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Original Article

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Association Between Proposed Definitions of Clinical Remission/Response and Well-Being in Patients With Crohn's Disease

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Abstract

Background and Aims: Patient-reported outcomes are recommended endpoints in Crohn's disease [CD] trials. The association between patient-reported general well-being relative to symptoms of diarrhoea and abdominal pain [AP] in patients with moderate to severe CD was explored.

Methods: Patients from three randomized, placebo-controlled, double-blind adalimumab or upadacitinib studies with average daily very soft/liquid stool frequency [SF] ≥4 and/or AP score ≥2 at baseline were included. Using electronic diaries, patients reported general well-being [seven-point Likert scale; 1 = worst; 7 = best] in item 10 of the Inflammatory Bowel Disease Questionnaire [IBDQ]. Changes in well-being and clinical outcomes of SF and AP from baseline to week 12 or 16, and the relationship between well-being and clinical outcomes were evaluated using cumulative distribution function and probability density function curves.

Results: In total, 858 patients with CD were included [adalimumab, *n* = 695; upadacitinib, *n* = 163]. Patients who achieved clinical remission [SF ≤2.8, AP score ≤1.0, neither worse than baseline] were more likely than those not in clinical remission to report IBDQ item 10 response in the 6–7 group category but not IBDQ categories ≤5. Higher IBDQ score for item 10 [6–7] was associated with lower SF and AP score. Greater point increases in IBDQ item 10 were associated with a greater percentage decrease in clinical parameters; a ≥25–30% decrease in SF or AP was associated with a ≥1-point improvement in IBDQ.

Conclusions: An association between improvements in patient-reported general well-being and clinical remission/response was observed using outcomes of SF and AP, supporting the clinical remission/response endpoint definitions used in clinical studies of CD.

Clinical Trial Registrations [ClinicalTrials.gov]: NCT00077779 [CHARM]; NCT00348283 [EXTEND]; NCT02365649 [CELEST].

Key Words: Stool frequency; abdominal pain; patient-reported outcomes

1. Introduction

Endpoints in randomized controlled trials in patients with Crohn's disease [CD] are evolving due to identification of relevant therapeutic targets and changes in regulatory perspective.[1] The Crohn's Disease Activity Index [CDAI] has been one of the most widely used endpoints, but has been under scrutiny as a primary efficacy endpoint by regulatory authorities in the USA and European Union, with a greater focus on patient-reported outcome [PRO] and endoscopic-related endpoints.[1,2] The PRO would reflect clinically relevant measures for patients, whereas the endoscopic assessment would add an objective measure of intestinal mucosal inflammation.[2] Recently, new definitions for clinical remission using the CDAI subcomponents of mean daily liquid or very soft stool frequency [SF] and abdominal pain [AP] score have been used in clinical trials.[3–5] For patients with mild to moderate CD, a clinical remission definition of SF ≤1.5 and AP score ≤1.0 has been proposed,[4] whereas a less stringent definition of SF ≤3.0 and AP score ≤1.0 seems more relevant in patients with moderate to severe CD.[3,5] However, data to support the relevance of these PRO-based clinical endpoints for patients are still lacking.

One way to assess the relevance of remission endpoints for patients is to evaluate the association of these endpoints with health-related quality of life [HRQoL]. Remission [assessed by CDAI] was associated with better HRQoL as assessed by the Inflammatory Bowel Disease Questionnaire [IBDQ].[6] The IBDQ is a 32-item questionnaire that assesses patients' overall HRQoL with item 10 specifically evaluating patients' general well-being and can serve as an anchor in assessing the relevance of PRO cut-offs.[7] A good correlation between IBDQ and CDAI has been reported, indicating that the IBDQ is a valid instrument for HRQoL evaluation in patients with CD.[8]

We sought to investigate whether more recent definitions of clinical remission or clinical response based on the PROs of SF and AP are relevant for patients based on their report of general well-being, that is, specifically item 10 in IBDQ. Pooled data were included from three studies in patients with CD who received either adalimumab, a tumour necrosis factor [TNF] inhibitor approved for the treatment of paediatric and adult CD,[9–14] or upadacitinib, an oral selective and reversible inhibitor of Janus kinase 1 approved for the treatment of rheumatoid arthritis and which is being studied as a therapy for CD, ulcerative colitis and other immune-mediated inflammatory diseases.[15]

2. Materials and Methods

2.1. Studies and participants

This analysis included data from two adalimumab phase 3 CD trials [CHARM and EXTEND][12,14] and one upadacitinib phase 2 CD trial [CELEST].[16] The methods and primary results of these trials have been previously reported.

Briefly, CHARM [NCT00077779] was a randomized, placebo-controlled, double-blind, multicentre study that enrolled 854 patients with moderately to severely active CD; patients who received prior TNF inhibitors other than adalimumab were eligible if they did not exhibit initial non-response to the agent.[12] At the baseline visit, patients received open-label adalimumab 80 mg subcutaneously [SC] followed by adalimumab 40 mg SC at week 2. At week 4, patients were randomized 1:1:1 to double-blind treatment with adalimumab 40 mg SC every other week, adalimumab 40 mg SC every week or placebo through week 56.

EXTEND [NCT00348283] was a randomized, placebo-controlled, double-blind, multicentre study that enrolled 135 patients with moderately to severely active CD; patients who received prior TNF inhibitors other than adalimumab were eligible if they did not exhibit initial non-response to the agent.[14] At baseline, patients received open-label adalimumab 160 mg SC followed by adalimumab 80 mg SC at week 2. At week 4, patients were randomized to double-blind maintenance therapy with adalimumab 40 mg SC every other week or placebo through week 52.

CELEST [NCT02365649] was a randomized, double-blind, placebo-controlled study that enrolled 220 patients with moderate to severe CD who had inadequate response/intolerance to immunomodulators or TNF inhibitors.[16] At baseline, patients were randomized equally to induction therapy with placebo or upadacitinib at 3, 6, 12, or 24 mg twice daily or 24 mg once daily for 16 weeks, followed by blinded extension therapy for 36 weeks.

This analysis included only patients from the three studies who met the criteria of baseline average daily SF ≥4 and/or average daily AP score ≥2, who made up 71% of the total population studied.

2.2. Outcomes

The main analysis was to assess the association between patient-reported general well-being, based on IBDQ item 10, and clinical remission/response, based on the CDAI subcomponents of SF and AP score. The IBDQ was completed at baseline and week 12 [adalimumab trials] or week 16 [upadacitinib trial]. IBDQ item 10 asks, 'How often during the last 2 weeks have you felt generally unwell?' with scores ranging from 1 to 7, and higher scores indicating better well-being. Answers include 'All of the time' [1], 'Most of the time' [2], 'A good bit of the time' [3], 'Some of the time' [4], 'A little of the time' [5], 'Hardly any of the time' [6] and 'None of the time' [7].[7] In the main analysis, IBDQ item 10 responses were grouped into three categories based on the scores [1–2, 3–5 and 6–7].

Patients reported their symptoms of SF and AP daily using an electronic diary. Data were collected as an average of the last 7 days before the week 12 or 16 visit. Clinical remission was defined as average daily SF ≤2.8 and AP score ≤1.0[3,5] and neither worse than baseline at weeks 12 or 16. Changes from baseline to week 12 or 16 in SF and AP score were also evaluated. Clinical response was defined as a decrease from baseline ≥30% in average daily SF and/or AP score and neither worse than baseline at week 12 or 16.

2.3. Statistical analysis

All patients who met the inclusion PRO criteria were combined for the analyses regardless of whether they were randomized to the active treatment or placebo group. The proportion of patients with clinical remission and clinical response defined by the individual components of SF and AP score at week 12 or 16 were compared among IBDQ item 10 response categories [1–7] or grouped categories [1–2, 3–5 and 6–7]. Changes from baseline in IBDQ item 10 response categories were determined as a category point change from baseline [≤–2-point change, –1-point change, 0-point change, +1-point change and >+2-point change] and were compared with change from baseline to week 12 or 16 in SF and AP score.

This analysis used the cumulative distribution function [CDF] and probability density function [PDF] by Kernel density estimation curves of each SF and AP score by each item response category of the IBDQ item [1–7] or grouped categories [1–2, 3–5 and 6–7]. Statistical differences were based on Mood's two-sample median test or chi-square test [two-sided $\alpha = 0.05$]. The trend between change of SF/AP and grouped IBDQ item response change category was examined using a Jonckheere–Terpstra test.

3. Results

This analysis included 858 patients [695 from adalimumab and 163 from upadacitinib trials] who met the PRO inclusion criteria. In the adalimumab studies, mean age at baseline was 37.1 years, 62–63% were female, and the mean CDAI scores were 313.1 and 319.9 in CHARM and EXTEND, respectively.[12,14] In the upadacitinib CELEST study, mean age at baseline was 40.7 years, 57% were female and the mean CDAI score was 302.8. Mean disease duration at baseline was 10.2 years in CHARM, 10.1 years in the EXTEND study and 13.2 years in the CELEST study. At baseline, higher SF and AP score were generally reported in patients with lower IBDQ item 10 responses in the CDF and PDF curves [Supplementary Figure 1].

3.1. Association between IBDQ item 10 and clinical remission at week 12 or 16

Significantly more patients in IBDQ item 10 category 6–7 [61.9% at week 12 in the adalimumab dataset, 60.5% at week 16 in the upadacitinib dataset] met the proposed definition of clinical remission compared with patients who reported their well-being status in categories 1–2 or 3–5; 3.1% of patients in the adalimumab dataset and 10.5% in the upadacitinib dataset who met the definition of clinical remission reported feeling generally unwell [category 1–2; Table 1]. The proportion of patients meeting the definition of clinical remission was correlated with the general well-being item-10 score on the IBDQ [$p < 0.001$ for adalimumab and $p < 0.001$ for upadacitinib].

The median SF and AP score were below the previously identified cutoffs for clinical remission [≤2.8 and ≤1.0, respectively] among patients who were in the grouped IBDQ category 6–7 in the adalimumab [median SF, 1.93; median AP, 0.29] and upadacitinib datasets [median SF, 1.21; median AP, 0.57; Table 2]. In contrast, median SF and AP score were >2.8 and >1.0, respectively, in patients who were feeling unwell at least a little of the time [scores of 5 or lower; Table 2]. Similar results were observed when assessed by the individual IBDQ categories in the adalimumab dataset; median SF and median AP score were 2.0 and 0.43 for patients in IBDQ category 6 and 1.71 and 0 for patients in IBDQ category 7, respectively [Supplementary Figure 2; upadacitinib data not assessed due to small patient numbers per category who were also in clinical remission].

In the adalimumab trials, median percentage changes from baseline to week 12 in SF and AP score were significantly greater in patients with IBDQ item 10 response categories 6–7 and 3–5 vs category 1–2 [Table 2]. Similarly, in the upadacitinib trial, median percentage changes from baseline to week 16 in SF and AP score were significantly greater in patients with IBDQ item 10 response category 6–7 vs category 1–2.

The response to IBDQ item 10 was more often reported in the higher category [6–7] by patients with lower SF and AP score, while the IBDQ item 10 response was more often reported in the lower categories [1–2 and 3–5] by patients with higher SF and AP score. These data demonstrated that the IBDQ item 10 responses feeling well [category 6–7] correlated with lower SF [≤2.8] and AP score [≤1.0; Figure 1]. In both the adalimumab and the upadacitinib datasets, ~70% of patients with SF ≤2.8 [Figure 1A] and 80% of patients with an AP score ≤1.0 [Figure 1B] were in the grouped IBDQ category 6–7. Similar results were observed when assessing data using the individual IBDQ categories in the adalimumab studies [Supplementary Figure 2].

3.2. Association between IBDQ item 10 and clinical response at week 12 or 16

Greater point increases in IBDQ item 10 responses correlated with a greater percentage decrease from baseline in SF and AP score [Figure 2; Supplementary Figure 3]. In both the adalimumab and the upadacitinib datasets, ~70% of patients with ≥30% reduction from baseline in daily average SF [Figure 2A] and ~80% of patients with ≥30% reduction from baseline in AP score [Figure 2B] reported at least a 2-point improvement in their general well-being status. We also evaluated the magnitude of improvement in SF and AP score.

Table 1. Proportion of patients who met the proposed clinical remission definition at week 12 [adalimumab] or week 16 [upadacitinib] by IBDQ item category

Drug [Studies]	Response category for IBDQ item 10, 'How often during the last 2 weeks have you felt generally unwell?'	n	Clinical remission		*p* value*
			Individual category, %	Grouped categories, %	
Adalimumab	1.All of the time	37	0	3.1	
	2. Most of the time	91	4.4		
	3.A good bit of the time	110	10.9	19.6	
	4.Some of the time	119	13.4		
	5. A little of the time	144	31.3		
	6.Hardly any of the time	134	58.2	61.9	<0.001
	7. None of the time	60	70.0		
Upadacitinib	1.All of the time	11	9.1	10.5	
	2. Most of the time	27	11.1		
	3.A good bit of the time	32	6.3	21.8	
	4.Some of the time	28	14.3		
	5. A little of the time	27	48.1		
	6.Hardly any of the time	27	48.1	60.5	<0.001
	7. None of the time	11	90.9		

IBDQ, Inflammatory Bowel Disease Questionnaire.

[a]Versus combined group response categories 1–5 using chi-square test.

Clinical remission defined as very soft/liquid stool frequency ≤2.8 and/or abdominal pain score ≤1.0, neither worse than baseline.

Statistical analysis: $p < 0.001$ compared with patients with IBDQ item 10 response categories 1–5 using chi-square test.

Table 2. Very soft or liquid SF and AP score median values and change from baseline at week 12 [adalimumab] or week 16 [upadacitinib]

Study	Response category for IBDQ item 10, 'How often during the last 2 weeks have you felt generally unwell?'	*n*	Very soft/liquid SF, median				AP score, median			
			Baseline	Week 12/16	% Change	*p* value	Baseline	Week 12/16	% Change	*p* value
Adalimumab	1.All of the time 2.Most of the time	128	6.00	5.00	−12.8[a]		2.14	2.00	−2.6	
	3.A good bit of the time 4.Some of the time 5.A little of the time	373	5.57	3.71	−31.8[a]	<0.001	2.00	1.14	−38.7[a]	<0.001
	6. Hardly any of the time 7. None of the time	194	5.29	1.93	−62.0	<0.001	2.00	0.29	−83.3[a]	<0.001
Upadacitinib	1.All of the time 2.Most of the time	38	6.43	5.21	−14.3		2.00	1.57	0	
	3.A good bit of the time 4. Some of the time 5.A little of the time	87	5.86	3.71	−31.3	0.222	2.00	1.14	−36.4	<0.001
	6. Hardly any of the time 7.None of the time	38	6.07	1.21	−76.0	<0.001	1.86	0.57	−72.6	<0.001

AP, abdominal pain; IBDQ, Inflammatory Bowel Disease Questionnaire; SF, stool frequency.

[a]Two patients with baseline SF = 0 were excluded from the calculation of SF percentage change; six patients with baseline AP = 0 were excluded from the calculation of AP percentage change.

Statistical analysis: $p < 0.001$ compared with patients with IBDQ item 10 response category 1–2 using Mood's two-sample median test.

A greater than 30% median percentage decrease in SF was observed among patients who reported 1-point [−32% with adalimumab and −35% with upadacitinib; from baseline to week 12, consistent with clinical response] or 2-point improvement [−50% with adalimumab and −68% with upadacitinib] in the IBDQ item 10 from baseline to week 12 or 16 [Table 3]. In the upadacitinib study, a 25% median percentage decrease in AP score was observed among patients who reported a 1-point improvement from baseline in the IBDQ item 10, whereas a 55% median percentage decrease in AP score was observed among patients reporting a ≥2-point improvement in the IBDQ item 10 [Table 3].

Overall, patients with a higher increase from baseline in the IBDQ item 10 response category had significantly greater median percentage reduction in SF and AP score from baseline compared with patients with lower change from baseline in both the adalimumab and the upadacitinib trials [$p < 0.0001$; Table 3].

4. Discussion

The predominant symptoms of active CD are diarrhoea and AP, which can greatly affect quality of life. This analysis of two adalimumab studies and one upadacitinib study in patients with moderate to severe CD evaluated the association between patient-reported general well-being [assessed by the IBDQ item 10] and SF/AP score to support the new PRO-based endpoint definitions of clinical remission and clinical response. The findings demonstrated that higher scores of general well-being, based on categories 6 and 7 responses of the IBDQ item 10, were associated with lower SF and AP score [SF ≤2.8 and AP score ≤1.0, respectively], indicating a status of clinical remission. In addition, greater improvements in well-being [defined as ≥2-point improvements in IBDQ item 10 responses] correlated with at least a 30% decrease in SF or AP score, supporting the definition of clinical response.

Adalimumab is an approved therapy for adult and paediatric CD and upadacitinib was recently approved for the treatment of rheumatoid arthritis,[17] with phase 3 studies in CD ongoing [NCT03345849, NCT03345836, NCT03345823]. Our findings were consistent between the adalimumab and upadacitinib studies, indicating that these endpoints perform similarly among patients with moderate to severe CD regardless of treatment. The only difference was that patients with 1-point improvement from baseline in the IBDQ item 10 achieved a ≥30% median percentage reduction in AP score in the adalimumab dataset while only a 25% median percentage reduction in AP score was observed in the upadacitinib dataset. This may be due to the smaller sample size in the upadacitinib dataset or that the trial enrolled a more refractory patient population with a longer disease duration and who had failed or been intolerant to a mean of two previous TNF inhibitors.[16]

The identification of clinically relevant PRO endpoints for patients with CD with varying disease severity is of great interest in light of the new regulatory guidances.[1] Clinical endpoints using the CDAI subcomponents of SF and AP score have been investigated in clinical trials. Although the clinical remission definition of SF ≤1.5 and AP score ≤1.0 may indicate better disease control, it has proven to be too stringent for the assessment of patients with moderate to severe CD. In contrast, defining clinical remission as SF ≤2.8 and AP score ≤1.0 seems appropriate for this patient population, as this analysis indicated that a significantly greater proportion of patients achieving these treatment targets reported improvements in their well-being.[3,5]

The strengths of this analysis include using large datasets from randomized controlled clinical trials of two therapeutic agents with different mechanisms of action. In addition, the population was reflective of patients with active, moderate to severe disease, exposed to various treatment options for CD. Limitations of this analysis include the IBDQ assessment that included a 2-week recall, which may be subject to memory bias. Additionally, patient-reported general well-being in the IBDQ was based on a single question and factors unrelated to CD may have also influenced well-being.

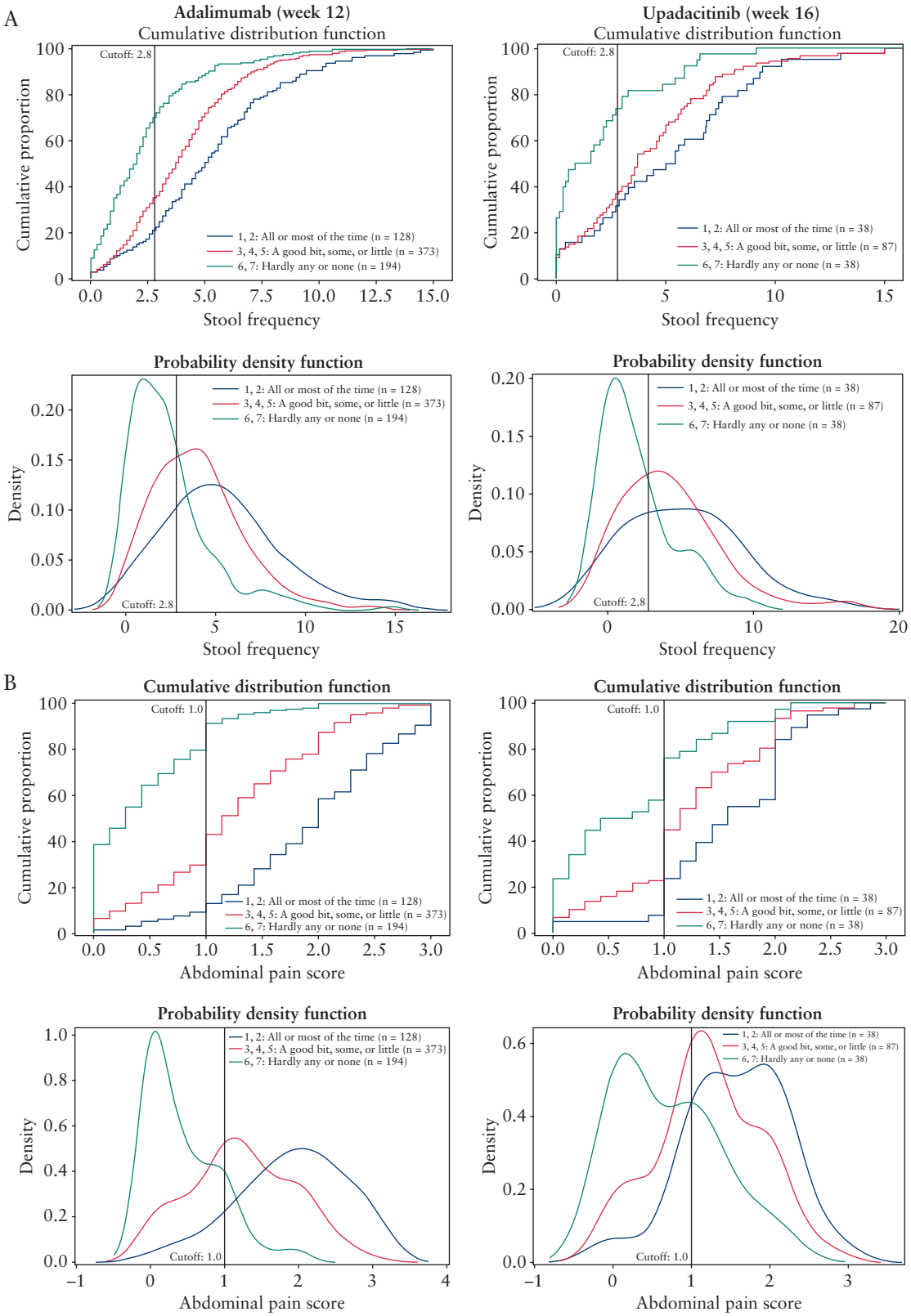

Figure 1. CDF and PDF of average daily very soft and liquid stool frequency [A] and abdominal pain score [B] by the grouped IBDQ item 10 response category at week 12 [adalimumab] and at week 16 [upadacitinib]. CDF, cumulative distribution function; IBDQ, Inflammatory Bowel Disease Questionnaire; PDF, probability density function.

In conclusion, these data demonstrated a significant association between improvements in general well-being and clinical remission and clinical response as reported by patients using the outcomes of very soft or liquid SF and AP score. The results support the definitions of these clinical remission and response endpoints used in the ongoing phase 3 clinical programmes in CD.

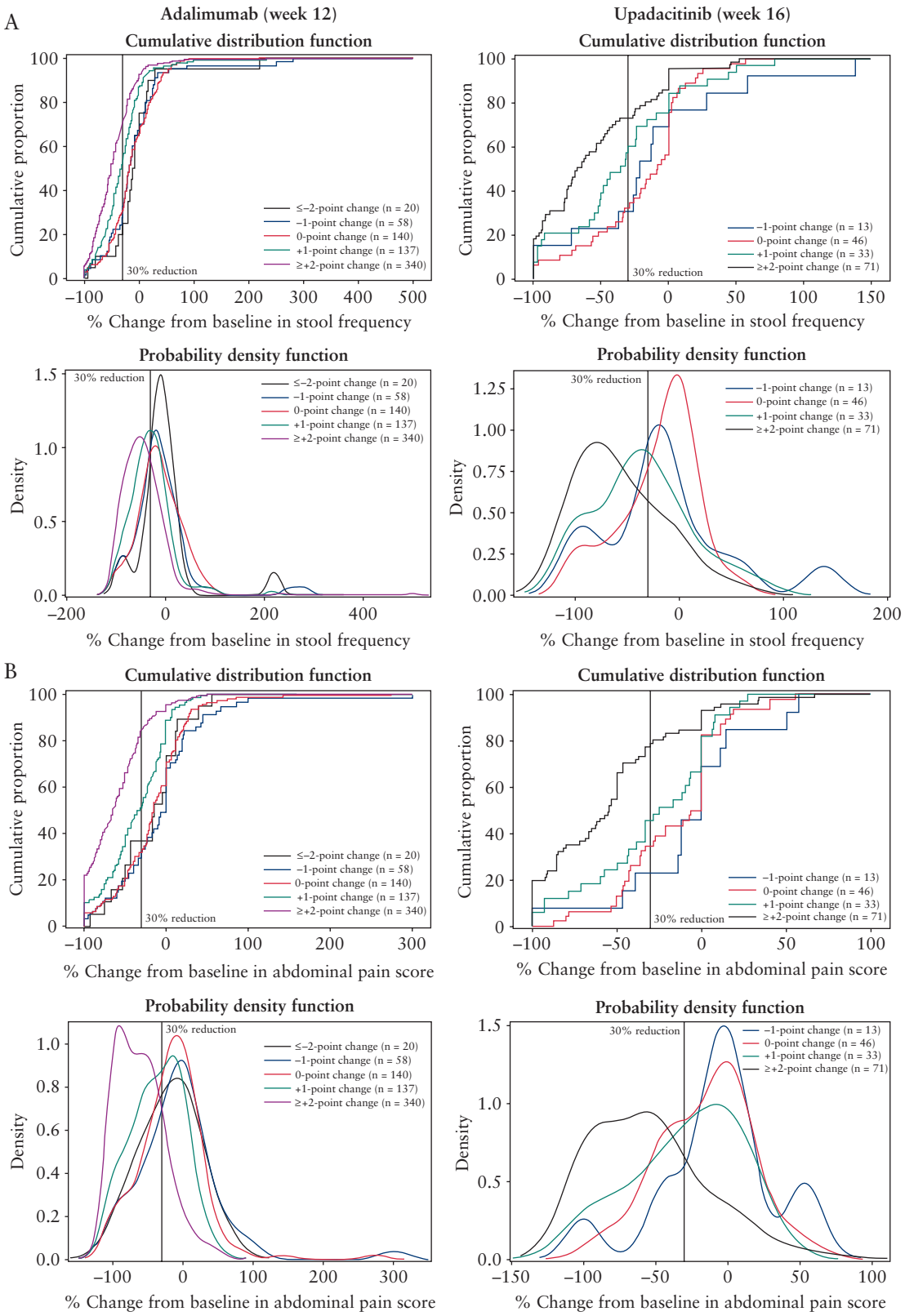

Figure 2. CDF and PDF of percentage change from baseline in average daily very soft and liquid stool frequency [A] and abdominal pain score [B] by the grouped IBDQ item 10 response category at week 12 [adalimumab] and at week 16 [upadacitinib]. CDF, cumulative distribution function; IBDQ, Inflammatory Bowel Disease Questionnaire; PDF, probability density function.

Table 3. Very soft or liquid SF and AP score median values and change from baseline at week 12 [adalimumab] or week 16 [upadacitinib] by IBDQ item response change category

Drug [study]	Response category for IBDQ item 10, 'How often during the last 2 weeks have you felt generally unwell?'	*n*	Very soft/liquid SF				AP score			
			Baseline	Week 12/16	Median % change	*p* value[a]	Baseline	Week 12/16	Median % change	*p* value[a]
Adalimumab	≤–2-point change	20	6.36	5.86	–10.6	<0.0001	2.00	1.29	–14.3[b]	<0.0001
	–1-point change	58	6.21	4.64	–18.5		1.93	1.64	0.0[a]	
	0-point change	140	5.71	4.57	–17.4[b]		2.00	1.71	–14.3[b]	
	+1-point change	137	5.57	3.57	–31.7		2.00	1.29	–31.3	
	≥+2-point change	340	5.29	2.43	–50.0[b]		2.14	0.71	–64.3[b]	
Upadacitinib	≤–2-point change	0	–	–	–	<0.001	–	–	–	<0.001
	–1-point change	13	6.29	5.43	–21.6		2.00	1.29	0.0	
	0-point change	46	5.79	5.50	–8.3		1.93	1.43	–3.3	
	+1-point change	33	5.86	3.57	–34.9		2.00	1.29	–25.0	
	≥+2-point change	71	6.14	2.14	–67.6		2.00	1.00	–55.0	

AP, abdominal pain; IBDQ, Inflammatory Bowel Disease Questionnaire [score range 1–7]; SF, stool frequency.

[a]Statistical analysis: $p < 0.0001$ comparing median percentage decrease trend against the increase of IBDQ item 10-point change using a Jonckheere–Terpstra trend test.

[b]Two patients with baseline SF = 0 were excluded from the calculation of SF percentage change; six patients with baseline AP = 0 were excluded from the calculation of AP percentage change.

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Conflict of Interest

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Author Contributions

All authors have made substantial contributions to the conception and design of the study, or acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content,

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Data Availability Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data [analysis data sets], as well as other information [e.g. protocols and Clinical Study Reports], as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan [SAP] and execution of a Data Sharing Agreement [DSA]. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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