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Long-term safety and tolerability of oral tofacitinib in patients with Crohn's disease: results from a phase 2, open-label, 48-week extension study

Running title: Tofacitinib long-term safety Crohn's disease

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Summary (255/250 words)

Background: Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for inflammatory bowel disease.

Aims: This 48-week, open-label extension study primarily investigated long-term safety of tofacitinib 5 and 10 mg b.d., and secondarily investigated efficacy as maintenance therapy in patients with Crohn's disease (CD).

Methods: Patients who had completed the phase 2b maintenance study, or withdrawn due to treatment failure, were enrolled. Patients in remission (CD-Crohn's disease activity index <150) at baseline received tofacitinib 5 mg b.d.; all others received 10 mg b.d. A single dose adjustment was allowed after 8 weeks' fixed, open-label treatment.

Results: Sixty-two patients received tofacitinib 5 mg b.d.; 88 received 10 mg b.d. Both groups had similar rates of adverse events (AEs) and serious infections. CD-Crohn's disease worsening was the most frequent AE adverse event for tofacitinib 5 (33.9%) and 10 mg b.d. (19.3%). Patients not in remission at baseline, receiving 10 mg b.d., had higher rates of serious AEs-adverse events (19.3%) and discontinuation attributed to insufficient clinical response (ICR; 30.7%) vs 5 mg b.d. (8.1% and 9.7%, respectively). At week 48, of patients with baseline remission receiving 5 mg b.d., 87.9% maintained remission and 75.0% sustained remission as observed (46.8% and 38.7%, respectively, by non-responder imputation). Study design prevented between-dose efficacy comparisons.

Conclusions: No new safety signals emerged. Although both doses showed generally similar safety outcomes for overall AEs-adverse events, serious AEs-adverse events were more frequent for tofacitinib 10 than 5 mg b.d. Discontinuation due to ICR insufficient clinical response was lower among patients in remission at baseline. ClinicalTrials.gov, NCT01470599.

Keywords: Crohn's disease, Inflammatory bowel disease, Clinical pharmacology

1 INTRODUCTION

Crohn's disease (CD) is a chronic, progressive inflammatory disease of the gastrointestinal (GI) tract¹ that has a significant impact on patients' quality of life (QoL).² Current therapies

for ~~CD~~-Crohn's disease include corticosteroids, thiopurines, methotrexate, anti-tumour necrosis factor-(TNF) α antibodies, anti-integrin antibodies and anti-p40 antibodies.³ However, not all patients respond to these medications, leaving an unmet need for novel therapies.⁴

Tofacitinib is an oral, small molecule Janus kinase inhibitor approved in several countries for the treatment of ulcerative colitis. It has also been investigated for ~~CD~~-Crohn's disease. The efficacy and safety of tofacitinib for inducing and maintaining clinical remission (defined as ~~CD~~-Crohn's disease activity index [CDAI] score <150) in patients with moderate-to-severe ~~CD~~-Crohn's disease has previously been investigated in two phase 2b studies.⁵ These induction and maintenance studies showed a modest treatment effect of tofacitinib compared with placebo, although the primary induction efficacy endpoint of clinical remission at week 8 was not significantly different from placebo. After 26 weeks of maintenance therapy, a higher proportion of patients receiving tofacitinib 10 mg twice daily (b.d.) showed clinical response-100 (defined as a CDAI score reduction of at least 100 points from baseline) or remission vs placebo, although these differences were also not statistically significant.⁵

Here, we present results of a phase 2b open-label extension (~~OLE~~) study that evaluated the safety and tolerability of tofacitinib, and exploratory efficacy over 48 weeks of treatment and 4 weeks of follow-up.

2 MATERIALS AND METHODS

2.1 Study design

This was a phase 2b, open-label, multicentre, 48-week extension study, followed by a 4-week safety follow up (ClinicalTrials.gov, NCT01470599). Patients in clinical remission at week 26 of the phase 2b maintenance study (NCT01393899; baseline of ~~OLE~~ open-label extension study), who were receiving either placebo, tofacitinib 5 or 10 mg b.d., were assigned to tofacitinib 5 mg b.d. in this ~~OLE~~ open-label extension study. All other patients, who were not in clinical remission at week 26 of the phase 2b maintenance study, including those with an early termination visit due to treatment failure, received tofacitinib 10 mg b.d., regardless of blinded prior maintenance study treatment. A single dose adjustment from 5 to 10 mg b.d. or vice versa was allowed at the physician's discretion after the initial 8 weeks of fixed, open-label treatment (Figure 1). This study was conducted at 57 centres in 17 countries (Online Supporting Information File S1), between 23 April 2012 and 25 July 2016. Details of protocol amendments are presented in Online Supporting Information File S2.

This study was approved by the institutional review board or independent ethics committee for each centre and conducted in accordance with the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent.

2.2 Study patients

To be eligible for this study, patients with ~~CD~~-Crohn's disease had either completed the 26-week, double-blind, maintenance study, or had withdrawn from the maintenance study after meeting prespecified treatment failure criteria. Maintenance study treatment failure was defined as meeting both of the following criteria on two consecutive visits, at least 2 weeks apart, in patients who had completed ≥ 4 weeks of treatment in the maintenance study: an increase in CDAI ≥ 100 points from maintenance study baseline value, and an absolute CDAI score ≥ 175 points. Patients with active (draining) fistulae, intra-abdominal or perineal collection, or abscess were excluded. Full details of eligibility criteria and prohibited concomitant medications are included in Online Supporting Information Files S3 and S4.

All patients who withdrew early or completed the ~~OLE~~ open-label extension study received a safety follow-up visit approximately 4 weeks after the last study medication dose.

For patients who discontinued, study procedures were completed as per end of treatment/early termination.

2.3 Primary objective: safety outcomes

The primary objective was to investigate the long-term safety and tolerability of tofacitinib 5 and 10 mg b.d. in patients with CD-Crohn's disease during the 48-week study and the 4-week follow-up. Safety outcomes included incidence and severity of adverse events, (AEs), classified by Medical Dictionary for Regulatory Activities version 19.0 coding.

Abnormalities and changes from baseline were monitored for clinical laboratory values, vital sign measurements, electrocardiogram measurements and clinically significant changes in physical examination. Safety endpoints of special interest were adjudicated, including major adverse cardiovascular events, hepatic injury, opportunistic infection, malignancy, GI gastrointestinal perforation and interstitial lung disease. There was a histopathological central over-read of specimens from potential malignancies, and the malignancy adjudication committee reviewed clinical and histopathological results. Safety outcomes were assessed at baseline, weeks 8, 16, 24, 36, 48 and 52. The 4-week safety follow-up visit at week 52 represented the end of study.

2.4 Secondary objective and secondary efficacy outcomes

The secondary objective was to investigate the effects of tofacitinib maintenance therapy on clinical remission, patient QoL-quality of life, and biomarkers measured by C-reactive protein (CRP) and faecal calprotectin (FCP), through 48 weeks.

Secondary binary efficacy outcomes included clinical remission, sustained clinical remission (achieved clinical remission at both weeks 24 and 48) and steroid-free clinical remission at week 48 among patients receiving steroids at baseline. Other endpoints included CDAI scores over time, time to relapse, serum high-sensitivity CRP C-reactive protein and FCP faecal calprotectin over time, changes from baseline, and corticosteroid use. Relapse was defined as an increase in CDAI of >100 points from baseline, and an absolute CDAI score of >220 points. The proportion of patients who relapsed, and the time to relapse, were analysed for patients in clinical remission at baseline who initially received tofacitinib 5 mg b.d. Also evaluated was the proportion of patients switching (at the investigator's discretion) from tofacitinib 5 to 10 mg b.d., or vice versa. Efficacy outcomes were monitored through 48 weeks, to end of treatment, or to early termination for those who discontinued the study.

2.5 Patient-reported outcomes (PROs)

The following PROs patient-reported outcomes were collected during this OLE open-label extension study: the Inflammatory Bowel Disease Questionnaire (IBDQ),⁶ the Short Form-36 v2 (SF-36v2; physical and mental component summary scores [PCS/MCS] and eight domain scores, with a 1-week recall)⁷ and the European QoL-Quality of Life Five Dimensions Questionnaire (EQ-5D) and Visual Analogue Scale (VAS) EQ-5D/VAS.⁸ The IBD inflammatory bowel disease Patient-Reported Treatment Impact (PRTI; v2) comprised three endpoints (patient satisfaction, preference for the study medication over their previous treatment, and willingness to use the study treatment again).^{9, 10}

Endpoints for IBDQ included: absolute scores and change from baseline in IBDQ total score and domain scores (i.e. bowel symptoms, systemic symptoms, emotional function and social function) over time, IBDQ clinical remission (total score ≥ 170) at week 48, absolute scores and change from baseline in SF-36v2, EQ-5D/VAS over time, and absolute scores for PRTI at week 48. IBDQ scores were recorded at baseline, weeks 8, 24 and 48. SF-36v2 and EQ-5D/VAS scores were recorded at baseline, weeks 24 and 48, and PRTI was recorded at week 48. The number of patients hospitalised, and the length of hospitalisations related to CD-Crohn's disease, was collected at every study visit.

2.6 Statistical analyses

Descriptive summary statistics, including two-sided 95% confidence intervals (CIs) for efficacy, biomarkers and PRO patient-reported outcome endpoints, were calculated based on observed data (no imputation of missing data) by initially assigned dose group from the full analysis set, defined as all patients who enrolled in the OLE open-label extension study. Additional summaries for clinical remission and sustained clinical remission were also completed, based on non-responder imputation (NRI) and last observation carried forward (LOCF). Kaplan-Meier estimates and the median time to relapse for patients in clinical remission at baseline were also reported. In accordance with the study design, which assigned patients who were not in clinical remission at baseline to tofacitinib 10 mg b.d., no statistical comparisons between 5 and 10 mg b.d. treatment groups were performed, due to the difference in study population. Safety endpoints were summarised for the safety analysis set, defined as all patients enrolled in the OLE open-label extension study who received ≥ 1 dose of study medication. All analyses were performed using SAS[®] 9.0 in Linux.

3 RESULTS

3.1 Patients

A total of 150 patients were enrolled in this study. Of these, 62 patients in remission at entry were assigned to tofacitinib 5 mg b.d., and 88 patients with active disease were assigned to 10 mg b.d. Of those enrolled, 19 (30.6%) and 43 (48.9%) patients discontinued in the 5 and 10 mg b.d. groups, respectively (Figure 2).

Patient demographics were similar between the tofacitinib groups. There was a geographical spread of patients recruited to the study from across the study site locations (geographic regions shown in Online Supporting Information Table S1). A greater proportion of patients assigned to 10 mg b.d. were taking corticosteroids and had higher mean CDAI scores and higher median CRP C-reactive protein and FCP faecal calprotectin concentrations, compared with those receiving 5 mg b.d. (Table 1). Ileocolonic disease location was recorded in a numerically higher proportion of patients receiving tofacitinib 10 mg b.d. than 5 mg b.d.

3.2 Safety outcomes

The proportion of patients with AEs adverse events was 79.0% and 76.1% for tofacitinib 5 and 10 mg b.d., respectively (Table 2), and the most frequently observed AEs adverse events were CD-Crohn's disease worsening (33.9% and 19.3%, respectively). Nasopharyngitis and urinary tract infection were the most frequently occurring infections for tofacitinib 5 mg b.d. (both AEs adverse events, 12.9%) and 10 mg b.d. (both AEs adverse events, 8.0%). Serious AEs adverse events (SAEs) were recorded in 8.1% and 19.3% of patients' assigned tofacitinib 5 and 10 mg b.d., of which CD-Crohn's disease worsening accounted for 4.8% and 10.2%, respectively. Both tofacitinib 5 and 10 mg b.d. showed similar rates of serious infections, with 3.2% and 2.3%, respectively.

Discontinuation due to insufficient clinical response (ICR) was more frequent for patients who entered the study not in remission, receiving 10 mg b.d. (30.7%), compared with 5 mg b.d. (9.7%). By investigator decision, some cases of discontinuation due to ICR insufficient clinical response did not have an associated AE adverse event of worsening CD-Crohn's disease recorded, and one patient discontinued due to an AE adverse event of worsening CD-Crohn's disease but did not have this specified as a reason for ICR insufficient

clinical response. Laboratory values meeting predetermined laboratory criteria for re-test or discontinuation were similarly low for both tofacitinib groups.

During this study, there were no deaths, adjudicated cases of cardiovascular events, interstitial lung disease or hepatic injury, or malignancy (excluding non-melanoma skin cancer [NMSC]) (Table 2). One case of basal cell carcinoma of the skin was reported in the tofacitinib 10 mg b.d. group, and no cases of squamous cell carcinoma. Three cases of non-serious herpes zoster (investigator-determined) occurred; one in the 5 mg b.d. group, and two in the 10 mg b.d. group (one of which was a case of acute, primary varicella infection, confirmed by the study site, that was misadjudicated as a multidermatomal herpes zoster reactivated infection). There were two opportunistic infections: a single, mild (investigator-determined) case of multidermatomal (non-adjacent or >2-6 adjacent dermatomes) herpes zoster reported in the 5 mg b.d. group (study drug continued, infection resolved with antiviral treatment); and one case of moderate, systemic, disseminated, multidermatomal primary varicella infection in the 10 mg b.d. group (study drug discontinued, infection resolved with antiviral therapy).

No cases with a preferred term of 'intestinal perforation' were reported, but one perineal fistula and one anal abscess in the tofacitinib 10 mg b.d. group were adjudicated as GI-gastrointestinal perforation.

3.3 Exploratory efficacy outcomes

This study had no primary efficacy endpoints; all efficacy endpoints, PROs patient-reported outcomes and biomarkers were exploratory endpoints. Dose adjustments were permitted post-week 8 at the investigator's discretion. Twenty-two patients (35.5%) adjusted from tofacitinib 5 to 10 mg b.d.: 16 patients at week 8, 4 patients at week 16 and 2 patients at week 24. Three patients (3.4%) adjusted from tofacitinib 10 to 5 mg b.d.: two at week 24 and one at week 36.

Among patients receiving tofacitinib 5 mg b.d. at week 48, 87.9% were in clinical remission and 75.0% in sustained clinical remission, as observed (Figures 3A and 3B). At week 48, when analysed by LOCF last observation carried forward and NRI non-responder imputation, 85.5% and 46.8% of patients, respectively, achieved clinical remission; and 77.4% and 38.7%, respectively, achieved sustained clinical remission. In the 5 mg b.d. group, median baseline CRP C-reactive protein was 3.6 mg/L. At week 48, of the 27 patients with baseline hsCRP high-sensitivity C-reactive protein <3 mg/L, 14 patients (51.9%) maintained

clinical remission, and of the 35 patients with baseline ~~hs~~CRP high-sensitivity C-reactive protein ≥ 3 mg/L, 15 patients (42.9%), maintained clinical remission. Median baseline ~~FCP~~ faecal calprotectin was 255.0 mg/kg. Similarly, at week 48 of the 31 patients with baseline ~~FCP~~ faecal calprotectin < 250 mg/kg and 31 patients with baseline ~~FCP~~ faecal calprotectin ≥ 250 mg/kg: 15 and 14 patients (48.4% and 45.2%), respectively, maintained clinical remission for tofacitinib 5 mg b.d.

The median time to relapse for patients in clinical remission at baseline was 366 days for patients receiving tofacitinib 5 mg b.d. The estimated relapse rate increased gradually over time for patients in remission at baseline, and was greatest at week 48 (24.7%). A Kaplan-Meier plot of probability of relapse is shown up to day 365 for patients receiving 5 mg b.d. who were in remission at baseline (Figure 3C). Among all patients receiving 5 mg b.d., seven (11.3%) were hospitalised due to ~~CD~~Crohn's disease during the study.

At week 48, patients receiving tofacitinib 5 mg b.d. showed generally consistent mean CDAI scores through week 48 (excepting week 8), showing a median CDAI score at week 48 of 67.0, and a week 48 mean change from baseline in CDAI score of -4.8. Decreases from baseline in ~~CRP~~ C-reactive protein (-4.6 mg/L) and ~~FCP~~ faecal calprotectin levels (-189.6 mg/kg) (Figure 4) were also observed at week 48.

For patients receiving tofacitinib 10 mg b.d., 55.6% achieved clinical remission and 34.3% achieved sustained clinical remission at week 48, as observed (Figure 5). At week 48, when analysed by ~~LOCF~~ last observation carried forward and ~~NRI~~ non-responder imputation, respectively; 39.8% and 22.7% of patients achieved clinical remission, and 29.6% and 13.6% achieved sustained clinical remission. In the tofacitinib 10 mg b.d. group, in which patients were not in remission at baseline, 45 patients (51.1%) achieved remission at some point during the study. The median time to remission, for those who achieved it, was 60 days. Patients showed improvements in mean CDAI score from baseline (-121.9), with a median CDAI score of 147.5 at week 48, and decreases from baseline in ~~CRP~~ C-reactive protein (-11.5 mg/L) and ~~FCP~~ faecal calprotectin levels (-123.9 mg/kg) (Figure 6). Fourteen patients (15.9%) receiving tofacitinib 10 mg b.d. were hospitalised due to ~~CD~~Crohn's disease during the study.

For tofacitinib 5 and 10 mg b.d. groups in this ~~OLE~~ open-label extension study, remission data over time were summarized by doses previously received in the maintenance study (data for baseline through week 48 are shown in Supporting Information Table S2). For

patients initially assigned to tofacitinib 5 mg b.d. in this OLE open-label extension study, who by study design were in remission at baseline, there were 15, 20 and 27 patients who received placebo, tofacitinib 5 mg b.d. and 10 mg b.d. in the maintenance study, respectively. Of these patients, 11, 11, and 11 patients remained in this OLE open-label extension study to week 48; and 10 (90.9%), 9 (81.8%), and 10 (90.9%) of these patients were in remission at week 48, respectively.

For patients initially assigned to tofacitinib 10 mg b.d. in this OLE open-label extension study, who by study design were not in remission at baseline, there were 33, 32 and 23 patients who received placebo, tofacitinib 5 mg b.d. and 10 mg b.d. in the maintenance study, respectively. Among them, 14, 10, and 12 patients remained in this OLE open-label extension study to week 48; and 7 (50.0%), 8 (80.0%), and 5 (41.7%) of these patients were in remission at week 48, respectively. These data support the potential efficacy of regaining therapeutic benefit with retreatment or dose escalation of therapy with 10 mg b.d., in achieving remission in those who had previously failed in the maintenance study with placebo or 5 mg b.d., respectively.

At baseline of the OLE open-label extension study, 2 (3.2%) and 22 (25.0%) patients in the tofacitinib 5 and 10 mg b.d. groups, respectively, received corticosteroids. As expected, this proportion was low for the 5 mg b.d. group, as these patients were in clinical remission, and corticosteroids had been tapered during the parent study. For tofacitinib 5 and 10 mg b.d., 3 (4.8%) and 19 (21.6%) patients, respectively, received corticosteroids at week 8, and 1 (1.6%) and 7 (8.0%) patients, respectively, at week 48.

3.4 PROs Patient-reported outcomes

For patients who entered the study in remission receiving tofacitinib 5 mg b.d., the majority (range: 69.5-81.0%) showed high (≥ 170) IBDQ total scores at baseline, weeks 8, 24 and 48 (Figure 7). At week 48, mean change from baseline IBDQ total score (-2.8) and individual IBDQ domains showed a general maintenance of values over time, with change from baseline range -3.1-0.1 (see Online Supporting Information Table S3). At week 48, small mean changes from baseline were observed for SF-36v2 domains (-0.2 and -1.2 for PCS and MCS, respectively), and for EQ-5D/VAS score (1.2). For PRTI assessment, 66.7% and 33.3% of patients reported being 'extremely satisfied' or 'satisfied', respectively, with their study drug, 88.1% of patients reported they preferred their study drug, and 83.3% reported they would use the same drug again.

In the tofacitinib 10 mg b.d. group, comprising patients who entered the study not in remission, there was a numerically increasing proportion of patients with high (≥ 170) total IBDQ score through week 48, among those who remained in the study (see Online Supporting Information Table S3). Substantial improvements (37.2) in mean change from baseline for IBDQ total score were observed at week 48. Each individual IBDQ domain showed increases in values (range: 6.6-12.6) at week 48.

At week 48 with tofacitinib 10 mg b.d., there were clinically relevant improvements in PCS and MCS of 8.4 and 7.6, respectively, greater than the previously published minimal clinically important differences (MCID) of 1.6-4.0 and 2.3-5.7, respectively, using either a distribution- or effect size anchor-based approach.¹¹ At week 48, there were clinically relevant increments from baseline for the EQ-5D/VAS score of 21.2, greater than the MCID minimal clinically important differences of 4.2-14.8.¹¹ For the PRTI assessment, 32.6% and 41.3% of patients reported being 'extremely satisfied' or 'satisfied' with their study drug, respectively. 56.5% of patients reported they preferred their study drug, and 60.9% reported they would use the same drug again.

4 DISCUSSION

No new or unexpected safety signals were observed during this study. Rates of AEs adverse events were generally similar for patients receiving tofacitinib 5 and 10 mg b.d. (79.0% and 76.1%, respectively), and were consistent with the previous 26-week maintenance study (83.3% and 78.7%, respectively).⁵ In the maintenance study, CD-Crohn's disease worsening was also the most frequently occurring AE adverse event, reported by 18.3% and 14.8% of patients receiving tofacitinib 5 or 10 mg b.d., respectively,⁵ although rates were lower than those reported here. rates of CD worsening reported as an AE reported here were higher than those observed in the maintenance study, at 33.9% and 19.3% for tofacitinib 5 and 10 mg b.d. respectively. Patient-years (PY) of tofacitinib exposure in the maintenance study were naturally lower for tofacitinib 5 mg b.d. and 10 mg b.d., at 22.9 PY-patient-years and 23.6 PY patient-years, respectively, compared with the longer extension study (47.0 PY and 57.1 PY for tofacitinib 5 and 10 mg b.d., respectively) shown here. As such, although only OLE open-label extension events are reported here, the longer study duration and length of exposure might impact upon rates of safety events.

Consistent with the maintenance study, AEs adverse events of special interest were similarly infrequent among both treatment groups, and there were no deaths during the study.

This is consistent with the maintenance study, where no deaths and an infrequent numbers of events were observed, including There was one case of large intestinal colon perforation (microperforation of the sigmoid) in the maintenance study.⁵ Additionally, the rates of AEs adverse events of special interest were generally similar between this OLE open-label extension study and the maintenance, 52-week OCTAVE Sustain study in patients with ulcerative colitis and clinical response to induction therapy, with neither study observing cases of intestinal perforation, malignancies (excluding NMSC), and generally similar proportions of NMSC (0% and 1.5%) and herpes zoster (1.5% and 5.1%), for tofacitinib 5 and 10 mg b.d., respectively.¹²

Infections were reported in approximately half of patients receiving tofacitinib in this study. The safety profile reported here is generally consistent with previous studies in rheumatoid arthritis with up to 114 months' observation.¹³ No new safety signals emerged and, as in the rheumatoid arthritis programme, the most frequently occurring AEs adverse events were infections, including nasopharyngitis.¹³

Rates of discontinuation due to AEs adverse events and ICR insufficient clinical response were higher for tofacitinib 10 mg b.d. than 5 mg b.d., indicating that patients who entered the OLE open-label extension study in remission had a lower probability of experiencing ICR insufficient clinical response resulting in discontinuation. Rates of discontinuation due to AEs for 10 mg b.d. were generally consistent with those observed in the maintenance study (9.8%), and were lower for 5 mg b.d. than those observed in the maintenance study (11.7%). Compared with the maintenance study, rates of discontinuation due to adverse events and rates of discontinuation due to ICR insufficient clinical response reported here were generally similar for tofacitinib 10 mg b.d. (26.2% and 30.7%) and lower for 5 mg b.d. (35.0% and 9.7%)⁵

In this OLE open-label extension study, rates of SAEs serious adverse events were higher with tofacitinib 10 mg b.d. than 5 mg b.d., and compared with rates observed in the maintenance study (13.1% and 10.0% for tofacitinib 10 and 5 mg b.d., respectively).⁵ However, it is important to note that patients assigned to 10 mg b.d. were not in remission at baseline, and were therefore likely to have more severe CD-Crohn's disease symptoms, compared with patients in remission at baseline receiving 5 mg b.d.

In comparison, a long-term extension study of adalimumab (ADHERE) included patients with moderately-to-severely active CD-Crohn's disease who had completed the

maintenance period of the 56-week CHARM study, which provides some context for this OLE open-label extension study.^{14, 15} Analyses were based on the intent-to-treat population, comprising patients who entered CHARM (maintenance study) after open-label induction with adalimumab and achieved CDAI ≥ 70 decrease while receiving adalimumab. Rates of remission (CDAI < 150) at week 104 from the CHARM maintenance study baseline, for patients in remission at ADHERE baseline, were 77.2%, 86.2% and 86.8%, as NRI non-responder imputation, LOCF last observation carried forward and observed data, respectively.¹⁴ Median CDAI scores at week 92 from the CHARM baseline, as observed, were 107 and 94 for adalimumab 40 mg dosed every other week and weekly, respectively.¹⁵ The rates of remission presented in this OLE open-label extension study at week 48 (90 weeks from maintenance study baseline) for tofacitinib 5 mg b.d. (patients in remission at OLE open-label extension baseline) were 46.8%, 85.5% and 87.9%, for NRI non-responder imputation, LOCF last observation carried forward and observed data, respectively, and median CDAI scores at week 48, as observed, were 67.0 and 147.5 for tofacitinib 5 and 10 mg b.d., respectively.

However, there were several key differences between study entry criteria for the CHARM study and the study presented here, which precludes direct comparisons of efficacy data. Safety is the primary consideration for this OLE open-label extension study. Any comparisons of efficacy data are provided for context purposes only. The results presented for this OLE open-label extension study included patients who had previously withdrawn in the maintenance study due to treatment failure; whereas in the ADHERE study, only patients who had completed CHARM were included in the ADHERE extension, which might exclude some patients with severe disease activity who were non-responders to adalimumab. As such, some patients in this OLE open-label extension study might have been more refractory than those in the CHARM study. Additionally, differences between patient group sizes mean that it is not appropriate to directly compare the results between these studies; as for tofacitinib 5 and 10 mg b.d. only 33 and 36 patients, respectively, had non-missing data at week 48, vs a range of 129-154 patients for efficacy outcomes at 104 weeks from CHARM baseline. In addition, there were dose adjustments for patients in both treatment groups.

Among patients initially assigned tofacitinib 5 mg b.d. who were in clinical remission at baseline, and remained in the study at week 48, approximately three-quarters achieved sustained clinical remission at week 48, as observed and with LOCF last observation carried forward, and approximately one-third as NRI non-responder imputation. By week 48, three-

quarters of patients had not relapsed, and there were decreases in ~~CRP~~ C-reactive protein and ~~FCP~~ faecal calprotectin from baseline at each timepoint through week 48. The aggregate data for time to relapse, clinical remission rate and sustained clinical remission rate, CDAI value, and ~~CRP~~ C-reactive protein and ~~FCP~~ faecal calprotectin values appear to show a maintenance of efficacy for some patients receiving tofacitinib 5 mg b.d.

For patients initially assigned tofacitinib 10 mg b.d., because they were not in remission at baseline, approximately one-third achieved sustained remission, as observed or with ~~LOCF~~ last observation carried forward. Decreases in ~~CRP~~ C-reactive protein and ~~FCP~~ faecal calprotectin from baseline were observed at each timepoint through week 48, and the magnitude of the decrease in ~~CRP~~ C-reactive protein from baseline was greater at each timepoint for 10 mg b.d. than for 5 mg b.d. However, patients assigned 10 mg b.d. were not in remission at baseline by study design, and had higher values of ~~CRP~~ C-reactive protein and ~~FCP~~ faecal calprotectin. This patient population included patients who had previously received either placebo, or tofacitinib 5 or 10 mg b.d., in the maintenance study; these data might indicate treatment effect with 10 mg b.d., although no control group data are available.

Changes from baseline for ~~PRO~~ patient-reported outcome endpoints over time were generally maintained for patients receiving tofacitinib 5 mg b.d. ~~The proportions of patients, as observed, with IBDQ clinical remission (≥ 170 mean total score) remained high, and there were generally small changes from baseline in SF-36v2 domains and little change observed from baseline for EQ-5D.~~ For patients receiving tofacitinib 10 mg b.d., clinically relevant improvements from baseline in ~~PRO~~ patient-reported outcome endpoints were observed in SF-36v2 domains and EQ-5D, and improvements in PCS and MCS and the proportions of patients with IBDQ clinical remission increased over time.

The ~~IBD~~ inflammatory bowel disease PRTI tool has previously been used to evaluate patient preference in tofacitinib studies for patients with ulcerative colitis, where it was shown to have approximately linear associations with Mayo scores.^{9, 10} The majority of patients receiving tofacitinib reported positive outcomes of ‘extremely satisfied’ and ‘satisfied’ for the PRTI assessments of patient satisfaction. Proportions of patients responding positively were slightly higher for 5 mg b.d. than 10 mg b.d.

This study had several limitations. Only patients not in remission were assigned to tofacitinib 10 mg b.d.; therefore, as the two patient populations had different disease activity at the outset, this precluded definitive comparison of efficacy outcomes between doses.

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Patients were permitted to switch doses after 8 weeks of receiving their initially assigned study dose and, as such, efficacy and safety outcomes were analysed by initial dose assignment, not taking dose changes into account. Additionally, this was an open-label study, without a control group.

In summary, no new safety signals were observed through week 52 of this ~~OLE~~ open-label extension study of tofacitinib in patients with ~~CD~~ Crohn's disease. Rates of ~~AEs~~ adverse events were generally similar among both groups, and were consistent with rates observed in the previous tofacitinib ~~CD~~ Crohn's disease maintenance study. There were higher rates of ~~SAEs~~ serious adverse events and discontinuation due to ~~AEs~~ adverse events in the tofacitinib 10 mg b.d. group. However, as patients were only assigned tofacitinib 10 mg b.d. if they were not in remission at baseline and therefore had more active disease than those receiving 5 mg b.d., and because dose switching was permitted, direct comparisons between dose groups were not conducted. Patients in remission at ~~OLE~~ open-label extension study entry had a lower rate of discontinuation due to ~~ICR~~ insufficient clinical response than those not in remission at study entry. Exploratory efficacy analyses at week 48 appeared to show that many patients receiving tofacitinib 5 mg b.d. maintained remission and achieved sustained remission by week 48, and although fewer patients receiving 10 mg b.d. achieved remission (approximately one-quarter by ~~NRI~~ non-responder imputation), these patients did show improvement in mean CDAI scores from baseline. For those patients who had received placebo or 5 mg b.d. in the maintenance study, but entered the ~~OLE~~ open-label extension not in remission, 50.0% and 80.0% respectively who subsequently received retreatment or dose escalation with 10 mg b.d. were able to achieve remission by week 48 in this ~~OLE~~ open-label extension study.

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STATEMENT OF INTERESTS

1. Authors' declaration of personal interests

J. Panés has received consulting fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Ferring, Genentech/Roche, GSK, Janssen, MSD, Oppilan, Pfizer Inc, Robarts, Shire, Takeda, TiGenix and Theravance. G. R. D'Haens has served as an advisor for AbbVie, Ablynx, Amakem, AM Pharma, Avaxia, Biogen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmo, Covidien, Dr. Falk Pharma, Engene, Ferring, Galapagos, Gilead, GSK, Hospira, Johnson and Johnson, Medimetrics, Millennium/Takeda, Mitsubishi Pharma, MSD, Mundipharma, Novo Nordisk, Pfizer Inc, Prometheus Laboratories/Nestle, Receptos, Robarts Clinical Trials, Salix, Sandoz, Setpoint, Shire, Teva, TiGenix, Tillotts, Topivert, Versant and Vifor; and has received speaker fees from AbbVie, Ferring, Johnson and Johnson, Millennium/Takeda, MSD, Mundipharma, Norgine, Pfizer Inc, Shire, Tillotts and Vifor. P. D. R. Higgins has received consulting fees from AbbVie, Genentech/Roche, GSK, Takeda, PRIME Medical Education and Lycera. L. Mele, M. Moscariello, G. Chan, W. Wang, W. Niezychowski, C. Su and E. Maller are all employees and stockholders of Pfizer Inc.

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AUTHORSHIP STATEMENT

Guarantor of article: Julián Panés

Specific author contributions: All authors substantially contributed in the acquisition, analysis or interpretation of data. All authors drafted the work and/or revised it critically for important intellectual content; approved the final published version of the manuscript; and are accountable for all aspects of this work.

DATA SHARING STATEMENT

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Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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TABLE 1 Patient demographics and baseline characteristics

	Tofacitinib 5 mg b.d. (N = 62)[†]	Tofacitinib 10 mg b.d. (N = 88)[†]
Female, n (%)	30 (48.4)	41 (46.6)
Race, n (%)		
White	49 (79.0)	71 (80.7)
Black	2 (3.2)	1 (1.1)
Asian	11 (17.7)	14 (15.9)
Other	0 (0.0)	2 (2.3)
Mean age, years (SD)	41.0 (12.6)	38.2 (11.6)
Mean age of onset of CD-Crohn's disease, years (SD) [‡]	28.0 (9.8)	26.6 (10.9)
Duration of CD-Crohn's disease, n (%) [‡]		
<5 years	17 (27.4)	26 (29.5)
5-<10 years	13 (21.0)	19 (21.6)
≥10 years	32 (51.6)	43 (48.9)
Disease location, n (%) [‡]		
Ileal alone	18 (29.0)	21 (23.9)
Colonic alone	22 (35.5)	23 (26.1)
Ileocolonic	22 (35.5)	43 (48.9)
Missing	0 (0.0)	1 (1.1)
Prior TNFi tumour necrosis factor inhibitor failure, n (%) [‡]	42 (67.7)	69 (78.4)
Prior immunosuppressant failure, n (%) [‡]	43 (69.4)	68 (77.3)
Use of corticosteroids at study entry, n (%) [†]	2 (3.2)	22 (25.0)

Baseline CDAI score, mean (SD) [§]	77.1 (43.2)	291 (95.8)
Baseline CRP C-reactive protein concentration, mg/L; median (SD) [†]	3.6 (18.6)	8.4 (30.1)
Baseline FCP faecal calprotectin concentration, mg/kg; median (SD) [†]	255.0 (483.3)	512.0 (305.4)

b.d., twice daily; ~~CD, Crohn's disease~~; CDAI, Crohn's disease activity index; ~~CRP, C-reactive protein~~; ~~FCP, faecal calprotectin~~; SD, standard deviation.; ~~TNFi, tumour necrosis factor inhibitor~~.

[†]Baseline characteristics at open-label extension study entry.

[‡]Baseline information from the induction study (NCT01393626).

[§]Baseline information from the maintenance study week 26 central laboratory measurement.

Only patients not in remission were assigned tofacitinib 10 mg b.d.

TABLE 2 AEs Adverse events and events of special interest in the open-label extension study

	Tofacitinib 5 mg b.d. (N = 62)[†]	Tofacitinib 10 mg b.d. (N = 88)[†]
Duration of treatment, days; median (SD)	333.5 (95.1)	284.5 (114.7)
Exposure, PY patient-years	47.0	57.1
Switched dose groups after week 8, n (%)	22 (35.5)	3 (3.4)
Treatment-emergent AEs adverse events, all causalities		
Patients with AEs adverse events, n (%)	49 (79.0)	67 (76.1)

Patients with SAEs serious adverse events, n (%)	5 (8.1)	17 (19.3) [‡]
Discontinuations		
Due to AEs adverse events, n (%) [§]	3 (4.8)	10 (11.4)
Due to infections	2 (3.2)	3 (3.4)
Due to insufficient clinical response	6 (9.7)	27 (30.7)
Infections, n (%)	31 (50.0)	42 (47.7)
Serious infections, n (%)	2 (3.2)	2 (2.3)
Diarrhoea infectious	1 (1.6)	0 (0.0)
Pyelonephritis	1 (1.6)	0 (0.0)
Anal abscess	0 (0.0)	1 (1.1)
Vulvar abscess	0 (0.0)	1 (1.1)
AEs Adverse events of special of interest, n (%)		
Deaths	0 (0.0)	0 (0.0)
Herpes zoster [¶]	1 (1.6)	2 (2.3)
Opportunistic infections ^{#,††}	1 (1.6)	1 (1.1)
Malignancy (excluding NMSC) [#]	0 (0.0)	0 (0.0)
NMSC [#]	0 (0.0)	1 (1.1) ^{‡‡}
Hepatic injury [#]	0 (0.0)	0 (0.0) ^{§§}
Intestinal perforation ^{#,¶¶}	0 (0.0)	0 (0.0)
Interstitial lung disease [#]	0 (0.0)	0 (0.0)
Most frequently observed AEs adverse events by preferred term (frequency ≥8.0%), n (%)		
CD-Crohn's disease worsening	21 (33.9)	17 (19.3)
Nasopharyngitis	8 (12.9)	7 (8.0)
Urinary tract infection	8 (12.9)	7 (8.0)
Abdominal pain	7 (11.3)	7 (8.0)
Gastroenteritis	7 (11.3)	2 (2.3)
Influenza	5 (8.1)	8 (9.1)
Nausea	2 (3.2)	9 (10.2)
Pyrexia	1 (1.6)	7 (8.0)
Arthralgia	5 (8.1)	8 (9.1)

Most frequently observed ~~SAEs~~-serious adverse events by preferred term (frequency $\geq 8.0\%$), n (%)

CD-Crohn's disease worsening	3 (4.8)	9 (10.2)
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Laboratory changes of interest

Alanine aminotransferase increased	1 (1.6)	0 (0.0)
Blood alkaline phosphatase increased	2 (3.2)	0 (0.0)
Blood cholesterol increased	1 (1.6)	0 (0.0)
Blood creatine phosphokinase increased	3 (4.8)	5 (5.7)
Liver function test increased	0 (0.0)	1 (1.1)

Two sequential laboratory measurements, meeting criteria for discontinuation^{##}

Neutrophil counts <750 neutrophils/mm ³	0 (0.0)	0 (0.0)
Lymphocyte counts <500 lymphocytes/mm ³	0 (0.0)	1 (1.1)
Creatinine kinase elevation $>10 \times$ ULN	0 (0.0)	0 (0.0)
Haemoglobin <0.8 g/L or a decrease of $>30\%$ from baseline value	1 (1.6)	1 (1.1)

AE, adverse event b.d., twice daily; CD, Crohn's disease; NMSC, non-melanoma skin cancer; PY, patient years; SAE, serious adverse event; SD, standard deviation; ULN, upper limit of normal.

[†]Patients evaluable for AEs-adverse events by initially assigned dose group.

[‡]Three out of 17 patients experienced SAEs serious adverse events after the 4-week safety follow-up.

[§]Excluding worsened Crohn's disease attributed to insufficient clinical response.

[¶]No serious cases of herpes zoster were reported.

[#]Events based upon adjudication.

^{††}Adjudicated opportunistic infections included the single case of herpes zoster multidermatomal (non-adjacent or $>2-6$ adjacent dermatomes) in the tofacitinib 5 mg b.d. group, and one case of primary varicella infection in the tofacitinib 10 mg b.d. group.

^{‡‡}Adjudicated malignancy events, including one case of basal cell carcinoma.

^{§§}One case of biliary colic was adjudicated as unrelated to drug-induced liver injury.

^{¶¶}AE Adverse event PF preferred term, including 'perforation'. However, one event of perineal fistula and one event of anal abscess in the tofacitinib 10 mg b.d. group were

adjudicated as intestinal perforation.

##Laboratory values meeting predetermined criteria for discontinuation.

The ~~AE~~ adverse event of worsening Crohn's disease leading to discontinuation was termed insufficient clinical response. Only patients who were not in remission were assigned to tofacitinib 10 mg b.d.

Infections that were reported as an ~~SAE~~ serious adverse event are described in the table as 'serious infections'.

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FIGURE LEGENDS

FIGURE 1

Open-label extension study design.

Patients were permitted to switch dose after week 8. If a patient discontinued early from the open-label therapy, study procedures were to be completed as per end of treatment/early termination. b.d., twice daily; CDAI, Crohn's disease activity index

FIGURE 2

Patient disposition diagram.

Safety analyses patient population. Includes enrolled patients who received ≥ 1 dose of study medication. N represents the total number of patients in each group; n represents the number of patients with events. †Dose assignment was determined based on last available haematocrit result prior to open-label extension study entry. Baseline CDAI scores were recalculated using baseline haematocrit results received after treatment assignment was determined.

Therefore, one patient in the tofacitinib 5 mg b.d. group and four patients in the 10 mg b.d. group had remission status that did not correspond to their initial dose assignment. b.d., twice daily; CDAI, Crohn's disease activity index

FIGURE 3

Proportion of patients in clinical remission at baseline and assigned to tofacitinib 5 mg b.d., who had (A) clinical remission at week 48, and (B) sustained clinical remission at weeks 24 and 48, and also (C) Kaplan-Meier plot showing probability of relapse among those in clinical remission at baseline (full analysis set).

Clinical remission was defined as CDAI < 150 . Sustained clinical remission was defined as remission at both weeks 24 and 48. Relapse was defined as an increase in CDAI of > 100 points from baseline, and an absolute CDAI score of > 220 points. Patients who discontinued due to lack of efficacy were treated as a relapse event, with an event time at the time of drop out. All data represent full analysis set. N represents the total number of patients analysed, n

represents number of patients achieving clinical remission or sustained clinical remission. Clopper-Pearson 95% confidence intervals are shown in panels A and B. The Kaplan-Meier plot for relapse is shown to 365 days, as there were 3 patients or fewer at risk from days 365 through 458. b.d., twice daily; CDAI, Crohn's disease activity index; ~~LOCF, last observation carried forward; NRI, non-responder imputation~~; SE, standard error

FIGURE 4

(A) Mean CDAI score through week 48, and mean changes from baseline at week 48 for (B) CDAI, (C) ~~CRP~~ C-reactive protein and (D) ~~FCP~~ faecal calprotectin, for tofacitinib 5 mg b.d. (observed data; full analysis set).

All data represent full analysis set (observed). N represents the total number of patients analysed at each timepoint, n represents the number of patients with data at week 48 or at baseline and week 48. b.d., twice daily; CDAI, Crohn's disease activity index; ~~CRP, C-reactive protein; FCP, faecal calprotectin~~; SD, standard deviation

FIGURE 5

Proportion of patients assigned to tofacitinib 10 mg b.d. at baseline who had (A) clinical remission at week 48 and (B) sustained clinical remission at weeks 24 and 48 (full analysis set).

Clinical remission was defined as CDAI <150. Sustained clinical remission was defined as remission at both week 24 and week 48. All data represent full analysis set. N represents the total number of patients analysed, n represents number of patients achieving clinical remission or sustained clinical remission. Clopper-Pearson 95% confidence intervals are shown. b.d., twice daily; CDAI, Crohn's disease activity index; ~~LOCF, last observation carried forward; NRI, non-responder imputation~~

FIGURE 6

(A) Mean CDAI score through week 48, and mean changes from baseline at week 48 for (B) CDAI, (C) ~~CRP~~ C-reactive protein and (D) ~~FCP~~ faecal calprotectin for tofacitinib 10 mg b.d. (observed data; full analysis set).

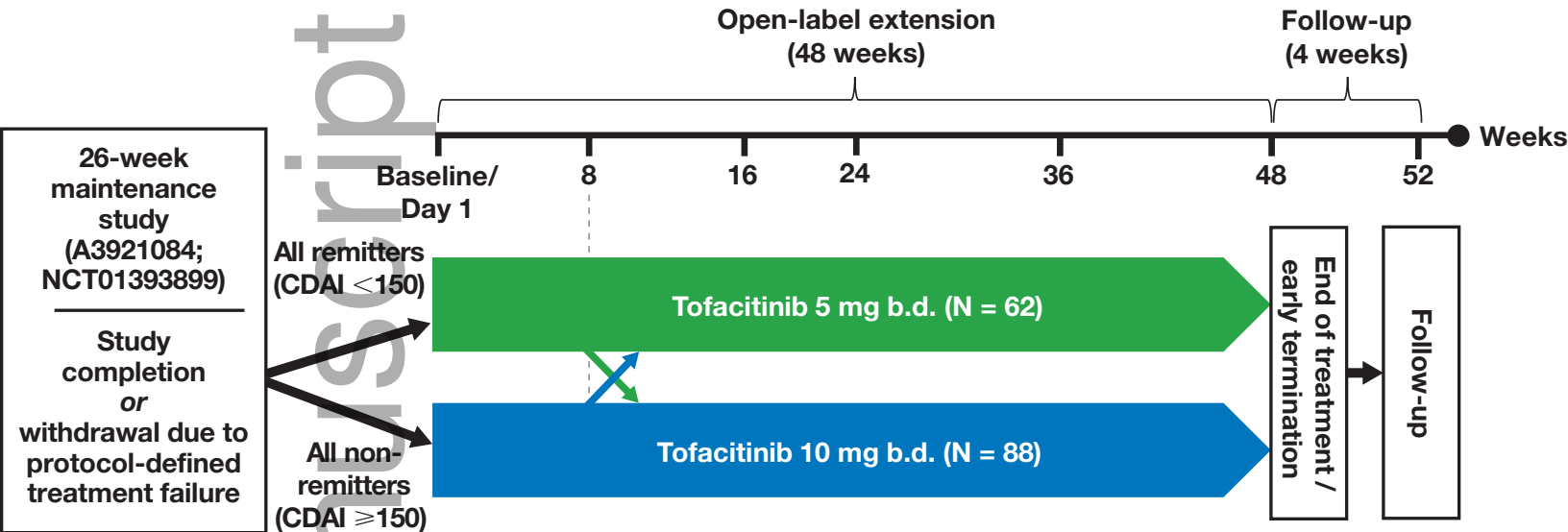
All data represent full analysis set (observed). N represents the total number of patients analysed at each timepoint, n represents the number of patients with data at week 48, or at baseline and week 48. b.d., twice daily; CDAI, Crohn's disease activity index; ~~CRP, C-reactive protein; FCP, faecal calprotectin~~; SD, standard deviation

FIGURE 7

Proportion of patients with IBDQ clinical remission (total score ≥ 170) ~~PRO~~ patient-reported outcome endpoint, by baseline and weeks 8, 24 and 48.

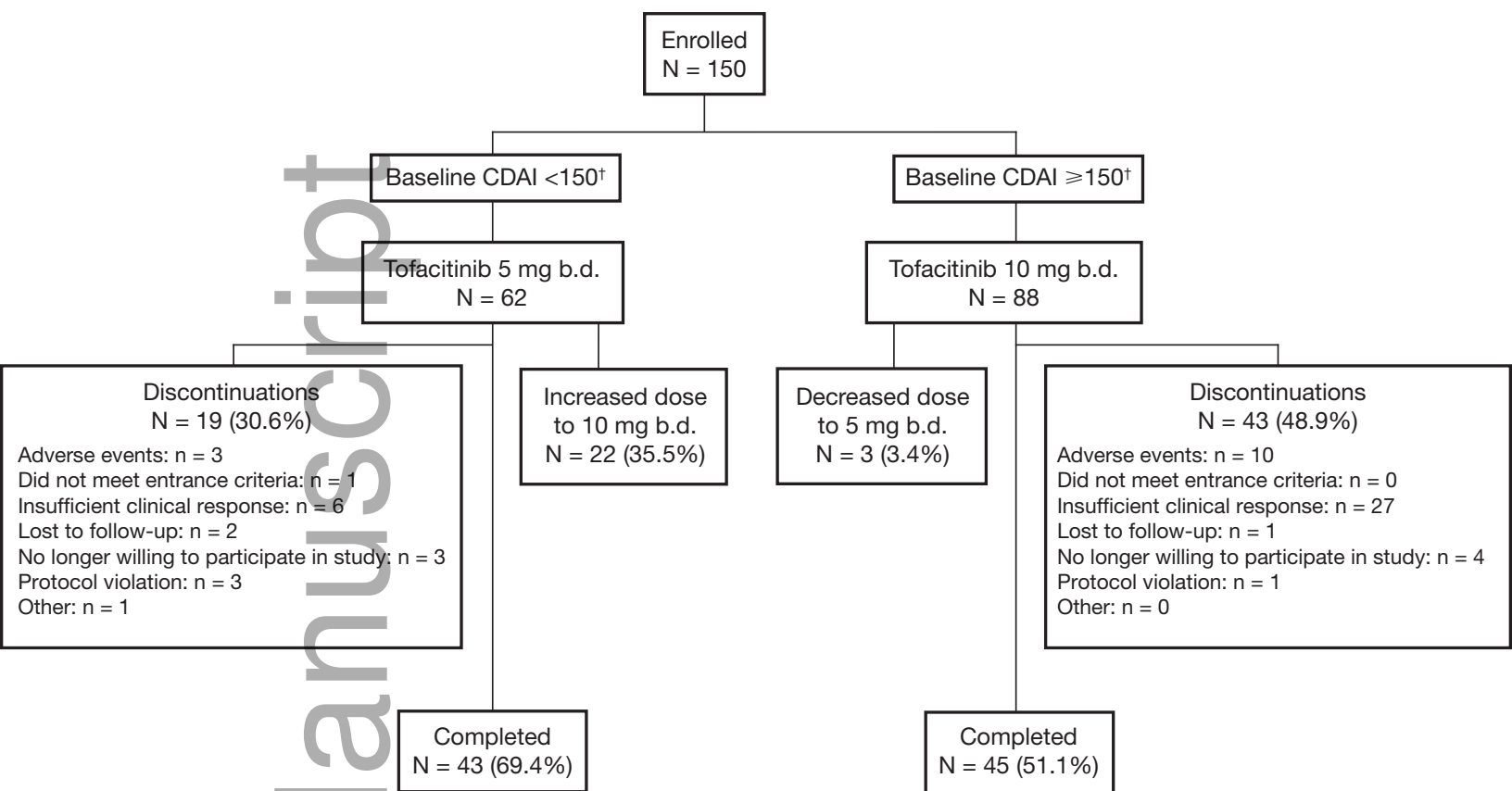
N represents the total number of patients analysed at each timepoint, n represents number of patients achieving IBDQ clinical remission. 95% Clopper-Pearson exact confidence intervals are shown for proportions. b.d., twice daily; IBDQ, Inflammatory Bowel Disease Questionnaire; ~~PRO, patient-reported outcome~~

Figure 1



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Figure 2



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Figure 3

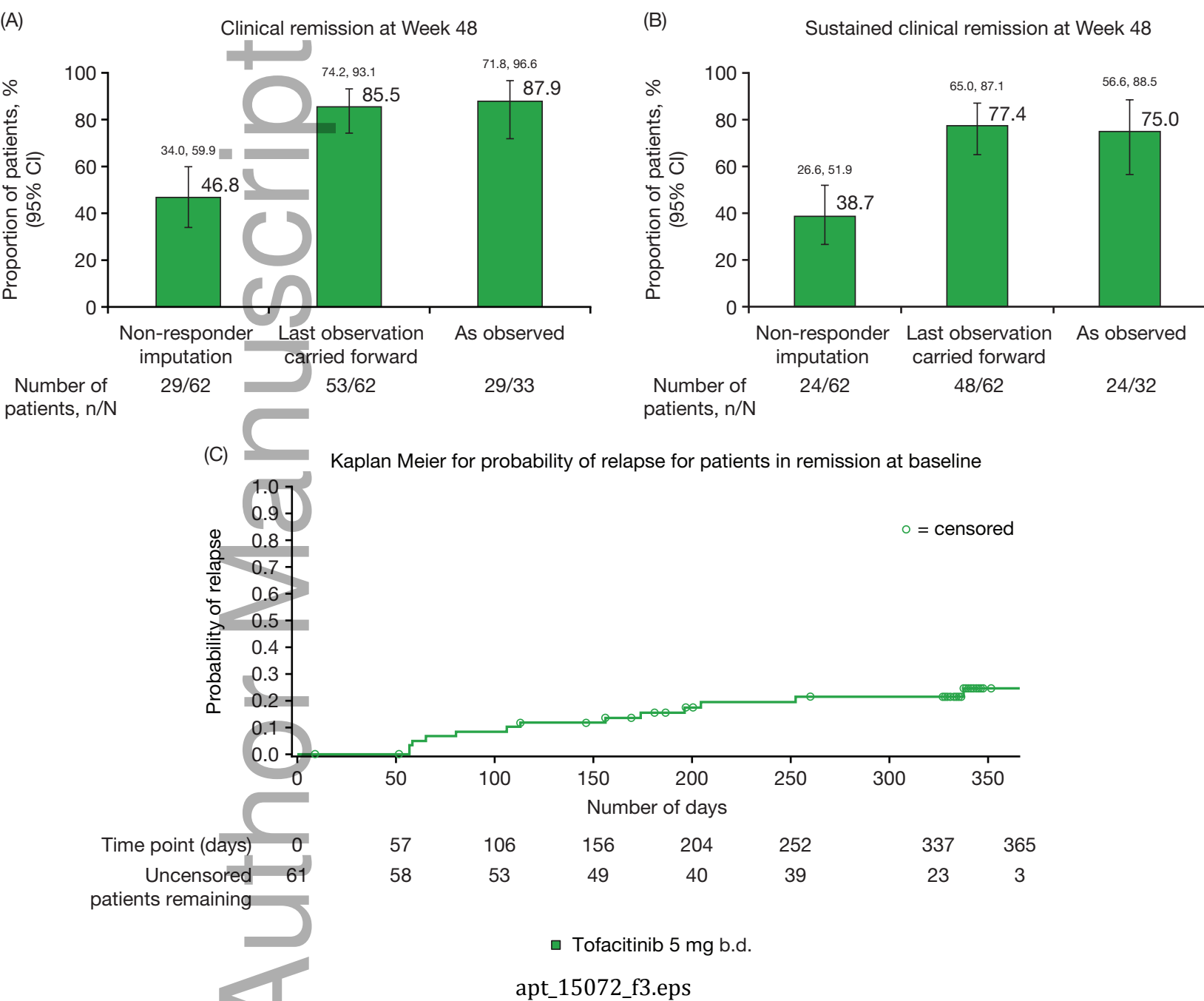


Figure 4

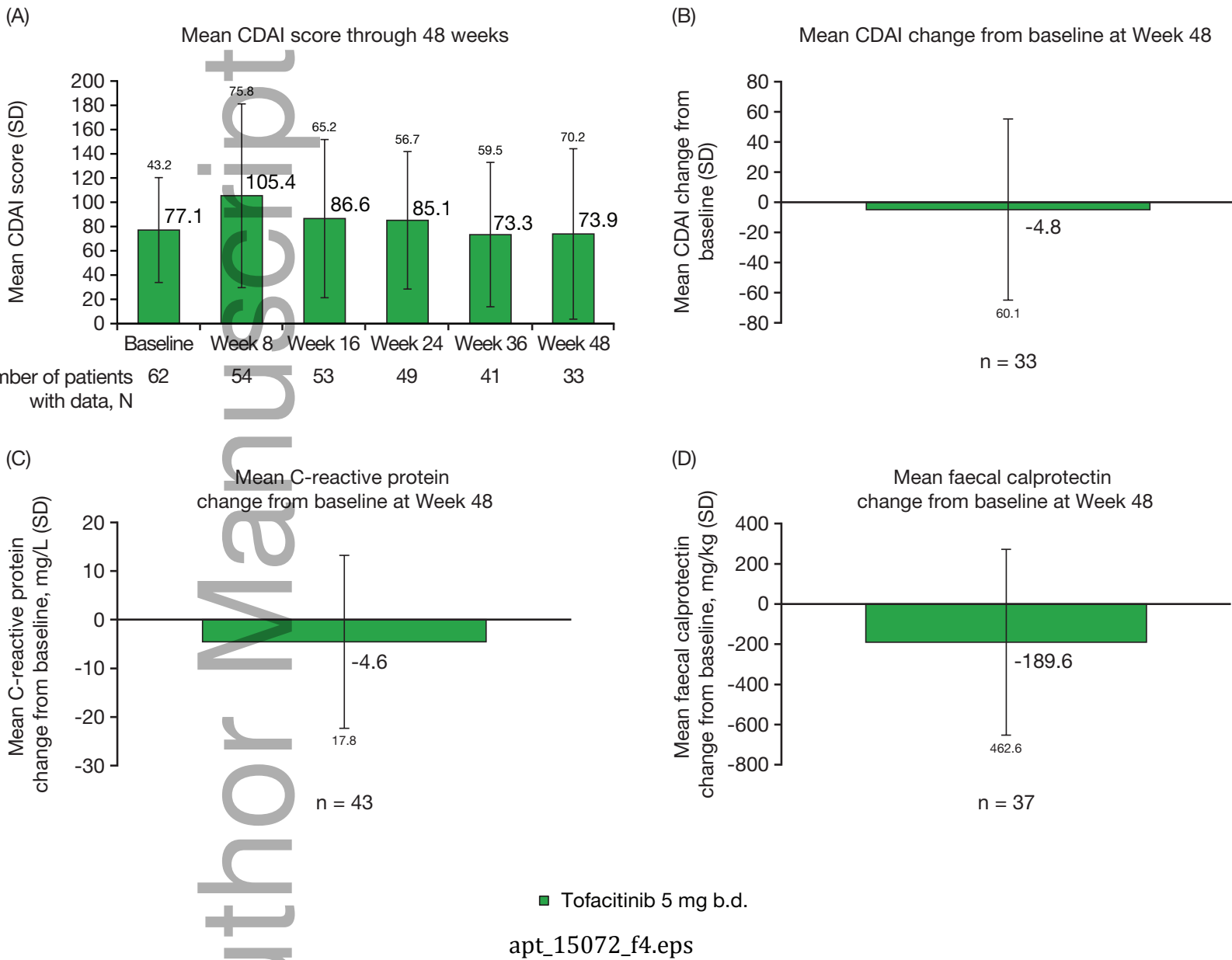


Figure 5

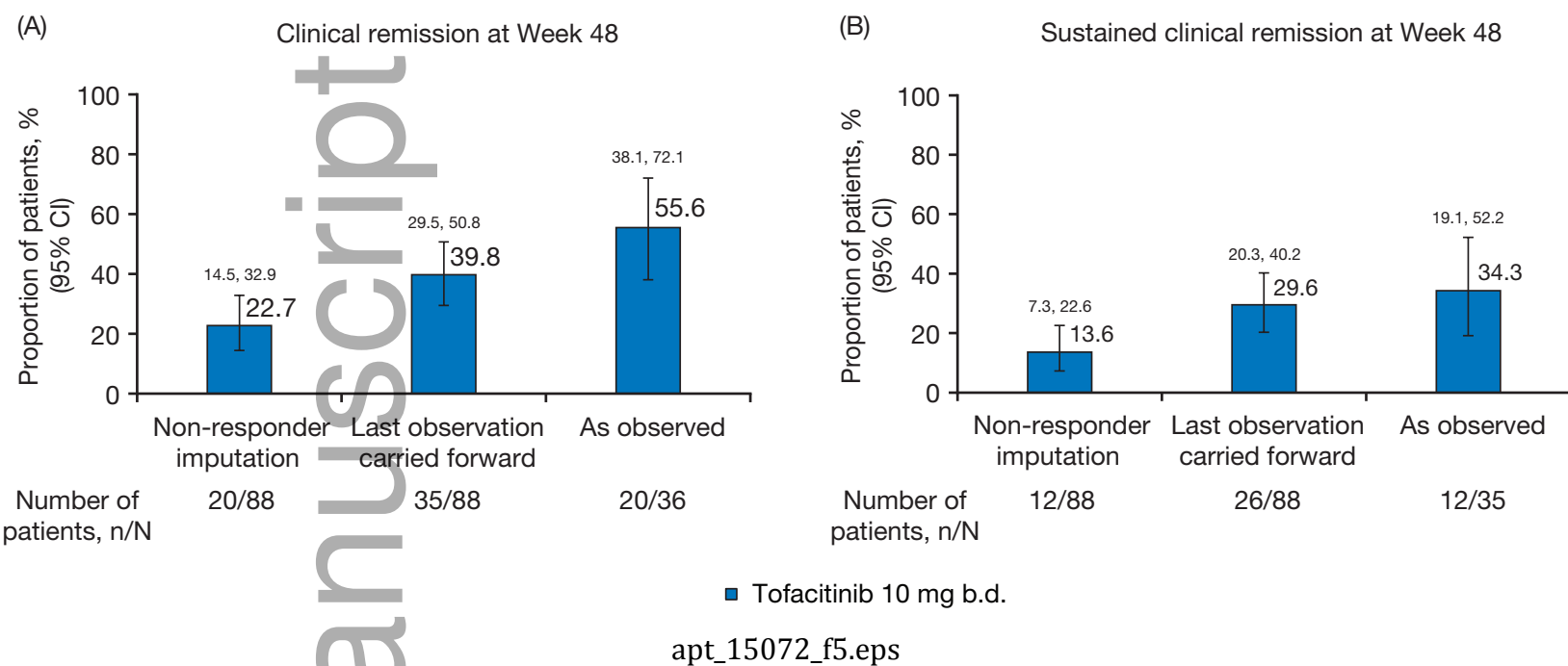


Figure 6

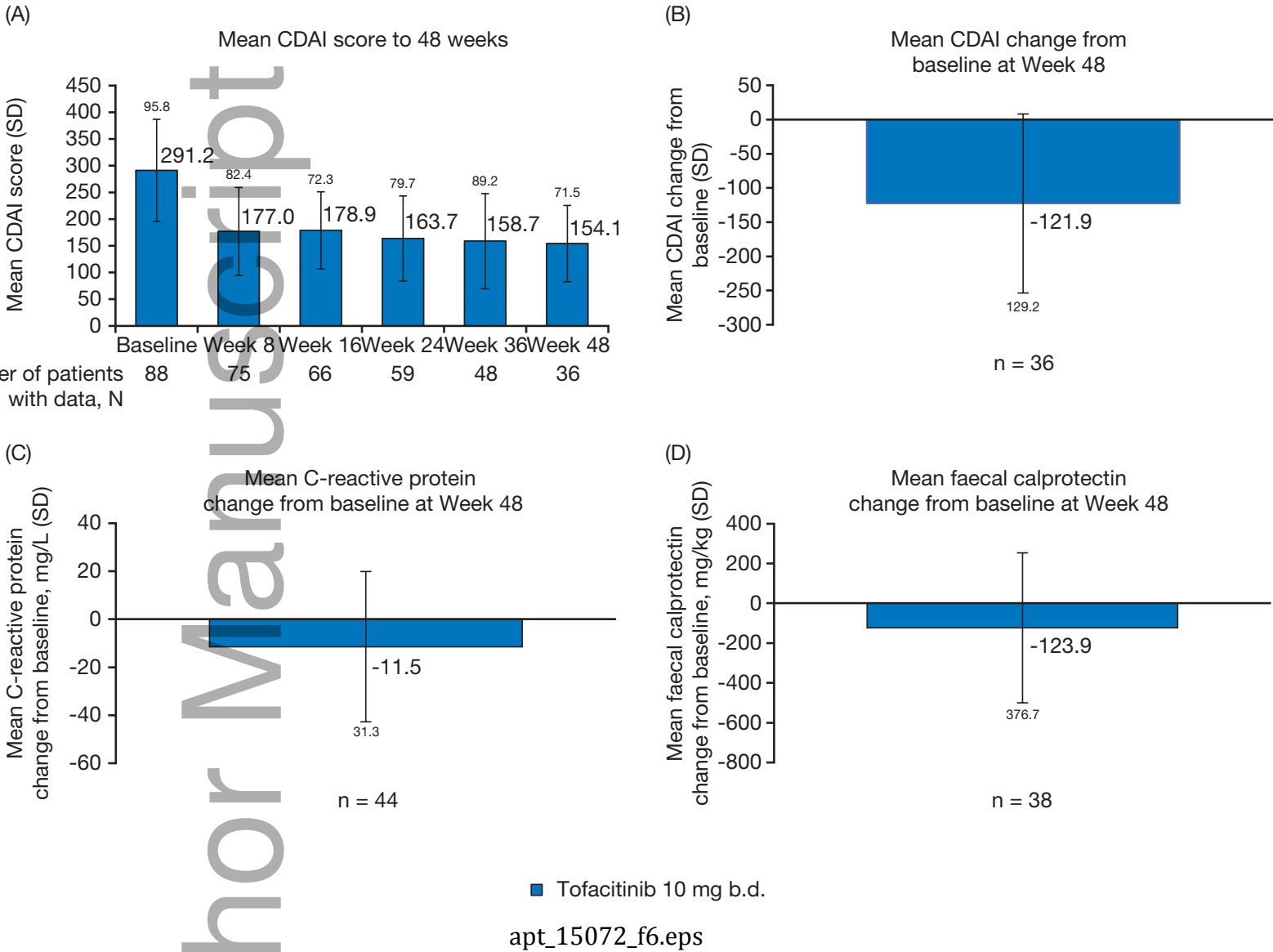
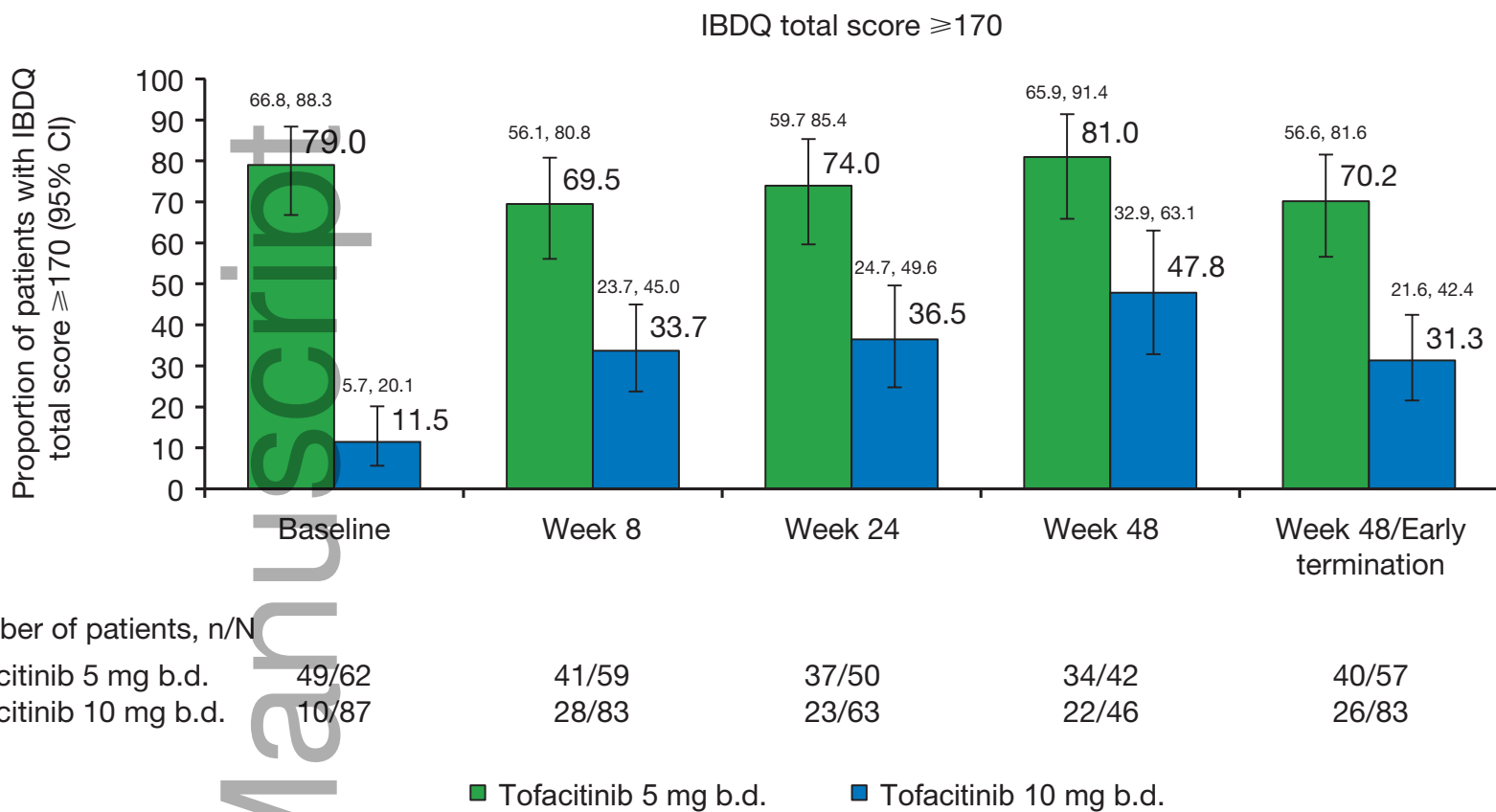


Figure 7



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