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Original Article

# Eldelumab [Anti-IP-10] Induction Therapy for Ulcerative Colitis: A Randomised, Placebo-Controlled, Phase 2b Study

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## Abstract

**Background and Aims:** Interferon-γ-inducible protein-10 [IP-10] mediates immune cell trafficking from the circulation to the inflamed colon and decreases gut epithelial cell survival. IP-10 expression is increased in patients with ulcerative colitis [UC]. We report efficacy and safety results from a dose-ranging induction study of eldelumab, a fully human monoclonal antibody to IP-10, in moderately to severely active UC.

**Methods:** A total of 252 adults with UC [Mayo score ≥ 6 and endoscopic subscore ≥ 2] were randomised 1:1:1 to placebo or eldelumab 15 or 25 mg/kg administered intravenously on Days 1 and 8 and every other week thereafter. The primary endpoint was clinical remission [Mayo score ≤ 2; no individual subscale score > 1] at Week 11. Key secondary endpoints included Mayo score clinical response and mucosal healing at Week 11.

**Results:** Neither eldelumab 15 or 25 mg/kg resulted in significant increases vs placebo in the proportion of patients achieving Week 11 clinical remission. Remission and response rates were 17.6% and 47.1% with eldelumab 25 mg/kg, 13.1% and 44.0% with eldelumab 15 mg/kg, and 9.6% and 31.3% with placebo. Clinical remission and response rates were higher in anti-tumour necrosis factor [TNF]-naïve patients treated with eldelumab compared with placebo. Eldelumab treatment was well tolerated and no immunogenicity was observed.

**Conclusions:** The primary endpoint was not achieved with induction treatment with eldelumab 15 or 25 mg/kg in patients with UC. Trends towards clinical remission and response were observed

in the overall population and were more pronounced in anti-TNF naïve patients. Eldelumab safety signals were consistent with those reported previously [ClinicalTrials.gov number, NCT01294410].

**Keywords:** Inflammatory bowel diseases; ulcerative colitis

## 1. Introduction

Ulcerative colitis [UC] is a chronic, relapsing-remitting inflammatory disease of the colonic mucosa related to an abnormal immune response.[1] The global prevalence of UC is about 8 million,[2,3] and both incidence and prevalence are increasing.[4] Patients with UC cite symptom frequency, related psychological burden, and disruption of daily activities as having the greatest impact on their quality of life.[5,6,7] Despite recent advances in the treatment of UC, both 'conventional' standard-of-care agents [8,9,10] and tumour necrosis factor [TNF] antagonists [anti-TNFs] have low long-term remission rates,[11,12,13] and/or treatment-limiting toxicities.[10,14] Hence, new treatment options are required. Anti-adhesion molecules, which prevent the trafficking of lymphocytes to the gut mucosa, are the most recently approved novel drug class for UC.[15]

Interferon-γ-inducible protein-10 [IP-10; also referred to as CXCL10] mediates trafficking of immune cells from the circulation to the inflamed colon, and decreases survival of gut epithelial cells.[16] IP-10 expression is increased in patients with UC[17] and IP-10 blockade has been shown to promote crypt cell survival, protect against epithelial ulceration, and reduce inflammation intensity in *in vivo* models of UC.[18,19,20] IP-10 may therefore be a novel therapeutic target in UC.

Eldelumab [BMS-936557], a fully human monoclonal antibody to IP-10, has been investigated for the treatment of moderately to severely active UC in a phase IIa randomised, double-blind, placebo-controlled, 8-week study, using a dose of 10 mg/kg every other week [EOW].[21] This study indicated an exposure-response relationship with eldelumab: response rates were 88% in patients in the highest eldelumab trough concentration tertile [minimum plasma concentration at steady state [$C_{minss}$], 108 to 235 µg/ml, 53% in the lowest eldelumab trough concentration tertile [26.4 to 78.6 µg/ml], and 37% in the placebo arm [$p < 0.001$ for highest tertile vs placebo]. Eldelumab was well tolerated, and patients who had $C_{minss} \geq 100$ µg/ml had safety results comparable to the overall study population. Thus, 100 µg/ml was considered the target trough concentration for efficacy in the present phase IIb dose-ranging induction study to evaluate the clinical efficacy and safety of two doses of eldelumab in patients with moderately to severely active UC.

## 2. Methods

### 2.1. Study design and patients

This was a phase IIb, randomised, placebo-controlled trial of eldelumab, conducted at 75 sites in 14 countries [Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hungary, Italy, Mexico, The Netherlands, Poland, South Africa, and the USA] between March 27, 2011 and January 15, 2013. The study comprised an 11-week induction period [Figure 1] and a 12-month exploratory maintenance period [ClinicalTrials.gov number NCT01294410]. Only results of the induction period are available and reported here. All patients gave written informed consent, and the study was approved by local ethics committees and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All authors had access to study data and reviewed and approved the final manuscript.

Eligible patients were ≥ 18 years of age and had moderately to severely active UC [confirmed by endoscopic evidence; Mayo score of ≥ 6 and a Mayo endoscopic subscore ≥ 2 within the 2 weeks prior to study drug administration][22] of ≥ 6 months' duration. Endoscopy subscores were determined by the local investigator who was blinded to treatment assignment; central reading was not employed. Enrolled patients had an inadequate response to one or more of oral aminosalicylates, prednisone, immunosuppressants, intravenous [IV] hydrocortisone, or an anti-TNF agent; were intolerant to one or more of the above; and/or were currently receiving oral aminosalicylates, prednisone or azathioprine, or 6-mercaptopurine.

Key exclusion criteria were: diagnosis of Crohn's disease or indeterminate colitis; UC that was limited to the rectum; or current evidence of fulminant colitis, toxic megacolon, or bowel perforation. Additional exclusion criteria were: impending requirement for colostomy or ileostomy; previous total or subtotal colectomy; *Clostridium difficile* toxin present in stool [study entry of patients testing positive for *C. difficile* was permitted following a negative retest upon treatment completion]; anti-TNF therapy or any monoclonal antibody or immunoglobulin-based fusion protein within the 8 weeks prior to study treatment, or any experimental therapy within the 4 weeks prior to eldelumab administration.

### 2.2. Randomisation, treatment, and dose

Eldelumab 15 and 25 mg/kg doses were selected, as the target $C_{minss}$ of 100 µg/ml was expected to be achieved by 75% and 96% to 99% of patients, respectively, assuming dose-proportional pharmacokinetics.

Randomisation numbers were assigned in the order in which patients qualified for treatment; a sponsor-owned central randomisation system allocated treatment based on these numbers. Randomisation was stratified by concomitant immunosuppressant use and previous anti-TNF use, and was performed centrally using dynamic treatment allocation. Treatment assignment was blinded for patients and study site personnel; blinding was maintained throughout the study. Two time-staggered cohorts of eight patients were used to ensure that at least six patients achieved the dose-escalation safety criteria for eldelumab 15 and 25 mg/kg IV, respectively, by Day 15. Dose escalation was included to confirm the safety of the higher dose of eldelumab.[21] Dose escalation to the next cohort would be halted if two patients experienced the same treatment-related adverse event [AE]/laboratory parameter abnormality during review of the preliminary blinded safety data. Once an in-depth safety review had been performed, the study could be continued as planned or data could be unblinded for one or more patients. As patients in the two preliminary cohorts achieved the pre-specified treatment safety criteria, the post-amendment group [approximately 270 patients] was randomised 1:1:1 to treatment with placebo or eldelumab 15 or 25 mg/kg.

Oral 5-aminosalicylic acid, prednisone-equivalent dose of ≤ 30 mg, azathioprine, and 6-mercaptopurine were continued at stable
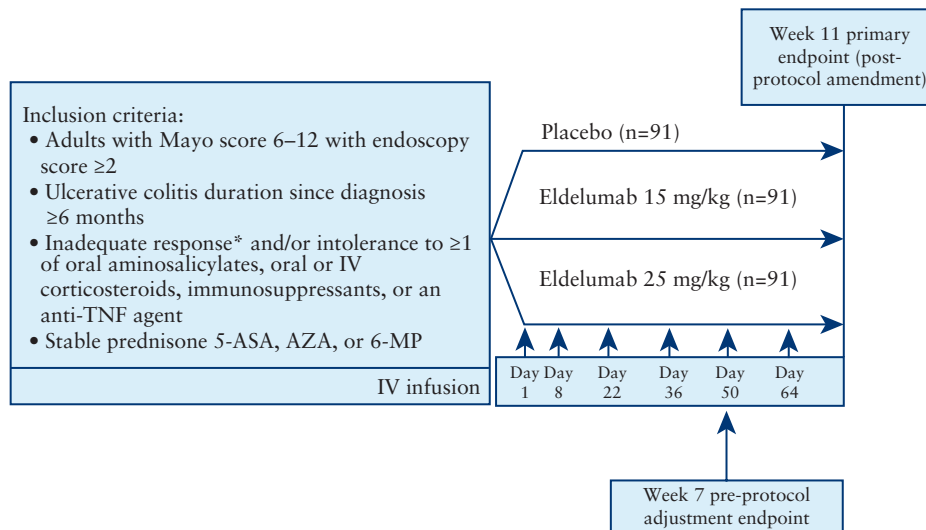
**Figure 1.** Design of study. Asterisk defines no response, insufficient response, or loss of response. Induction period stratified by anti-tumour necrosis factor [TNF] failure and concomitant immunosuppressant use. The planned number of patients per arm was 91. Study amended to change the primary endpoint to Week 11 after 53 patients completed induction at Week 7. 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, azathioprine; IV, intravenous.

doses throughout the induction period. Study drugs were administered as an intravenous [IV] infusion over 90 min on Days 1, 8, and EOW thereafter.

At the end of the induction period, all patients who had achieved a response entered the randomised, double-blind, placebo-controlled maintenance study for up to 2 years.

### 2.3. Efficacy endpoints

#### 2.3.1. Primary endpoint

The primary endpoint was the proportion of patients in each treatment group in clinical remission, defined as a Mayo score < 2 points with no individual subscore >1 point, at Week 11. Although blinding was maintained, an amendment was issued to change the primary endpoint time frame from Week 7 to Week 11, after 53 patients had completed the 7-week induction period. This change was based on blinded review of the aggregate efficacy data in the two preliminary dose-escalation cohorts: clinical improvement continued in patients in the preliminary cohorts who were enrolled in the open-label treatment phase after failing to demonstrate clinical response by Week 7 of the induction period. Furthermore, eldelumab efficacy in UC may be partially mediated by inhibition of IP-10–induced epithelial cell apoptosis,[16,19] an effect that may take time to manifest, suggesting that an 11-week endpoint may be more appropriate for demonstrating optimal efficacy. The present publication reports the primary analyses with patients who completed the induction period at Week 11. Efficacy and safety data from patients assessed according to the original primary endpoint schedule [Week 7] were analysed separately from the overall population [pre-amendment group data].

#### 2.3.2. Secondary and exploratory endpoints

Key secondary endpoints at Week 11 were clinical response [reduction from baseline ≥ 3 points and ≥ 30% in Mayo score, reduction ≥ 1 in rectal bleeding subscore, or absolute rectal bleeding subscore ≤ 1], mucosal healing [endoscopy subscore ≤ 1], and Inflammatory Bowel Disease Questionnaire [IBDQ] response [≥ 16-point change from baseline]. Additional secondary endpoints and subanalyses included Week 11 response/remission/mucosal healing subgroup analyses according to previous anti-TNF status, concomitant

immunosuppressant use [ie azathioprine or 6-mercaptopurine], baseline high-sensitivity C-reactive protein [hsCRP] value, and geographical region. Additional assessments included change in partial Mayo score from baseline over time; changes from baseline to Week 11 in concentrations of faecal calprotectin and serum hsCRP; the proportion of patients achieving histological remission [Geboes Index < 2.0] at Week 11; and eldelumab pharmacokinetics and the exposure–response relationship at Week 11.

#### 2.3.3. Efficacy assessments

The Mayo score is a composite index of four disease variables [stool frequency, rectal bleeding, endoscopy findings, and physician global assessment], each scored on a scale of 0 to 3, with higher scores indicating greater frequency or severity [total score: 0 to 12].[22] Partial Mayo scores [endoscopy subscore omitted] range from 0 to 9. Mayo scores [including endoscopy] were assessed at baseline and Week 11; partial Mayo scores were recorded at Weeks 1, 2, 5, 7, and 9. Patient diaries were used to assist in Mayo score calculations.

The IBDQ is a self-administered 32-item questionnaire that evaluates quality of life across four dimensions [bowel, systemic symptoms, emotional function, and social function], with responses ranging from 1 [severe impact] to 7 [normal health]. Total IBDQ scores range from 32 to 224, with higher scores indicating better quality of life.[23,24] The IBDQ was administered at baseline and Week 11. IBDQ response was defined as a ≥ 16 point increase in IBDQ.

Blood for assessment of hsCRP was drawn at baseline and Weeks 1, 3, 5, 7, 9, and 11. Faecal calprotectin was assessed in stool samples at baseline and Week 11. Histological assessment of gut mucosa following biopsy was performed using the Geboes Index, a seven-component index where 0 [lack of architectural change or other histological abnormalities] indicates the least severe damage and 4 [crypt destruction] indicates the most severe damage.

#### 2.3.4. Pharmacokinetic assessments

In the post-amendment group, venous blood samples were taken on Days 1 and 8 [pre-dose and end of infusion], and at Weeks 3 and 7 [pre-dose], Week 5 [pre-dose and end of infusion], and Week 11. Results for eldelumab in human serum were analysed by enzyme-linked immunosorbent assay.

## 2.4. Safety endpoints

The frequency and severity of adverse events [AEs] and their relationship to study drug, including AEs that worsened relative to the pre-treatment state and all treatment-related AEs, were monitored throughout the study and for up to 56 days after the last dose of study drug. Treatment-related AEs were defined as those possibly, probably, or definitely related to the study drug, with missing relationships presumed to be 'related'. Infusion reactions were defined as any AE that could potentially constitute a reaction to infusion, occurring within 1 h of infusion completion. No routine prophylactic premedication was administered unless indicated by previous infusion reaction experience in an individual patient. Vital sign monitoring, clinical laboratory tests, and physical examinations were performed at each time point. Laboratory abnormalities were defined as laboratory test results that were clinically significant or met the definition of a serious AE, required discontinuation or interruption of study drug, or required treatment with a specific therapy.

## 2.5. Immunogenicity

A validated electrochemiluminescent bridging immunoassay [Meso-Scale Discovery platform; Rockville, MD, USA] was used to screen, confirm, and measure anti-eldelumab antibody titres in serum. Immuno-analysis was performed at baseline and Week 11.

## 2.6. Statistical analysis

Administration of study drug to 81 patients in each treatment arm was calculated to be sufficient to provide 85% power to demonstrate the superiority of eldelumab in terms of achieving clinical remission at Week 11, with a Bonferroni adjustment for the primary endpoint that yielded a significance level of $p = 0.025$ for each comparison with a two-sided test. Splitting of the α in this way meant that the primary endpoint would be met only if at least one of the two dose arms achieved a $p$-value of < 0.025. A placebo remission rate of 15%, and a treatment difference for the proportion of patients attaining remission of 24% between eldelumab and placebo, were used to calculate the sample size required. The values were based on a previous phase IIa eldelumab study [Medarex, data on file, 2013].

The intent-to-treat population [primary efficacy population] comprised all randomised patients who had received any study medication. The safety population comprised all patients who had received at least one dose of study drug or placebo through to the end of the induction period.

For the binary endpoints of response, remission, and mucosal healing, patients who prematurely discontinued were considered to be non-responders for the primary efficacy analysis. The Cochran–Mantel–Haenszel chi-square test was used for the primary analysis, with previous use of anti-TNF therapy and concomitant use of immunosuppressants as stratification factors. The primary endpoint [remission] and the key secondary endpoints [response and mucosal healing] were tested in order using a hierarchical testing procedure within each dose group; only if the previous endpoint was statistically significant was the next endpoint tested, otherwise testing was halted. A linear logistic regression model was used to assess the exposure-response relationship between the average $C_{minss}$ from Weeks 5 to 11 in serum and the efficacy endpoints [clinical response, clinical remission, and mucosal healing] excluding placebo.

## 3. Results

### 3.1. Patient disposition and demographic characteristics

In total, 252 patients were randomised and treated in the 11-week induction period [post-amendment group; Figure 2]; approximately 85% of patients completed this part of the study. Treatment discontinuations due to AEs were comparable across the three treatment arms. Demographic and disease baseline characteristics were comparable across groups in the post-amendment group [Table 1], with a slightly higher percentage of men in the eldelumab 15-mg/kg group vs the other treatment arms [64.3% vs 51.8% for both placebo and eldelumab 25 mg/kg]. Mean [median] duration of UC was lowest in the eldelumab 25-mg/kg arm (6.5 [5.0] year). Concomitant immunosuppressant use and inadequate response/intolerance to anti-TNFs were most common in the eldelumab 25-mg/kg group [43.5% and 44.7% of patients, respectively]. Pre-amendment group baseline characteristics are shown in Supplementary Table 1 [available as Supplementary data at *ECCO-JCC* online].

### 3.2. Primary endpoint

The primary endpoint was not met. Treatment with neither eldelumab 15 mg/kg nor eldelumab 25 mg/kg resulted in a significant difference from placebo in the proportion of patients achieving clinical remission at Week 11 [Figure 3A]. The treatment difference (97.5% confidence interval [CI]) vs placebo was 3.1% [–8.3% to 14.5%] for eldelumab 15 mg/kg and 7.6% [–3.9% to 19.2%] for eldelumab 25 mg/kg.

### 3.3. Key secondary endpoints

In line with the hierarchical testing procedure, clinical response and mucosal healing were not tested statistically vs placebo as the primary endpoint was not met; however, nominal $p$-values were provided. The proportion of patients who achieved clinical response at Week 11 was not significantly different in the eldelumab and placebo treatment groups [Figure 3B]. Treatment differences [97.5% CI] vs placebo were 12.4% [–4.2% to 29.0%] and 16.6% [–0.2% to 33.3%] in the eldelumab 15- and 25-mg/kg groups, respectively.

A similar proportion of patients achieved mucosal healing in the eldelumab 15- and 25-mg/kg and placebo groups [Figure 3C]: treatment difference vs placebo [97.5% CI] was 1.7% [–14.0% to 17.3%] with eldelumab 15 mg/kg and 3.9% [–11.4% to 19.2%] with eldelumab 25 mg/kg. Remission rates, response, and mucosal healing findings in the pre-amendment group were similar [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online].

IBDQ response rates [95% CI] at Week 11 were higher in the eldelumab 15- and 25-mg/kg treatment arms vs placebo (45.2% [34.6% to 55.9%], 51.8% [41.1% to 62.4%], and 38.6% [28.1% to 49.0%], respectively). Mean adjusted changes from baseline were 25.5, 27.4, and 13.2 points in the eldelumab 15- and 25-mg/kg and placebo groups, respectively [nominal $p$-values: 0.0328 and 0.0152 for eldelumab 15 and 25 mg/kg, respectively, vs placebo].

### 3.4. Other endpoints

Greater decreases were observed in partial Mayo score components [stool frequency, rectal bleeding, and physician global assessment] over time with eldelumab 15 mg/kg compared with placebo as early as Day 36 [Week 5], and persisting through to Day 64 [Week 9] before equalising at Day 78 [Week 11; Figure 3D]. Partial Mayo score reductions with eldelumab 15 and 25 mg/kg were comparable at Day 78.

Median decreases [interquartile range] in faecal calprotectin concentrations were greater with eldelumab 15 and 25 mg/kg vs placebo (–51.5 [502.5], –74.5 [782.0], and –3.0 [439.0] μg/g, respectively). Throughout the induction period, mean decreases in serum hsCRP concentrations were greatest in placebo-treated patients. At Week 11, mean change [standard error] from baseline in hsCRP with
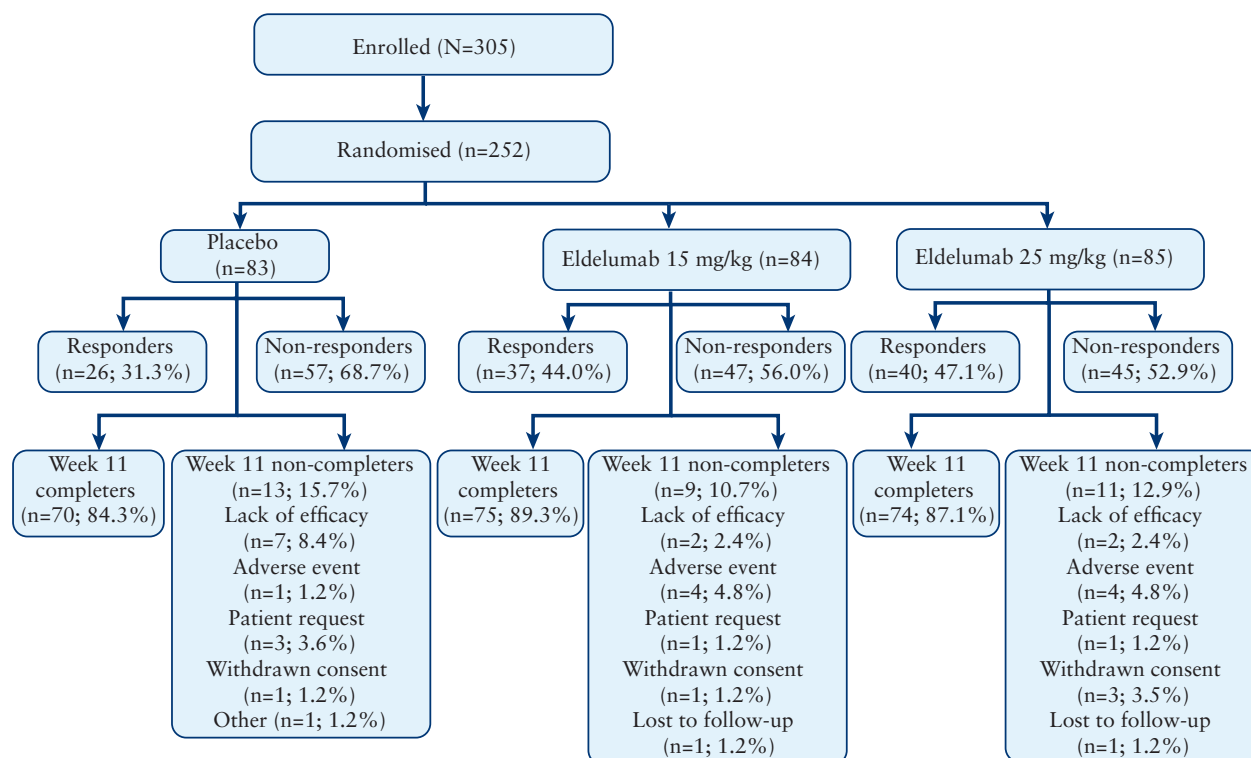
**Figure 2.** Disposition of patients. Patients were classified as responders or non-responders based on the clinical response endpoint.

eldelumab 15 and 25 mg/kg and placebo was –0.6 [1.9], –1.4 [1.7], and –4.6 [2.2] mg/l, respectively.

Increases in eldelumab minimum plasma concentration [$C_{min}$] were approximately dose-proportional. At Week 11, 78.6% and 97.0% of patients in the 15- and 25-mg/kg arms had an eldelumab plasma concentration ≥ 100 μg/ml. The geometric mean eldelumab $C_{min}$ increased from 120 μg/ml at Day 8 to 144 μg/ml at Week 11 in the 15-mg/kg group, and from 195 μg/ml to 293 μg/ml in the 25-mg/kg group. $C_{min}$ profiles over time indicated that steady state was reached at Week 3. There were no meaningful differences in $C_{minss}$ in patients with or without concomitant immunosuppressant use [data not shown].

Clinical remission, response, and mucosal healing were moderately increased with increasing $C_{minss}$ from Week 5 to Week 11. With a 2.0-fold increase in eldelumab exposure, clinical remission, response, and mucosal healing [95% CI] increased by approximately 2.0-fold [1.0 to 4.0], 1.4-fold [0.9 to 2.2], and 2.1-fold [1.2 to 3.6], respectively, compared with lower $C_{minss}$.

Histological remission [Geboes Index < 2.0; assessed in 150 patients] was achieved in a comparable percentage [95% CI] of patients in each treatment arm: eldelumab 15 mg/kg, 28.6% [16.7% to 40.4%]; eldelumab 25 mg/kg, 19.1% [7.9% to 30.4%]; and placebo, 23.4% [11.3% to 35.5%].

No instances of immunogenicity per anti-eldelumab antibody assay were observed.

### 3.5. Subgroup analyses
In anti-TNF naïve patients, higher rates of remission, response, and mucosal healing were reported with eldelumab 15 and 25 mg/kg compared with placebo [Figure 4A].

Among those receiving concomitant immunosuppressants [azathioprine or 6-mercatopurine], the proportion of patients achieving clinical remission was higher with eldelumab 25 mg/kg than with eldelumab 15 mg/kg or placebo [Figure 4B]. Among those receiving concomitant immunosuppressants, more patients in the eldelumab 15- and 25-mg/kg groups achieved clinical response and mucosal healing compared with the placebo group [Figure 4B].

No clear patterns in terms of effect of eldelumab on remission, response, and mucosal healing according to baseline level of inflammatory markers were observed [Figure 4C].

Placebo rates of remission and response were lowest in Eastern Europe, and treatment differences with eldelumab 25 mg/kg for both of these endpoints were highest in this region compared with North America, South America, or Western Europe [Figure 4D].

### 3.6. Safety
Safety data for the post-amendment group during the induction period are summarised in Table 2 [pre-amendment group safety data are reported in Supplementary Table 3[available as Supplementary data at ECCO-JCC online]]. No deaths occurred during the study. There were three treatment-related serious AEs during the induction period: one in the eldelumab 15-mg/kg group [UC] and two in the eldelumab 25-mg/kg group [hypersensitivity and an infusion-related reaction]. In the post-amendment group, 32.1% [27/84], 38.8% [33/85], and 19.3% [16/83] of patients in the eldelumab 15- and 25-mg/kg and placebo groups, respectively, had treatment-related AEs. The treatment-related AEs reported most commonly in the eldelumab 15- and 25-mg/kg and placebo groups were headache [7.1%, 11.8%, and 2.4%, respectively], hypersensitivity [4.8%, 7.1%, and 1.2%], and nausea [3.6%, 2.4%, and 2.4%].

**Table 1**. Baseline demographics and disease characteristics.

| Parameter | Placebo [n = 83] | Eldelumab 15 mg/kg [n = 84] | Eldelumab 25 mg/kg [n = 85] | Total [N = 252] |
|---|---|---|---|---|
| Age, years | | | | |
|   Mean [SD] | 42.7 [14.2] | 40.8 [15.1] | 39.0 [12.7] | 40.8 [14.1] |
|   Median [range] | 41.0 [18–73] | 39.0 [20–77] | 37.0 [19–77] | 39.0 [18–77] |
| Male, n [%] | 43 [51.8] | 54 [64.3] | 44 [51.8] | 141 [56.0] |
| Geographical region, n [%] | | | | |
|   North America | 16 [19.3] | 23 [27.4] | 19 [22.4] | 58 [23.0] |
|   South America | 11 [13.3] | 13 [15.5] | 15 [17.6] | 39 [15.5] |
|   Europe[a] | 48 [57.8] | 42 [50.0] | 43 [50.6] | 133 [52.8] |
|   Rest of World | 8 [9.6] | 6 [7.1] | 8 [9.4] | 22 [8.7] |
| Duration of UC, years | | | | |
|   Mean [SD] | 7.9 [7.4] | 6.8 [7.2] | 6.5 [5.6] | 7.1 [6.8] |
|   Median [range] | 5.7 [0.5–31.2] | 3.9 [0.5–39.6] | 5.0 [0.5–27.0] | 4.7 [0.5–39.6] |
| Extent of disease, n [%] | | | | |
|   Left-sided only | 46 [55.4] | 41 [48.8] | 47 [55.3] | 134 [53.2] |
|   Extensive disease | 37 [44.6] | 43 [51.2] | 38 [44.7] | 118 [46.8] |
| Concomitant immunosuppressant[b] use, n [%] | | | | |
|   Yes | 29 [34.9] | 29 [34.5] | 37 [43.5] | 95 [37.7] |
|   No | 54 [65.1] | 55 [65.5] | 48 [56.5] | 157 [62.3] |
| Concomitant corticosteroid use, n [%] | | | | |
|   Methylprednisolone | 4 [4.8] | 6 [7.1] | 4 [4.7] | 16 [6.3] |
|   Prednisolone | 12 [14.5] | 6 [7.1] | 8 [9.4] | 26 [10.3] |
|   Prednisone | 26 [31.3] | 31 [36.9] | 23 [27.1] | 80 [31.7] |
| Previous inadequate response/intolerance to anti-TNFs, n [%] | | | | |
|   Yes | 30 [36.1] | 30 [35.7] | 38 [44.7] | 98 [38.9] |
|   No | 53 [63.9] | 54 [64.3] | 48 [56.5] | 155 [61.1] |
| Mean Mayo score [SD] | 8.6 [1.7] | 8.3 [1.5] | 8.5 [1.7] | 8.5 [1.7] |
|   Mean partial Mayo score [SD] | 6.1 [1.5] | 5.8 [1.4] | 6.0 [1.5] | 5.9 [1.5] |
|   Rectal bleeding score [SD] | 1.4 [0.9] | 1.3 [0.8] | 1.5 [0.9] | NR |
|   Stool frequency [SD] | 2.5 [0.7] | 2.3 [0.8] | 2.4 [0.8] | NR |
| Mean faecal calprotectin, µg/g [SD] | 562.2 [535.9] | 553.4 [297.6] | 688.4 [302.7] | NR |
| Mean serum hsCRP, mg/l [SD] | 12.9 [19.7] | 13.9 [24.6] | 9.8 [15.7] | 12.2 [20.2] |

SD, standard deviation; hsCRP, high-sensitivity C-reactive protein; NR, not reported; TNF, tumour necrosis factor; UC, ulcerative colitis.

*[a]Eastern Europe, n = 54 patients; Western Europe, n = 79.

[b]Permitted concomitant immunosuppressants were azathioprine or 6-mercaptopurine.

A higher proportion of patients [25.9%] in the eldelumab 25-mg/kg group had infections/infestations, compared with the eldelumab 15-mg/kg [17.9%] and placebo [18.1%] groups. The most common type of infection was nasopharyngitis [10.6%, 3.6%, and 3.6%, respectively]. There was one serious infection in the placebo arm [severe cytomegalovirus colitis] and none in the eldelumab arms. Compared with the placebo group, more patients receiving eldelumab 15 and 25 mg/kg had an infusion reaction (4 [4.8%], 12 [14.3%], and 16 [18.8%], respectively). Most infusion events were mild to moderate; one patient in each eldelumab group experienced a severe acute infusion reaction [15 mg/kg: vomiting and urticaria; 25 mg/kg: dyspnoea, vertigo, vomiting, and tachycardia]. Both severe acute infusion reactions occurred during the first infusion and resolved with corticosteroid and antihistamine treatment. None of the patients with acute infusion reactions had anti-eldelumab antibodies. The occurrence of marked laboratory abnormalities was comparable across treatment arms.

## 4. Discussion

In this 11-week, phase IIb, dose-ranging induction study in moderately to severely active UC, remission rates at Week 11 for eldelumab 15 and 25 mg/kg were not significantly increased vs placebo, and the study did not meet its primary endpoint. The 11-week induction period was likely of sufficient duration to assess remission rates in UC, and further prolongation of the study endpoint was unlikely to have resulted in a different outcome. The extension of study duration at the time of amendment was supported by the partial Mayo score over time for both eldelumab doses, which reached a plateau at Day 78. Subjects randomized before the amendment to extend study duration were not included in the primary efficacy analyses and therefore unlikely to have caused any bias in study results.

During the 11-week induction period, higher proportions of patients in the eldelumab treatment arms than in the placebo arm achieved clinical response, whereas rates of mucosal healing were comparable across the three groups. Furthermore, meaningful improvements in quality of life were observed with eldelumab compared with placebo. Effects on inflammatory biomarkers with eldelumab were inconsistent; eldelumab resulted in greater decreases from baseline in faecal calprotectin concentrations vs placebo, but no difference was observed in change in serum hsCRP concentrations between treatment groups.

Consistent with observations in other inflammatory bowel disease studies,[15,25,26,27] efficacy was more robust in patients who were anti-TNF naïve. Among patients receiving immunosuppressants, remission rates were higher in those treated with eldelumab 25 mg/
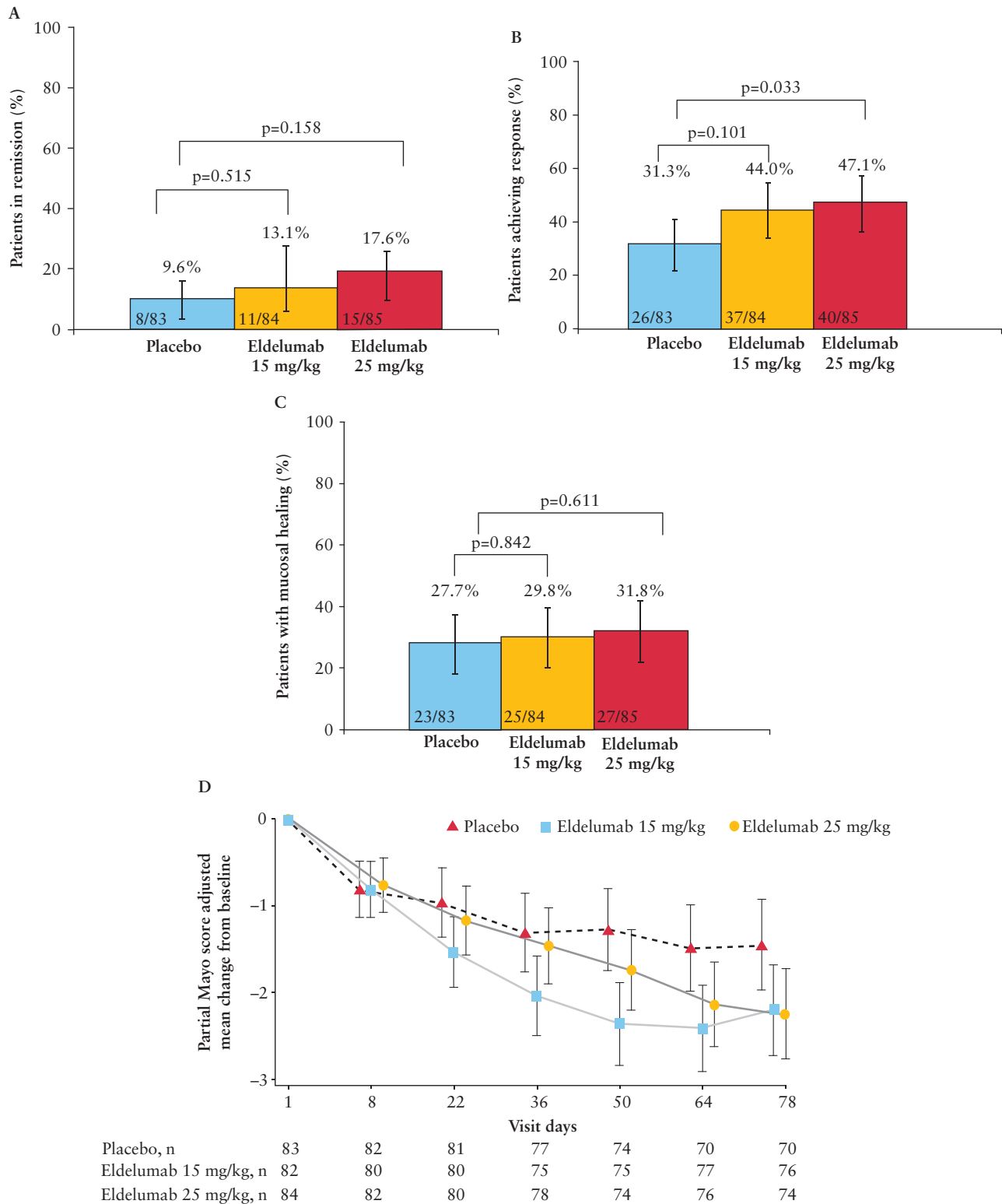
**Figure 3.** [A] Clinical remission rate* at week 11 [intent-to-treat [ITT] analysis]; [B] clinical response rate† according to Mayo score at Week 11 [ITT analysis]; [C] mucosal healing‡ at Week 11 [ITT analysis]; and [D] adjusted mean change from baseline in partial Mayo score over time [as observed analysis]. *Remission defined as Mayo score ≤ 2 with no individual subscore > 1; †response defined as a reduction from baseline ≥ 3 and ≥ 30% in Mayo score, reduction ≥ 1 in rectal bleeding subscore, or absolute rectal bleeding subscore ≤ 1; ‡defined as endoscopy subscore ≤ 1. Error bars represent 95% confidence intervals.

kg than in other treatment arms, whereas rates of clinical response and mucosal healing were higher in patients receiving either dose of eldelumab vs placebo. Concomitant immunosuppressant use

did not appear to increase exposure to eldelumab to an extent that could account for the higher efficacy observed in this subgroup. Rather, the higher efficacy rates with eldelumab and concomitant

**A**



Anti-TNF naïve
(n=155)

Anti-TNF failure
(n=97)

**B**



Immunosuppressant use:
No (n=157)

Immunosuppressant use:
Yes (n=95)
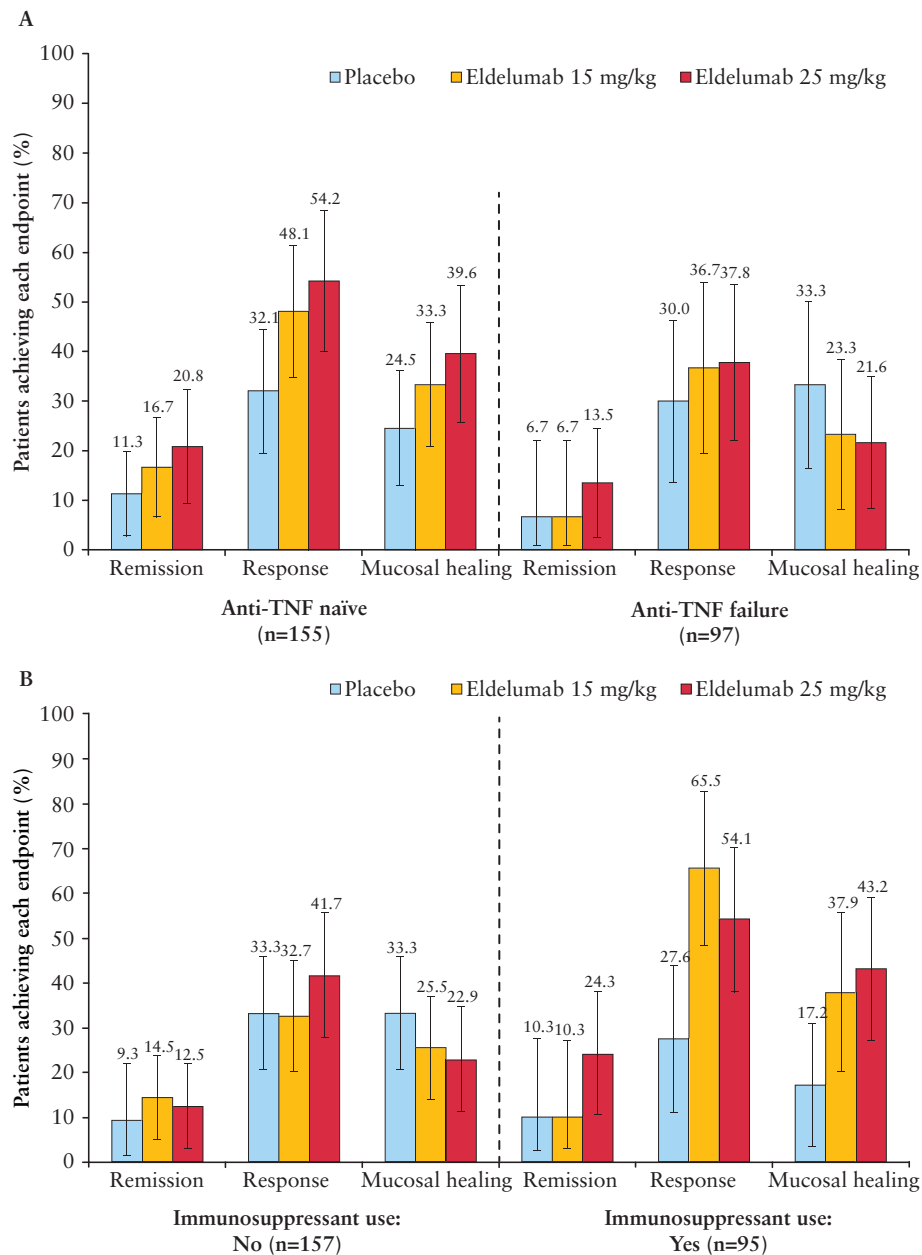
immunosuppressants may have been related to mechanistic synergy, a possibility that warrants further characterisation.

Placebo remission, response, and mucosal healing rates were high [9.6%, 31.3%, and 27.7%, respectively] and could have been reduced by central reading of endoscopy to prevent scoring variability between study centres; however, the current results were comparable to placebo rates reported in other recent trials of induction therapies in UC.[15,28,29] Meta-analyses have shown that placebo remission and response rates are highly variable in UC and are influenced by factors that include the country in which the trial was performed, trial length, number of visits, and the stringency and objectivity of study endpoints.[30,31] The mechanisms driving geographical variation in placebo response remain unclear,[28] although in the current study, small sample sizes in regional efficacy analyses may have led to the differences in placebo response occurring through chance. In the present study, patients in Eastern Europe had the lowest placebo remission and response rates and the largest effect sizes. The larger

effect size may have in part been driven and confounded by the higher percentage of patients on concomitant immunosuppressants in Eastern Europe. These data suggest that controlling for factors that influence placebo remission and response rates with appropriate study design could increase sensitivity in UC trials. Intriguingly, patients in Eastern Europe also demonstrated the highest rates of clinical remission vs other regions when assessed in a recent trial of etrolizumab as induction therapy in UC, although this difference did not reach statistical significance owing to the small number of Eastern European patients.[32]

This was a well-powered phase IIb study, designed with a target drug exposure for efficacy based on an earlier study. Targeted $C_{minss}$ of 100 µg/ml was achieved in both eldelumab arms during the induction period and increases in $C_{min}$ were approximately dose-proportional. Exposure-response analyses indicate that optimal exposure [ie associated with the highest efficacy] was achieved across the 15- to 25-mg/kg doses tested. Although target exposure was attained
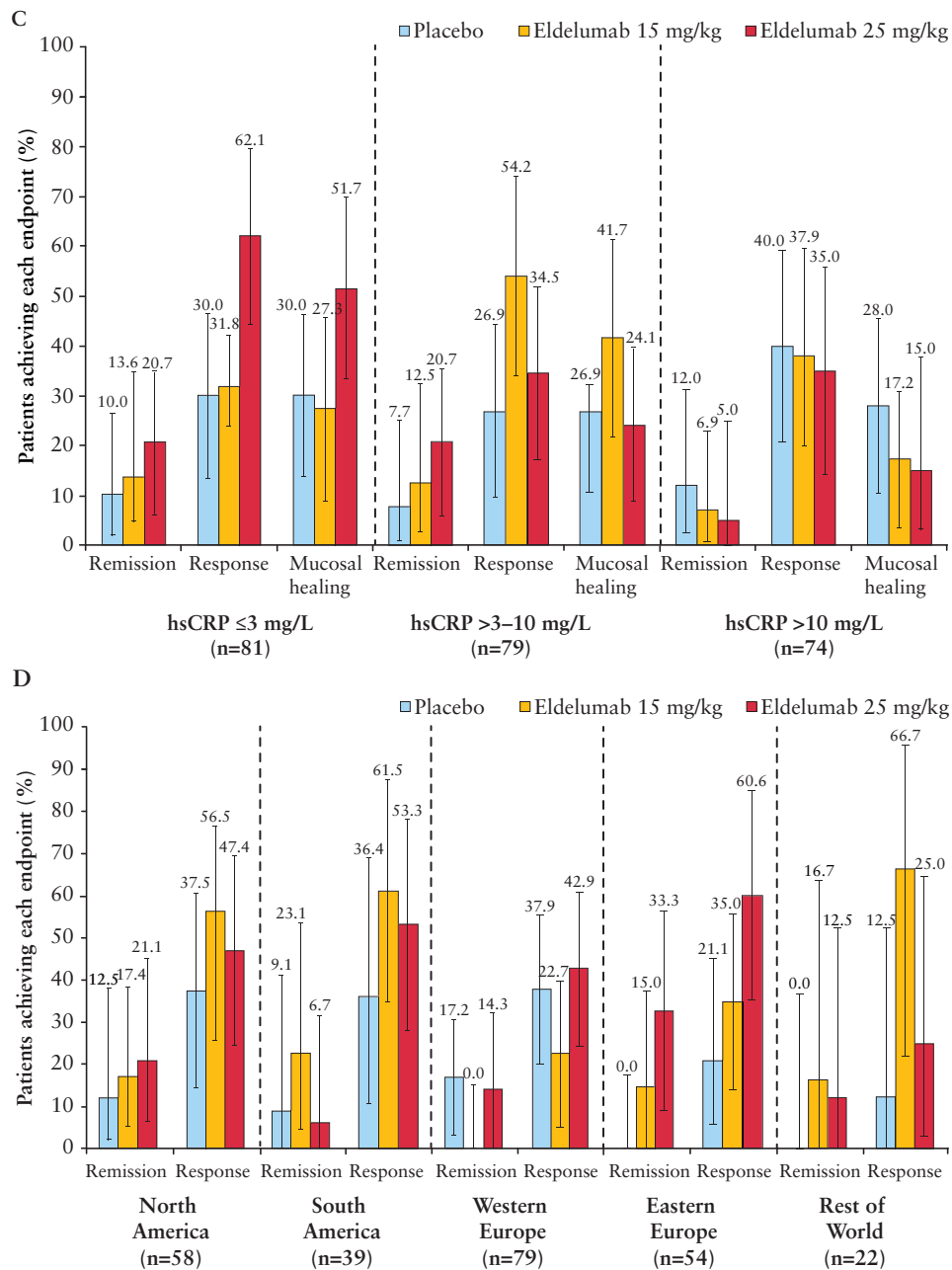
**Figure 4.** Subgroup analyses according to: [A] anti-tumour necrosis factor [TNF] status;* [B] concomitant immunosuppressant use;† [C] baseline high-sensitivity C-reactive protein [hsCRP] value;‡ and [D] geographical region.§ *Numbers for anti-TNF naïve and anti-TNF failure groups were 155 and 97, respectively. †Permitted concomitant immunosuppressants were azathioprine or 6-mercaptopurine. N, numbers for no concomitant immunosuppressant use and concomitant immunosuppressant use were 157 and 95, respectively. ‡N, numbers for hsCRP ≤ 3, > 3 to 10 and > 10 mg/l were 81, 79, and 74, respectively. §Mucosal healing results followed a similar pattern to those of remission and response but have not been shown owing to space limitations. N, numbers for North America, South America, Western Europe, Eastern Europe, and Rest of the World were 58, 39, 79, 54, and 22, respectively. Error bars represent 95% confidence intervals.

and eldelumab demonstrated signals for activity, it did not confer robust efficacy despite the carefully considered study design.

Eldelumab treatment was well tolerated and no new safety signal was identified relative to the completed study in UC.[21] Infection rates were slightly higher in the eldelumab 25-mg/kg group relative to the eldelumab 15-mg/kg and placebo groups, although serious infection rates did not differ across treatment groups. The present study confirmed a safety signal for acute infusion reaction; moderate-to-severe reactions occurred more frequently in the high-dose eldelumab group and were more common early in the treatment schedule.

In conclusion, this 11-week induction study did not meet its primary endpoint of higher clinical remission with eldelumab compared with placebo. However, there was a consistent trend suggesting eldelumab activity, as measured by clinical response, quality of life, and reduced levels of the biomarker faecal calprotectin; although there were inconsistencies across pharmacokinetic parameters. Eldelumab efficacy was more pronounced in subgroups of patients who were anti-TNF naïve or who were receiving concomitant immunosuppressants. No new safety concerns emerged.

**Table 2**. Overall summary of adverse events.

| Category, n [%] | Placebo [n = 83] | Eldelumab 15 mg/kg [n = 84] | Eldelumab 25 mg/kg [n = 85] |
|---|---|---|---|
| Total AEs | 57 [68.7] | 56 [66.7] | 60 [70.6] |
| Treatment-related AEs | 16 [19.3] | 27 [32.1] | 33 [38.8] |
| Total serious AEs | 8 [9.6] | 4 [4.8] | 4 [4.7] |
| Treatment-related serious AEs | 0 | 1 [1.2] | 2 [2.4] |
| Discontinuation owing to AEs | 4 [4.8] | 5 [6.0] | 4 [4.7] |
| Discontinuation owing to serious AEs | 4 [4.8] | 2 [2.4] | 2 [2.4] |
| Deaths | 0 | 0 | 0 |
| Serious infections | 1 [1.2] | 0 | 0 |
| Infections and infestations | 15 [18.1] | 15 [17.9] | 22 [25.9] |
| Infusion reaction[a] | 4 [4.8] | 12 [14.3] | 16 [18.8] |

AE, adverse event.

[a]Potentially infusion-related AEs occurring from the start of study drug infusion until 1h after the end of infusion.

## Conflict of Interest

WS has received consulting fees from Abbott, ActoGeniX NV, AGI Therapeutics Inc., Alba Therapeutics Corp., Albireo, Alfa Wassermann, Amgen, AM-Pharma BV, Anaphore Inc., Astellas, Athersys Inc., Atlantic Healthcare Ltd, Aptalis, BioBalance Corp., Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis Inc., Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals Inc., EnGene Inc., Eli Lilly, EnteroMedics Inc., Exagen Diagnostics Inc., Ferring Pharmaceuticals, Flexion Therapeutics Inc., Funxional Therapeutics Ltd, Genzyme Corp., Gilead Sciences, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood Pharmaceuticals, Janssen Pharmaceutical Research & Development, LLC, KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera Corp., Meda Pharmaceuticals Inc., Merck Research Laboratories, Merck Serono, Millennium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics Inc., PDL Biopharma Inc., Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Ltd, Purgenesis Technologies Inc., Relypsa Inc., Roche, Salient Pharmaceuticals, Salix Pharmaceuticals Inc., Santarus Inc. [a wholly owned subsidiary of Salix Pharmaceuticals Inc.], Schering Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Sirtris Pharmaceuticals Inc., SLA Pharma UK Ltd, Targacept Inc., Teva Pharmaceuticals, Therakos Inc., Tilliotts Pharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals Inc., Vascular Biogenics Ltd, Warner Chilcott UK Ltd, and Wyeth; research grants from Abbott Laboratories, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen Pharmaceutical Research & Development, LLC, Millennium Pharmaceuticals, Novartis, Pfizer, Procter and Gamble, Shire Pharmaceuticals, and UCB Pharma; payments for lectures/speaker bureaus from Abbott Laboratories, Bristol-Myers Squibb, and Janssen Pharmaceutical Research & Development, LLC. J-FC has served as consultant or advisory board member for AbbVie, ABScience, Amgen, Bristol-Myers Squibb, Celltrion, Danone, Ferring, Genentech, Giuliani SPA, Given Imaging, Janssen, Immune Pharmaceuticals, Medimmune, Merck & Co., Millennium Pharmaceuticals Inc., Neovacs, Nutrition Science Partners Ltd., Pfizer Inc., Prometheus Laboratories, Protagonist, Receptos, Sanofi, Schering Plough Corporation, Second Genome, Shire, Takeda, Teva Pharmaceuticals, Tigenix, UCB Pharma, Vertex, Dr. August Wolff GmbH & Co; and as speaker for AbbVie, Ferring, Janssen, Merck & Co., Nutrition Science Partners Ltd, and Takeda. SG has received consulting and/or lecture fees from AbbVie, Shire, Pfizer, Bristol-Myers Squibb, Janssen, and Merck; served on an advisory committee or review panel for AbbVie and Merck; and received research support from AbbVie. BS has received honoraria for advisory activities as a member of an advisory board for AbbVie, Bristol-Myers Squibb, Forest Research Institute, Janssen Research and Development, Luitpold Pharmaceuticals, Millennium Pharmaceuticals, Pfizer, Salix, Shire, Takeda, and Vedanta Biosciences. GD has received funding for acting as a speaker, consultant, or advisory board member for AbbVie, Entera Health, Forest/Ironwood, Salix, and Takeda; and has received research support from AbbVie, Bristol-Myers Squibb, Coronado Biosciences, Genentech, Janssen, Johnson & Johnson, Takeda, and Millennium. XH has received funding for advisory activities as a member of an advisory board from AbbVie, Baxter, Fresenius Kabi, Nestlé Health Sciences, and Takeda, and for educational activities from AbbVie, ARARD, Mayoli-Spindler, MSD, Nestlé Health Sciences, Norgine, Nutricia, and Vifor. RL has served as a speaker and/or advisory board member for AbbVie, Aspen, Ferring, Hospira, Janssen, and Takeda. 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WR has served as a speaker, consultant, and/or advisory board member for Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, Aptalis, Astellas, AstraZeneca, Avaxia, Bioclinica, Biogen Idec, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Grünethal, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, Millennium, Mitsubishi Tanabe Pharma Corp., MSD, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, SetPoint Medical, Shire, Takeda, Therakos, Togenix, UCB, Vifor, Yakult, Zyngenia, and 4SC. L-AX is an employee of Bristol-Myers Squibb and owns Bristol-Myers Squibb stock. AL was previously an employee of Bristol-Myers Squibb and owns Bristol-Myers Squibb stock.

## Author Contributions

## Supplementary Data

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

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