SUPPLEMENTARY FILE

Randomised trial and open-label extension study of an anti-interleukin-6 antibody in Crohn's disease (ANDANTE I and II)

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METHODS

In the phase 2 randomised study, patients were screened at 128 sites across 18 countries (Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, New Zealand, Romania, Switzerland, UK and the USA).

Patients

Sub-groups of TNF experience

Relapsed patients included those who relapsed after an initial clinical response or remission to one or more anti-tumour necrosis factor (TNF) treatment(s) with an adequate dose and regimen. Non-responders were those who experienced no clinical response to one or more anti-TNF treatment(s) with adequate dose and regimen. Intolerant patients experienced clinically significant side effects, including hypersensitivity, to one or more anti-TNF treatment(s). The 'other' category was patients who discontinued one or more anti-TNF treatment(s) for reasons that could include financial or insurance-based issues.

Permitted and prohibited treatments

Patients could continue to receive mesalamine, immunosuppressive (azathioprine, 6-mercaptopurine or methotrexate) at stable doses for >6 weeks, and/or oral prednisone ≤20 mg/day or oral budesonide ≤6 mg/day. Corticosteroid dose tapering was permitted following clinical remission (CDAI score <150) or in response to adverse events. The regular use of nonsteroidal anti-inflammatory drugs was not permitted; however, occasional use of ibuprofen ≤800 mg on any day was allowed during the study.

Exclusion criteria

Exclusion criteria included: prior exposure to anti-interleukin-6 biologic agent, natalizumab, vedolizumab or an unapproved biologic agent (within the previous 12 months); any investigational procedure, drug or live vaccine within 4 weeks of baseline; diverticulitis or active fistulae or abscess. Computed tomography or magnetic resonance enterography was required within 6 months of screening to exclude active fistulae or abscess.

Sample size calculation

At the planning stage, assuming true CDAI-70 response rates of 35% with placebo and 60% with at least one PF-04236921 dose, a sample size of 240 patients (~60 per group) would have at least 78% probability to detect a greater CDAI-70 response rate with PF-04236921 versus placebo at Weeks 8 or 12. This calculation assumed that the family-wise error rate was controlled at one-sided 0.05 using the Bonferroni method for Weeks 8 and 12 (but did not account for the dose comparisons), and also counted a potential loss of about 3% in the overall power, introduced by a futility interim analysis.

End points

CDAI response and remission rates

The generalized linear mixed effects model (GLMM) is a pre-specified primary analysis method in the statistical analysis plan. Because the sample size is modest for phase 2, the GLMM analysis integrates all available data points (vs a landmark/cross-sectional analysis at a particular time point).[1, 2] The GLMM does not impute missing data; however, it does not ignore dropouts since it takes into account all available data. Multiplicity adjustment was applied for the CDAI-70 response rate for the two time points: Weeks 8 and 12 using the

Hochberg method of accounting for multiplicity only for the two time points (but not adjusting for doses). As per the pre-specified criteria in the statistical analysis plan, the results were considered to be statistically significant if the one-sided test p-value is less than 0.05 after consideration of the strategy for controlling the type I error. Outcomes for the 200 mg dose were analysed separately using the same GLMM. As a sensitivity (post-hoc) analysis and to align with the analyses commonly used for phase 3 studies, CDAI-70 and CDAI remission rate were also analysed using non-responder imputation (NRI) method.

Statistical comparisons for mean changes from baseline in CDAI scores at Weeks 2 through 12 were performed using a mixed effect repeated measures analysis, with treatment group, visit and treatment by visit as fixed effects, and a random effect for patient and baseline covariates.

Assessment of responders and non-responders (OLE)

At OLE study baseline, responders (CDAI-70 at Week 12) and non-responders could be enrolled. Mean change from baseline (and standard error) in Harvey-Bradshaw Index (HBI) score were assessed at each visit. In the OLE, responders were defined by one of the following: being a responder at baseline and maintaining response, or having a ≥3-point decrease in HBI in this study or from the baseline in the prior induction study. The HBI (online supplementary table S1) was selected for the long-term extension study as a simpler approach than the CDAI, given that it has a one-day recall period and the primary objective was safety rather than efficacy. Patients who discontinued from the treatment period were considered non-responders. The proportions (n, %) of patients who were HBI responders and remitters were analysed and reported using NRI analysis method.

Patients were considered to be adequately controlled if the HBI score was <8.

Pharmacokinetic, pharmacodynamic and immunogenicity assessments

In the induction study, serum was collected before dosing at baseline and every 2 weeks during the induction period and at follow-up visits and, except for the baseline visit, every 4 weeks in the open-label extension (OLE) study, for measurement of PF-04236921 concentrations (secondary end point) and C-reactive protein concentrations (exploratory end point). Serum samples were analysed for PF-04236921 concentrations using a validated enzyme-linked immunosorbent assay. Serum concentrations of PF-04236921 were plotted for all patients with at least one PF-04236921 concentration who received at least one treatment.

Serum samples were also collected for measurement of PF-04236921 anti-drug antibodies (ADAs) and neutralising antibodies (Nab), by semi-quantitative electrochemiluminescent immunoassay, at Weeks 4, 8, 12, 16, 24, 32 and 40 (induction study), and Weeks 8, 16, 24, 32, 40 and 48 (OLE), and at early withdrawal and postwithdrawal visits, and during the follow-up periods of the respective studies. Percentages of patients with ADAs and Nab were reported.

Faecal calprotectin was measured through stool samples collected every 4 weeks in the induction study and every 8 weeks in the OLE study.

Safety assessments

Investigators graded the severity of any events as mild, moderate or severe, and possible causality of the study drug. Standardised Medical Dictionary for Regulatory Activities Queries (SMQs) were used to identify cases of possible treatment-emergent gastrointestinal (GI) perforation, and included broad terms of perforation and abscess. Follow-up endoscopy was not mandated by protocol but was performed at the investigator's discretion in cases of worsening disease. Findings were not required to be reported into the study databases.

An independent Data Monitoring Committee (DMC) reviewed the safety data throughout the trial. For any cases of GI perforation or abscess, DMC members reviewed available information on concomitant medications, disease localisation and duration, surgical history and surgical/pathology reports.

RESULTS

Patient demographics

The proportion of patient screen failures was high with >65% of reasons for not meeting entry criteria based on C-reactive protein (CRP) <5 mg/L (44.4%), positive for *C. difficile* (12.5%), or CDAI score <200 (10.5%).

Since randomisation was not stratified according to current corticosteroid use, rates of use varied across groups, from 25.4% (10 mg) to 50.7% (placebo). Corticosteroid use was numerically lower in the 50 mg treatment group. All but one patient had the presence of ulcers at baseline based on endoscopy and, using the Simple Endoscopic Score for CD (SES-CD), the left colon was the most common of the sites of ulcer involvement (157/247 patients; 63.6%), followed by the ileum (148/247 patients; 59.9%). The SES-CD sub-scores for each of the sites of involvement were similar across the placebo, 10 and 50 mg groups.

Efficacy of induction therapy

As a sensitivity analysis, a separate longitudinal model was used to evaluate the efficacy outcomes of all the treatment arms in the same model. Estimates for CDAI-70 response rates at Week 12 were 28.2% for placebo and 35.0%, 47.4% and 43.7% for 10 mg, 50 mg and 200 mg, respectively, which is comparable to the estimates from the primary analyses.

Post-hoc sub-group analyses were conducted to evaluate whether baseline characteristics impacted CDAI response. Data indicated small variations in outcome by baseline demographics, CD characteristics and treatment history (online supplementary figure S2); these require corroboration in a prospective study.

Pharmacokinetic and pharmacodynamics outcomes

Increases in serum concentrations of PF-04236921 in the induction trial were approximately dose-proportional (online supplementary figure S5) and serum CRP concentrations were continuously suppressed from Weeks 2 to 12 (online supplementary figure S6). At Week 12, median serum concentrations of PF-04236921 were 0.44, 1.76 and 9.62 μg/mL with 10, 50 and 200 mg, respectively. Corresponding median percent changes from baseline in CRP concentrations were -66.4%, -86.3% and -95.5%, compared with -12.3% for placebo at Week 12.

During the treatment period in the OLE, patients who received placebo or PF-04236921 10, 50 or 200 mg subcutaneously (SC) on Days 1 and 28 in the induction study were dosed with PF-04236921 50 mg SC (and 100 mg SC, if dose was escalated). Median serum PF-04236921 concentrations of all patients increased slightly over the 48-week treatment period and decreased to concentrations close to the lower limit of quantitation (ie, 100 ng/mL) by the end of the follow-up period (online supplementary figure S7).

Safety outcomes

There was one death in the induction study, which occurred in the 50 mg group, in a patient in their mid-70s who had a 54-year history of ileocolonic Crohn's disease without prior surgery. The patient was hospitalised due to exacerbation of Crohn's disease, one day prior to receiving a second 50-mg dose. Eight days after receiving the second dose, the patient was hospitalised with exacerbation of Crohn's disease, which was treated with intravenous (IV) steroids (100 mg every 8 h). Two days later, the patient was diagnosed with a *Clostridium difficile* infection and treated with oral vancomycin 250 mg four times per day for 12 days. Thirteen days after the second hospitalisation, the patient was started on IV infliximab 500

mg every 6 weeks, but received only one dose. On the same day, a colonoscopy showed a colonic stricture with resolution of the *C. difficile* infection. Exacerbation of Crohn's disease continued, and the patient was subsequently re-admitted to the hospital twice more within a 2-week period, first receiving treatment with two units of packed cells for Crohn's disease, and a combination of IV vancomycin 125 mg four times daily and oral rifampicin 300 mg two times daily for the recurring *C. difficile* infection. During the second of these hospitalisations, the patient experienced a perforation of the colon and peritonitis, and underwent a sub-total colectomy with ileostomy. The peritonitis was treated with IV piperacillin/tazobactam (3.375 mg every 8 h) and IV metronidazole (500 mg every 8 h). The investigator considered it a reasonable possibility that the exacerbation of Crohn's disease with the colonic stricture, and gastrointestinal perforation, were related to the study drug. Pathology indicated the colon pathology was consistent with Crohn's disease and that there were multiple areas of ulceration. Postoperative respiratory failure necessitated temporary intubation and the patient died 17 days after surgery due to worsening respiratory failure, considered attributable to the underlying chronic obstructive pulmonary disease.

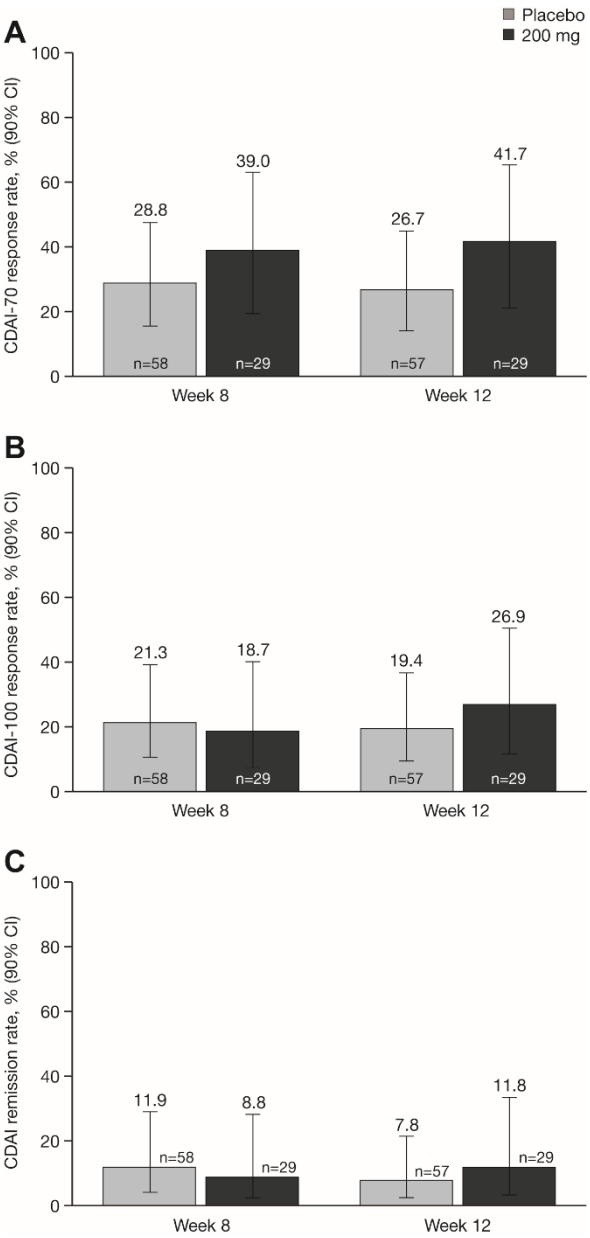
References

1 National Research Council. The prevention and treatment of missing data in clinical trials. Washington, DC: The National Academies Press 2010.

2 Siddiqui O, Hung HM, O'Neill R. MMRM vs LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. *J Biopharm Stat* 2009;19:227-46 doi:10.1080/10543400802609797.

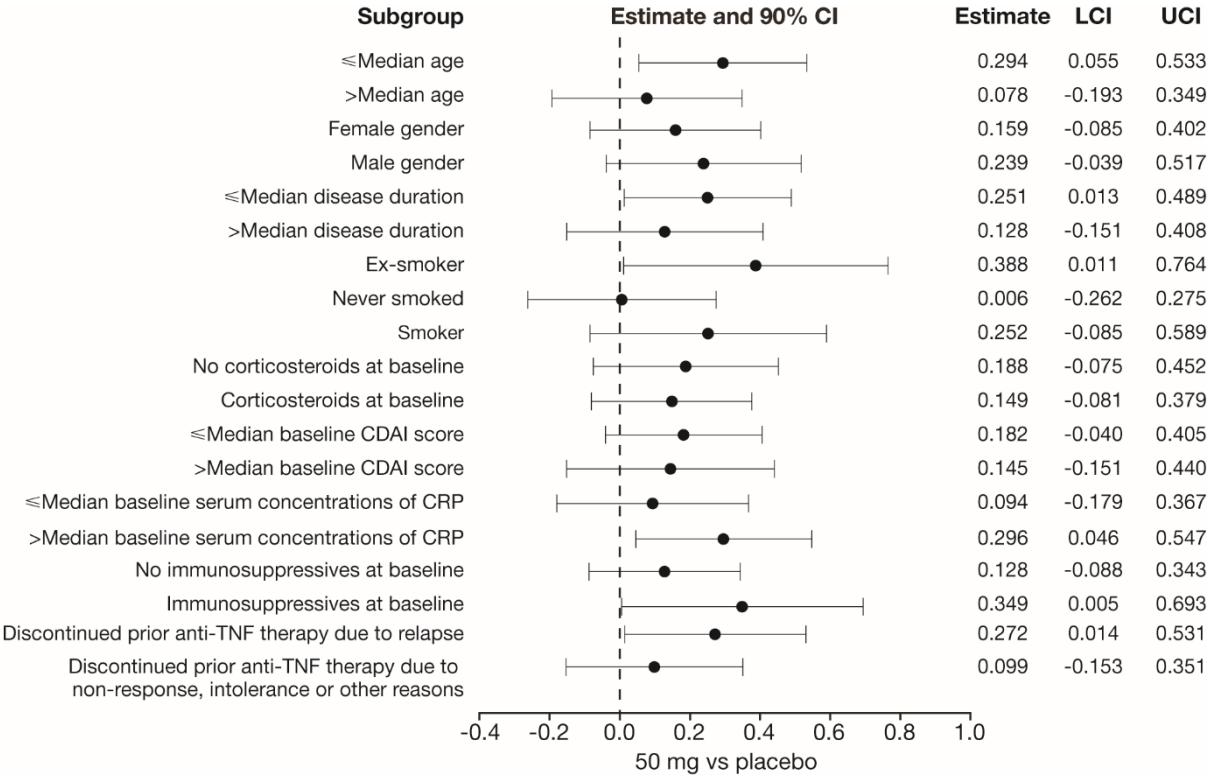
SUPPLEMENTARY FIGURES

Online Supplementary Figure S1 CDAI outcomes at Weeks 8 and 12 for the 200 mg group: (A) CDAI-70 response rate; (B) CDAI-100 response rate; and (C) CDAI remission rate (generalised linear mixed model; mITT population).



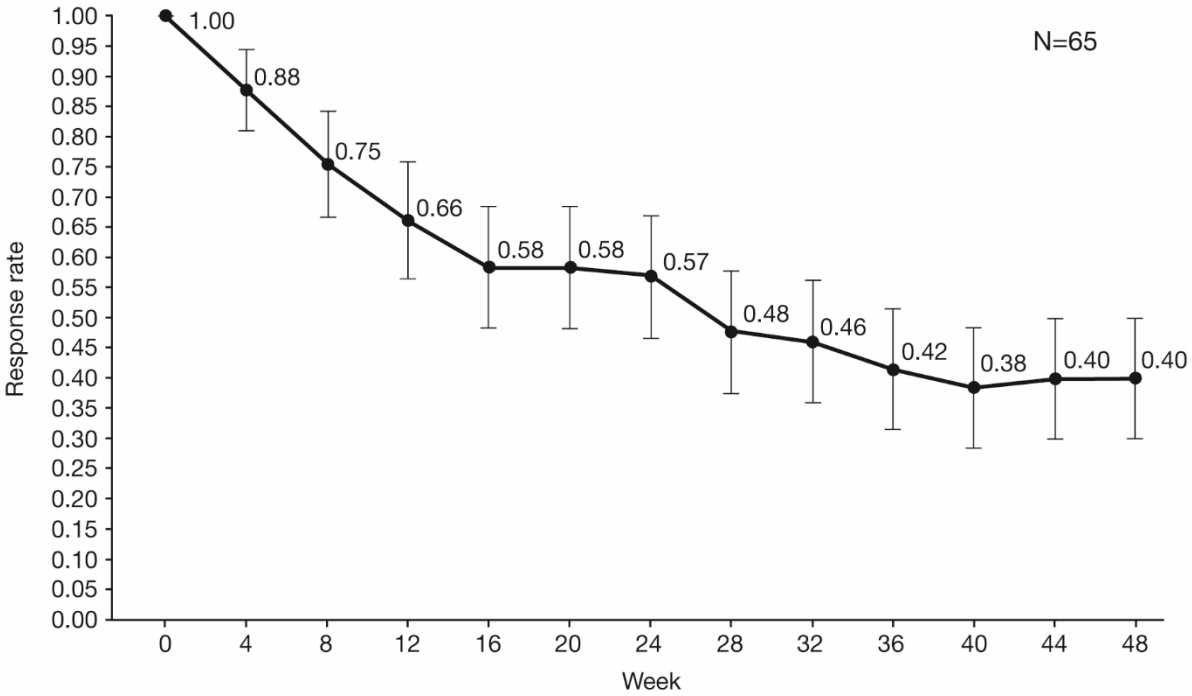
CDAI, Crohn's Disease Activity Index; CDAI-70/-100, proportion of patients who achieved a 70-/100-point reduction in CDAI score; CI, confidence interval; mITT, modified intent-to-treat.

Online Supplementary Figure S2 Sub-group analysis of CDAI-70 response rates at Week 12 for 50 mg versus placebo (generalised linear mixed model; mITT population).



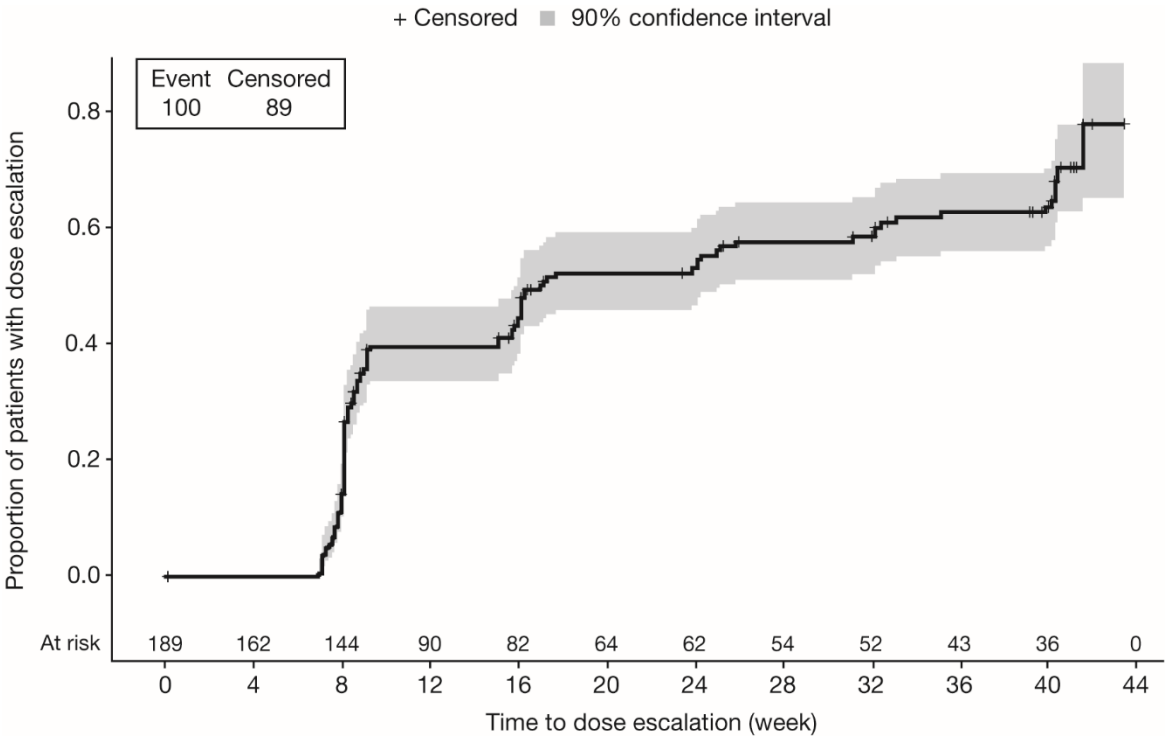
CDAI, Crohn's Disease Activity Index; CDAI-70, proportion of patients who achieved a ≥70-point reduction in CDAI score; CI, confidence interval; CRP, C-reactive protein; LCI, lower CI; mITT, modified intent-to-treat; TNF, tumour necrosis factor; UCI, upper CI.

Online Supplementary Figure S3 Harvey-Bradshaw Index response rate (90% CIs) for patients who were on active treatment in the induction trial and who entered the open-label extension as CDAI-70 responders.

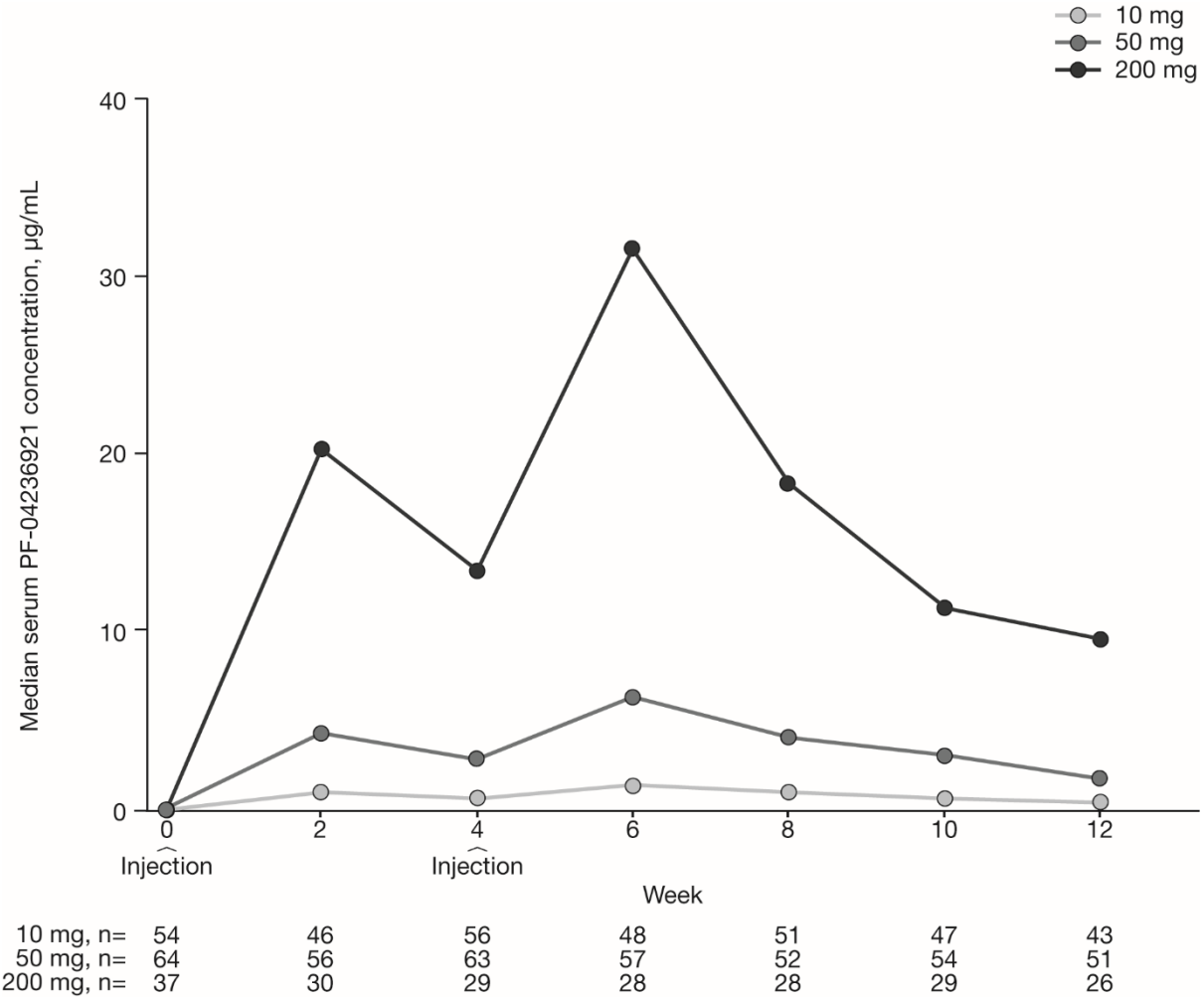


CDAI-70, proportion of patients who achieved a ≥70-point reduction in Crohn's Disease Activity Index score; CI, confidence interval.

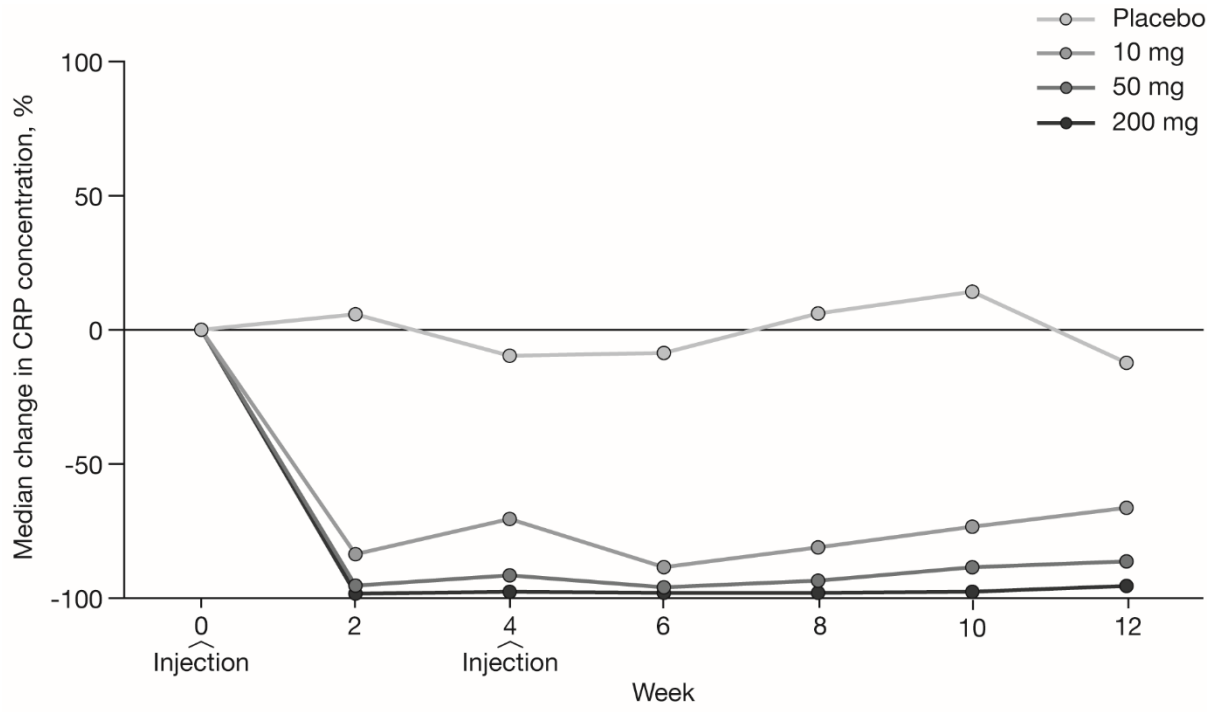
Online Supplementary Figure S4 Kaplan-Meier plot for time to dose escalation.



Online Supplementary Figure S5 Serum concentrations of PF-04236921 over time by treatment group.



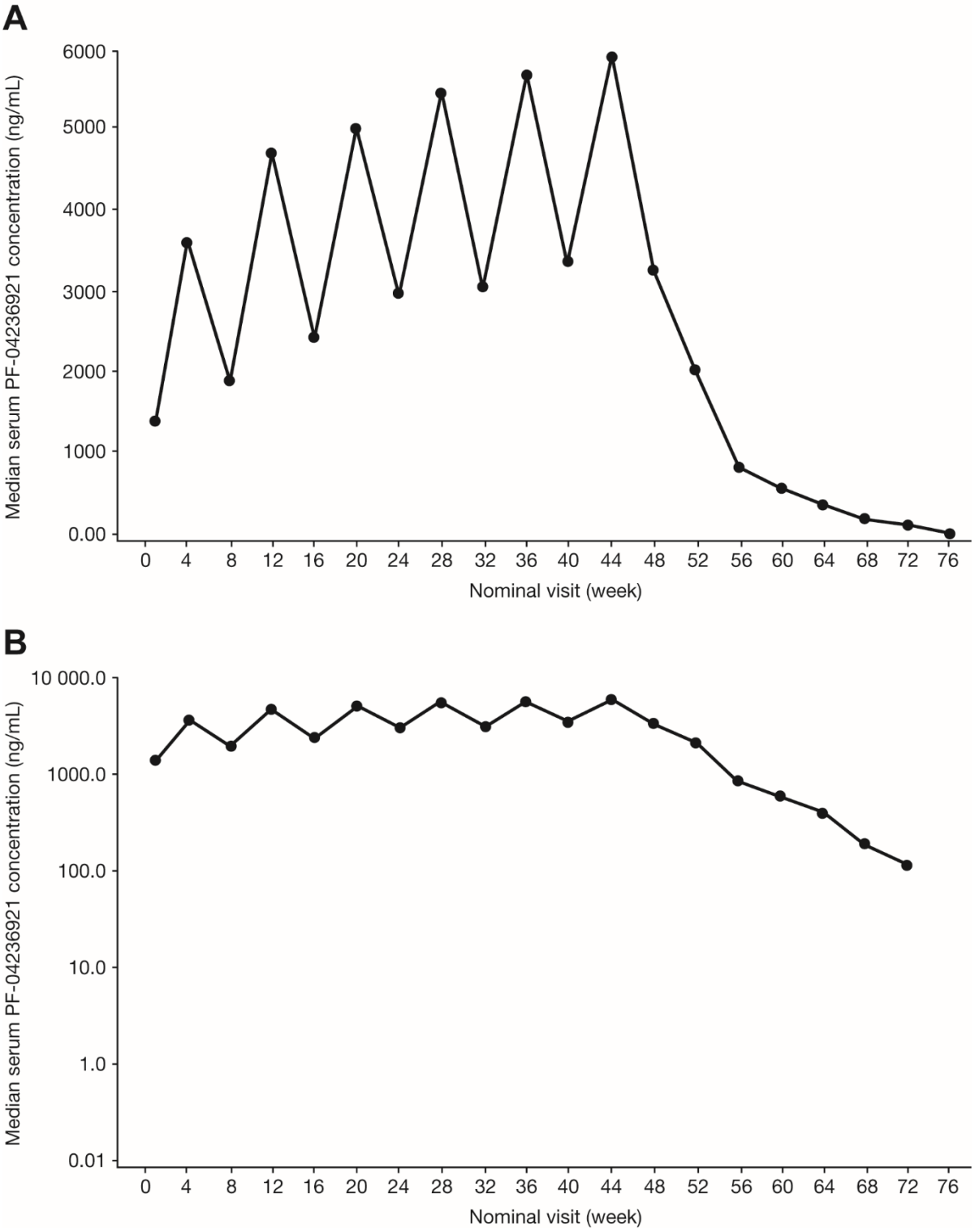
Online Supplementary Figure S6 Serum concentrations of CRP over time by treatment group.



Placebo, n=	69	66	66	60	61	56	59
10 mg, n=	65	61	58	57	56	53	56
50 mg, n=	71	69	68	64	57	59	58
200 mg, n=	40	36	36	33	31	32	33

CRP, C-reactive protein.

Online Supplementary Figure S7 Median serum PF-04236921 concentration-time profiles – linear scale (upper panel), semi-logarithmic scale (lower panel).



SUPPLEMENTARY TABLES

Online Supplementary Table S1 Harvey-Bradshaw Index criteria

Clinical status	HBI score
Remission	<5
Mildly active	5–7
Moderately active	8–16
Severely active	>16
Response at baseline in OLE	Decrease of ≥70 CDAI points at Week 12 in the induction study
Response at postbaseline in OLE	1) Being a responder at baseline and never relapsed by that time point 2) ≥3-point decrease in HBI score from the baseline of either the OLE baseline or the induction study baseline. This condition applied to patients who were non-responders at baseline or relapsed after baseline
Relapse	≥3-point increase relative to the lowest HBI score measured following a response, with total HBI score of ≥8

CDAI, Crohn's Disease Activity Index; HBI, Harvey-Bradshaw Index; OLE, open-label extension.

Online Supplementary Table S2 Treatment-emergent adverse events (all causalities, Weeks 0–48) in the open-label extension study

Number (%) of patients	**PF-04236921 N=191**
Adverse events	171 (89.5)
Serious adverse events	58 (30.4)
Treatment-emergent adverse events in ≥5 patients by system organ class preferred term	
Blood and lymphatic system disorders	**14 (7.3)**
Anaemia	10 (5.2)
Ear and labyrinth disorders	**6 (3.1)**
Vertigo	5 (2.6)
Gastrointestinal disorders	**116 (60.7)**
Abdominal pain	31 (16.2)
Abdominal pain upper	8 (4.2)
Abdominal tenderness	5 (2.6)
Anal fistula	7 (3.7)
Constipation	6 (3.1)
Crohn’s disease	53 (27.7)
Diarrhoea	16 (8.4)
Dyspepsia	7 (3.7)
Flatulence	5 (2.6)
Nausea	16 (8.4)

Rectal haemorrhage	5 (2.6)
Vomiting	17 (8.9)
General disorders and administration conditions	**44 (23.0)**
Fatigue	6 (3.1)
Injection-site erythema	8 (4.2)
Oedema peripheral	5 (2.6)
Pyrexia	9 (4.7)
Swelling	8 (4.2)
Infections and infestations	**94 (49.2)**
Bronchitis	9 (4.7)
Gastroenteritis	11 (5.8)
Influenza	5 (2.6)
Nasopharyngitis	23 (12.0)
Oral herpes	5 (2.6)
Pharyngitis	5 (2.6)
Pneumonia	5 (2.6)
Sinusitis	6 (3.1)
Upper respiratory tract infections	9 (4.7)
Urinary tract infection	8 (4.2)
Metabolism and nutrition disorders	**22 (11.5)**
Hypokalaemia	5 (2.6)
Vitamin D deficiency	6 (3.1)

Musculoskeletal and connective tissue disorders	**52 (27.2)**
Arthralgia	17 (8.9)
Back pain	11 (5.8)
Muscle spasms	7 (3.7)
Pain in extremity	7 (3.7)
Nervous system disorders	**31 (16.2)**
Headache	17 (8.9)
Migraine	6 (3.1)
Psychiatric disorders	**20 (10.5)**
Anxiety	8 (4.2)
Insomnia	6 (3.1)
Respiratory disorders	**25 (13.1)**
Cough	12 (6.3)
Oropharyngeal pain	5 (2.6)
Skin and subcutaneous tissue disorders	**63 (33.0)**
Eczema	7 (3.7)
Erythema	12 (6.3)
Pruritus	6 (3.1)
Rash	12 (6.3)
Skin lesion	5 (2.6)
Vascular disorders	**8 (4.2)**
Hypertension	6 (3.1)

Online Supplementary Table S3 Events identified by the SMQ for potential gastrointestinal perforations during the 12-week induction period and the open-label extension

Event	Start/stop day	Severity/outcome	Action taken: study drug/patient	Causality
12-week induction period				
PF-04236921 10 mg				
Anal abscess	29/29	Severe/resolved	Permanently discontinued/treatment given, surgery, discontinued from study	Study drug
Abscess intestinal	31/77	Severe/resolved	No action taken/permanently discontinued	Study drug
PF-04236921 50 mg				
Large intestine perforation	79/80	Severe/resolved	No action taken/treatment given	Study drug
Peritonitis	80/>96	Severe/still present	No action taken/treatment given	Study drug
Anal fistula	28/77	Moderate/resolved	No action taken/resection of ileum	Study drug
Anal abscess	28/77	Moderate/resolved	Permanently discontinued/discontinued from study	Study drug

Anal fistula	15/43	Severe/resolved	No action taken/treatment given	Study drug
Anal abscess	49/57	Severe/resolved	No action taken/treatment given	Disease under study
Anal abscess	80/>84	Moderate/still present	No action taken/treatment given	Disease under study
PF-04236921 200 mg				
Anal fistula	15/83	Mild/resolved	No action taken/no action	Disease under study
Intestinal perforation	79/87	Moderate/resolved	No action taken/treatment given	Disease under study
Open-label extension period				
PF-04236921 50 mg				
Small intestinal perforation	280/286	Moderate/resolved	No action taken/small bowel resection	Disease under study
Small intestinal perforation	23/31	Moderate/resolved	No action taken/treatment given/small bowel resection	Disease under study
Perirectal abscess	182/351	Moderate/resolved	Permanently discontinued/treatment given/discontinued from study	Study drug
Perianal abscess	47/58	Severe/resolved	Permanently discontinued/treatment	Study drug

			given/discontinued from study	
Abdominal abscess	69/189	Severe/resolved	No action taken/treatment given	Study drug
Abdominal abscess	97/122	Severe/resolved	Permanently discontinued/discontinued from study	Disease under study
Abdominal abscess	135/156	Severe/resolved	No action taken/treatment given, hospitalisation - surgery	Disease under study
PF-04236921 100 mg				
Large intestinal perforation	143/155	Severe/resolved	No action taken/treatment given	Study drug
Small intestinal perforation	207/209	Severe/resolved	No action taken/small bowel resection	Disease under study
Rectal abscess	138/218	Moderate/resolved	Permanently discontinued/treatment given/discontinued from study	Disease under study
Intra-abdominal abscess	259/260	Moderate/resolved	No action taken/treatment given/small bowel resection	Disease under study

SMQ, Standardised Medical Dictionary for Regulatory Activities Queries.

Online Supplementary Table S4 NRI analysis for CDAI-70 from Week 2 to Week 12 using the exact method

Week	Treatment	n/N	Estimate (90% CI)	Difference from placebo Estimate (90% CI)
CDAI response				
2	Placebo	11/69	0.159 (0.097 to 0.241)	
	PF-04236921 50 mg	15/65	0.231 (0.148 to 0.326)	0.071 (-0.047 to 0.189)
	PF-04236921 100 mg	13/71	0.183 (0.119 to 0.271)	0.024 (-0.088 to 0.132)
4	Placebo	14/69	0.203 (0.127 to 0.293)	
	PF-04236921 50 mg	23/65	0.354 (0.255 to 0.460)	0.151 (0.015 to 0.282)
	PF-04236921 100 mg	23/71	0.324 (0.236 to 0.417)	0.121 (-0.005 to 0.244)
6	Placebo	17/69	0.246 (0.163 to 0.342)	
	PF-04236921 50 mg	22/65	0.338 (0.241 to 0.445)	0.092 (-0.042 to 0.224)
	PF-04236921 100 mg	29/71	0.408 (0.316 to 0.509)	0.162 (0.023 to 0.291)
8	Placebo	23/69	0.333 (0.241 to 0.431)	
	PF-04236921 50 mg	22/65	0.338 (0.241 to 0.445)	0.005 (-0.132 to 0.141)
	PF-04236921 100 mg	29/71	0.408 (0.316 to 0.509)	0.075 (-0.065 to 0.211)
10	Placebo	22/69	0.319 (0.227 to 0.416)	
	PF-04236921 50 mg	22/65	0.338 (0.241 to 0.445)	0.020 (-0.017 to 0.155)
	PF-04236921 100 mg	29/71	0.408 (0.316 to 0.509)	0.090 (-0.047 to 0.224)

12	Placebo	22/69	0.319 (0.227 to 0.416)	
	PF-04236921 50 mg	22/65	0.338 (0.241 to 0.445)	0.020 (-0.117 to 0.155)
	PF-04236921 100 mg	28/71	0.394 (0.297 to 0.491)	0.076 (-0.061 to 0.211)
CDAI remission				
2	Placebo	1/69	0.014 (0.002 to 0.059)	
	PF-04236921 50 mg	2/65	0.031 (0.008 to 0.086)	0.016 (-0.036 to 0.078)
	PF-04236921 100 mg	6/71	0.085 (0.037 to 0.159)	0.070 (-0.007 to 0.146)
4	Placebo	2/69	0.029 (0.008 to 0.081)	
	PF-04236921 50 mg	2/65	0.031 (0.008 to 0.086)	0.002 (-0.060 to 0.067)
	PF-04236921 100 mg	11/71	0.155 (0.095 to 0.236)	0.126 (0.044 to 0.217)
6	Placebo	5/69	0.072 (0.036 to 0.139)	
	PF-04236921 50 mg	3/65	0.046 (0.017 to 0.110)	-0.026 (-0.106 to 0.048)
	PF-04236921 100 mg	14/71	0.197 (0.123 to 0.284)	0.125 (0.023 to 0.227)
8	Placebo	9/69	0.130 (0.072 to 0.214)	
	PF-04236921 50 mg	5/65	0.077 (0.038 to 0.148)	-0.054 (-0.149 to 0.038)
	PF-04236921 100 mg	14/71	0.197 (0.123 to 0.284)	0.067 (-0.042 to 0.174)
10	Placebo	7/69	0.101 (0.054 to 0.176)	
	PF-04236921 50 mg	9/65	0.138 (0.079 to 0.228)	0.037 (-0.062 to 0.137)
	PF-04236921 100 mg	16/71	0.225 (0.154 to 0.316)	0.124 (0.013 to 0.233)
12	Placebo	6/69	0.087 (0.039 to 0.163)	
	PF-04236921 50 mg	5/65	0.077 (0.038 to 0.148)	-0.010 (-0.095 to 0.078)
	PF-04236921 100 mg	16/71	0.225 (0.154 to 0.316)	0.138 (0.033 to 0.244)

N is based on observed data using the full analysis set population (defined as all randomised subjects who received at least one dose of investigational product).

Baseline is the latest CDAI score prior to the first dose on Day 1.

90% CI for point estimate is based on Blyth-Still-Casella exact method.

The risk difference is based on the Chan and Zhang method.

CDAI-70, proportion of patients who achieved a ≥70-point reduction in Crohn's Disease Activity Index score; CI, confidence interval; n, number of subjects with CDAI-70 response or remission; NRI, non-responder imputation.