US Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

Biologics License Application

Clinical Studies

BLA:	125-544
Drug Name:	CT-P13
Indication:	Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis [1], rheumatoid arthritis in combination with methotrexate, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis
Applicant:	Celltrion
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[1] This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

Contents

List of Tables

List of Figures

1 Executive Summary

This review considers the therapeutic protein product CT-P13 as a potential biosimilar to US-licensed Remicade (infliximab). We focus on two 54-week, randomized, double-blind, parallel-group clinical trials that compared the efficacy and safety of CT-P13 and EU-approved Remicade. Study 3.1 was the primary comparative clinical study in 606 patients with active rheumatoid arthritis who had an inadequate response to methotrexate. Study 1.1 was a clinical study in 250 patients with ankylosing spondylitis designed to compare pharmacokinetic profiles, with safety and efficacy comparisons as secondary objectives.

In Study 3.1, the primary endpoint was the proportion of patients who remained in the study and achieved an American College of Rheumatology 20% (ACR20) response at Week 30. Approximately 60.9% of patients randomized to CT-P13 and 58.9% of patients randomized to EU-Remicade were ACR20 responders, for an estimated absolute difference between treatments of 2.0% (90% confidence interval [CI]: -4.6%, +8.7%). The 90% CI successfully ruled out the similarity margin of ±12% that the Agency has determined reasonable. ACR20, ACR50, and ACR70 responses over time, in addition to mean changes from baseline in the components of the ACR composite endpoint, the disease activity score (DAS28), and the radiographic damage score, were also similar between the treatment arms.

In Study 1.1, among the subset of randomized patients remaining in the study at Week 30, 70.5% of patients randomized to CT-P13 and 72.4% of patients randomized to EU-Remicade achieved an Assessment of SpondyloArthritis International Society 20% (ASAS20) response, for an estimated odds ratio comparing treatments of 0.91 (95% CI: 0.51, 1.62). In a supportive FDA analysis in all randomized patients, 63.2% of patients on CT-P13 and 67.2% on EU-Remicade remained in the study and achieved an ASAS20 response at Week 30, for an estimated difference of -4.0% (95% CI: -15.9%, 8.0%). Mean changes from baseline in important patient-reported outcome assessments, including the ASAS components, were also similar between the arms.

Patients who discontinued treatment early were also withdrawn from the clinical studies, leading to substantial dropout: 25% and 16% failed to complete the 54-week double-blind periods in Studies 3.1 and 1.1, respectively. The high dropout rates led to substantial missing data in important analyses, such as the evaluations of ACR20 and DAS28 at Week 30 in all randomized patients regardless of adherence in Study 3.1. Therefore, we conducted tipping point analyses to explore the sensitivity of results to violations in assumptions about the missing data. Confidence intervals for the differences between CT-P13 and EU-Remicade failed to rule out concerning losses in efficacy only under the assumption that patients who dropped out on CT-P13 had much worse outcomes than dropouts on EU-Remicade. Given the similar proportions of patients and distributions of reasons for early withdrawal on the two treatment arms, in addition to the similar baseline characteristics between dropouts on the two arms, an assumption of such large differences between the outcomes in dropouts on the two treatments seems implausible. That is, the finding of similar efficacy is highly credible notwithstanding the number of dropouts.

To reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must have assay sensitivity, or the ability to detect meaningful differences between the products, if such differences exist. Historical evidence of sensitivity to drug effects and appropriate trial conduct may be used to support the presence of assay sensitivity and a conclusion that the treatments are similarly effective rather than similarly ineffective. Based on an evaluation of five historical, randomized, placebo-controlled clinical trials of infliximab, we concluded that (1) the design of the historical trials were largely similar to that of comparative clinical Study 3.1; and (2) there were relatively large and consistent treatment effects across the five historical studies. We did not identify any issues with the quality of study conduct, with the exception of the high rate of study withdrawal. The totality of available information largely supports the assay sensitivity of Study 3.1.

2 Introduction

2.1 Background

The applicant has submitted a Biologics License Application (BLA) under section 351(k) of the Public Health Service (PHS) Act to support marketing of CT-P13 as a biosimilar to US-licensed Remicade (infliximab). Section 351(i) of the PHS Act defines biosimilarity to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." As noted in the FDA draft guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* [1], protein products are typically more complex than small molecule drugs and analytical methods may not be able to identify all relevant structural differences between the proposed biosimilar and the reference product. Because even minor differences in structure (e.g., higher order structure such as protein folding) may significantly affect safety, purity, or potency, comparative data from clinical studies designed to rule out important differences in safety and efficacy will often need to be part of the evaluation of biosimilarity.

Infliximab is a monoclonal antibody that inhibits the activity of tumor necrosis factor α (TNFα), an inflammatory cytokine thought to play a role in many disease processes. Infliximab was first approved in the United States in 1998 and is currently indicated for the treatment of Crohn's disease (CD), pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis [1], rheumatoid arthritis (RA) in combination with methotrexate, ankylosing spondylitis (AS), psoriatic arthritis, and plaque psoriasis. The approved dose for treatment of RA is 3 mg/kg at 0, 2, and 6 weeks, and then every 8 weeks thereafter, with the possibility of increasing the dose up to 10 mg/kg or increasing the frequency up to every 4 weeks in some patients. The approved dose for AS is 5 mg/kg at 0, 2, and 6 weeks, and then every 6 weeks thereafter. The approved dose for all other indications is 5 mg/kg at 0, 2, and 6 weeks, followed by every 8 weeks, with the possibility of increasing the dose to 10 mg/kg in adult CD patients.

The applicant has submitted results from several nonclinical, analytical, and clinical studies to support the claim of no clinically meaningful differences between CT-P13 and US-Remicade. The proposed indications for CT-P13 sought by Celltrion are identical to those of the reference product[1]. This review primarily considers the safety and efficacy evaluation of CT-P13 in clinical studies.

2.2 History of Product Development

The clinical development program for CT-P13 was introduced to the Division of Pulmonary, Allergy, and Rheumatology Products under IND 118,135. The comparative clinical studies were already complete at the time of the first correspondence between FDA and the applicant. However, there were several interactions with the applicant during product development that are potentially relevant to this review.

At a Biosimilar Biological Product Development (BPD) Type 3 meeting in July 2013, FDA noted that an adequately justified, prespecified similarity margin for the comparative clinical study was recommended, and that a randomized, controlled transition study was preferred. Because the studies were already complete, FDA acknowledged that the applicant would need to provide a post hoc justification of the margin, and that more than one analysis, each with important limitations, would be needed to explore the uncontrolled transition data. At a BPD Type 4 meeting in April 2014, the Agency stated that analyses of adverse events of special interest based on integrated data from multiple studies should use a statistical approach that appropriately accounts for the potential differences between studies. The Agency also reiterated

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a request from the BPD Type 3 meeting for additional analyses of the transition from EU-infliximab to CT-P13 based on comparisons of safety and immunogenicity rates within the same patients before and after the transition. In addition, FDA requested sensitivity analyses to explore the potential effect of violations in assumptions about the missing data in important analyses of continuous secondary efficacy endpoints. The applicant also agreed to further justify that the confidence interval for the difference in the primary endpoint in the comparative clinical study in RA was able to rule out an appropriately selected similarity margin.

2.3 Specific Studies Reviewed

The applicant has submitted results from seven completed clinical studies. Study 1.4 was a randomized, double-blind, parallel-group, single-dose clinical trial in 213 healthy volunteers to compare the pharmacokinetic (PK) profiles of CT-P13, EU-Remicade, and US-Remicade. Study 3.1 was a randomized, double-blind, parallel-group clinical trial to compare the safety and efficacy of CT-P13 and EU-Remicade in 606 patients with active RA who had an inadequate response to methotrexate (MTX). Study 3.2 was an open-label, single-arm extension study in 302 RA patients who had completed Study 3.1. Study 1.2 was a randomized, double-blind, parallel-group pilot trial to compare CT-P13 and EU-Remicade in 19 RA patients in the Philippines. Study B1P13101 was a randomized, double-blind, parallel-group clinical trial to compare the PK profiles of CT-P13 and EU-Remicade in 108 Japanese patients with active RA who had an inadequate response to MTX. Study 1.1 was a randomized, double-blind, parallel-group clinical trial to perform PK, safety, and efficacy comparisons of CT-P13 and EU-Remicade in 250 patients with AS. Study 1.3 was an open-label, single-arm extension study in 174 AS patients who had completed Study 1.1. There are also a number of ongoing studies.

Our evaluation of the similarity of CT-P13 and US-Remicade centers on Studies 3.1 and 1.1, the randomized, double-blind comparative studies in RA and AS, respectively. Our major focus is on Study 3.1, the comparative clinical study in which a comparison of efficacy and safety was the primary objective. We also briefly discuss safety results from the long-term extension Studies 3.2 and 1.3. Table 1 provides a summary of the two comparative clinical studies that are the focus of this review.

2.4 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, program code, and study reports were accessed under the network path \\cdsesub1\evsprod\bla125544\125544.enx.

Table 1: Overview of Key Clinical Studies

Study	Population	Design	Treatment Arms	Number Subjects	Date[1]
CT-P13 3.1	RA	54-week, R, DB, PG	CT-P13 EU-Remicade	302 304	12/2010 – 07/2012
CT-P13 1.1	AS	54-week, R, DB, PG	CT-P13 EU-Remicade	125 125	12/2010 – 07/2012

Source: Reviewer

[1] Dates correspond to the start and end of the study.

Abbreviations: RA = rheumatoid arthritis; AS = ankylosing spondylitis; R = randomized; DB = double-blind; PG = parallel-group

3 Statistical Evaluation

3.1 Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented. We were able to reproduce the results of all important primary and secondary analyses. In key analyses, the applicant excluded 11 randomized patients from Study 3.1 and 7 randomized patients from Study 1.1 who were enrolled at potentially fraudulent study centers. Results were similar when including data from patients treated at these centers. The FDA Office of Scientific Investigations (OSI) identified issues with one clinical site during an inspection, but results did not change in a sensitivity analysis removing data from this site.

3.2 Study Design

3.2.1 Study 3.1

Study 3.1 was a 54-week, randomized, double-blind, parallel-group clinical trial to compare the safety and efficacy of CT-P13 and EU-Remicade in 606 patients with active rheumatoid arthritis despite treatment with methotrexate. The study consisted of patients ages 18 to 75 years who had been diagnosed with RA according to the revised 1987 American College of Rheumatology (ACR) classification criteria for at least 1 year prior to screening. Active disease was defined by the presence of six or more swollen joints, six or more tender joints, and at least two of the following: morning stiffness lasting at least 45 minutes, an erythrocyte sedimentation rate (ESR) greater than 28 mm/h, and a serum C-reactive protein (CRP) concentration greater than 2.0 mg/dL. Patients had been on methotrexate (12.5 to 25 mg/week) for at least 3 months, with a stable dose for at least 4 weeks, and they also received $\geq$ 5 mg/week folic acid during the study. Patients previously treated with a biological agent at any time for RA or who had received disease-modifying antirheumatic drugs (DMARDs) other than methotrexate (e.g., hydroxychloroquine, chloroquine, or sulfasalazine) in the past 4 weeks were excluded. Subjects were randomized 1:1 to CT-P13 or EU-Remicade administered via single 2-hour intravenous (IV) infusion at a dose of 3 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter. Dose increases were not permitted. Randomization was stratified by region (European versus non-European) and CRP ($\leq$ 2 versus $>$ 2 mg/dL).

Withdrawal *from the treatment* was equivalent to withdrawal *from the study* because patients who stopped taking the therapy early were not followed up for safety and efficacy assessment for the remainder of the 54-week treatment period. Possible protocol-specified reasons for withdrawal included adverse event, loss to follow-up, significant protocol violation, and signs of disease progression. If possible, an early withdrawal visit was conducted 8 weeks after the last dose of study medication. The many potential reasons for stopping treatment, combined with the fact that the applicant did not continue to collect information on patients who stopped therapy early, led to substantial missing data in intention-to-treat safety and efficacy analyses (see 5.1 for further discussion).

The prespecified primary efficacy endpoint was the proportion of patients achieving an ACR20 response at Week 30. An ACR20 response was defined as at least 20% improvement from baseline in both the tender and swollen joint counts, in addition to at least 20% improvement in at least three of the following: patient assessment of pain on a visual analog scale (VAS), patient global assessment of disease status (VAS), physician global assessment of disease status (VAS), Health Assessment Questionnaire (HAQ) physical ability score, and either serum CRP concentration or ESR. Patients who discontinued treatment early (and therefore the study, as well), had a protocol-prohibited change in medication, required a surgical joint procedure, or had missing or incomplete data for the evaluation of ACR20 at Week 30 were considered non-responders. Therefore, the primary efficacy endpoint was in fact a composite endpoint consisting of the following components: (1) remaining on treatment and in the study; (2) not receiving a protocol-prohibited medication or a surgical joint procedure; and (3) achieving an ACR20 response at Week 30. Secondary efficacy endpoints included the components used to define ACR20 response, time to onset of ACR20 response, the Disease Activity Score in 28 joints (DAS28), EULAR response, ACR50 response, ACR70 response, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), total van der Heijde radiographic joint score, SF-36 total score, fatigue (SF-36 vitality subscale score), and the number of patients requiring salvage treatments. Most were evaluated at Weeks 14, 30, and 54.

The study was unblinded at Week 30 for reporting, although patients and investigators remained blinded to treatment assignment until the end of the study. Patients and investigators may have been exposed to summary-level interim results that were announced publicly, and it is possible that unblinding to interim results could have altered study conduct and biased Week 54 results. However, unblinding would not have affected Week 30 results, which are the primary focus of this review.

3.2.2 Study 1.1

Study 1.1 was a 54-week, randomized, double-blind, parallel-group clinical trial to compare the PK, safety, and efficacy of CT-P13 and EU-Remicade in 250 patients with active ankylosing spondylitis. The study consisted of patients ages 18 to 75 years who had been diagnosed with AS according to the 1984 modified New York classification criteria for at least 3 months prior to screening. Active disease was defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 (range 0 to 10) despite conventional treatment for AS for at least 3 months. Subjects also had a VAS score for spinal pain of ≥ 4 (range 0 to 10). Patients previously treated with a biological agent at any time for AS or who had received DMARDs (e.g., methotrexate) in the past 4 weeks were excluded. Subjects were randomized 1:1 to CT-P13 or EU-Remicade administered via 2-hour IV infusion at 5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter. Randomization was stratified by region and baseline BASDAI score (< 8 versus ≥ 8). As in Study 3.1, there were many reasons for treatment discontinuation, and patients who stopped treatment early were withdrawn from the study. This led to substantial missing data in intention-to-treat safety and efficacy analyses (see 5.1 for further discussion).

The primary objective was to demonstrate comparable PK at steady state between CT-P13 and EU-Remicade. Secondary objectives were to compare CT-P13 and EU-Remicade with respect to long-term safety and efficacy endpoints. Efficacy endpoints included the Assessment of SpondyloArthritis International Society 20% improvement scale (ASAS20), ASAS40, BASDAI score, Bath Ankylosing Spondylitis Functional Index (BASFI) score, Bath Ankylosing Spondylitis Metrology Index (BASMI) score, chest expansion, and SF-36 total score, assessed at Weeks 14, 30, and 54 (or an end-of-study visit for patients who stopped treatment early). The ASAS20 response is defined as improvement of at least 20% and an absolute improvement of at least 1 unit on a 0 to 10 scale in at least 3 of the following domains: patient global assessment of disease status, patient assessment of spinal pain, function according to BASFI score, and morning stiffness determined using the last 2 questions of BASDAI. Additionally, ASAS20 responders could not show worsening of at least 20% and 1 unit on any of the domains. As with Study 3.1, Study 1.1 was unblinded at Week 30 for reporting, although patients and investigators remained blinded to treatment assignment until the end of the study.

3.2.3 Additional Studies

Studies 1.3 and 3.2 were open-label, single-arm, long-term extensions of Studies 1.1 and 3.1, respectively. Patients who had completed all scheduled visits and had no major protocol violations during Study 1.1 or 3.1 were eligible. Patients who had previously received CT-P13 during the double-blind, controlled treatment period of Study 1.1 or 3.1 continued to receive CT-P13 during the long-term extension. Those who had previously received EU-Remicade transitioned to CT-P13. The last dosing of double-blind study therapy in Studies 1.1 and 3.1 occurred at Week 54; patients who entered the extension studies were unblinded and dosed with CT-P13 every 8 weeks through Week 102 (i.e., at Weeks 62, 70, 78, 86, 94, and 102). An end-of-study visit occurred 8 weeks after the last dose of study treatment. Efficacy and safety assessments, as well as withdrawal criteria, were similar to those of Studies 1.1 and 3.1.

3.3 Statistical Methodologies

3.3.1 Planned Analyses

The applicant completed the comparative clinical studies before corresponding with FDA, so the Agency was not able to review the statistical analysis plan prior to data unblinding. However, the applicant did have statistical analysis plans for the clinical studies finalized and documented prior to the completion of the studies. In Study 3.1, a sample size of 584 patients was planned to rule out a similarity margin of ±15% at the 2.5% overall significance level with 80% power under the alternative hypothesis of no difference, assuming a response rate of 50% in both groups. This allowed for approximately 20% of patients to be excluded from the per-protocol population. The primary analysis was based on an exact binomial approach in which the null hypothesis would be rejected if the 95% confidence interval (CI) for the difference in ACR20 response proportions was contained within the similarity margin. The applicant modified the proposed similarity margin to ±13% after discussions with the Agency (see 3.3.3 for additional discussion).

The applicant also carried out a supportive logistic regression analysis of ACR20 response, adjusting for region and CRP category. Analyses of ACR20, ACR50, and ACR70 responses over time were also based on the exact binomial approach, and linear regression models (analyses of covariance) adjusting for baseline value, region, and CRP category were used to evaluate mean changes from baseline in DAS28 (CRP) and DAS28 (ESR).

All analyses were carried out in both the all-randomized population and the per-protocol population. The per-protocol population was defined as patients who received all doses of study treatment, had an ACR assessment, did not discontinue or reduce their methotrexate dose below 12.5 mg/week for more than two consecutive weeks because of toxicity or noncompliance, and did not have any major protocol deviations. The following were considered major protocol deviations: misrandomizations, potentially fraudulent study centers, noncompliance of inclusion/exclusion criteria, changes in joint assessor where the data were questionable, a Week 30 assessment out of window by more than 2 weeks, and receipt of certain protocol-prohibited medications. Sensitivity analyses were carried out including data on patients from potentially fraudulent study centers. The applicant provided only descriptive statistics for several additional important secondary endpoints, such as the ACR components and the total van der Heijde radiographic joint damage score.

For the evaluation of key continuous secondary efficacy endpoints (e.g., HAQ score and DAS28), the applicant performed post hoc sensitivity analyses based on single and multiple imputation to explore the potential effect of missing data. However, all of the sensitivity analyses performed by the applicant were based on the strong and unverifiable assumption that unobserved data in dropouts were missing at random.

In Study 1.1, a sample size of 246 was planned to provide 90% power to show PK similarity. Analyses of ASAS20 and ASAS40 response were based on logistic regression models adjusting for region and baseline BASDAI score. Patients who withdrew from the study prior to the time point of assessment were excluded from analyses rather than considered non-responders (the latter was the approach in Study 3.1). There were no similarity margins prespecified and no hypothesis tests carried out. The applicant presented only descriptive statistics for additional efficacy endpoints.

3.3.2 Additional Reviewer Analyses

We conducted several additional analyses to support those carried out by the applicant. Because FDA generally expects the type I error rate of a test of similarity to be controlled at 5%, we calculated a 90% rather than 95% CI as part of the primary analysis for Study 3.1. We used 95% CIs for all additional analyses in this review in order to match the applicant's results. The applicant presented only descriptive statistics for the components of the composite primary endpoint and other important secondary efficacy endpoints, and performed limited analyses to explore the sensitivity of the findings to possible violations in key assumptions. Therefore, we carried out several additional supportive analyses that we considered important.

In Studies 3.1 and 1.1, we compared mean changes from baseline in important continuous secondary efficacy endpoints using linear regression models adjusting for the baseline value of the endpoint and the stratification factors, with robust Huber-White standard errors. These endpoints included the ACR components, DAS28, and the total van der Heijde radiographic joint score in Study 3.1, and the ASAS components, BASDAI score, and BASMI score in Study 1.1. Such continuous endpoints may be more sensitive to small but important differences between treatments in efficacy than the primary binary ACR and ASAS response endpoints. In addition, we gave importance to endpoints that directly measure how patients function or feel in daily life, such as the tender and swollen joint counts and HAQ physical ability score in RA and the BASDAI, BASFI, and BASMI scores in AS. Although the primary ACR20 endpoint in Study 3.1 is largely composed of such direct measures, it is also based on the changes in ESR and CRP, which are both surrogate endpoints.

We also compared the utility of the two treatments by presenting empirical distribution function plots for these continuous endpoints in which patients who discontinued the assigned treatment were assigned the worst outcomes. In Study 1.1, we carried out additional supportive analyses of the binary ASAS20 and ASAS40 endpoints in all randomized patients to calculate exact confidence intervals for the difference in response probabilities between the arms. In these analyses, patients who withdrew from the study prior to the time point of assessment were considered non-responders.

We carried out all key analyses in all randomized patients to evaluate mean differences between treatment groups at key time points in all randomized patients regardless of adherence to the treatment or to the protocol (i.e., the *intention-to-treat* or *de facto* estimand). We also carried out analyses in the per-protocol population to evaluate mean differences between treatment groups at key time points in the subset of patients who tolerate and adhere. Draft FDA Guidance [2] and ICH guidelines [3] indicate that the evaluation of both estimands is important in the context of a study designed to establish similarity between treatments. The de facto evaluation is critical because, unlike the per-protocol evaluation, it preserves the integrity of randomization and therefore guarantees reliable inference regarding possible differences in effects of the treatment strategies (if there are no missing data). However, in the presence of true differences between treatments, the per-protocol effect may be larger and easier to detect than the de facto effect because of the restriction to the subsets of patients who adhere.

Because patients were not followed after treatment discontinuation, there were substantial missing outcome data at Weeks 30 and 54 in the comparative clinical studies. Therefore, evaluations of de facto estimands based on data in completers rely on untestable assumptions about the unobserved missing values at the follow-up time of interest (e.g., 30 weeks). In particular, these analyses, in addition to the sensitivity analyses carried out by the applicant, assume that patients who discontinued treatment went on to have similar outcomes to those patients on that treatment arm who remained in the study through the time point of endpoint ascertainment (and who had similar values of baseline characteristics included in the model). This assumption may not be plausible given the known efficacy of infliximab and the fact that early symptomatic improvement on treatment within a patient who does not tolerate or adhere to the treatment regimen might go away within a few weeks of treatment discontinuation. In addition, the subsets of patients who withdrew from the study on the two treatment arms may have been inherently different with respect to important, unmeasured prognostic characteristics, thus leading to different future (unobserved) outcomes.

Therefore, we carried out additional analyses to explore the sensitivity of results to violations in the assumptions about the missing data. We used simple tipping point analyses to determine how much worse outcomes in patients who discontinue early on CT-P13 (relative to CT-P13 completers) would have to be than outcomes in dropouts on EU-Remicade (relative to EU-Remicade completers) such that there would be a concerning difference in efficacy (see Appendix for methodology details). This allows for a follow-up discussion of the plausibility of those assumptions under which the conclusions change.

Dr. Juwaria Waheed, the Medical Reviewer, conducted the complete safety evaluation, but we conducted supplementary analyses to compare CT-P13 and EU-Remicade with respect to the incidence of adverse events of special interest. Selected safety endpoints included active tuberculosis (TB), latent TB, infection, serious infection, pneumonia, malignancy and lymphoma, infusion-related reaction, drug-induced liver injury in accordance with Hy's law, vascular disorder, cardiac disorder, and opportunistic infection. Detailed methods and results for these safety analyses can be found in 3.5.

3.3.3 Similarity Margin for Study 3.1

The determination of an equivalence margin is a critical aspect of the design of the comparative clinical study because it determines the null hypothesis being tested in the primary analysis, i.e., the differences in efficacy that the study will need to rule out at an acceptable significance level. The term *equivalence margin* is a misnomer because it is not possible to statistically demonstrate that two products are equivalent with respect to a particular endpoint. Instead, we describe the margin as a *similarity margin* to better reflect the goal of the efficacy evaluation: to determine whether the two products are similar, in that a certain magnitude of difference (the margin) in efficacy can be ruled out.

The applicant prespecified a similarity margin of ±15%, but did not seek Agency feedback on the margin until the study was complete and the data unblinded. In response to comments from FDA indicating that the margin was not acceptable, the applicant provided justification for a revised margin of ±13% based on a meta-analysis of historical data from randomized clinical trials of infliximab and the goal of preserving at least 50% of the effect size of the reference product. We do not agree with the applicant's selection of historical studies, as one important study [4] is not included in the meta-analysis, and we do not agree with the proposed ±13% margin. We believe that a margin of ±12% is more appropriate.

Our selection of a ±12% similarity margin was based on discussions with clinicians aimed at weighing the clinical importance of different losses in effect against the feasibility of different study sizes. In a comparative clinical study designed with 90% power to reject absolute differences greater than 12% in magnitude, observed differences larger than approximately 6% will result in failure to establish similarity, as the 90% confidence interval for the estimated difference will not rule out the 12% margin. Therefore, the comparative clinical study will be able to rule out differences in ACR20 response greater than 12% with high (at least 95%) statistical confidence, and will be able to rule out differences greater than around 6% with moderate (at least 50%) statistical confidence. The lower bound of the proposed similarity margin (-12%) also corresponds to the retention of approximately 50% of conservative estimates of treatment effect sizes relative to placebo for infliximab (Table 2).

Table 2: Historical Effect of Infliximab on ACR20 Response in Randomized Clinical Trials of Patients with Active RA Despite Treatment with Methotrexate (MTX)

Study	Week	MTX + Placebo		MTX + Infliximab		Difference in Response
		N	ACR Response	N	ACR20 Response	
Maini [5]	30	88	20%	86	50%	30%
Westhovens [6]	22	361	24%	360	55%	31%
Schiff [4]	28	110	42%	165	59%	18%
Zhang [7]	18	86	49%	87	76%	27%
Abe [8]	14	47	23%	49	61%	38%
Meta-Analysis (Fixed Effects[1]): Difference (95% CI)						28.4% (23.6%, 33.3%)
Meta-Analysis (Random Effects[2]): Difference (95% CI)						28.3% (22.6%, 34.1%)

Source: Reviewer

[1] Based on Mantel-Haenszel weights

[1] Based on DerSimonian-Laird approach

3.4 Evaluation of Efficacy

3.4.1 Patient Disposition, Demographic, and Baseline Characteristics

Baseline characteristics for Studies 3.1 and 1.1 are presented in Tables 3 and 4, respectively. There were no large imbalances in the distributions of baseline characteristics across the treatment arms. In Study 3.1, there were 606 subjects enrolled at 100 sites in 19 countries worldwide. None of the sites were in the United States. Seventy-three percent of patients were White, 83% were female, and the mean age was 49 years. The average swollen and tender joint counts were 16 and 25, respectively, and the average disease activity score (DAS28 [CRP]; scale: 0–10) was 5.8. In Study 1.1, there were 250 patients enrolled at 46 sites in 10 countries worldwide, with no U.S. sites. Seventy-six percent of subjects were White, 19% were female, and the mean age was 39 years. The average disease activity score (BASDAI; scale: 0–10) was 6.7.

As described previously, the design of the clinical studies was such that subjects who stopped treatment early were also withdrawn from the study. There were many prespecified reasons for withdrawal, such as adverse event, lack of efficacy, and protocol deviation. As a result, there was substantial patient dropout. The proportions of patients withdrawing over time in Studies 3.1 and 1.1 are displayed by treatment group in Figures 1 and 2. In Studies 3.1 and 1.1, 25% and 16% failed to complete the 54-week double-blind follow-up periods, respectively (Tables 5 and 6). In Study 3.1, the dropout rate was approximately 15% at Week 30, the time point of the primary analysis. The proportions of patients withdrawing early from the study and the distributions of reasons for dropout were largely similar between CT-P13 and EU-Remicade in the two studies. There was slightly lesser dropout due to adverse events on CT-P13 (8%) than EU-Remicade (13%) in Study 3.1, but such small differences would not be unusual by random chance if there was no true difference between treatments. In addition, this observed trend was not replicated in Study 1.1. Of note, six patients on CT-P13 discontinued therapy due to a life-threatening infusion-related reaction in Study 3.1, as compared to zero patients on EU-Remicade. However, the overall incidence of infusion-related reactions was similar between the treatments (see 3.5).

Table 3: Baseline Characteristics in RA Patients in Study 3.1

	CT-P13	EU-Remicade	Overall
N	302	304	606
Female	245 (81%)	256 (84%)	501 (83%)
Age (years)	49.0 (12.2)	48.6 (11.5)	48.8 (11.8)
Age Group (years)			
< 35	40 (13%)	43 (14%)	83 (14%)
35-50	100 (33%)	107 (35%)	207 (34%)
50-65	138 (46%)	136 (45%)	274 (45%)
≥ 65	24 (8%)	18 (6%)	42 (7%)
Race			
White	220 (73%)	222 (73%)	442 (73%)
Black	2 (1%)	1 (0%)	3 (0%)
Asian	34 (11%)	37 (12%)	71 (12%)
Other	46 (15%)	44 (14%)	90 (15%)
Weight (kg)	70.7 (16.3)	69.9 (15.8)	70.3 (16.0)
Height (cm)	163.2 (8.7)	162.9 (9.0)	163.0 (8.9)
BMI (kg/m^2)	26.5 (5.3)	26.3 (5.3)	26.4 (5.3)
Region			
Eastern Europe	180 (60%)	182 (60%)	362 (60%)
Western Europe	16 (5%)	17 (6%)	33 (5%)
Latin America	71 (24%)	67 (22%)	138 (23%)
Asia	34 (11%)	38 (12%)	72 (12%)
Swollen Joint Count	16.2 (8.7)	15.2 (8.3)	15.7 (8.5)
Tender Joint Count	25.6 (13.8)	24.0 (12.9)	24.8 (13.4)
HAQ Score	1.6 (0.6)	1.6 (0.6)	1.6 (0.6)
Patient Pain Score	65.9 (17.5)	65.5 (17.2)	65.7 (17.3)
Patient Global Assessment	65.7 (17.2)	65.4 (17.0)	65.5 (17.1)
Physician Global Assessment	64.8 (14.2)	65.0 (13.5)	64.9 (13.8)
CRP (mg/dL)	1.9 (2.5)	1.9 (2.2)	1.9 (2.4)
ESR (mm/h)	46.6 (22.4)	48.5 (22.6)	47.5 (22.5)
DAS28 (ESR)	6.7 (0.8)	6.6 (0.8)	6.6 (0.8)
DAS28 (CRP)	5.9 (0.8)	5.8 (0.9)	5.8 (0.9)

Source: Reviewer

Cell contents are mean (standard deviation) or frequency (percent)

Table 4: Baseline Characteristics in AS Patients in Study 1.1

	CT-P13	EU-Remicade	Overall
N	125	125	250
Female	26 (21%)	22 (18%)	48 (19%)
Age (years)	39.2 (12.1)	38.7 (10.5)	38.9 (11.3)
Age Group (years)			
< 35	52 (42%)	45 (36%)	97 (39%)
35-50	45 (36%)	58 (46%)	103 (41%)
50-65	26 (21%)	20 (16%)	46 (18%)
≥ 65	2 (2%)	2 (2%)	4 (2%)
Race			
White	97 (78%)	92 (74%)	189 (76%)
Asian	16 (13%)	13 (10%)	29 (12%)
Other	12 (10%)	20 (16%)	32 (13%)
Weight (kg)	74.3 (15.7)	76.7 (14.3)	75.5 (15.0)
Height (cm)	171.7 (9.6)	171.4 (8.6)	171.5 (9.1)
BMI (kg/m^2)	25.1 (4.2)	26.1 (4.3)	25.6 (4.2)
Region			
Eastern Europe	80 (64%)	83 (66%)	163 (65%)
Asia	16 (13%)	12 (10%)	28 (11%)
Latin America	22 (18%)	27 (22%)	49 (20%)
Western Europe	7 (6%)	3 (2%)	10 (4%)
BASDAI Score	6.7 (1.4)	6.6 (1.6)	6.7 (1.5)
BASDAI Score ≥ 8	33 (26%)	30 (24%)	63 (25%)
BASFI Score	6.2 (1.9)	6.2 (2.2)	6.2 (2.1)
BASMI Score	4.0 (2.1)	4.1 (2.1)	4.0 (2.1)
Patient Spinal Pain Score	68.7 (15.4)	69.2 (17.0)	68.9 (16.2)
Physician Disease Status Score	65.9 (16.9)	65.8 (19.7)	65.8 (18.3)

Source: Reviewer

Cell contents are mean (standard deviation) or frequency (percent)

Figure 1: Patient Withdrawal over Time in Study 3.1 (Source: Reviewer)

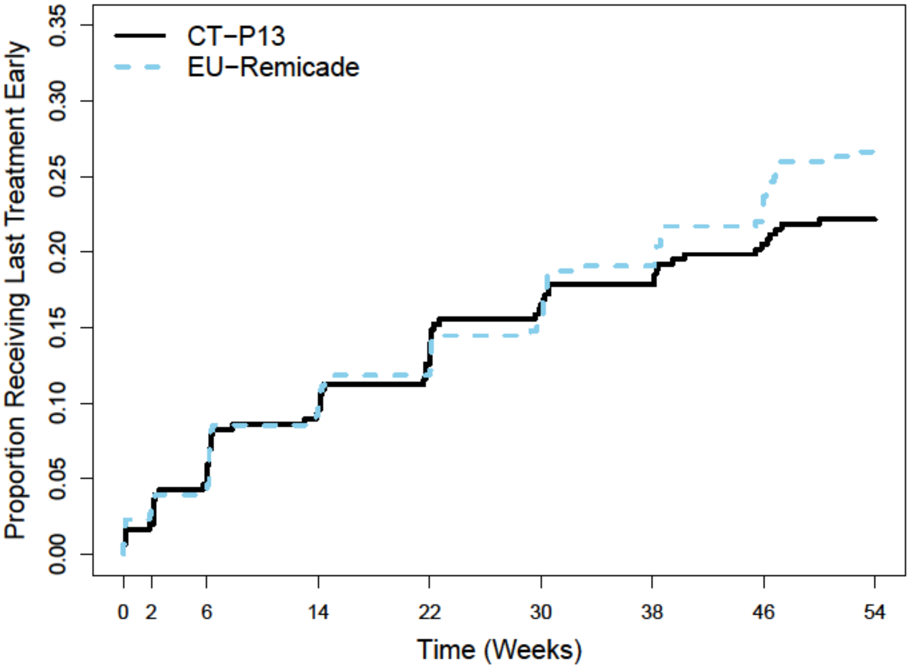

Figure 2: Patient Withdrawal over Time in Study 1.1 (Source: Reviewer)

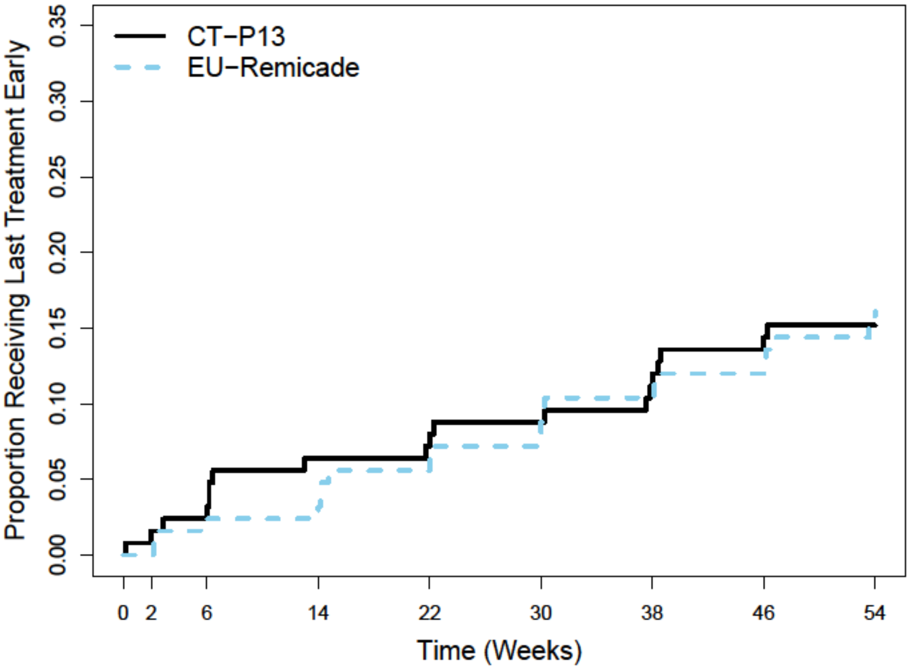

Table 5: Patient Dropout, by Reason for Withdrawal, in Study 3.1

	CT-P13	EU-Remicade	Overall
Completed Study	233 (77%)	222 (73%)	455 (75%)
Withdrew from Study	69 (23%)	82 (27%)	151 (25%)
Adverse Event	25 (8%)	41 (13%)	66 (11%)
Any malignancy diagnosed	0 (0%)	2 (1%)	2 (0%)
Investigator Decision	1 (0%)	0 (0%)	1 (0%)
Lack of Efficacy	10 (3%)	6 (2%)	16 (3%)
Life-threatening infusion-related reaction	6 (2%)	0 (0%)	6 (1%)
Other	1 (0%)	2 (1%)	3 (0%)
Patient consent withdrawn	16 (5%)	21 (7%)	37 (6%)
Patient died	0 (0%)	1 (0%)	1 (0%)
Patient lost to follow-up	3 (1%)	2 (1%)	5 (1%)
Pregnancy	0 (0%)	1 (0%)	1 (0%)
Significant protocol violation	2 (1%)	2 (1%)	4 (1%)
Sponsor decision	5 (2%)	4 (1%)	9 (1%)

Source: Reviewer

Table 6: Patient Dropout, by Reason for Withdrawal, in Study 1.1

	CT-P13	EU-Remicade	Overall
Completed Study	106 (85%)	104 (83%)	210 (84%)
Withdrew from Study	19 (15%)	21 (17%)	40 (16%)
Adverse Event	10 (8%)	8 (6%)	18 (7%)
Any malignancy diagnosed	1 (1%)	0 (0%)	1 (0%)
Investigator Decision	1 (1%)	1 (1%)	2 (1%)
Lack of Efficacy	2 (2%)	0 (0%)	2 (1%)
Other	0 (0%)	1 (1%)	1 (0%)
Patient consent withdrawn	3 (2%)	6 (5%)	9 (4%)
Patient died	0 (0%)	2 (2%)	2 (1%)
Patient lost to follow-up	0 (0%)	2 (2%)	2 (1%)
Significant protocol violation	0 (0%)	1 (1%)	1 (0%)
Sponsor decision	2 (2%)	0 (0%)	2 (1%)

Source: Reviewer

3.4.2 Key Results in Study 3.1

Table 7 displays results from the primary efficacy analysis in Study 3.1. Approximately 60.9% of patients randomized to CT-P13 and 58.9% of patients randomized to EU-Remicade remained in the study and achieved an ACR20 response at Week 30, for an estimated absolute difference between treatments of 2.0% (90% CI: -4.6%, +8.7%; 95% CI: -5.8%, +9.9%). The 90% CI ruled out the margin of ±13% proposed by the applicant, in addition to the margin of ±12% that the Agency has determined reasonable. The lower CI bound of -4.6% also corresponds to the preservation of approximately 80% of conservative estimates of the effect of infliximab from historical trials (Table 2). A little more than half of the non-responders were patients who completed the study and did not satisfy the ACR20 response criteria. The majority of the remaining non-responders were patients who withdrew from the study prior to Week 30. There were no large differences between the treatment arms in the distributions of reasons for non-response (Table 7).

In a supportive analysis of ACR20 response in the subset of patients who completed the study and adhered to the protocol (per-protocol population), 73.4% and 70.1% responded on CT-P13 and EU-Remicade, respectively, for an estimated difference of 3.3% (90%: -3.4%, +10.0%). The proportions of patients remaining in the study and achieving ACR20 responses at Weeks 14 and 54, in addition to ACR50 and ACR70 response probabilities over time, were similar between the treatment arms (Figure 3). Mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28) were also similar between the arms in all randomized patients who completed the study (Table 8), as well as in the per-protocol population (results not shown). In particular, the 95% CI (-0.28, 0.16) for the mean difference in DAS28 (CRP) ruled out relatively large increases on CT-P13 as compared to EU-Remicade. The upper CI bound of 0.16 is considerably less than 0.6, which has been used as a non-inferiority margin in a European study and has been specified by EULAR as the threshold for a moderate within-patient response. See 3.4.5 for additional discussion on the potential effect of missing data on these comparisons. On both treatment arms, improvements in these continuous secondary endpoints were evident as early as Week 14, and trends over time were similar (see Appendix: Figures 7 – 13). Empirical distribution functions were also comparable between the treatment arms for key continuous efficacy endpoints (e.g., see DAS28 comparison in Figure 14).

Table 9 presents results for the radiographic evaluation at Week 54. Based on the original assessment, although mean changes from baseline were similar between the arms (difference: 2.6; 95% CI: -2.7, 7.9), the within-group mean changes on the two arms (-28.5 and -31.9) were noticeably different than those observed in historical clinical trials (typically closer to zero). Therefore, the applicant performed a post hoc reassessment of the radiographs. In the original assessment, a single reader evaluated a patient's radiographs with knowledge of the chronological order of the images. In the reassessment, two readers independently evaluated a patient's paired radiographs without knowledge of the order, and the scores of the two readers were averaged. Based on the reassessment, average changes on the two arms remained similar (difference: 0.7; 95% CI: -0.4, 1.9), and the within-group changes from baseline were more in line with those of historical trials. The substantial change in the results upon reassessment illustrates the importance of the approach used to read radiographic images. Our results differ slightly from those of the applicant because the applicant excluded 73 patients who had radiographs assessed after the first date of treatment. Fifty and 66 of these 73 patients had radiographs within 2 and 4 weeks of treatment initiation, respectively. Although radiographic results appeared similar between CT-P13 and EU-Remicade, the need for a post hoc reassessment and the large number of patients with radiographs weeks after first treatment infusion cloud the interpretability of the radiographic data.

Figure 3: ACR Response Probabilities over Time in Study 3.1 (Source: Reviewer)

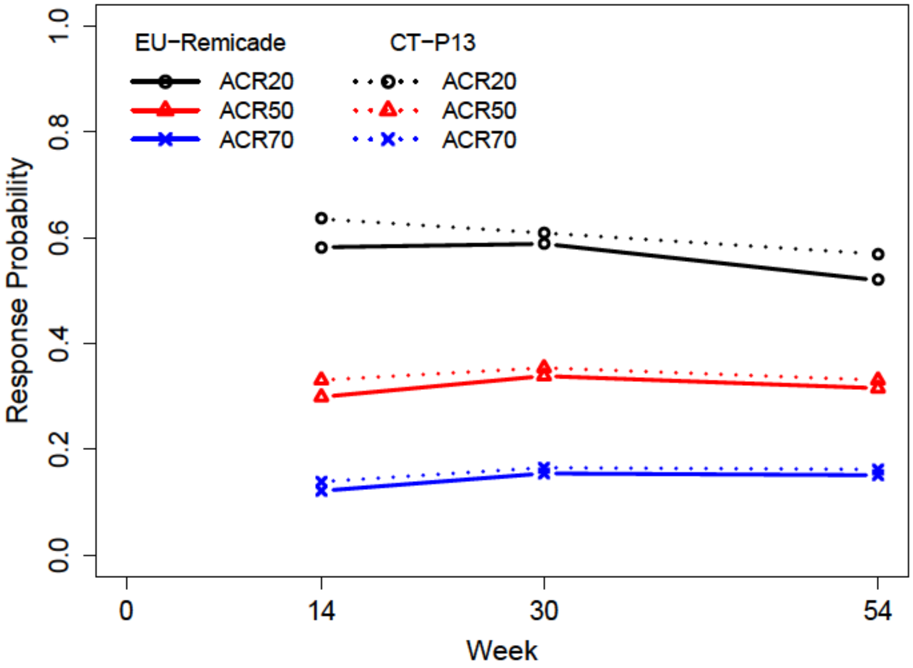

Table 7: Proportions of Responders, and Distributions of Reasons for Non-Response, with Respect to Composite ACR20-Based Primary Endpoint at Week 30 in Study 3.1

	CT-P13 (N=302)	EU-Remicade (N=304)
Responder[1]	184 (60.9%)	179 (58.9%)
	Difference: 2.0% (90% CI: -4.6%, 8.7%)[2]	
Non-Responder	118 (39.1%)	125 (41.1%)
ACR20 Criteria Not Met	63 (20.9%)	73 (24.0%)
Withdrew from Study	46 (15.2%)	44 (14.5%)
Lack of Efficacy	4 (1.3%)	0 (0%)
Adverse Event	24 (7.9%)	20 (6.6%)
Malignancy	0 (0%)	2 (0.7%)
Withdrawal of Consent	11 (3.6%)	14 (4.6%)
Protocol Violation	2 (0.7%)	2 (0.7%)
Sponsor Decision	5 (1.7%)	4 (1.3%)
Other	0 (0%)	2 (0.7%)
Prohibited Medication Change	7 (2.3%)	5 (1.6%)
Surgical Joint Procedure	1 (0.3%)	1 (0.3%)
Incomplete ACR Assessment	1 (0.3%)	2 (0.7%)

Source: Reviewer

Cell contents are frequency (percent of column total)

Abbreviations: CI = confidence interval

[1] Defined by remaining in the study and without a protocol-prohibited medication change or surgical joint procedure through Week 30, and meeting ACR20 response criteria at Week 30

[2] Difference between CT-P13 and EU-Remicade, with exact confidence interval

Table 8: Mean Changes from Baseline in the ACR Components and DAS28 at Week 30 in Study 3.1 Completers

	CT-P13 (N=302)		EU-Remicade (N=304)		Difference (95% CI)[2]
	N[1]	Mean	N[1]	Mean	
Swollen Joint Count	260	-12.2	257	-11.5	-0.1 (-1.0, 0.7)
Tender Joint Count	260	-16.3	257	-15.6	0.2 (-1.2, 1.7)
HAQ Score	261	-0.60	256	-0.51	-0.06 (-0.15, 0.04)
Patient Pain	260	-29.3	256	-27.7	-1.5 (-5.4, 2.4)
Patient Global	260	-27.7	255	-26.8	-1.1 (-5.0, 2.8)
Physician Global	260	-35.8	256	-35.4	-0.6 (-3.9, 2.6)
ESR	261	-15.1	255	-15.7	-0.4 (-3.8, 2.9)
CRP	261	-0.68	256	-0.74	0.03 (-0.25, 0.30)
DAS28 (ESR)	259	-2.42	253	-2.31	-0.10 (-0.32, 0.13)
DAS28 (CRP)	259	-2.14	254	-2.22	-0.06 (-0.28, 0.16)

Source: Reviewer

Abbreviations: CI = confidence interval

[1] Number of patients with complete data included in analysis

[2] Mean difference between CT-P13 and EU-Remicade based on linear regression model adjusting for baseline value, region, and CRP category, with Huber-White standard errors

Table 9: Mean Changes from Baseline in Radiographic Score[1] at Week 54 in Study 3.1 Completers Based on Original Assessment and Post Hoc Re-Assessment

	CT-P13 (N=302)		EU-Remicade (N=304)		Difference (95% CI)[3]
	N[2]	Mean	N[2]	Mean	
Original Assessment[4]					
Baseline	252	105.7	248	106.4	
Week 54	220	72.4	227	71.2	
Change	179	-28.5	188	-31.9	2.6 (-2.7, 7.9)
Re-Assessment[5]					
Baseline	275	69.1	271	65.4	
Week 54	206	66.0	201	63.7	
Change	197	1.1	192	0.4	0.7 (-0.4, 1.9)

Source: Reviewer

Abbreviations: CI = confidence interval

[1] Total van der Heijde radiographic joint score (range: 0–448), which is the sum of erosion and joint space narrowing scores based on evaluations of joints in hands, wrist, and feet

[2] Number of patients with complete data included in analysis

[3] Mean difference between CT-P13 and EU-Remicade based on linear regression model adjusting for baseline value, region, and CRP category, with Huber-White standard errors

[4] Based on score from single reader evaluating each patient's paired radiographs with knowledge of chronological order of images

[5] Based on average score from two readers independently evaluating each patient's paired radiographs without knowledge of order

3.4.3 Key Results in Study 1.1

According to the applicant's planned analysis in the subset of patients remaining in Study 1.1 at Week 30, approximately 70.5% of patients randomized to CT-P13 and 72.4% of patients randomized to EU-Remicade achieved an ASAS20 response, for an estimated odds ratio comparing treatments of 0.91 (95% CI: 0.51, 1.62). In a supportive FDA analysis in all randomized patients, 63.2% of patients on CT-P13 and 67.2% on EU-Remicade remained in the study and achieved an ASAS20 response at Week 30, for an estimated difference of -4.0% (95% CI: -15.9%, 8.0%). The proportions of patients remaining in the study and achieving ASAS20 responses at Weeks 14 and 54, in addition to the proportions achieving ASAS40 responses over time, were also similar between the treatment arms (Figure 4). Mean changes from baseline in important patient-reported outcome assessments, including the ASAS components, were also similar between the arms (Table 10). On both treatment arms, improvements in these continuous secondary endpoints were evident as early as Week 14, and trends over time were similar (see Appendix: Figures 15 – 19).

Figure 4: ASAS Response Probabilities over Time in Study 1.1 (Source: Reviewer)

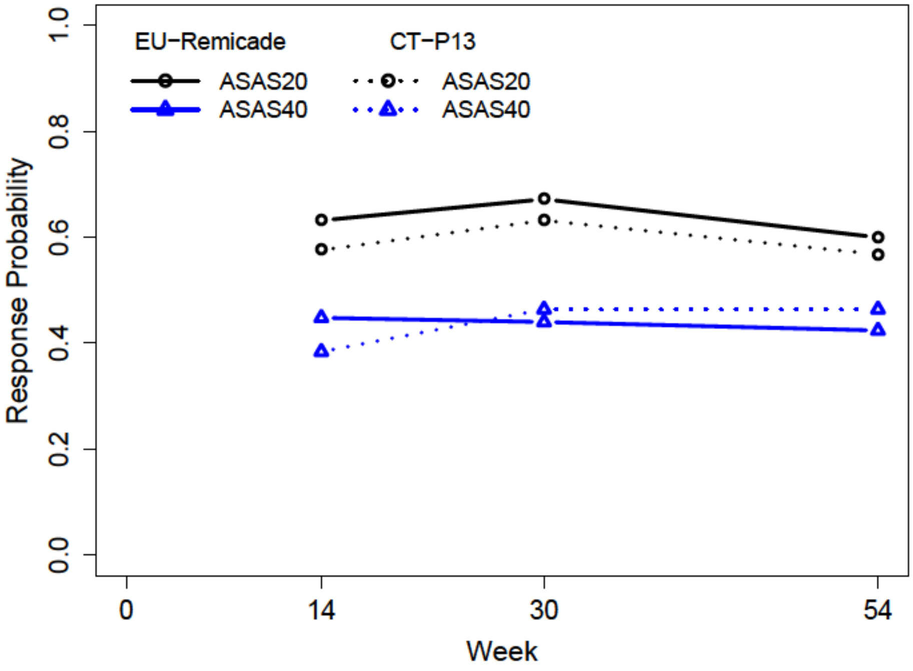

Table 10: Mean Changes from Baseline in Continuous Secondary Efficacy Endpoints at Week 30 in Study 1.1 Completers

	CT-P13 (N=125)		EU-Remicade (N=125)		Difference (95% CI)[2]
	N[1]	Mean	N[1]	Mean	
BASDAI Score	114	-3.0	116	-2.7	-0.3 (-0.8, 0.3)
BASFI Score	112	-2.6	116	-2.5	-0.0 (-0.6, 0.5)
BASMI Score	111	-1.0	115	-0.9	-0.1 (-0.4, 0.3)
Spinal Pain Score	114	-34.8	116	-36.0	1.6 (-4.5, 7.7)
Disease Status Score	114	-30.4	116	-27.5	-2.5 (-8.4, 3.3)

Source: Reviewer

Abbreviations: CI = confidence interval

[1] Number of patients with complete data included in analysis

[2] Mean difference between CT-P13 and EU-Remicade based on linear regression model adjusting for baseline value, region, and CRP category, with Huber-White standard errors

3.4.4 Assay Sensitivity and the Constancy Assumption

In order to reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must have assay sensitivity, or the ability to detect meaningful differences between the products, if such differences exist. In addition, to reliably evaluate whether the experimental treatment retains a certain proportion of the effect of the reference product versus placebo, the constancy assumption must be reasonable. This is the assumption that estimates of the effect of the reference product from historical, placebo-controlled trials are unbiased for the setting of the comparative clinical study. The absence of a placebo arm in an active-controlled study makes it difficult to determine whether evidence of similarity between the experimental and control arms implies that the two products were similarly effective or similarly ineffective. As discussed in the ICH E10 guidelines [9] and in the literature [10], historical evidence of sensitivity to drug effects and appropriate trial conduct may be used to support the presence of assay sensitivity and a conclusion that the treatments are similarly effective.

Table 11 describes key characteristics of five historical randomized, double-blind, parallel-group, placebo-controlled clinical trials of infliximab in patients with active RA despite treatment with methotrexate, alongside key characteristics of Study 3.1. Important aspects of the design of the historical studies, including key inclusion/exclusion criteria, permitted concomitant medications, and baseline disease severity, were largely similar if not identical across the six studies. One notable difference was the timing of the ACR20 assessment, which ranged from Week 14 to Week 30. However, the ATTRACT study demonstrated large treatment effects as early as Week 6 [5], and there was no apparent trend in effect size as a function of the timing of endpoint assessment across the historical studies. Estimated treatment effects with respect to ACR20 for the five historical trials were displayed earlier in Table 2. The estimated effects ranged from 18% to 38% on the absolute difference scale, with an overall estimated effect size of 28%. Thus, the information in Tables 2 and 11 indicates that (1) the design of the five historical placebo-controlled clinical trials were largely similar to that of comparative clinical Study 3.1; and (2) there were relatively large and consistent treatment effects across the five historical studies. This evidence of historical sensitivity to effects of infliximab in similarly designed clinical trials provides some support for a conclusion that Study 3.1 had assay sensitivity.

It is also important that a study designed to evaluate similarity has quality conduct, because conduct issues such as violations in eligibility criteria, poor adherence, cross-over between arms, or missing data tend to bias results toward the alternative hypothesis of equivalence. In Study 3.1, there were only 5 (0.8%) patients with failed eligibility criteria and only 1 patient received the wrong treatment prior to Week 30. In addition, examination of minutes from Data

Monitoring Committee meetings did not identify any clear concerns with the quality of study conduct. However, approximately 15% of patients discontinued treatment prior to Week 30 – this proportion is greater than the historical discontinuation rates, which ranged from 5% to 11% (Table 11). This is concerning because adherence at a level lower than that which is best achievable in real clinical practice will tend to bias comparisons between treatments toward equivalence and therefore decrease the sensitivity of the comparative study. Decreased adherence on the active control may also result in decreased efficacy and therefore violations in the constancy assumption. In addition, because patients who discontinued treatment were not retained for safety and efficacy assessments through the double-blind period, this led to substantial missing data in important analyses. The need for a post hoc reassessment of radiographic data, as well as the large number of patients with radiograph assessments weeks after treatment initiation, were additional study conduct issues that we identified.

We also examined whether the within-group responses in the comparative clinical study were similar to those observed in previous placebo-controlled trials. The 59% ACR20 response rate on EU-Remicade in Study 3.1 is in line with the historical rates, which ranged from 50% to 76%. The definition of ACR20 in Study 3.1 was slightly different than in historical studies, in that a 20% improvement in either ESR or CRP could contribute to a determination of response. However, when we modified the ACR20 criteria to match that of historical studies (with only a 20% improvement in CRP contributing to a determination of response), the response probability declined only slightly to 58%, remaining similar to the response rates of the historical trials.

In summary, there are some concerns about study conduct, including the high rates of treatment discontinuation and missing data in Study 3.1, an issue that will be discussed in greater detail in 3.4.5. However, the design, conduct, and within-group responses rates of Study 3.1 were largely similar to those characteristics in five historical clinical trials that demonstrated relatively large and consistent treatment effects of infliximab over placebo. Therefore, the totality of available information largely supports the assay sensitivity of Study 3.1, in addition to the constancy assumption.

Table 11: Comparison of Key Characteristics of Historical Randomized, Placebo-Controlled Clinical Trials[1] of Infliximab in RA and Comparative Clinical Study 3.1

	Study					
	Maini [5]	Westhovens [6]	Schiff [4]	Zhang [7]	Abe [8]	Study 3.1
Selected Inclusion / Exclusion Criteria	≥6 SJ, ≥6 TJ, 2 of: morning stiffness ≥45 min, ESR >28 mm/h, CRP >2 mg/dL	≥6 SJ, ≥6 TJ	Disease duration ≥1 year, ≥10 SJ, ≥12 TJ, CRP ≥1 mg/dL	≥3 SJ, ≥8 TJ, 2 of: morning stiffness ≥45 min, ESR >28 mm/h, CRP >1.5 X ULN	≥6 SJ, ≥6 TJ, 2 of: morning stiffness ≥45 min, ESR >28 mm/h, CRP >2 mg/dL	≥6 SJ, ≥6 TJ, 2 of: morning stiffness ≥45 min, ESR >28 mm/h, CRP >2 mg/dL
Anti-TNF experience allowed?	No	No	No	Yes	No	No
Concomitant DMARDs	stable MTX	stable MTX + additional DMARDs allowed	stable MTX	stable MTX + additional DMARDs allowed?	stable (low-dose) MTX	stable MTX
Region / Country	NA, EU	NA, EU, AU, SA	NA, EU, AU, AF, SA	China	Japan	EU, SA, NA, AS
Baseline Characteristics of Study Population[2]	SJ: 19; TJ: 32; Disease Duration: 8 yrs; HAQ: 1.8	SJ: 15; TJ: 22 Disease Duration: 8 yrs; HAQ: 1.5	SJ: 20; TJ: 32; Disease Duration: 7 yrs; HAQ: 1.7	Disease Duration: 7 yrs	SJ: 15; TJ: 19; Disease Duration: 9 yrs	SJ: 15; TJ: 24; HAQ: 1.6
Time of ACR20 Evaluation	Week 30	Week 22	Week 28	Week 18	Week 14	Week 30
ACR20 Response on Infliximab	50%	55%	59%	76%	61%	59%
Withdrawal on Infliximab	11%	7%	8%	10%	5%	15%

Source: Reviewer

Abbreviations: SJ=swollen joint count; TJ=tender joint count; ULN = upper limit of normal; DMARD=disease-modifying anti-rheumatic drug; NA=North America; EU=Europe; AU=Australia; SA=South America; AF=Africa; AS=Asia

[1] Based on best attempts to identify/estimate characteristics from literature review

[2] Means or medians, depending on what was reported in publication

3.4.5 Potential Effect of Missing Data

As described in detail in 3.4.1, there was substantial early patient withdrawal in Studies 3.1 and 1.1. Our missing data sensitivity analyses focused on comparative clinical Study 3.1, in which the efficacy comparison was a primary objective. In Study 3.1, the primary endpoint was a composite measure of treatment success defined by remaining in the study and on treatment through Week 30 and achieving an ACR20 response at Week 30. Therefore, outcomes in patients who withdrew early were not missing – these patients were non-responders according to the composite endpoint definition. However, comparing treatments with respect to this composite measure of treatment success may confound differences between treatments in efficacy with differences in tolerability. The composite measure could fail to identify clinically meaningful differences in efficacy, for example, if the proposed biosimilar was better tolerated than the reference product but had lesser efficacy in the subset of patients who adhere. Therefore, it is important to evaluate differences in the components of the composite primary endpoint. This includes an evaluation of ACR20 at Week 30 in all randomized patients regardless of adherence (an evaluation of the de facto or intention-to-treat estimand), in addition to de facto evaluations of the components of ACR20 (and other important endpoints such as DAS28). However, such evaluations are subject to substantial missing data and rely on the strong and unverifiable assumption that outcomes in patients who withdrew early are missing at random. Therefore, we conducted tipping point analyses to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing-not-at-random assumptions).

Tables 12 and 13 display estimated de facto differences between CT-P13 and EU-Remicade in the ACR20 response and mean DAS28 change at Week 30, with varying assumptions about the differences on each treatment arm between outcomes in patients who withdrew from the study early and outcomes in patients who completed the study. In order for the 90% CI to fail to rule out a 12% absolute loss in the probability of ACR20 response, the response among CT-P13 dropouts would need to be around 70 percentage points lower than the response in CT-P13 completers, while the response among EU-Remicade dropouts would need to be only slightly worse (e.g., 17.5 percentage points less) than the response among EU-Remicade completers. As a point of reference, the response probabilities among completers on CT-P13 and EU-Remicade were 75% and 72%, respectively. Similarly, inference on DAS28 rules out large mean increases (e.g., 0.6 units) on CT-P13 as compared to EU-Remicade unless there is an assumption of much worse outcomes (3–4 unit increases) in CT-P13 dropouts than CT-P13 completers, along with only slight worse outcomes (0–2 unit increases) in EU-Remicade dropouts than EU-Remicade completers. As a point of reference, mean changes among completers on CT-P13 and EU-Remicade were -2.2 and -2.1, respectively. The tipping points for ruling out large increases in efficacy, while not as extreme as those for ruling out efficacy losses, still require the assumption of relatively large differences between responses in CT-P13 dropouts and responses in EU-Remicade dropouts (relative to completers on the two arms). Given the similar proportions of patients and distributions of reasons for early withdrawal on the two treatment arms (see Figure 1 and Table 5), in addition to the similar baseline characteristics between dropouts on the two arms (see Appendix: Table 16), an assumption of such large differences between the outcomes in dropouts on the two arms seems implausible. Therefore, these tipping point sensitivity analyses largely support the findings of the key efficacy analyses in Study 3.1.

Table 12: Tipping Point Analysis in Study 3.1: Inference on the Difference Between CT-P13 and EU-Remicade in the Probability of Week 30 ACR20 Response under Varying Assumptions About the Differences on Each Treatment Arm Between Responses in Patients who Withdrew from the Study Early and Responses in Patients who Completed the Study

Shift for	Shift for EU-Remicade[1]				
CT-P13[2]	-0.700	-0.525	-0.350	-0.175	0.00
-0.700	0.03 (-0.04, 0.10)	0.00 (-0.07, 0.07)	-0.02 (-0.09, 0.05)	-0.05 (-0.12, 0.02)	-0.07 (-0.14, -0.01)
-0.525	0.06 (-0.01, 0.13)	0.03 (-0.04, 0.10)	0.00 (-0.06, 0.07)	-0.02 (-0.09, 0.05)	-0.05 (-0.11, 0.02)
-0.350	0.08 (0.01, 0.15)	0.06 (-0.01, 0.13)	0.03 (-0.03, 0.10)	0.01 (-0.06, 0.07)	-0.02 (-0.08, 0.05)
-0.175	0.11 (0.04, 0.18)	0.09 (0.02, 0.15)	0.06 (-0.01, 0.12)	0.03 (-0.03, 0.10)	0.01 (-0.06, 0.07)
0.000	0.14 (0.07, 0.21)	0.11 (0.05, 0.18)	0.09 (0.02, 0.15)	0.06 (0.00, 0.13)	0.03 (-0.03, 0.10)

Source: Reviewer

Cell contents are estimated difference (90% confidence interval). Shaded cells represent assumptions under which the confidence interval fails to rule out the ±12% margin.

[1] Assumed difference in Week 30 ACR20 response between completers and dropouts on EU-Remicade. Response in EU-Remicade completers was 0.72.

[2] Assumed difference in Week 30 ACR20 response between completers and dropouts on CT-P13. Response in CT-P13 completers was 0.75.

Table 13: Tipping Point Analysis in Study 3.1: Inference on the Difference Between CT-P13 and EU-Remicade in the Mean Change from Baseline in DAS28 (CRP) at Week 30 under Varying Assumptions About the Differences on Each Treatment Arm Between Mean Changes in Patients who Withdrew from the Study Early and Mean Changes in Patients who Completed the Study

Shift for CT-P13[2]	Shift for EU-Remicade[1]				
	0	+1	+2	+3	+4
0	-0.1 (-0.3, 0.1)	-0.2 (-0.4, 0.0)	-0.4 (-0.6, -0.2)	-0.5 (-0.7, -0.3)	-0.7 (-0.9, -0.4)
+1	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.1)	-0.2 (-0.4, 0.0)	-0.4 (-0.6, -0.1)	-0.5 (-0.7, -0.3)
+2	0.2 (0.0, 0.4)	0.1 (-0.1, 0.3)	-0.1 (-0.3, 0.2)	-0.2 (-0.4, 0.0)	-0.3 (-0.6, -0.1)
+3	0.4 (0.2, 0.6)	0.3 (0.0, 0.5)	0.1 (-0.1, 0.3)	0.0 (-0.3, 0.2)	-0.2 (-0.4, 0.1)
+4	0.6 (0.3, 0.8)	0.4 (0.2, 0.6)	0.3 (0.0, 0.5)	0.1 (-0.1, 0.4)	0.0 (-0.3, 0.2)

Source: Reviewer

Cell contents are estimated difference (90% confidence interval). Shaded cells represent assumptions under which the confidence interval fails to rule out 0.6-unit differences.

[1] Assumed difference in Week 30 mean DAS28 change between completers and dropouts on EU-Remicade. Mean change in EU-Remicade completers was -2.1.

[2] Assumed difference in Week 30 mean DAS28 change between completers and dropouts on CT-P13. Mean change in CT-P13 completers was -2.2.

3.5 Evaluation of Safety

Dr. Juwaria Waheed, the Medical Reviewer, conducted the complete safety evaluation, and the reader is referred to Dr. Waheed's review for more detailed information on safety. We conducted supplementary analyses to compare CT-P13 and EU-Remicade with respect to the incidence of adverse events of special interest (AESIs) in the double-blind clinical Studies 1.1 and 3.1, in addition to the transition Studies 1.3 and 3.2. The applicant analyzed the following adverse events of special interest based on the known safety profile of infliximab: active TB, latent TB, infection, serious infection, pneumonia, malignancy and lymphoma, infusion-related reaction, drug-induced liver injury in accordance with Hy's law, and vascular disorder. In addition to these events, we evaluated two additional AESIs: cardiac disorder and opportunistic infection. The captions under Tables 14 and 15 provide definitions for these safety endpoints. The applicant reported no occurrences of drug-induced liver injury, so this event is not included in the tables.

Within each study, we calculated the cumulative incidence of each event, i.e., the proportion of patients who remained in the study, on treatment, and experienced an event during the 54-week treatment period. We also calculated on-treatment incidence rates per 100 person-years. It was not possible to calculate the 54-week cumulative incidence or incidence rate regardless of adherence to treatment because patients who discontinued treatment were withdrawn from the study. We also integrated results from the studies in RA and AS to compare treatment groups with respect to the relative risk (RR) of each AESI, i.e., the ratio of cumulative incidences. Following the applicant's approach, we performed as-treated rather than as-randomized analyses and calculated integrated relative risks based on DerSimonian-Laird random effects meta-analyses. Many of the statistics presented here differ from those in the applicant's summaries because: (1) we applied slightly different definitions of pneumonia (additionally including lower respiratory tract infection) and malignancy and lymphoma (additionally including neoplasm and Myeloprofilerative disorder) than the applicant; (2) we calculated the incidence rate of the *first* event per person, whereas the applicant appears to have counted only incident (first) events in the numerator but included all time at risk (including follow-up time after an incident event) in the denominator; and (3) we only evaluated Studies 3.1 and 1.1 in integrated analyses, whereas the applicant also included results from two additional small studies.

Table 14 describes the incidence of AESIs during the 54-week, double-blind, controlled treatment periods of Studies 1.1 and 3.1. There was a trend toward a greater incidence of active TB on CT-P13 (5 total events) than EU-Remicade (1 total event), with an estimated integrated relative risk of 3.2 (95% CI: 0.5, 20.4). There were also slight trends toward greater incidences of pneumonia (RR: 1.8; 95% CI: 0.6, 5.1) and vascular disorder (RR: 1.7; 95% CI: 0.9, 3.0) on CT-P13 than

EU-Remicade. Given the multiple statistical comparisons being carried out here, and because the confidence intervals do not exclude equality (RR=1), these observed differences may have been due to chance alone. That being said, the upper bounds of the confidence intervals also include the possibility of very large relative risks. Therefore, these clinical data alone cannot rule out the possibility of meaningful increases in the risk of important adverse events on CT-P13.

Table 15 describes the incidence of AESIs during the 54-week, open-label, extension Studies 1.3 and 3.2, in which patients previously treated with CT-P13 (in the double-blind, randomized, controlled Studies 1.1 and 3.1, respectively) continued on CT-P13 and patients previously treated with EU-Remicade transitioned to CT-P13. There were no striking differences between the groups. However, the interpretability of these data is limited. A more appropriate design to reliably evaluate the potential effect of transitioning from a reference product to a proposed biosimilar would randomize patients on the reference product to either continue on the reference or transition to the proposed biosimilar. The applicant's evaluation of the transition was based on a non-randomized comparison of patients transitioning from EU-Remicade to CT-P13 to the wrong control group: patients continuing on CT-P13. Therefore, this evaluation relies on the strong assumptions that (1) the subsets of patients on EU-Remicade and CT-P13 entering the transition studies were comparable; and (2) rates of events in patients continuing on CT-P13 are similar to rates of events in patients continuing on the reference product. Alternatively, one can compare the incidence of adverse events after transition to the incidence prior to transition in those same patients. The interpretability of this alternative analysis is also limited because differences (or lack therefore) observed before and after transition could be due to the effect of the transition or to effects of age or time on treatment. Results presented by the applicant based on this alternative approach also did not identify any striking differences.

Table 14: Evaluation of the Incidence of Adverse Events of Special Interest During the 54-Week Controlled Treatment Periods of Studies 1.1 and 3.1

	Study 1.1				Study 3.1				
	CT-P13		EU-Remicade		CT-P13		EU-Remicade		Integrated RR
	(N=128)		(N=122)		(N=302)		(N=300)		(95% CI)
	n (%)	Rate	n (%)	Rate	n (%)	Rate	n (%)	Rate	
Latent TB	10 (7.8%)	7.3	6 (4.9%)	4.6	28 (9.3%)	9.3	26 (8.7%)	8.6	1.2 (0.7, 1.8)
Active TB	2 (1.6%)	1.4	1 (0.8%)	0.7	3 (1.0%)	0.9	0 (0.0%)	0.0	3.2 (0.5, 20.4)
Infection	55 (43.0%)	52.5	49 (40.2%)	48.4	127 (42.1%)	53.8	137 (45.7%)	60.4	1.0 (0.8, 1.1)
Serious Infection	2 (1.6%)	1.4	3 (2.5%)	2.2	13 (4.3%)	4.2	7 (2.3%)	2.2	1.4 (0.6, 3.5)
Pneumonia	2 (1.6%)	1.4	0 (0.0%)	0.0	8 (2.6%)	2.5	5 (1.7%)	1.6	1.8 (0.6, 5.1)
Malignancy and Lymphoma	2 (1.6%)	1.4	0 (0.0%)	0.0	3 (1.0%)	0.9	4 (1.3%)	1.3	1.2 (0.2, 5.7)
Infusion-related Reaction	11 (8.6%)	8.2	15 (12.3%)	11.8	30 (9.9%)	9.8	43 (14.3%)	14.8	0.7 (0.5, 1.0)
Vascular Disorder	4 (3.1%)	2.9	1 (0.8%)	0.7	25 (8.3%)	8.3	16 (5.3%)	5.3	1.7 (0.9, 3.0)
Cardiac Disorder	5 (3.9%)	3.6	6 (4.9%)	4.6	5 (1.7%)	1.6	12 (4.0%)	3.9	0.6 (0.3, 1.2)
Opportunistic Infection	0 (0.0%)	0.0	2 (1.6%)	1.5	4 (1.3%)	1.3	6 (2.0%)	1.9	0.6 (0.2, 1.8)

Source: Reviewer

[1] n (%) is number (percent) of patients having at least one on-treatment event

[2] Rate is incidence rate of first on-treatment event per 100 person-years

[3] Relative risk (RR) of event (95% confidence interval [CI]) compares CT-P13 with EU-Remicade based on DerSimonian-Laird random effects meta-analysis of results from Studies 1.1 and 3.1

[4] Definitions of Adverse Events of Special Interest:

Latent TB: All preferred terms with latent tuberculosis or Mycobacterium tuberculosis complex test

Active TB: All preferred terms with tuberculosis not classified as latent TB

Infection: All events in infections and infestations system organ class

Serious Infection: All events in infections and infestations system organ class classified as serious

Pneumonia: All preferred terms with pneumonia, bronchopneumonia, lobar pneumonia, or lower respiratory tract infection

Malignancy and Lymphoma: All preferred terms with cancer, carcinoma, lymphoma, neoplasm, or Myeloproliferative disorder

Infusion-related Reaction: See applicants ISS SAP Appendix 2 for definition

Vascular Disorder: All events in vascular disorders system organ class

Cardiac Disorder: All events in cardiac disorders system organ class

Opportunistic Infection: All preferred terms with Herpes zoster, Oesophageal candidiasis, Oral candidiasis, or Varicella

Table 15: Evaluation of the Incidence of Adverse Events of Special Interest During the 54-Week Transition Periods of Extension Studies 1.3 and 3.2

	Study 1.3				Study 3.2				
	EU-Remicade to CT-P13 Transition (N=84)		CT-P13 Maintenance (N=90)		EU-Remicade to CT-P13 Transition (N=143)		CT-P13 Maintenance (N=159)		Integrated RR (95% CI)
	n (%)	Rate	n (%)	Rate	n (%)	Rate	n (%)	Rate	
Latent TB	7 (8.3%)	5.3	5 (5.6%)	4.1	7 (4.9%)	3.4	11 (6.9%)	5.0	1.0 (0.3, 3.2)
Active TB	1 (1.2%)	0.7	1 (1.1%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0.0	1.1 (0.1, 16.9)
Infection	29 (34.5%)	30.5	23 (25.6%)	25.4	47 (32.9%)	34.9	50 (31.4%)	32.3	1.1 (0.9, 1.5)
Serious Infection	1 (1.2%)	0.7	2 (2.2%)	1.5	3 (2.1%)	1.4	4 (2.5%)	1.7	0.7 (0.2, 2.6)
Pneumonia	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (0.6%)	0.4	NA
Malignancy and Lymphoma	0 (0.0%)	0.0	1 (1.1%)	0.8	4 (2.8%)	1.9	1 (0.6%)	0.4	1.7 (0.1, 18.6)
Infusion-related Reaction	6 (7.1%)	4.5	7 (7.8%)	5.7	4 (2.8%)	1.9	11 (6.9%)	5.0	0.6 (0.3, 1.4)
Vascular Disorder	2 (2.4%)	1.4	3 (3.3%)	2.3	3 (2.1%)	1.4	4 (2.5%)	1.7	0.8 (0.3, 2.4)
Cardiac Disorder	3 (3.6%)	2.1	4 (4.4%)	3.2	1 (0.7%)	0.5	1 (0.6%)	0.4	0.9 (0.2, 3.2)
Opportunistic Infection	1 (1.2%)	0.7	1 (1.1%)	0.8	1 (0.7%)	0.5	1 (0.6%)	0.4	1.1 (0.2, 7.7)

Source: Reviewer

[1] n (%) is number (percent) of patients having at least one on-treatment event

[2] Rate is incidence rate of first on-treatment event per 100 person-years

[3] Relative risk (RR) of event (95% confidence interval [CI]) compares EU-Remicade to CT-P13 transition with CT-P13 maintenance based on DerSimonian-Laird random effects meta-analysis of results from Studies 1.1 and 3.1

[4] Definitions of Adverse Events of Special Interest:

Latent TB: All preferred terms with latent tuberculosis or Mycobacterium tuberculosis complex test

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Pneumonia: All preferred terms with pneumonia, bronchopneumonia, lobar pneumonia, or lower respiratory tract infection

Malignancy and Lymphoma: All preferred terms with cancer, carcinoma, lymphoma, neoplasm, or Myeloproliferative disorder

Infusion-related Reaction: See applicants ISS SAP Appendix 2 for definition

Vascular Disorder: All events in vascular disorders system organ class

Cardiac Disorder: All events in cardiac disorders system organ class

Opportunistic Infection: All preferred terms with Herpes zoster, Oesophageal candidiasis, Oral candidiasis, or Varicella

4 Findings in Special/Subgroup Populations

Figures 5 and 6 present the results of subgroup analyses by sex, race (White, Asian, or Other), age (≤35, 35–50, 50–65, ≥65), and geographic region (non-European versus European) in Studies 3.1 and 1.1, respectively. As would be expected, there was considerable heterogeneity in the estimated differences in response probabilities comparing CT-P13 and EU-Remicade across the many subgroups (some very small in size). However, estimated differences were largely centered around similarity, and there were no striking trends across the two studies. The numbers of Black patients in both studies, and the number of patients ages ≥ 65 years in Study 1.1, were too small to calculate sufficiently reliable estimated differences to report. There were no U.S. sites in either study so subgroup analyses in the United States are not possible.

Figure 5: Estimated Differences Between CT-P13 and EU-Remicade in the Probability of Remaining in the Study and Achieving an ACR20 Response at Week 30, Stratified by Selected Subgroups, in Study 3.1. Solid Vertical Line Represents Estimated Difference in Overall Population, and Dashed Vertical Line Represents No Difference. (Source: Reviewer)

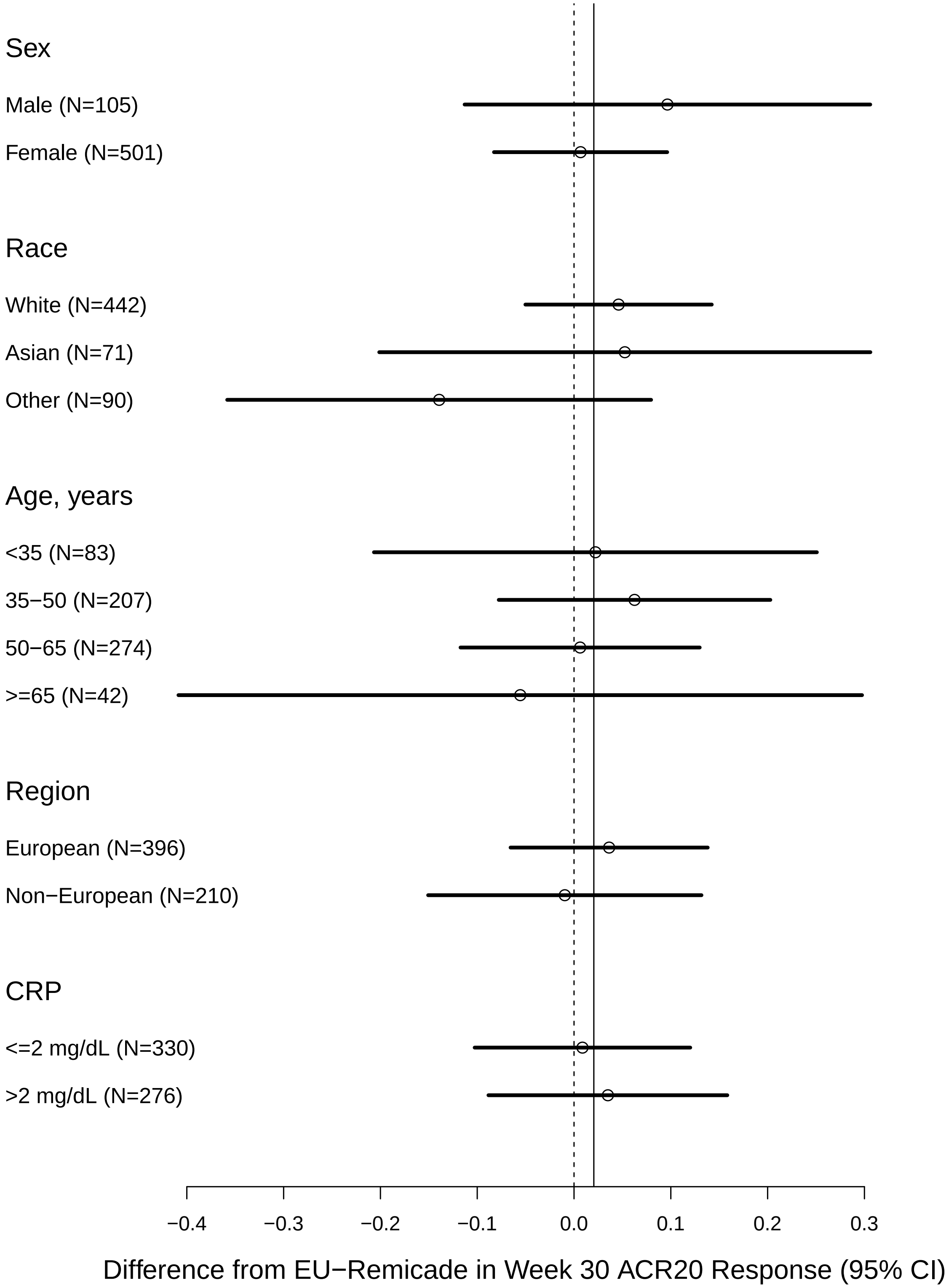
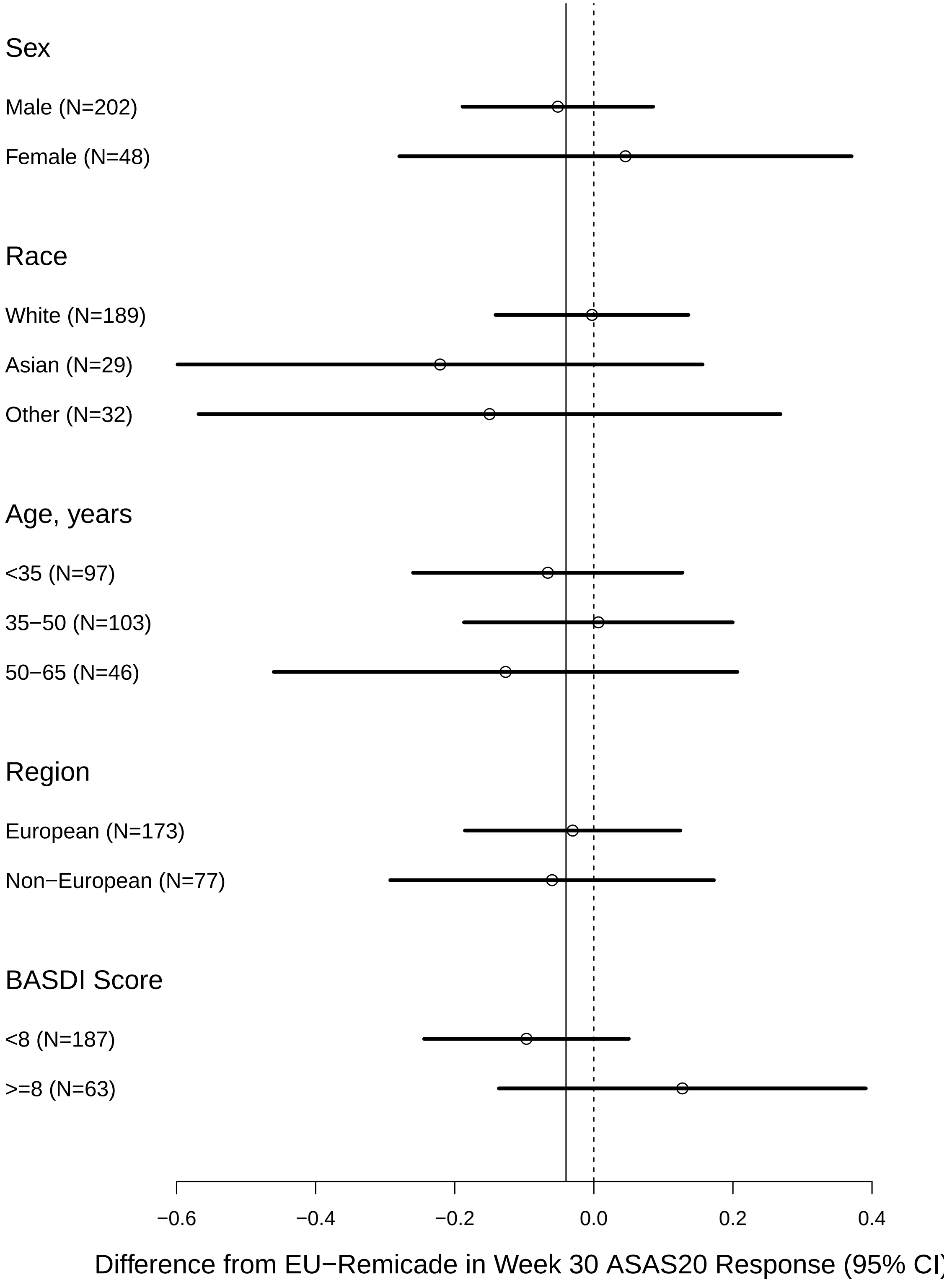


Figure 6: Estimated Differences Between CT-P13 and EU-Remicade in the Probability of Remaining in the Study and Achieving an ASAS20 Response at Week 30, Stratified by Selected Subgroups, in Study 1.1. Solid Vertical Line Represents Estimated Difference in Overall Population, and Dashed Vertical Line Represents No Difference. (Source: Reviewer)



5 Summary and Conclusions

5.1 Statistical Issues

During this statistical review, we identified the following important issues:

- Margin selection and evidence of similarity

  The determination of a similarity margin is a critical aspect of the design of a comparative clinical study because it determines the null hypothesis being tested in the primary analysis, i.e., the differences in efficacy that need to be ruled out at an acceptable significance level. The applicant prespecified a similarity margin of ±15% and later modified the margin to ±13% in response to feedback from FDA. We do not agree with the applicant's justification for the proposed margins. We selected a margin of ±12% based on meta-analyses of historical effects of infliximab and discussions with clinicians aimed at weighing the clinical importance of different losses in effect against the feasibility of different study sizes. Despite the lack of agreement on an appropriate similarity margin, results from the primary analysis of Study 3.1 (90% CI: -4.6%, +8.7%) successfully ruled out the ±12% margin we consider to be reasonable. In addition, there were similar improvements from baseline in the components of the composite primary endpoint, as well as additional important secondary endpoints, on the two treatment arms. Results in Study 1.1 in AS also suggested similar efficacy on CT-P13 and EU-Remicade. Therefore, the totality of the evidence from the comparative clinical studies supports a demonstration of no clinically meaningful differences between CT-P13 and US-Remicade.

- Potential effect of missing data on the reliability of efficacy results

  This issue was discussed in detail in 3.3.2 and 3.4.5. Our missing data sensitivity analyses focused on comparative clinical Study 3.1, in which the efficacy comparison was a primary objective. In Study 3.1, 25% of patients failed to complete the 54-week double-blind period. This led to substantial missing data in important analyses, such as the evaluations of ACR20 and DAS28 at Week 30 in all randomized patients regardless of adherence. Because such evaluations rely on the strong and unverifiable assumption that outcomes in patients who withdraw early are missing at random, we conducted tipping point analyses to explore the sensitivity of results to violations in this assumption. Confidence intervals for the differences between CT-P13 and EU-Remicade failed to rule out concerning losses in efficacy only under the assumption that patients who dropped out on CT-P13 had much worse outcomes than dropouts on EU-Remicade. Given the similar proportions of patients and distributions of reasons for early withdrawal on the two treatment arms, in addition to the similar baseline characteristics between dropouts on the two arms, an assumption of such large differences between the outcomes in dropouts on the two treatments seems implausible. Therefore, these tipping point sensitivity analyses largely support the findings of the key efficacy analyses in Study 3.1.

The substantial missing data in important analyses of endpoints at specific follow-up times was largely due to the design of the study, in particular, the fact that patients who discontinued treatment early were also withdrawn from the study. Future studies should clearly differentiate treatment discontinuation from study withdrawal, and the only reason for study withdrawal should be a patient's withdrawal of consent for additional follow-up. This will help prevent missing data and improve the reliability of key results.

- Assay sensitivity and the constancy assumption

  This issue was discussed in detail in 3.4.4. It is critical that a comparative clinical study has assay sensitivity, or the ability to detect meaningful differences between products, if such differences exist. In addition, the constancy assumption should be reasonable. This is the assumption that estimates of the reference product effect from historical, placebo-controlled trials are unbiased for the setting of the comparative study. Our evaluation of the literature indicated historical sensitivity to effects of infliximab over placebo in five clinical trials with similar designs to that of comparative clinical Study 3.1. Within-group responses in Study 3.1 were also similar to those of historical trials. It is also important that a study designed to evaluate similarity has appropriate conduct because conduct issues tend to bias results toward the alternative hypothesis of equivalence. Despite some concerns about the high rates of treatment discontinuation and missing data, the totality of available information largely supports the assay sensitivity of Study 3.1, in addition to the constancy assumption.

- Extrapolation to other indications

  The collective evidence from the comparative clinical studies supports a demonstration of no clinically meaningful differences between CT-P13 and US-Remicade in the studied indications (RA and AS). However, these studies would not be sensitive to clinically meaningful differences in another approved indication if those differences were caused by changes in function unique to the mechanism of action of infliximab in that additional indication. In addition, because the approved dose of infliximab is near the plateau of the dose-response curve in RA, potential differences in potency between the products may not translate into meaningful differences in efficacy. But such differences could translate into clinically meaningful differences in other indications. Therefore, extrapolation of findings of no clinically meaningful differences to other indications needs to additionally rely on data from other studies, such as results from analytical and PK comparisons.

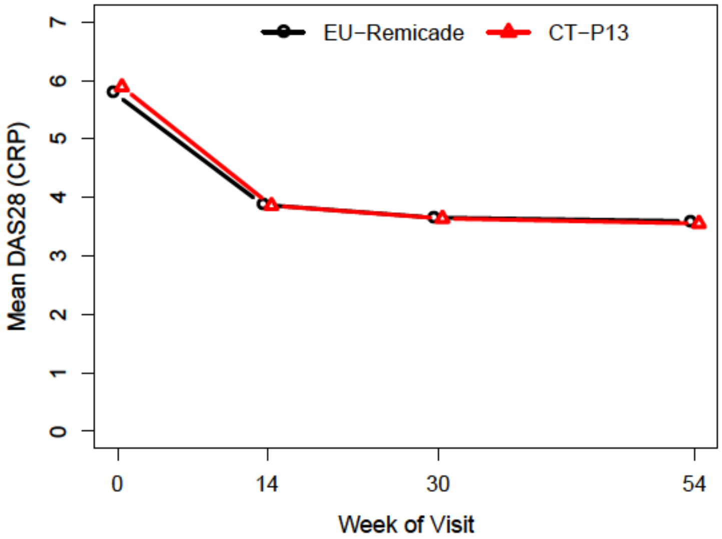
5.2 Collective Evidence

The collective evidence from the comparative clinical studies supports a demonstration of no clinically meaningful differences between CT-P13 and US-Remicade. In Study 3.1 in RA, 60.9% of CT-P13 patients and 58.9% of EU-Remicade patients were ACR20 responders, for an estimated absolute difference between treatments of 2.0% (90% CI: -4.6%, +8.7%). The confidence interval successfully ruled out the similarity margin of ±12% that the Agency has determined reasonable. ACR20, ACR50, and ACR70 responses over time, in addition to mean changes from baseline in the components of the ACR composite endpoint, the disease activity score (DAS28), and the radiographic damage score, were also similar between the treatment arms. Results in Study 1.1 in AS also suggested similar efficacy on CT-P13 and EU-Remicade. There was substantial missing data in important analyses, but tipping point analyses largely support the findings of key efficacy results in Study 3.1. In addition, the totality of available information largely supports the assay sensitivity of Study 3.1, in addition to the constancy assumption.

Appendix

A.1 Additional Tables and Figures

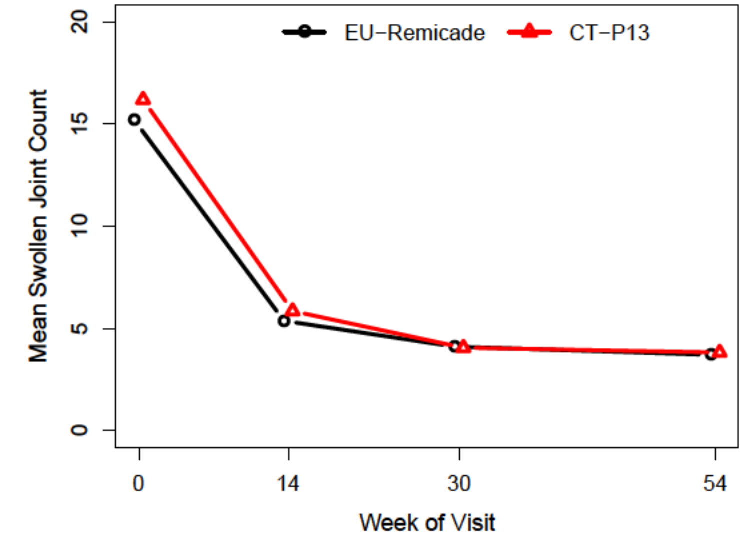
Figure 7: Mean Disease Activity Score (DAS28 [CRP]) among Patients Remaining in Study over Time in Study 3.1 (Source: Reviewer)



Number of Patients with Data

EU−Remicade	302	280	259	223
CT−P13	299	276	254	231

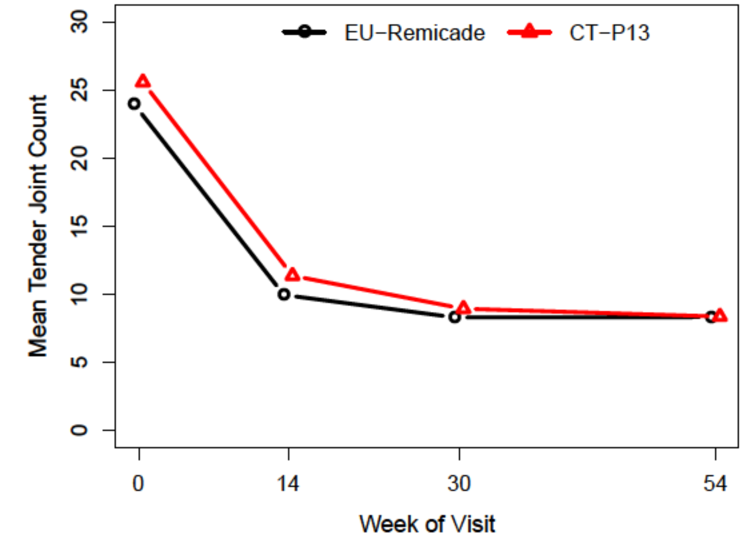
Figure 8: Mean Swollen Joint Count among Patients Remaining in Study over Time in Study 3.1 (Source: Reviewer)



Number of Patients with Data

	0	14	30	54
EU−Remicade	304	281	260	226
CT−P13	302	278	257	235

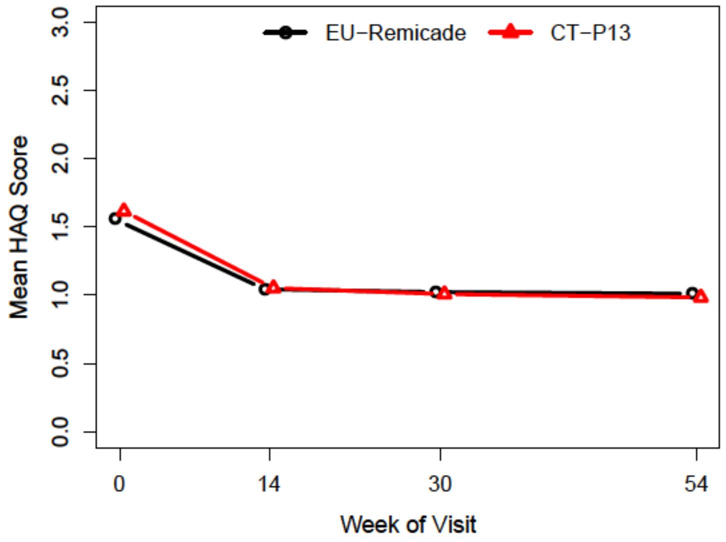
Figure 9: Mean Tender Joint Count among Patients Remaining in Study over Time in Study 3.1 (Source: Reviewer)



Number of Patients with Data

	0	14	30	54
EU−Remicade	304	281	260	226
CT−P13	302	278	257	235

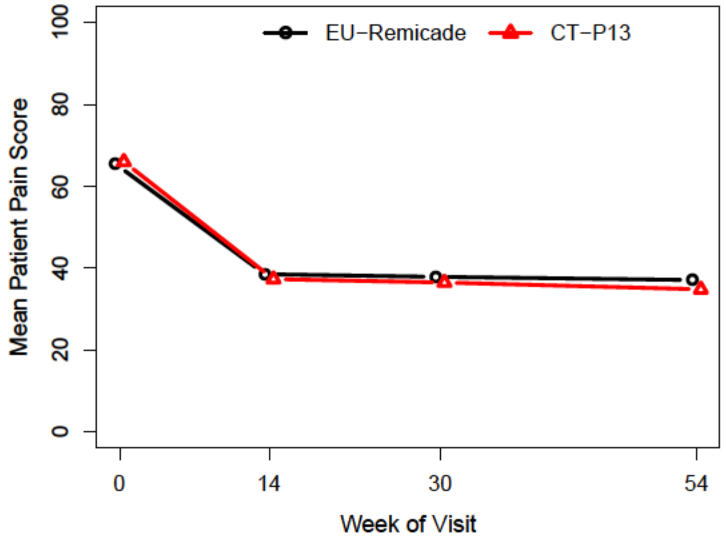
Figure 10: Mean Health Assessment Questionnaire (HAQ) Physical Ability Score among Patients Remaining in Study over Time in Study 3.1 (Source: Reviewer)



Number of Patients with Data

	0	14	30	54
EU−Remicade	303	282	261	226
CT−P13	302	278	256	235

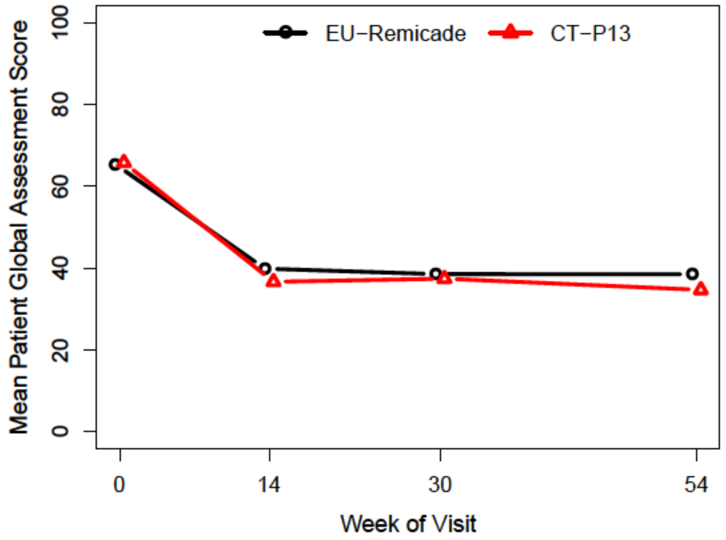
Figure 11: Mean Patient Pain Score among Patients Remaining in Study over Time in Study 3.1 (Source: Reviewer)



Number of Patients with Data

	0	14	30	54
EU−Remicade	302	281	260	226
CT−P13	302	278	256	235

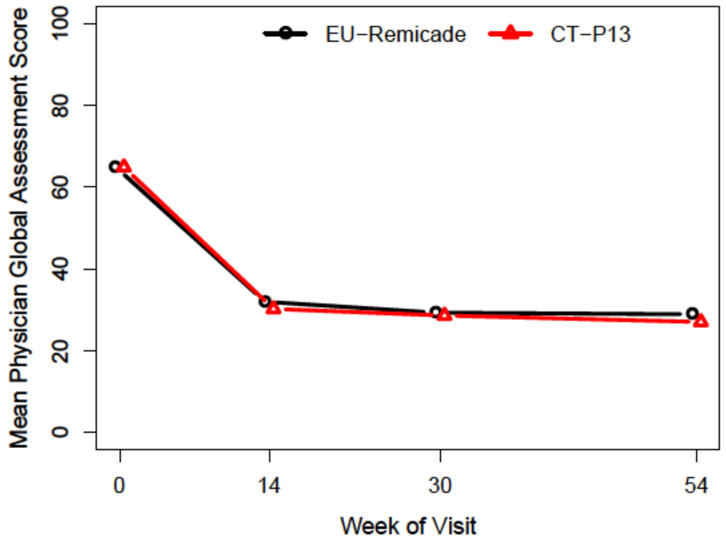
Figure 12: Mean Patient Global Assessment Score among Patients Remaining in Study over Time in Study 3.1 (Source: Reviewer)



Number of Patients with Data

EU−Remicade	302	280	260	226
CT−P13	302	278	255	234

Figure 13: Mean Physician Global Assessment Score among Patients Remaining in Study over Time in Study 3.1 (Source: Reviewer)



Number of Patients with Data

EU−Remicade	302	282	260	226
CT−P13	302	277	256	235

Figure 14: Empirical Distribution Function for Change from Baseline in Disease Activity Score (DAS28 [CRP]) at Week 30 in Study 3.1 (Source: Reviewer)

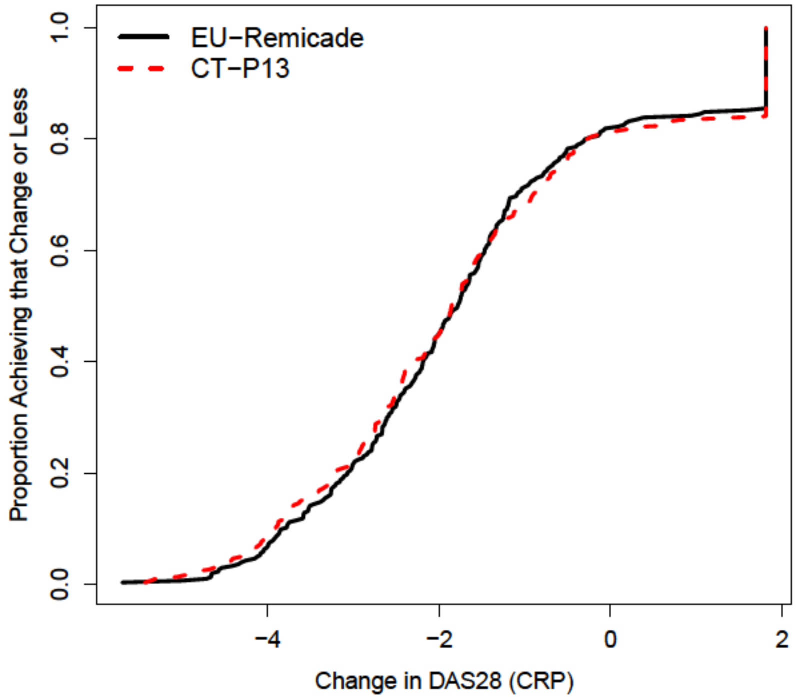
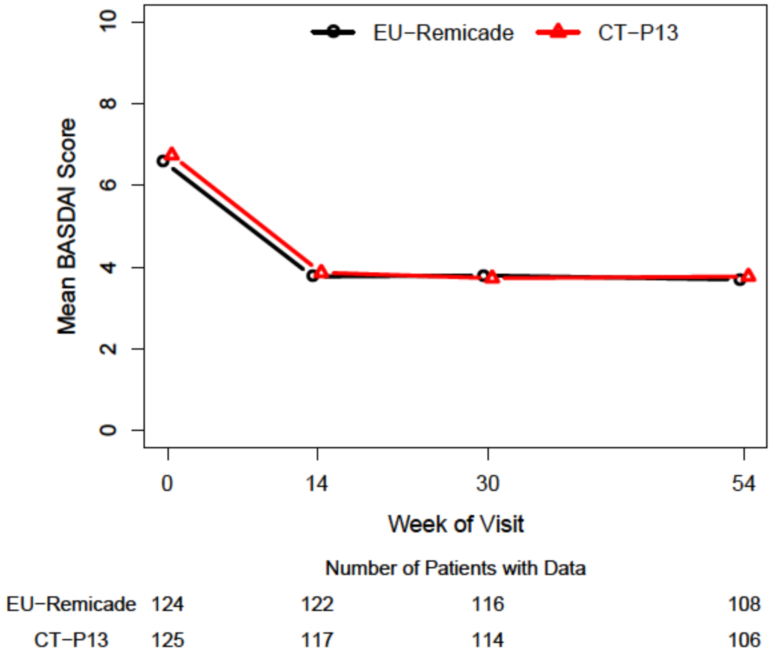


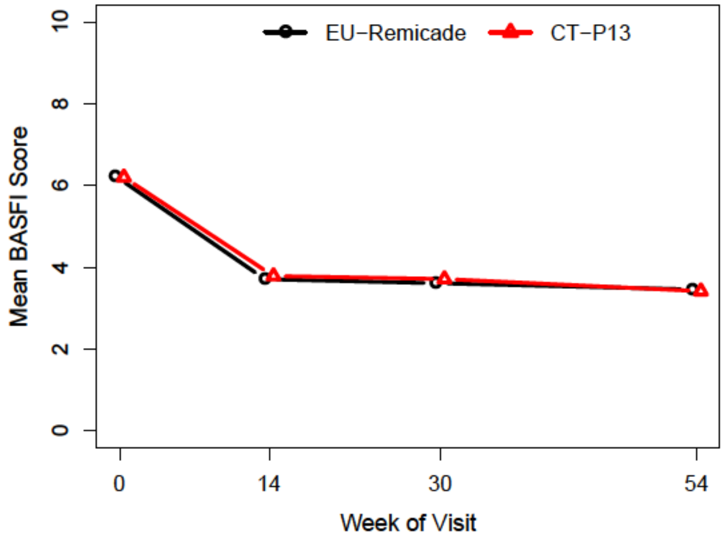
Figure 15: Mean BASDAI Score among Patients Remaining in Study over Time in Study 1.1 (Source: Reviewer)



Number of Patients with Data

EU−Remicade	124	122	116	108
CT−P13	125	117	114	106

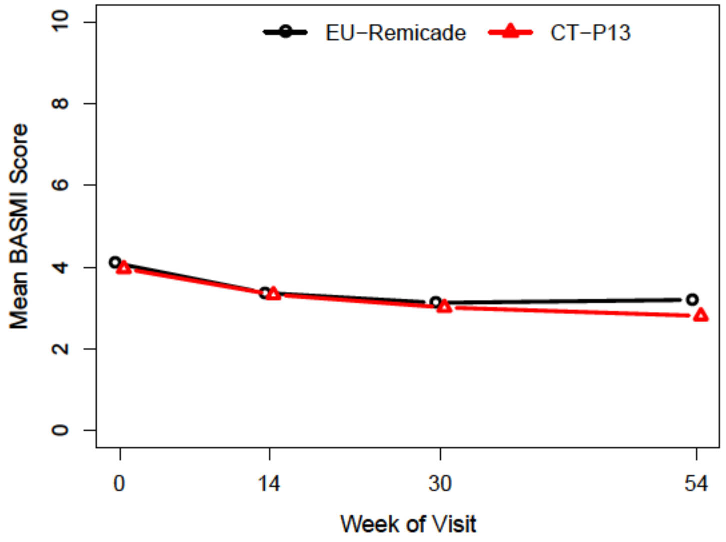
Figure 16: Mean BASFI Score among Patients Remaining in Study over Time in Study 1.1 (Source: Reviewer)



Number of Patients with Data

EU−Remicade	125	122	116	108
CT−P13	123	117	114	106

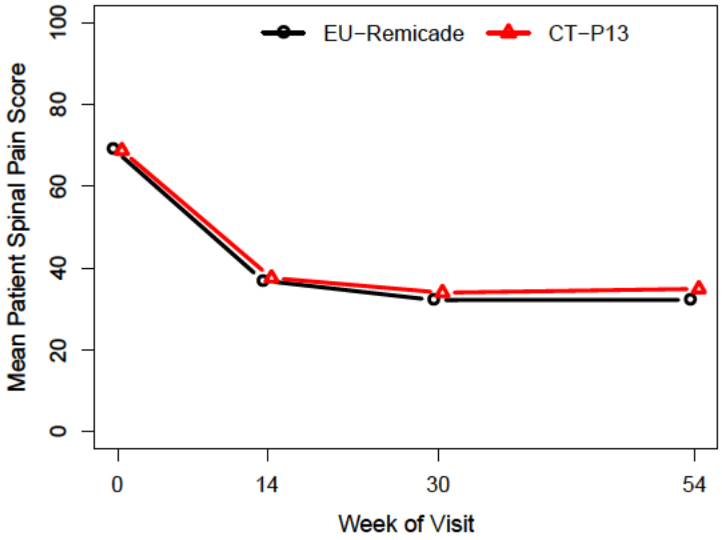
Figure 17: Mean BASMI Score among Patients Remaining in Study over Time in Study 1.1 (Source: Reviewer)



Number of Patients with Data

EU−Remicade	125	121	115	108
CT−P13	124	118	111	106

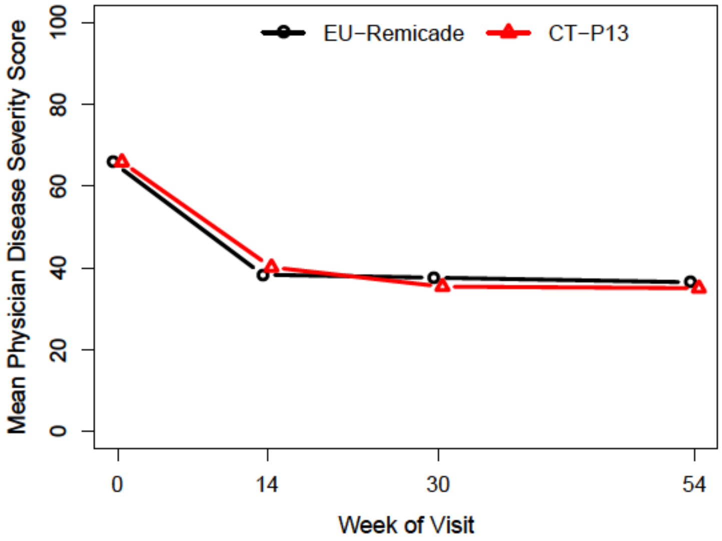
Figure 18: Mean Patient Spinal Pain Score among Patients Remaining in Study over Time in Study 1.1 (Source: Reviewer)



Number of Patients with Data

EU−Remicade	125	122	116	108
CT−P13	125	117	114	106

Figure 19: Mean Physician Disease Status Score among Patients Remaining in Study over Time in Study 1.1 (Source: Reviewer)



Number of Patients with Data

EU−Remicade	125	122	116	108
CT−P13	125	117	114	106

Table 16: Baseline Characteristics in RA Patients who Withdrew from the Study Early in Study 3.1

	CT-P13	EU-Remicade	Overall
N	69	82	151
Female	57 (83%)	72 (88%)	129 (85%)
Age (years)	51.7 (13.1)	48.5 (12.0)	50.0 (12.6)
Age Group (years)			
< 35	9 (13%)	13 (16%)	22 (15%)
35-50	20 (29%)	28 (34%)	48 (32%)
50-65	30 (43%)	34 (41%)	64 (42%)
≥ 65	10 (14%)	7 (9%)	17 (11%)
Race			
White	46 (67%)	59 (72%)	105 (70%)
Asian	7 (10%)	11 (13%)	18 (12%)
Other	16 (23%)	12 (15%)	28 (19%)
Weight (kg)	69.2 (15.8)	68.1 (16.4)	68.6 (16.1)
Height (cm)	161.1 (9.5)	162.3 (8.3)	161.7 (8.9)
BMI (kg/m^2)	26.5 (5.0)	25.8 (5.6)	26.1 (5.4)
Region			
Eastern Europe	34 (49%)	41 (50%)	75 (50%)
Western Europe	4 (6%)	6 (7%)	10 (7%)
Latin America	24 (35%)	23 (28%)	47 (31%)
Asia	7 (10%)	12 (15%)	19 (13%)
Swollen Joint Count	16.3 (8.4)	13.8 (6.9)	15.0 (7.7)
Tender Joint Count	27.0 (15.9)	25.0 (12.5)	25.9 (14.2)
HAQ Score	1.7 (0.6)	1.6 (0.6)	1.6 (0.6)
Patient Pain Score	67.9 (15.2)	65.1 (16.4)	66.4 (15.9)
Patient Global Assessment	67.2 (16.5)	65.5 (16.1)	66.2 (16.2)
Physician Global Assessment	66.9 (13.1)	65.4 (13.1)	66.1 (13.1)
CRP	2.7 (3.8)	2.0 (2.2)	2.3 (3.0)
ESR	50.0 (27.7)	51.2 (27.0)	50.6 (27.2)
DAS28 (ESR)	6.8 (0.9)	6.7 (0.8)	6.7 (0.8)
DAS28 (CRP)	6.0 (0.8)	5.8 (0.8)	5.9 (0.8)

Source: Reviewer

Cell contents are mean (standard deviation) or frequency (percent)

A.2 Tipping Point Analysis Methodology

The goal is to evaluate the potential effect of violations in assumptions about missing data on the reliability of conclusions. Suppose that outcomes Y are independently distributed on the control and test drug arms. The parameter of interest is the difference in means θ. Consider the following parameterization and notation to describe the probabilities of completing the study (non-missingness), the true means in completers and dropouts, and the numbers of completers and total patients on the two treatment arms:

Table 17: Relevant Parameters and Notation for Setting with Missing Data

Treatment Arm	Probability Non-Missing	Mean in Completers	Mean in Dropouts	Number of Completers	Total Sample Size
Control	π_c	μ_c	$\mu_c + \delta_c$	N_c	n_c
Test	π_t	μ_t	$\mu_t + \delta_t$	N_t	n_t

Given this parameterization, the paramter of interest is $\theta = [\pi_t\,\mu_t + (1-\pi_t)\,(\mu_t+\delta_t)] - [\pi_c\,\mu_c + (1-\pi_c)\,(\mu_c+\delta_c)] \equiv [\mu_t + (1-\pi_t)\,\delta_t] - [\mu_c + (1-\pi_c)\,\delta_c]$. An analysis in completers will only provide reliable inference on θ if the strong and unverifiable missing-at-random assumption, i.e., the assumption that $\delta_c = \delta_t = 0$, is valid. We will perform sensitivity analyses that allow for the possibility that outcomes among dropouts are not missing at random by performing inference under different assumed values of the parameters δ_c and δ_t.

Let $M_{j,i}$ be an indicator that patient i on treatment group j is a completer, i.e., his or her outcome is observed ($i = 1, ..., n_j$; $j = c, t$). Assuming specific values of the sensitivity parameters δ_c and δ_t, we consider the following estimator of θ:

$$\hat{\theta} = [\hat{\mu_t} + (1-\hat{\pi_t})\,\delta_t] - [\hat{\mu_c} + (1-\hat{\pi_c})\,\delta_c]$$

where $\hat{\mu_j} = \frac{1}{N_j}\sum_{i=1}^{n_j} Y_{j,i}|M_{j,i} = 1$ is the sample mean in the completers and $\hat{\pi_j} = \frac{N_j}{n_j} \equiv \frac{1}{n_j}\sum_{i=1}^{n_j} M_{j,i}$ is the observed proportion of completers on treatment arm j, with $j = c, t$.

One can show that:

$$\frac{\hat{\theta} - \theta}{\sqrt{s_t^2/N_t + s_c^2/N_c + \delta_t^2\hat{\pi}_t(1-\hat{\pi}_t)/n_t + \delta_c^2\hat{\pi}_c(1-\hat{\pi}_c)/n_c}} \xrightarrow{d} N[\,0,\,1\,]$$

where s_j^2 is the sample variance of the outcomes in completers on treatment j, with $j = c, t$. Thus, we can compute a Wald-type $(1-\alpha) * 100\%$ confidence interval for θ of the form

$$\hat{\theta} \pm z_{\alpha/2}\sqrt{s_t^2/N_t + s_c^2/N_c + \delta_t^2\hat{\pi}_t(1-\hat{\pi}_t)/n_t + \delta_c^2\hat{\pi}_c(1-\hat{\pi}_c)/n_c}$$

where $z_{\alpha/2}$ is the upper $(1-\alpha/2)$ quantile of the standard normal distribution.

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/s/

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I concur