Journal of Crohn's and Colitis, 2018, 1014–1020
doi:10.1093/ecco-jcc/jjy070
Advance Access publication May 29, 2018
Original Article

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A Phase 2, Randomized, Placebo-Controlled Study Evaluating Matrix Metalloproteinase-9 Inhibitor, Andecaliximab, in Patients With Moderately to Severely Active Crohn's Disease

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Conference: Presented at UEG Week 2017, Barcelona, Spain.

Abstract

Background and Aims: Matrix metalloproteinase-9 [MMP9] is implicated in the pathogenesis of Crohn's disease and may serve as a potential biomarker. A phase 2 trial was conducted to examine the efficacy and safety of the anti-MMP9 antibody andecaliximab [GS-5745] in patients with moderately to severely active Crohn's disease.

Methods: Patients were randomized 1:2:2:2 to receive subcutaneous injections of placebo weekly [QW], andecaliximab 150 mg every 2 weeks [Q2W], andecaliximab 150 mg QW, or andecaliximab 300 mg QW. The co-primary study efficacy endpoints were evaluation of a clinical response, defined as liquid or very soft stool frequency and abdominal pain composite [from Patient-Reported Outcome 2] score ≤ 8 at week 8, and an endoscopic response, defined as a ≥ 50% reduction from baseline in the Simple Endoscopic Score for Crohn's Disease, following 8 weeks of treatment.

Results: A total of 187 participants were randomized to treatment; 53 participants were randomized to each andecaliximab treatment group and 28 participants were randomized to placebo. Proportions of patients receiving andecaliximab were not different from proportions of patients receiving placebo based on clinical and endoscopic response and Crohn's disease activity index-defined remission at week 8. Rates of adverse events were comparable among the andecaliximab and placebo groups.

Conclusions: Eight weeks of induction treatment with 150 mg andecaliximab Q2W, 150 mg andecaliximab QW, or 300 mg andecaliximab QW in patients with Crohn's disease did not induce a clinically meaningful symptomatic or endoscopic response. Andecaliximab was well tolerated.

Clinical trial registration: ClinicalTrials.gov NCT02405442.

Key Words: Crohn's disease; inflammation; matrix metalloproteinase-9

1. Introduction

Crohn's disease [CD], one of the main subtypes of inflammatory bowel disease, is characterized by chronic mucosal inflammation resulting in diarrhoea, abdominal pain, weight loss, and passage of blood or mucus. Active disease alternates with remission phases during which symptoms and inflammatory loads are greatly reduced.[1,2] Symptomatic activity and complexity of patients trigger choice of therapies.[2] Management goals are to rapidly induce and maintain remission, withdraw corticosteroid therapy and avoid surgery.[3] Non-specific immunosuppressant or targeted biologic treatments produce poor long-term or durable remission rates generally < 40%.[4–9] Immunosuppressive side effects impact the utility of anti-tumour necrosis factor alpha [TNF-α] therapies. Infection and malignancy risk may limit long-term use in vulnerable populations.[2]

Matrix metalloproteinase-9 [MMP9] is implicated in the pathogenesis of CD and its activation has been investigated as a biomarker of disease.[10,11] MMP9-related destruction of basement membranes, altered barrier permeability, activation and/or recruitment of pro-inflammatory cytokines, and altered angiogenesis may contribute to the compromised barrier function observed in CD.[12–15]

Andecaliximab [GS-5745; Gilead Sciences, Inc.], a recombinant chimeric IgG4 monoclonal antibody, was engineered to remove T-cell epitopes to reduce immunogenicity risk. Andecaliximab selectively binds and inhibits MMP9 with minimal cross-reactivity to other matrix metalloproteinases, including the highly homologous matrix metalloproteinase-2.[16] In a phase 1 dose-ranging study of andecaliximab in patients with ulcerative colitis [UC] over 5 weeks of treatment, more patients demonstrated clinical response to andecaliximab vs placebo;[17] however, a phase 2 study in UC patients failed to meet its endpoints [Sandborn et al., this issue].[18] Here, we report phase 2 study results evaluating the safety and efficacy of andecaliximab in patients with moderately to severely active CD.

2. Methods

2.1. Study design

This phase 2, randomized, placebo-controlled, double-blind, multicentre, 8-week study was conducted from April 2015 to December 2016 [NCT02405442], in accordance with the Declaration of Helsinki, International Conference on Harmonisation, and Good Clinical Practice guidelines. The protocol was reviewed and approved by institutional review boards or independent ethics committees at each site; all participants provided written informed consent prior to our initiating study procedures.

Eligible patients were randomized 1:2:2:2 to receive subcutaneous [SC] injections of placebo weekly [QW], andecaliximab 150 mg every 2 weeks [Q2W], andecaliximab 150 mg QW, or andecaliximab 300 mg QW. The dose range was chosen based on target saturation in healthy volunteers and patients with UC.[17] Treatments were provided as single-use 150-mg/ml [1-ml] prefilled syringes with matching placebo; all patients received two injections per week of placebo and/or andecaliximab over 8 weeks. Treatment randomization was stratified by concomitant use of oral corticosteroids, prior exposure to TNF-α antagonists and evidence of fistula at screening.

2.2. Patients

Males and non-lactating, non-pregnant females aged 18 to 75 years with moderately or severely active CD were eligible. Moderate to severe activity was defined as Crohn's Disease Activity Index [CDAI] total score of 220 to 450, Patient Reported Outcome 2 [PRO2] score ≥ 11, and Simple Endoscopic Score for Crohn's Disease [SES-CD] total score ≥ 6 or ulcer presence and size score of 2 or 3 or a combined score ≥ 4 in the ileum and/or right colon, for patients with disease limited to these two segments. Participants also demonstrated inadequate clinical response, loss of response or intolerance to corticosteroids, immunomodulators, TNF-α antagonists or vedolizumab. Concomitant administration of the following was permitted: oral 5-aminosalicylate compounds; prednisone ≤ 30 mg/day or budesonide ≤ 9 mg/day at a stable dose for ≥ 2 weeks prior to screening; anti-diarrheals; azathioprine, 6-mercaptopurine or methotrexate at a stable dose for 4 weeks prior to screening; and antibiotics for treatment of CD at stable doses for ≥ 2 weeks prior to screening or doses consistent with the subject's standard low-dose regimen. Thiopurines or methotrexate could be initiated up to 4 weeks prior to screening. Key exclusion criteria included evidence of abscess at screening; extensive colonic resection; current use of oral corticosteroids at a dose equivalent to > 30 mg/day prednisone; and treatment with infliximab [or similar biologic], vedolizumab, or any other monoclonal antibody within 4 weeks of screening; additional exclusion criteria are provided in the Supplementary Material.

2.3. Study objectives

The co-primary study efficacy endpoints, based on PRO2 score, included liquid or very soft stool frequency and abdominal pain composite score ≤ 8 at week 8, and an endoscopic response defined as a ≥ 50% reduction from baseline in the SES-CD following an 8-week induction regimen of SC 150 mg Q2W, 150 mg QW, or 300 mg QW andecaliximab vs placebo.

Additional efficacy endpoints included the proportion of patients achieving CDAI ≤ 150 and changes in systemic or localized biomarkers C-reactive protein [CRP], faecal calprotectin and faecal lactoferrin in response to treatment. Safety was evaluated by documentation of adverse events [AEs], physical examination, vital signs, and laboratory evaluations. Patients were provided a CDAI diary to complete daily.

2.4. Assessments

Centrally read ileocolonoscopy was performed at baseline and week 8. Stool specimens were collected at baseline and week 8 for assessment of faecal calprotectin [fCAL ELISA; EL-CAL, Bühlmann] and faecal lactoferrin [IBD-SCAN T5009; TECHLAB] levels. High-sensitivity CRP [hsCRP] levels were measured from blood samples [CRP HS, Siemens Medical Solutions] by immunonephelometry [BN II Nephelometer, Siemens Medical Solutions]. Cutoffs for normal biomarker levels were < 7.24 µg/g for faecal lactoferrin[19] and < 2.87 mg/ml for hsCRP;[20] faecal calprotectin ≤ 250 µg/g has been associated with endoscopic remission in CD.[21]

2.5. Statistics

Demographic and baseline characteristics were summarized using descriptive statistics. No formal statistical hypothesis testing was performed; two-sided 95% confidence intervals [CIs] were provided for point-estimates in each treatment group. The sample size was selected to achieve a desired width of confidence interval for the proportion difference. With a sample size of 50 patients in each of the three andecaliximab groups and 25 patients in the placebo group, a two-sided 95% exact CI of the proportion of patients achieving a positive outcome at week 8 ranged between 28.9% and 40.9%, respectively.

3. Results

Of 187 participants randomized to treatment, 53 were randomized to each andecaliximab treatment group and 28 to placebo [Figure 1]. Baseline demographics and clinical characteristics, particularly disease activity, concomitant steroid use, and prior exposure to anti-TNF-α and vedolizumab, were similar between treatment groups [Table 1].

Proportions of patients achieving clinical and endoscopic response and CDAI remission at week 8 were not different between andecaliximab treatment groups and placebo [Figure 2]. Proportions of patients below clinically relevant levels of disease biomarkers were similar at baseline and week 8 for each treatment group [Table 2].

Thirty-two andecaliximab 150 mg Q2W-treated patients, 33 andecaliximab 150 mg QW-treated patients, 37 andecaliximab 300 mg QW-treated patients, and 19 placebo-treated patients experienced at least one treatment emergent AE [TEAE]. Most events were mild or moderate. In the andecaliximab 150 mg Q2W group, one patient had serious TEAEs [pneumonia, acute prerenal failure, hypercalcaemia, and peripheral ischaemia]; in the andecaliximab 150 mg QW group, six patients had serious TEAEs (anaemia, CD [*n* = 3], abdominal pain, proctalgia, rectal haemorrhage, and acute kidney injury); in the andecaliximab 300 mg QW group, eight patients had serious TEAEs (anaemia, CD [*n* = 2], abdominal pain, anal fistula, large intestine perforation, postprocedural haematoma, postprocedural haemorrhage, procedural pain, hypokalaemia, and acne); three placebo-treated patients had serious TEAEs [anal fistula, perirectal abscess, paresthesia and pulmonary embolism]. Three patients receiving andecaliximab 150 mg QW, four receiving andecaliximab 300 mg QW, and one receiving placebo discontinued treatment due to TEAEs; one patient each receiving andecaliximab 150 mg QW and andecaliximab 300 mg QW experienced an AE leading to dose modification or treatment interruption. Most commonly experienced TEAEs were nausea, abdominal pain, pyrexia, anaemia, CD, headache, hypokalaemia, and fatigue. Percentages of AEs were similar between treatment groups [Table 3].

4. Discussion

In this phase 2 study evaluating the safety and efficacy of andecaliximab in patients with moderately to severely active CD, clinical or endoscopic response did not differ relative to placebo. Secondary endpoint results were consistent with the primary endpoint; biomarker results were consistent with clinical endpoints.

This was a well-conducted phase 2 evaluation in CD based on phase 1b data in UC. Although suggestive signs of efficacy were observed in the phase 1 UC study,[17] treatment differences were not present in this CD study. The results parallel the failed phase 2 UC study indicating MMP9 may be a less relevant target than suggested by animal models of human disease pathophysiology. Alternatively, target coverage may not have been achieved; however, molecular tools to assess this are not yet available. Although both biomarkers and other endpoints were in line with the endoscopic findings, endoscopic evaluation was performed at week 8, and may have been too early in light of other clinical trials' use of week 14. Additionally, as patients were allowed to enter the study 4 weeks after their last change in thiopurine therapy or last administration of another biological therapy, a carry-over effect may have influenced the results.

Importantly, this trial included a difficult-to-treat population typically excluded from studies, including high proportions of patients with prior biologic exposure, and penetrating disease and/or fistula. A higher treatment dose of andecaliximab [300 mg QW] was chosen, relative to doses included in the phase 2 UC study, as it may be a more difficult disease to treat. A study in murine models resembling aspects of UC and CD yielded mixed results; some indicated benefit with MMP9 knockout or inhibition and others did not.[16,22,23] These data, in combination with the phase 2 studies of andecaliximab

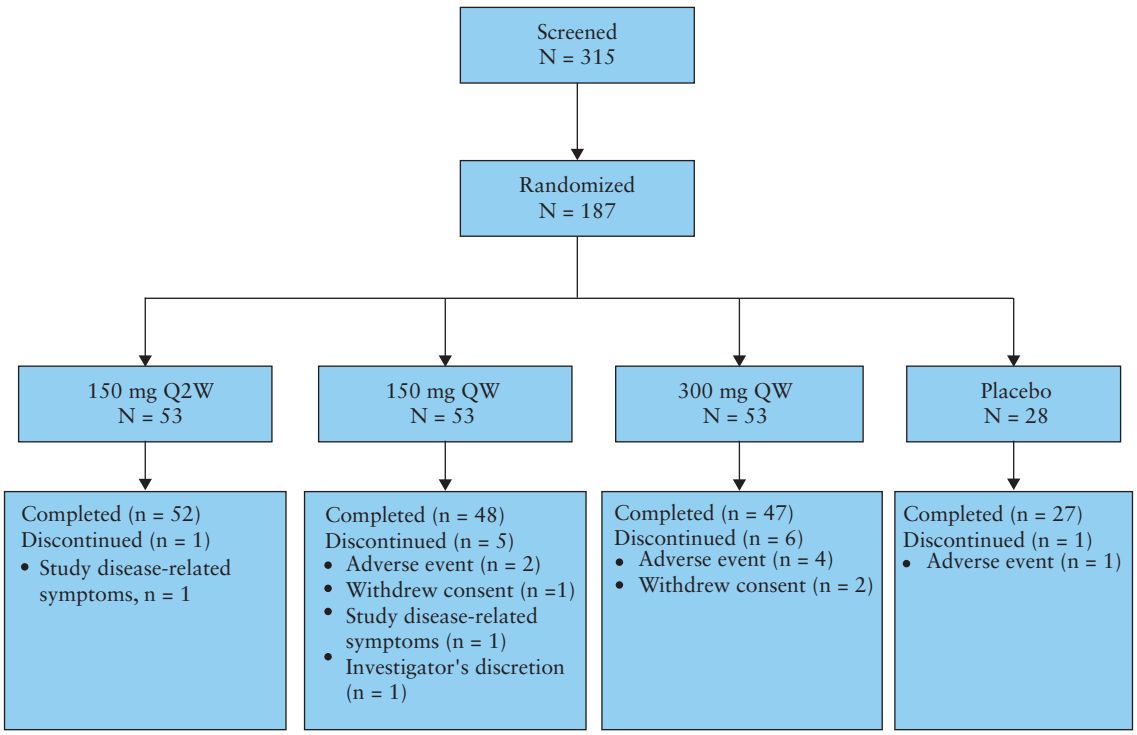

Figure 1. CONSORT diagram. Q2W, once every 2 weeks; QW, once weekly.

Table 1. Subject demographics and baseline characteristics

	Andecaliximab 150 mg Q2W *n* = 53	Andecaliximab 150 mg QW *n* = 53	Andecaliximab 300 mg QW *n* = 53	Placebo *n* = 28	Total *N* = 187
Age, years	38 [12.8]	39 [13.5]	42 [11.7]	38 [13.5]	39 [12.8]
Sex, *n* [%]					
Male	28 [52.8]	25 [47.2]	31 [58.5]	13 [46.4]	97 [51.9]
Race, *n* [%]					
American Indian or Alaskan Native	0	0	0	0	0
Asian	1 [1.9]	1 [1.9]	0	1 [3.6]	3 [1.6]
Black or African American	3 [5.7]	4 [7.5]	3 [5.7]	1 [3.6]	11 [5.9]
White	48 [90.6]	42 [79.2]	48 [90.6]	22 [78.6]	160 [85.6]
Other	1 [1.9]	0	1 [1.9]	3 [10.7]	5 [2.7]
Not reported	0	6 [11.3]	1 [1.9]	1 [3.6]	8 [4.3]
Ethnicity, *n* [%]					
Hispanic or Latino	1 [1.9]	1 [1.9]	5 [9.4]	1 [3.6]	8 [4.3]
Not Hispanic or Latino	52 [98.1]	46 [86.8]	47 [88.7]	26 [92.9]	171 [91.4]
Not reported	0	6 [11.3]	1 [1.9]	1 [3.6]	8 [4.3]
BMI, kg/m^2	26.4 [6.26]	25.8 [7.26]	26.6 [5.64]	24.6 [5.79]	26.0 [6.32]
Smoking status					
Current	11 [20.8]	11 [20.8]	12 [22.6]	4 [14.3]	38 [20.3]
Former	11 [20.8]	8 [15.1]	17 [32.1]	8 [28.6]	44 [23.5]
Never	31 [58.5]	34 [64.2]	24 [45.3]	16 [57.1]	105 [56.1]
Duration of Crohn's disease, years					
Mean [SD]	12.7 [8.60]	11.4 [9.23]	12.6 [10.80]	13.4 [9.30]	12.4 [9.49]
Median [Q1, Q3]	10.5 [7.2, 16.2]	7.7 [4.5, 17.8]	9.2 [4.4, 16.5]	9.9 [6.1, 19.6]	9.4 [5.6, 16.8]
SES-CD Score					
Mean [SD]	13 [6.3]	16 [8.1]	13 [8.8]	13 [7.7]	14 [7.8]
Median [Q1, Q3]	12 [8, 18]	14 [10, 23]	12 [5, 17]	12 [8, 17]	12 [7, 19]
CDAI Score					
Mean [SD]	320 [54.8]	335 [61.4]	329 [60.7]	298 [61.6]	323 [60.2]
Median [Q1, Q3]	324 [278, 346]	331 [298, 376]	319 [294, 365]	297 [258, 330]	320 [280, 362]
PRO2 Score					
Mean [SD]	22 [7.5]	23 [6.6]	22 [7.5]	20 [6.7]	22 [7.2]
Median [Q1, Q3]	21 [18, 26]	23 [18, 25]	20 [17, 25]	18 [16, 22]	21 [17, 25]
Faecal calprotectin, µg/g	1377 [1992.7]	2112 [2306.9]	2138 [4005.0]	2459 [3154.1]	1960 [2958.0]
Faecal lactoferrin, µg/g	131.17 [173.8]	295.61 [251.8]	170.02 [211.6]	247.51 [259.4]	206.10 [230.0]
hsCRP [mg/l]	19.38 [24.3]	26.55 [34.8]	17.49 [22.2]	22.03 [21.5]	21.27 [26.9]
Concomitant use of oral corticosteroid at randomization, *n* [%]					
Yes	24 [45.3]	26 [49.1]	24 [45.3]	9 [32.1]	83 [44.4]
No	29 [54.7]	27 [50.9]	29 [54.7]	19 [67.9]	104 [55.6]
Prior exposure to vedolizumab					
Yes	20 [37.7]	13 [24.5]	14 [26.4]	9 [32.1]	56 [29.9]
No	33 [62.3]	40 [75.5]	39 [73.6]	19 [67.9]	131 [70.1]
Prior exposure to TNF-α antagonist					
Yes	46 [86.8]	45 [84.9]	43 [81.1]	24 [85.7]	158 [84.5]
No	7 [13.2]	8 [15.1]	10 [18.9]	4 [14.3]	29 [15.5]
Fistula at screening					
Present	9 [17.0]	11 [20.8]	9 [17.0]	4 [14.3]	33 [17.6]
Not present	44 [83.0]	42 [79.2]	44 [83.0]	24 [85.7]	154 [82.4]
Concomitant use of immunomodulator					
Yes	19 [35.8]	17 [32.1]	8 [15.1]	8 [28.6]	52 [27.8]
No	34 [64.2]	36 [67.9]	45 [84.9]	20 [71.4]	135 [72.2]
Location of Crohn's disease, *n* [%]					
Colonic	10 [18.9]	13 [24.5]	11 [20.8]	4 [14.3]	38 [20.3]
Ileal	7 [13.2]	5 [9.4]	9 [17.0]	4 [14.3]	25 [13.4]
Ileocolonic	36 [67.9]	35 [66.0]	33 [62.3]	20 [71.4]	124 [66.3]

Data presented as mean [SD] if not otherwise noted.

BMI, body mass index; CDAI, Crohn's disease activity index; hsCRP, high-sensitivity C-reactive protein; PRO2, Patient Reported Outcome 2; Q1, first quartile; Q2W, once every 2 weeks; Q3, third quartile; QW, once weekly; SD, standard deviation; SES-CD, simple endoscopic score for Crohn's disease; TNF-α, tumour necrosis factor-α.

in UC and CD, suggest MMP9 upregulation is a consequence of inflammation in UC and CD, but not a primary driver of disease pathogenesis.

Andecaliximab did not achieve a clinical or endoscopic response, but all doses were well tolerated. Improving barrier function in inflammatory bowel disease merits further investigation.

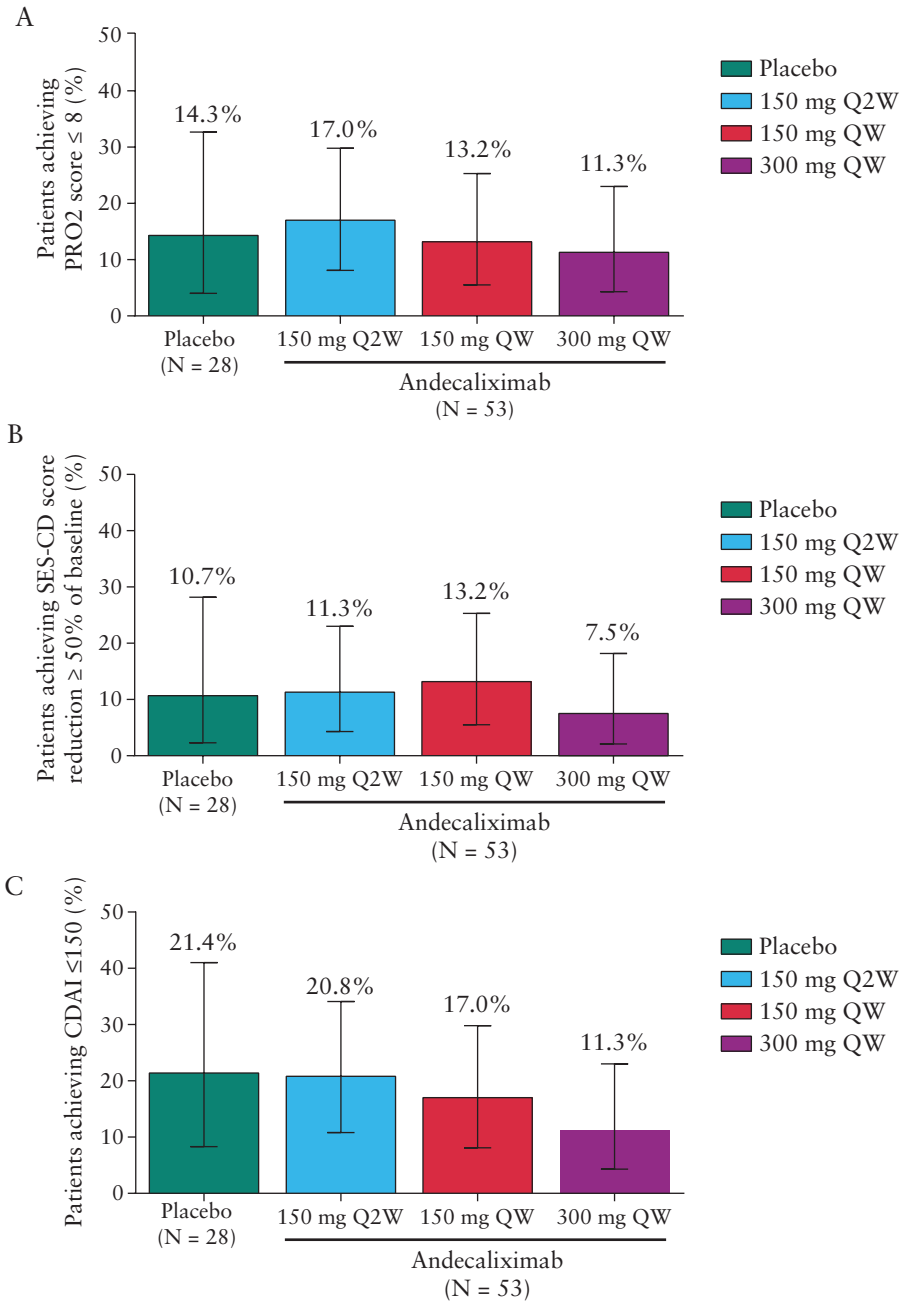

Figure 2. Proportion of patients achieving clinical response by [A] PRO2 score ≤ 8; [B] ≥ 50% baseline reduction in SES-CD; or [C] CDAI ≤ 150 at week 8. Bars denote 95% confidence interval. CDAI, Crohn's Disease Activity Index; PRO2, Patient-Reported Outcome 2; Q2W, once every 2 weeks; QW, once weekly; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Table 2. Proportion of patients below benchmark levels in disease biomarkers at baseline and week 8

Biomarker, *n*/*N* [%]	Andecaliximab 150 mg Q2W		Andecaliximab 150 mg QW		Andecaliximab 300 mg QW		Placebo QW	
	Baseline	Week 8	Baseline	Week 8	Baseline	Week 8	Baseline	Week 8
Serum hsCRP < 2.87 mg/l	12/53 [22.6]	10/53 [19.6]	5/53 [9.4]	2/53 [4.1]	14/53 [26.4]	9/49 [18.4]	1/28 [3.6]	0/27 [0]
Faecal calprotectin ≤ 250 µg/g	14/53 [26.4]	15/50 [30.0]	6/49 [12.2]	7/46 [15.2]	15/53 [28.3]	8/45 [17.8]	3/28 [10.7]	5/25 [20.0]
Faecal lactoferrin < 7.24 µg/g	5/52 [9.6]	4/48 [8.3]	2/52 [3.8]	2/46 [4.3]	7/52 [13.5]	4/45 [8.9]	1/27 [3.7]	1/25 [4.0]

Data presented as *n*/*N* [%].
hsCRP, high-sensitivity C-reactive protein; Q2W, once every 2 weeks; QW, once weekly.

Table 3. Treatment-emergent adverse events occurring in > 5% of the treatment group

	Andecaliximab 150 mg Q2W [*n* = 53]	Andecaliximab 150 mg QW [*n* = 53]	Andecaliximab 300 mg QW [*n* = 53]	Placebo [*n* = 28]
Any AE	32 [60.4]	33 [62.3]	37 [69.8]	19 [67.9]
Any SAE	1 [1.9]	6 [11.3]	8 [15.1]	3 [10.7]
Any serious infection	1 [1.9]	0	0	1 [3.6]
Any premature discontinuation of study drug due to AE or SAE	0	3 [5.7]	4 [7.5]	1 [3.6]
Nausea	3 [5.7]	1 [1.9]	7 [13.2]	5 [17.9]
Abdominal pain	1 [1.9]	8 [15.1]	4 [7.5]	3 [10.7]
Pyrexia	1 [1.9]	3 [5.7]	0	4 [14.3]
Anaemia	0	3 [5.7]	6 [11.3]	0
Fatigue	6 [11.3]	0	5 [9.4]	1 [3.6]
Dizziness	0	5 [9.4]	2 [3.8]	0
Headache	0	4 [7.5]	5 [9.4]	1 [3.6]
Hypokalaemia	1 [1.9]	3 [5.7]	5 [9.4]	1 [3.6]
Crohn's disease	1 [1.9]	4 [7.5]	4 [7.5]	2 [7.1]
Arthralgia	0	4 [7.5]	1 [1.9]	2 [7.1]
Nasopharyngitis	2 [3.8]	1 [1.9]	4 [7.5]	0
Urinary tract infections	1 [1.9]	2 [3.8]	1 [1.9]	1 [3.6]
Back pain	1 [1.9]	2 [3.8]	0	2 [7.1]
Herpes zoster	0	0	0	2 [7.1]
Upper respiratory tract infection	1 [1.9]	0	1 [1.9]	2 [7.1]
Nephrolithiasis	0	0	1 [1.9]	2 [7.1]

Data presented as *n* [%].
AE, adverse event; Q2W, once every 2 weeks; QW, once weekly; SAE, serious adverse event.

Funding

These studies were funded by Gilead Sciences, Inc.

Conflict of Interest

SS reports grants from Gilead Sciences, Inc., during the conduct of the study. CAS reports grants or personal fees from AbbVie, Agency for Health Research and Quality, Amgen, Broad Medical Research Program, Celgene, Crohn's and Colitis Foundation of America, Eli Lilly, Janssen, Sandoz, Pfizer, Prometheus, Sebela, and Takeda; and is an inventor and co-founder of MiTest Health [LLC pending] and ColonaryConcepts [LLC pending]. KAF has nothing to disclose. US reports grants from Gilead Sciences, Inc., during the conduct of the study; grants from Allergan; Boehringer Ingelheim; Celgene Corp.; Pfizer, Inc.; Roche; and Takeda outside the submitted work; and grants and personal fees from Janssen outside the submitted work. BRB has nothing to disclose. ZY reports grants from Gilead Sciences, Inc., during the conduct of the study; grants from AbbVie; Arena Pharmaceuticals; Celgene Corp.; Eli Lilly; Genentech; Janssen; Pfizer, Inc.; and Takeda outside the submitted work; and others from AbbVie; Gilead Sciences, Inc.; and Takeda outside the submitted work. KW, EW, MM, SZ, and JS are employees of and hold stock in Gilead Sciences, Inc. SDL has received grants from or served as a consultant for AbbVie; Atlantic Pharmaceuticals; Arena Pharmaceuticals; Celgene; Celltrion; Cornerstones; Eli Lilly; Gilead Sciences, Inc.; Janssen; Mesoblast Ltd.; Pfizer, Inc.; Salix Pharmaceuticals; Shield Pharmaceuticals; Takeda; Tetherex; and UCB Pharma. EVL reports grants or consulting fees from AbbVie; Amgen; Celgene Corp.; Celltrion; CVS Caremark; Eli Lilly; Genentech; Gilead Sciences, Inc.; Janssen; MedImmune; LLC; Mesoblast, Ltd; Pfizer, Inc.; Receptos, Inc.; Robarts Clinical Trials, Inc.; Salix Pharmaceuticals; Seres Therapeutics; Takeda; and UCB Pharma.

Acknowledgments

We extend our thanks to the patients, their families, and the study-site personnel, as well as Karim Sajwani of Gilead Sciences, Inc., for his contributions to the conduct of the study. Writing and editorial support was provided by Terri Schochet, PhD, of AlphaBioCom, LLC, and funded by Gilead Sciences, Inc.

Author Contributions

All authors had full access to all of the study data and had the final responsibility for the decision to submit the manuscript for publication.

Supplementary Data

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

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