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Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, Patients With Moderate to Severe Crohn's Disease: a Phase 2a Study

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Conflicts of interest

The authors disclose the following: **Bruce E. Sands** has served as a consultant for AbbVie, Akros Pharma Inc, Amgen, Arena Pharmaceuticals, Boehringer-Ingelheim, Forest Research Institute, Immune Pharmaceuticals, Salix Pharmaceuticals, Shire, Synergy Pharmaceuticals, Takeda, Theravance Pharmaceuticals, and Vedanta Biosciences; has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Luitpold Pharmaceuticals, MedImmune, Millennium Pharmaceuticals, Pfizer, Prometheus Laboratories, TiGenix, and TopiVert Pharma Ltd; has received research funding from Abbvie, Amgen, Celgene, Janssen, MedImmune, Millennium Pharmaceuticals, Pfizer, and Takeda. **Brian G. Feagan** has served as a board member for Abbott/AbbVie, Amgen, AstraZeneca, Avaxia Biologics, Bristol-Myers Squibb, Celgene, Centocor, Elan/Biogen, Ferring Pharma, Johnson & Johnson, Janssen, Merck, Novartis, Novo Nordisk Inc, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharmaceuticals, Takeda, Teva Pharmaceuticals, Tillotts Pharma AG, and UCB Pharma; has served as a consultant for Abbott/AbbVie, Actogenix, Albireo Pharma, Amgen, AstraZeneca, Avaxia Biologics, Axcan Pharma, Baxter Healthcare Corp, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, enGene, Ferring Pharma, Roche/Genentech, GIcare Pharma, Gilead, Given Imaging, GlaxoSmithKline, Ironwood Pharmaceuticals, Janssen Biotech (Centocor), Johnson & Johnson/Janssen, Kyowa Hakko Kirin Co, Lexicon, Lilly, Merck, Millennium, Nektar Therapeutics, Novo Nordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Protagonist, Receptos, Inc, Salix Pharmaceuticals, Serono, Shire, Sigmoid Pharma, Synergy Pharmaceuticals, Takeda, Teva Pharmaceuticals, Tillotts Pharma AG, UCB Pharma, Vertex Pharmaceuticals, Warner Chilcott, Wyeth (Pfizer), Zealand Pharma, and Zyngenia; and has received lecture fees from Abbot/AbbVie, Johnson & Johnson, Janssen, Takeda, UCB Pharma, and Warner Chilcott. **Silvio Danese** has served as a board member for AbbVie, AstraZeneca, Danone, Johnson & Johnson, Merck, Mundipharma, Pfizer, Salix Pharmaceuticals, Takeda, TiGenix, and Vifor Pharma; has served as a consultant for AbbVie, AstraZeneca, Celltrion Healthcare, Danone, Johnson & Johnson, Merck, Mundipharma, Pfizer, Salix Pharmaceuticals, Takeda, TiGenix, and Vifor Pharma; has provided expert testimony for AbbVie, AstraZeneca, Danone, Johnson & Johnson, Merck, Mundipharma, Pfizer, Salix Pharmaceuticals, Takeda, TiGenix, and Vifor Pharma; has received lecture fees from AbbVie, AstraZeneca, Johnson & Johnson, Merck, Mundipharma, Pfizer, Takeda, and Vifor Pharma; and has received payment for development of educational presentations from AbbVie, AstraZeneca, Johnson & Johnson, Merck, Mundipharma, Pfizer, Takeda,

and Vifor Pharma. **Peter D. R. Higgins** has no conflicts to disclose. **René van der Merwe** is an employee of MedImmune and owns patents with MedImmune. **Paul Klekotka** was an employee of and owned stock in Amgen at the time of the study. **William A. Rees** owns patents both with MedImmune and independently. **William A. Rees, Paul Newbold, Raffaella Faggioni, Jing Li, Chris Morehouse, Erik Pulkstenis, Jörn Drappa,** and **Robert A. Gasser, Jr.** are employees of MedImmune and may own stock in AstraZeneca. **Jingjing Chen, Mark Penney,** and **Kaushik Patra** were employees of MedImmune at the time the study was conducted.

Author Roles

The authors designed the study in collaboration with MedImmune. Study data were collected and analyzed by MedImmune and were interpreted jointly with the authors. All authors had full access to the data. Dr. Sands wrote the first draft of the manuscript, and all authors contributed to the critical review and revision of subsequent drafts. The authors made a collective decision to submit the manuscript for publication and vouch for the completeness and veracity of the data analyses and for adherence to the protocol.

Short Summary

In this double-blind, placebo-controlled trial, MEDI2070 resulted in clinical improvement after 8 weeks in adults with moderate to severe Crohn's disease after tumor necrosis factor antagonist failure.

Abbreviations

CI, confidence interval; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IRB, institutional review board; TNF, tumor necrosis factor

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ABSTRACT

BACKGROUND & AIMS: MEDI2070 is a human monoclonal antibody that selectively inhibits interleukin 23 (IL23), a cytokine implicated in the pathogenesis of Crohn's disease (CD). We analyzed its safety and efficacy in treatment of CD in a phase 2a study.

METHODS: We conducted a double-blind, placebo-controlled, study of 119 adults with moderate to severe CD failed by treatment with tumor necrosis factor (TNF) antagonists. Patients were randomly assigned (1:1) to groups given MEDI2070 (700 mg) or placebo intravenously at weeks 0 and 4. Patients received open-label MEDI2070 (210 mg) subcutaneously every 4 weeks from weeks 12 to 112. The CD Activity Index (CDAI) was used to measure disease activity.

RESULTS: The primary outcome, clinical response (either a 100-point decrease in CDAI score from baseline or clinical remission, defined as CDAI score below 150]) at week 8 occurred in 49.2% of patients receiving MEDI2070 (n=59) compared with 26.7% receiving placebo (n=60; absolute difference, 22.5%; 95% CI, 5.6%–39.5%, *P*=.010). Clinical response at week 24 occurred in 53.8% of patients who continued to receive open-label MEDI2070 and in 57.7% of patients who had received placebo during the double-blind period and open-label MEDI2070 thereafter. The most common adverse events were headache and nasopharyngitis. Higher baseline serum concentrations of IL22, a cytokine whose expression is induced by IL23, were associated with greater likelihood of response to MEDI2070 compared to placebo.

Conclusions: In a phase 2a trial of patients with moderate to severe Crohn's disease who had failed treatment with TNF antagonists, 8 and 24 weeks of treatment with MEDI2070 were associated with clinical improvement. Clinicaltrials.gov no: NCT01714726.

KEY WORDS: IL23, IL22, clinical trial, phase II

Crohn's disease is a chronic inflammatory disorder characterized by diarrhea, abdominal pain, fatigue, and anemia.[1] Although tumor necrosis factor (TNF) antagonists are effective, approximately one third of patients with Crohn's disease fail to respond (primary nonresponse) to these agents.[2-6] Furthermore, a substantial proportion of patients lose response (secondary nonresponse) or manifest intolerance to TNF antagonists, resulting in dose escalation, use of other therapies, or surgery.[7-9] Response rates in patients switched to alternative TNF antagonists are generally lower than those of patients naive to these agents.[2,5,10]

Interleukin-23 is a pro-inflammatory cytokine comprising two disulfide-linked subunits: p19, which is unique to interleukin-23, and p40, which is shared with interleukin-12.[11-13] Interleukin-23 induces expression of interleukin-22, interleukin-17A, and interleukin-17F and stabilizes TH17 cells. Interleukin-22 is an effector cytokine that plays a key role in maintaining mucosal barrier integrity, directly stimulating gut epithelial cell proliferation,[14,15] and is an indicator of interleukin-23 axis activity.[16] Interleukin-23 also inhibits regulatory T-cell responses in the intestine, thereby enhancing local inflammation.[11] Genome-wide association studies strongly implicate the interleukin-23 axis in Crohn's disease pathogenesis.[17-19] In animal studies, blockade of interleukin-23 receptor activation prevents development of colitis.[12] In clinical studies, ustekinumab, a monoclonal antibody that targets p40, inhibiting both interleukin-12 and IL-23, has shown efficacy in treating Crohn's disease.[20]

MEDI2070 (formerly known as AMG 139) is a human immunoglobulin G2 monoclonal antibody that selectively binds the p19 subunit, specifically blocking binding

of interleukin-23 to its receptor.[21] We evaluated MEDI2070 as an induction therapy for Crohn's disease.

Materials and Methods

This phase 2a, 12-week randomized, double-blind, placebo-controlled, and 100-week open-label study was conducted at 49 centers in nine countries (see Supplementary Appendix for list of study investigators and sites).

Patients

Eligible patients were aged 18 to 65 years, with at least a 6-month history of Crohn's disease, a score of 220 to 450 points on the Crohn's Disease Activity Index (CDAI; scores range from 0–600, with higher scores indicating worse disease), and evidence of active inflammation (serum C-reactive protein [CRP] concentration ≥5 mg/L, fecal calprotectin concentration ≥250 µg/g, or endoscopic findings of at least 3 non-anastomotic ulcerations, each >0.5 cm in diameter, or 10 aphthous ulcerations involving ≥10 cm of contiguous intestine) within 12 weeks before screening. Patients must have received at least one TNF antagonist at the approved dosage, with primary or secondary nonresponse or intolerance. Primary nonresponse to TNF antagonists was defined as signs and symptoms of persistently active disease, despite a history of at least one induction regimen of a TNF antagonist (consisting of at least 2 doses given at least 2 weeks apart). Secondary nonresponse was defined as initial response followed by loss of response with continued therapy. Key exclusion criteria included previous allogeneic bone marrow transplant or cell-based transplantation; clinical manifestation

of short bowel syndrome; a stricture with obstructive symptoms within 3 months, bowel surgery within 12 weeks, bowel perforation or evidence of noninflammatory obstruction within 6 months, or evidence of an infected abscess or fistula prior to first study dose; an ileostomy and/or colostomy; positive stool test for *C. difficile*; prior treatment with a biologic agent targeting interleukin-12 or -23; treatment with cyclosporine, mycophenolate mofetil, sirolimus, thalidomide, or tacrolimus within 4 weeks, or topical aminosalicylic acid or topical steroids within 2 weeks prior to first study dose; intravenous or intramuscular steroids within 2 weeks prior to or during screening; positive test for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus at screening; history of cancer, except for basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy at least 12 months prior to screening; or myocardial infarction or acute coronary syndrome within 12 months of screening. Treatment with oral 5-aminosalicylates and prednisone (≤20 mg per day or budesonide ≤6 mg per day) or azathioprine, mercaptopurine, or methotrexate was required to be at stable doses for 2 and 8 weeks before randomization, respectively, and to remain stable through week 8. Patients receiving biologic therapy were required to discontinue these agents before study entry, according to the following schedule; infliximab, 8 weeks; adalimumab or certolizumab, 10 weeks; and natalizumab, 12 weeks. All patients provided written informed consent. See the Supplementary Appendix for additional eligibility and exclusion criteria.

Study Design

The study included a blinded, 12-week induction period and a 100-week open-label period. This report describes the induction period and the first 12 weeks of the open-label period. Patients were randomized 1:1 to receive intravenous MEDI2070 700 mg or placebo at weeks 0 and 4. Randomization was performed centrally and stratified by prior TNF antagonist failure status (number of agents). Eligible patients were registered in an interactive voice/web response system (Perceptive Informatics; Berlin, Germany), which assigned a unique randomization code. Patients, investigators, and the sponsor were unaware of treatment assignment until last patient completed week 12, when the primary analysis was conducted. During the open-label period (weeks 12 through 112), all patients received MEDI2070 210 mg subcutaneously every 4 weeks, up to a maximum of 26 doses over 100 weeks.

Patients were seen at weeks 0 (baseline), 2, 4, 8, and 12 during the double-blind period, and every 4 weeks during the open-label period. The CDAI, adverse events, laboratory values, vital signs, and concomitant medications were assessed at each visit through week 24. Blood samples were taken for analysis of serum CRP concentrations and biomarkers at screening (CRP only) and at weeks 0, 4 (CRP only), 8, 12, and 24, and for anti-MEDI2070 antibodies at weeks 0, 8, and 24. Stool samples were collected at screening and at weeks 8, 12, and 24 for measurement of fecal calprotectin concentration.

The CDAI score was used to measure disease activity.[22] The primary outcome was clinical response (a CDAI decrease of 100 points from baseline or clinical remission [CDAI <150]) at week 8. Secondary outcomes included clinical remission at week 8, clinical response at week 12, safety and tolerability, and immunogenicity of MEDI2070.

Prespecified exploratory analyses included clinical response by visit, clinical remission by visit, sustained response and remission at week 8 and week 24, the composite outcomes of clinical response and at least a 50% reduction from baseline in either fecal calprotectin or CRP concentration at weeks 8, 12, and 24, and clinical remission and at least a 50% reduction from baseline in either fecal calprotectin or CRP concentration at weeks 8, 12, and 24, change from baseline in the concentrations of CRP, fecal calprotectin, and other biomarkers, including interleukin-22,[23] and the value of baseline serum interleukin-22 concentration to predict clinical response. A complete list of all prespecified outcomes can be found in the study protocol, submitted with the Supplementary Appendix.

Statistical Analysis

Sample size was calculated using a two-sided chi-square test (without continuity correction) of equal proportions, assuming response rates of 20% and 45% at week 8 in the placebo and MEDI2070 700-mg groups, respectively. Approximately 54 subjects per treatment arm provided 87% power to detect a 25% difference in response rates at week 8 between MEDI2070 700 mg versus placebo, using a significance level of α=0.1. Assuming a 10% dropout rate per treatment arm and nonresponder imputation adjustment, approximately 60 patients per treatment arm were randomized.

Demographic and baseline characteristics were summarized using descriptive statistics.

Analyses of the primary and CDAI-based dichotomous efficacy outcomes were performed using a logistic regression model,[24] with treatment assignment and number

of prior TNF antagonists (1 vs >1) as covariates. Significance was tested using a two-sided test of α=0.10 as prespecified in the analysis plan; however, 95% confidence intervals (CIs) for the absolute treatment differences for all efficacy outcomes are reported. Analyses were not adjusted for multiple comparisons, and nominal P values are presented.

Continuous measures were analyzed using inverse probability weighted generalized estimating equation, and mixed-effects repeated-measure methods.

The association between baseline serum interleukin-22 concentrations and treatment effect was analyzed in patients with evaluable baseline interleukin-22 concentrations using a logistic regression model with treatment, number of prior TNF antagonists (1 vs >1), baseline interleukin-22 concentrations (continuous), and interaction between treatment by baseline interleukin-22 concentrations. Based on a statistically significant interaction (eg, $P < .15$), further evaluation of subgroups was conducted for patients with high (defined as a baseline median of ≥15.6 pg/mL) and low baseline interleukin-22 concentrations (<15.6 pg/mL).

Efficacy analyses during the double-blind period were performed according to a modified intention-to-treat principle and included all randomized patients who received MEDI2070 or placebo. Efficacy analyses for the open-label period (up to week 24) were reported by cohorts defined by treatment in the double-blind and open-label periods. Safety analyses were based on actual treatment received.

Nonresponder imputation was applied to dichotomous measures for missing data. The imputed nonresponders before week 8 were considered nonresponders for all

subsequent visits. Per protocol, patients with an increased corticosteroid dose were also considered nonresponders.

The study was registered at clinicaltrials.gov with registration number NCT01714726. The protocol was approved by the institutional review board (IRB) at each center (*see Supplementary Appendix for list of IRB names and protocol approval numbers*). All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Patient Characteristics

In total, between March 20, 2013, and February 26, 2014, 121 patients underwent randomization, of whom 119 received study drug (Supplementary Figure 1). A total of 104 (52 of 59 and 52 of 60 patients treated with MEDI2070 and placebo, respectively) of the 119 patients (87.4%) completed the double-blind period and entered the open-label period (Figure 1). Baseline demographics and disease characteristics were similar between treatment groups (Table 1).

Efficacy

At week 8, the primary outcome of clinical response occurred in 49.2% of patients receiving MEDI2070 700 mg compared with 26.7% of patients receiving placebo (absolute difference, 22.5%; 95% CI, 5.6–39.5; P = .01) at week 8. Clinical remission at week 8 occurred in 27.1% of patients receiving MEDI2070 700 mg and in 15.0% of patients receiving placebo (absolute difference, 12.2%; 95% CI, −2.3–26.7;

P = .10). A significantly greater proportion of patients receiving MEDI2070 700 mg achieved the composite end point of clinical response and at least a 50% reduction from baseline in either fecal calprotectin or CRP concentration at week 8 compared with those receiving placebo (42.4% vs. 10.0%; absolute difference, 32.4%; 95% CI, 17.8–47.1; *P* < .001). Outcomes at weeks 8 and 12 are summarized in Figure 2A and B.

Clinical response, clinical remission, and the composite outcome of clinical response and at least a 50% reduction from baseline in either fecal calprotectin or CRP concentration occurred in a similar proportion of patients receiving continued treatment with MEDI2070 at week 24 (Figure 2C) of the open-label period, as at week 8 of the double-blind period. Sustained clinical response at weeks 8 and 24 occurred in 42.3% of patients receiving MEDI2070 during both study periods compared with 23.1% of patients receiving placebo in the double-blind period; sustained clinical remission occurred in 23.1% and 11.5% of patients, respectively. Similar proportions of patients receiving placebo during the double-blind period achieved clinical response, clinical remission, and the composite outcome of clinical response and at least a 50% reduction from baseline in either fecal calprotectin or CRP at week 24 during the open-label period, as did patients receiving MEDI2070 during both study periods. See the Supplementary Appendix for additional details about changes in CDAI scores from baseline over time (Supplementary Figure 1) and through week 24 (Supplementary Figure 2).

Within the range of serum levels of MEDI2070 produced by the double-blind and open-label doses of MEDI2070, no difference was observed for the serum MEDI2070 levels between responders and nonresponders at weeks 8, 12, and 24. See the

Supplementary Appendix for additional details about pharmacokinetics and exposure-response data (Supplementary Figures 3 and 4).

Safety

Similar proportions of patients had treatment-emergent adverse events, serious adverse events, and events of grade 3 or greater severity in both study groups during the double-blind period (Table 2). Twice as many patients receiving placebo experienced treatment-related adverse events (21.7% vs 10.2% of patients receiving MEDI2070). Similar proportions of patients in both groups discontinued treatment owing to adverse events.

Clinically significant infections (ie, serious, at least grade 3 in severity, or requiring treatment with oral or parenteral antimicrobials) occurred in 4 patients with 4 events in the MEDI2070 group, and in 7 patients with 11 events in the placebo group (Table 3).

Treatment-emergent adverse events in the open-label period (up to week 24) occurred in 67.3% of patients receiving MEDI2070 during both study periods and in 65.4% of patients receiving placebo in the double-blind period. Serious adverse events occurred in 15.4% of patients receiving MEDI2070 during both study periods and in 7.7% of patients receiving placebo in the double-blind period. Treatment discontinuation owing to adverse events occurred in 9.6% of patients receiving MEDI2070 during both study periods and in 3.8% of patients receiving placebo in the double-blind period. An equal number (n=13) of clinically significant infections occurred in patients receiving

MEDI2070 in both study periods and in those receiving placebo in the double-blind period (Supplementary Table 1).

Biomarkers

Patients receiving MEDI2070 had significantly greater reductions in fecal calprotectin and CRP concentrations at weeks 8 and 12 of the double-blind period compared with those receiving placebo (Table 4). Patients who continued receiving MEDI2070 in the open-label period maintained these reductions, whereas patients receiving placebo in the double-blind period had significant reductions from weeks 12 to 24 in fecal calprotectin ($P < .001$) and CRP concentrations ($P = .002$). From weeks 12 to 24, fecal calprotectin concentrations decreased by a mean of 65.7 µg/g from weeks 12 to 24 in patients receiving MEDI2070 in both periods (95% CI, −179.7–48.2; $P = .25$), and 207.8 µg/g (95% CI, −326.4– −89.1; $P < .001$) in those receiving placebo during the double-blind period. A similar pattern was observed for CRP; from weeks 12 to 24, serum concentrations decreased by 1.8 mg/L in patients receiving MEDI2070 in both periods (95% CI, −8.3–4.7; $P = .58$), and 10.8 mg/L (95% CI, −17.5– −4.0; $P = .002$) in those receiving placebo during the double-blind period.

Patients receiving MEDI2070 had greater reductions in serum interleukin-22 levels than did patients receiving placebo (Figure 3A). The P values for the treatment-by-baseline interleukin-22 interaction term were significant for clinical response at week 8 ($P = .04$), suggesting that treatment effect at week 8 differed by baseline serum interleukin-22 concentrations. Baseline serum interleukin-22 concentrations with a median value of at least 15.6 pg/mL were associated with an increased likelihood of

clinical response and clinical remission at week 8 in patients receiving MEDI2070 (Figures 3B and 3C), whereas patients receiving MEDI2070 with concentrations below this threshold had clinical response and remission rates similar to patients receiving placebo. This suggests that interleukin-22 may have value as a potential predictive biomarker.

Immunogenicity

Antidrug antibodies were detected in 3 of 119 patients. One patient receiving MEDI2070 during both study periods had antidrug antibodies at baseline and at no subsequent time points, one patient receiving placebo during the double-blind period had antidrug antibodies at week 24 during the open-label period, and 1 patient receiving MEDI2070 during both study periods had antidrug antibodies at week 24 during the open-label period.

DISCUSSION

In this phase 2a trial of patients with moderate to severe active Crohn's disease who failed treatment with a TNF antagonist, two infusions of MEDI2070 700 mg 4 weeks apart resulted in significantly greater rates of clinical response at week 8 than placebo. Continued treatment with subcutaneous injections of MEDI2070 210 mg resulted in sustained clinical response and remission at 24 weeks. Patients who switched at week 12 from placebo to open-label treatment with subcutaneous MEDI2070 210 mg every 4 weeks achieved similar rates of clinical outcomes at week 24 as those who had received continuous treatment with MEDI2070. This study also evaluated a composite

outcome that included both clinical response and at least a 50% reduction from baseline concentrations of either fecal calprotectin or CRP. Significantly more patients receiving MEDI2070 achieved this outcome at week 8 compared with those on placebo. The placebo rate decreased when this more stringent outcome definition was applied, further supporting a meaningful treatment effect. The proportion of patients receiving MEDI2070 who achieved this outcome at week 24 was similar to week 8 and, at week 24, the proportions did not differ between patients who had received continuous treatment with MEDI2070 and those who received placebo during the double-blind period.

Treatment with MEDI2070 also resulted in significant decreases from baseline in both fecal calprotectin and CRP compared with placebo at weeks 8 and 12. These reductions were sustained at week 24 with continued treatment with MEDI2070 during the open-label period. Similar to the clinical effects, patients who received placebo during the double-blind period also had significant reductions in fecal calprotectin and CRP concentrations from weeks 12 to 24 after switching to open-label treatment with MEDI2070. The combined clinical and biologic effects of treatment with MEDI2070 are considerable given that greater than 65% of the patients in this study had failed prior treatment with two or more TNF antagonists.

MEDI2070 was well tolerated, with rates of treatment-emergent adverse events generally similar to those of placebo. However, the duration of follow-up was limited to week 24, and relatively small numbers of patients were treated. Other limitations of this study include the evaluation of only one dose during the double-blind period, as well as

the limited number of subjects enrolled. Additionally, no endoscopic evaluation of the bowel nor imaging studies were conducted to assess end-organ healing.

Interleukin-22 is an effector cytokine whose expression is induced by interleukin-23.[25-27] Although a specific role in Crohn's disease pathogenesis is undefined, interleukin-22 has been identified as a potential biomarker for Crohn's disease activity.[16] In this study, serum interleukin-22 levels declined after treatment with MEDI2070 providing evidence for inhibition of the interleukin-23 pathway, and for mechanistic differentiation from the TNF antagonist adalimumab, which, while clinically effective, did not reduce interleukin-22 concentrations in Crohn's disease patients.[28] We identified interleukin-22 concentrations above the baseline median associated with improved treatment effect in this study. Patients with baseline serum interleukin-22 concentrations above the median threshold concentration of 15.6 pg/mL treated with MEDI2070 had higher rates of clinical response and remission compared with those with baseline concentrations below this threshold, whose clinical outcomes approximated those of patients treated with placebo. These results provide support for further research on the value of interleukin-22 serum concentrations to predict response to MEDI2070.

In conclusion, this phase 2a study provides evidence for clinical and biologic effects of MEDI2070 for the treatment of Crohn's disease refractory to TNF antagonists, and may support use of interleukin-22 serum concentrations to predict clinical response to treatment with MEDI2070. Although larger studies are required, short-term treatment with MEDI2070 was well tolerated.

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FIGURES

Figure 1. Patient Disposition Through Week 24.

[a]Patient decision (n=1), adverse events (n=5); other (n=2).
[b]Patient decision (n=1), adverse events (n=5); other (n=1).
[c]Patient decision (n=2), adverse events (n=1), lack of therapeutic response (n=2), development of study-specific withdrawal criteria (n=1), other (n=3).
[d]Patient decision (n=3); adverse events (n=5), lack of therapeutic response (n=1), other (n=3).

Figure 2. Efficacy outcomes during the double-blind (weeks 8 and 12) and open-label (week 24) periods. Shown are the proportions of patients who achieved a clinical response (defined as a 100-point decrease in CDAI score from baseline or clinical remission [CDAI score <150]), clinical remission, or the composite outcome of clinical response and a ≥50% reduction in fecal calprotectin or CRP concentration from baseline at week 8 (mITT population, n = 119; *A*) and week 12 (mITT population, n = 119; *B*) of the double-blind period, and week 24 (open-label population, n = 104; *C*) of the open-label period.

Figure 3. Percent change from baseline in serum interleukin-22 levels in MEDI2070 and placebo groups (*A*) and percentage of patients with clinical response (*B*) and with clinical remission (*C*) over time, by baseline serum interleukin-22 levels. Error bars represent median absolute deviation.

TABLES

Table 1. Baseline Characteristics and Demographics[a]

Characteristic	MEDI2070 (n = 59)	Placebo (n = 60)	Total (N = 119)
Age, y	34.9 ± 11.2	38.1± 10.7	36.5± 11.0
Female, n (%)	37 (62.7)	37 (61.7)	74 (62.2)
Mean weight, kg	70.4 ± 20.7	71.9± 15.4	71.2± 18.2
Mean disease duration, y	13.1 ± 9.4	11.2± 8.5	12.2± 9.0
≥2 y, n %	57 (96.6)	54 (90.0)	111 (93.3)
Sites of disease, n (%)			
Ileal only	14 (23.7)	18 (30.0)	32 (26.9)
Colonic only	16 (27.1)	18 (30.0)	34 (28.6)
Ileo-colonic	28 (47.5)	24 (40.0)	52 (43.7)
Other[b]	1 (1.7)	0	1 (0.8)
Crohn's Disease Activity Index score[c]			
Mean	325.0±59.2	312.4±56.3	318.6±57.8
Minimum, maximum	222, 440	221, 450	221, 450
CDAI <250, n (%)	8 (13.6)	10 (16.7)	18 (15.1)
Mean C-reactive protein, mg/L	29.8± 35.4	21.1± 24.2	25.4±30.4
C-reactive protein ≥5 mg/L, n (%)	46 (78.0)	39 (65.0)	85 (71.4)
Mean fecal calprotectin,[d] µg/g	536.7 ± 303.2	616.9 ± 420.7	578.2 ± 369.3
Fecal calprotectin ≥250 µg/g, n (%)	41 (73.2)	47 (78.3)	88 (75.9)
Mean interleukin-22,[e] pg/mL	38.0 ± 96.4	20.7 ± 25.3	29.0 ± 69.6
Interleukin-22 ≥15.6 pg/mL, n (%)	30 (53.6)	28 (46.7)	58 (50.0)

Characteristic	MEDI2070 (n = 59)	Placebo (n = 60)	Total (N = 119)
Prior anti–tumor necrosis factor-α agents, n (%)			
1	18 (30.5)	19 (31.7)	37 (31.1)
2	35 (59.3)	35 (58.3)	70 (58.8)
≥3	6 (10.2)	6 (10.0)	12 (10.1)
Prior use of anti–tumor necrosis factor-α agents, n (%)			
Infliximab	51 (86.4)	50 (83.3)	101 (84.9)
Adalimumab	45 (76.3)	45 (75.0)	90 (75.6)
Certolizumab	10 (16.9)	11 (18.3)	21 (17.6)
Reason for discontinuing prior anti–tumor necrosis factor-α agent, n (%)			
Primary failure	23 (39.0)	23 (38.3)	46 (38.7)
Secondary failure	34 (57.6)	33 (55.0)	67 (56.3)
Intolerance	27 (45.8)	26 (43.3)	53 (44.5)
Other[f]	7 (11.9)	11 (18.3)	18 (15.1)
Not identified[f]	0	2 (3.3)	2 (1.7)
5-aminosalicylate use at baseline, n (%)	18 (30.5)	18 (30.0)	36 (30.3)
Corticosteroid use at baseline, n (%)	24 (40.7)	24 (40.0)	48 (40.3)
Immunomodulators use at baseline, n (%)	18 (30.5)	14 (23.3)	32 (26.9)
Prior surgery for Crohn's disease, n (%)	29 (49.2)	26 (43.3)	55 (46.2)

[a]Plus-minus values are means ± SD. No significant differences were observed between the groups.
[b]This single patient had perineal disease but did not have documented ileal or colonic lesions, as specified in the study inclusion criteria.
[c]This index consists of eight factors, with each factor totaled after adjustment with a weighting factor that ranged from 1 to 30. Total scores can range from 0 to 600, with higher scores indicating more severe disease activity and a 50-point change indicating the minimum clinically important difference.
[d]Three patients in the MEDI2070 group had missing fecal calprotectin assessments.
[e]Three patients in the MEDI2070 group had missing interleukin-22 assessments.

[f]All patients who had discontinued treatment with a TNF antagonist owing to reasons listed as “other” or “not identified” had received prior treatment with either two or three TNF antagonists before study participation. In all cases, at least one TNF antagonist had been discontinued for primary failure, secondary failure, or intolerance.

Table 2. Adverse Events During the Double-blind Period (Week 0–Week 12)

Event	MEDI2070 (n = 59)	Placebo (n = 60)
Total number of adverse events	107	112
Patients with event, n (%)		
Adverse event	40 (67.8)	41 (68.3)
Serious adverse event[a]	5 (8.5)	5 (8.3)
Adverse event with severity grade of 3 or greater[b]	6 (10.2)	7 (11.7)
Treatment-related adverse event	6 (10.2)	13 (21.7)
Adverse event leading to study drug discontinuation[c]	5 (8.5)	6 (10.0)
Adverse events occurring in ≥5% of patients in either treatment group		
Headache	10 (16.9)	4 (6.7)
Nasopharyngitis	8 (13.6)	6 (10.0)
Abdominal pain	6 (10.2)	6 (10.0)
Crohn's disease	5 (8.5)	5 (8.3)
Vomiting	3 (5.1)	2 (3.3)
Arthralgia	3 (5.1)	2 (3.3)
Proctalgia	3 (5.1)	0
Dizziness	3 (5.1)	0
Pyrexia	2 (3.4)	4 (6.7)
Nausea	2 (3.4)	3 (5.0)
Diarrhea	0	5 (8.3)
Sinusitis	0	4 (6.7)
Insomnia	0	3 (5.0)
Cough	0	3 (5.0)

[a]Serious adverse events occurred in five patients in each treatment group; Crohn's disease (3

events in 3 patients), colonoscopy-associated colon perforation (n = 1), pyrexia (n = 1), and cellulitis (n = 1) in the MEDI2070 group, and anemia (n = 1), Crohn's disease (two events in two patients), diarrhea (n = 1), gastrointestinal hemorrhage (n = 1), and abdominal abscess (n = 1) in the placebo group.

[b]Defined as severe, life-threatening, or fatal.

[c]Gastrointestinal disorders (6.8%) and infection (1.7%) in the MEDI2070 group and gastrointestinal disorders (6.7%), infection (1.7%), and eye disorder (1.7%) in the placebo group.

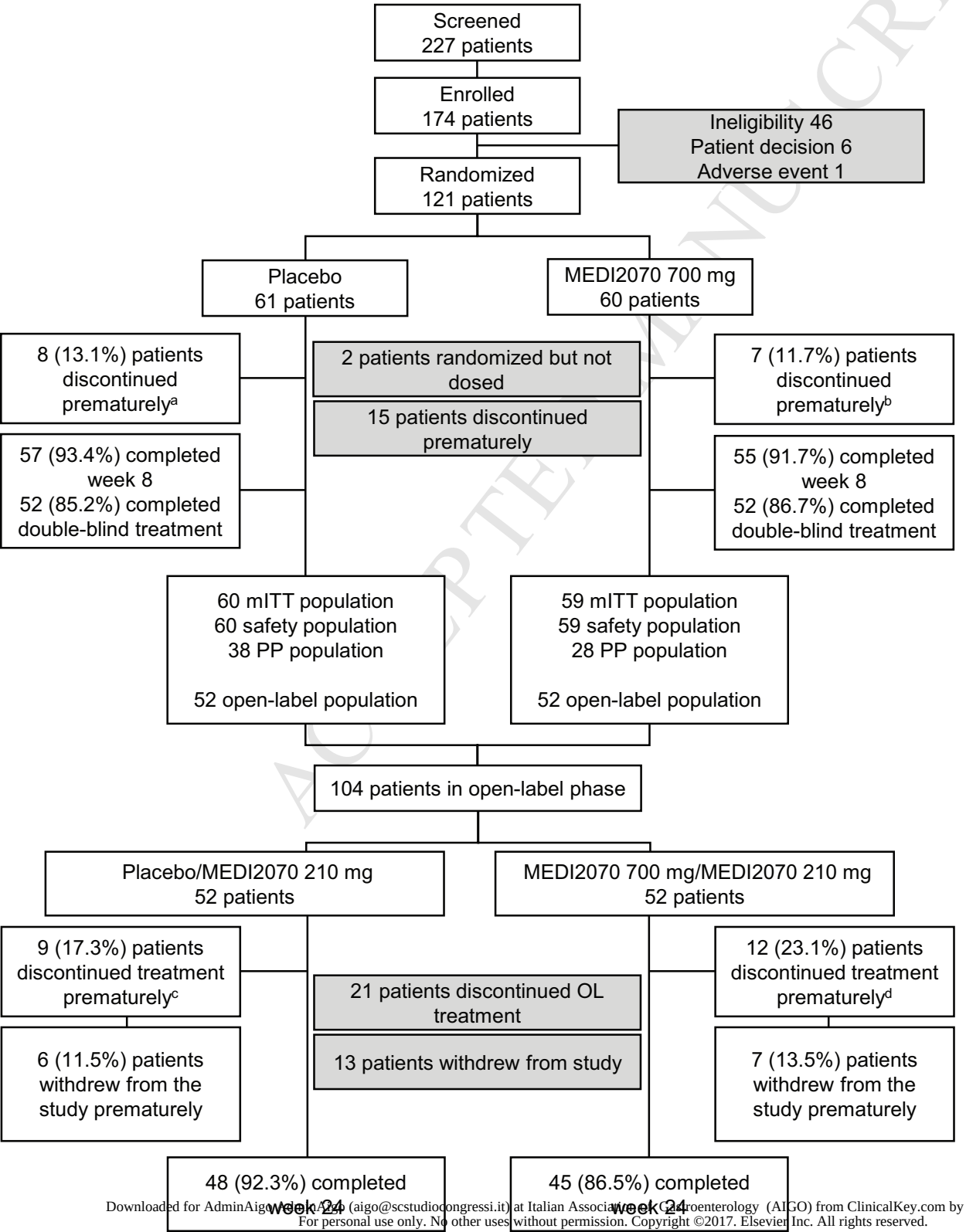
Table 3. Clinically Significant Infections in the Double-blind Period (Through Week 12)

System Organ Class **Preferred Term**	**MEDI2070 700 mg** **(n = 59)**	**Placebo** **(n = 60)**	**Total** **(N = 119)**
Infections and infestations	4	11	15
Abdominal abscess	0	1	1
Bronchitis	1	0	1
Cellulitis	1	0	1
Clostridium difficile infection	0	1	1
Gastroenteritis	1	0	1
Sinusitis	0	4	4
Subcutaneous abscess	1	0	1
Sweat gland infection	0	1	1
Tooth abscess	0	1	1
Tracheobronchitis	0	1	1
Urinary tract infection	0	1	1
Vulvovaginal mycotic infection	0	1	1

Table 4. Change From Baseline in Fecal Calprotectin and C-reactive Protein

Parameter	Least Squares Mean Placebo (n = 60)	Least Squares Mean MEDI2070 (n = 59)	Least Squares Mean Difference	95% CI	P value
Fecal calprotectin, µg/g					
Week 8	-47.9	-153.5	-105.6	-199 to -12.2	.027
Week 12	-55.1	-179.6	-124.6	-239.8 to -9.3	.034
C-reactive protein, mg/L					
Week 8	5.1	-12.6	-17.6	-30.4 to -4.9	.007
Week 12	-2.6	-13.4	-10.8	-18.9 to -2.8	.008

Values for fecal calprotectin were available for 52 and 42 patients in the placebo group and for 45 and 40 patients in the MEDI2070 group at weeks 8 and 12, respectively. Values for C-reactive protein (CRP) were available for 57 and 54 patients in the placebo group and for 55 and 52 patients in the MEDI2070 group at weeks 8 and 12, respectively. Missing data were accounted for statistically using the inverse probability weighting generalized estimating equations model.



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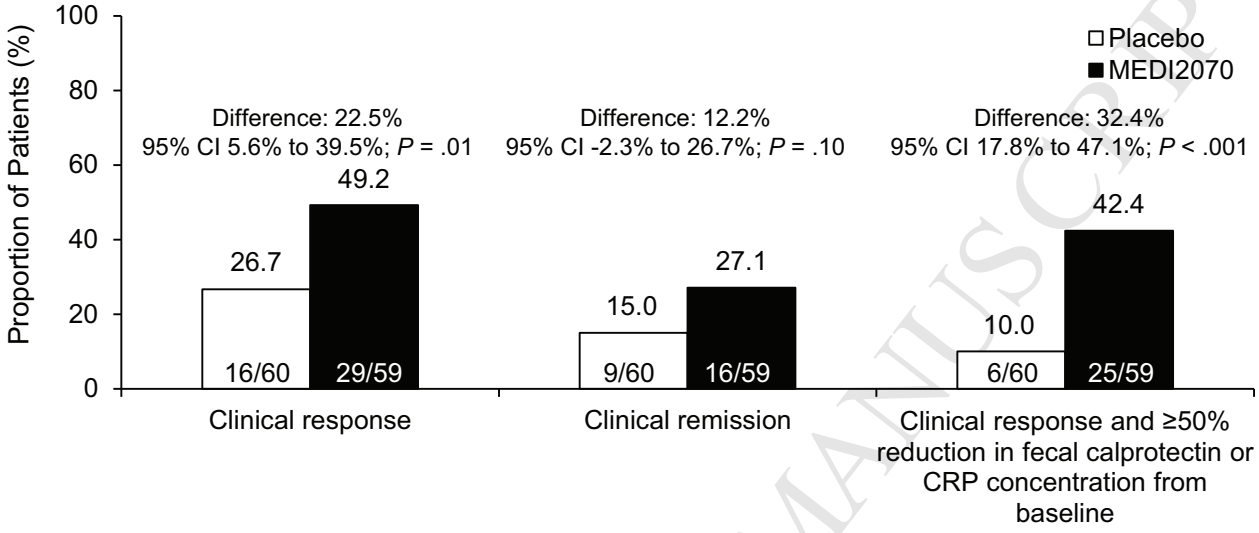

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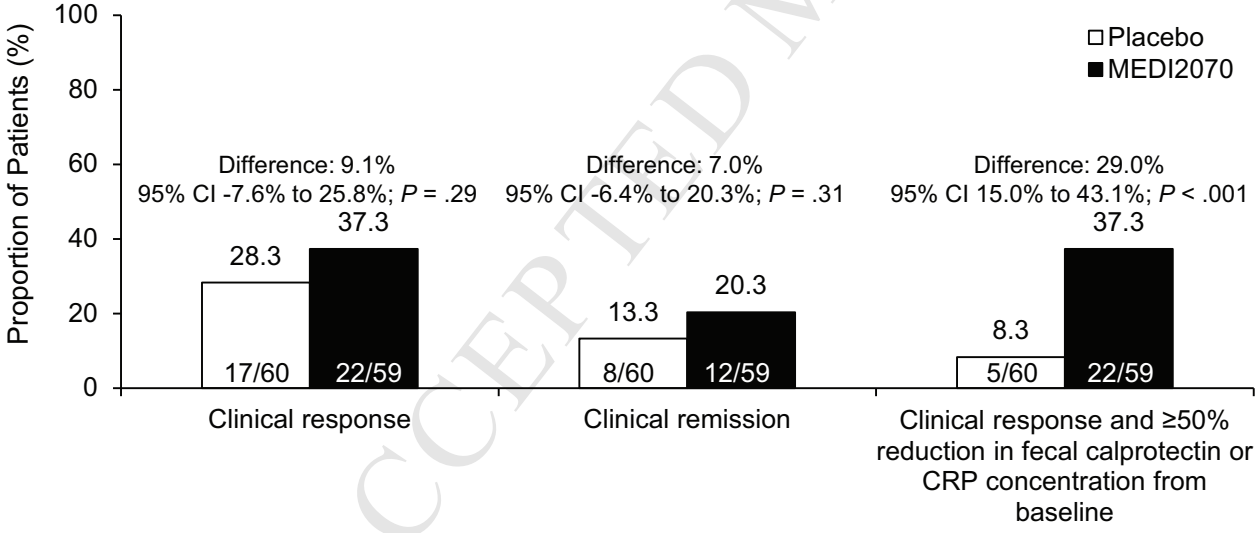

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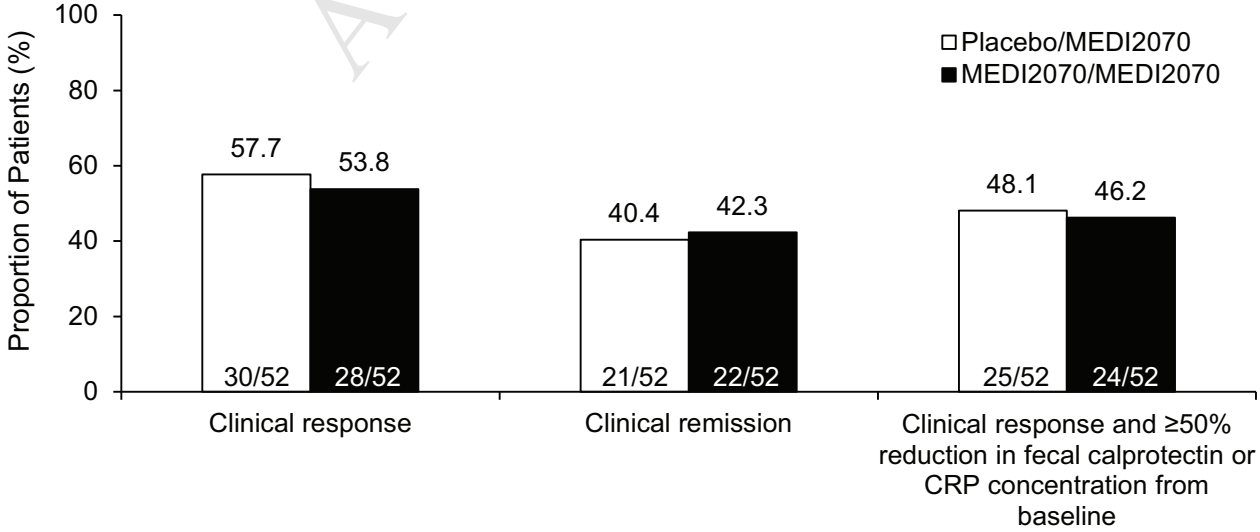

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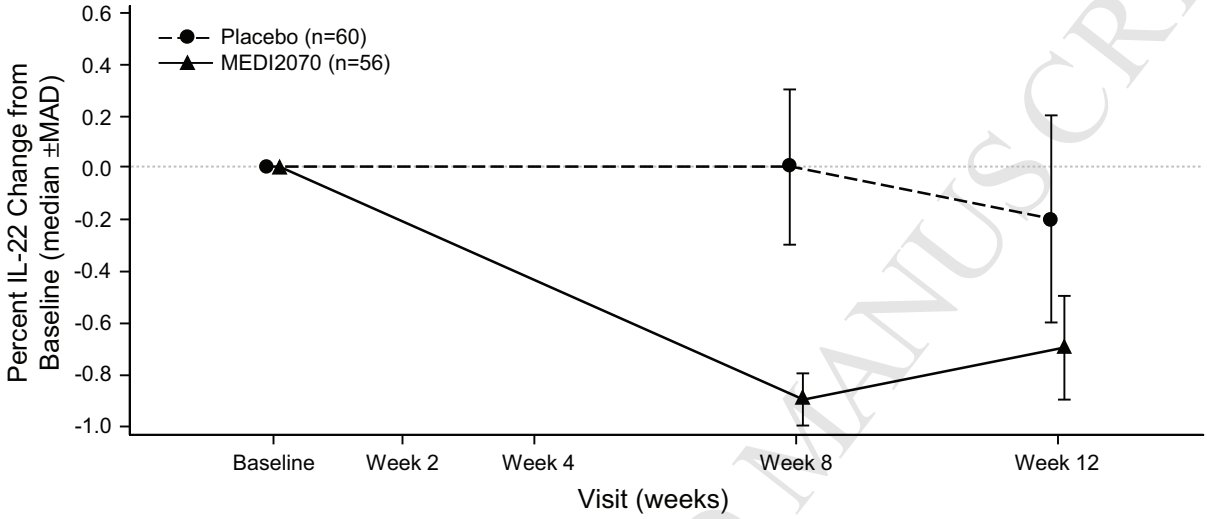

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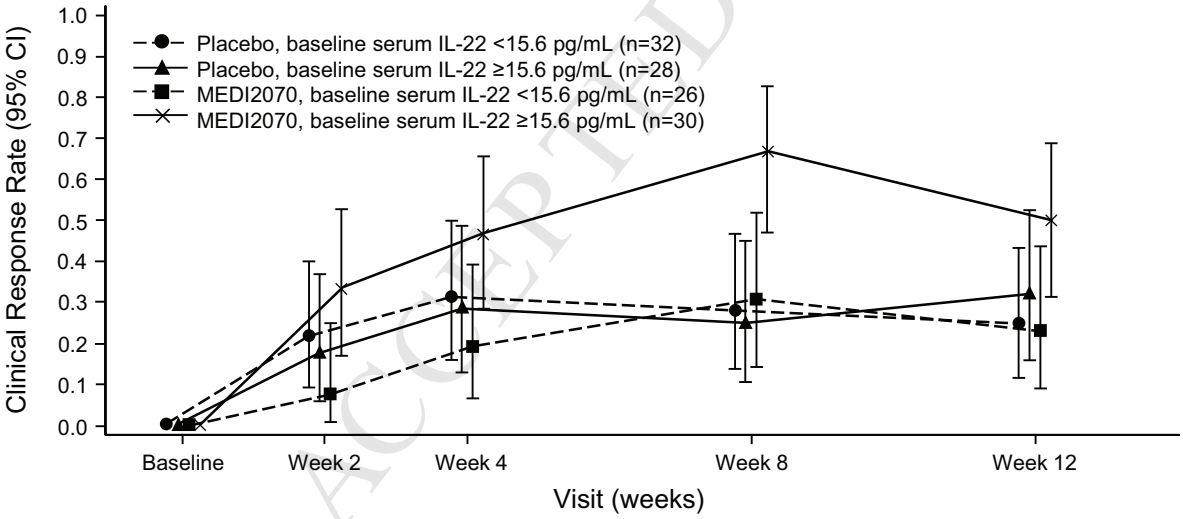

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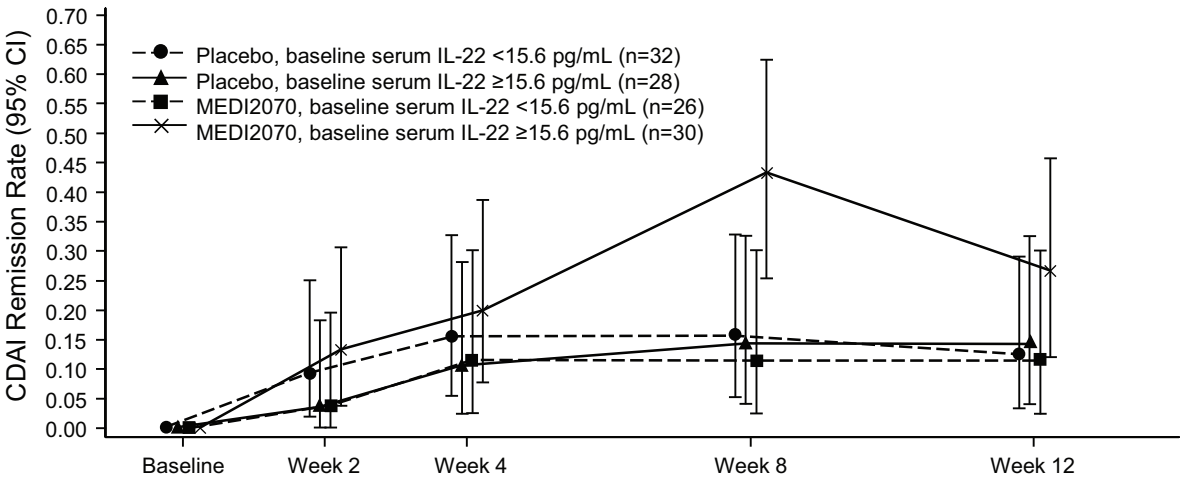

SUPPLEMENTARY APPENDIX

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Ethics Committees/Internal Review Boards That Approved the Study Protocol (With the Study Approval Numbers)

Canada: IRB Services, Autora, ON; Mount Sinai Hospital Ethics Committee, Toronto, ON; Ontario Hall Queens University, Kingston, ON; Ottawa Health Science Network Research Ethics Board, Ottawa, ON; University of Alberta Health Research Ethics Board, Edmonton, AB; Western University REB, London, ON; Protocol approval numbers do not apply in Canada.

Czech Republic: Ethics Committee FN Hradec Kralove, Hradec Kralove (201302 D02M); Eticka Komise ISCARE, Praha 7 (52/a); Eticka Komise Fakultni Nemocnice

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Hungary: Ethics Committee of Hungary–Central, Budapest (4386-0/2013-EKL)

Italy: CE Seconda Universitá degli Studi di Napoli, Naples (SUN-AORN OSPE, Prot. 179); Comitato Etico Indipendente Fondazione PTV Tor Vergata, Rome (37/13); Comitato Etico A O della Seconda Universitá di Napoli, Naples (Prot. 179); Comitato Etico A O Policlinico S Orsola-Malpighi, Bologna (26/2013/U/Sper); Comitato Etico dell' IRCCS Istituto Clinico Humanitas, Rozzano (CE ICH – 87/13); Comitato Etico Indipendente AOU Bologna, Bologna (26/2013/U/Sper); Comitato Etico dell' Universitá Cattolica del Sacro Cuore E, Rome (27376/13); Comitato Etico Universitá Cattolica Policlinico Gemelli, Rome (27376/13); Firenze–Comitato Etico Area Vasta Centro, Florence (833/13).

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Supplementary Text

Inclusion Criteria

The following criteria were also required for study inclusion: primary or secondary nonresponse or treatment intolerance to TNF antagonists defined as signs and symptoms of persistently active disease despite a history of at least one induction regimen of a TNF antagonist consisting of at least 2 doses at least 2 weeks apart (ie, primary nonresponse), initial response followed by loss of response with continued therapy (ie, secondary nonresponse), or history of intolerance to at least one TNF antagonist (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, infection); use of adequate birth control measures during the study and for 36 weeks after the last dose of study treatment**;** no known history of tuberculosis and a negative test for tuberculosis at screening, or no symptoms, a documented history of a completed course of adequate tuberculosis prophylaxis, no known exposure to a case of tuberculosis after prophylaxis, and no evidence of active tuberculosis on chest radiograph within 1 month of the first study dose for patients with either a positive purified protein derivative or positive or indeterminate QuantiFERON-TB test, or a chest radiograph with no evidence of active tuberculosis within 1 month of the first study dose for patients with a history of treatment with a TNF antagonist at least 1 year or who discontinued treatment with a TNF antagonist within 6 months of screening.

Exclusion Criteria

Exclusion criteria also included the following: previous allogenic bone marrow transplant or history of cell-based transplantation; clinical manifestation of short bowel syndrome (defined as requiring oral or parenteral supplemental or total nutrition to maintain stable body weight); a stricture with obstructive symptoms within 3 months, bowel surgery within 12 weeks, bowel perforation or evidence of noninflammatory obstruction within 6 months, or evidence of an infected abscess or fistula prior to first study dose; an ileostomy and/or colostomy; positive stool test for *C. difficile*; clinically significant concomitant systemic disease; prior treatment with a biologic agent targeting interleukin-12 or -23; treatment with cyclosporine, mycophenolate mofetil, sirolimus, thalidomide, or tacrolimus within 4 weeks, or topical aminosalicylic acid or topical steroids within 2 weeks prior to first study dose; intravenous or intramuscular steroids within 2 weeks or during screening; evidence of a recent (within 6 months of first study dose) systemic fungal infection, requiring inpatient hospitalization, or oral antifungals (within 14 days prior to first study dose); treatment for infection with intravenous or oral antibiotics or antivirals (within 14 days prior to first study dose); receipt of a live attenuated vaccine within 4 weeks of first study dose; positive test for hepatitis B virus surface antigen, hepatitis C virus antibody, or human immunodeficiency virus at screening; any underlying condition that predisposes to infections; known history of drug or alcohol abuse within 1 year of first study dose; history of cancer, except for basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy at least 12 months prior to screening; abnormal laboratory results at screening, including aspartate aminotransferase, alanine aminotransferase, or alkaline

phosphatase greater than 2.0 × upper limit of normal or total bilirubin greater than 1.5 × ULN (except for patients with Gilbert Syndrome), white blood cell count less than 3000 cells/mm^3, or hemoglobin less than 10 g/dL; current enrollment in another investigational device or drug study of less than 30 days or 5 half-lives, whichever is longer, since ending another investigational device or drug study(s), or receiving other investigational agent(s); donation or transfusion of blood, plasma, or platelets within 90 days prior to screening; or myocardial infarction or acute coronary syndrome within 12 months of screening.

Supplementary Table 1. Clinically Significant Infections in the Open-label Period (Week 12 to Week 24)

System Organ Class Preferred Term	MEDI2070 700 mg/ MEDI2070 210 mg (n = 52)	Placebo/ MEDI2070 210 mg (n = 52)	Total (N = 104)
Infections and infestations	13	13	26
Anal abscess	1	0	1
Bronchitis	2	2	4
Clostridium difficile colitis	1	0	1
Gingivitis	1	0	1
Mastoiditis	1	0	1
Esophageal candidiasis	1	0	1
Pelvic abscess	0	1	1
Peritonitis	0	1	1
Pharyngitis	1	0	1
Pharyngitis streptococcal	1	0	1
Pilonidal cyst	1	0	1
Sinusitis	0	3	3
Tonsillitis	0	2	2
Tooth abscess	0	1	1
Tooth infection	2	0	2
Upper respiratory tract infection	0	1	1
Urinary tract infection	1	2	3

Time Course of Responses

The mean change from baseline in the Crohn's Disease Activity Index (CDAI) in the mITT population (n = 119) during the double-blind period (to week 12) and in the open-label population (n = 104) to week 24 are shown in Supplementary Figures 1 and 2, respectively. Open-label treatment with MEDI2070 210 mg administered subcutaneously every 4 weeks began at week 12.

Supplementary Figure 1. Mean change from baseline in CDAI scores over time for the double-blind period (mITT population)

Error bars represent standard error.

Supplementary Figure 2. Mean change from baseline in CDAI scores over time for the double-blind and open-label periods (open-label population)

Pharmacokinetics

As shown in Supplementary Figure 3, MEDI2070 maximum mean serum concentration (194 µg/mL) was achieved at the end of the second infusion at week 4. In the open-label extension phase, MEDI2070 trough serum concentration at week 24 following 210 mg SC every 4 weeks was similar to the serum concentration at week 12 (13.8 vs 16.0 µg/mL). MEDI2070 concentration at week 24 also was similar between patients who received two 700-mg IV doses and those who received placebo during the induction phase (13.8 vs 16.0 µg/mL). No difference was observed for the serum MEDI2070 concentration levels between responders and nonresponders at weeks 8, 12, and 24 (Supplementary Figure 4).

Supplementary Figure 3. Mean (+ standard deviation) serum concentration-time profiles of MEDI2070 following intravenous administration of MEDI2070 700 mg at weeks 0 and 4 or placebo, followed by subcutaneous administration of MEDI2070 210 mg every 4 weeks from week 12.

Supplementary Figure 4. Individual concentration of MEDI2070 by CDAI response (*A* and *B*) and CDAI Remission (*C* and *D*) during the double-blind phase (*A* and *C*) and the open-label extension phase (*C* and *D*)