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Presented at the 14th Congress of European Crohn’s and Colitis Organisation • Copenhagen, Denmark • March 6 – 9, 2019

BACKGROUND

- Crohn’s disease (CD) is a chronic, debilitating disease that negatively impacts patients’ lives<sup>1</sup>
- Upadacitinib, an oral selective JAK1 inhibitor,<sup>2</sup> was investigated for the treatment of patients with CD in the phase 2 CELEST study<sup>3</sup> and demonstrated improvements in stool frequency, abdominal pain, and severity of mucosal inflammation versus placebo during a 16-week induction period
- However, the impact of upadacitinib on patients’ general clinical condition is less known
- Body weight and serum albumin levels are common measures used in clinical practice to assess the impact of CD on patients’ clinical condition
- Furthermore, diarrhoea is a common clinical feature of CD,<sup>4</sup> and the Bristol Stool Chart (BSC) is a validated and widely used patient-reported outcome measure to assess stool consistency in patients with functional bowel disorders and favoured by regulatory agencies<sup>5-8</sup>

OBJECTIVE

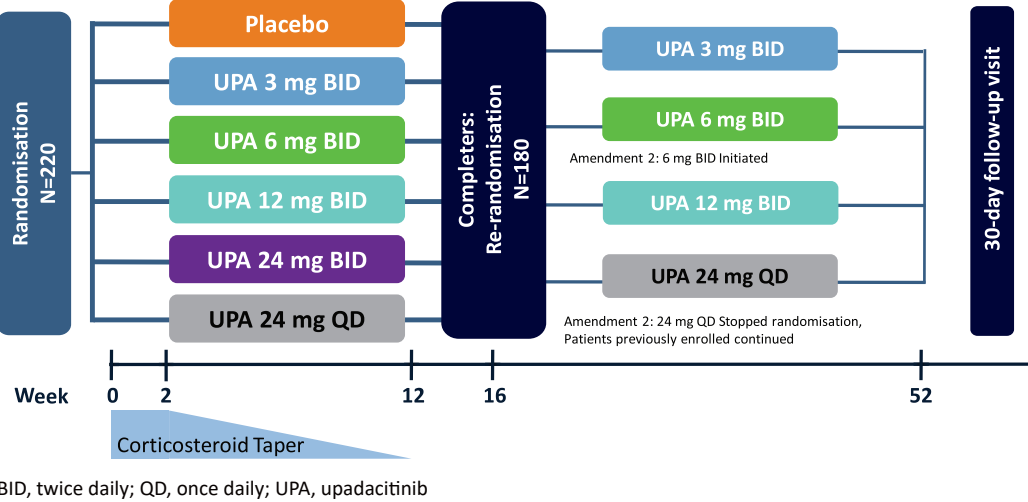
- The objective of this analysis of data from the CELEST study was to assess the impact of upadacitinib on the general clinical condition of patients with CD by evaluating body weight, serum albumin levels, and improvement in stool consistency

METHODS

STUDY DESIGN AND PATIENTS

- The placebo-controlled phase 2 CELEST study (NCT02365649) enrolled adults with moderately to severely active CD refractory or intolerant to immunosuppressants or biologics (**Figure 1**)
  - Patients with CD Activity Index (CDAI) score of 220–450, an average daily liquid/very soft stool frequency (SF) ≥2.5 or daily abdominal pain (AP) score ≥2.0, and evidence of mucosal inflammation, defined as SES-CD ≥6 (or ≥4 for those with isolated ileal disease), were enrolled
- At the start of the 16-week induction period, patients were randomised (1:1:1:1:1:1) to placebo or upadacitinib 3 mg, 6 mg, 12 mg, or 24 mg twice daily (BID) or 24 mg once daily (QD)
- All patients who completed the 16-week induction phase were re-randomised (1:1:1) to receive double-blind upadacitinib at 3 mg BID, 12 mg BID, or 24 mg QD for 36 weeks, with a total study duration of 52 weeks
  - When data from the phase 2 rheumatoid arthritis and phase 1 trials became available, the 24-mg QD arm in the extension phase was stopped and a 6-mg BID arm was initiated in a protocol amendment; patients who were on 24 mg QD continued to receive this dose

FIGURE 1. STUDY DESIGN



OUTCOMES

- Changes over time from baseline in body weight and serum albumin levels (reference range: 35–50 g/L) were assessed at weeks 2, 4, 8, 12, and 16 during the induction period and at weeks 20, 28, 36, 44, and 52 during the extension period
- Stool consistency was assessed by BSC (**Table 1**):
  - The BSC is an ordinal scale of stool types ranging from type 1 (hard, difficult to pass) to type 7 (liquid)<sup>5</sup>
  - In this analysis, change from baseline in the BSC score (defined as the proportion of days over the last week prior to the visit with BSC type 6 [very soft] or 7 [liquid] stool) was assessed at weeks 4 and 16 (induction period) and weeks 28 and 52 (extension period), with a higher BSC score indicating a greater proportion of days with soft to liquid stools over the last week
  - The proportion of patients who achieved BSC response (defined as ≥50% reduction in number of days over the last week with ≥1 BSC type 6 or 7 stool versus baseline) was assessed at weeks 4 and 16 (induction period) and weeks 28 and 52 (extension period)

Table 1. Bristol Stool Chart<sup>5</sup>

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces, entirely liquid

STATISTICAL ANALYSIS

- Analyses included all patients during the induction period and patients who achieved clinical response at week 16 (Clinical Responders) during the extension period
  - Clinical Response was defined as average daily SF reduction ≥30% from baseline or average daily AP score reduction ≥30% from baseline and both not worse than baseline
- Observed data were used for the changes from baseline in BSC score analysis, and nonresponder imputation was used for the proportion of patients who achieved BSC response analysis
- Statistical differences between upadacitinib versus placebo were evaluated at the two-sided 0.1 level of significance

RESULTS

- Among 220 randomised patients, mean±SD weight was 75.3±20.1 kg, mean albumin levels were 38.6–39.7 g/L, and mean±SD BSC score was 0.9±0.3 at baseline (**Table 2**)

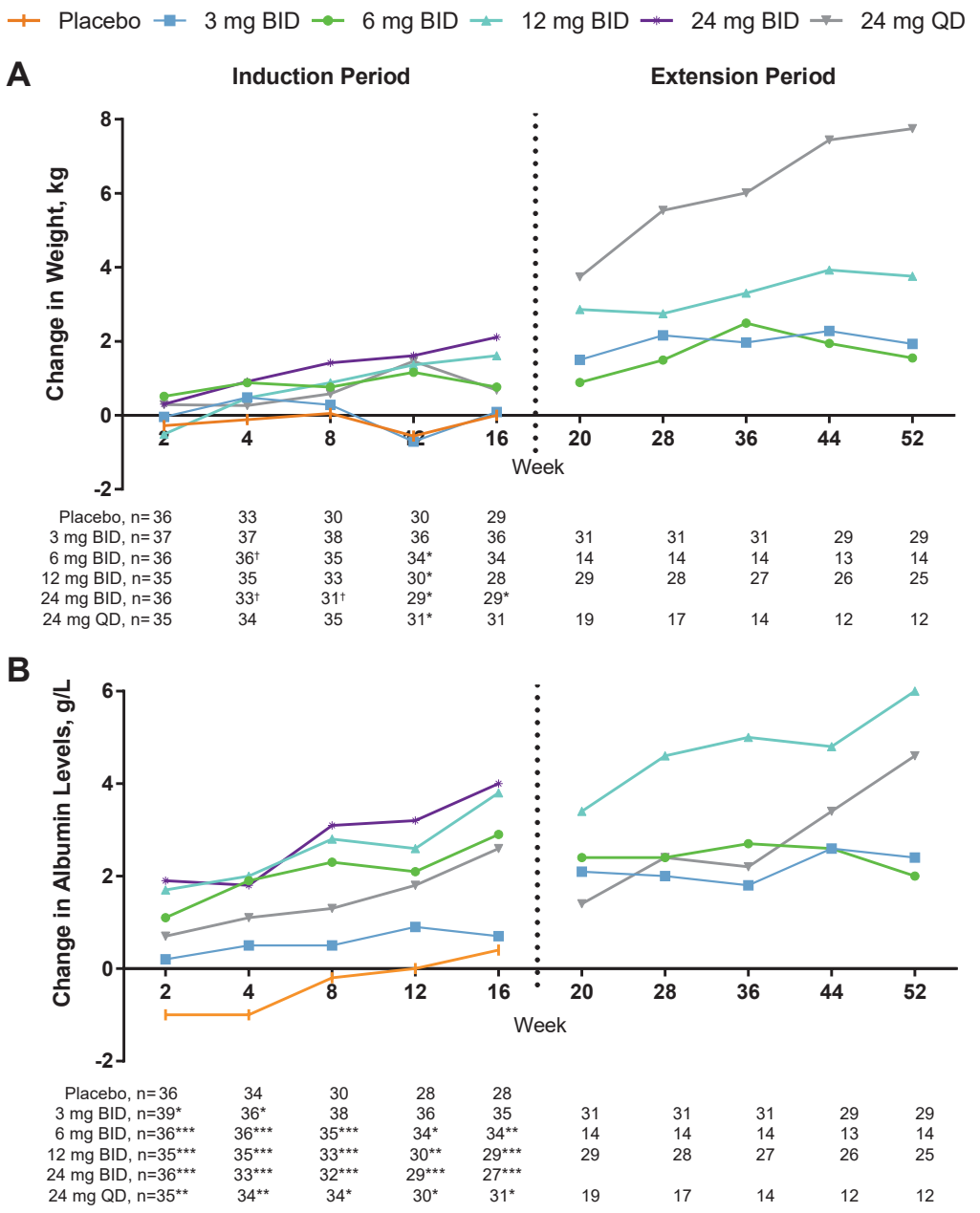
Table 2. Patient Demographics at Baseline

	Placebo n=37	3 mg BID n=39	6 mg BID n=37	12 mg BID n=36	24 mg BID n=36	24 mg QD n=35	Overall N=220
Age, y, mean (SD)	40.5 (12.1)	39.7 (14.0)	40.5 (13.4)	40.8 (15.2)	42.5 (10.0)	40.2 (12.6)	40.7 (12.9)
Female, n (%)	24 (64.9)	19 (48.7)	21 (56.8)	17 (47.2)	25 (69.4)	19 (54.3)	125 (56.8)
CD duration, y, mean (SD)	11.8 (9.7)	13.3 (10.7)	11.8 (10.1)	13.3 (10.6)	14.9 (9.6)	14.2 (9.7)	13.2 (10.0)
Weight, kg, mean (SD)	77.3 (21.5)	70.9 (13.8)	74.9 (19.5)	76.7 (18.5)	71.0 (19.4)	81.8 (25.9)	75.3 (20.1)
Albumin, g/L, mean (SD)	39.7 (4.4)	39.5 (4.9)	38.8 (4.4)	38.6 (4.0)	38.8 (3.6)	39.7 (4.2)	39.2 (4.2)
BSC score, mean (SD)	0.9 (0.2)	0.8 (0.3)	0.9 (0.3)*	0.9 (0.2)	0.9 (0.3)*	0.8 (0.3)*	0.9 (0.3)*
CDAI, mean (SD)	288.4 (60.0)	298.0 (60.7)	316.5 (72.1)	305.1 (60.0)	294.3 (70.2)	315.1 (54.6)	302.8 (63.4)
SES-CD, mean (SD)	15.8 (8.6)	14.7 (8.8)	16.3 (8.9)	15.6 (9.4)	14.3 (7.3)	13.4 (7.4)	15.0 (8.4)

BSC, Bristol Stool Chart; BID, twice daily; CD, Crohn’s disease; CDAI, CD Activity Index; QD, once daily; SD, standard deviation.  
\*6 mg BID, n=36; 24 mg BID, n=35; 24 mg QD, n=34; Overall, n=217.  
BSC score defined as the proportion of days over the last week prior to the visit with BSC type 6 (very soft) or 7 (liquid) stool.

- Mean weight was significantly increased from baseline as early as week 4 with the upadacitinib 6 mg BID and 24 mg BID doses (both 0.9 kg) versus placebo (–1.2 kg;  $P<0.1$ ; **Figure 2A**)
- By week 12, significant increases in mean weight were observed with upadacitinib doses ≥6 mg (range: 1.2–1.6 kg) versus placebo (–0.6 kg;  $P<0.05$ )
  - Mean weight increase remained significant with upadacitinib 24 mg BID (2.1 kg;  $P<0.05$ ) at week 16
- Mean changes from baseline in serum albumin levels were significantly increased as early as week 2 with all upadacitinib doses (range: 0.2–1.9 g/L) versus placebo (–1.0 g/L; 3 mg BID,  $P<0.05$ ; ≥6 mg,  $P<0.01$ ; **Figure 2B**)
  - Significant increases from baseline in mean serum albumin levels were maintained through week 16 with upadacitinib doses ≥6 mg (range: 2.6–4.0 g/L) versus placebo (0.4 g/L;  $P≤0.05$ )
- During the extension period, mean weight and serum albumin levels generally continued to increase among Clinical Responders (**Figure 2A and 2B**)

Figure 2. Changes From Baseline in Mean Weight (A) And Serum Albumin Level (B) in All Patients During the Induction Period and in Clinical Responders During the Extension Period



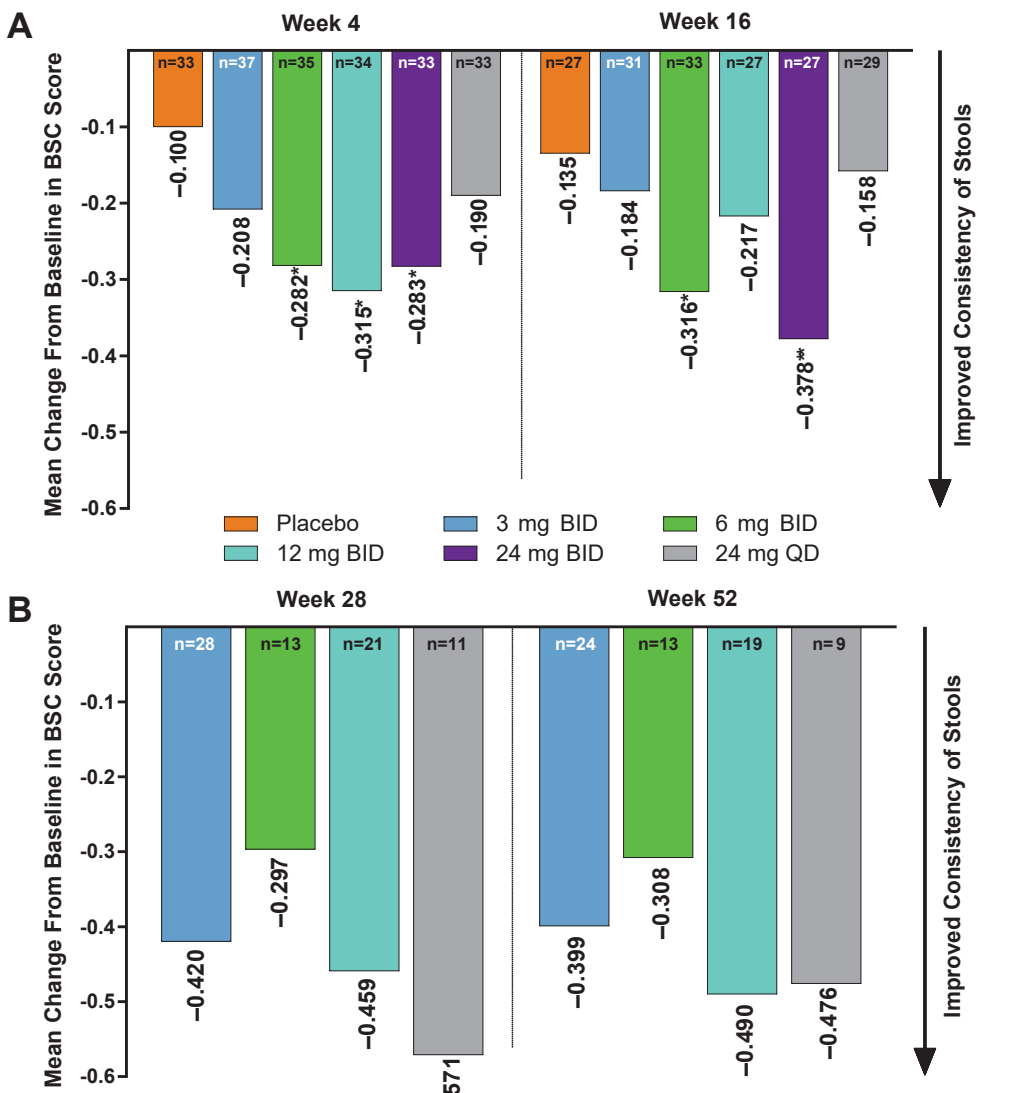
BID, twice daily; QD, once daily.  
Statistical comparisons between each upadacitinib dose group and placebo during the induction period used a one-way analysis of variance. Extension period data are presented for clinical responders in the safety set (all patients who entered the extension period, regardless of induction period treatment).  
† $P<0.1$ , \* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$ , vs placebo.

- BSC scores were significantly improved (ie, reduced number of days with soft to liquid stool consistency over the last week) from baseline by week 4 with upadacitinib 6 mg, 12 mg, and 24 mg BID versus placebo and were maintained to week 16 with the 6-mg and 24-mg BID doses ( $P≤0.05$ ; **Figure 3A**)
- During the extension period, BSC scores continued to improve among Clinical Responders receiving continuous upadacitinib treatment (**Figure 3B**)

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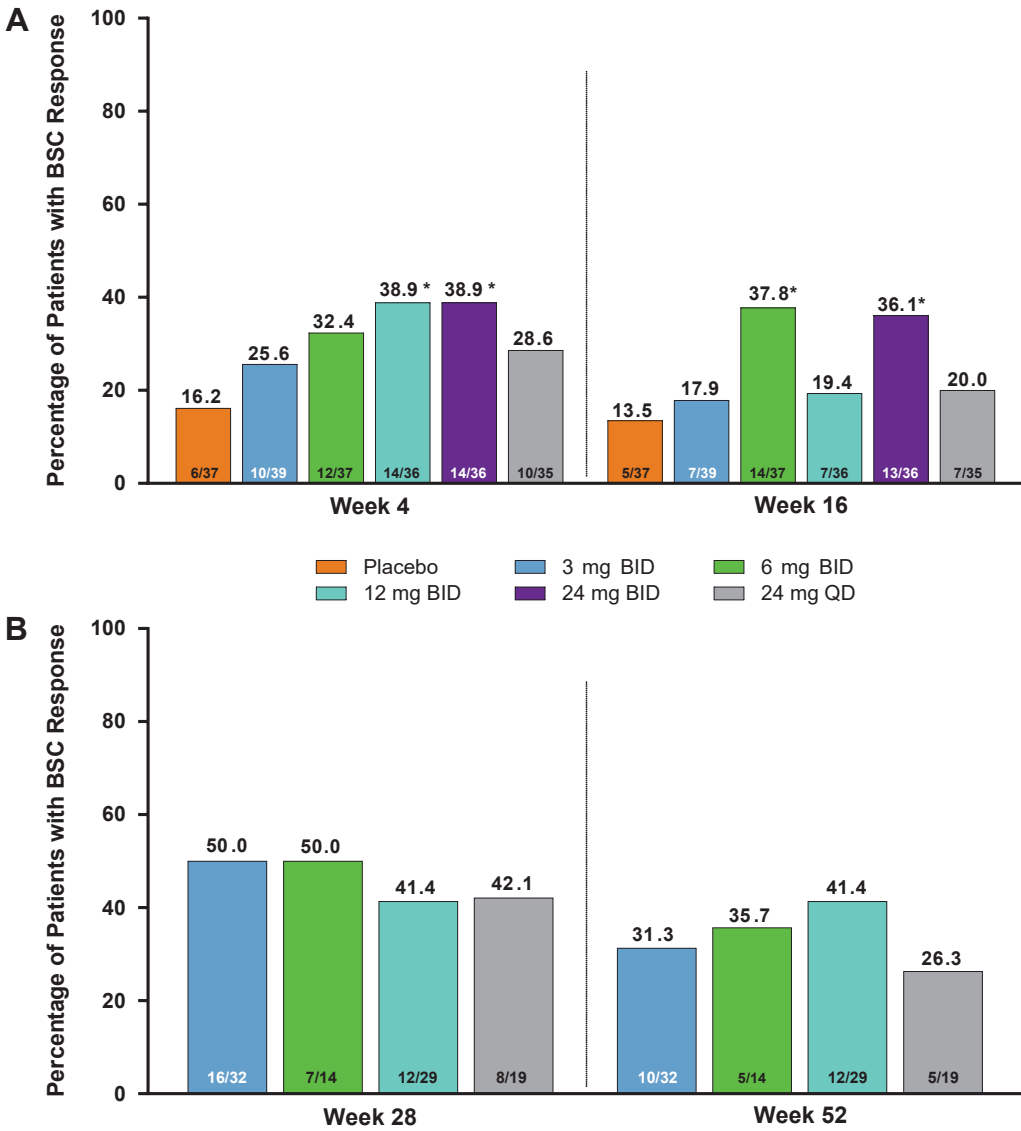
Figure 3. Change from Baseline in Bristol Stool Chart Score at Weeks 4 and 16 of the Induction Period (A) and at Weeks 28 and 52 of the Extension Period Among Clinical Responders (B)



BID, twice daily; BSC, Bristol Stool Chart; QD, once daily; SES-CD, Simplified Endoscopic Score for Crohn’s Disease.  
BSC score defined as the proportion of days over the last week prior to the visit with BSC type 6 (very soft) or 7 (liquid) stool. Panel A: Statistical comparison between each upadacitinib dose group and placebo using analysis of covariance with treatment, baseline disease severity (SES-CD <15 and SES-CD ≥15), and baseline value as covariate (observed analysis). \* $P<0.05$ , \*\* $P<0.01$  vs placebo. Panel B: During the extension period, data are presented for clinical responders in the intent-to-treat set (all patients who received continuous treatment with upadacitinib [any dose] during both the induction and extension periods).

- A significantly greater proportion of patients receiving upadacitinib 12 mg and 24 mg BID at week 4 and 6 mg and 24 mg BID at week 16 achieved BSC response (ie, less frequent very soft or liquid stools compared with baseline) versus placebo ( $P<0.05$ ; **Figure 4A**)
- During the extension period, proportions of patients with BSC response continued to improve among Clinical Responders receiving continuous upadacitinib treatment (**Figure 4B**)

Figure 4. Proportion of Patients With Bristol Stool Chart Response at Weeks 4 and 16 of the Induction Period (A) and at Weeks 28 and 52 of the Extension Period Among Clinical Responders (B)



BID, twice daily; BSC, Bristol Stool Chart; QD, once daily.  
BSC response defined as ≥50% reduction in number of days over the last week with ≥1 BSC type 6 or 7 stool versus baseline. Panel A: Statistical comparison between each upadacitinib dose group and placebo based on Cochran-Mantel-Haenszel test stratified by baseline SES-CD (SES-CD <15 and SES-CD ≥15) (non-responder imputation). \* $P<0.05$  vs placebo. Panel B: During the extension period, data are presented for clinical responders in the intent-to-treat set (all patients who received continuous treatment with upadacitinib [any dose] during both the induction and extension periods).

CONCLUSIONS

- Upadacitinib induction treatment resulted in significant increases in body weight, serum albumin levels, and improvements in stool consistency compared with placebo in patients with CD
  - These improvements were maintained during the extension period
- Improvements in these parameters paralleled conventional outcomes such as CDAI and mucosal healing<sup>3</sup>

DISCLOSURES & ACKNOWLEDGEMENTS

EVL has provided consultancy to AbbVie, UCB, Janssen, Takeda, Celgene, Eli Lilly, Amgen, Pfizer, Celltrion Healthcare, Allergan, and Bristol-Myers Squibb; received research support from AbbVie, UCB, Genentech, Janssen, Amgen, Pfizer, Takeda, Roberts Clinical Trials, Gilead, Receptos, Seres Therapeutics, and MedImmune. DTR has provided consultancy to AbbVie, UCB, Janssen, Takeda, Celgene, Eli Lilly, Amgen, Pfizer, Celltrion Healthcare, Napo Pharmaceuticals, Abgenomics, Shire; received research support from AbbVie, Janssen, Pfizer, Takeda. JP has provided consultancy to AbbVie, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Ferring, Genentech, Glaxo-Smith-Kline, GoodGut, Janssen, MSD, Nestle, Opplan, Pfizer, Progenity, Roberts, Roche, Takeda, Theravance, TiGenix, and Topivert; received lecture fees from AbbVie, Ferring, Janssen, MSD, Pfizer, Shire Pharmaceuticals, Takeda, and Theravance; received research support from AbbVie and MSD. ST has received research support from AbbVie, IOIBD, Lilly, UCB, Vifor and Norman Collison Foundation; received lecture fees from AbbVie, Amgen, Asahi, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chemocentryx, Cosmo, Ferring, Giuliani SpA, GlaxoSmithKline, Janssen, Lilly, MSD, Neovacs, NovoNordisk, Novartis, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma, Takeda, Topivert, UCB, VHSquared and Vifor; has provided consultancy to AbbVie, Amgen, Asahi, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chemocentryx, Cosmo, Ferring, Giuliani SpA, GlaxoSmithKline, Janssen, Lilly, MSD, Neovacs, NovoNordisk, Novartis, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma, Takeda, Topivert, UCB, VHSquared and Vifor. DP, WZ, SG, and AL are AbbVie employees and may own AbbVie stock and/or options.

AbbVie funded the study, contributed to its design, and was involved in the collection, analysis, and interpretation of the data, and in the writing, review, and approval of the publication. Medical writing support was provided by Maria Hovenden, PhD, Complete Publication Solutions, LLC (North Wales, PA), a CHC Group company, and was funded by AbbVie.