RMD Open

Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Use of multibiomarker disease activity scores in biosimilarity studies for the treatment of patients with rheumatoid arthritis

Jonathan Kay [ID],[1,2,3] Amy E Bock,[4] Muhammad Rehman,[5] Wuyan Zhang,[6] Min Zhang,[7] Noriko Iikuni,[8] Daniel F Alvarez[9]

ABSTRACT

Objectives This exploratory analysis investigated the potential use of the multibiomarker disease activity (MBDA) score to support biosimilarity assessments using data from two randomised controlled trials (RCTs) of biosimilar infliximab (IFX-qbtx) and biosimilar adalimumab (ADL-afzb) versus EU-sourced infliximab (Remicade; IFX-EU) and adalimumab (Humira; ADL-EU) reference products, respectively, both conducted in adult patients with active rheumatoid arthritis.

Methods In one study, patients (N=650) were randomised 1:1 to IFX-qbtx or IFX-EU (3 mg/kg intravenous at weeks 0, 2 and 6, then every 8 weeks). In the other, patients (N=597) were randomised 1:1 to ADL-afzb or ADL-EU (40 mg subcutaneous every other week). All treatments were given with MTX. Mean values of MBDA scores were calculated at baseline (BL), based on the concentrations of 12 serum proteins using the Vectra disease activity algorithm, and at timepoints throughout treatment period 1 (TP1) of the IFX (weeks 6, 14, 30) and ADL (weeks 6, 12, 26) studies. Data were summarised using descriptive statistics for the intent-to-treat population, without imputation for missing data.

Results At BL, mean (±SD) MBDA scores were 61.3 (±12.5) and 58.8 (±13.2) for IFX-qbtx (n=236) and IFX-EU (n=248), respectively, and 57.2 (±14.44) and 58.3 (±15.34) for ADL-afzb (n=292) and ADL-EU (n=293), respectively. Mean MBDA scores were highly comparable between IFX-qbtx and IFX-EU and between ADL-afzb and ADL-EU at all measured timepoints during TP1 in each study.

Conclusions These RCTs are the first to incorporate MBDA score as an exploratory assessment of biosimilarity. MBDA scores may provide objective, quantitative evidence of biosimilarity using an assessment of disease activity that is independent of the potential subjectivity inherent in joint counts, or in patient or physician global assessments.

Trial registration numbers NCT02222493 and NCT02480153.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ The multibiomarker disease activity (MBDA) score provides an objective, quantitative measure of disease activity in patients with rheumatoid arthritis (RA) based on the concentrations of 12 serum proteins using the Vectra disease activity algorithm.

WHAT THIS STUDY ADDS
⇒ This study reports an exploratory analysis of the potential for use of the MBDA score to support biosimilarity assessments.
⇒ The analysis was conducted using data from two randomised controlled trials of biosimilar infliximab (IFX-qbtx) versus EU-sourced infliximab reference product (Remicade; IFX-EU) and biosimilar adalimumab (ADL-afzb) versus EU-sourced adalimumab reference product (Humira; ADL-EU), both conducted in adult patients with active RA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Our analysis demonstrates that mean MBDA scores were highly comparable between IFX-qbtx and IFX-EU and between ADL-afzb and ADL-EU at all measured timepoints during the first treatment period in each study.
⇒ These results suggest that MBDA scores may provide objective, quantitative evidence of biosimilarity using an assessment of disease activity that is independent of the potential subjectivity inherent in joint counts, or in patient or physician global assessments.

INTRODUCTION

Biosimilars are developed and approved according to an abbreviated clinical development pathway in comparison to their reference or originator products.[1] The biosimilar approval pathways specified by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for monoclonal antibodies usually require a comparative clinical efficacy and safety trial conducted in a patient population which is sensitive to detect potential differences between the proposed biosimilar and its
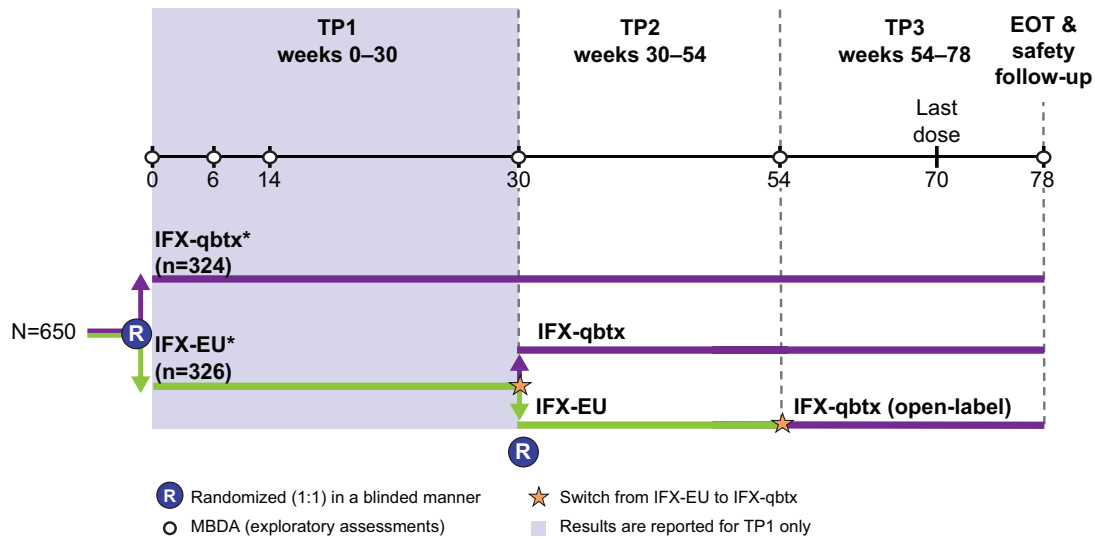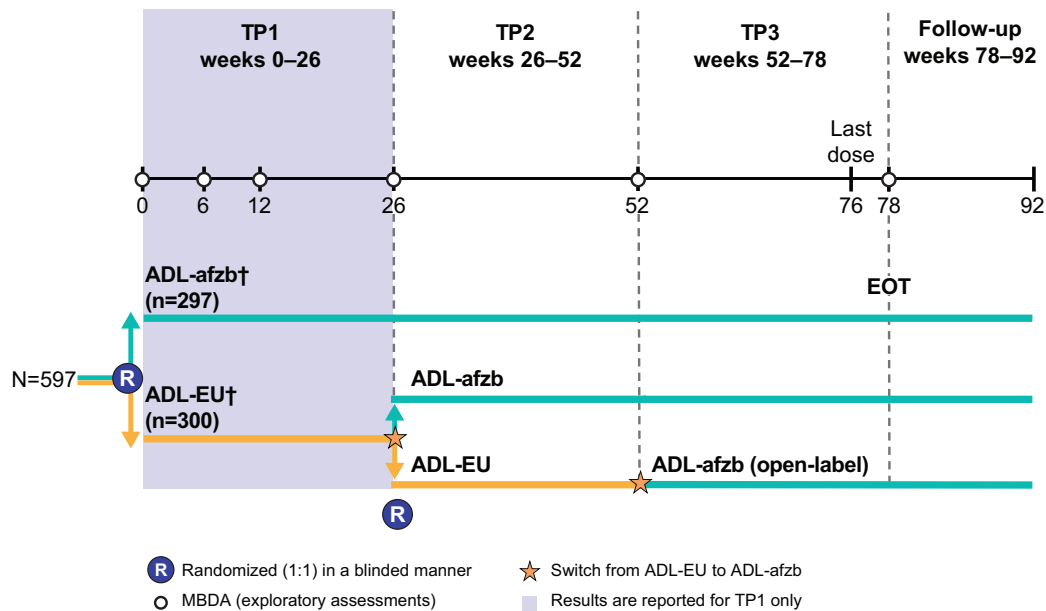
A.

B.

Figure 1 Design of the comparative clinical studies of (A) IFX-qbtx and IFX-EU and (B) ADL-afzb and ADL-EU. (A) Comparative clinical study of IFX-qbtx and IFX-EU. (B) Comparative clinical study of ADL-afzb and ADL-EU. *Intravenous IFX-qbtx or IFX-EU (3 mg/kg) in combination with MTX (10–25 mg/week) were administered at weeks 0, 2 and 6 and then every 8 weeks thereafter. †ADL-afzb or ADL-EU 40 mg subcutaneously Q2W+MTX. ADL-afzb, adalimumab biosimilar PF-06410293; ADL-EU, adalimumab reference product sourced from the European Union; EOT, end of treatment; IFX-EU, infliximab reference product sourced from the European Union; IFX-qbtx, infliximab biosimilar PF-06438179/GP1111; MBDA, multi-biomarker disease activity; MTX, methotrexate; Q2W, every 2 weeks; TP, treatment period.

reference products, should they exist.[1] The clinical assessment of biosimilarity in such trials relies on measures of disease activity.

PF-06438179/GP1111 (infliximab (IFX)-qbtx; Pfizer, New York, USA; Sandoz GmbH, Kundl, Austria) and PF-06410293 (adalimumab (ADL)-afzb; Pfizer, New York,

USA; Pfizer Europe MA EEIG, Brussels, Belgium) were approved as IFX and ADL biosimilars, respectively, by both the US FDA and the EMA for the treatment of all eligible indications of their respective reference products.[2–5] IFX-qbtx and ADL-afzb were evaluated in separate biosimilar development programmes. The regulatory approval of

Table 1 Baseline demographics and clinical characteristics (ITT population) in the comparative clinical studies of IFX-qbtx and IFX-EU and ADL-afzb and ADL-EU

	IFX-qbtx (n=324)	IFX-EU (n=326)	ADL-afzb (n=297)	ADL-EU (n=300)
Female, n (%)	258 (79.4)	264 (81.0)	241 (81.1)	229 (76.3)
Age, years	52.8 (13.3)	52.8 (12.9)	51.5 (13.6)	53.5 (12.9)
Weight, kg	73.3 (19.8)	74.2 (20.0)	74.7 (17.5)	76.2 (20.8)
BMI, kg/m^2	27.2 (6.4)	27.7 (7.0)	27.5 (6.1)	28.1 (7.3)
Race, n (%)				
White	257 (79.3)	247 (75.8)	261 (87.9)	256 (85.3)
Black	5 (1.5)	9 (2.8)	6 (2.0)	9 (3.0)
Asian	46 (14.2)	45 (13.8)	16 (5.4)	17 (5.7)
Other	15 (4.6)	25 (7.7)	14 (4.7)	18 (6.0)
Unspecified	1 (0.3)	0	0	0
Ethnicity, n (%)				
Not Hispanic/Latino	292 (90.1)	294 (90.2)	272 (91.6)	271 (90.3)
RA duration, years	7.3 (8.6)	6.4 (6.7)	6.8 (7.2)	6.8 (6.9)
Swollen joint count	16.1 (9.4)	16.3 (8.7)	15.4 (7.8)	17.0 (9.8)
Tender joint count	24.7 (13.9)	25.7 (12.9)	24.3 (12.3)	26.7 (14.8)
PGA	65.4 (20.7)	63.9 (23.0)	64.4 (19.3)	68.2 (19.5)
DAS28-CRP	6.0 (1.0)	6.0 (0.9)	5.9 (0.9)	6.1 (0.9)
hs-CRP, mg/L	25.8 (24.3)	25.3 (28.4)	21.3 (22.7)	22.8 (25.2)
MTX dose, mg/week	14.2 (4.5)*	14.4 (4.5)	15.2 (4.4)	15.2 (4.5)
MBDA score	61.3 (12.45)†	58.8 (13.17)†	57.2 (14.44)‡	58.3 (15.34)‡

Data are mean (SD) unless otherwise stated.
*Total weekly dose of MTX was 16 mg/week for one patient (IFX-qbtx) but incorrectly recorded as 32 mg/week; incorrect dose was the maximum value of the MTX dose range and was used for calculation of mean dose.
†Mean MBDA score was calculated based on 236 (IFX-qbtx) and 248 (IFX-EU) patients with baseline data.
‡Mean MBDA score was calculated based on 292 (ADL-afzb) and 293 (ADL-EU) patients with baseline data.
ADL-afzb, adalimumab biosimilar PF-06410293; ADL-EU, adalimumab reference product sourced from the European Union; BMI, body mass index; CRP, C reactive protein; hs-CRP, high-sensitivity CRP; IFX-EU, infliximab reference product sourced from the European Union; IFX-qbtx, infliximab biosimilar PF-06438179/GP1111; ITT, intent-to-treat; MBDA, multibiomarker disease activity; MTX, methotrexate; PGA, patient's global assessment of arthritis; RA, rheumatoid arthritis.

IFX-qbtx and ADL-afzb was each based on the 'totality of the evidence' obtained from comparative analytical assessments, a comparative clinical pharmacology study in healthy volunteers and a randomised, double-blind clinical trial that assessed comparative efficacy and safety in patients with active rheumatoid arthritis (RA).[6–11]

In the randomised controlled clinical trial that compared IFX-qbtx to reference IFX sourced from the European Union (IFX-EU; Janssen Biologics B.V., Leiden, The Netherlands), therapeutic equivalence was demonstrated using the American College of Rheumatology (ACR) 20% improvement (ACR20) response at week 14 as the primary endpoint.[7] Likewise, in the clinical trial that confirmed therapeutic equivalence of ADL-afzb to reference ADL sourced from the European Union (ADL-EU; AbbVie Deutschland GmbH Co. KG, Ludwigshafen, Germany), the ACR20 response at week 12 served as the primary efficacy endpoint.[10] In addition, comparable safety and immunogenicity of IFX-qbtx and

ADL-afzb to their respective reference products were also established.[7–10]

Patient global self-assessment and physician global assessment are both components of composite measures that are used to evaluate disease activity in patients with RA; however, these subjective assessments can be confounded by pain amplification, comorbidities or structural accumulated joint damage resulting from past disease activity.[12 13] Thus, use of these established composite disease activity measures as efficacy endpoints in clinical trials comparing biosimilar candidates to their reference products may not be sensitive to detect potential differences in efficacy between the biosimilar candidate and its reference product, should they exist. The results of the AMPLE study, which compared the efficacy of two dissimilar biological agents with distinct mechanisms of action, support this assertion in that adalimumab could not be differentiated from abatacept using traditional efficacy endpoints, including ACR20 responses

Figure 2 Mean (±SD) MBDA scores over time and ACR response rates and change from baseline in DAS28-CRP by study visit in patients with RA treated with IFX-qbtx or IFX-EU (ITT population). (A) Mean (±SD) MBDA scores over time up to week 30 in patients with RA treated with IFX-qbtx or IFX-EU (ITT population). (B) ACR response rates by study visit up to week 30 in patients with RA treated with IFX-qbtx or IFX-EU (ITT population). (C) Mean (±SE) change from baseline in DAS28-CRP by study visit up to week 30 in patients with RA treated with IFX-qbtx or IFX-EU (ITT population). *Baseline was defined as the measurement taken at the week 0 visit. For postbaseline visits, patients with both baseline and postbaseline data at each visit were counted. (B,C) ACR20/50/70, American College of Rheumatology criteria for ≥20%/50%/70% clinical improvement; DAS28-CRP, Disease Activity Score in 28 joints, four components based on C-reactive protein; IFX-EU, infliximab reference product sourced from the European Union; IFX-qbtx, infliximab biosimilar PF-06438179/GP1111; ITT, intent-to-treat; MBDA, multi-biomarker disease activity; SD, standard deviation. Reproduced with permission from Cohen SB, Alten R, Kameda H. *et al*. A randomized controlled trial comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis despite methotrexate therapy. *Arthritis Res Ther* 2018;20:155. https://doi.org/10.1186/s13075-018-1646-4.
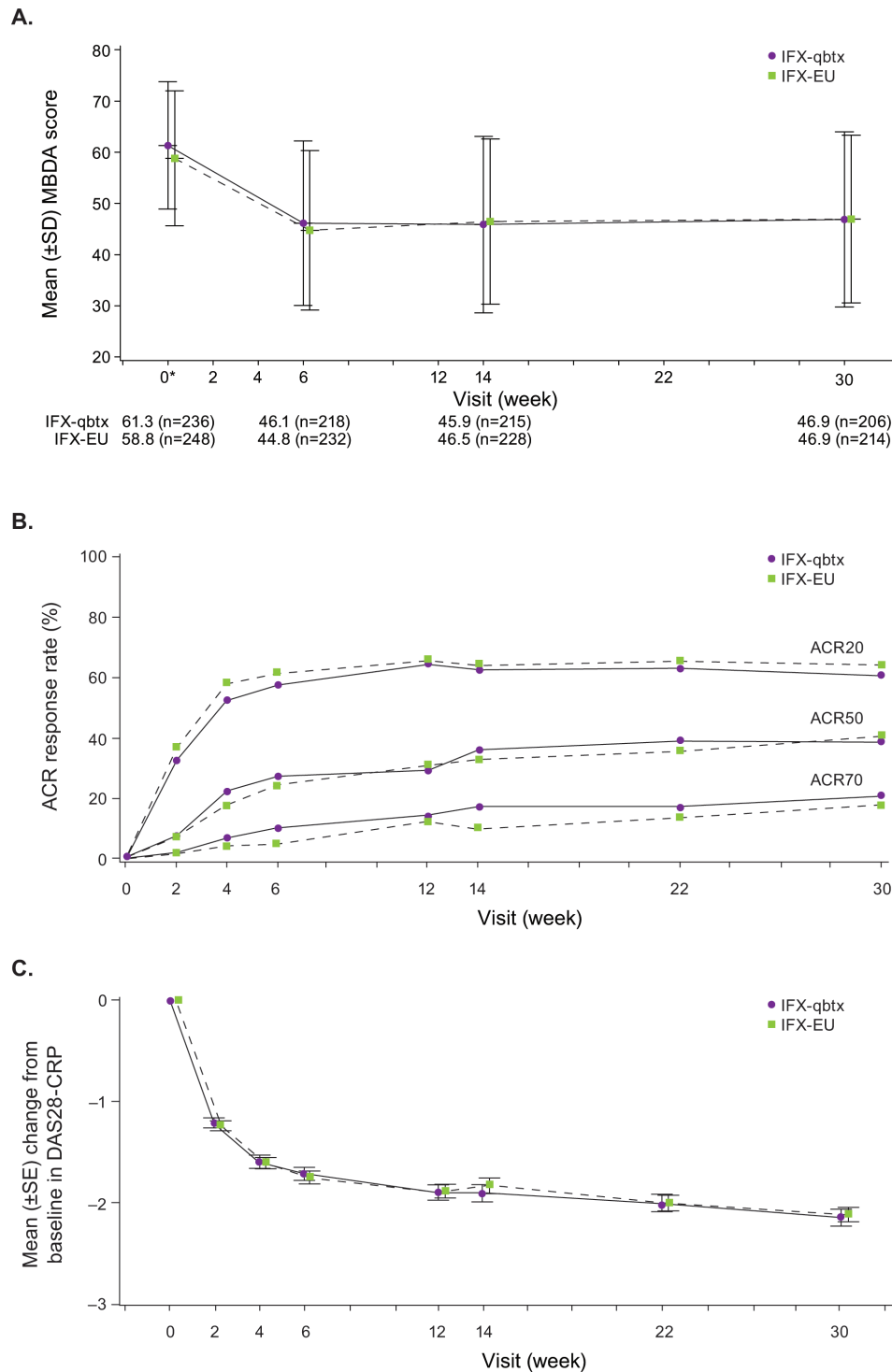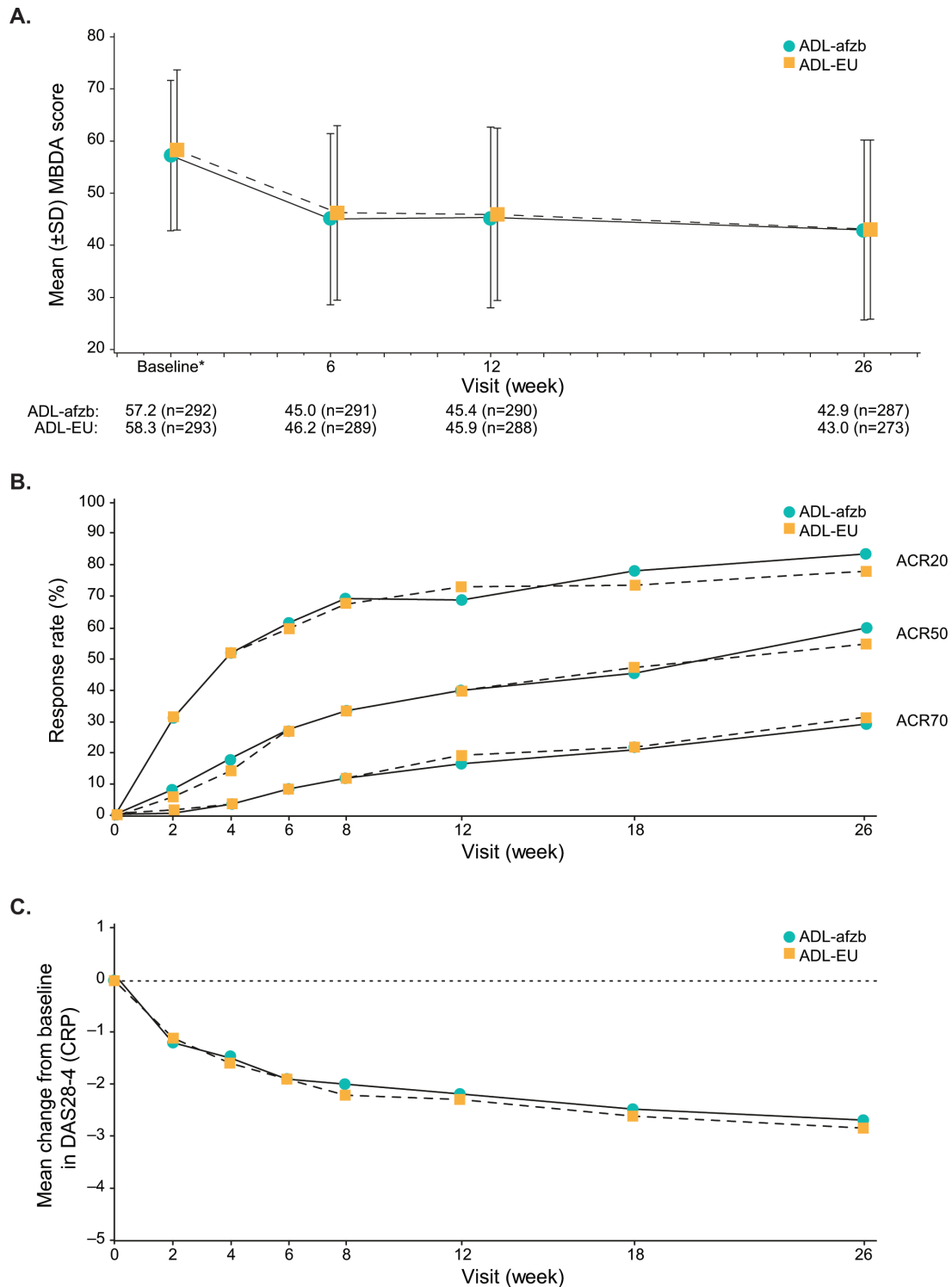
Figure 3 Mean (±SD) MBDA scores over time and ACR response rates and change from baseline in DAS28-CRP by study visit in patients with RA treated with ADL-afzb or ADL-EU (ITT population). (A) Mean (±SD) MBDA scores over time up to week 26 in patients with RA treated with ADL-afzb or ADL-EU (ITT population). (B) ACR response rates by study visit up to week 26 in patients with RA treated with ADL-afzb or ADL-EU (ITT population). (C) Mean (±SE) change from baseline in DAS28-CRP by study visit up to week 30 in patients with RA treated with ADL-afzb or ADL-EU (ITT population). *Baseline was defined as the last non-missing measurement taken on or before study day 1. (B,C) ACR20/50/70, American College of Rheumatology criteria for ≥20%/50%/70% clinical improvement; ADL-afzb, adalimumab biosimilar PF-06410293; ADL-EU, adalimumab reference product sourced from the European Union; DAS28-CRP, Disease Activity Score in 28 joints, four components based on C-reactive protein; ITT, intent-to-treat; MBDA, multi-biomarker disease activity; SD, standard deviation. Reproduced with permission from Fleischmann, R.M., Alten, R., Pileckyte, M. *et al*. A comparative clinical study of PF-06410293, a candidate adalimumab biosimilar, and adalimumab reference product (Humira®) in the treatment of active rheumatoid arthritis. *Arthritis Res Ther* 2018;20:178. https://doi.org/10.1186/s13075-018-1676-y.
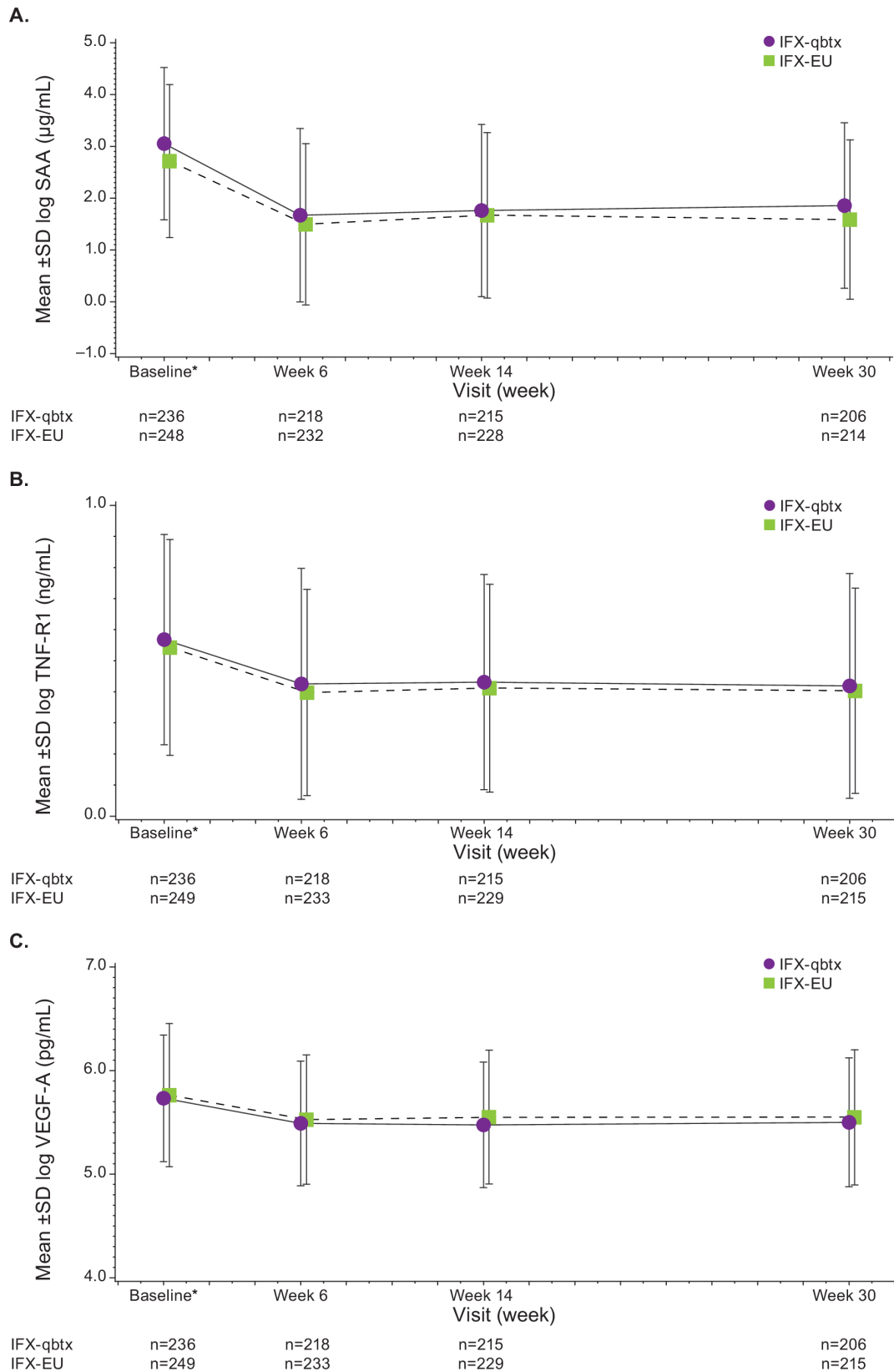
Figure 4 Mean (±SD) log biomarker values over time for (A) SAA (µg/mL), (B) TNF-R1 (ng/mL) and (C) VEGF-A (pg/mL) during TP1 (ITT population) of the comparative clinical study of IFX-qbtx and IFX-EU. (A) Mean (±SD) log biomarker values (µg/mL) over time for SAA. (B) Mean (±SD) log biomarker values (ng/mL) over time for TNF-R1. (C) Mean (±SD) log biomarker values (pg/mL) over time for VEGF-A. *Baseline was defined as the last non-missing measurement taken on or before study day 1. IFX-EU, infliximab reference product sourced from the European Union; IFX-qbtx, infliximab biosimilar PF-06438179/GP1111; ITT, intent-to-treat; SAA, serum amyloid A; TNF-R1, tumour necrosis factor receptor 1; TP1, treatment period 1; VEGF-A, vascular endothelial growth factor-A.
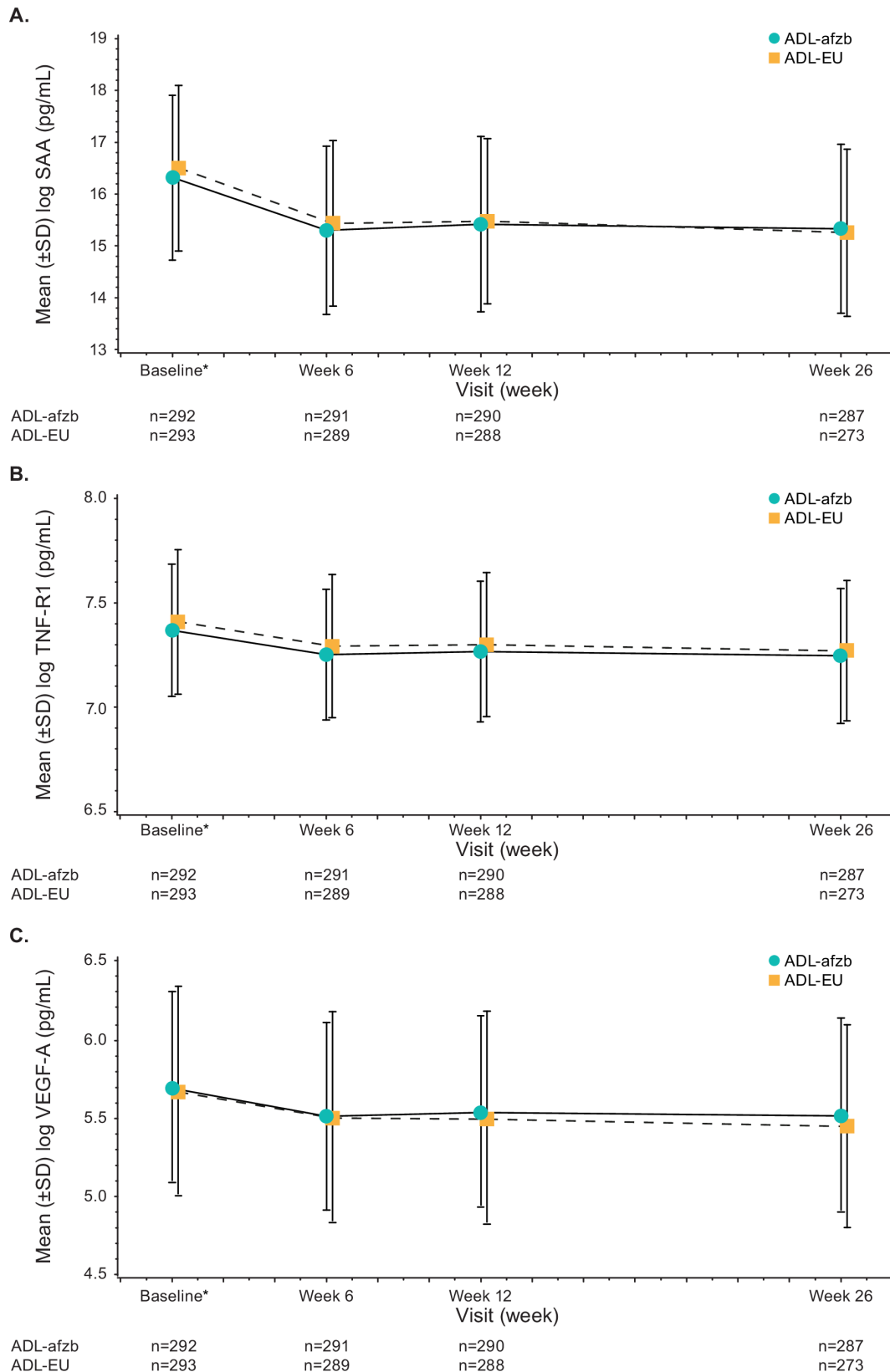
Figure 5 Mean (±SD) log biomarker values (pg/mL) over time for (A) SAA, (B) TNF-R1 and (C) VEGF-A during TP1 (ITT population) of the comparative clinical study of ADL-afzb and ADL-EU. (A) Mean (±SD) log biomarker values (pg/mL) over time for SAA. (B) Mean (±SD) log biomarker values (pg/mL) over time for TNF-R1. (C) Mean (±SD) log biomarker values (pg/mL) over time for VEGF-A. *Baseline was defined as the last non-missing measurement taken on or before study day 1. ADL-afzb, adalimumab biosimilar PF-06410293; ADL-EU, adalimumab reference product sourced from the European Union; ITT, intent-to-treat; SAA, serum amyloid A; TNF-R1, tumour necrosis factor receptor 1; TP1, treatment period 1; VEGF-A, vascular endothelial growth factor-A.

and DAS28.[14 15] Accordingly, such limitations when using composite measures of efficacy have prompted regulatory authorities to encourage the use of biomarkers as endpoints in clinical trials comparing biosimilar candidates to their reference products.[16 17] The data submitted to support the approval of pegfilgrastim biosimilars in the EU and in the USA included the results of comparative pharmacodynamic studies measuring changes in the absolute neutrophil count in healthy subjects, which obviated the need to conduct confirmatory comparative clinical trials in patients.[18 19] However, no suitable biomarker is yet available to assess biosimilarity in patients with inflammatory diseases.

The multibiomarker disease activity (MBDA) score (Vectra, Myriad Genetics, Salt Lake City, Utah, USA) has been validated to provide a quantitative measure of disease activity in patients with RA.[12 13] Using a proprietary algorithm, the concentrations of 12 biomarkers, including C reactive protein (CRP), are combined to calculate a score that ranges from 1 to 100.[12 13] This MBDA score has been validated to correlate with the disease activity score that includes a 28-joint count and CRP (DAS28-CRP) in patients with RA.[12]

The present analysis, using data from the randomised, double-blinded clinical trials that compared IFX-qbtx to IFX-EU and ADL-afzb to ADL-EU, each in adult patients with active RA, was performed to explore the potential of using the MBDA score to support assessments of biosimilarity in the future.

METHODS
Study designs and treatments
The multinational, randomised, double-blind, parallel-group study comparing the efficacy, safety and immunogenicity of IFX-qbtx and IFX-EU in patients with active, moderate to severe RA inadequately responsive to methotrexate (MTX) (ClinicalTrials.gov identifier: NCT02222493) consisted of an initial 30-week treatment period (treatment period (TP) 1) followed by two subsequent 24-week TPs (figure 1A).[7 20 21] At the start of TP1 (weeks 0–30), patients (N=650) were randomised 1:1 to receive intravenous infusions of either IFX-qbtx (n=324) or IFX-EU (n=326) (3 mg/kg at weeks 0, 2 and 6, then every 8 weeks thereafter) in addition to a stable background dose of MTX (10–25 mg/week).[7] The primary efficacy endpoint of this study was the percentage of patients achieving ACR20 at week 14. In TP2 (weeks 30–54), patients receiving IFX-EU remained blinded and were rerandomised 1:1, at week 30, either to continue receiving IFX-EU or to switch to IFX-qbtx.[20] Throughout TP3 (weeks 54–78), all patients received open-label treatment with IFX-qbtx.[21]

The multinational, randomised, double-blind study comparing the efficacy, safety and immunogenicity of ADL-afzb and ADL-EU in adult patients with active, moderate to severe RA inadequately responsive to MTX (ClinicalTrials.gov Identifier: NCT02480153) consisted of three 26-week TPs and a 16-week follow-up period after the last dose of study drug (figure 1B).[10 22] At the start of TP1 (weeks 0–26), patients (N=597) were randomised 1:1 to receive subcutaneous injections of either ADL-afzb (n=297) or ADL-EU (n=300) (40 mg every other week) in addition to a stable background dose of MTX (10–25 mg/week).[10] The primary efficacy endpoint of this study was the proportion of patients achieving ACR20 at week 12. In TP2 (weeks 26–52), patients receiving ADL-EU remained blinded and were rerandomised 1:1 at week 26 either to continue receiving ADL-EU or to switch to ADL-afzb.[22] Throughout TP3 (weeks 52–78), all patients received open-label treatment with ADL-afzb.[23]

Study populations
Eligibility criteria were similar for both studies. Briefly, eligible patients were adults (aged ≥18 years) who met the 2010 ACR/European Alliance of Associations for Rheumatology classification criteria for RA for ≥4 months and the 1991 revised ACR criteria for functional status classes I–III. Active RA was defined as ≥6 tender and ≥6 swollen joints (at screening and baseline) with high-sensitivity-CRP ≥10 mg/L (IFX study) or ≥8 mg/L (ADL study) at screening. In addition, patients must have received MTX for ≥12 weeks and been on a stable dose (10–25 mg/week) for ≥4 weeks before the first dose of study drug. Full study inclusion and exclusion criteria have been described in detail elsewhere.[7 10]

Exploratory endpoints and assessments
For each study, MBDA scores were calculated using a proprietary algorithm (Vectra disease activity).[12 13] In this algorithm, the concentrations of 12 biomarkers (epidermal growth factor; interleukin-6; leptin; matrix metalloproteinase (MMP)-1; MMP-3; resistin; serum amyloid A (SAA); tumour necrosis factor receptor 1 (TNFR1); vascular cell adhesion molecule-1; vascular endothelial growth factor-A (VEGF-A); human cartilage glycoprotein-39 (YKL-40); and CRP) were combined to produce the MBDA score, which ranged from 1 to 100 on an integer scale and was categorised into low (<30), moderate (30–44) and high (>44) disease activity.[12 13] For each study, MBDA scores were compared from TP1 only, during which patients were randomised 1:1 to receive either biosimilar or reference product.

Statistical analysis
Analyses were performed using the intent-to-treat populations, without imputation for missing data. Data were summarised using descriptive statistics for MBDA scores and for each of the 12 biomarkers. As the distributions of each of the 12 biomarkers were right skewed, results were log-transformed before data analysis.

Patient involvement statement
Patient and members of the public were not involved in any aspect of this study, including the design, management and conduct of the study and were not involved in choosing the methods or agreeing plans for dissemination

of the study results to participants and linked communities.

Ethics approval and consent to participate

The main studies were conducted in compliance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. All patients provided informed consent prior to undergoing any screening procedures.[7 10 20–23]

RESULTS

As previously reported, no notable differences were observed between biosimilar and reference product groups in baseline demographics or RA characteristics in either study (table 1).[7 10] At baseline, mean (±SD) MBDA scores were 61.3 (±12.5) and 58.8 (±13.2) for the IFX-qbtx (n=236) and IFX-EU (n=248) groups, respectively, and were 57.2 (±14.44) and 58.3 (±15.34) for the ADL-afzb (n=292) and ADL-EU (n=293) groups, respectively.

Mean MBDA scores and changes from baseline in MBDA scores, ACR20/50/70 response rates and changes from baseline in DAS28-CRP were comparable between the biosimilar and its reference product at all timepoints measured during TP1 in each study: for the IFX-qbtx and IFX-EU groups through week 30 (figure 2 and online supplemental figure S1) and for the ADL-afzb and ADL-EU groups through week 26 (figure 3 and online supplemental figure S2).[7 10 24 25] For each treatment group in each study, mean MBDA scores plateaued at week 6 (figures 2A, 3A) while ACR response rates and changes from baseline in DAS28-CRP continued to improve throughout TP1 (figures 2B,C, 3B,C).[24 25]

Decreases in the proportions of patients with high MBDA scores from baseline to the end of TP1 and in mean MBDA scores from baseline to week 6 were comparable between the biosimilar and its reference product in each study.[24 25] At baseline, 66.0% of patients in the IFX-qbtx and 66.9% of those in the IFX-EU treatment group had high (>44) MBDA scores; these proportions decreased comparably to 42.3% and 40.2%, respectively, at week 30. Likewise, these proportions decreased from 78.5% to 45.5% for patients in the ADL-afzb treatment group and from 81.7% to 41.7% for those in the ADL-EU treatment group from baseline to week 26.[24 25] Mean MBDA scores decreased comparably from baseline in the IFX-qbtx and IFX-EU groups, respectively: by 15.2 and 14.1 at week 6, by 15.5 and 12.1 at week 14 and by 14.7 and 12.0 at week 30. Mean MBDA scores also decreased comparably from baseline in the ADL-afzb and ADL-EU groups, respectively, by 11.9 and 12.4 at week 6, by 11.7 and 12.4 at week 12 and by 14.3 and 15.5 at week 26.[24 25]

Overall, changes in the concentrations of individual biomarkers over time were comparable between IFX-qbtx and IFX-EU groups and between ADL-afzb and ADL-EU groups (figures 4 and 5; Online supplemental figures S3 and S4).[24 25] Plots showing the mean (±SD) log-transformed values for the individual biomarkers SAA,

TNFR1 and VEGF-A are presented to highlight the variety (largest change, moderate change and smallest change) in the range in the magnitude of changes from baseline to week 30 that were observed for individual biomarkers in the IFX-qbtx and IFX-EU groups (figure 4) and from baseline to week 26 for individual biomarkers in the ADL-afzb and ADL-EU groups (figure 5).

DISCUSSION

These clinical trials that compared IFX-qbtx with IFX-EU, and ADL-afzb with ADL-EU, are the first studies to incorporate an MBDA score as an exploratory assessment of biosimilarity. It was anticipated that MBDA scores would change in a similar fashion between the reference product and the biosimilar product. Accordingly, in TP1 of each study, mean MBDA scores were comparable between the biosimilar and its reference product at each timepoint measured: over 30 weeks for IFX-qbtx and IFX-EU and over 26 weeks for ADL-afzb and ADL-EU.

For TNF inhibitors, the ACR responses and change in DAS28 over time typically reach a plateau around 6 months after initiation of treatment.[26–32] Our results demonstrate that, although ACR responses for the reference and biosimilar products continued to improve in parallel over the first 30 and 26 weeks of treatment for IFX and ADL, respectively, MBDA scores reached plateau phase within the first 6 weeks of treatment. Thus, using MBDA scores at week 6 instead of ACR responses or change in DAS28 as the primary outcome measure has the potential to demonstrate comparable disease activity earlier. Conversely, as in the AMPLE study of two biological agents with dissimilar protein structure and mechanisms of action, use of MBDA scores may demonstrate differences over time when ACR responses and change in DAS28 do not.[33] Additionally, unlike ACR response criteria and DAS28, each of which includes a subjective assessment of disease activity by the patient and a tender joint count that is susceptible to the bias of both the patient and the examiner, the MBDA is derived from objective measurement of the concentrations of 12 biomarkers without any subjective component.

A limitation of the current study is that, because this was an exploratory analysis of two biosimilar comparative effectiveness trials, only a limited number of timepoints were included for the assessment of MBDA scores; MBDA scores were not evaluated before week 6. Earlier timepoints might be more sensitive to detecting potential differences between a biosimilar candidate and its reference product.[34] Also, the power calculations for these studies were based on the primary endpoints of the proportion of patients achieving ACR20 responses at week 12 or 14, and not the MBDA scores. Nevertheless, in the current analysis, similar trends in the mean MBDA scores over time for the biosimilar and its reference product were observed for both IFX and ADL. Prospective study in a clinical trial comparing a biosimilar to its

reference product is warranted to validate this disease activity measure as an assessment of biosimilarity.

In conclusion, the MBDA score may provide objective, quantitative and potentially earlier evidence of biosimilarity using an assessment of disease activity that is independent of the potential subjectivity inherent to counts of tender joints or global assessments of disease activity by the patient or assessor.

Author affiliations
[1]Division of Rheumatology, Department of Medicine, UMass Chan Medical School, Worcester, Massachusetts, USA
[2]Division of Epidemiology, Department of Population and Quantitative Health Sciences, UMass Chan Medical School, Worcester, Massachusetts, USA
[3]Division of Rheumatology, Department of Medicine, UMass Memorial Medical Center, Worcester, Massachusetts, USA
[4]Pfizer Inc, Cambridge, Massachusetts, USA
[5]Pfizer Inc, Andover, Massachusetts, USA
[6]Pfizer Inc, Lake Forest, Illinois, USA
[7]Pfizer Inc, La Jolla, California, USA
[8]Pfizer Inc, New York, New York, USA
[9]Pfizer Inc, Collegeville, Pennsylvania, USA

Twitter Jonathan Kay @RheumKay

Contributors JK and DFA contributed to the design and implementation of the study. All authors contributed to the analysis of the results and to the writing of the manuscript. JK is the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Competing interests JK reports grant support (paid to his institution) from Aker BioMarine, Alliance for Lupus Research, AMPEL BioSolutions, Gilead Sciences, Inc., Novartis Pharmaceuticals Corp., Pfizer and UCB Inc; royalty fees from UpToDate; consulting fees from AbbVie, Alvotech Suisse AG, Arena Pharmaceuticals, Inc., Boehringer Ingelheim GmbH, Celltrion Healthcare Co. Ltd., Horizon Therapeutics PLC, Jubilant Radiopharma, Merck Sharp & Dohme Corp., Mylan Inc., Novartis AG, Pfizer, Samsung Bioepis, Sandoz Inc., Scipher Medicine, and UCB Inc.; and fees for participation in data monitoring boards from Bristol Myers Squibb Co., Inmagene Biopharmaceuticals and Kolon TissueGene Inc. DFA, AEB, MR and MZ are full-time employees of, and declare shareholdings, stock holdings and/or stock options from, Pfizer. NI was a full-time employee of Pfizer at the time of the studies and declares shareholdings, stock holdings and/or stock options from Pfizer. WZ is a full-time employee of Pfizer and declares shareholdings, stock holdings and/or stock options from Abbot, AbbVie and Pfizer.

Patient consent for publication Not applicable.

Ethics approval The studies' protocols, all amendments and informed consent documentation were reviewed and approved by an institutional review board or independent ethics committee(s) at each of the participating investigational sites in each of the studies. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. On request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iD
Jonathan Kay http://orcid.org/0000-0002-8970-4260

REFERENCES
1 US Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product, 2015. Guidance for industry. Available: https://www.fda.gov/media/82647/download [Accessed 11 Nov 2019].
2 European Medicines Agency. Amsparity (adalimumab) Europoean public assessment report, 2020. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/amsparity#product-information-section [Accessed 17 Sep 2020].
3 European Medicines Agency. Zessly (infliximab) European public assessment report, 2020. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/zessly [Accessed 16 Sep 2020].
4 Pfizer Inc. ABRILADA (adalimumab-afzb) US prescribing information, 2020. Available: http://labeling.pfizer.com/ShowLabeling.aspx?id=12780 [Accessed 17 Sep 2020].
5 Pfizer Ireland Pharmaceuticals. IXIFI (infliximab-qbtx) US prescribing information, 2017. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761072s000lbl.pdf [Accessed 16 Sep 2020].
6 ClinicalTrials.gov. A study of PF-06410293 (adalimumab-Pfizer) and adalimumab (Humira) in healthy subjects (reflections B538–07)) (B538–07), 2014. Available: https://clinicaltrials.gov/ct2/show/NCT02237729 [Accessed 17 Sep 2020].
7 Cohen SB, Alten R, Kameda H, *et al*. A randomized controlled trial comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis despite methotrexate therapy. *Arthritis Res Ther* 2018;20:155.
8 Derzi M, Johnson TR, Shoieb AM, *et al*. Nonclinical evaluation of PF-06438179: a potential biosimilar to Remicade® (Infliximab). *Adv Ther* 2016;33:1964–82.
9 Derzi M, Shoieb AM, Ripp SL, *et al*. Comparative nonclinical assessments of the biosimilar PF-06410293 and originator adalimumab. *Regul Toxicol Pharmacol* 2020;112:104587.
10 Fleischmann RM, Alten R, Pileckyte M, *et al*. A comparative clinical study of PF-06410293, a candidate adalimumab biosimilar, and adalimumab reference product (Humira®) in the treatment of active rheumatoid arthritis. *Arthritis Res Ther* 2018;20:178.
11 Palaparthy R, Udata C, Hua SY, *et al*. A randomized study comparing the pharmacokinetics of the potential biosimilar PF-06438179/GP1111 with Remicade® (infliximab) in healthy subjects (reflections B537-01). *Expert Rev Clin Immunol* 2018;14:329–36.
12 Centola M, Cavet G, Shen Y, *et al*. Development of a multi-biomarker disease activity test for rheumatoid arthritis. *PLoS One* 2013;8:e60635.
13 Segurado OG, Sasso EH. Vectra dA for the objective measurement of disease activity in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2014;32:S-29–34.
14 Schiff M, Weinblatt ME, Valente R, *et al*. Head-To-Head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis* 2014;73:86–94.
15 Weinblatt ME, Schiff M, Valente R, *et al*. Head-To-Head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIB, multinational, prospective, randomized study. *Arthritis Rheum* 2013;65:28–38.
16 US Food and Drug Administration. Biosimilars action plan: balancing innovation and competition, 2018. Available: https://www.fda.gov/media/114574/download [Accessed 17 September 2020].
17 Li J, Florian J, Campbell E, *et al*. Advancing Biosimilar development using pharmacodynamic biomarkers in clinical pharmacology studies. *Clin Pharmacol Ther* 2020;107:40–2.
18 European Medicines Agency. Pelmeg (pegfilgrastim) European public assessment report, 2018. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/pelmeg [Accessed 6 September 2022].
19 US Food and Drug Administration. Udenyca (pegfilgrastim-cbqv) summary review, 2018. Available: https://www.accessdata.fda.gov/

drugsatfda_docs/nda/2018/761039Orig1s000SumR.pdf [Accessed 25 July 2022].

20 Alten R, Batko B, Hala T, *et al*. Randomised, double-blind, phase III study comparing the infliximab biosimilar, PF-06438179/GP1111, with reference infliximab: efficacy, safety and immunogenicity from week 30 to week 54. *RMD Open* 2019;5:e000876.

21 Cohen SB, Radominski SC, Kameda H, *et al*. Long-Term efficacy, safety, and immunogenicity of the infliximab (IFX) biosimilar, PF-06438179/GP1111, in patients with rheumatoid arthritis after switching from reference IFX or continuing biosimilar therapy: week 54-78 data from a randomized, double-blind, phase III trial. *BioDrugs* 2020;34:197–207.

22 Fleischmann RM, Alvarez DF, Bock AE, *et al*. Randomised study of PF-06410293, an adalimumab (ADL) biosimilar, compared with reference ADL for the treatment of active rheumatoid arthritis: results from weeks 26-52, including a treatment switch from reference ADL to PF-06410293. *RMD Open* 2021;7:e001578.

23 Fleischmann RM, Alvarez DF, Bock AE, *et al*. Long-Term efficacy, safety, and immunogenicity of the adalimumab biosimilar, PF-06410293, in patients with rheumatoid arthritis after switching from reference adalimumab (Humira®) or continuing biosimilar therapy: week 52-92 data from a randomized, double-blind, phase 3 trial. *Arthritis Res Ther* 2021;23:248.

24 Kay J, Alvarez D, Rehman M. Use of Multi-Biomarker Disease Activity Scores to Assess Biosimilarity in a Phase 3 Randomized Controlled Trial Comparing Biosimilar Infliximab-qbtx (PF-06438179/GP1111) with EU-Sourced Reference Infliximab in Patients with Active RA [abstract]. *Arthritis Rheumatol* 2020;72 https://acrabstracts.org/abstract/use-of-multi-biomarker-disease-activity-scores-to-assess-biosimilarity-in-a-phase-3-randomized-controlled-trial-comparing-biosimilar-infliximab-qbtx-pf%e2%80%9106438179-gp1111-with-eu-sourced-refere/

25 Kay J, Bock AE, Iikuni N. Use of Multi-Biomarker Disease Activity Scores to Compare Biosimilar Adalimumab-afzb (PF-06410293) with EU-Sourced Reference Adalimumab in a Phase 3, Randomized, Double-Blind Trial in Patients with Active RA [abstract]. *Arthritis Rheumatol* 2020;72 https://acrabstracts.org/abstract/use-of-multi-biomarker-disease-activity-scores-to-compare-biosimilar-adalimumab-afzb-pf-06410293-with-eu-sourced-reference-adalimumab-in-a-phase-3-randomized-double-blind-trial-in-patients-with-ac/

26 Bathon JM, Martin RW, Fleischmann RM, *et al*. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586–93.

27 Keystone E, Genovese MC, Klareskog L, *et al*. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis* 2010;69:1129–35.

28 Keystone E, Heijde Dvander, Mason D, *et al*. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;58:3319–29.

29 Keystone EC, Kavanaugh AF, Sharp JT, *et al*. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400–11.

30 Lipsky PE, van der Heijde DM, St Clair EW, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy Study Group. *N Engl J Med* 2000;343:1594–602.

31 Maini R, St Clair EW, Breedveld F, *et al*. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. attract Study Group. *Lancet* 1999;354:1932–9.

32 Smolen JS, Kay J, Landewé RBM, *et al*. Golimumab in patients with active rheumatoid arthritis who have previous experience with tumour necrosis factor inhibitors: results of a long-term extension of the randomised, double-blind, placebo-controlled GO-AFTER study through week 160. *Ann Rheum Dis* 2012;71:1671–9.

33 Fleischmann R, Connolly SE, Maldonado MA, *et al*. Brief report: estimating disease activity using multi-biomarker disease activity scores in rheumatoid arthritis patients treated with abatacept or adalimumab. *Arthritis Rheumatol* 2016;68:2083–9.

34 Kay J, Smolen JS. Biosimilars to treat inflammatory arthritis: the challenge of proving identity. *Ann Rheum Dis* 2013;72:1589–93.