Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis (TURANDOT): a phase 2, randomised, double-blind, placebo-controlled trial

Séverine Vermeire, William J Sandborn, Silvio Danese, Xavier Hébuterne, Bruce A Salzberg, Maria Klopocka, Dino Tarabar, Tomas Vanasek, Miloš Greguš, Paul A Hellstern, Joo Sung Kim, Miles P Sparrow, Kenneth J Gorelick, Michelle Hinz, Alaa Ahmad, Vivek Pradhan, Mina Hassan-Zahraee, Robert Clare, Fabio Cataldi, Walter Reinisch**

Summary

Background PF-00547659 is a fully human monoclonal antibody that binds to human mucosal addressin cell adhesion molecule-1 (MAdCAM-1) to selectively reduce lymphocyte homing to the intestinal tract. We aimed to assess the efficacy and safety of PF-00547659 in patients with moderate to severe ulcerative colitis.

Methods This phase 2, randomised, double-blind, placebo-controlled clinical trial recruited patients aged 18–65 years from 105 centres in 21 countries, with a history (≥3 months) of active ulcerative colitis extending more than 15 cm beyond the anal verge (with a total Mayo score ≥6 and a Mayo endoscopic subscore ≥2) who had failed or were intolerant to at least one conventional therapy. Patients were stratified by previous anti-TNFα treatment, and randomly assigned by a computer-generated randomisation schedule to receive a subcutaneous injection of 7·5 mg, 22·5 mg, 75 mg, or 225 mg PF-00547659 or placebo at baseline, then every 4 weeks. Patients, investigators, and sponsors were blinded to the treatment. The primary endpoint was the proportion of patients achieving remission (total Mayo score ≤2 with no individual subscore >1 and rectal bleeding subscore ≤1) at week 12. The efficacy analysis included all patients who received at least one dose of the randomised treatment; the safety analysis was done according to treatment received. All p values were one-sided and multiplicity-adjusted. This study is registered with ClinicalTrials.gov, number NCT01620255.

Findings Between Nov 2, 2012, and Feb 4, 2016, we screened 587 patients; 357 were eligible and randomly assigned to receive placebo (n=73) or PF-00547659 at doses of 7·5 mg (n=71), 22·5 mg (n=72), 75 mg (n=71), or 225 mg (n=70). Remission rates at week 12 were significantly greater in three of four active-treatment groups than in the placebo group (2·7% [two of 73]): 7·5 mg (11·3% [eight of 71]), 22·5 mg (16·7% [12 of 72]), 75 mg (15·5% [11 of 71]), and 225 mg (5·7% [four of 70]). These rates corresponded to a stratum-adjusted (anti-TNFα-naive and anti-TNFα-experienced) risk difference versus placebo of 8·0% for 7·5 mg (90% CI 1·9 to 14, p=0·0425), 12·8% for 22·5 mg (5·6 to 19·9, p=0·0099), 11·8% for 75 mg (4·8 to 18·8, p=0·0119), and 2·6% for 225 mg (–1·2 to 6·4, p=0·1803). Four of 73 (5·5%) patients had a serious adverse event in the placebo group, ten of 71 (14·1%) in the 7·5 mg group, one of 70 (1·4%) in the 22·5 mg group, three of 73 (4·1%) in the 75 mg group, and three of 70 (4·3%) in the 225 mg group. No safety signal was observed for the study drug.

Interpretation PF-00547659 was safe and well tolerated in this patient population, and better than placebo for induction of remission in patients with moderate to severe ulcerative colitis. The greatest clinical effects were observed with the 22·5 mg and 75 mg doses.

Funding Pfizer.

Lancet 2017; 390: 135–44

Published Online
May 17, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30930-3

See Comment page 98

*Joint last authors

Leuven University Hospital and University of Leuven, Leuven, Belgium (Prof S Vermeire MD); **University of California San Diego, La Jolla, CA, USA** (Prof W J Sandborn MD); **Humanitas University, Clinical and Research Center, Humanitas Research Hospital, Rozzano, Milan, Italy** (Prof S Danese MD); **Centre Hospitalier Universitaire de Nice Sophia Antipolis, Nice, France** (Prof X Hébuterne MD); **Atlanta Gastroenterology Specialists PC, Atlanta, GA, USA** (B A Salzberg MD); **Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland** (M Klopocka MD); **Military Medical Academy, Clinic for Gastroenterology and Hepatology, Belgrade, Serbia** (D Tarabar MD); **Charles University Hospital, Hradec Kralove, Czech Republic** (T Vanasek MD); **Gastroenterology Center, Nitra, Slovakia** (M Greguš MD); **Nature Coast Clinical Research, Inverness, FL, USA** (P A Hellstern MD); **Seoul National University College of Medicine, Seoul, South Korea** (J S Kim MD); **Alfred Hospital, Melbourne, VIC, Australia** (M P Sparrow MBBS); **Pfizer, Cambridge, MA, USA** (K J Gorelick MD, M Hinz MS, A Ahmad PhD, V Pradhan MS, M Hassan-Zahraee PhD, R Clare PhD, F Cataldi MD); **Medical University of Vienna, Vienna, Austria** (Prof W Reinisch MD); **and McMaster University, Hamilton, ON, Canada** (Prof W Reinisch)

Introduction

Ulcerative colitis is a chronic, relapsing disorder of unknown cause, characterised by inflammation and ulceration of the colonic mucosa.[1,2] The disorder contributes to substantial morbidity globally, with incidence and prevalence continuing to increase over time.[3] However, despite advances in treatment, many patients do not respond to conventional therapies such as 5-aminosalicylic acid, thiopurines, corticosteroids, or anti-tumour necrosis factor (TNFα) antibodies. Therefore, compounds with novel mechanisms of action are needed to induce and maintain clinical and endoscopic remission.[4]

The role of adhesion molecules in mediating the migration of lymphocytes into sites of inflammation in the gut has made them an attractive target in the treatment of inflammatory bowel disease.[5] Mucosal addressin cell adhesion molecule (MAdCAM) is mostly expressed on the cell surface of high endothelial venules of organised intestinal lymphoid tissue such as Peyer's patches and mesenteric lymph nodes, and binds the α4β7 integrin on populations of gut-homing CD4+ and CD8+ memory T cells.[6] Anti-α4β7 integrin antibody therapy with vedolizumab is effective for induction and maintenance of clinical and endoscopic remission in ulcerative colitis.[7] Agents directly blocking MAdCAM have not yet been studied in this indication.

PF-00547659 is a fully human monoclonal antibody that inhibits binding of the α4β7 integrin to human

Correspondence to:
Prof Séverine Vermeire,
Department of Gastroenterology,
Leuven University Hospital,
Herestraat 49, 3000 Leuven,
Belgium
severine.vermeire@uzleuven.be

Research in context

Evidence before this study

Patients with ulcerative colitis often do not respond to treatment, so there is a need for new treatment options. Cell adhesion molecules have an important role in mediating lymphocyte migration into the gut and represent a promising target for treatment in ulcerative colitis. Mucosal addressin cell adhesion molecule (MAdCAM) is expressed primarily on the cell surface of endothelial venules in gastrointestinal and associated lymphoid tissues. We searched PubMed using the terms "ulcerative colitis", "mucosal addressin cell adhesion molecule", and "randomised clinical trial". We found one first-in-human phase 1 study, which explored the safety and efficacy of PF-00547659, a monoclonal antibody to MAdCAM, in 80 patients with active ulcerative colitis. This study reported a favourable short-term safety profile and preliminary clinical efficacy and endoscopic response in patients treated with PF-00547659 compared with placebo.

Added value of this study

This is the first study to assess an anti-MAdCAM antibody as a potential treatment for ulcerative colitis. The study met its primary endpoint of inducing clinical and endoscopic remission by week 12. Importantly, although clinical studies in patients with ulcerative colitis have typically used locally read endoscopy scores in efficacy assessments, our data also indicate that blinded central endoscopy reads result in a more robust assessment of potential efficacy than that obtained with historical approaches based on local endoscopy reading.

Implications of all the available evidence

This study contributes to the growing body of evidence that cell adhesion has an important role in ulcerative colitis and suggests that inhibition of cell adhesion mediated by MAdCAM could result in an effective therapy for ulcerative colitis. A large phase 3 programme is underway.

MAdCAM with high affinity and selectivity.[8] This phase 2, randomised, double-blind, placebo-controlled clinical trial was designed to assess the efficacy and safety of PF-00547659 in patients with moderate to severe ulcerative colitis.

Methods

Study design

TURANDOT was a 12-week, phase 2, randomised, double-blind, placebo-controlled, parallel-group study done from Nov 2, 2012 (first patient, first visit), to Feb 4, 2016 (last patient visit), at 105 centres in 21 countries in Europe, North America, Africa, Asia, and Oceania. The protocol was approved by the institutional review board or ethics committee at each centre. All patients gave written informed consent.

The protocol was amended twice. Amendment 1 clarified exclusion criteria, added withdrawal criteria, and added details for the planned interim analysis. Amendment 2 clarified the definitions of intolerance and treatment failure, deleted inflammatory bowel disease serology biomarker testing, and made administrative changes to the protocol.

Patients

Eligible patients were aged 18–65 years, with a history of active ulcerative colitis (≥3 months) extending more than 15 cm beyond the anal verge (with a total Mayo score[9] ≥6 and a Mayo endoscopic subscore ≥2), without fulminant colitis, who had not responded or were intolerant to at least one conventional therapy, such as 5-aminosalicylic acid, steroids, immunosuppressants (azathioprine, mercaptopurine, or methotrexate), or anti-TNFα agents. For eligibility assessment, the Mayo score was calculated with an endoscopic subscore provided by the central reader. For efficacy analysis, the endoscopic subscore was measured by a central reader (Robarts Clinical Trials, London, ON, Canada) who was blinded to treatment allocation.[10] The endoscopic subscore was independently assessed by the local reader for comparison. For anti-TNFα agents, treatment failure was defined as either inability to respond to initial therapy or relapse after an original response to therapy, and intolerance was defined as the presence of clinically significant side-effects, including hypersensitivity. For immunosuppressants, treatment failure was defined as continued disease activity despite treatment with a therapeutic dose of azathioprine, mercaptopurine, or methotrexate; intolerance was defined as a history of having an unacceptable or dose-limiting toxicity associated with the use of the agent. Patients were excluded if they had received more than 20 mg per day of prednisone or an equivalent oral systemic corticosteroid dose within 2 weeks before randomisation, more than 6 mg per day of oral budesonide within 2 weeks before randomisation, or other biological agents (including any anti-TNFα agents) within 6 weeks from baseline or at randomisation.

Randomisation and masking

Patients were randomly assigned to one of five treatment groups (placebo or PF-00547659 at doses of 7·5 mg, 22·5 mg, 75 mg, or 225 mg) in a 1:1:1:1:1 ratio according to a computer-generated randomisation schedule by use of a stratified block randomisation method with a block size of ten. Randomisation was stratified by the status of previous treatment with anti-TNFα agents (with patients classified as naive or experienced). The study drug was administered by unblinded personnel who were separate from the study team. Patients, investigators, and sponsors were blinded to study treatment.

Procedures

The study drug (PF-00547659) was administered as three subcutaneous injections of solutions containing either 75 mg/mL active treatment (7·5 mg, 22·5 mg, 75 mg, or 225 mg doses) or matching placebo into the lateral thigh, abdomen, or deltoid. The study drug was administered at baseline, then every 4 weeks. Patients attended the clinic at screening, for randomisation (week 0=baseline), and for follow-up visits at weeks 2, 4, 8, and 12. For the Mayo score, we measured stool and bleeding subscores as the average of three values obtained 3 days before endoscopy, and before initiation of a bowel preparation. Soluble MAdCAM (sMAdCAM) was measured at baseline and week 12 (Q² Solutions, Ithaca, NY, USA). At the follow-up visits, patients were assessed for safety, tolerability, and clinical efficacy. At week 12, endoscopic efficacy was also assessed.

Outcomes

The primary endpoint was the proportion of patients achieving remission (defined as a Mayo score ≤2 with no individual subscore >1 and rectal bleeding subscore ≤1) at week 12; the endoscopic subscore was centrally assessed and also independently assessed by the local reader for comparison. Secondary efficacy endpoints were the proportion of patients with a clinical response (defined as a decrease from baseline of Mayo score ≥3 with ≥30% change, accompanied by ≥1 point decrease or absolute score of ≤1 in rectal bleeding subscore) at week 12; the proportion of patients with mucosal healing (defined as Mayo endoscopy subscore ≤1) at week 12; the proportion of patients with a decrease from baseline in partial Mayo score of 2 or less with no individual subscore greater than 1 at weeks 4, 8, and 12; change from baseline in total Mayo score at week 12, and in individual Mayo subscores at weeks 4, 8, and 12; change from baseline in faecal calprotectin and high-sensitivity C-reactive protein (hsCRP) at weeks 4, 8, and 12; and change from baseline in the simple clinical colitis activity index (SCCAI) score at weeks 4, 8, and 12, and the proportion of patients with anti-PF-00547659 antibodies at each follow-up visit and cumulative through to week 12. The safety, tolerability, and pharmacokinetic profile of PF-00547659 were also assessed. Safety and tolerability were assessed by recording observed or reported adverse events and by physical examination, monitoring of vital signs, and clinical laboratory assessments.

Statistical analysis

The sample size calculation was based on the three-parameter maximum drug response (E_{max}) model, which assumes a monotone dose response; hence, multiplicity adjustment was not required in the power calculation. The null hypothesis was that there is no difference from placebo in remission at week 12, with a remission rate of 15% for all groups. The alternative hypothesis was that there is an increasing dose–response relationship, with a remission rate of 15% for placebo and remission rates for all active doses falling on an underlying E_{max} curve. This remission rate was selected on the basis of the sponsor's internal meta-analysis of previous pivotal studies of biological agents for ulcerative colitis. The confidence interval for the placebo remission rate included the value of 15%, which provided a conservative estimate for sample size planning consistent with the available information at the time the study was designed. The dose concentration required to produce 50% maximal effect was unknown and simulation studies based on a three-parameter E_{max} model assessed the robustness of the design to varying fixed values of 50% maximal effect. We estimated that a total sample size of 300 patients (n=60 per group) would give acceptable power to make decisions about characterisation of dose response in an ulcerative colitis population based on various simulation studies. Determination of sample size was also based on assessment of treatment difference among the active-treatment and placebo groups. With one-sided alpha of 0·05, 60 patients per group (n=300 in total) provides approximately 83% power to detect a 20% difference in clinical remission at week 12 between active-treatment and placebo groups, assuming a placebo remission rate of 15% at week 12. An interim analysis with gamma (–4) futility stopping boundary was planned for 50% completers.

Statistical analysis was done with SAS (version 9.4). Since the observed data showed a non-monotonic dose–response, fitting of an E_{max} model was inappropriate; furthermore, the model failed to converge. Consequently, the prespecified fixed sequence testing procedure, as stated in the statistical analysis plan, was not applied. We analysed all primary and key secondary endpoints with the Cochran-Mantel-Haenszel test stratified by previous anti-TNFα exposure,[11] and we computed the multiplicity-adjusted p values with the Hochberg step-up method. The one-sided alpha of 0·05 was used as the significance level for all other tests. Efficacy analysis was done on a modified intention-to-treat population, which was defined as all patients who received at least one dose of randomised treatment. Safety analysis was done according to actual treatment received.

We analysed binary secondary and exploratory endpoints with the Cochran-Mantel-Haenszel method to detect the stratum-adjusted risk difference, and assessed continuous endpoints with analysis of covariance using a linear mixed model to detect mean difference. A treatment failure approach was used for imputation of missing values for dropout patients in analyses of binary primary, secondary, and exploratory endpoints for which the Cochran-Mantel-Haenszel method was used. While fitting linear mixed models, all missing values were assumed to be missing at random or missing completely at random. Since the linear mixed model can effectively handle missing data under these assumptions, no imputation was done for missing data. In the linear mixed model, we used the following covariates as the

fixed effects: treatment, time, treatment and time interaction, baseline, and stratum. With repeated statement, the prespecified unstructured covariance structure was used to fit the linear mixed model.

An independent data monitoring committee met once every 3 months to review all clinical trials of PF-00547659. The data monitoring committee also intended to review all potential cases of progressive multifocal leukoencephalopathy and do a planned interim analysis for futility when 50% of patients had been randomly assigned and completed 12 weeks of treatment. This analysis was not done because the enrolment rate was such that all participants would have been randomly assigned by the time the interim analysis would occur. Sample size computation was done with one-sided alpha of 0·05. Also, as per the statistical analysis plan, two-sided 90% CIs were computed for all primary and key secondary endpoints.

This study is registered with ClinicalTrials.gov, number NCT01620255.

Deviations from the protocol

Four patients were enrolled despite failure to meet all entry criteria. 14 patients received at least one incorrect dose of the study drug. Five patients were missing total Mayo score calculations for baseline or week 12.

Role of the funding source

Employees of the sponsor (Pfizer) are included as authors of this manuscript and were involved in the design of the study, acquisition and analysis of data, and writing of the manuscript. These activities were carried out in full collaboration with the study investigators and all authors had full access to the source data, were collectively responsible for the decision to submit the manuscript, and have reviewed and approved the final version for submission.

Results

We screened 587 patients for eligibility (a complete list of principal investigators and sites is provided in the appendix). Of these, 357 were recruited and randomly assigned to receive at least one dose of the study drug (figure). During randomisation, 71 patients were assigned to receive 7·5 mg, 72 to receive 22·5 mg, 71 to receive 75 mg, and 70 to receive 225 mg PF-00547659; 73 patients were assigned to the placebo group. The treatment groups were similar at baseline with respect to age, sex, race, body-mass index, total Mayo score, and SCCAI score[12] (table 1). Distribution of previous anti-TNFα exposure was similar among groups, as was previous treatment with immunosuppressants, corticosteroids, and 5-aminosalicylic acid (table 1). Among the patients who received treatment, 336 of 357 (94·1%) completed the week 12 study visit. All patients who enrolled in the study while continuing to receive immunosuppressants had discontinued treatment by week 12.

See Online for appendix

Remission rates at week 12 were highest in patients receiving 22·5 mg and 75 mg of PF-00547659, and were significantly greater than placebo in three of the four PF-00547659 treatment groups: 7·5 mg, 22·5 mg, and 75 mg (table 2). In all treatment groups, remission rates were substantially higher among anti-TNFα-naive patients (10·0–25·8%) than among those previously treated with anti-TNFα agents (2·5–9·8%), and in both groups the highest remission rates were in patients receiving 22·5 mg and 75 mg PF-00547659 (table 2). Remission rates for all groups were higher with locally read endoscopy scores than with central endoscopy scores (table 2).

Compared with placebo, the response rate was significantly increased in patients allocated to receive the 22·5 mg dose, 75 mg dose, and 225 mg dose of PF-00547659 (table 2). The mucosal healing rate was greatest in patients allocated to receive 22·5 mg or 75 mg of PF-00547659 (table 2); moreover, patients given these doses had significantly improved rates of mucosal healing compared with those who received placebo (table 2). There was no difference in remission or response rate based on concurrent use of systemic glucocorticoids (data not shown).

Change from baseline in Mayo score at week 12 was significantly greater in all patients receiving PF-00547659 than in those receiving placebo, and was greatest among patients receiving the 22·5 mg dose (appendix p 6). At week 12, the proportion of patients with a decrease from baseline in partial Mayo score of 2 or less, with no individual subscore greater than 1, was greatest in the 22·5 mg group (risk difference [RD] 24·2%, 90% CI 11.5–36·9, p=0·0043) and 75 mg group (13·1%, 1·3–25·0, p=0·1186) versus placebo (appendix p 7). Between-group differences in the partial Mayo score were observed at 8 weeks. (appendix p 7). Other secondary and exploratory endpoints, including Mayo subscore values and SCCAI values, are shown in the appendix (pp 2–10). Results of secondary and exploratory analyses supported the findings for the primary analysis (appendix). Analyses of health outcomes and biomarkers have not yet been completed.

Faecal calprotectin concentration was reduced by week 4 in all PF-00547659 dose groups and continued to decline up to week 12 (appendix p 9). Decline in faecal calprotectin concentration from baseline was less substantial in patients receiving placebo than in those receiving active treatment. At week 12, the decrease in geometric means from baseline was –23% (SD 3·9) with placebo, –56% (SD 4·8) with 7·5 mg, –58% (SD 6·4) with 22·5 mg, –57% (SD 6·9) with 75 mg, and –65% (SD 6·3) with 225 mg PF-00547659 (appendix).

Decline in hsCRP concentrations from baseline was reported in the active-treatment groups at week 4 (appendix p 10). Concentrations continued to decrease through to week 8 for all study doses, except for patients in the 7·5 mg dose group, whose hsCRP concentrations did not show much further change (appendix p 10). In all

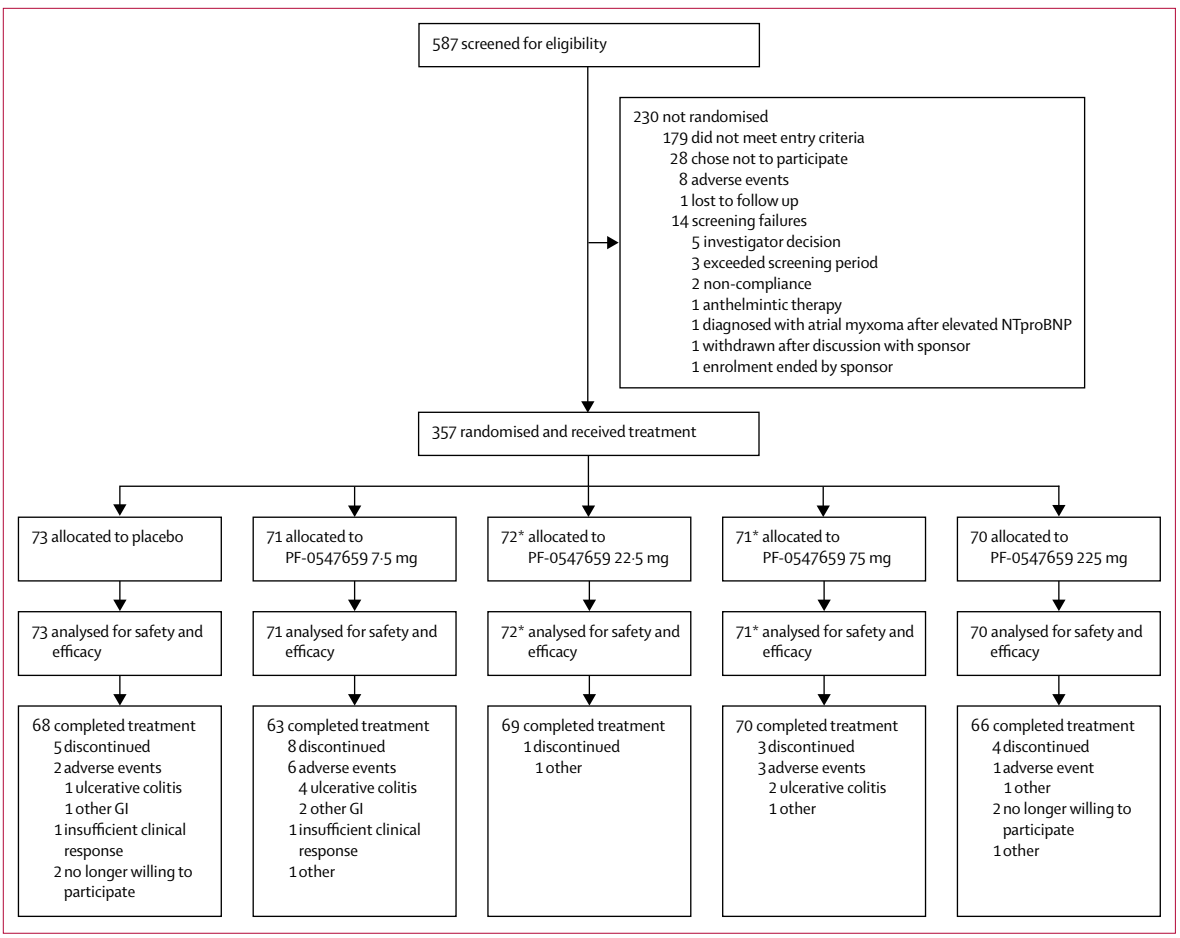

***Figure*: Trial profile**

GI=gastrointestinal. NTproBNP= N-terminal pro-brain natriuretic peptide. Primary endpoint assessed at week 12. *Two patients were initially randomly assigned to the 22·5 mg group but mistakenly received the 75 mg dose instead. For efficacy analysis they were included in the initial randomised group but for safety analysis they were counted in the as-treated group.

active-treatment groups hsCRP concentrations showed a trend to return towards baseline by week 12; the greatest and most persistent reductions were observed in the 22·5 mg and 75 mg groups (appendix p 10). The placebo group did not show much change over time. At week 12, the change from baseline in geometric means was +15% (SD 3·5) for placebo, +5% (SD 3·1) for 7·5 mg, –20% (SD 3·6) for 22·5 mg, –16% (SD 3·2) for 75 mg, and +2% (SD 3·0) for 225 mg PF-00547659 (appendix p 10).

Concentrations of sMAdCAM in active-treatment, but not placebo, groups declined significantly across all doses during the study, and the decreases levelled off at PF-00547659 doses of 22·5 mg or more (data not shown). After 12 weeks, mean suppression of sMAdCAM after monthly dosing of PF-00547659 was 67% (SD 3·0) for the 7·5 mg dose, 90% (SD 2·1) for the 22·5 mg dose, 94% (SD 2·0) for the 75 mg dose, and 98% (SD 1·8) for the 225 mg dose, and increased by 3% (SD 1·4) in the placebo group (data not shown).

Analysis showed that 709 (93·5%) of 758 samples from 284 patients on active treatment analysed up to week 12 reported negative for antidrug antibodies. Of the 35 patients who were confirmed positive, eight received 7·5 mg, six received 22·5 mg, 11 received 75 mg, and ten received 225 mg PF-00547659. Of the 12 patients who had confirmed antidrug antibodies at baseline, nine were also positive post baseline (three in the 7·5 mg group, one in the 22·5 mg group, four in the 75 mg group, and one in the 225 mg group) with no indication of treatment-enhanced antidrug antibody response (ie, greater antidrug antibody titre after treatment than at baseline). The overall confirmatory positive rate was 6·4%, with titres generally low and close to the cutoff point (4·64), and none higher than 11·9. Assessments in patients with post-baseline confirmatory antidrug antibodies (n=26) indicated no obvious effect of positive antidrug antibodies on exposure, safety, or efficacy. There was no indication of neutralising antibody activity based on pharmacokinetic levels (data not shown).

Overall, PF-00547659 appeared safe and well tolerated in this patient population. There was no substantial difference in the occurrence of adverse events between

	Placebo (n=73)	PF-00547659			
		7·5 mg (n=71)	22·5 mg* (n=70)	75 mg* (n=73)	225 mg (n=70)
Mean age, years (SD)	38·6 (12·7)	41·3 (12·5)	42·1 (14·7)	37·7 (12·4)	41·3 (13·2)
Women	29 (39·7%)	32 (45·1%)	25 (35·7%)	35 (47·9%)	28 (40·0%)
Race					
White	65 (89·0%)	64 (90·1%)	64 (91·4%)	64 (87·7%)	57 (81·4%)
Black	3 (4·1%)	1 (1·4%)	0	0	2 (2·9%)
Asian	3 (4·1%)	5 (7·0%)	5 (7·1%)	7 (9·6%)	8 (11·4%)
Other	2 (2·7%)	1 (1·4%)	1 (1·4%)	2 (2·7%)	3 (4·3%)
Mean BMI, kg/m² (SD)	25·5 (6·0)	24·3 (4·2)	24·3 (4·5)	25·4 (6·0)	25·4 (5·8)
Anti-TNFα exposure					
Naive	31 (42·5%)	30 (42·3%)	30 (42·9%)	31 (42·5%)	30 (42·9%)
Experienced	42 (57·5%)	41 (57·7%)	40 (57·1%)	42 (57·5%)	40 (57·1%)
Current immunosuppressant therapy					
Azathioprine	12 (16·4%)	18 (25·4%)	15 (21·4%)	15 (20·5%)	17 (24·3%)
Mercaptopurine	1 (1·4%)	4 (5·6%)	4 (5·7%)	4 (5·5%)	2 (2·9%)
Methotrexate	2 (2·7%)	1 (1·4%)	4 (5·7%)	0	1 (1·4%)
Tioguanine	0	0	0	0	1 (1·4%)
None	58 (79·5%)	48 (67·6%)	47 (67·1%)	54 (74·0%)	49 (70·0%)
Current corticosteroid use					
Yes	28 (38·4%)	35 (49·3%)	34 (48·6%)	34 (46·6%)	33 (47·1%)
No	45 (61·6%)	36 (50·7%)	36 (51·4%)	39 (53·4%)	37 (52·9%)
Current 5-aminosalicylic acid use					
Yes	48 (65·8%)	37 (52·1%)	36 (51·4%)	44 (60·3%)	36 (51·4%)
No	25 (34·2%)	34 (47·9%)	34 (48·6%)	29 (39·7%)	34 (48·6%)
Smoking status					
Never smoked	47 (64·4%)	40 (56·3%)	46 (65·7%)	48 (65·8%)	45 (64·3%)
Smoker	4 (5·5%)	4 (5·6%)	2 (2·9%)	5 (6·8%)	5 (7·1%)
Ex-smoker	22 (30·1%)	27 (38·0%)	22 (31·4%)	20 (27·4%)	20 (28·6%)
Extent of disease					
Proctosigmoiditis	15 (20·5%)	13 (18·3%)	9 (12·9%)	11 (15·1%)	7 (10·0%)
Left-sided colitis	21 (28·8%)	18 (25·4%)	21 (30·0%)	20 (27·4%)	24 (34·3%)
Extensive colitis	37 (50·7%)	40 (56·3%)	40 (57·1%)	42 (57·5%)	39 (55·7%)
Mean disease duration since diagnosis, years (range)	6·7 (0·3–30·4)	7·7 (0·7–24·3)	7·1 (0·4–39·2)	9·0 (0·6–36·2)	8·5 (0·3–51·2)
Median hsCRP, nmol/L (geometric mean); IQR	46·7 (44·8); 21·9–121·0	50·5 (41·0); 14·3–96·2	42·9 (40·0); 15·2–139·0	40·0 (43·8); 17·1–100·0	33·3 (33·3); 11·4–82·9
Median faecal calprotectin, µg/g (geometric mean); IQR	2095 (1958); 966–3912	1904 (2034); 1072–4626	1928 (1376); 492–4063	2198 (1942); 826–4745	1835 (1486); 653–3650
Mean Mayo score (SD)†	8·4 (1·7)	8·7 (1·7)	8·1 (1·6)	8·4 (1·9)	8·7 (1·6)
Mean Mayo score, partial (SD)	5·9 (1·5)	6·1 (1·4)	5·5 (1·5)	5·7 (1·7)	6·0 (1·5)
Mean SCCAI score (SD)	7·4 (2·9)	7·9 (2·8)	7·4 (2·8)	7·2 (2·6)	7·4 (2·4)

Values of n are per randomised treatment for efficacy analysis, and by actual treatment received for safety analysis. BMI=body-mass index. TNFα=tumour necrosis factor-α. hsCRP=high-sensitivity C-reactive protein. SCCAI=simple clinical colitis activity index. *Two patients assigned to receive 22·5 mg PF-00547659 mistakenly received the 75 mg dose. †Calculated with locally read endoscopy subscores.

***Table 1*: Baseline characteristics of patients**

placebo and active-treatment groups and no evidence for a dose-related increase in adverse events (table 3). Common adverse events (ie, observed in four or more patients in one or more treatment groups) were abdominal pain, ulcerative colitis (worsening or ongoing disease activity), nausea, vomiting, headache, cough, and anaemia. The most common adverse event was headache, reported by approximately 10% of patients, followed by ulcerative colitis and abdominal pain (table 3). There was no evidence of a dose effect for any of these events. The frequency of infections was similar across treatment groups. The most common infection was nasopharyngitis, reported in three of 73 patients in the placebo group, and none to five patients in the active-treatment group. Treatment-related injection-site reactions (reported as erythema, pain, swelling, or burning sensation) were

	Placebo (n=73)	PF-00547659			
		7·5 mg (n=71)	22·5 mg (n=72)	75 mg (n=71)	225 mg (n=70)
Central endoscopy reading					
Remission rate, n/N					
Overall	2/73 (2·7%)	8/71 (11·3%)	12/72 (16·7%)	11/71 (15·5%)	4/70 (5·7%)
Anti-TNFα-naive, n/N	2/31 (6·5%)	5/30 (16·7%)	8/31 (25·8%)	7/30 (23·3%)	3/30 (10·0%)
Anti-TNFα-experienced, n/N	0/42 (0·0%)	3/41 (7·3%)	4/41 (9·8%)	4/41 (9·8%)	1/40 (2·5%)
Risk difference *vs* placebo (90% CI)*	..	0·08 (0·019 to 0·14)	0·128 (0·056 to 0·199)	0·118 (0·048 to 0·188)	0·026 (–0·012 to 0·064)
p value†	..	0·0425	0·0099	0·0119	0·1803
Response rate, n/N	21/73 (28·8%)	27/71 (38·0%)	39/72 (54·2%)	32/71 (45·1%)	35/70 (50·0%)
Risk difference *vs* placebo (90% CI)*	..	0·089 (–0·037 to 0·214)	0·254 (0·121 to 0·388)	0·163 (0·032 to 0·293)	0·213 (0·08 to 0·347)
p value†	..	0·1379	0·0044	0·0479	0·0157
Mucosal healing rate, n/N	6/73 (8·2%)	11/71 (15·5%)	20/72 (27·8%)	18/71 (25·4%)	10/70 (14·3%)
Risk difference *vs* placebo (90% CI)*	..	0·081 (0 to 0·162)	0·187 (0·091 to 0·284)	0·159 (0·068 to 0·25)	0·069 (–0·013 to 0·151)
p value†	..	0·0099	0·0038	0·0080	0·0099
Local endoscopy reading					
Remission rate, n/N					
Overall	4/73 (5·5%)	10/71 (14·1%)	17/72 (23·6%)	13/71 (18·3%)	9/70 (12·9%)
Anti-TNFα-naive, n/N	2/31 (6·5%)	6/30 (20·0%)	9/31 (29·0%)	8/30 (26·7%)	6/30 (20·0%)
Anti-TNFα-experienced, n/N	2/42 (4·8%)	4/41 (9·8%)	8/41 (19·5%)	5/41 (12·2%)	3/40 (7·5%)
Risk difference *vs* placebo (90% CI)*	..	0·08 (0·002 to 0·159)	0·178 (0·083 to 0·272)	0·122 (0·036 to 0·208)	0·066 (–0·009 to 0·142)
p value†	..	0·0927	0·0056	0·0375	0·0927
Response rate, n/N	24/73 (32·9%)	27/70 (38·6%)	39/72 (54·2%)	34/70 (48·6%)	36/70 (51·4%)
Risk difference *vs* placebo (90% CI)*	..	0·056 (–0·075 to 0·186)	0·212 (0·077 to 0·347)	0·156 (0·022 to 0·290)	0·185 (0·050 to0·320)
p value†	..	0·2617	0·0231	0·0652	0·0435
Mucosal healing rate, n/N	16/73 (21·9%)	16/71 (22·5%)	27/72 (37·5%)	25/71 (35·2%)	20/70 (28·6%)
Risk difference *vs* placebo (90% CI)*	..	0·001 (–0·111 to 0·114)	0·154 (0·030 to 0·278)	0·130 (0·008 to 0·253)	0·066 (–0·053 to 0·186)
p value†	..	0·5225	0·0982	0·1393	0·4000

TNFα=tumour necrosis factor-α. *The stratum-adjusted risk difference and the corresponding 90% CIs were obtained with the Cochran-Mantel-Haenszel test.[11] †One-sided adjusted p value due to the Hochberg step up method.

***Table 2*: Remission, response, and mucosal healing rates at week 12 with central and local endoscopy readings**

uncommon and observed more frequently in the 225 mg treatment group (10% [7 of 70]) than in the other three active-treatment groups (3–4% [2–4 of 70–73]), including the placebo group (5% [4 of 73]). The frequency of serious adverse events was highest in the 7·5 mg treatment group; all other groups, including placebo, had similar rates (table 3). The most common serious adverse event was ulcerative colitis, reported by nine patients (one in the placebo group, six in the 7·5 mg group, and two in the 75 mg group), followed by migraine in two patients (one each in the 75 mg and 225 mg groups). Other gastrointestinal serious adverse events included constipation in two patients (one each in the 7·5 mg and 22·5 mg groups), appendicitis in one patient (in the placebo group), and diarrhoea in one patient (in the placebo group). Adenocarcinoma of the colon, anal abscess, anal fistula, and vomiting occurred in the 7·5 mg group; *Clostridium difficile* infection in the 75 mg group (in a patient who also had concurrent active ulcerative colitis); and abdominal pain in the 225 mg group.

Before randomisation, there were 15 serious adverse events in 13 patients, including six cases of ulcerative colitis, one case of anal fistula and perirectal abscess, and one case of proctalgia. During the 12-week study, 21 patients discontinued treatment, including 12 who withdrew because of adverse events. Most withdrawals related to adverse events were attributable to worsening of ulcerative colitis (n=7) and other gastrointestinal events (n=3) in the placebo and active-treatment groups (figure). Most of these adverse events occurred in the 7·5 mg group (n=6) during the first 30 days of the study.

One patient in the 7·5 mg group died from adenocarcinoma of the colon. Before enrolment, the patient had substantial weight loss over a short time, with a body-mass index of 15·8 kg/m² at screening. The pre-study colonoscopy was abnormal with a stenotic area in the rectum, but biopsy did not show dysplasia. A further 10% weight loss occurred within the first 4 weeks on the study drug; repeat sigmoidoscopy at that time revealed more significant stenosis than previously observed, and biopsy of the stenotic lesion showed adenocarcinoma. The patient discontinued the study drug and died from metastatic colon cancer 3 months later. The cancer was considered to be present before enrolment (despite the

	Placebo (n=73)	PF-00547659			
		7·5 mg (n=71)	22·5 mg (n=70)	75 mg (n=73)	225 mg (n=70)
All adverse events					
Number of adverse events	83	121	79	85	117
Patients with an adverse event	39 (53·4%)	41 (57·7%)	36 (51·4%)	43 (58·9%)	43 (61·4%)
Infections and infestations	13 (17·8%)	13 (18·3%)	12 (17·1%)	17 (23·3%)	17 (24·3%)
Gastrointestinal disorders	14 (19·2%)	22 (31·0%)	9 (12·9%)	9 (12·3%)	12 (17·1%)
Nervous system disorders	8 (11·0%)	8 (11·3%)	8 (11·4%)	6 (8·2%)	15 (21·4%)
Musculoskeletal disorders	7 (9·6%)	10 (14·1%)	11 (15·7%)	8 (11·0%)	7 (10·0%)
General disorders and administration site conditions*	5 (6·8%)	7 (9·9%)	7 (10·0%)	11 (15·1%)	8 (11·4%)
Patients with serious adverse events	4 (5·5%)	10 (14·1%)	1 (1·4%)	3 (4·1%)	3 (4·3%)
Study discontinuation because of adverse events	2 (2·7%)	5 (7·0%)	0	3 (4·1%)	1 (1·4%)
Deaths	0	1 (1·4%)	0	0	0
Adverse events occurring in ≥4 patients in ≥1 treatment group					
Gastrointestinal disorders					
Ulcerative colitis	3 (4·1%)	7 (9·9%)	0	0	0
Abdominal pain	1 (1·4%)	6 (8·5%)	0	0	0
Nausea	2 (2·7%)	4 (5·6%)	0	0	4 (5·7%)
Vomiting	2 (2·7%)	0	4 (5·7%)	0	0
Nervous system disorders					
Headache	5 (6·8%)	5 (7·0%)	7 (10·0%)	4 (5·5%)	8 (11·4%)
Respiratory, thoracic, and mediastinal disorders					
Cough	4 (5·5%)	1 (1·4%)	0	1 (1·4%)	0
Blood and lymphatic system disorders					
Anaemia	0	0	0	4 (5·5%)	0

Values are n (%) unless otherwise noted. *Including non-treatment-related adverse events.

***Table 3*: Safety characteristics of patients**

negative biopsy) and therefore unlikely to be associated with the study drug. The external data monitoring committee agreed on this causality.

Discussion

Among patients with moderate to severe ulcerative colitis, the remission rate after 12 weeks of treatment with PF-00547659 at all doses was greater than that observed with placebo. The highest remission rates were recorded in the 22·5 mg and 75 mg dose groups. This inverse bell-shaped dose response—sometimes referred to as hormesis[13]—mirrored other clinical endpoints, with maximum effects observed at a dose below the highest dose studied. Mucosal healing rates were also greatest in patients receiving 22·5 mg and 75 mg PF-00547659, and the highest peak clinical response rate was seen in the 22·5 mg group. Endoscopy scores based on locally read results were consistently higher than those based on central reading. Change from baseline in total Mayo score was greatest with 22·5 mg PF-00547659, and the proportion of patients with a decrease from baseline in partial Mayo score of 2 or less at week 12 was highest in the 22·5 mg and 75 mg groups.

Assuming a placebo remission rate of 15%, the study was powered to detect a treatment difference of 20%. The observed placebo remission rate, however, was 2·7%, with the highest risk difference of 12·8%. Statistical significance was achieved with a reduced effect size while controlling for type-1 error with multiplicity adjustment, which still suggests a strong efficacy signal for PF-00547659. The placebo remission rate with locally read endoscopy scores in our study was 5·5%, which is consistent with that of published data,[14,15] and the greatest observed remission rate was 23·6%, with a risk difference of 17·8%, consistent with the original design. Centrally read endoscopy scores were consistently lower than locally read values, as has now been reported in various studies.[15,16]

The bell-shaped dose–response curve seen with different clinical parameters in this trial is consistent with the dose–response observed with etrolizumab in this indication.[15] In a previous phase 2 study of etrolizumab as induction therapy for ulcerative colitis, although maximum β7 occupancy was observed with both study doses (100 mg and 300 mg) and a drug concentration quartile versus response analysis did not show an exposure–response correlation, patients receiving 300 mg etrolizumab had reduced remission compared with those who received the 100 mg dose.[15] We believe that decreased activity at increased doses is related to over-depletion of regulatory T cells. In addition to regulatory T-cell depletion, over-depletion of the leucocyte subsets known to express α4β7 integrin, including intraepithelial lymphocytes,[17] mucosa-associated invariant T cells,[18] and eosinophils,[19] is likely to be undesirable and could underlie the weaker responses seen at higher doses. Our findings support the hypothesis that the gut effector cell population is more sensitive than the regulatory T-cell population to MAdCAM blockade, resulting in a net immunoregulatory phenotype in the intestine at decreasing efficacious doses, and a loss of this phenotype with increasing doses of PF-00547659.

The proportion of patients in each treatment group who achieved clinical remission at week 12 when analysed by previous anti-TNFα treatment exposure was similar to that reported in the overall study population. Among both anti-TNFα-naive and anti-TNF-experienced patients, treatment with PF-00547659 at all doses provided a greater response than that observed with placebo, with peak remission rates observed in the 22·5 mg and 75 mg dose groups. For all PF-00547659 doses, higher rates of remission were seen among patients who had not previously received an anti-TNFα agent than in patients who had. Similar findings were noted in a previous phase 2 study[15] with etrolizumab, in which clinical remission was mainly reported in a subgroup of patients who had not previously been given anti-TNFα agents.

Importantly, our primary efficacy analysis was based on blinded central endoscopy reading, although blinded local endoscopy readings were also made. Across all treatment groups, analysis based on blinded local endoscopy reads resulted in higher remission rates than those seen with blinded central endoscopy readings. A detailed analysis of the reasons for this discrepancy is beyond the scope of this Article. Results of previous studies have suggested that differences between local and central reading might be due to higher measurement noise with local endoscopy reading and point towards a need for standardisation and increased adoption of blinded central endoscopy reading as a means of ensuring that comparisons of efficacy between studies are valid.[9]

Faecal calprotectin has shown substantial promise as a non-invasive biomarker for detection of intestinal inflammation. Concentrations of faecal calprotectin have been found to correlate significantly with endoscopic activity of ulcerative colitis,[20] and a significant decrease in faecal calprotectin has been shown in association with clinical response and also with mucosal healing after drug therapy.[21,22] In our analysis, faecal calprotectin declined by 55–60% from baseline in all PF-00547659 dose groups compared with a 20% reduction among patients receiving placebo, although this decline did not directly reflect the clinical dose response. Reduction in hsCRP, another predictive factor and marker of inflammation in ulcerative colitis,[23] was also greater after treatment with PF-00547659 than with placebo. Consistent with clinical findings, the largest decreases in hsCRP concentration were observed in the 22·5 mg and 75 mg PF-00547659 groups and, in contrast to faecal calprotectin, seemed to correlate well with clinical outcomes.

All doses of PF-00547659 seemed safe and well tolerated in this patient population. The most common adverse events were related to the underlying disease, with no evidence of relationship to dose for any adverse event. However, since this trial was only 12 weeks in duration, these safety data should be interpreted with some degree of caution; a larger patient population treated for a longer period will be needed to fully assess the safety of PF-00547659 in patients with ulcerative colitis.

Although our study supports the efficacy of PF-00547659 in induction therapy for ulcerative colitis, its short duration leaves open the question of the efficacy and safety of PF-00547659 for maintenance therapy of ulcerative colitis. The unexpectedly low remission rate with placebo may be considered a further limitation; however, this rate was in line with that of other studies that used central rather than locally read endoscopy scores,[15] and the consistency and magnitude of the efficacy signal we observed suggest that PF-00547659 is worthy of further investigation.

In conclusion, PF-00547659 was better than placebo for induction of remission, response, and mucosal healing in patients with moderate to severe ulcerative colitis. The greatest clinical effects were observed in patients who received the 22·5 mg or 75 mg doses. The safety profile of PF-00547659 seemed to be similar to that of placebo. Further studies are required to define the long-term efficacy and safety of PF-00547659 in the treatment of ulcerative colitis.

Contributors

All authors contributed to the design of the study, the acquisition, analysis, and interpretation of the data, and development of the manuscript. All authors approved the final version of the manuscript for submission.

Declaration of interests

SV has received research support from AbbVie, MSD, and Takeda; consulting fees from AbbVie, Celgene, Ferring, Galapagos, Genentech/Roche, Hospira, Janssen, MSD, Mundipharma, Pfizer, Second Genome, Shire, and Takeda; and speaker fees from AbbVie, Falk Pharma, Ferring, Hospira, MSD, Takeda, and Tillotts. WJS reports grant support, personal fees, and non-financial support from Pfizer during the conduct of the study; grant support from Pfizer, Exact Sciences, Amgen, the American College of Gastroenterology, and the Broad Foundation; grant support and personal fees from Prometheus Laboratories, AbbVie, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, and Nutrition Science Partners; and personal fees from Kyowa Hakko Kirin, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Catabasis Pharmaceuticals, Vertex Pharmaceuticals, Warner Chilcott, Gilead Sciences, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid Biotechnologies, Tillotts Pharma, Am Pharma BV, Dr August Wolff, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, Index Pharmaceuticals, Nestlé, Lexicon Pharmaceuticals, UCB Pharma, Orexigen, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, Amgen, Novo Nordisk, Mesoblast, Shire, Ardelyx, Actavis, Seattle Genetics, MedImmune (AstraZeneca), Actogenix NV, Lipid Therapeutics Gmbh, Eisai, Qu Biologics, Toray Industries, Teva Pharmaceuticals, Eli Lilly, Chiasma, TiGenix, Adherion Therapeutics, Immune Pharmaceuticals, Celgene, Arena Pharmaceuticals, Ambrx, Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos, Seres Health, Ritter Pharmaceuticals, Theravance, Palatin, Biogen, and the University of Western Ontario (owner of Robarts Clinical Trials) outside the submitted work. WSJ also has a patent issued for topical azathioprine to treat inflammatory bowel disorders (US 5,691,343), a patent issued for topical formulations of azathioprine to treat inflammatory bowel disorders (US 5,905,081), patents issued for colonic delivery of nicotine to treat inflammatory bowel disease (South African patent 97/1020; US 5,846,983, 5,889,028, and 6,166,044; Mexico patent 209636; Europe patents 0954337 and 893998; Hong Kong patent HK1019043; China patent ZL97192177; Czech patent 293616; Canada patent 2,246,235), a patent issued for the use of azathioprine to treat Crohn's disease (US 5,733,915), a patent issued for azathioprine compositions for colonic administration (New Zealand patent 306062; Singapore patent 45647; Australia patent 707168; Czech patent 290428), patents issued for intestinal absorption of nicotine to treat nicotine-responsive conditions (Australia patent 718052; US 6,238,689), a patent issued for the use of topical azathioprine and thioguanine to treat colorectal adenomas (US 6,166,024), a patent issued for enterically coated oral dosage forms of azathioprine for enema (US 6,432,967), a patent issued for pharmaceutical composition for the treatment of inflammatory bowel disease (US 7,341,741), a patent issued for intestinal absorption of nicotine to treat nicotine-responsive conditions (Canada patent 2,260,909), and a patent licensed to Enteromedics for an obesity treatment and device (US 7,803,195 B2). SD has been a speaker, consultant, and advisory board member for AbbVie, Ferring, Hospira, Johnson & Johnson, Merck, Millennium, Takeda, Mundipharma, Pfizer, TiGenix, UCB Pharma, and Vifor, and has received personal fees from MSD, Allergan, Sandoz, Boehringer Ingelheim, and Celltrion. XH has served on advisory boards for AbbVie, Fresenius Kabi, Janssen, and Takeda, and has been involved in educational activities for AbbVie, Arard Pharma, Ferring, Fresenius Kabi, Mayoly Spindler, MSD, Nestlé, Norgine, Nutricia, and Takeda. BAS has received research support from AbbVie, Celgene, Gilead, Janssen,

Millennium, Pfizer, Prometheus, Redhill, and Takeda, and speaker fees from Janssen and Takeda. MK has received speaker fees from AbbVie, Alvogen, Ferring, and Takeda, and travel, accommodation, and meeting expenses from AbbVie, Alvogen, and Ferring, and research support from Pfizer. DT declares no competing interests. TV has served on advisory boards for Hospira, Pfizer, and Takeda. MG has received speaker or consultant fees from AbbVie, Alfa Wasserman, Ferring Pharmaceuticals, Hospira, MSD, Pfizer, and Takeda, and has been involved in the development of educational presentations, including speakers' bureaux, for Alfa Wasserman, Egis, Hospira, MSD, Takeda, and Vifor. PAH has received personal fees from Nature Coast Clinical Research, Cubist, Evoke, Ferring, Forest, Furiex, Gilead, GSK, Intercept, Ironwood, Menarini, Pfizer, Rhythm, Salix, Synergy, Takeda, Theravance, and Vivus. JSK declares no competing interests. MPS has received educational grants and research support from Ferring and Orphan; speaker's fees from AbbVie, Ferring, Hospira, Janssen, and Takeda; and has served on advisory boards for Janssen, Hospira, and Takeda. KJG was a contract employee of Pfizer during the course of the TURANDOT study. MH, AA, VP, MH-Z, RC, and FC were employees of Pfizer during the TURANDOT study. WR has received research support from Abbott Laboratories, AbbVie, AESCA, Centocor Biotech, Falk Pharma, Immundiagnostik, and MSD; consulting fees from 4SC, Abbott Laboratories, AbbVie, AESCA, Amgen, AM Pharma, Astellas, AstraZeneca, Avaxia Biologics, BioClinica, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix, ChemoCentryx, Celgene, Celltrion, Centocor, Covance, Danone Austria, Elan, Falk Pharma, Ferring, Galapagos, Genentech, Gilead, Grünenthal Group, ICON, Index Pharma, iNova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millennium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestlé, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trials, Schering-Plough, Second Genome, SetPoint Medical, Takeda, Therakos, TiGenix, UCB, Vifor, and Zyngenia; and speaker fees from Abbott Laboratories, AbbVie, AESCA, Aptalis, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult.

Acknowledgments

The TURANDOT study was funded by Pfizer. Medical writing support was provided by John Bilbruck and Paul Hassan of Engage Scientific Solutions, and was funded by Pfizer. The authors acknowledge statistical support from Pfizer, provided by Shen Mei Liao, and programming assistance from Pfizer, provided by Qiong Hua Zhao, Yan Shen, and Fang Wang. The authors are grateful to all investigators who participated in the TURANDOT study and to the members of the data monitoring committee: Colm O'Morain (Chair), Paola Cinque, David Clifford, Lauren Krupp, Glen Cooke, and Dan Anbar.

References

1 Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis. *Lancet* 2017; **389:** 1756–70.

2 Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. *BMJ* 2013; **346:** f432.

3 Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142:** 46–54 e42.

4 Allocca M, Fiorino G, Vermeire S, Reinisch W, Cataldi F, Danese S. Blockade of lymphocyte trafficking in inflammatory bowel diseases therapy: importance of specificity of endothelial target. *Expert Rev Clin Immunol* 2014; **10:** 885–95.

5 Ghosh S, Panaccione R. Anti-adhesion molecule therapy for inflammatory bowel disease. *Therap Adv Gastroenterol* 2010; **3:** 239–58.

6 Briskin M, Winsor-Hines D, Shyjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol* 1997; **151:** 97–110.

7 Parikh A, Leach T, Wyant T, et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. *Inflamm Bowel Dis* 2012; **18:** 1470–79.

8 Pullen N, Molloy E, Carter D, et al. Pharmacological characterization of PF-00547659, an anti-human MAdCAM monoclonal antibody. *Br J Pharmacol* 2009; **157:** 281–93.

9 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317:** 1625–29.

10 Gottlieb K, Travis S, Feagan B, Hussain F, Sandborn WJ, Rutgeerts P. Central reading of endoscopy endpoints in inflammatory bowel disease trials. *Inflamm Bowel Dis* 2015; **21:** 2475–82.

11 Mehrotra DV, Railkar R. Minimum risk weights for comparing treatments in stratified binomial trials. *Stat Med* 2001; **19:** 811–25.

12 Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998; **43:** 29–32.

13 Calabrese EJ, Blain RB. The hormesis database: the occurrence of hormetic dose responses in the toxicological literature. *Regul Toxicol Pharmacol* 2011; **61:** 73–81.

14 Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; **369:** 699–710.

15 Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet* 2014; **384:** 309–18.

16 Feagan BG, Sandborn WJ, D'Haens G, et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. *Gastroenterology* 2013; **145:** 149–57 e2.

17 Sheridan BS, Lefrancois L. Intraepithelial lymphocytes: to serve and protect. *Curr Gastroenterol Rep* 2010; **12:** 513–21.

18 Serriari NE, Eoche M, Lamotte L, et al. Innate mucosal-associated invariant T (MAIT) cells are activated in inflammatory bowel diseases. *Clin Exp Immunol* 2014; **176:** 266–74.

19 Jung Y, Rothenberg ME. Roles and regulation of gastrointestinal eosinophils in immunity and disease. *J Immunol* 2014; **193:** 999–1005.

20 D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18:** 2218–24.

21 De Vos M, Dewit O, D'Haens G, et al. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNFα naïve patients with ulcerative colitis. *J Crohns Colitis* 2012; **6:** 557–62.

22 Sipponen T, Björkesten CG, Färkkilä M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. *Scand J Gastroenterol* 2010; **45:** 325–31.

23 Henriksen M, Jahnsen J, Lygren I, et al. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. *Gut* 2008; **57:** 1518–23.