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Effects of Mongersen (GED-0301) on Endoscopic and Clinical Outcomes in Patients With Active Crohn's Disease

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GED-0301 is an antisense oligodeoxynucleotide with a sequence complementary to the *Smad7* mRNA transcript. Smad7 is a negative regulator of transforming growth factor-β, which is increased in the intestinal mucosa of patients with active Crohn's disease (CD). We randomly assigned 63 CD patients to 4-, 8-, or 12-week treatment groups receiving oral GED-0301 (160 mg/day). The primary objective was to determine GED-0301's effect on endoscopic CD measures; secondary objectives included effects on clinical activity. Endoscopic improvement was observed in 37% of participants with evaluable endoscopy results at week 12. At week 12, 32% (4 weeks), 35% (8 weeks), and 48% (12 weeks) of patients receiving GED-0301 were in remission (CD activity index score <150); corresponding reductions from baseline in mean CD activity index scores were −124, −112, and −133 points. No new safety signals were observed. These findings support a GED-0301 benefit in active CD. ClinicalTrials.gov no: NCT02367183.

Keywords: CDAI; Clinical Efficacy; IBD; Randomized.

Crohn's disease (CD) frequently affects the terminal ileum and/or proximal colon.[1] Smad7 is a key regulator of transforming growth factor-beta (TGF-β), a cytokine suppressing chronic inflammation.[2] In CD patients, high Smad7 concentrations in intestinal mucosa contribute to sustained production of pro-inflammatory cytokines by inhibiting TGF-β intracellular signaling.[3]

GED-0301 is an antisense oligodeoxynucleotide (21-mer) with a sequence complementary to the mRNA of Smad7. Although a phase 2 study showed potential GED-0301 efficacy in active CD, no endoscopic data were collected.[4] A recent consensus conference concluded the CD treatment target should comprise patient-reported outcomes (stool frequency, abdominal pain) and ileocolonoscopy,[5] given that endoscopic response is associated with prolonged clinical remission and reductions in hospitalizations and surgeries.[5–7] We report results from a 12-week, randomized study evaluating 3 GED-0301 treatment regimens in patients with active CD. The primary study objective was to explore the effect of GED-0301 on endoscopic outcomes; effects on clinical activity were secondary objectives.

Sixty-three CD patients from 34 international sites were randomized (1:1:1) to 4, 8, or 12 weeks of oral, blinded GED-0301 160 mg daily (Supplementary Materials and Methods; Supplementary Figure 1). Baseline characteristics were similar amongst the 3 groups, comprising approximately 20 patients each (Supplementary Table 1). In the overall population, mean age was 41.5 years; mean Crohn's disease activity index (CDAI) score, 294.4; mean Simple Endoscopic Score for Crohn's Disease (SES-CD), 11.2; mean high-sensitivity C-reactive protein (hsCRP) level, 12.6 mg/L; and mean fecal calprotectin, 1,606.7 mcg/g. Forty-six percent had prior tumor necrosis factor (TNF)-α antagonist exposure. In addition to ileal or right-sided colonic disease on ileocolonoscopy, 46% of patients had involvement distal to the mid-transverse colon. Fifty-four (86%) patients completed the 12-week induction phase: 15/19 (79%), 20/23 (87%), and 19/21 (91%) in the 4-, 8-, and 12-week treatment groups, respectively (Supplementary Figure 2). Fifty-two (83%) patients had evaluable endoscopy at week 12.

Among patients with evaluable endoscopy at week 12 (n = 52), 37% achieved endoscopic response (ie, reduction in SES-CD of $\geq$25% from baseline) (Figure 1*A*), with no meaningful difference between treatment groups (data not shown). Two patients had endoscopic remission (SES-CD $\leq$2), with SES-CD = 0 at week 12. Sixty-three percent of patients with greater baseline endoscopic disease severity (SES-CD >12) achieved endoscopic response (Figure 1*A*). Similar results were demonstrated when endoscopic response was defined as reduction from baseline in SES-CD $\geq$50% (Figure 1*B*). Endoscopic response (SES-CD reduction $\geq$25%) was greater in patients with no prior TNF-antagonist exposure (Figure 1*C*) and with proximal and distal disease (Figure 1*D*).

Figure 2 shows change in CDAI score for all patients receiving active treatment over time. All treatment groups had clinically relevant improvements as early as week 2. Mean changes from baseline in CDAI score at week 12 ranged from −112 to −133 points (Supplementary Figure 3); 48% in the 12-week treatment group achieved

Abbreviations used in this paper: **CD, Crohn's disease; CDAI, Crohn's disease activity index; hsCRP, high-sensitivity C-reactive protein; SES-CD, Simple Endoscopic Score for Crohn's Disease; TGF, transforming growth factor; TNF, tumor necrosis factor.**

Most current article

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

GED-0301 is an antisense oligodeoxynucleotide with a sequence complementary to the Smad7 mRNA transcript. Smad7 is a negative regulator of transforming growth factor-β which is increased in the intestinal mucosa of patients with active Crohn's disease (CD).

NEW FINDINGS

Endoscopic improvement was observed in 37% of CD participants randomly assigned to 4-, 8-, or 12-week treatment groups receiving oral GED-0301 (160 mg/day). At week 12, 32% (4 weeks), 35% (8 weeks), and 48% (12 weeks) of patients receiving GED-0301 were in remission (CD activity index score <150). No new safety signals were observed.

LIMITATIONS

A study period > 12 weeks may be needed to determine maximum benefit of GED-0301.

IMPACT

These findings are consistent with a GED-0301 benefit in active CD and support continued development of this agent.

clinical remission (CDAI <150), and 67% achieved clinical response (≥100-point CDAI reduction) (Supplementary Table 2). Similar results were obtained for clinical remission when defined only using clinical symptoms (stool frequency score ≤3; abdominal pain score ≤1), with the 12-week treatment group achieving the highest rate (43%) (Supplementary Table 2). Subset analyses showed greater clinical benefit in patients without prior TNF-α antagonist exposure (Supplementary Figure 4). Patients with lesser baseline disease severity (SES-CD ≤12 or CDAI score ≤300) and those with only proximal disease achieved greater clinical benefit (Supplementary Figure 4). Moderate correlation was observed between changes in CDAI and endoscopic scores ($r = 0.37$), which was more pronounced when patients with prior surgery were excluded ($r = 0.48$).

Reductions from baseline in biomarkers hsCRP and fecal calprotectin were observed in patients with increased values at baseline. Patients with baseline hsCRP ≥10 mg/L had median percent changes of −16.6% (week 4), −22.0% (week 8), and −10.2% (week 12). Patients with elevated baseline fecal calprotectin levels (>250 mg/kg) had median percent changes of −24.9% (week 4), −39.9% (week 8), and −31.4% (week 12).

Adverse event and serious adverse event rates were low and similar across groups (Supplementary Table 3). The

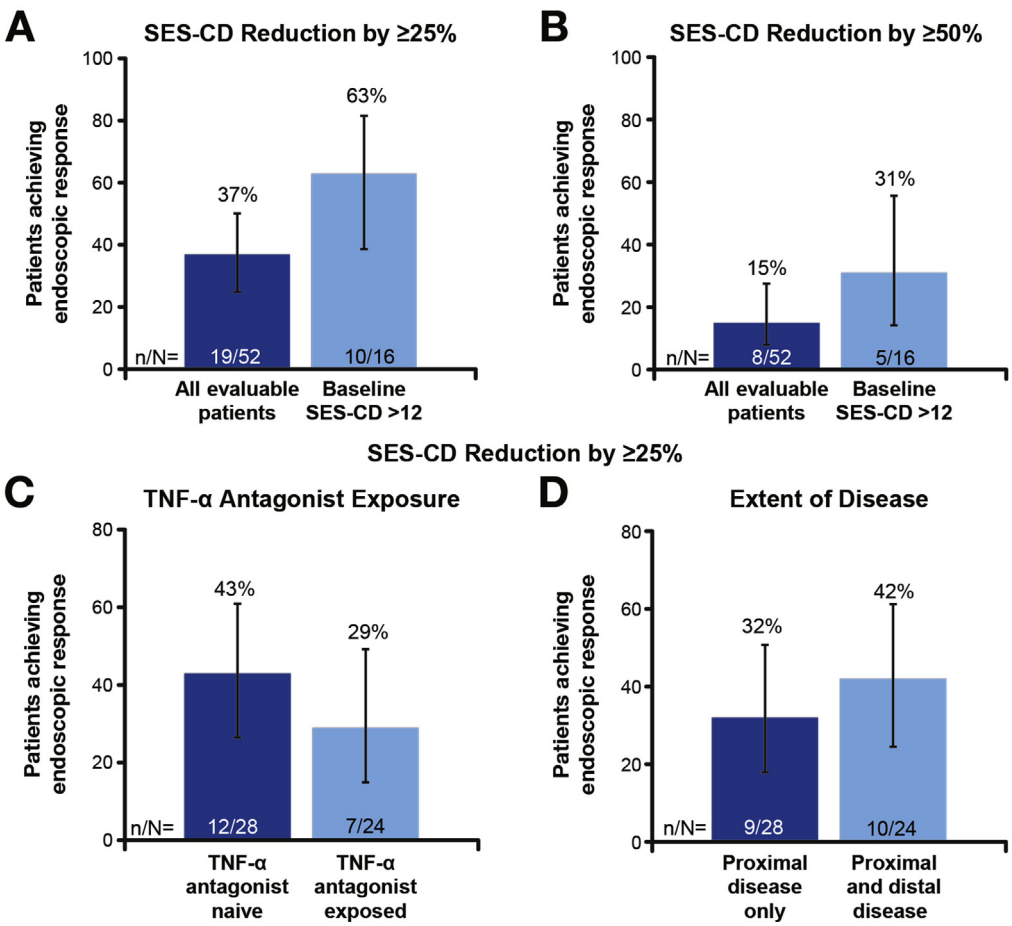

Figure 1. Week 12 endoscopic response: SES-CD reduction from baseline of (*A*) ≥25% and (*B*) ≥50%, and (*C*, *D*) SES-CD reduction from baseline of ≥25% in select patient subgroups. *Bars* indicate 95% CI. Data as observed.

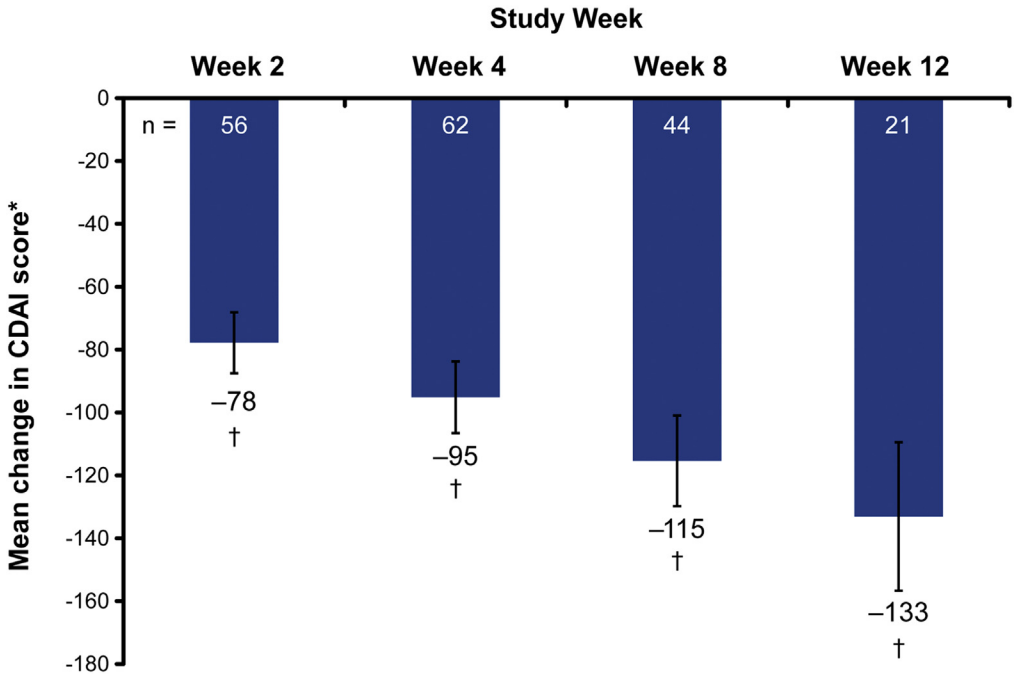

Figure 2. Mean change in CDAI score in all patients receiving active treatment through each time point. *CDAI mean change from baseline was determined in the intent-to-treat population using last-observation-carried-forward methodology. Bars indicate standard error. †$P < .0001$.

most frequent adverse events were gastrointestinal. Of 315 pharmacokinetic samples, only 2 had quantifiable drug plasma concentrations.

These results are consistent with the placebo-controlled study by Monteleone et al.[4] All 3 GED-0301 regimens showed rapid, clinically meaningful decreases in CDAI scores. Week 12 pooled reduction in scores for 4, 8, or 12 weeks of treatment was −123 points, similar to the 122-point reduction observed by Monteleone at week 12.[4] Our participants had endoscopically confirmed disease activity at entry, a criterion not required in the Monteleone study, and had more severe disease activity and prior TNF-α antagonist exposure. Lack of a placebo comparator in our study might have resulted in sufficient patient expectation bias to explain these favorable results; however, this possibility is unlikely given the magnitude of clinical benefit observed. A meta-analysis of 67 randomized controlled studies of diverse patient populations estimated a CDAI-defined pooled placebo remission rate of 18% (95% CI, 16%–21%)[8] compared with the 37% (week 8) and 38% (week 12) overall rates we observed, which were similar to those in controlled studies of effective induction drugs.[9] Longer treatment duration (4, 8, or 12 weeks) was associated with greater reductions in CDAI scores; moderate correlation was demonstrated between improvement in CDAI and SES-CD scores. Consistent therapeutic benefit for CDAI stool frequency and abdominal pain components was demonstrated (Supplementary Table 2). This study, the first to evaluate GED-0301's effects on endoscopic CD outcomes, showed results consistent with therapeutic benefit. Data were pooled to increase precision of estimation. Based on the predefined criterion (SES-CD reduction ≥25%), 37% with evaluable endoscopies had an endoscopically defined response, a benefit more pronounced in the subset with higher endoscopic disease activity at baseline (SES-CD >12), such that 63% of these patients met this endpoint. Patients with prior TNF antagonist exposure (surrogate for more refractory disease) were less likely to respond than those naïve to these agents (29% vs 43%). Absence of a placebo arm does not diminish the importance of our endoscopic findings, as centrally read endoscopic response in placebo patients is expected to be low (<15%), as evidenced in recently published and presented data.[10–12] However, these data should be interpreted cautiously because of limited experience available with endoscopic outcomes in CD induction trials. Sparse data for other agents suggest a treatment duration >12 weeks may be needed for optimal response.[6,13] GED-0301 has the potential to positively affect downstream regulatory mechanisms through TGF-β signaling, which may intrinsically require >12 weeks to achieve maximal benefit.[14]

GED-0301 safety and tolerability were consistent with previous experience; no important concerns were identified in this relatively small, short-term evaluation. Our results confirm systemic drug exposure is negligible in patients with more significant mucosal inflammation and longer treatment periods.

Our findings are consistent with a beneficial effect in active CD and support continued development of this agent.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2017.08.035.

References

1. Torres J, et al. Lancet 2016;389:1741–1755.
2. Monteleone G, et al. Gastroenterology 2005;129:1420–1429.
3. Monteleone G, et al. Mol Ther 2012;20:870–876.
4. Monteleone G, et al. N Engl J Med 2015;372:1104–1113.
5. Peyrin-Biroulet L, et al. Am J Gastroenterol 2015;110:1324–1338.
6. Ferrante M, et al. Gastroenterology 2013;145:978–986.
7. Colombel JF, et al. Gastroenterology 2017;152:351–361.
8. Jairath V, et al. Aliment Pharmacol Ther 2017;45:1021–1042.
9. Hanauer SB, et al. Gastroenterology 2006;130:323–333.
10. Feagan BG, et al. Lancet 2017;389:1699–1709.
11. Vermeire S, et al. Lancet 2017;389:266–275.
12. Sandborn WJ, et al. Gastroenterology 2017;152(suppl 1):S1308–S1309; Abstract 874.
13. Neurath MF, Travis SP. Gut 2012;61:1619–1635.
14. Laudisi F, et al. Curr Drug Metab 2016;17:303–306.

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Conflicts of interest
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Supplementary Materials

I. Materials and Methods

This randomized, double-blind, multicenter phase 1b study was designed to explore the efficacy of oral GED-0301 on endoscopic activity and clinical effects in both tumor necrosis factor (TNF)-α antagonist-naive and TNF-α antagonist-experienced patients with active Crohn's disease (CD). Men and women $\geq$18 years of age were eligible for inclusion if they met the following key inclusion criteria: active CD, defined as a Crohn's disease activity index (CDAI) score of $\geq$220 to $\leq$450 at screening; ileal, colonic, or ileocolonic CD; Simple Endoscopic Score for Crohn's Disease (SES-CD) $\geq$7 at screening, or SES-CD $\geq$4 for patients with ileitis only; and therapeutic failure or intolerance to $\geq$1 of the following: aminosalicylates, budesonide, systemic corticosteroids, immunosuppressants, or TNF-α antagonists. Key exclusion criteria were: Crohn's colitis restricted to the left colon; CD complications; surgical resection within the past 6 months or intra-abdominal surgery within the past 3 months; and prior treatment with $>$2 TNF-α antagonists or any prior treatment with integrin antagonists.

This study included a screening phase (up to 4 weeks); a 12-week, double-blind induction phase; an observation phase (up to 52 weeks); a 100-week extension phase; and a 4-week follow-up phase. This publication reports the results of the 12-week double-blind induction phase; the other phases of the study are ongoing. Eligible patients were randomized (1:1:1) to 4, 8, or 12 weeks of treatment with GED-0301 160 mg daily (Supplementary Figure 1).

The primary objective of this study was to evaluate endoscopic outcomes with GED-0301, as measured by SES-CD. Endoscopic assessments were carried out at baseline and week 12. Images were sent to a centralized reader for assessment, and the assessment was used to calculate the SES-CD. Endoscopic outcomes included endoscopic response, defined as $\geq$25% reduction in SES-CD from baseline, and endoscopic remission, defined as an SES-CD of $\leq$2 at week 12.

Secondary objectives included clinical activity of GED-0301, as measured by the CDAI, and safety and tolerability of GED-0301.

To assess clinical outcomes, an electronic diary was given to each patient at the first screening visit, and data on CD symptoms were collected from daily electronic diary records. Diary data were used to determine the CDAI score, the stool frequency score, and the abdominal pain score. Stool frequency was defined as the number of liquid or very soft stools per 24 hours. Abdominal pain was measured on a 4-point scale (0 = none; 1 = mild [aware but tolerable]; 2 = moderate [interferes with usual activities]; 3 = severe [incapacitating]). Clinical remission was defined as a CDAI score $<$150 at week 12. Remission of clinical symptoms was defined as a stool frequency score $\leq$3 or an abdominal pain score $\leq$1 at week 12. Clinical response was defined as a decrease in the CDAI score of $\geq$100 points from baseline.

GED-0301 is formulated as a gastro-resistant, delayed-release, pH-dependent tablet designed to deliver the active substance in the distal GI tract. This formulation is not intended to achieve systemic absorption, but rather to obtain a local release and therapeutic benefit directly on the intestinal inflammatory lesions. To assess systemic exposure to GED-0301, all enrolled participants underwent 2 blood draws at 4, 8, and 12 weeks, for a total of 6 blood specimens per patient. Blood draws occurred at 2 time points: pre-dose ($>$23 hours after the previous dose) and 1 to 6 hours post-dose.

The intent-to-treat population is the primary population for the efficacy analysis, whereas analysis of safety data is based on the safety population, which consists of all patients who were randomized and received at least 1 dose of GED-0301. Endoscopic analyses were carried out using data as observed methodology. Clinical remission (CDAI score $<$150), clinical response (decrease in CDAI score from baseline of $\geq$100), and remission of clinical symptoms (stool frequency score $\leq$3 and abdominal pain score $\leq$1) were determined using non-responder imputation methodology. For binary end points, 95% CIs for within-group estimates were calculated by the Wilson score method. For continuous endpoints, analysis of covariance was used for within-group estimation, with change from baseline as the response variable, treatment regimen (where applicable), and randomization stratification as factors and the baseline value as a covariate. No inferential testing for statistical significance in the safety analysis was performed.

The study protocol (GED-0301-CD-001) was approved by the institutional review board or ethics committee at each study center. Written informed consent was obtained from all patients before they underwent screening for eligibility.

II. GED-0301-CD-001 Study Investigators

Scott Lee (University of Washington, Seattle, WA); Jonathan Terdiman (UCSF Medical Center, San Francisco, CA); Gil Melmed (Cedars Sinai Medical Center, Los Angeles, CA); John Valentine (University of Utah, Salt Lake City, UT); Jeffry Katz (University Hospitals Cleveland Medical Center, Cleveland, OH); Gerald Dryden (University of Louisville, Louisville, KY); Sarah Glover (University of Florida, Gainesville, FL); Jason Hou (Baylor College of Medicine, Houston, TX); Kevin Casey (Rochester General Hospital, Rochester, NY); William Pandak (McGuire VA Medical Center, Richmond, VA); Alex Sherman (Concorde Medical Group, New York, NY); Timothy Ritter (Texas Digestive Disease Consultants, Southlake, TX); Valli Kodali (Cumberland Research Associates, Fayetteville, NC); Robert Herring (Nashville Gastro Specialists, Nashville, TN); Maria Abreu (University of Miami, Miami, FL); Douglas Wolf (Atlanta Gastroenterology, Atlanta, GA); Charles Sninsky (Florida Research Network, Gainesville, FL); Steven Klein (Trial Management Associates, Wilmington, NC); Ira Shafran (Shafran Gastroenterology Center, Winter Park, FL); Bruce Salzberg (Atlanta Gastroenterology Specialists, Atlanta, GA); Paul Moayyedi (Hamilton Health Science Center, Hamilton, ON, Canada); Andrew Singh (PerCuro Clinical Research,

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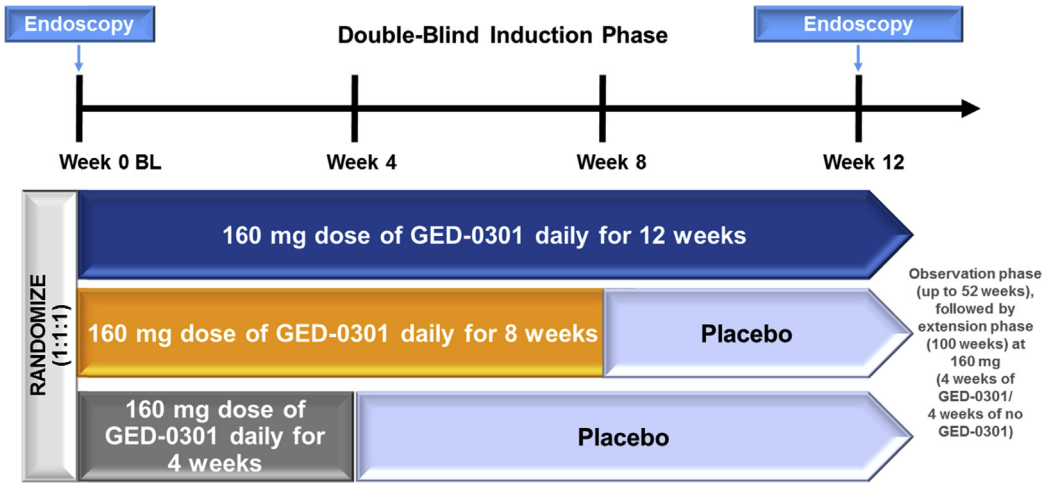
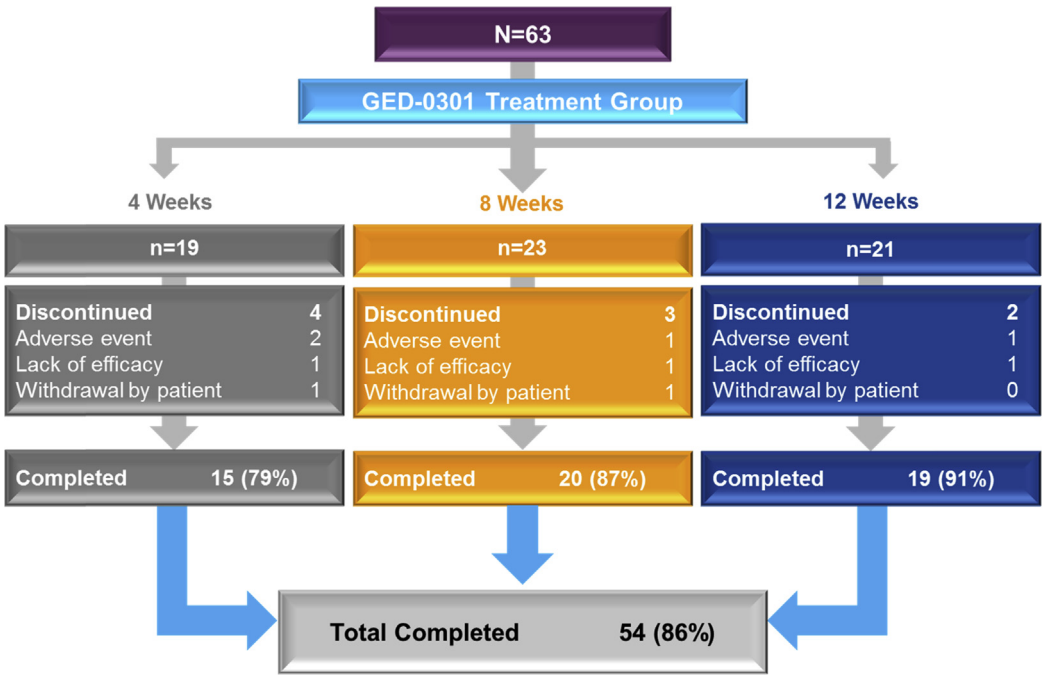
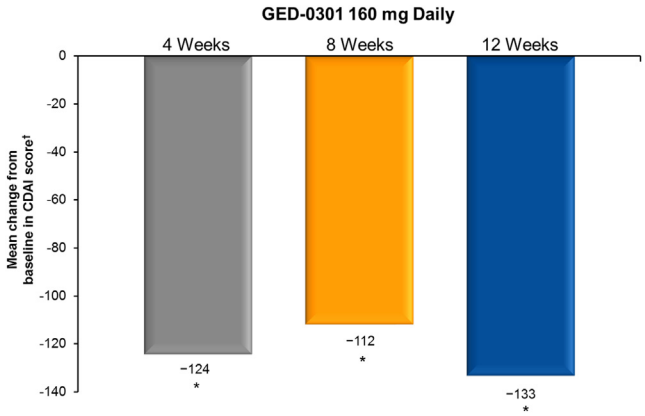


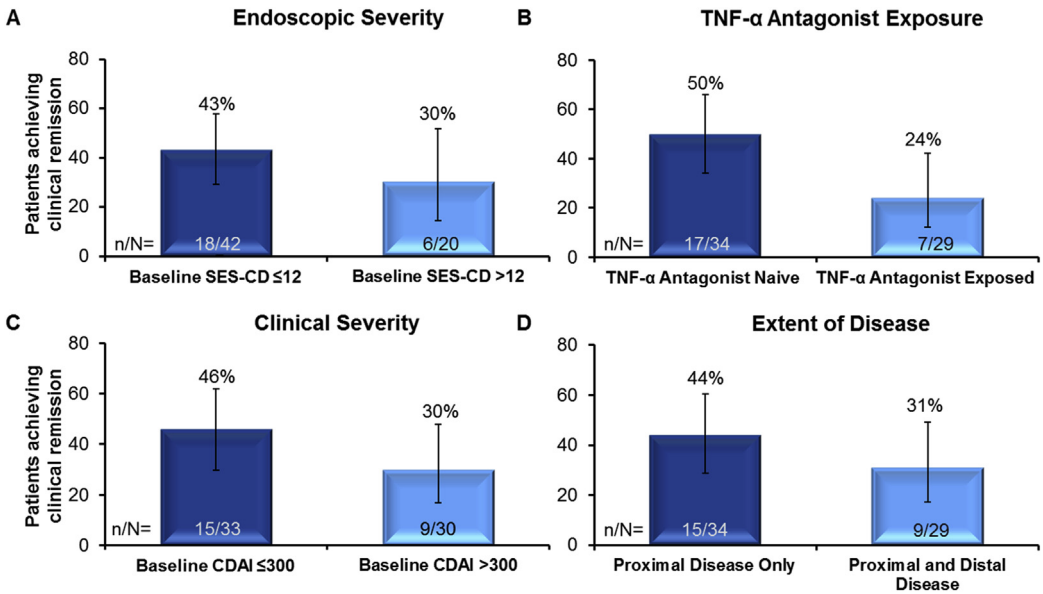
Supplementary Figure 1. Study design. Randomization stratified by distal colon involvement (yes/no) and prior biologic exposure (yes/no).



Supplementary Figure 2. Patient disposition through week 12. Note: 52 patients had an evaluable post-baseline endoscopy at week 12.



Supplementary Figure 3. Change from baseline in CDAI score at week 12 by treatment group. *$P < .0001$ vs baseline. †Mean change from baseline was determined in the intent-to-treat population using the last-observation-carried-forward methodology.



Supplementary Figure 4. Clinical remission (CDAI score <150) by patient subgroup at week 12 (all patients). Bars indicate 95% CIs. Remission (CDAI <150) at week 12 was determined in all patients regardless of randomized group using the non-responder imputation methodology.

Supplementary Table 1. Baseline Patient Demographics and Disease Characteristics

	GED-0301 160 mg daily			
Intent-to-Treat Population	4 Weeks N = 19	8 Weeks N = 23	12 Weeks N = 21	Total N = 63
Age, mean (SD), *y*	41.9 (16.2)	41.6 (15.3)	41.0 (14.4)	41.5 (15.0)
Female, %	42	61	57	54
Duration of CD, mean (SD), *y*	11.1 (12.1)	10.8 (13.0)	13.0 (14.1)	11.6 (13.0)
Disease inclusive distal to mid-transverse colon, %	42	52	43	46
TNF-α antagonist exposed, %	42	48	48	46
Corticosteroids,[a] %	32	26	19	25
CDAI score, mean (SD)	294.1 (81.1)	302.7 (60.7)	285.6 (74.9)	294.4 (71.3)
SES-CD (centrally read), mean (SD)	11.5 (8.2)	11.0 (6.7)	11.1 (6.9)	11.2 (7.2)
Daily stool frequency score, mean (SD)	5.2 (2.7)	5.2 (2.6)	5.8 (2.7)	5.4 (2.6)
Daily abdominal pain score, mean (SD)	1.7 (0.54)	1.9 (0.36)	1.8 (0.44)	1.8 (0.45)
hsCRP, mean (SD), *mg/L*	11.7 (12.6)	12.6 (22.6)	13.5 (12.4)	12.6 (16.6)
Fecal calprotectin, mean (SD), *mcg/g*	1,858.9 (2243.6)	1005.5 (962.0)	2023.5 (2067.2)	1606.7 (1837.2)

CD, Crohn's disease; CDAI, Crohn's disease activity index; hsCRP, high-sensitivity C-reactive protein; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor.
[a]Oral prednisone ($\leq$20 mg/day or equivalent) or budesonide $\leq$9 mg/day was permitted during the induction phase, provided that the dose was stable for the 3 weeks prior to screening.

Supplementary Table 2. Clinical Remission (Defined as Either CDAI Score $<$150 or Stool Frequency Score $\leq$3 and Abdominal Pain Score $\leq$1) and Clinical Response (CDAI Decrease $\geq$100) at Week 12 by Treatment Group

	GED-0301 160 mg daily		
	4-Week treatment	8-Week treatment	12-Week treatment
Clinical remission (CDAI $<$150) at week 12, *n/N* (%)	6/19 (32)	8/23 (35)	10/21 (48)
Clinical remission (stool frequency scores $\leq$3 and abdominal pain scores $\leq$1) at week 12, *n/N* (%)	5/19 (26)	7/23 (30)	9/21 (43)
Clinical response (CDAI decrease $\geq$100), *n/N* (%)	10/19 (53)	10/23 (44)	14/21 (67)

NOTE. Determined using the non-responder imputation methodology.

Supplementary Table 3. Overview of Adverse Events

	GED-0301 (160 mg daily)			
Study Population, n (%)	4 Weeks N = 19	8 Week N = 23	12 Week N = 21	Total N = 63
≥1 Adverse event	13 (68)	16 (70)	12 (57)	41 (65)
Drug-related adverse events	3 (16)	4 (17)	2 (10)	9 (14)
Adverse events leading to discontinuation	2 (11)	1 (4)	1 (5)	4 (6)
Serious adverse events[a]	1 (5)	1 (4)	1 (5)	3 (5)
Deaths	0	0	0	0

[a]One drug-related serious adverse event was reported (intestinal obstruction/perforation at day 15 in a patient with a history of terminal ileum stricture by computed tomography who had significant baseline ileal stenosis).