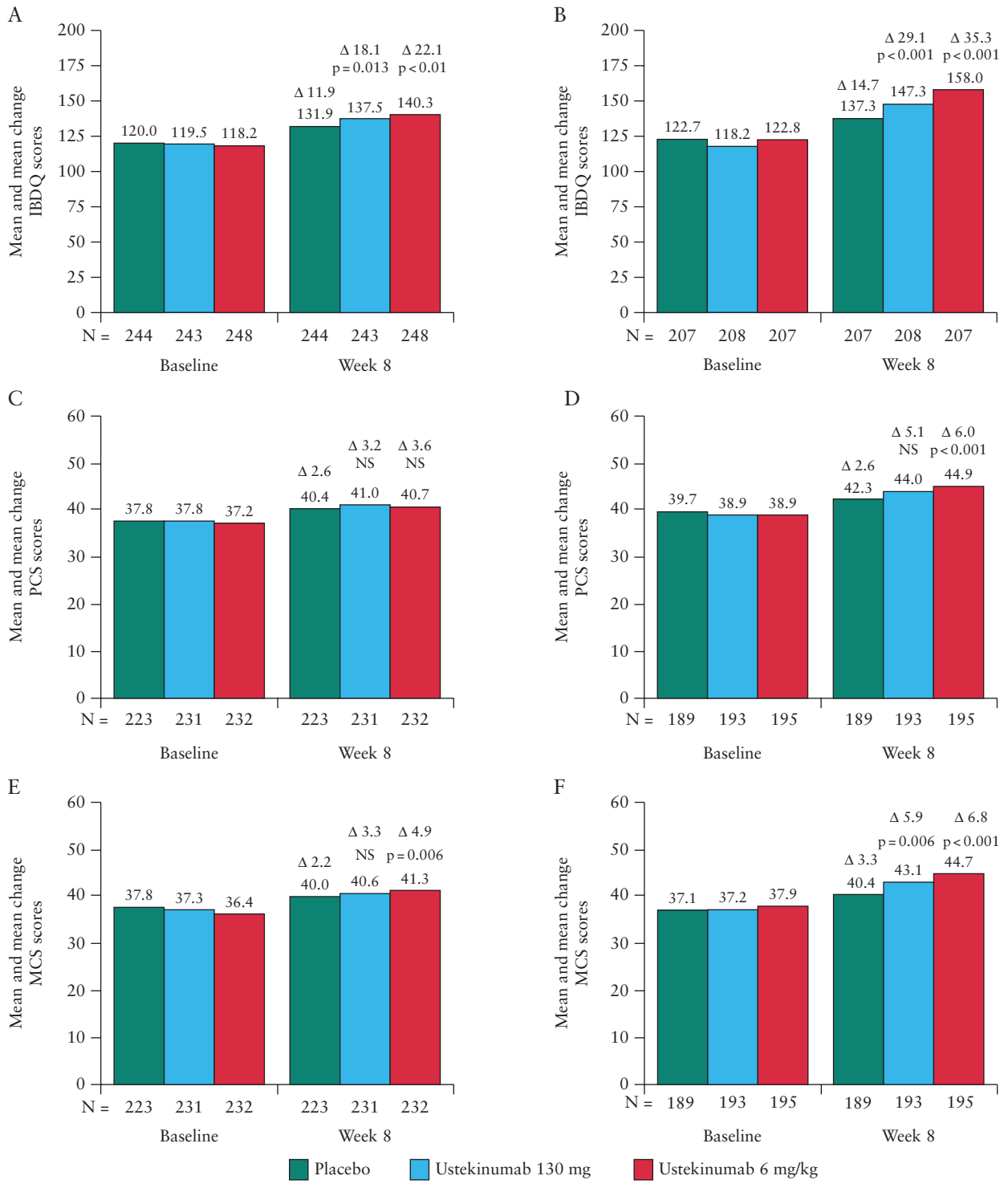
[c]Patients who had insufficient data at Week 8 had their last value carried forward.

*p <0.050; **p <0.010; ***p <0.001.

2.1. Assessments

Disease-specific HRQOL was measured using the Inflammatory Bowel Disease Questionnaire [IBDQ],[2] and generic HRQOL was measured using the SF-36[1] summary scores [PCS and MCS] and individual item scores, which were completed at Weeks 0 and 8 of the induction studies and at Weeks 20 and 44 of the maintenance study.

Clinically meaningful improvements of these measures were defined as an increase of ≥16 points in IBDQ score[2,6,7] and ≥5 points



Key: Δ, change from baseline; IBDQ, inflammatory bowel disease questionaire; PCS, physical component score; MCS, mental component score; NS, not statistically significant

Figure 1. Mean baseline and Week 8, and mean change in IBDQ, PCS, and MCS scores with induction therapy [UNITI-1: A, C, E; UNITI-2: B, D, F].

Table 2. Mean [SD] and mean change [SD] from baseline in IBDQ domain and SF-36 scale scores at Week 8 of induction therapy.

	UNITI-1			UNITI-2		
		Ustekinumab			Ustekinumab	
Patient-reported outcome	Placebo	130 mg	6 mg[a]	Placebo	130 mg	6 mg[a]
IBDQ *score, n*[b,c]	**247**	**245**	**249**	**209**	**209**	**209**
Bowel symptoms						
Baseline, *n*	245	244	248	207	209	208
Mean [SD]	38.6 [9.28]	38.2 [8.81]	38.5 [8.27]	38.8 [9.14]	38.2 [9.21]	38.9 [9.19]
Week 8, *n*	245	244	248	207	209	208
Mean [SD]	42.6 [10.31]	43.7 [11.27]	45.1 [10.01]	43.9 [11.02]	47.5[10.96]	50.6 [10.88]
Change at Week 8, *n*	245	244	248	207	209	208
Mean [SD]	4.0 [8.81]	5.5 [9.04]	6.6*** [8.56]	5.1 [8.78]	9.3*** [10.76]	11.7*** [11.21]
Emotional functions						
Baseline, *n*	245	243	248	207	209	208
Mean [SD]	46.5 [13.32]	47.0 [13.75]	45.9 [11.93]	46.7 [14.17]	44.3 [13.56]	46.8 [14.44]
Week 8, *n*	245	243	248	207	209	208
Mean [SD]	50.7 [14.99]	52.8 [16.06]	53.7 [14.20]	51.2 [15.71]	54.5 [15.28]	58.6 [14.43]
Change at Week 8, *n*	245	243	248	207	209	208
Mean [SD]	4.2 [10.52]	5.8 [11.53]	7.7*** [11.82]	4.5 [10.79]	10.1*** [13.95]	11.9*** [14.88]
Systemic symptoms						
Baseline, *n*	245	245	248	209	209	208
Mean [SD]	15.2 [5.25]	14.9 [4.74]	14.6 [4.97]	15.7 [5.35]	15.2 [5.11]	15.8 [5.23]
Week 8, *n*	245	245	248	209	209	208
Mean [SD]	17.3 [6.09]	18.3 [6.52]	18.5 [6.60]	18.5 [6.46]	20.0 [6.61]	21.8 [5.94]
Change at Week 8, *n*	245	245	248	209	209	208
Mean [SD]	2.1 [5.10]	3.4* [5.65]	3.9*** [5.57]	2.8 [5.17]	4.8*** [6.09]	6.0*** [6.29]
Social functions						
Baseline	244	244	248	209	208	209
Mean [SD]	19.8 [7.35]	19.3 [7.44]	19.2 [7.15]	21.5 [7.21]	20.4 [7.44]	21.4 [7.37]
Week 8 *n*	244	244	248	209	208	209
Mean [SD]	21.3 [8.09]	22.6 [8.23]	23.0 [7.99]	23.8 [7.75]	25.2 [7.65]	26.9 [6.97]
Change at Week 8, *n*,	244	244	248	209	208	209
Mean [SD]	1.5 [6.03]	3.3** [6.14]	3.8*** [6.63]	2.3 [5.67]	4.8*** [6.69]	5.6*** [7.12]
SF-36 Score, n=[b,c]	225	231	235	190	194	196
Physical functioning						
Baseline, *n*	224	231	234	190	193	196
Mean [SD]	44.2 [8.52]	44.3 [8.61]	43.5 [8.70]	44.9 [9.57]	44.2 [9.38]	43.7 [9.13]
Week 8, *n*	224	231	234	190	193	196
Mean [SD]	45.9 [8.67]	46.7 [9.23]	45.9 [9.52]	46.6 [9.21]	47.9 [8.45]	47.9 [8.65]
Change at Week 8, *n*	224	231	234	190	193	196
Mean [SD]	1.7 [6.58]	2.4 [6.76]	2.4 [7.27]	1.8 [6.68]	3.7* [7.36]	4.2** [7.09]
Role-physical						
Baseline, *n*	223	231	234	190	193	195
Mean [SD]	35.2 [8.87]	35.5 [9.51]	34.7 [9.45]	37.7 [9.36]	37.2 [9.92]	37.1 [9.64]
Week 8, *n*	223	231	234	190	193	195
Mean [SD]	39.1 [10.09]	39.6 [10.95]	39.7 [11.17]	40.8 [10.30]	43.3 [10.36]	44.3 [10.07]
Change at Week 8, *n*	223	231	234	190	193	195
Mean [SD]	3.9 [8.70]	4.1 [8.95]	5.0 [9.51]	3.1 [7.67]	6.1*** [8.60]	7.2*** [9.87]
Bodily pain						
Baseline, *n*	224	231	233	190	193	195
Mean [SD]	37.8 [8.11]	36.3 [7.03]	36.3 [7.72]	36.8 [7.27]	36.6 [8.20]	37.3 [7.27]
Week 8, *n*	224	231	233	190	193	195
Mean [SD]	40.3 [9.09]	40.5 [8.87]	41.7 [9.20]	40.6 [8.91]	43.3 [9.61]	45.8 [9.04]
Change at Week 8, *n*	224	231	233	190	193	195
Mean [SD]	2.5 [7.75]	4.1 [8.02]	5.4*** [8.07]	3.8 [7.31]	6.8** [9.47]	8.5*** [10.00]
General health						
Baseline, *n*	224	231	234	190	193	196
Mean [SD]	31.7 [7.59]	31.7 [6.70]	30.4 [6.89]	33.6 [8.69]	32.9 [8.45]	33.4 [7.47]
Week 8, *n*	224	231	234	190	193	196
Mean [SD]	33.2 [8.46]	34.0 [8.56]	33.4 [8.18]	36.3 [9.17]	37.8 [10.50]	38.9 [10.40]
Change at Week 8, *n*	224	231	234	190	193	196
Mean [SD]	1.6 [6.30]	2.4 [6.51]	2.9 [6.54]	2.7 [7.20]	4.8* [8.79]	5.6*** [9.36]

Table 2. Continued

Patient-reported outcome	UNITI-1			UNITI-2		
		Ustekinumab			Ustekinumab	
	Placebo	130 mg	6 mg[a]	Placebo	130 mg	6 mg[a]
Vitality						
Baseline, *n*	224	231	232	189	193	196
Mean [SD]	35.5 [9.21]	35.3 [8.28]	34.8 [8.29]	36.9 [9.15]	36.3 [9.13]	37.7 [9.57]
Week 8, *n*	224	231	232	189	193	196
Mean [SD]	38.8 [10.05]	39.7 [10.49]	39.8 [10.19]	40.7 [10.95]	43.4 [11.82]	45.2 [10.91]
Change at Week 8, *n*	224	231	232	189	193	196
Mean [SD]	3.3 [8.12]	4.5 [9.43]	5.0* [9.05]	3.8 [9.17]	7.2** [10.46]	7.6*** [10.32]
Social functioning						
Baseline, *n*	224	231	234	190	193	195
Mean [SD]	35.2 [10.04]	35.6 [9.57]	34.1 [9.41]	36.8 [10.50]	36.6 [10.18]	36.2 [9.95]
Week 8, *n*	224	231	234	190	193	195
Mean [SD]	38.2 [10.97]	39.0 [11.03]	40.0 [10.63]	40.2 [11.36]	43.2 [10.79]	44.1 [9.86]
Change at Week 8, *n*	224	231	234	190	193	195
Mean [SD]	3.0 [9.24]	3.5 [9.76]	5.9** [9.50]	3.4 [9.55]	6.6** [11.04]	7.9*** [11.11]
Role-emotional						
Baseline, *n*	223	231	234	190	193	195
Mean [SD]	38.9 [12.51]	38.5 [12.17]	37.7 [12.48]	38.5 [12.39]	38.4 [12.86]	38.7 [11.97]
Week 8, *n*	223	231	234	190	193	195
Mean [SD]	40.7 [12.53]	41.9 [13.09]	41.5 [12.74]	41.3 [12.34]	43.7 [11.85]	44.8 [10.78]
Change at Week 8, *n*	223	231	234	190	193	195
Mean [SD]	1.9 [10.72]	3.4 [10.84]	3.8 [11.30]	2.8 [10.80]	5.3* [10.47]	6.1** [12.34]
Mental health						
Baseline, *n*	224	231	232	189	193	196
Mean [SD]	40.5 [10.63]	39.5 [10.26]	38.8 [9.34]	38.6 [11.16]	38.8 [10.51]	39.6 [11.37]
Week 8, *n*	224	231	232	189	193	196
Mean [SD]	42.4 [11.35]	42.3 [11.49]	43.3 [10.24]	41.6 [11.94]	44.0 [11.32]	45.7 [11.00]
Change at Week 8, *n*	224	231	232	189	193	196
Mean [SD]	1.9 [8.17]	2.8 [9.34]	4.5** [8.59]	3.0 [8.56]	5.2* [10.29]	6.1*** [10.91]

IBDQ, Inflammatory Bowel Disease Questionnaire; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

[a]Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg [weight ≤55 kg], 390 mg [weight >55 kg and ≤85 kg], 520 mg [weight >85 kg].

[b]Patients who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes before Week 8 had their baseline value carried forward.

[c]Patients who had insufficient data at Week 8 had their last value carried forward.

*p <0.050; **p <0.010; ***p <0.001.

in SF-36 PCS and MCS scores.[8,9] Patients with an IBDQ score ≥170 points were considered to be in clinical remission.[10] Additionally, IBDQ normalisation defined as a score ≥210 points,[7] and SF-36 PCS or MCS normalisation defined as scores ≥50 points[11] among patients with abnormal baseline values, were also evaluated in post hoc analyses.

2.2. Statistical analysis

The Type 1 error rate within each study was controlled at 0.05 for the primary and major secondary endpoints, using a hierarchical testing procedure. The HRQOL outcomes described herein were pre-specified; however, statistical contrasts were not adjusted for multiplicity. thus p-values should be considered nominal. Each ustekinumab group [induction: ustekinumab 130 mg, ustekinumab 6 mg/kg, ustekinumab combined; maintenance: ustekinumab 90 mg q12w, ustekinumab 90 mg q8w] was compared with the placebo group. Continuous outcomes [mean change from baseline in SF-36 component summary and scale scores at Week 8, Week 20, and Week 44; mean change from baseline in IBDQ total and domain scores at Week 8, Week 20, and Week 44] were analysed by analysis of covariance on van der Waerden normal scores. Proportions of patients with dichotomous outcomes [clinically meaningful improvements or normalised values] in IBDQ, PCS, and MCS at Week 8 and Week 44 were compared using a Cochran-Mantel-Haenszel chi-square test.

The following missing data conventions were used for these analyses. Each of the four individual IBDQ dimensions was calculated when ≤1 item was missing in the dimension. The missing item was estimated using the average value across the non-missing items. If any one of the dimensions within the IBDQ could not be calculated, then the total IBDQ score was not be calculated.

For SF-36 scores, subscales were calculated whenever ≥50% of the items that comprised the individual subscale were available [non-missing]. Any missing items were estimated using the average value across the non-missing items for that subscale. If <50% of the items that comprised the subscale were available, the subscale was not calculated. If any of the individual subscales that comprised the PCS or MCS score was missing, then these scores could not be calculated.

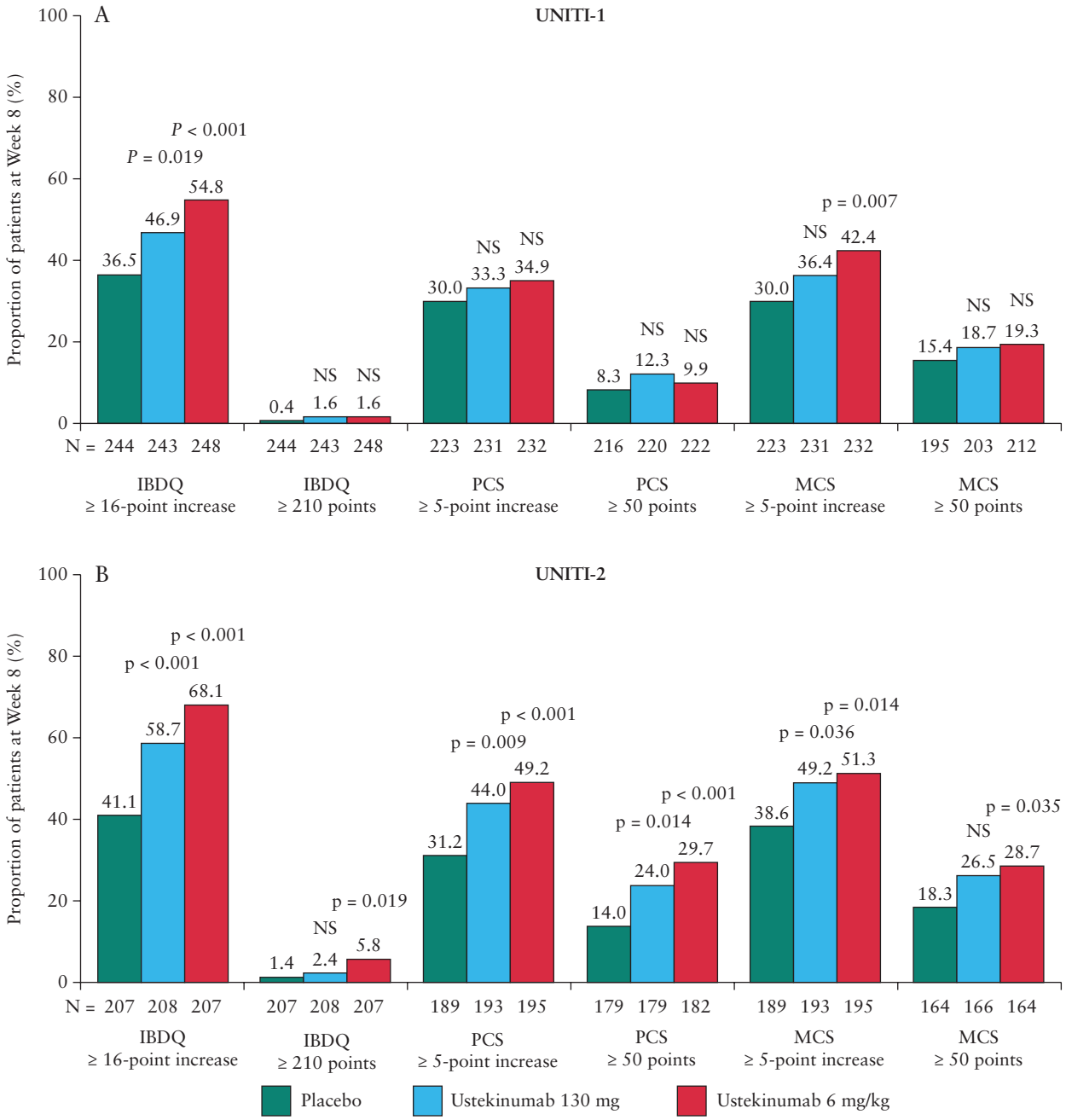


Figure 2. Proportions of patients at Week 8 who achieved ≥16-point improvement in or normalised [≥210] IBDQ total scores and proportions of patients who achieved ≥5-point improvement in or normalized [≥50] SF-36 MCS and PCS scores with induction therapy. IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary Score; NS, not statistically significant; PCS, Physical Component Summary Score; SF-36, 36-item Short Form Health Survey.

3. Results

3.1. Induction studies

Baseline disease characteristics in both the UNITI-1 and UNITI-2 study populations were representative of patients with moderately to severely active CD refractory to either TNF antagonists [UNITI-1] or conventional therapies [UNITI-2]. Median disease duration was 6.4 and 10.1 years and median CDAI scores were 292.5 and 317.0 in UNITI-2 and 1, respectively. Median C-reactive protein [CRP] concentrations were 8.05 mg/L in UNITI-2 and 9.88 mg/L in UNITI-1. Higher values for CDAI score and CRP concentrations are consistent with higher disease activity in the TNF-antagonist failure UNITI-1 population.

3.1.1. IBDQ results

In both UNITI-1 and UNITI-2, mean (standard deviation[SD]) baseline IBDQ scores for placebo, ustekinumab 130 mg, and ustekinumab 6 mg/kg (UNITI-1: 120.0 [29.27], 119.5 [29.47], and 118.2 [26.64], respectively; UNITI-2: 122.7 [31.32], 118.2 [30.99], and 122.8 [31.62], respectively) were similar across treatment groups, consistent with substantially impaired HRQOL. Following initiation of induction therapy, significantly greater improvement was observed for both ustekinumab doses in comparison with placebo [Table 1; Figure 1A, B]. A numerically greater treatment effect relative to placebo was seen in UNITI-2 than UNITI-1 [ustekinumab 130 mg, 14.4 versus 6.2; ustekinumab 6 mg/kg, 20.6 versus 10.2, respectively].

Table 3. Mean [SD] and mean change [SD] from baseline in the IBDQ score at Week 20 and Week 44 of maintenance therapy.

		Ustekinumab	
	Placebo SC[a] [*n* = 131]	90 mg SC q12w [*n* = 129]	90 mg SC q8w [*n* = 128]
Baseline, *n*	130	129	126
Mean [SD]	163.6 [31.76]	165.8 [32.82]	170.5 [29.33]
Week 20, *n*	130	129	126
Mean [SD]	150.8 [40.99]	159.6 [40.96]	161.6 [40.27]
Change from baseline			
Week 20[b,c], *n*	130	129	126
Mean [SD]	-12.8 [34.05]	-6.3 [37.04]*	-8.9 [31.46]
Week 44, *n*	130	128	126
Mean [SD]	142.1 [42.46]	156.9 [43.54]	160.5 [40.71]
Change from baseline			
Week 44[b,c], *n*	130	128	126
Mean [SD]	-21.5 [39.26]	-8.9 [43.08]***	-9.9 [34.83]**

IBDQ, inflammatory bowel disease questionnaire; IV, intravenous; SC, subcutaneous; SD, standard deviation; q8w, every 8 weeks; q12w, every 12 weeks.

[a]Patients who were in clinical response to ustekinumab IV induction dosing and were randomised to placebo SC on entry into this maintenance study.

[b]Patients who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be worsened Crohn's disease before the designated analysis timepoint had their induction baseline value carried forward.

[c]Patients who had insufficient data at the designated analysis timepoint had their last value carried forward.

*p <0.050; **p <0.010; ***p <0.001.

For both studies, changes in the mean IBDQ scores at Week 8 were significantly greater in both ustekinumab dose groups compared with placebo and across all dimensions [p <0.05 for all comparisons]. In both studies, changes in the mean IBDQ dimension scores at Week 8 were significantly greater in the ustekinumab 6 mg/kg group compared with placebo and across all dimensions [p <0.001 for all comparisons]. In the ustekinumab 130 mg group, mean changes at Week 8 were significantly greater for the social and systemic dimensions [p <0.05 for both comparisons], and numerically greater for the bowel and emotional dimensions compared with placebo in UNITI-1 [Table 2]. Mean changes at Week 8 were significantly greater across all four dimensions when compared with placebo [p <0.001 for both comparisons] in UNITI-2 [Table 2].

With both ustekinumab doses in both studies, significantly greater proportions of patients experienced clinically meaningful improvement in IBDQ at Week 8 [UNITI-1: 54.8% and 46.9%, respectively, versus 36.5%; p <0.001 and p = 0.019, respectively; UNITI-2: 68.1% and 58.7%, respectively, versus 41.1%; p <0.001 and p <0.001, respectively; Figure 2A, B]. All patients had impaired baseline IBDQ scores [<210 points]. In both ustekinumab dose groups at Week 8, a greater proportion of patients had normal scores [≥210 points] than placebo [Figure 2A, B]. In UNITI-2, this comparison was only statistically significant for the comparison of ustekinumab 6 mg/kg with placebo [5.8% versus 1.4%, p = 0.019].

3.1.2. SF-36 results

In both studies, the mean baseline SF-36, PCS, and MCS scores were similar among the three treatment groups [Table 1; Figure 1C-F]. In UNITI-1 at Week 8, the mean change from baseline in the PCS score was numerically, but not significantly, greater in the both ustekinumab dose groups compared with the placebo group. The mean change from baseline in the MCS score at that time was significantly greater in the ustekinumab 6 mg/kg group [p = 0.006], but only numerically greater for the ustekinumab 130 mg group compared with the placebo group. In UNITI-2, the mean changes from baseline in the MCS and PCS scores were significantly greater for both ustekinumab groups compared with the placebo group [p <0.05 for all comparisons; Table 1].

In UNITI-1, mean changes from baseline in norm-based scores of the SF-36 scales at Week 8 were numerically greater in both ustekinumab groups compared with placebo; however, the ustekinumab 6 mg/kg group showed relatively greater differences, with statistically significant differences observed for bodily pain, vitality, social functioning, and mental health scales [Table 2]. In UNITI-2, the mean changes from baseline in norm-based scores of the SF-36 scales at Week 8 were significantly greater in both ustekinumab groups compared with the placebo group [p <0.05 for all comparisons; Table 2].

In UNITI-2, the proportion of patients with a clinically meaningful improvement in PCS was significantly greater for the ustekinumab 6 mg/kg and 130 mg groups than for the placebo group [49.2% and 44.0%, respectively versus 31.2%; p <0.001 and p = 0.009, respectively]. More patients experienced clinically significant improvement in MCS in both the ustekinumab 6 mg/kg and 130 mg groups than the placebo group [51.3% and 49.2%, respectively, versus 38.6%; p = 0.014 and p = 0.036, respectively]. In UNITI-1, MCS scores were only significantly greater for the ustekinumab 6 mg/kg group in comparison with the placebo group [42.4% versus 30.0%; p = 0.007] [Figure 2A, B].

For patients with impaired SF-36 scores at baseline, defined as less than the US population norm of 50 points, greater proportions of patients receiving either ustekinumab dose had normal MCS and PCS scores compared with placebo at Week 8 [Figure 2A, B]. These differences were statistically significant in UNITI-2 for the MCS [with both ustekinumab doses] and for the PCS in the ustekinumab 6 mg/kg group.

3.2. Maintenance study

3.2.1. IBDQ results

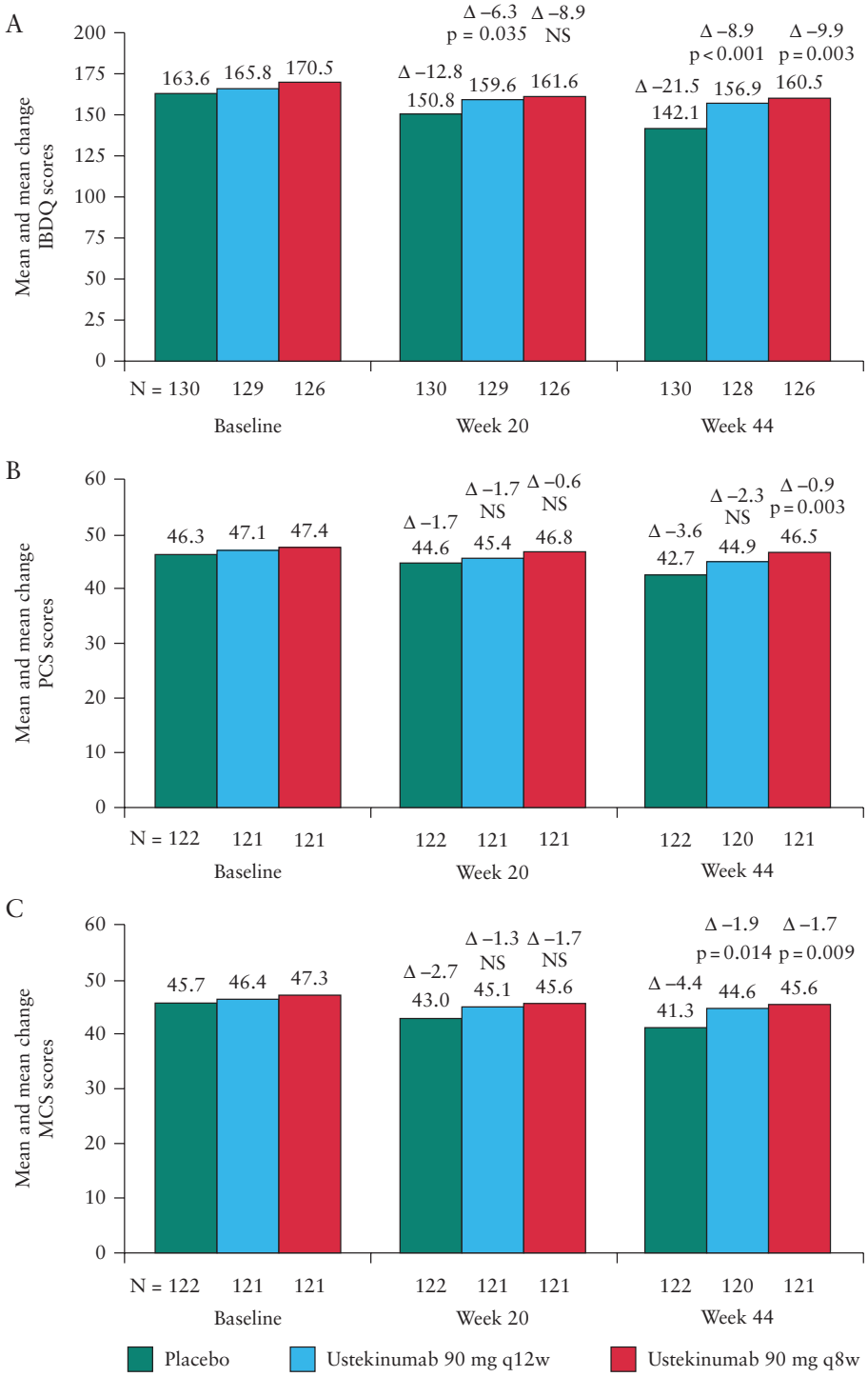
At baseline of the maintenance study [induction Week 8], the mean [SD] IBDQ scores for randomised ustekinumab responders were generally similar among the placebo and ustekinumab q12w and q8w groups (163.6 [31.75], 165.8 [32.82], and 170.5 [29.33], respectively) [Table 3; Figure 3A]. At Week 20, the mean decrease [worsening] in IBDQ score from maintenance baseline was significantly less in the ustekinumab 90 mg q12w group and numerically less in the ustekinumab q8w dose group compared with the placebo group [p = 0.035 and p = 0.183, respectively; Table 3]. At Week 44, the mean decreases in IBDQ scores from maintenance baseline were significantly less in the ustekinumab q12w and q8w dose groups (-8.9 [43.08] versus -9.9 [34.83], respectively) compared with the placebo group (-21.5 [39.26]; p < 0.001 and p = 0.003, respectively; Table 3; Figure 3A]. These results indicate that patients who received ustekinumab were more likely to maintain the improvement in their IBDQ scores achieved during induction compared with patients who discontinued ustekinumab treatment.

The proportion of patients with a clinically meaningful improvement in IBDQ score at Week 44 was significantly greater than placebo for the ustekinumab q8w dose but not for the ustekinumab q12w

dose group [67.9% and 61.3%, respectively, versus placebo 50.4%; $p = 0.014$ and $p = 0.140$, respectively; Figure 4]. Among patients with IBDQ scores of <210 points at baseline of an induction study, greater proportions of patients receiving either ustekinumab dose, than placebo, achieved normal scores at Week 44 following maintenance treatment [Figure 4].

3.2.2. SF-36 results

The mean PCS and MCS scores of the SF-36 at baseline of maintenance [induction Week 8] were similar among the three treatment groups [Table 4; Figure 3B, C]. For the ustekinumab q8w group, the mean decreases from baseline [worsening] of the maintenance study in the PCS and MCS scores were significantly less at Week 44



Key: Δ, change from baseline; IBDQ, inflamatory bowel disease questionaire; PCS, physical component score; MCS, mental component score; NS, not statistically significant; q8w, every 8 weeks; q12w, every 12 weeks.

Figure 3. Mean and mean change from baseline, Week 20, and Week 44 in IBDQ [A], PCS [B] and MCS [C] scores with maintenance therapy.

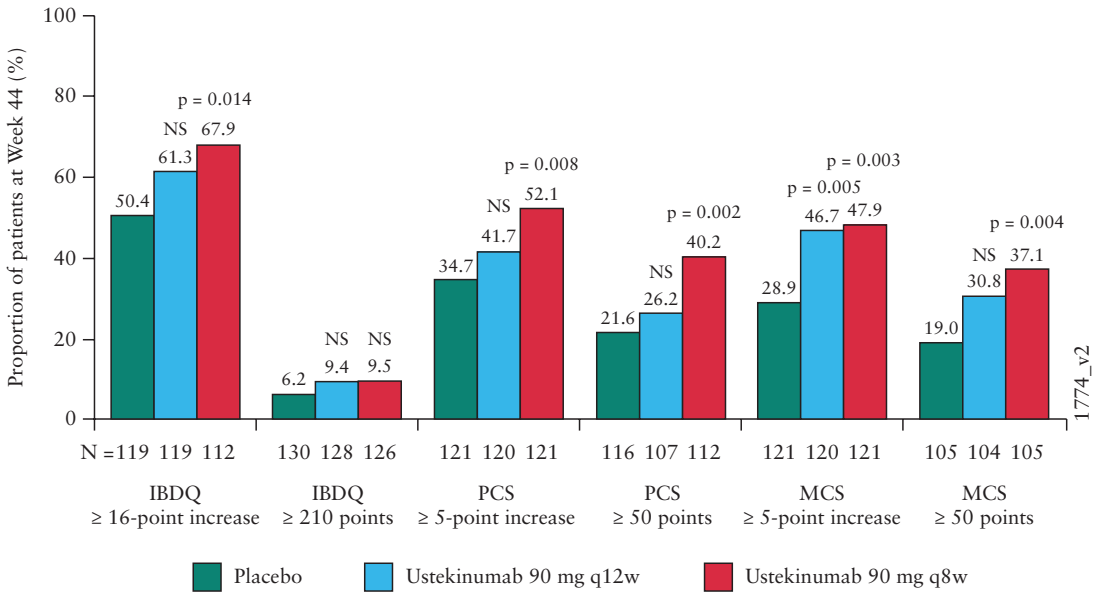


Figure 4. Proportions of patients at Week 44 who achieved ≥16-point improvement in or normalised [≥210] IBDQ total score and proportions of patients who achieved ≥5-point improvement in or normalised [≥50] SF-36 PCS and MCS scores from the baseline of an induction study. IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary Score; NS, not statistically significant; PCS, Physical Component Summary Score; q8w, every 8 weeks; q12w, every 12 weeks. SF-36, 36-item Short Form Health Survey.

Table 4. Mean [SD] and mean change [SD] from baseline in the physical and mental component summary scores of the SF-36 at Week 20 and Week 44 of maintenance therapy.

		Ustekinumab	
SF-36 Component Summary Scores	Placebo SC[a] [*n* = 122]	90 mg SC q12w [*n* = 121]	90 mg SC q8w [*n* = 121]
Physical Component Summary			
Baseline, *n*	122	121	121
Mean [SD]	46.3 [8.21]	47.1 [8.10]	47.4 [7.52]
Week 20[b,c], *n*	122	121	121
Mean [SD]	44.6 [9.71]	45.4 [8.86]	46.8 [9.08]
Change from baseline			
Week 20[b,c], *n*	122	121	121
Mean [SD]	-1.7 [7.67]	-1.7 [7.18]	-0.6 [6.37]
Week 44[b,c], *n*	122	120	121
Mean [SD]	42.7 [9.96]	44.9 [9.62]	46.5 [8.98]
Change from baseline			
Week 44[b,c], *n*	122	120	121
Mean [SD]	-3.6 [9.33]	-2.3 [9.31]	-0.9 [7.14]**
Mental component summary			
Baseline, *n*	122	121	121
Mean [SD]	45.7 [10.89]	46.4 [10.66]	47.3 [9.91]
Week 20[b,c], *n*	122	121	121
Mean [SD]	43.0 [11.34]	45.1 [11.40]	45.6 [10.57]
Change from baseline			
Week 20[b,c], *n*	122	121	121
Mean [SD]	-2.7 [10.78]	-1.3 [11.53]	-1.7 [9.01]
Week 44[b,c], *n*	122	120	121
Mean [SD]	41.3 [11.79]	44.6 [11.81]	45.6 [11.22]
Change from baseline			
Week 44[b,c], *n*	122	120	121
Mean [SD]	-4.4 [11.06]	-1.9 [12.68]*	-1.7 [9.76]**

IV, intravenous; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; SD, standard deviation; SF-36, 36-item Short-Form Health Survey.

[a]Patients who were in clinical response to ustekinumab IV induction dosing and were randomised to placebo SC on entry into this maintenance study.

[b]Patients who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be worsened Crohn's disease before the designated analysis timepoint had their induction baseline value carried forward.

[c]Patients who had insufficient data at the designated analysis timepoint had their last value carried forward.

*p <0.050; **p <0.010; ***p <0.001.

Table 5. Mean [SD] and mean change [SD] from baseline in IBDQ and SF-36 dimension and scale scores at Week 44 of maintenance therapy.

		Ustekinumab	
Patient-reported outcome	Placebo SC[a]	90 mg SC q12w	90 mg SC q8w
IBDQ[b,c]	131	129	128
Bowel symptoms			
Baseline, *n*	131	129	128
Mean [SD]	52.2 [9.86]	53.7 [8.93]	54.0 [8.92]
Week 44, *n*	131	128	127
Mean [SD]	45.5 [12.70]	50.4 [13.48]	51.4 [12.63]
Change from baseline Week 44, *n*	131	128	127
Mean [SD]	-6.7 [11.62]	-3.3** [12.26]	-3.0*** [11.06]
Emotional functions			
Baseline, *n*	131	129	127
Mean [SD]	60.4 [13.39]	61.1 [14.52]	62.8 [12.44]
Week 44, *n*	131	128	127
Mean [SD]	53.8 [16.26]	58.6 [17.05]	59.9 [15.99]
Change from baseline Week 44, *n*	131	128	127
Mean [SD]	-6.6 [15.76]	-2.6** [17.46]	-2.9** [13.42]
Systemic symptoms			
Baseline, *n*	130	129	128
Mean [SD]	23.1 [5.79]	23.2 [6.04]	23.9 [5.55]
Week 44, *n*	130	128	128
Mean [SD]	18.9 [7.78]	20.9 [7.41]	21.9 [7.14]
Change from baseline Week 44, *n*	130	128	128
Mean [SD]	-4.2 [7.42]	-2.3* [7.77]	-2.0** [6.19]
Social functions			
Baseline, *n*	131	129	127
Mean [SD]	27.8 [6.31]	27.9 [7.18]	28.8 [6.25]
Week 44, *n*	131	128	127
Mean [SD]	24.1 [8.98]	27.1 [8.20]	27.0 [7.80]
Change from baseline Week 44, *n*	131	128	127
Mean [SD]	-3.7 [7.67]	-0.8*** [8.49]	-1.8* [7.38]
SF-36[b,c]	122	121	121
Physical functioning			
Baseline, *n*	122	121	121
Mean [SD]	49.8 [7.70]	50.4 [8.51]	51.0 [7.33]
Week 44, *n*	122	121	121
Mean [SD]	46.7 [9.35]	48.5 [9.67]	50.6 [7.94]
Change from baseline Week 44, *n*	122	121	121
Mean [SD]	-3.2 [8.42]	-1.9 [7.94]	-0.4** [5.63]
Role-physical			
Baseline, *n*	122	121	121
Mean [SD]	45.6 [9.75]	46.3 [9.93]	47.6 [9.37]
Week 44, *n*	122	121	121
Mean [SD]	40.8 [12.01]	43.4 [11.89]	46.0 [10.94]
Change from baseline Week 44, *n*	122	121	121
Mean [SD]	-4.8 [11.87]	-2.9 [12.73]	-1.6** [8.79]
Bodily pain			
Baseline, *n*	122	121	121
Mean [SD]	47.1 [8.04]	48.8 [8.17]	48.2 [8.67]
Week 44, *n*	122	120	121
Mean [SD]	42.1 [10.65]	45.1 [11.34]	46.5 [10.97]
Change from baseline Week 44, *n*	122	120	121
Mean [SD]	-5.0 [10.61]	-3.8 [11.73]	-1.7** [8.87]
General health			
Baseline, *n*	122	121	121
Mean [SD]	39.5 [10.37]	40.0 [10.54]	40.7 [10.06]
Week 44, *n*	122	121	121
Mean [SD]	37.2 [10.94]	39.9 [11.31]	40.1 [11.03]
Change from baseline Week 44, *n*	122	121	121
Mean [SD]	-2.3 [10.18]	-0.1* [10.25]	-0.6 [8.78]

Table 5. Continued

Patient-reported outcome	Placebo SC[a]	Ustekinumab	
		90 mg SC q12w	90 mg SC q8w
Vitality			
Baseline, *n*	122	121	121
Mean [SD]	46.4 [10.27]	47.2 [10.82]	48.6 [10.94]
Week 44, *n*	122	120	121
Mean [SD]	41.4 [12.25]	44.8 [12.83]	45.6 [12.45]
Change from baseline Week 44, *n*	122	120	121
Mean [SD]	-5.0 [11.77]	-2.4* [12.42]	-2.9* [10.38]
Social functioning			
Baseline, *n*	122	121	121
Mean [SD]	45.7 [8.89]	46.4 [10.17]	46.5 [9.54]
Week 44, *n*	122	121	121
Mean [SD]	41.5 [11.79]	44.1 [11.76]	45.3 [10.96]
Change from baseline Week 44, *n*	122	121	121
Mean [SD]	-4.2 [12.23]	-2.3 [13.41]	-1.2* [10.06]
Role-emotional			
Baseline, *n*	122	121	121
Mean [SD]	45.5 [11.95]	46.4 [10.90]	47.9 [9.64]
Week 44, *n*	122	121	121
Mean [SD]	42.2 [13.46]	44.6 [12.80]	46.5 [11.69]
Change from baseline Week 44, *n*	122	121	121
Mean [SD]	-3.3 [11.59]	-1.8 [14.04]	-1.4 [9.29]
Mental health			
Baseline, *n*	122	121	121
Mean [SD]	46.9 [10.68]	47.7 [10.11]	48.1 [10.30]
Week 44, *n*	122	120	121
Mean [SD]	42.0 [10.98]	45.6 [11.57]	47.0 [10.81]
Change from baseline Week 44, *n*	122	120	121
Mean [SD]	-4.9 [10.52]	-2.3** [11.93]	-1.1*** [9.85]

IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

[a]Patients who were in clinical response to ustekinumab IV induction dosing and were randomised to placebo SC on entry into this maintenance study.

[b]Patients who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be worsened Crohn's disease before the designated analysis timepoint had their induction baseline value carried forward.

[c]Patients who had insufficient data at the designated analysis timepoint had their last value carried forward.

*p <0.050; **p <0.010; ***p <0.001.

compared with the placebo group [Table 4]. For the ustekinumab q12w group, only the mean decrease from baseline during maintenance in the MCS score at Week 44 was significantly less compared with the placebo group.

For the SF-36 PCS and MCS scores, both the ustekinumab q8w and q12w dose groups had significantly greater proportions of patients with a clinically meaningful [≥5-point] improvement, except for the PCS in the ustekinumab q12w group [Figure 4]. A significantly greater proportion of patients in the ustekinumab q8w group achieved clinically-meaningful improvement in PCS than in the placebo group [52.1% versus placebo, 34.7%; p = 0.008], and a significantly greater proportion of patients in the ustekinumab q8w and q12w dose groups achieved a clinically meaningful improvement in MCS than the placebo group at Week 44 [47.9% and 46.7%, respectively, versus placebo, 28.9%; p = 0.003 and p = 0.005, respectively; Figure 4].

For patients with baseline SF-36 scores lower than the US population norm, greater proportions of patients in both ustekinumab dose groups had normal MCS and PCS scores at Week 44 [Figure 4]. These results were significantly greater with ustekinumab q8w for both MCS and PCS.

The mean SF-36 dimension scores [i.e. physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health] were generally consistent across all groups at baseline of the maintenance study. At Week 44, the mean worsening from baseline in the SF-36 dimension scores was generally less in the ustekinumab q12w and q8w groups compared with the placebo group [Table 5]. Specifically, the mean decreases [worsening] in general health, vitality, and mental health dimension scores in the ustekinumab q12w group were significantly less than those observed in the placebo group at Week 44, whereas the mean worsening in six of the eight dimension scores [physical functioning, role-physical, bodily pain, vitality, social functioning, and mental health] in the ustekinumab q8w group were significantly less than those observed for the placebo group at Week 44.

4. Discussion

At study entry, participants in the UNITI trials had active CD with IBDQ and SF-36 scores consistent with moderate to severe impairment of HRQOL.[10] Following treatment with IV ustekinumab 6 mg/kg or 130 mg, HRQOL scores improved considerably relative to placebo.

At Week 8, greater proportions of patients receiving either ustekinumab 6 mg/kg or 130 mg demonstrated clinically important improvement in total IBDQ scores compared with placebo, with a greater effect evident in those who received the regulatory approved 6 mg/kg dose. Consistent with these observations, greater

proportions of patients receiving ustekinumab 6 mg/kg and 130 mg demonstrated clinically significant improvement compared with placebo in both the PCS and MCS scores. Likewise, greater proportions of patients in the ustekinumab 6 mg/kg group achieved normal IBDQ, PCS, and MCS scores. It is noteworthy that HRQOL normalisation was more pronounced among ustekinumab-treated patients with an inadequate response or intolerance to conventional CD therapy [UNITI-2 population] than to TNF antagonists [UNITI-1 population]. This phenomenon, which was also observed in a recent analysis of patients treated with vedolizumab, is likely due to the greater prevalence of structural bowel damage in UNITI-1 participants who had higher disease activity and longer disease duration than those evaluated in UNITI-2.

At the baseline visit of IM-UNITI, the mean baseline IBDQ scores approached the criterion for remission [≥170 points] and both PCS and MCS scores approximated the general US population mean norms of 50. At Week 44 in IM-UNITI, a dose-response relationship was observed with patient-reported outcomes, as was previously reported for improvements in signs and symptoms.[5] This dose-response relationship favoured patients receiving q8w maintenance dosing compared with q12w dosing. Mean reductions in IBDQ scores from baseline at entry to IM-UNITI [i.e. Week 8] for the ustekinumab q12w and q8w dose groups were both significantly less compared with those assigned to placebo. This was also observed with SF-36 scores, where ustekinumab q8w was more likely to maintain improvement from induction therapy than ustekinumab q12w as measured by both the MCS and the PCS scores.

This dose-response between q8w and q12w dosing at Week 44 was more apparent in parameters evaluating the more stringent endpoints of patients achieving clinically-important improvement in IBDQ, PCS, or MCS, or normalisation of IBDQ, PCS, or MCS scores. These results are consistent with the Week 44 primary endpoint [clinical remission] and major secondary endpoints [clinical response, remission in remitters, corticosteroid-free remission, and remission in TNF-naïve patients] where the ustekinumab q8w group was numerically greater than the q12w group for all endpoints.[5] Collectively, these findings support the choice of the q8w dose regimen as being optimal for maintaining improved quality of life in patients who responded to induction therapy with ustekinumab.

Previous studies with TNF antagonists, including infliximab, natalizumab, adalimumab, and vedolizumab, have shown that maintenance treatment with these therapies results in improved HRQOL in patients as assessed by multiple patient-reported outcome instruments.[12–15]

In conclusion, ustekinumab improved general health status and inflammatory bowel disease-specific HRQOL after a single intravenous infusion in patients with moderately to severely active CD, particularly ustekinumab 6 mg/kg, and improvements were better maintained with subcutaneous ustekinumab 90 mg q8w or q12w as compared with placebo. These results mirror the efficacy in clinical outcomes and inflammatory biomarkers reported previously.[5]

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Conflict of Interest

BES has received honoraria for speaking in a CME conference from American Academy of CME, Inc., Catrille & Associates, Ltd, Creative Educational Concepts, Inc., Curatio CME Institute, Focus Medical Communications, LLC, Med-IQ, LLC, Rockpoint, Inc., IMEDEX, Scripps, Strategic Consultants International, and Vindico Medical Education; received consultant fees from Akros Pharma, Arena Pharmaceuticals, Cowen Services Company, LLC, Forest Research Institute, Inc., Forward Pharma, Immune Pharmaceuticals, Inc., MedImmune, Salix Pharmaceuticals, Inc., Strategic Consultants International, Synergy Pharmaceuticals, Theravance Biopharma R&D, Inc., TiGenix, UCB, and Vedanta Biosciences; received consulting fees for services on an advisory board for AbbVie, Amgen, AstraZeneca LP, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Luitpold Pharmaceuticals, Inc., Pfizer, Prometheus Laboratories, Receptos, Takeda, TopiVert Pharma; and received research grants from AbbVie, Amgen, Celgene, Janssen, Pfizer, Prometheus Laboratories, and Takeda. ST reports receiving consulting fees from Janssen Research & Development, LLC. WJS reports grants, personal fees, and non-financial support from AbbVie; grants and personal fees from Prometheus Laboratories, AbbVie, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen Research & Development, LLC, Bristol-Myers Squibb, Genentech, and Nutrition Science Partners; personal fees from Kyowa Hakko Kirin, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Catabasis Pharmaceuticals, Vertex Pharmaceuticals, Warner Chilcott, Gilead Sciences, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid Biotechnologies, Tillotts Pharma, Am Pharma BV, Dr August Wolff, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, Index Pharmaceuticals, Nestle, Lexicon Pharmaceuticals, UCB Pharma, Orexigen, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, Amgen, Novo Nordisk, Mesoblast, Inc., Shire, Ardelyx Inc., Actavis, Seattle Genetics, MedImmune [AstraZeneca], Actogenix NV, Lipid Therapeutics GmbH, Eisai, Qu Biologics, Toray Industries, Inc., Teva Pharmaceuticals, Eli Lilly, Chiasma, TiGenix, Adherion Therapeutics, Immune Pharmaceuticals, Celgene, Arena Pharmaceuticals, Ambrx, Inc., Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos, Seres Health, Ritter Pharmaceuticals, Theravance, Palatin, Biogen, and Western University [owner of Robarts Clinical Trials]. BGF has received consulting fees from Abbott/AbbVie, Ablynx, Actogenix, Akebia Therapeutics, Akros, Albireo Pharma, Allergan, Amgen, Applied Molecular Transport, Inc., Astra Zeneca, Atlantic Pharma, Avaxia Biologics, Inc., Avir Pharma, Baxter Healthcare Corp., Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, Galapagos, GiCare Pharma, Gilead, Given Imaging, Inc., GSK, Inception IBD, Inc., Ironwood Pharma, Janssen Research & Development, LLC, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Lycera BioTech, Merck, Mesoblast Pharma, Millennium, Nektar, Nestles, Nextbiotix, Novo Nordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Progenity, Protagonist, Receptos, Roche/Genentech, Salix Pharma, Serano, Shire, Sigmoid Pharma, Synergy Pharma, Inc., Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, Vivelix Pharma, VHsquared Ltd, Warner-Chilcott, Wyeth, Zealand, Zyngenia; grant/research support from AbbVie, Inc., Amgen, Inc., AstraZeneca/MedImmune Ltd, Atlantic Pharmaceuticals Ltd, Boehringer-Ingelheim, Celgene Corporation, Celltech, Genentech ,Inc.,/Hoffmann-La Roche Ltd, Gilead Sciences, Inc., GlaxoSmithKline [GSK], Janssen Research & Development LLC, Pfizer, Inc., Receptos, Inc./Celgene International, Sanofi, Santarus, Inc., Takeda Development Center Americas, Inc., Tillotts Pharma AG, UCB; served as a Scientific Advisory Board member for Abbott/AbbVie, Allergan, Amgen, Astra Zeneca, Atlantic Pharma, Avaxia Biologics, Inc., Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Inc., Elan/Biogen, Ferring, Galapagos, Genentech/Roche, Janssen Research & Development, LLC, Merck, Nestles, Novartis, Novo Nordisk, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharma, Takeda, Teva, TiGenix, Tillotts Pharma AG, UCB Pharma; has been on the speakers bureau for Abbott/AbbVie, Janssen Research & Development, LLC, Lilly, Takeda, Tillotts, and UCB Pharma; and is a member of the Board of Directors for Robarts Clinical Trials, Inc., Western University, London, ON. CH is an employee of Janssen Biotech, Inc., CG, YL, DJ, L-LG, and PS are employees of Janssen Research & Development, LLC.

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Author Contributions

The study concept and design were developed by BES, ST, WJS, and BGF in collaboration with the sponsor, Janssen Research & Development, LLC, and interpretation of data. BES, ST, WJS, and BGF were involved in the recruitment of study patients. All authors were involved in the analysis and/or interpretation of the data, and were involved in drafting the manuscript and critically reviewing it for important intellectual content. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

References

1. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey [SF-36]. I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.
2. Irvine EJ, Feagan B, Rochon J, *et al*. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology* 1994;**106**:287–96.
3. Sands BE, Han C, Gasink C, *et al*. Ustekinumab improves general health status and disease-specific health related quality of life of patients with moderate to severe Crohn's disease: results from the UNITI and IMUNITI phase 3 clinical trials. *Gastroenterology* 2016;**150**:S1004 [abstract].
4. Bernklev T, Jahnsen J, Lygren I, Henriksen M, Vatn M, Moum B. Health-related quality of life in patients with inflammatory bowel disease measured with the short form-36: psychometric assessments and a comparison with general population norms. *Inflamm Bowel Dis* 2005;**11**:909–18.
5. Feagan BG, Sandborn WJ, Gasink C, *et al*.; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016;**375**:1946–60.
6. Pallis AG, Vlachonikolis IG, Mouzas IA. Assessing health-related quality of life in patients with inflammatory bowel disease, in Crete, Greece. *BMC Gastroenterol* 2002;**2**:1.
7. Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1999;**28**:S23–7.
8. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE Jr. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:1478–87.
9. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics* 1999;**15**:141–55.
10. Hlavaty T, Persoons P, Vermeire S, *et al*. Evaluation of short-term responsiveness and cutoff values of inflammatory bowel disease questionnaire in Crohn's disease. *Inflamm Bowel Dis* 2006;**12**:199–204.
11. Ware JE, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: Health Institute; 1994.
12. Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. *Am J Gastroenterol* 2003;**98**:2232–8.
13. Feagan BG, Sandborn WJ, Hass S, Niecko T, White J. Health-related quality of life during natalizumab maintenance therapy for Crohn's disease. *Am J Gastroenterol* 2007;**102**:2737–46.
14. Loftus EV, Feagan BG, Colombel JF, *et al*. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008;**103**:3132–41.
15. Feagan BG, Patel H, Colombel JF, *et al*. Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial. *Aliment Pharmacol Ther* 2017;**45**:264–75.