

# Effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in patients with Crohn's disease or ulcerative colitis who had failed conventional therapy

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## SUMMARY

### Background

Adalimumab is approved for use in patients with moderate to severe Crohn's disease (CD) or ulcerative colitis (UC) who have not achieved disease control with conventional therapies including corticosteroids and/or immunomodulators (IMM).

### Aim

To analyse six studies that examined efficacy, pharmacokinetics and safety of combination IMM/adalimumab therapy, compared with adalimumab monotherapy in patients with inadequate disease control on conventional therapy.

### Methods

Patients with moderate to severe CD or UC from randomised, double-blind, placebo-controlled trials were analysed. Adalimumab was added to background therapy; patients were categorised as receiving adalimumab monotherapy (CD induction,  $n = 245$ , maintenance,  $n = 185$ ; UC induction,  $n = 213$ , maintenance,  $n = 157$ ) or combination therapy (CD induction,  $n = 139$ , maintenance,  $n = 139$ ; UC induction,  $n = 140$ , maintenance,  $n = 100$ ) according to baseline immunomodulator use. Efficacy was reported for the intent-to-treat populations from each study, with remission defined as CD activity index  $<150$  for CD and Mayo score  $\leq 2$  with no subscore  $>1$  for UC. Safety was assessed via adverse events.

### Results

The proportions of patients achieving remission were similar for adalimumab monotherapy and immunomodulator combination therapy in all studies. Median adalimumab concentrations at week 4 or 8 were numerically but not significantly higher with adalimumab combination therapy vs. monotherapy in the CD and UC studies respectively. Incidence and rate of adverse events was similar for adalimumab monotherapy and combination therapy.

### Conclusions

*Post hoc* analysis of six randomised, controlled trials demonstrated no efficacy benefits with immunomodulator/adalimumab combination therapy, compared with adalimumab monotherapy in CD and UC patients with inadequate disease control on conventional therapy; the safety of the two treatment approaches was comparable.

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## INTRODUCTION

Adalimumab, a recombinant human immunoglobulin monoclonal antibody that binds to human tumour necrosis factor (TNF), is approved for use in patients with moderate to severe Crohn's disease (CD) or ulcerative colitis (UC) who have failed conventional therapy with corticosteroids and/or immunomodulators.<sup>1–6</sup> Opinions regarding whether anti-TNF therapies such as adalimumab should be given alone or in combination with immunomodulators have changed over the years, largely based on the evolving information about the benefits and risks of treatment.

The benefit of combination therapy in patients failing immunomodulators has not been studied in prospective clinical trials. However, randomised, controlled studies have demonstrated that a combination of immunomodulator and anti-TNF therapy is superior to either treatment alone in patients who are naïve to both. In SONIC, patients with CD, who were naïve to anti-TNF agents and thiopurines, experienced greater efficacy at weeks 26 and 50 with the combination of infliximab/thiopurine therapy compared with monotherapy with either agent.<sup>7</sup> Infliximab trough levels at week 30 were approximately twice as high and immunogenicity was less frequent in patients receiving combination therapy compared with those receiving infliximab alone.<sup>7</sup> Similarly, a greater percentage of patients with UC who were treated with a combination of infliximab and azathioprine achieved corticosteroid-free remission at week 16 in the SUCCESS clinical trial compared with patients treated with infliximab or azathioprine monotherapy.<sup>8</sup> Patients in SUCCESS were either azathioprine-naïve or azathioprine-free for 3 months before enrolment.

Based on the results of SONIC, many experts recommend the use of combination therapy for patients in whom any anti-TNF therapy is initiated; however, definitive data are lacking for anti-TNF therapies other than infliximab. In addition, in clinical practice, many patients do not initiate anti-TNF therapy until failure of immunomodulator therapy, and clinicians are faced with the question of whether continuation of previous immunomodulator therapy is advisable. The benefits and risks of combination therapy in this setting may differ from its use in patients naïve to either drug category.

Multiple studies have demonstrated that thiopurines are associated with an increased risk of malignancies including lymphoproliferative disorders and non-melanoma skin cancers (NMSC).<sup>9–14</sup> Patients treated with thiopurines had an increased risk of malignancies

compared with patients receiving anti-TNF therapy alone or in combination with thiopurines.<sup>15</sup> A pooled analysis of placebo-controlled registration trials of adalimumab in Crohn's disease revealed an increased risk of malignancies and NMSC with immunomodulator and anti-TNF combination therapy compared with adalimumab alone.<sup>16</sup> Furthermore, a recent retrospective cohort study in patients with CD identified no efficacy and safety benefit of infliximab or adalimumab combination therapy compared with immunomodulator monotherapy, whereas the risk of opportunistic infections was significantly increased with infliximab combination therapy.<sup>17</sup> However, all occurrences of hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease (IBD) were reported in patients treated with thiopurine monotherapy or thiopurine/anti-TNF combination therapy.<sup>18</sup> Therefore, the use of immunomodulator and anti-TNF combination therapy in patients with IBD warrants weighing of the benefits and risks.

The current analysis examined the efficacy, pharmacokinetics (PK) and safety of combination immunomodulator/adalimumab therapy compared with adalimumab monotherapy in patients with inadequate disease control on conventional therapy. Data from six randomised, double-blind, placebo-controlled, phase 3 clinical studies from the CD and UC development programme for adalimumab were included.

## METHODS

### Study designs and patients

Patients with moderate to severe CD [Crohn's Disease Activity Index (CDAI) of 220–450] or moderately to severely active UC (Mayo score of 6–12; endoscopy subscore of 2–3) from randomised, double-blind, placebo-controlled trials for the induction or maintenance of remission or mucosal healing (CLASSIC-I, GAIN, CHARM, EXTEND, ULTRA 1 and ULTRA 2) were included in this analysis. The designs of these six trials have been described previously,<sup>1–6</sup> and a descriptive summary of the studies and patients included in these analyses is shown in Table S1. The CD induction (CLASSIC-I, GAIN) and maintenance studies (CHARM and EXTEND), the UC induction study (ULTRA 1), and the UC induction/maintenance study (ULTRA 2) were all analysed individually. In all studies, adalimumab was added to stable background therapy for CD or UC. Patients were categorised as receiving adalimumab monotherapy or combination therapy according to

baseline immunomodulator use (azathioprine, mercaptopurine or methotrexate). Patients receiving adalimumab monotherapy in this analysis may or may not have failed treatment with immunomodulators in the past, while patients receiving adalimumab combination therapy were those who entered the trial with active disease on immunomodulator therapy. By study design, immunomodulator therapy was to be continued with the dosage remaining constant throughout each study. Discontinuation or dose reduction was only permitted in the case of immunomodulator-related toxicity.

In this analysis, efficacy was reported for the patients from the intent-to-treat (ITT) populations from each study as outlined below. For patients with CD from the induction studies CLASSIC-I and GAIN, analysed patients were those randomised to blinded placebo or adalimumab 160 mg and 80 mg at weeks 0 and 2 respectively. For patients from EXTEND, analysed patients received open-label induction adalimumab 160 mg and 80 mg at weeks 0 and 2, respectively, followed by blinded placebo or adalimumab 40 mg every other week to week 52. For patients from CHARM, analysed patients were randomised responders (patients who received open-label induction adalimumab 80 and 40 mg at weeks 0 and 2, respectively, had a response at week 4, and were randomised to either blinded placebo, adalimumab 40 mg every other week, or 40 mg weekly to week 56). For patients with UC from the ULTRA 1 induction study, the population analysed included only patients who enrolled after amendment 3 and were randomised to blinded placebo or adalimumab 160 and 80 mg at weeks 0 and 2, respectively, followed by 40 mg every other week to week 8. ULTRA 1 had an open-label period from weeks 8 to 52 in which all patients received adalimumab 40 mg every other week, but those data are not included in this analysis. For the ULTRA 2 induction/maintenance study, analysed patients were those randomised to blinded placebo or adalimumab 160 and 80 mg at weeks 0 and 2, respectively, followed by 40 mg every other week up to week 52, except 24 patients who were excluded from the ITT population for noncompliance of the site with Good Clinical Practice. Safety analyses included all patients who received  $\geq 1$  dose of study drug in each of these studies, including patients who received 40/20 mg and 80/40 mg adalimumab induction dosing in CLASSIC-I, 80/40 mg adalimumab induction dosing in ULTRA 1, and patients excluded from the ITT population in ULTRA 2 due to study site noncompliance. Treatment-emergent adverse events experienced during the double-blind treatment period are reported.

### Concomitant medications

In the adalimumab CD and UC programmes, all enrolled patients were required to have failed current or past conventional therapy. Failure of conventional therapy was defined as inadequate disease control on concomitant therapy with corticosteroids and/or immunomodulator therapy at study baseline, or demonstrated inadequate disease control or intolerance to these agents in the past. For the CD studies, concurrent use at baseline of stable dosages of 5-aminosalicylates, azathioprine, mercaptopurine, methotrexate and CD-related antibiotics, prednisone (maximum allowable dosage ranged from 20 to 40 mg/day, depending on the study) and budesonide ( $\leq 9$  mg/day) was permitted in patients taking those medications at baseline.<sup>1–4</sup> In the UC studies, concurrent use of stable doses of UC-related medications was permitted in patients taking those medications at baseline.<sup>5, 6</sup> In all studies, concomitant immunomodulator doses were to remain stable (except in the case of immunomodulator-related toxicity, in which case doses could be reduced or discontinued). Corticosteroid tapers were defined in each protocol.

### PK assessments

Serial samples for PK analyses were collected at designated time points from all patients treated with adalimumab in the CLASSIC-I (week 4),<sup>1</sup> GAIN (week 4)<sup>2</sup> and ULTRA 2 (baseline, weeks 2, 4, 6, 32 and 52)<sup>6</sup> studies. Serum concentrations of adalimumab were measured by a validated enzyme-linked immunosorbent assay adapted from Weisman *et al.*<sup>19, 20</sup> Median trough levels were reported for adalimumab-treated patients according to baseline immunomodulator use. Missing data were not imputed; summaries are for patients receiving 40 mg every other week. Despite a known effect of methotrexate on adalimumab PK<sup>21</sup> and the lack of a similar effect of other immunomodulators,<sup>22, 23</sup> data from all immunomodulators were combined because of the relatively small number of patients receiving methotrexate.

### Statistical analysis

Remission was defined as a CDAI  $< 150$  in patients with CD and a Mayo score  $\leq 2$  with no subscore  $> 1$  for patients with UC. Mucosal healing in the UC studies was defined as an endoscopic subscore  $\leq 1$ . Nonresponder imputation was used for missing data and patients who received open-label adalimumab during the double-blind period of each study. Remission rates were compared between adalimumab and placebo for the monotherapy

and combination groups using the Fisher exact test. Statistical comparisons of effect size were based on Z-score. Odds ratios (ORs) and 95% CIs were calculated relative to placebo according to immunomodulator use at baseline.

A sensitivity analysis was performed to evaluate the efficacy of combination or monotherapy in patients with CD who had objective evidence of active inflammation, defined by baseline C-reactive protein (CRP) levels  $\geq 1$  mg/dL. A similar sensitivity analysis was performed for patients with UC who had active inflammatory disease defined by baseline rectal bleeding scores of  $\geq 1$ . Remission rates based on the presence of baseline rectal bleeding or baseline elevated CRP values in patients treated with adalimumab monotherapy and combination therapy were compared with patients receiving the respective placebo controls using the Fisher exact test.

The incidence of adverse events was presented for adalimumab- and placebo-treated patients according to baseline immunomodulator use for the induction studies (CLASSIC-I, GAIN and ULTRA 1). For the maintenance studies (CHARM, EXTEND and ULTRA 2), which were of longer duration, the number of events and rate of events per 100 patient-years was calculated. No statistical testing was performed with safety data.

## RESULTS

This analysis included 1382 patients with CD and 754 patients with UC. Baseline patient characteristics and demographics have been described and detailed previously.<sup>1–6</sup> A summary of baseline disease severity, disease duration, and concomitant corticosteroid and immunomodulator use at baseline is presented for patients with CD and UC in Tables S2 and S3 respectively.

In CD studies, baseline disease severity assessed by mean CDAI ranged from 285.7 to 322.7 among the analysis groups and mean disease duration ranged from 6.86 to 13.53 years (Tables S2 and S3); there were no notable differences among studies or in patients receiving combination therapy as compared with those receiving monotherapy. Across the analysis groups, 13.9–51.8% of patients were receiving concomitant steroids at baseline. In both the monotherapy and combination therapy cohorts in EXTEND, fewer patients randomised to adalimumab than placebo were receiving corticosteroids at baseline. Azathioprine was the most commonly used immunomodulator at baseline, followed by mercaptopurine or methotrexate. Discontinuation of

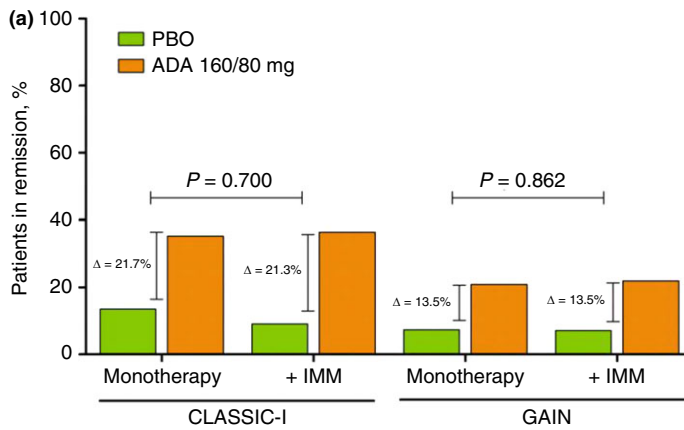
immunomodulators was only permitted in the cases of immunomodulator-related toxicity. Of patients with immunomodulator use at baseline, 93.5% (462/494) completed the studies receiving combination therapy. Mean CRP levels were  $\geq 1$  mg/dL in every analysis group; the mean (from 1.08 to 2.66 mg/dL) and median (range, 0.37–1.51 mg/dL) values were variable across groups and studies.

In UC studies, mean Mayo scores and rectal bleeding subscores across analysis groups reflected moderately to severely active UC (from 8.6 to 9.1 and 1.5 to 1.8 respectively; Table S3) and mean disease duration ranged from 6.93 to 9.04 years. Across groups, 45.1%–70.5% of patients with UC were receiving concomitant steroids at baseline. Concomitant use of azathioprine at baseline was more common than use of mercaptopurine. Of the patients with immunomodulator use at baseline, 94.6% (261/276) completed the studies receiving combination therapy.

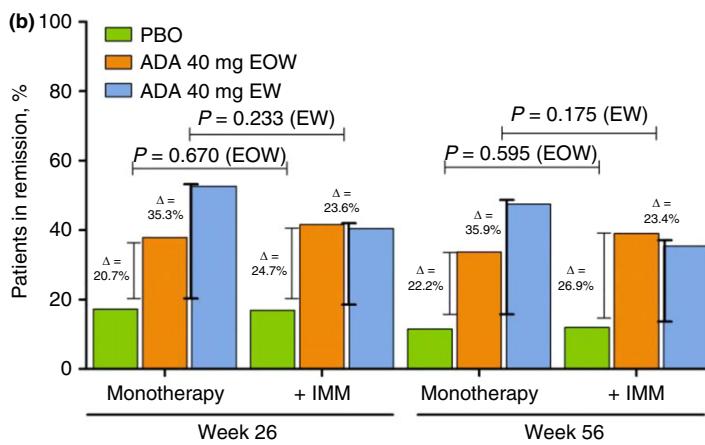
### Crohn's disease studies

**Efficacy.** The proportion of patients who achieved clinical remission along with treatment effect size (rates for adalimumab minus placebo) comparisons and odds ratios (with 95% CIs) are presented by adalimumab monotherapy and combination therapy subgroups and their placebo comparisons in Figure 1. The proportions of patients who achieved clinical remission (CDAI <150) at the reported time points in the induction studies and maintenance studies were generally similar in adalimumab monotherapy and combination therapy groups. Odds ratios for remission were similar in patients treated with adalimumab monotherapy compared with combination therapy at each time point (Figure 1). In the sensitivity analysis of patients with CRP levels  $\geq 1$  mg/dL at baseline, remission rates generally appeared similar between the adalimumab monotherapy and combination therapy groups, and no consistent pattern was observed (Table S4).

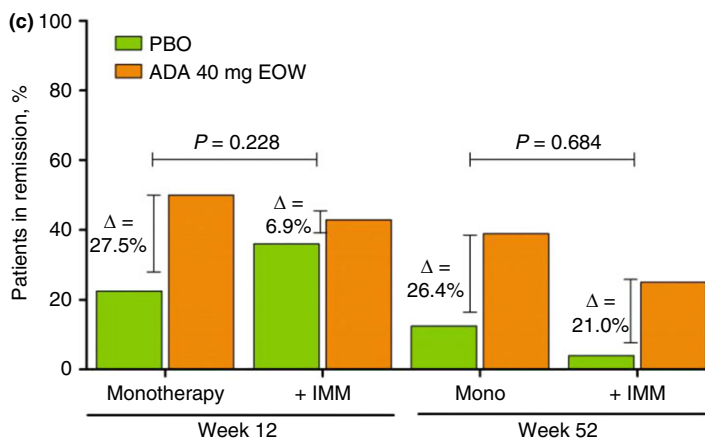
**Pharmacokinetics and immunogenicity.** In the CLASSIC-I and GAIN studies, median adalimumab trough levels at week 4 trended slightly higher but were not significantly different ( $P > 0.05$ ) in patients treated with adalimumab combination therapy compared with adalimumab monotherapy (CLASSIC-I, 12.90 vs. 11.40  $\mu\text{g/mL}$  respectively; GAIN, 13.30 vs. 11.40  $\mu\text{g/mL}$  respectively; Figure 2a and Figure 2b). All seven patients who were positive for anti-adalimumab antibodies were receiving adalimumab monotherapy.



	Odds ratio (95% CI) ADA vs PBO
<b>CLASSIC-I</b>	
Week 4	
Mono	3.49 (1.32, 9.23)
+ IMM	5.71 (1.05, 31.07)
<b>GAIN</b>	
Week 4	
Mono	3.31 (1.24, 8.82)
+ IMM	3.70 (1.36, 10.03)



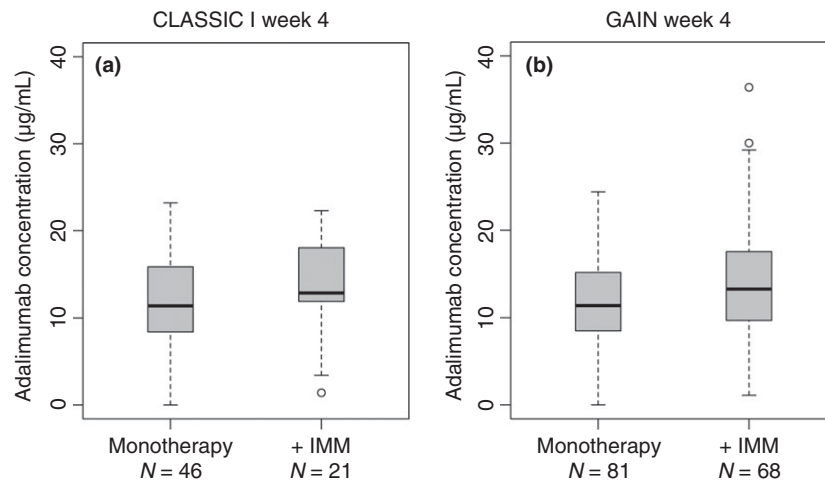
	Odds ratio (95% CI) ADA vs PBO	
<b>CHARM</b>		
Week 26		
Mono	40 mg EOW: 2.93 (1.46, 5.86)	40 mg EW: 5.32 (2.61, 10.84)
+ IMM	3.50 (1.69, 7.29)	3.36 (1.62, 6.96)
Week 52		
Mono	3.91 (1.79, 8.57)	6.95 (3.14, 15.38)
+ IMM	4.66 (2.08, 10.41)	4.01 (1.79, 8.97)



	Odds ratio (95% CI) ADA vs PBO
<b>EXTEND</b>	
Week 12	
Mono	3.44 (1.28, 9.26)
+ IMM	1.33 (0.44, 4.04)
Week 52	
Mono	4.45 (1.41, 14.10)
+ IMM	8.00 (0.91, 70.46)

**Figure 1** | Proportion of patients with Crohn’s disease receiving adalimumab monotherapy or combination therapy achieving clinical remission (CDAI <150). (a) Remission at week 4 in the induction CLASSIC-I and GAIN studies. (b) Remission at weeks 26 and 56 in the maintenance CHARM study. (c) Remission at weeks 12 and 52 in the maintenance EXTEND study. Differences in the percentage of patients achieving clinical remission between adalimumab and placebo are shown on the graph for each treatment, with P values for the comparison of effect sizes between monotherapy and combination therapy. Table shows odds ratio (95% CI) between adalimumab and placebo for each treatment group. ADA, adalimumab; EOW, every other week; EW, every week; IMM, immunomodulator; PBO, placebo.





**Figure 2** | Median adalimumab trough levels in patients with Crohn's disease receiving adalimumab monotherapy or combination therapy with immunomodulators (IMMs) in (a) CLASSIC-I and (b) GAIN at week 4. Patients received 160 mg of adalimumab at week 0 and 80 mg at week 2. Concentrations reported are for patients receiving adalimumab 40 mg every other week as maintenance therapy. In each plot, the middle line in the box represents the median, the bottom of the box represents the first quartile (Q1), and the top of the box represents the third quartile (Q3). The error bars represent  $\pm 1.5$  times the interquartile range (Q1–Q3). The open circles represent outliers beyond 1.5 times the interquartile range.

**Safety.** In general, the adverse event profiles of patients treated with adalimumab monotherapy or combination therapy were similar (Table 1). In the induction studies, the incidence of serious adverse events differed little between the adalimumab monotherapy and adalimumab combination therapy groups (1.6% vs. 1.4% respectively); serious adverse event rates in the maintenance studies were higher in the combination therapy group (16.1 vs. 21.9 events per 100 patient-years respectively). The incidence of infectious adverse events was similar with adalimumab monotherapy compared with adalimumab combination therapy (14.7% vs. 16.5% respectively) in induction studies and rates (159.8 vs. 176.1 events per 100 patient-years) in maintenance studies. In the induction studies, two patients receiving adalimumab monotherapy, but none receiving adalimumab combination therapy, experienced serious infectious adverse events. The rates of serious infectious adverse events in the maintenance studies were low in the adalimumab monotherapy and combination therapy groups (3.0 and 5.1 events per 100 patient-years respectively). One malignant adverse event (breast cancer) was reported by a patient receiving placebo monotherapy in the CHARM maintenance study, and no malignant adverse events were reported in patients treated with adalimumab monotherapy or combination therapy in any of the studies. No lymphoma occurred.

#### Ulcerative colitis studies

**Efficacy.** The proportion of patients who achieved clinical remission (full Mayo score  $\leq 2$  and no subscore  $>1$ ), along with treatment effect size (rates for adalimumab minus placebo) comparisons, and odds ratios (with 95% CIs) are presented by adalimumab monotherapy and combination therapy subgroups and their placebo comparisons for the ULTRA 1 and ULTRA 2 studies in Figure 3. The proportion of patients who achieved clinical remission was similar in patients treated with adalimumab monotherapy compared with adalimumab combination therapy in the induction and maintenance studies (Figure 3). Likewise, the percentage of patients who achieved mucosal healing (endoscopy score  $\leq 1$ ) was similar in patients treated with adalimumab monotherapy or adalimumab combination therapy in both studies. In the sensitivity analysis to evaluate efficacy in patients with inflammatory UC, defined by a rectal bleeding score of  $\geq 1$  at baseline, full Mayo score remission rates were numerically higher in patients treated with adalimumab monotherapy (20.3%) compared with adalimumab combination therapy (14.9%) at week 8 in ULTRA 1 and ULTRA 2 (19.4% vs. 13.3% respectively). However, by week 52 in ULTRA 2, the rates of Mayo remission were similar in the two cohorts (Table S5).

**Table 1 |** Comparison of treatment-emergent AE profiles in patients treated with adalimumab or placebo monotherapy or combination therapy in randomised, double-blind studies in patients with Crohn's disease

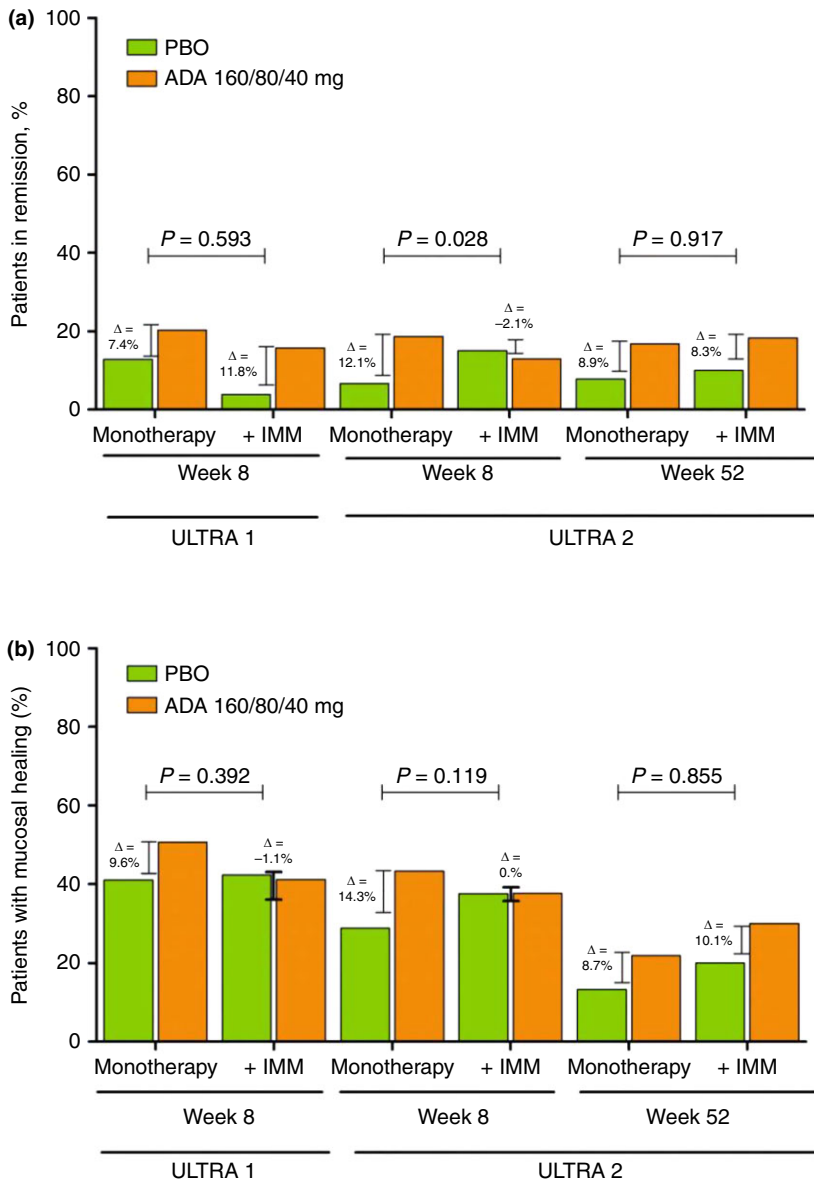
AE	Monotherapy		Combination therapy	
	Placebo	Adalimumab	Placebo	Adalimumab
CLASSIC-I and GAIN, n (%)	n = 133	n = 245	n = 107	n = 139
Any AE	88 (66.2)	155 (63.3)	88 (82.2)	94 (67.6)
Any severe AE	13 (9.8)	20 (8.2)	14 (13.1)	11 (7.9)
Any serious AE	4 (3.0)	4 (1.6)	7 (6.5)	2 (1.4)
Any AE leading to discontinuation of study drug	3 (2.3)	3 (1.2)	3 (2.8)	1 (0.7)
Any infectious AE	25 (18.8)	36 (14.7)	26 (24.3)	23 (16.5)
Any serious infectious AE	0	2 (0.8)	4 (3.7)	0
Any malignant AE	0	0	0	0
Any lymphoma AE	0	0	0	0
Any NMSC AE	0	0	0	0
CHARM and EXTEND, events (events/100 PY) [95% CI]	n = 168 (PYs = 55.6)	n = 185 (PYs = 99.5)	n = 158 (PYs = 58.2)	n = 139 (PYs = 77.8)
Any AE	621 (1116.9) [1032.4–1208.3]	812 (816.1) [761.8–874.2]	574 (986.3) [908.8–1070.3]	630 (809.8) [748.9–875.5]
Any severe AE	63 (113.3) [88.5–145.0]	41 (41.2) [30.3–56.0]	48 (82.5) [62.2–109.4]	32 (41.1) [29.1–58.2]
Any serious AE	33 (59.4) [42.2–83.5]	16 (16.1) [9.9–26.2]	20 (34.4) [22.2–53.3]	17 (21.9) [13.6–35.1]
Any AE leading to discontinuation of study drug	24 (43.2) [28.9–64.4]	22 (22.1) [14.6–33.6]	17 (29.2) [18.2–47.0]	11 (14.1) [7.8–25.5]
Any infectious AE	107 (192.4) [159.2–232.6]	159 (159.8) [136.8–186.7]	102 (175.3) [144.3–212.8]	137 (176.1) [148.9–208.2]
Any serious infectious AE	6 (10.8) [4.8–24.0]	3 (3.0) [1.0–9.3]	3 (5.2) [1.7–16.0]	4 (5.1) [1.9–13.7]
Any malignant AE	1 (1.8) [0.3–12.8]	0	0	0
Any lymphoma AE	0	0	0	0
Any NMSC AE	0	0	0	0

ADA, adalimumab; AE, adverse event; NMSC, nonmelanoma skin cancer; PY, patient-years.

**Pharmacokinetics and immunogenicity.** Pharmacokinetic analysis was performed only in the ULTRA 2 trial. Similar to studies in patients with CD, median adalimumab concentrations in the ULTRA 2 study at week 8 trended slightly higher (8.76 vs. 7.42 µg/mL) but were not significantly different ( $P > 0.05$ ) in patients treated with adalimumab combination therapy compared with adalimumab monotherapy (Figure 4a), with a similar trend observed with median adalimumab concentrations at week 52 (7.74 vs. 6.23 µg/mL; Figure 4b). All 19 patients who were positive for anti-adalimumab antibodies were receiving adalimumab monotherapy.

**Safety.** In the ULTRA 1 induction study, the adverse event profiles of patients treated with adalimumab monotherapy or combination therapy were similar. In the ULTRA 2 induction/maintenance study, the rates of

most categories of AEs appeared lower with adalimumab combination therapy compared with adalimumab monotherapy (Table 2). The incidence of serious adverse events was nearly identical between the adalimumab monotherapy and adalimumab combination therapy groups (4.2% vs. 4.3% respectively) in ULTRA 1, but the serious adverse event rate in ULTRA 2 was numerically higher with adalimumab monotherapy compared with adalimumab combination therapy (38.0 vs. 21.0 events per 100 patient-years respectively). Infectious adverse events occurred with a similar incidence in patients treated with adalimumab monotherapy compared with adalimumab combination therapy (17.4% vs. 17.9% in ULTRA 1 respectively), whereas rates were slightly higher with adalimumab monotherapy compared with adalimumab combination therapy (154.5 vs. 132.3 events per 100 patient-years in ULTRA 2). In ULTRA 1, the



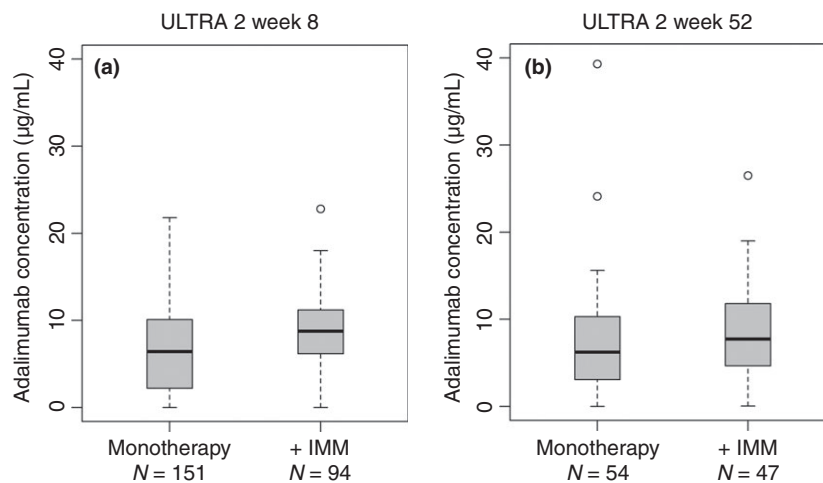
	Odds ratio (95% CI) ADA vs PBO
<b>ULTRA 1</b>	
Week 8	
Mono	1.73 (0.73, 4.09)
+ IMM	4.65 (0.94, 23.09)
<b>ULTRA 2</b>	
Week 8	
Mono	3.24 (1.56, 6.75)
+ IMM	0.84 (0.35, 1.99)
Week 52	
Mono	2.37 (1.17, 4.80)
+ IMM	2.01 (0.82, 4.95)
<b>ULTRA 1</b>	
Week 8	
Mono	1.47 (0.78, 2.77)
+ IMM	0.95 (0.44, 2.09)
<b>ULTRA 2</b>	
Week 8	
Mono	1.87 (1.18, 2.97)
+ IMM	1.01 (0.54, 1.86)
Week 52	
Mono	1.84 (1.02, 3.31)
+ IMM	1.72 (0.85, 3.49)

**Figure 3 | Efficacy in patients with ulcerative colitis treated with adalimumab monotherapy or combination therapy. (a) Proportion of patients with clinical remission (Full Mayo Score ≤2) at week 8 in ULTRA 1 and weeks 8 and 52 in ULTRA 2. (b) Proportion of patients with mucosal healing (endoscopy subscore ≤1) at week 8 in ULTRA 1 and weeks 8 and 52 in ULTRA 2. Differences in the percentages of patients achieving clinical remission or mucosal healing between adalimumab and placebo are shown on the graph for each treatment group, with P values for comparison of effect sizes between monotherapy and combination therapy. Table shows odds ratio (95% CI) between adalimumab and placebo for each treatment group. ADA, adalimumab; IMM, immunomodulator; PBO, placebo.**

incidence of serious infectious adverse events was low in patients who received adalimumab monotherapy (0.5%) or adalimumab combination therapy (1.4%). In ULTRA 2, the rate of serious infectious adverse events was 4.8 events for 100 patient-years for patients receiving adalimumab monotherapy and 0 for patients treated with

adalimumab combination therapy. In the ULTRA 1 study, one patient treated with placebo monotherapy and one patient treated with placebo combination therapy reported a malignant adverse event (basal cell carcinoma and breast cancer). In the ULTRA 2 study, one malignant adverse event was reported in a patient treated with





**Figure 4** | Median adalimumab trough levels in patients with ulcerative colitis receiving adalimumab monotherapy or combination therapy with immunomodulators (IMMs) in ULTRA 2 at (a) week 8 and (b) week 52. IMM, immunomodulator. Patients received 160 mg of adalimumab at week 0, 80 mg of adalimumab at week 2, and 40 mg every other week beginning at week 4. In each plot, the middle line in the box represents the median, the bottom of the box represents the first quartile (Q1) and the top of the box represents the third quartile (Q3). The error bars represent  $\pm 1.5$  times the interquartile range (Q1–Q3). The open circles represent outliers beyond 1.5 times the interquartile range.

adalimumab monotherapy and in one patient that received combination therapy (squamous cell carcinoma and 1 gastric cancer; Table 2). No lymphoma occurred.

## DISCUSSION

This exploratory *post hoc* analysis of placebo-controlled induction and maintenance studies in patients with CD or UC did not identify an efficacy advantage of adalimumab combination therapy (when added to background inadequately effective immunomodulator use) over adalimumab monotherapy in patients who entered these studies with moderate to severe disease activity. These results are consistent with the findings of an IBD-subgroup analysis of infliximab maintenance therapy across four randomised trials (two in patients with CD; two in patients with UC); no consistent trend in improved efficacy was observed between patients in whom infliximab was added to background immunomodulator therapy compared to patients who received infliximab monotherapy.<sup>24</sup> A recent retrospective cohort study of patients with CD who received Medicare benefits and were new to anti-TNF therapy examined the benefit of continuing immunomodulator therapy when stepping up to anti-TNF therapy with either infliximab or adalimumab. Continuation of the immunomodulator did not result in improved outcomes, but was associated with increased opportunistic

infections compared with anti-TNF monotherapy.<sup>17</sup> A meta-analysis of 11 randomised, controlled trials of anti-TNF therapies in patients with CD, excluding studies of patients naïve to both immunomodulators and thiopurines, concluded that nearly all clinical outcomes were similar with anti-TNF monotherapy compared with anti-TNF combination therapy.<sup>25</sup> However, with infliximab, a statistically significant protective effect of baseline immunomodulator vs. no baseline immunomodulator exposure was observed for the induction of treatment response and in a sensitivity analysis for remission at 6 months.<sup>25</sup> Finally, a systematic review and meta-analysis of adalimumab monotherapy vs. combination therapy included data from randomised, controlled trials, prospective open-label and observational studies.<sup>26</sup> That analysis showed an increased probability of induction of clinical remission with combination therapy; however, no advantage was observed with maintenance therapy.<sup>26</sup> A distinguishing feature of our analyses was the inclusion of pharmacokinetic data as well as detailed safety assessments.

Another key finding of the current analysis was that, although trough adalimumab levels in patients with CD and UC treated with immunomodulator combination therapy trended slightly higher than the trough adalimumab levels in patients treated with adalimumab monotherapy, the differences were not significant, and

**Table 2 | Comparison of treatment-emergent AE profiles in patients treated with adalimumab or placebo monotherapy or combination therapy in randomised, double-blind studies in patients with ulcerative colitis**

AE	Monotherapy		Combination therapy	
	Placebo	Adalimumab	Placebo	Adalimumab
ULTRA 1, <i>n</i> (%)	<i>n</i> = 136	<i>n</i> = 213	<i>n</i> = 87	<i>n</i> = 140
Any AE	71 (52.2)	117 (54.9)	49 (56.3)	71 (50.7)
Any severe AE	12 (8.8)	17 (8.0)	7 (8.0)	11 (7.9)
Any serious AE	10 (7.4)	9 (4.2)	8 (9.2)	6 (4.3)
Any AE leading to discontinuation of study drug	10 (7.4)	14 (6.6)	5 (5.7)	7 (5.0)
Any infectious AE	21 (15.4)	37 (17.4)	20 (23.0)	25 (17.9)
Any serious infectious AE	2 (1.5)	1 (0.5)	1 (1.1)	2 (1.4)
Any malignant AE	1 (0.7)	0	1 (1.1)	0
Any lymphoma AE	0	0	0	0
Any NMSC AE	0	0	1 (1.1)	0
ULTRA 2, events (events/100 PY) [95% CI]	<i>n</i> = 170 (PYs = 73.8)	<i>n</i> = 157 (PYs = 84.1)	<i>n</i> = 90 (PYs = 46.3)	<i>n</i> = 100 (PYs = 62.0)
Any AE	682 (923.8) [857.0–995.8]	679 (807.1) [748.7–870.2]	334 (722.1) [648.6–803.8]	407 (656.7) [595.9–723.7]
Any severe AE	28 (37.9) [26.2–54.9]	38 (45.2) [32.9–62.1]	25 (54.0) [36.5–80.0]	18 (29.0) [18.3–46.1]
Any serious AE	24 (32.5) [21.8–48.5]	32 (38.0) [26.9–53.8]	20 (43.2) [27.9–67.0]	13 (21.0) [12.2–36.1]
Any AE leading to discontinuation of study drug	36 (48.8) [35.2–67.6]	17 (20.2) [12.6–32.5]	12 (25.9) [14.7–45.7]	8 (12.9) [6.5–25.8]
Any infectious AE	122 (165.3) [138.4–197.3]	130 (154.5) [130.1–183.5]	55 (118.9) [91.3–154.9]	82 (132.3) [106.6–164.3]
Any serious infectious AE	3 (4.1) [1.3–12.6]	4 (4.8) [1.8–12.7]	4 (8.6) [3.2–23.0]	0
Any malignant AE	0	1 (1.2) [0.2–8.4]	0	1 (1.6) [0.2–11.5]
Any lymphoma AE	0	0	0	0
Any NMSC AE	0	1 (1.2) [0.2–8.4]	0	0

ADA, adalimumab; AE, adverse event; NMSC, nonmelanoma skin cancer; PY, patient-years.

there was a wide overlap in the range of trough values. Previously reported analyses of CLASSIC-I and II studies described similar findings; although adalimumab concentrations were numerically higher in patients taking concomitant immunomodulator, detectable adalimumab concentration was not a predictive factor for clinical remission.<sup>19</sup> These results are consistent with published findings for infliximab in immunomodulator-experienced patients, which failed to identify any consistent trend in median serum trough concentrations of infliximab by concomitant immunomodulator use.<sup>24</sup> These findings contrast with those observed in the SONIC study of patients naïve to both infliximab and azathioprine, in which median serum infliximab concentrations at week

30 were significantly higher with a combination of infliximab and immunomodulator therapy compared with infliximab alone (3.5 vs. 1.6 µg/mL;  $P < 0.001$ ).<sup>7</sup> In a recent retrospective cohort study that examined mucosal healing in 145 patients with IBD, median serum infliximab levels were significantly higher in patients treated with concomitant immunomodulator compared with patients treated with infliximab alone (3.7 vs. 2.2 µg/mL;  $P = 0.018$ ); however, concomitant immunomodulator use in IBD patients has not had a similar effect on adalimumab concentrations (4.2 vs. 3.4 µg/mL respectively;  $P = 0.37$ ).<sup>27</sup>

Much of the early data from infliximab studies, often describing intermittent administration of infliximab,

demonstrated increased serum infliximab concentrations and decreased antibody formation when administered with an immunomodulator. This suggested that the addition of an immunomodulator may be used as a rescue therapy in infliximab-treated patients with immunogenic loss of response.<sup>28–30</sup> Concomitant administration of MTX with adalimumab has been shown to decrease the clearance and increase the concentration of adalimumab.<sup>31, 32</sup> Considering the available PK and immunogenicity data for both adalimumab and infliximab, it is reasonable to expect a decrease in antibody formation, an increase in serum drug concentrations and a related improvement in efficacy with concomitant IMM use. Based on the results of our analysis, these effects may not translate into clinical benefit when adding adalimumab therapy in patients with inadequate disease control on immunomodulator therapy. These findings are in direct contrast to those of the SONIC and SUCCESS studies, which demonstrated a clear advantage of infliximab in combination with immunomodulator compared with either therapy alone.<sup>7, 8</sup> However, these results should be interpreted with caution because patients were not randomised to monotherapy vs. combination therapy in our analysis; study populations are not comparable to SONIC and SUCCESS; and unmeasured confounders may affect the observations. Notably, patients in the adalimumab monotherapy group may or may not have received prior immunomodulator therapy, as prior immunomodulator exposure data were not captured in these studies beyond a limited time frame (e.g. 90 days), whereas all patients in the combination group had inadequate disease control despite concurrent immunomodulator therapy.

In this analysis, the incidence and rate of AEs was broadly comparable with adalimumab monotherapy and combination therapy. This is consistent with a systematic review which concluded that the risks of serious infections in patients treated with anti-TNF and immunomodulator combination therapy do not appear to differ compared with the risks with anti-TNF or immunomodulator monotherapy, and that the increased risk of lymphoma with combination therapy appears to be attributed primarily to immunomodulator medication.<sup>33</sup> Similarly, a large pooled analysis detected an increased incidence of NMSC and malignancies other than NMSC (as a group) in patients with CD who were treated with adalimumab combination therapy, but not adalimumab monotherapy, suggesting a role for the immunomodulator component in raising the risk of malignancy.<sup>16</sup> Our safety analysis

did not reveal a signal for increased malignancy with combination therapy in studies of relatively short duration; however, the Osterman, *et al.* analysis included open-label adalimumab exposure in the adalimumab CD trials, in addition to the open-label extension study of CHARM [ADHERE], for a total of 3050 patient-years of exposure.<sup>16</sup>

Strengths of the current analysis include the large sample size of patients treated with combination therapy (nearly half of the population in each of the six studies) in randomised, placebo-controlled comparator trials and that all of the analyses used blinded treatment data. A limitation is that a pooled analysis of the data was not possible for these trials in two separate indications with varying study designs. A major limitation of the analysis is that the studies analysed were not designed or powered to address whether discontinuing immunomodulator therapy in patients with inadequate disease control is advisable after they start adalimumab. Another major limitation is that the adalimumab monotherapy and adalimumab combination therapy groups were not based on randomised assignment, but rather on immunomodulator use at baseline; therefore, the characteristics of the two therapy groups may have been dissimilar, which could confound comparisons. Furthermore, serum drug assays were not collected in all studies, and immunogenicity data are limited due to immunoassays available at the time of study, which were not drug tolerant, hampering interpretation of the efficacy differences between treatments. The studies were often of relatively short duration. Finally, as with all *post hoc* analyses, there is the risk of observational bias.

This manuscript highlights and emphasises the pharmacokinetics, efficacy and safety of adalimumab monotherapy and adalimumab combination therapy. Although analyses of efficacy by weight or other clinical variables would make an important contribution to treatment management, they are out of scope for this report. Future studies will need to address treatment optimisation.

In conclusion, remission rates in CD or UC patients with active disease were similar regardless of whether patients received adalimumab as monotherapy or as combination therapy with IMM. Randomised, controlled studies in patients failing immunomodulator therapy who are ready for anti-TNF therapy are needed to better assess the efficacy of continuing an immunomodulator when initiating anti-TNF therapy in the patient with inadequate disease control.

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Summary of studies included in this analysis.

**Table S2.** Baseline disease characteristics and concomitant medication use at baseline in patients with Crohn's disease in induction (A) and maintenance (B) studies.

**Table S3.** Baseline disease characteristics and concomitant medication use at baseline in patients with ulcerative colitis.

**Table S4.** Remission rates of patients with Crohn's disease who had CRP levels  $\geq 1$  mg/dL at baseline.

**Table S5.** Full Mayo score remission rates of patients with rectal bleeding scores  $\geq 1$  at baseline in patients with ulcerative colitis.

## AUTHORSHIP

*Guarantor of the article:* Dr Colombel.

*Author contributions:* J-FC, WJS, BF and LPB collected data; QZ performed statistical analyses; NMM performed PK analyses; JFC, BJ, WJS, BF, LPB, SE, AMR and RBT contributed to the design of the analyses. All authors contributed to the interpretation of data and critical review and revision of each draft of the manuscript.

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