Filgotinib for the Treatment of Small Bowel Crohn's Disease: The DIVERGENCE 1 Trial

Crohn's disease (CD) presents as chronic inflammation occurring anywhere in the gastrointestinal tract. The majority of patients have small bowel (SB) involvement with or without accompanying colitis.[1]

There is increasing evidence of differences in the biology of small bowel Crohn's disease (SBCD) vs colonic CD, with studies showing SBCD to be more refractory (eg, with slower endoscopic and magnetic resonance enterography [MRE] healing) to current therapies.[1–3]

Ileocolonoscopy offers limited information on the severity of SB mucosal inflammation and misses the transmural disease component. Therefore, MRE is used to complement the assessment of SBCD.[4] The validated magnetic resonance index of activity (MaRIA) was developed to score bowel wall thickness, bowel wall contrast enhancement after gadolinium injection, ulceration, and mural edema.[5] Transmural healing in CD (ie, resolution of abnormalities shown on MRE), assessed using MaRIA, is increasingly being recognized as a treatment goal.[6] However, it has not been formally evaluated as a primary endpoint in a clinical trial.

Filgotinib is a Janus kinase 1 (JAK1) preferential inhibitor previously shown to induce clinical and endoscopic remission in patients with active CD in a phase 2 trial.[7] We evaluated filgotinib efficacy and safety in patients with SBCD in the phase 2, double-blind, placebo-controlled, multicenter DIVERGENCE 1 trial (ClinicalTrials.gov identifier NCT03046056). Adults with moderately to severely active CD (Crohn's disease activity index [CDAI] of 200–450); active inflammation in at least 1 SB segment on MRE (segmental MaRIA [MaRIAseg], $\geq$7); and prior failure of corticosteroids, immunomodulators, tumor necrosis factor inhibitors, vedolizumab, or ustekinumab were randomly assigned (2:2:1) to receive filgotinib 200 mg, filgotinib 100 mg, or placebo orally once daily for up to 24 weeks. Treatment assignment was stratified based on concomitant corticosteroid and/or immunomodulator use and prior exposure to biologics, which were discontinued before screening.

Clinical nonresponders at week 10 (<70-point reduction in CDAI from baseline or no CDAI of <150 at any point up to and including week 10) and those with disease worsening after week 10 ($\geq$100-point increase in CDAI from week 10 and CDAI of $\geq$220 at 2 consecutive visits) discontinued treatment. The primary endpoint was the proportion of patients achieving clinical remission (CDAI of <150) at week 24. Secondary 24-week endpoints included patient-level SB MaRIA remission (MaRIAseg of <7 in all SB segments) and segment-level MaRIA remission in the terminal ileum, distal ileum, and/or jejunum (MaRIAseg of <7 in segments with baseline MaRIAseg of $\geq$7). MRE was read centrally with a single read. To our knowledge, this is the first clinical trial in SBCD to use serial MRE instead of endoscopy. Thus, the trial was exploratory in nature. Further details are provided in the Supplementary Methods.

In total, 78 patients were randomized, and 43 (55.1%) completed the study (Supplementary Figure 1). Overall, 32 of 78 (41.0%) patients had a history of CD-related strictures, 43 of 78 (55.1%) had a history of CD surgery, and 30 of 78 (38.5%) had previously received at least 3 biologic agents (Supplementary Table 1). At baseline, 68 of 78 (87.2%) had active disease in the terminal ileum (61 of 78 [78.2%] had ulcerative lesions, defined as MaRIAseg of >11), 24 of 78 (30.8%) in the distal ileum (22 of 78 [28.2%] had ulcerative lesions), and 17 of 78 (21.8%) in the jejunum (8 of 78 [10.3%] had ulcerative lesions).

Clinical remission at week 24 was attained in 3 of 18 (16.7%) patients receiving placebo, 8 of 32 (25.0%) receiving filgotinib 100 mg, and 7 of 28 (25.0%) receiving filgotinib 200 mg (difference not statistically significant) (Figure 1A). Week-24 SB MaRIA remission was observed in 0 of 18 patients treated with placebo, 2 of 32 (6.3%) receiving filgotinib 100 mg, and 2 of 25 (8.0%) receiving filgotinib 200 mg (Figure 1B). All 4 patients with MaRIA remission were also in clinical remission. Segment-level MaRIA remission results are shown in Figure 1C–E. Inflammatory biomarkers improved dose-dependently from baseline to week 24 (Figure 1F and G). Adverse events were experienced by 13 of 18 (72.2%) patients receiving placebo, 27 of 32 (84.4%) receiving filgotinib 100 mg, and 25 of 28 (89.3%) receiving filgotinib 200 mg. No deaths or cardiovascular events were reported.

In this unique proof-of-concept study in SBCD, 24 weeks of treatment with filgotinib did not result in statistically significant differences vs placebo in the proportion of patients who achieved clinical remission, SB MaRIA remission, or MaRIA remission in any of the SB segments. The numbers of patients who achieved MaRIA remission were very low, representing fewer than a quarter of those with clinical remission, although more pronounced inflammatory biomarker responses suggest a pharmacodynamic treatment effect. Filgotinib 100 mg and 200 mg were generally well tolerated in this patient population.

Although filgotinib and other JAK1 inhibitors (ie, upadacitinib) have been shown to induce clinical remission and
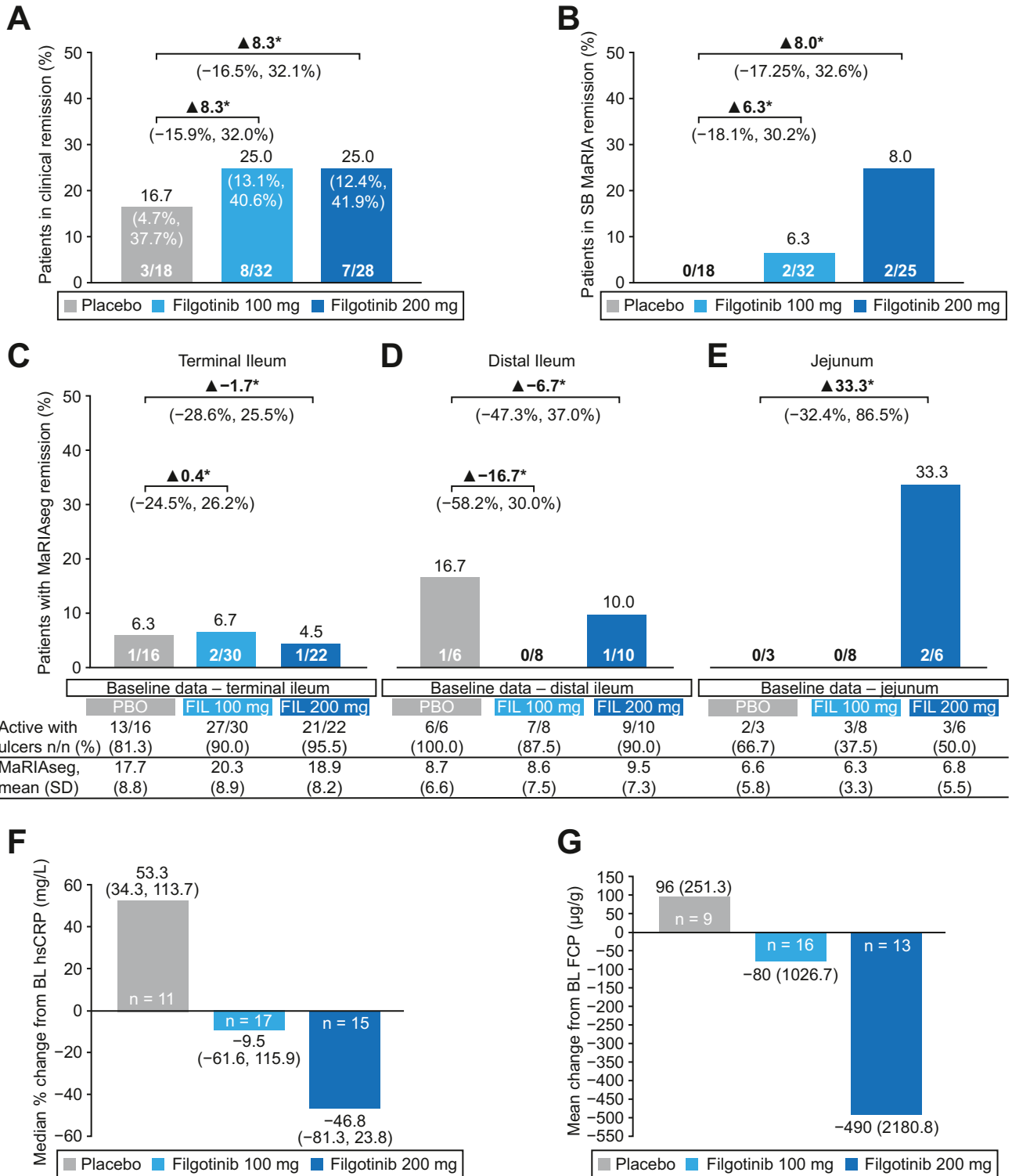
Figure 1. DIVERGENCE 1 efficacy results. (*A*) Proportions (90% CI) of patients in clinical remission (CDAI of <150) at week 24 (full analysis set). (*B*) Proportions of patients in SB MaRIA remission (MaRIAseg of <7 at week 24 in each of the SB segments [terminal ileum, distal ileum, and jejunum]) at week 24 (full analysis set). (*C–E*) Proportions of patients in segment-level MaRIA remission (MaRIAseg of <7 among segments with baseline MaRIAseg of ≥7) at week 24 in the (*C*) terminal ileum, (*D*) distal ileum, and (*E*) jejunum (full analysis set). (*F*) Median (interquartile range) percent change from baseline hsCRP concentrations at week 24 (biomarker analysis set). (*G*) Mean (SD) change from baseline FCP concentrations at week 24 (biomarker analysis set). *Risk difference in proportions (90% CI; nonresponder imputation). BL, baseline; CI, confidence interval; FCP, fecal calprotectin; FIL, filgotinib; hsCRP, high-sensitivity C-reactive protein; PBO, placebo; SD, standard deviation.

improve endoscopic outcomes in patients with CD,[7–9] it is possible that filgotinib may not be effective for the treatment of SBCD. There may also have been several other reasons why DIVERGENCE 1 did not meet its endpoints. First, discontinuation of patients with clinical "nonresponse" at week 10 led to a relatively small number of patients completing the 24-week treatment course and, hence, a heavily underpowered study.

Second, the stringency of the MaRIA remission endpoint, which had not been formally assessed as a primary endpoint in a clinical trial, may not have allowed an observation of treatment effects. Evidence suggests that transmural normalization does not occur in a significant proportion of patients with SBCD.[10] The application of different MaRIA thresholds or MRE-based endpoints (eg, MaRIA of <11 or intraclass correlation analysis based on visual analog scales) warrants future analysis. MRE-based endpoint research should also focus on better understanding how sensitive to change the various MaRIA components are because some may be more sensitive than others to short-term and midterm changes.

Third, failure to meet its endpoints could also have been driven by slower, less complete healing of SBCD vs colonic disease. This has been observed in other trial populations with longstanding refractory disease, albeit with drugs that have different modes of action from filgotinib.[11,12] However, no formal analysis of the colon was performed in DIVERGENCE 1, and therefore, we cannot be certain of the degree of colonic inflammation in this study, nor do we know if there were greater rates of healing in the colon than in the SB.

In summary, despite not meeting its endpoints, DIVERGENCE 1 may help inform the design of future trials assessing drugs for SBCD. A longer treatment exposure and follow-up may be necessary for efficacy assessment of patients with refractory SBCD. Moreover, further analysis of DIVERGENCE 1 data may yield insights into the optimal application of the MaRIA remission score and/or its components as a primary endpoint in SCBD clinical trials.

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.2023.03.234.

GEERT R. D'HAENS
Department of Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, the Netherlands

SCOTT LEE
Division of Gastroenterology
University of Washington
Seattle, Washington

STUART A. TAYLOR
Center for Medical Imaging
University College London
London, United Kingdom

ADRIAN SERONE
Gilead Sciences Inc
Foster City, California

JORDI RIMOLA
Inflammatory Bowel Disease Unit
Department of Radiology
Hospital Clinic of Barcelona
Barcelona, Spain

JEAN-FREDERIC COLOMBEL
The Dr. Henry D. Janowitz Division of Gastroenterology
Icahn School of Medicine at Mount Sinai
New York, New York

DIVERGENCE 1 STUDY GROUP

References

1. Atreya R, et al. Nat Rev Gastroenterol Hepatol 2021; 18:544–558.
2. Narula N, et al. Am J Gastroenterol 2022; 117:1106–1117.
3. Rimola J, et al. Aliment Pharmacol Ther 2020; 52:1563–1573.
4. Kumar S, et al. J Crohns Colitis 2022;16:1531–1539.
5. Rimola J, et al. Gut 2009;58:1113–1120.
6. Turner D, et al. Gastroenterology 2021;160:1570–1583.
7. Vermeire S, et al. Lancet 2017;389:266–275.
8. Danese S, et al. Lancet 2022;399:2113–2128.
9. Galápagos. https://www.glpg.com/press-release/3766/galapagos-announces-topline-results-from-phase-3-diversity-trial-of-filgotinib-in-crohn-s-disease. Accessed February 28, 2023.
10. Lafeuille P, et al. Aliment Pharmacol Ther 2021; 53:577–586.
11. Danese S, et al. Gastroenterology 2019;157:1007–1018.
12. Rimola J, et al. Oral presentation 175. Presented at the 26th United European Gastroenterology Week; October 20–24, 2018; Vienna, Austria.

RESEARCH LETTERS

Data Availability
Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non–conflict of interest. The request proposal must also include a statistician. Approval of such requests is at the discretion of Gilead Sciences and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

Supplementary Methods

Study Design

The DIVERGENCE 1 study (ClinicalTrials.gov identifier NCT03046056), which took place from April 11, 2017, until July 20, 2020, was a phase 2, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of filgotinib for the treatment of patients with SBCD.

It was planned that up to 100 men and nonpregnant, nonlactating women would be enrolled in this study. Patients were recruited from 39 study centers in 12 countries. Following a 30-day screening period, patients were randomized using a central interactive voice/web response system (2:2:1) to receive filgotinib 200 mg (and placebo-to-match [PTM] filgotinib 100 mg), filgotinib 100 mg (and PTM filgotinib 200 mg), or placebo (and PTM filgotinib 200 mg and 100 mg) orally once daily for up to 24 weeks. Men from the United States for whom ≥ 2 prior biologic therapies had not failed were randomized 2:1 to filgotinib 100 mg or placebo. Treatment assignment was stratified based on concomitant use of oral systemically absorbed corticosteroids, concomitant use of immunomodulators, and prior exposure to biologics.

Patients did not receive biologic therapy (ie, adalimumab, certolizumab/certolizumab pegol, infliximab, tumor necrosis factor [TNF] inhibitor biosimilars [to adalimumab, certolizumab/certolizumab pegol, or infliximab], natalizumab, vedolizumab, or ustekinumab) during screening or throughout study participation. Patients who completed all procedures per protocol were offered the option to continue into a separate long-term extension study. Nonresponders at week 10 (<70-point reduction in CDAI score from baseline or no CDAI score of <150 at any point up to and including week 10) and patients with disease worsening after week 10 ($\geq$100-point increase in CDAI score from week 10 and CDAI score of $\geq$220 at 2 consecutive visits) were discontinued and offered open-label filgotinib in the long-term extension study.

DIVERGENCE 1 was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Patients

The key inclusion criteria were patients aged 18−75 years with a documented diagnosis of CD for at least 6 months (by imaging, histopathology report, or ileoscopy report); moderately to severely active CD (CDAI score, 200–450) at screening; the presence of diseased SB segments on MRE with a MaRIAseg score of ≥ 7 in the terminal ileum, distal ileum, and/or jejunum; and an inadequate clinical response, loss of response, or intolerance to prior corticosteroids, immunomodulators, TNF inhibitors, vedolizumab, or ustekinumab.

Endpoints

The primary endpoint was the proportion of patients achieving clinical remission (CDAI score of <150) at week 24. Secondary endpoints included the proportion of patients with patient-level SB MaRIA remission (MaRIAseg score of <7 in each of the SB segments) at week 24 and the proportion of patients with segment-level MaRIA remission in the terminal ileum, distal ileum, and/or jejunum (MaRIAseg score of <7 among segments with baseline MaRIAseg score of ≥ 7). Changes from baseline in biomarker (serum high-sensitivity C-reactive protein or fecal calprotectin) concentrations were also assessed.

Assessments to determine the safety of filgotinib included documentation of adverse events (AEs), concomitant medications, vital signs, clinical laboratory evaluations (hematology, chemistry, urinalysis), and electrocardiograms.

Statistical Analysis

The full analysis set included all randomized patients who took at least 1 dose of the study drug. For the primary endpoint, the number and proportion of patients achieving clinical remission at week 24 for each treatment group was summarized with corresponding 90% exact confidence intervals based on the binomial distribution (Clopper-Pearson method). No formal hypothesis testing was performed. If patients had 3 or more of the 8 CDAI component subscores missing, they were considered to have insufficient data to determine their response status, and their CDAI score was considered missing. If patients had 1 or 2 components missing, then the missing component was imputed by the last observation carried forward method using the component score from the most recent analysis visit. If the component score from the most recent analysis visit was also missing, the missing value was imputed with the corresponding baseline component score.

Nonresponder imputation was used for the analysis of binary endpoints. Patients were considered nonresponders if they did not have sufficient measurements to evaluate the specific endpoint.

For secondary binary endpoints, the same statistical analysis method was used as for the primary endpoint. Continuous endpoints were summarized using descriptive statistics by treatment group and analysis visit. An analysis of covariance model, which included treatment and stratification factors as fixed-effect factors and baseline values as covariates, was implemented.

For patient-level SB MaRIA remission, if MaRIAseg scores at week 24 were missing for more than 1 SB segment identified at baseline, the patient was considered a nonresponder. If data were missing at week 24 for 1 SB segment identified at baseline, then the last observation carried forward was used to impute the missing segment.

For segment-level MaRIA remission, if a segment identified at baseline had a missing MaRIAseg score at week 24, no imputation was performed. The patient was considered to have insufficient data to determine segment-level remission status and was treated as a nonresponder for that specific segment.

The safety analysis set included all patients who took at least 1 dose of the study drug. AEs were summarized by

treatment group using descriptive statistics. Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1. AEs of interest were identified by either system organ class, standardized MedDRA queries, or Gilead MedDRA Search Term lists. AEs of interest included all infections, serious infections, herpes zoster infections, opportunistic infections, malignancies, gastrointestinal perforations, positively adjudicated major adverse cardiac events, arterial systemic thromboembolism, and venous thromboembolism. An independent cardiovascular safety endpoint adjudication committee periodically reviewed and adjudicated potential major adverse cardiac events and thromboembolic events.

The biomarker analysis set included all patients in the safety analysis set who had a baseline and at least 1 post-baseline measurement from 1 or more of the biomarkers. Biomarker data were summarized by treatment group using descriptive statistics.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).
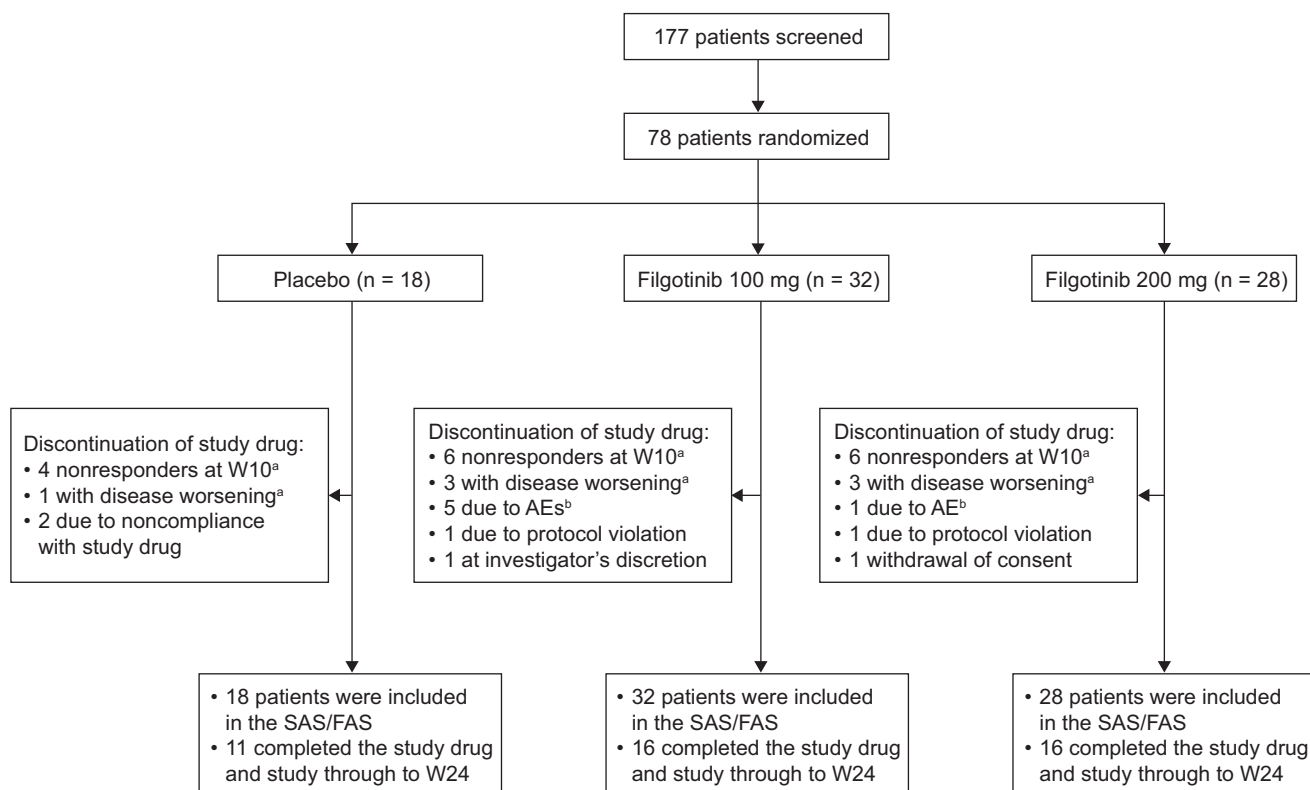
Supplementary Figure 1. DIVERGENCE 1 study design. [a]Nonresponders at week 10 and those with disease worsening after week 10 had the option to receive open-label filgotinib in a separate long-term extension study. [b]AEs leading to discontinuation included CD (filgotinib 200 mg: 1 patient [3.6%]; filgotinib 100 mg: 2 patients [6.3%]), anemia (filgotinib 100 mg: 1 patient [3.1%]), anal abscess (filgotinib 100 mg: 1 patient [3.1%]), and pneumonia (filgotinib 100 mg: 1 patient [3.1%]). AE, adverse event; FAS, full analysis set; SAS, safety analysis set; W, week.

Supplementary Table 1. Demographic and Baseline Characteristics

Demographic and baseline characteristics	Placebo (n = 18)	Filgotinib 100 mg (n = 32)	Filgotinib 200 mg (n = 28)
Age, *y*, mean (SD)	45 (12.9)	42 (12.9)	46 (16.3)
Women, n (%)	9 (50.0)	23 (71.9)	19 (67.9)
Duration of CD from diagnosis, *y*, mean (SD)	11.2 (9.1)	14.6 (13.7)	10.6 (8.4)
CDAI score, mean (SD)	300 (63.7)	297 (64.9)	309 (55.7)
Active disease in terminal ileum, n (%)	16 (88.9)	30 (93.8)	22 (78.6)
Active disease in distal ileum, n (%)	6 (33.3)	8 (25.0)	10 (35.7)
Active disease in jejunum, n (%)	3 (16.7)	8 (25.0)	6 (21.4)
Active disease in ≥2 SB segments, n (%)	7 (38.9)	11 (34.4)	12 (42.9)
Ulcerative lesions in terminal ileum, n (%)	13 (72.2)	27 (84.4)	21 (75.0)
Ulcerative lesions in distal ileum, n (%)	6 (33.3)	7 (21.9)	9 (32.1)
Ulcerative lesions in jejunum, n (%)	2 (11.1)	3 (9.4)	3 (10.7)
Ulcerative lesions in ≥2 SB segments, n (%)	5 (27.8)	7 (21.9)	9 (32.1)
Terminal ileum MaRIAseg, mean (SD)	17.7 (8.8)	20.3 (8.9)	18.9 (8.2)
Distal ileum MaRIAseg, mean (SD)	8.7 (6.6)	8.6 (7.5)	9.5 (7.3)
Jejunum MaRIAseg, mean (SD)	6.6 (5.8)	6.3 (3.3)	6.8 (5.5)
Prior CD-related fistula, n (%)	5 (27.8)	7 (21.9)	7 (25.0)
Prior CD-related stricture, n (%)	7 (38.9)	12 (37.5)	13 (46.4)
Prior CD-related abscess, n (%)	3 (16.7)	3 (9.4)	7 (25.0)
High-sensitivity C-reactive protein, *mg/L*, mean (SD)	7.3 (9.9)	9.4 (9.6)	16.4 (20.0)
Fecal calprotectin, *μg/g*, mean (SD)	933 (1289.3)	867 (985.1)	1133 (1475.6)
Prior failure of TNF inhibitors, n (%)	11 (61.1)	17 (53.1)	17 (60.7)
Prior failure of vedolizumab, n (%)	5 (27.8)	8 (25.0)	6 (21.4)
Prior failure of ustekinumab, n (%)	7 (38.9)	4 (12.5)	14 (50.0)
Prior failure of TNF inhibitors + vedolizumab, n (%)	4 (22.2)	5 (15.6)	5 (17.9)
Number of prior biologic agents used ≥ 3, n (%)	6 (33.3)	8 (25.0)	16 (57.1)
Concomitant use of systemic corticosteroids only, n (%)	4 (22.2)	8 (25.0)	8 (28.6)
Concomitant use of immunomodulators only, n (%)	3 (16.7)	3 (9.4)	3 (10.7)
Concomitant use of corticosteroids and immunomodulators, n (%)	0	1 (3.1)	0
History of surgeries for CD, n (%)	11 (61.1)	16 (50.0)	16 (57.1)

NOTE. Active disease, MaRIAseg ≥ 7; ulcerative lesions, MaRIAseg ≥ 11.
SD, standard deviation; TNF, tumor necrosis factor.