

BMJ Open Immunogenicity of adalimumab reference product and adalimumab-adbm in patients with rheumatoid arthritis, Crohn's disease and chronic plaque psoriasis: a pooled analysis of the VOLTAIRE trials

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ABSTRACT

Objective This post hoc analysis compared the immunogenicity of the biosimilar adalimumab-adbm (Cyltezo) with the adalimumab reference product (RP; Humira) across indications, including rheumatoid arthritis (RA), Crohn's disease (CD) and plaque psoriasis (PsO), and by patient sex in the VOLTAIRE trials programme.

Methods In each active-comparator randomised controlled trial (RCT), immunogenicity was assessed at various time points by the proportion of patients with antidrug antibodies (ADAs) and neutralising antibodies (nAbs), using acid dissociation followed by electrochemiluminescence assay. Assay sensitivity was 50 ng/mL, and drug tolerance was ≥ 30 µg/mL (free drug) at the low positive control level.

Results Minor differences in immunogenicity parameters (ADAs, ADA titres and nAbs) were evident between adalimumab-adbm and adalimumab RP across these three immune-mediated inflammatory diseases (IMiDs). The proportion of ADA-positive and nAb-positive patients increased from baseline over time in all three RCTs, as expected, and was similar in the RA and CD RCTs but with higher numbers of ADA-positive and nAb-positive patients reported in the PsO trial. Subgroup analysis by patient sex showed the same trend.

Conclusions Differences among the RCTs may partially be explained by concomitant background therapy (methotrexate) in the RA trial, stable doses of azathioprine, 6-mercaptopurine or methotrexate in 36% of patients with CD and absence of background therapy in the PsO RCT. The analyses further confirm the biosimilarity of adalimumab-adbm with the adalimumab RP across IMiDs and provide supporting evidence that adalimumab-adbm is an interchangeable biosimilar with consistent clinical results in patients originally treated with the RP.

Trial registration numbers VOLTAIRE-RA (NCT02137226; EudraCT 2012-002945-40); VOLTAIRE-CD (NCT02871635; EudraCT 2016-000612-14); VOLTAIRE-PsO (NCT02850965; EudraCT 2016-000613-79).

INTRODUCTION

The monoclonal antibody (mAb) adalimumab-adbm (Cyltezo, Boehringer Ingelheim) is

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study used a fully validated single-bridging electrochemiluminescence assay (ECLIA) following acid dissociation to measure the presence and titre of antidrug antibodies (ADAs).
- ⇒ ECLIA is not only simpler and faster than ELISA but also provides more sensitive and precise results. ECLIA has a far higher drug tolerance than ELISA, allowing ADA levels to be detected at any time point in the VOLTAIRE trials.
- ⇒ While the same treatments and analysis methods were used across the different VOLTAIRE trials, there were important differences between the background medications and patient populations that were included in each trial.
- ⇒ Comparisons to immunogenicity data from previous trials may be complicated by the increased sensitivity and stringency demonstrated by current immunogenicity assays and by the different visit schedules among the trials.

approved in the USA as an interchangeable biosimilar to the adalimumab reference product (RP; Humira, AbbVie).^{1–3} Adalimumab-adbm and adalimumab RP have structural similarity, comparable activity in blocking tumour necrosis factor (TNF), and are pharmacokinetically bioequivalent.^{4,5} The phase III VOLTAIRE clinical development programme demonstrated that the efficacy of adalimumab-adbm was equivalent to adalimumab RP with comparable safety and immunogenicity in patients with moderate to severely active rheumatoid arthritis (VOLTAIRE-RA), moderate to severely active Crohn's disease (VOLTAIRE-CD) or moderate-to-severe chronic plaque psoriasis (VOLTAIRE-PsO).^{6–8} In VOLTAIRE-RA and VOLTAIRE-CD, treatment benefits were



Table 1 Features and properties of the multicentre, active-comparator VOLTAIRE randomised controlled trials

RCT details	VOLTAIRE-RA ⁶ (NCT02137226)	VOLTAIRE-CD ⁷ (NCT02871635)	VOLTAIRE-PsO ⁸ (NCT02850965)
Participants	Moderate-to-severe RA	Active CD (CDAI 220–450)	Moderate-to-severe PsO
Primary outcome	ACR20 at weeks 12 and 24	CDAI decrease ≥ 70 points at week 4	PASI 75 at week 16
Background therapy	Methotrexate (15–25 mg/week; 10–14 mg/week permitted if intolerant)	Stable doses of DMARDs allowed	No
Study duration	58 weeks	56 weeks	34 weeks
Intervention (n)	Adalimumab-adbm (n=324) Adalimumab RP (n=321)	Adalimumab-adbm (n=72) Adalimumab RP (n=75)*	Adalimumab-adbm (n=159) Adalimumab RP (n=158)
Dosage regimen	40 mg every 2 weeks	Loading doses of 160 mg on day 1 and 80 mg on day 15 then 40 mg every 2 weeks maintenance	Loading doses of 80 mg on day 1 and 40 mg day 8 then 40 mg every 2 weeks every two maintenance
Previous biologics	Allowed	Allowed	Allowed
Key time points†	Week 24: Rerandomisation adalimumab RP group (either continued adalimumab RP or switched to adalimumab-adbm) and dummy rerandomisation adalimumab-adbm group (continued medication)‡	Week 4: CDAI response evaluated§; responders continued in trial to week 24: patients unmasked; adalimumab RP group switched to adalimumab-adbm, adalimumab-adbm group continued medication	Week 16 PASI 50 response evaluated¶; responders continued to week 24
Immunogenicity time points	Baseline, post dose: weeks 1, 2, 4, 12, 24, 40 and 48	Baseline, post dose: weeks 4, 24 and 48	Baseline, post dose: weeks 16 and 24

*Randomisation stratified by previous exposure to infliximab (yes vs no) and simple endoscopic score for CD at screening (<16 vs ≥ 16).

†Each trial included 10-week safety follow-up.

‡Qualifying patients could enter open-label extension (VOLTAIRE-RAext; NCT02640612).

§ ≥ 70 -point decrease from baseline.

¶ $\geq 50\%$ reduction from baseline.

ACR20, American College of Rheumatology 20% response criteria; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; DMARD, disease-modifying antirheumatic drug; PASI, Psoriasis Area and Severity Index; PASI 50/PASI 75, 50% or 75% reduction in PASI, respectively; PsO, chronic plaque psoriasis; RA, rheumatoid arthritis; RP, reference product.

maintained in patients who received adalimumab RP and were switched to adalimumab-adbm.⁶⁷

TNF inhibitor (TNFi) treatment is unsuccessful in up to 40% of patients according to European League Against Rheumatism response criteria, either because of failure to attain any response or loss of response over time.⁹ One reason for loss of response is the development of anti-drug antibodies (ADAs), as these newly formed immune complexes are biologically less active or cleared more readily by the kidneys.^{10–11} In essence, ADAs lower the effective dose of therapeutic mAb by limiting its bioavailability in the circulation. The presence of ADAs not only results in subtherapeutic serum drug concentrations and treatment resistance but also leads to adverse effects such as infusion reactions/anaphylaxis, drug-induced lupus and vasculitis-like events.^{12–14}

The incidence of ADAs to TNFi varies between mAbs due to factors such as structure, extent of humanisation and route of administration and between trials for various reasons, including patient-related factors (eg, genetic predisposition, concomitant medication use), disease activity, treatment-related factors (eg, sampling timing,

treatment duration) and the ADA detection methodology used (eg, type of assay and drug trough levels).^{9–14–17} Detecting and characterising ADAs with respect to serum titre and neutralising capacity are key to understanding their relationship with safety and efficacy outcomes.¹⁸ ELISAs are often used for ADA screening, but their utility is limited by a low drug tolerance—the maximal amount of free drug in the sample that still results in a detectable ADA signal—and their capacity to detect only free ADAs.

In VOLTAIRE, a fully validated single-bridging electrochemiluminescence assay (ECLIA) following acid dissociation was used to measure the presence of ADAs and their titres.⁵ ECLIA is not only simpler and faster than ELISA but also provides more sensitive and precise results.¹⁹ Importantly, ECLIA has a far higher drug tolerance than ELISA, allowing ADA levels to be detected at any time point in the VOLTAIRE trials.⁵ The aim of this post hoc analysis was to compare the immunogenicity of adalimumab-adbm and adalimumab RP in VOLTAIRE-RA, VOLTAIRE-CD and VOLTAIRE-PsO. ADAs and neutralising antibodies (nAbs) were assessed to identify at what point they were first detectable, determine the proportion of patients

Table 2 Patient demographics and clinical characteristics at baseline in VOLTAIRE-RA, VOLTAIRE-CD and VOLTAIRE-PsO RCTs (safety analysis sets)

Parameter	VOLTAIRE-RA			VOLTAIRE-CD			VOLTAIRE-PsO		
	Adalimumab-adbm (n=324)	Adalimumab RP (n=321)	Adalimumab RP (n=72)	Adalimumab-adbm (n=72)	Adalimumab RP (n=75)	Adalimumab-adbm (n=159)	Adalimumab RP (n=158)	Adalimumab RP (n=158)	Adalimumab RP (n=158)
Age, years									
Mean (SD)	53.7 (12.0)	53.6 (11.3)	37.4 (13.4)	33.2 (11.5)	42.1 (12.8)	44.7 (13.9)	44.7 (13.9)	44.7 (13.9)	44.7 (13.9)
Female, n (%)	267 (82.4)	269 (83.8)	33 (45.8)	31 (41.3)	58 (36.5)	56 (35.4)	56 (35.4)	56 (35.4)	56 (35.4)
Race, n (%)									
White	309 (95.4)	304 (94.7)	69 (95.8)	74 (98.7)	157 (98.7)	156 (98.7)	156 (98.7)	156 (98.7)	156 (98.7)
Asian	8 (2.5)	6 (1.9)	1 (1.4)	0	0	0	0	0	0
Black/African American	6 (1.9)	7 (2.2)	1 (1.4)	1 (1.3)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Other	1 (0.3)	4 (1.2)	1 (1.4)	0	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Prior biological agent, n (%)	85 (26.2)	86 (26.8)	3 (4.2)*	5 (6.7)*	30 (19.0)	30 (19.1)	30 (19.1)	30 (19.1)	30 (19.1)
Median number of previous DMARDs	2	2	-	-	-	-	-	-	-

*Infliximab.

CD, Crohn's disease; DMARDs, disease-modifying antirheumatic drugs; PsO, chronic plaque psoriasis; RA, rheumatoid arthritis; RCTs, randomised controlled trials; RP, reference product.

with ADAs and nAbs over time and explore any observed effects on clinical responses.

METHODS

Study designs and participants

The design, methods and conduct of the phase III VOLTAIRE-RA, VOLTAIRE-CD and VOLTAIRE-PsO randomised controlled trials (RCTs) have been described previously and are summarised in [table 1](#).⁶⁻⁸ In addition to the different patient populations, although prior adalimumab use was an exclusion criterion in all three trials, there are important differences between the background medications given in each trial. All patients in VOLTAIRE-RA had to have received stable background methotrexate therapy for ≥12 weeks prior to enrolment, which was not used in VOLTAIRE-CD or VOLTAIRE-PsO.⁶⁻⁸ Patients in VOLTAIRE-CD were either naive to TNFi therapy or had previously been treated with infliximab and developed secondary resistance due to anti-infliximab ADA formation or had become intolerant.⁷ Patients in VOLTAIRE-CD and VOLTAIRE-PsO received a loading dose of either adalimumab-adbm or adalimumab RP, whereas VOLTAIRE-RA patients were initiated on 40mg every 2 weeks (ie, the maintenance dose in all three trials). Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of the research.

Assessments

Immunogenicity

Fully validated assays for the detection and quantification of ADAs and nAbs have been described elsewhere.⁵ In brief, ADA positivity and titres were determined using acid dissociation followed by single-bridging ECLIA (MSD platform; Meso Scale Diagnostics, USA).⁵ Acid dissociation followed by ECLIA for detection of ADAs is independent of serum drug concentrations. In VOLTAIRE, assay sensitivity was 50ng/mL and drug tolerance was ≥30µg/mL (free drug) at the low positive control level. The presence of nAbs was determined using a cell-based antibody-dependent cell-mediated cytotoxicity method with a sensitivity of 1.5µg/mL.

Efficacy

The primary endpoints that were prospectively evaluated in VOLTAIRE-RA, VOLTAIRE-CD and VOLTAIRE-PsO were American College of Rheumatology 20% response criteria (ACR20), Crohn's Disease Activity Index (CDAI) decrease ≥70 points and 75% reduction in Psoriasis Area and Severity Index (PASI 75), respectively.⁶⁻⁸ In VOLTAIRE-RA, coprimary endpoints were the percentage of patients with ACR20 responses at weeks 12 and 24.⁶ The percentage of patients with CDAI scores ≥70 points at week 4 was the primary endpoint in VOLTAIRE-CD⁷ and the percentage of patients with PASI 75 responses at week 16 was the primary endpoint in VOLTAIRE-PsO.⁸

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Table 3 Immunogenicity in the phase III VOLTAIRE RCTs ⁶⁻⁸						
Status	VOLTAIRE-RA		VOLTAIRE-CD		VOLTAIRE-PsO	
	Adalimumab-adbm (n=324)	Adalimumab RP (n=321)	Adalimumab-adbm (n=72)	Adalimumab RP (n=75)	Adalimumab-adbm (n=159)	Adalimumab RP (n=158)
Antibody first detectable						
ADA	Baseline	Baseline	Baseline	Week 4	Baseline	Baseline
nAb	Baseline	Baseline	Week 4	Week 4	Baseline	Baseline
ADA titre at primary endpoint, median (Q1, Q3)						
	16 (4, 64) at W12 32 (8, 128) at W24	16 (4, 64) at W12 32 (8, 96) at W24	16.0 (2.0, 32.0) at W4	2.5 (1.0, 34.0) at W4	32.0 (16, 128) at W16	32.0 (16, 128) at W16
Proportion of patients with antibodies over time						
ADA positive	*	*				
Baseline	3.4% (11/323)	6.5% (21/321)	4.3% (3/69)	0% (0/74)	10.7% (17/159)	10.8% (17/158)
Week 4	20.1% (64/319)	19.9% (63/316)	20.6% (14/68)	5.5% (4/73)		
Week 16					68.2% (101/148)	71.8% (107/149)
Week 24	43.6% (129/296)	47.8% (144/301)	69.5% (41/59)	45.9% (28/61)	75.3% (113/150)	77.9% (113/145)
Week 48	41.9% (119/284)	42.6% (120/282)	63.5% (33/52)	51.8% (29/56)		
nAb positive	*	*				
Baseline	2.8% (9/323)	5.0% (16/321)	0% (0/69)	0% (0/74)	0.6% (1/159)	1.9% (3/158)
Week 4	6.6% (21/319)	7.6% (24/316)	8.8% (6/68)	2.7% (2/73)		
Week 16					54.1% (80/148)	55.7% (83/149)
Week 24	16.2% (48/296)	20.9% (63/301)	35.6% (21/59)	23.0% (14/61)	52.7% (79/150)	57.2% (83/145)
Week 48	19.4% (55/284)	17.7% (50/282)	25.0% (13/52)	19.6% (11/56)		
*Reported in the randomised population at baseline. ADA, antidrug antibody; CD, Crohn's disease; nAb, neutralising antibody; PsO, chronic plaque psoriasis; Q, quarter; RA, rheumatoid arthritis; RCTs, randomised controlled trials; RP, reference product; W, week.						

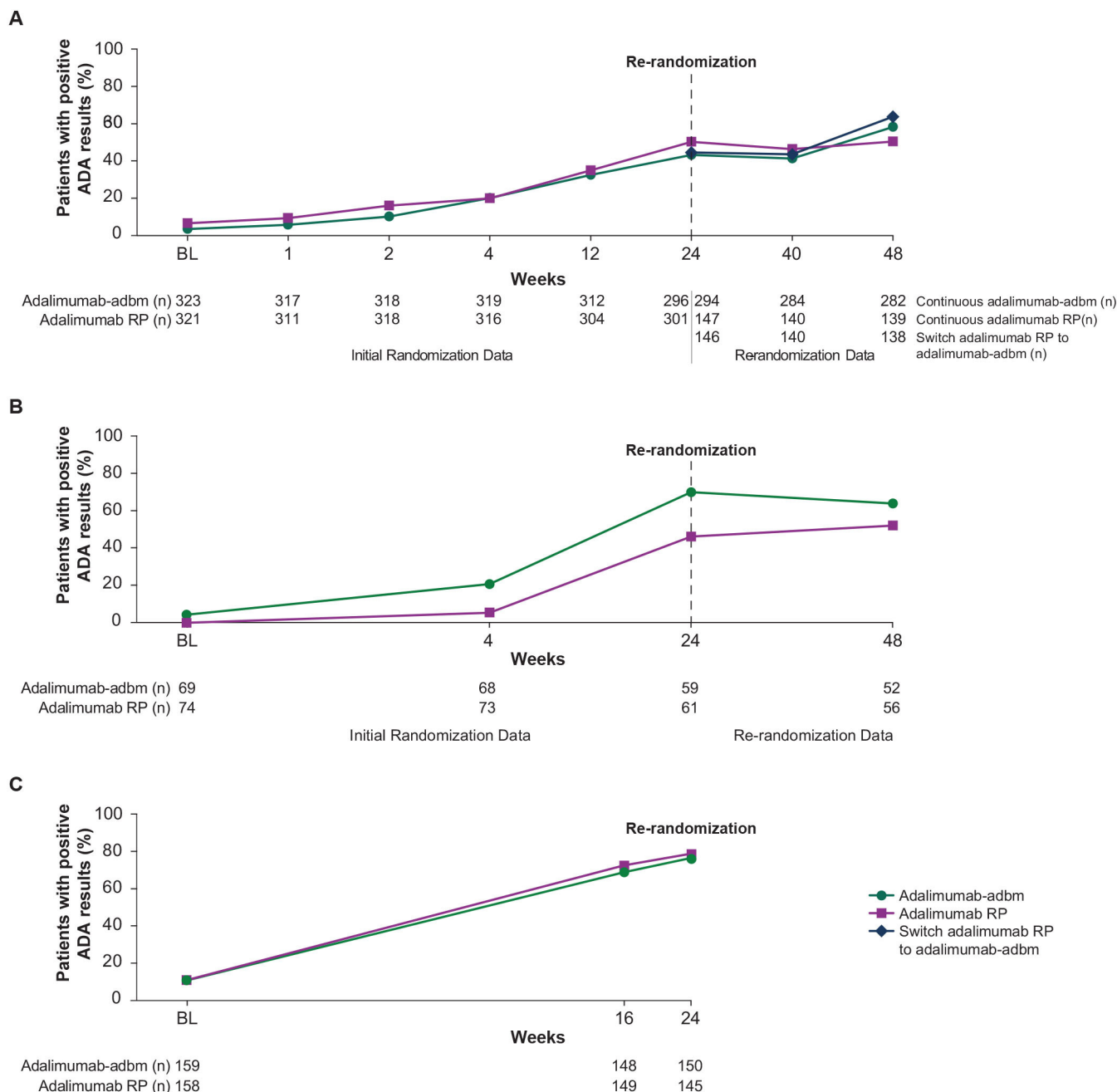


Figure 1 Time course of ADA development in (A) VOLTAIRE-RA, (B) VOLTAIRE-CD and (C) VOLTAIRE-PsO (safety analysis sets). ADA, antidrug antibody; CD, Crohn's disease; PsO, plaque psoriasis; RA, rheumatoid arthritis; RP, reference product.

Statistics

All patients who received ≥ 1 dose of adalimumab-adbm or adalimumab RP in the VOLTAIRE clinical trials were included in the immunogenicity analysis (safety analysis set). Immunogenicity was assessed as the proportion of patients with ADAs and/or nAbs at baseline and prespecified time points post dose (table 1). Patient-level immunogenicity data were analysed separately in each VOLTAIRE RCT and by sex. Differences in study population and methodology precluded formal comparisons between trials. Clinical responses based on the primary efficacy outcome for each RCT were reported according to ADA and nAb positivity. Non-responder imputation

was used for patients who discontinued prior to that time point and last observation carried forward for patients with missing data.

Continuous and categorical characteristics were summarised descriptively by treatment and by disease indication, with categorical data summarised as N (%), normal continuous data as mean (SD) and skewed continuous data as median (Q1, Q3). Incidence rates were calculated by disease indication and by treatment arm. Kaplan-Meier estimates will be used to display the distribution of time to first event for each treatment group by disease indication with 95% CIs found using Greenwood's variance estimate.

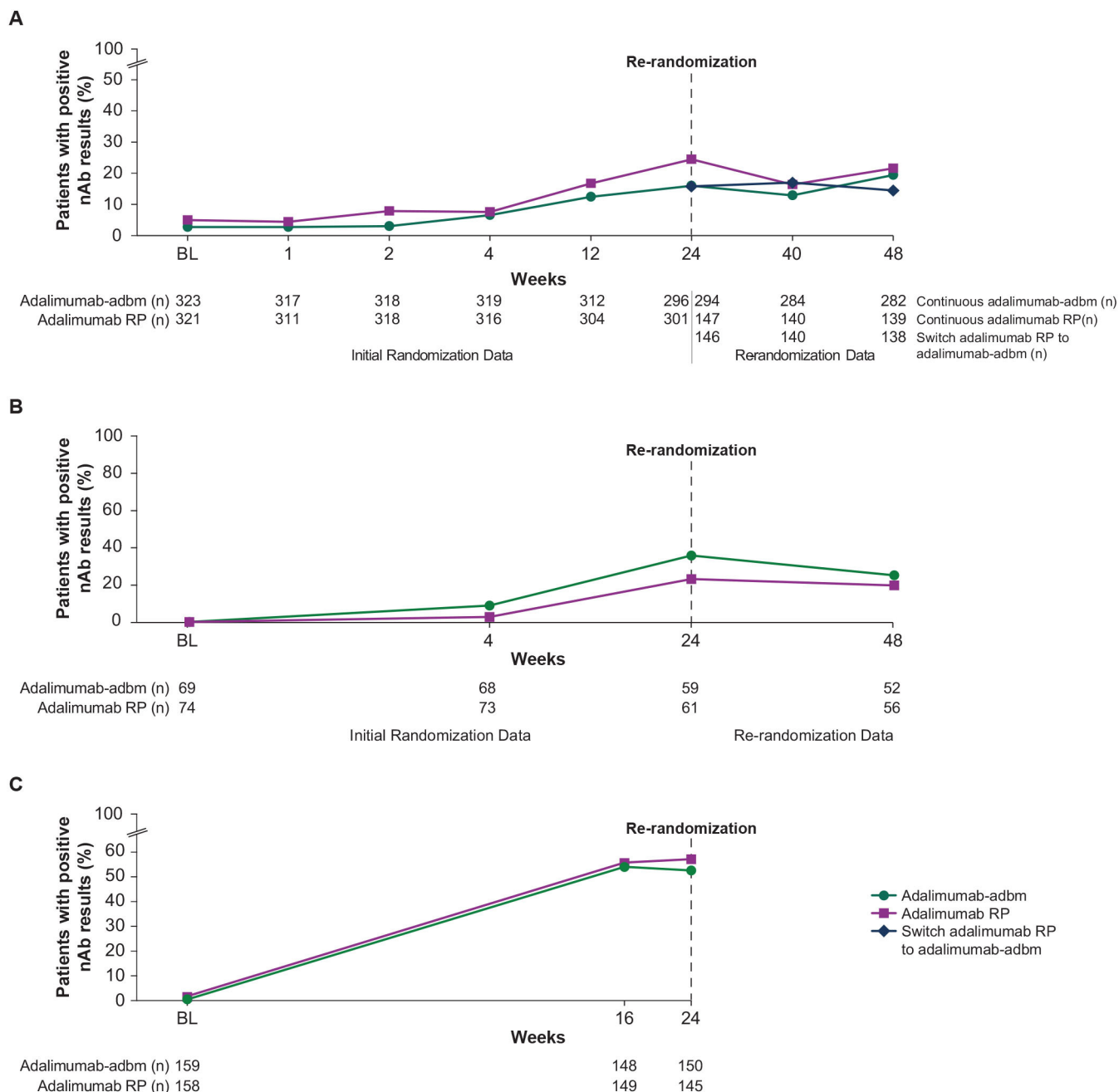


Figure 2 Time course of nAb development in (A) VOLTAIRE-RA, (B) VOLTAIRE-CD and (C) VOLTAIRE-PsO RCTs (safety analysis sets). CD, Crohn's disease; nAb, neutralising antibody; PsO, plaque psoriasis; RA, rheumatoid arthritis; RCT, randomised controlled trial; RP, reference product.

All data analyses were performed using descriptive statistics compiled by SAS software (SAS, Cary, North Carolina, USA; V.9.4 or higher).

RESULTS

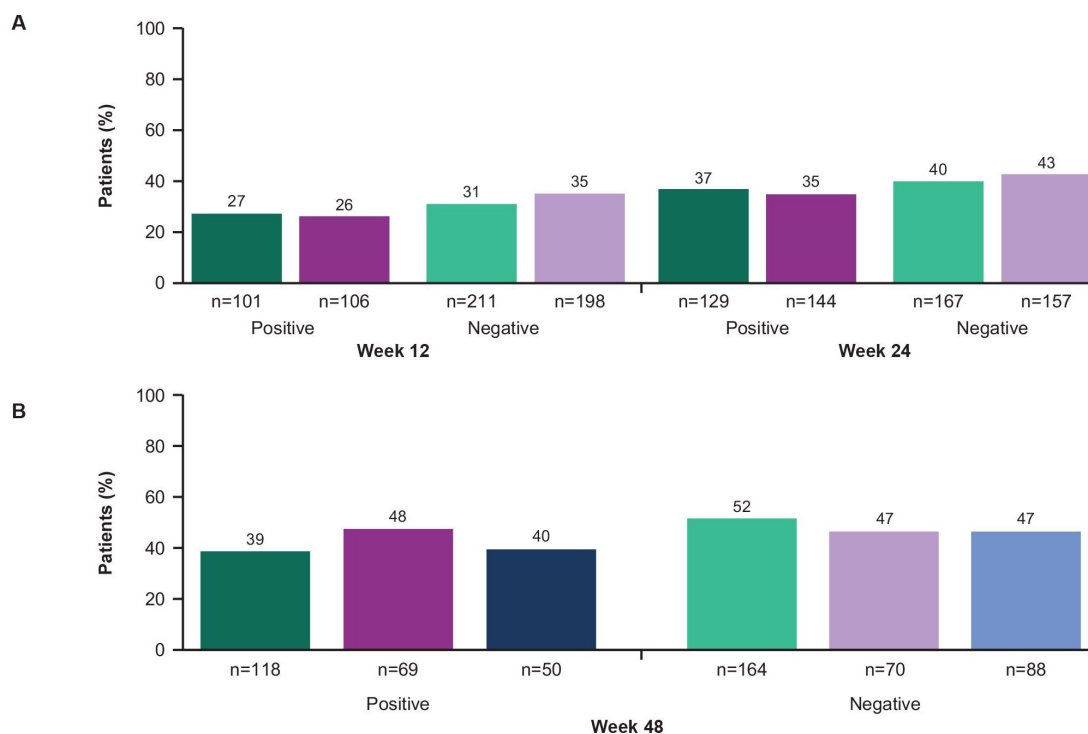
Study populations

The analysis populations are described in table 2. The average age of patients in the VOLTAIRE-RA population was around 10 years older than the VOLTAIRE-PsO population, which in turn was 5–10 years older than the average age of patients in the VOLTAIRE-CD population. More

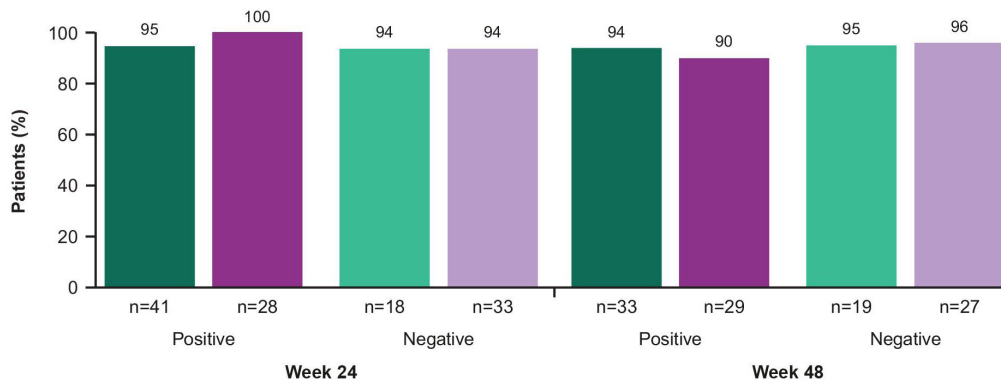
than three-quarters of patients (83.1%) in VOLTAIRE-RA were women, whereas women comprised less than half of the population in VOLTAIRE-CD (43.5%) and VOLTAIRE-PsO (36.0%). Across all VOLTAIRE trials, >95% were White patients.

A significant minority of patients in VOLTAIRE-RA and VOLTAIRE-PsO trials had previously received a biologic agent (19%–27%) compared with <10% of VOLTAIRE-CD patients. In VOLTAIRE-RA, the mean (SD) dosage of background methotrexate at baseline was 16.3 (3.6) mg/week in the adalimumab-adbm

VOLTAIRE-RA (ACR20)



VOLTAIRE-CD (CDAI decrease ≥ 70 points)



VOLTAIRE-PsO (PASI 75)

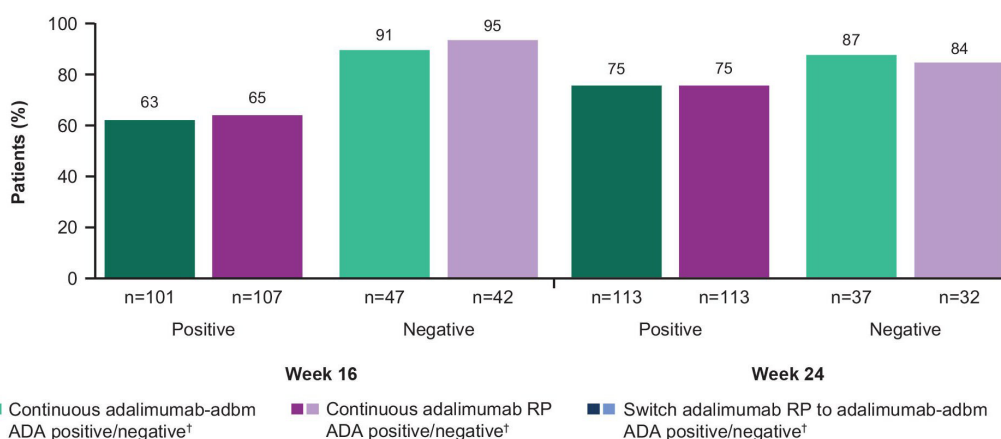


Figure 3 Frequency of patients meeting primary clinical response criteria per treatment arm stratified by ADA titre positivity (safety analysis sets) for VOLTAIRE-RA, VOLTAIRE-CD and VOLTAIRE-PsO RCTs. ACR20, American College of Rheumatology 20% response criteria; ADA, antidrug antibody; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; PASI, Psoriasis Area and Severity Index; PASI 50 / PASI 75, 50% or 75% reduction in PASI, respectively; PsO, plaque psoriasis; RA, rheumatoid arthritis; RCT, randomised controlled trial; RP, reference product.

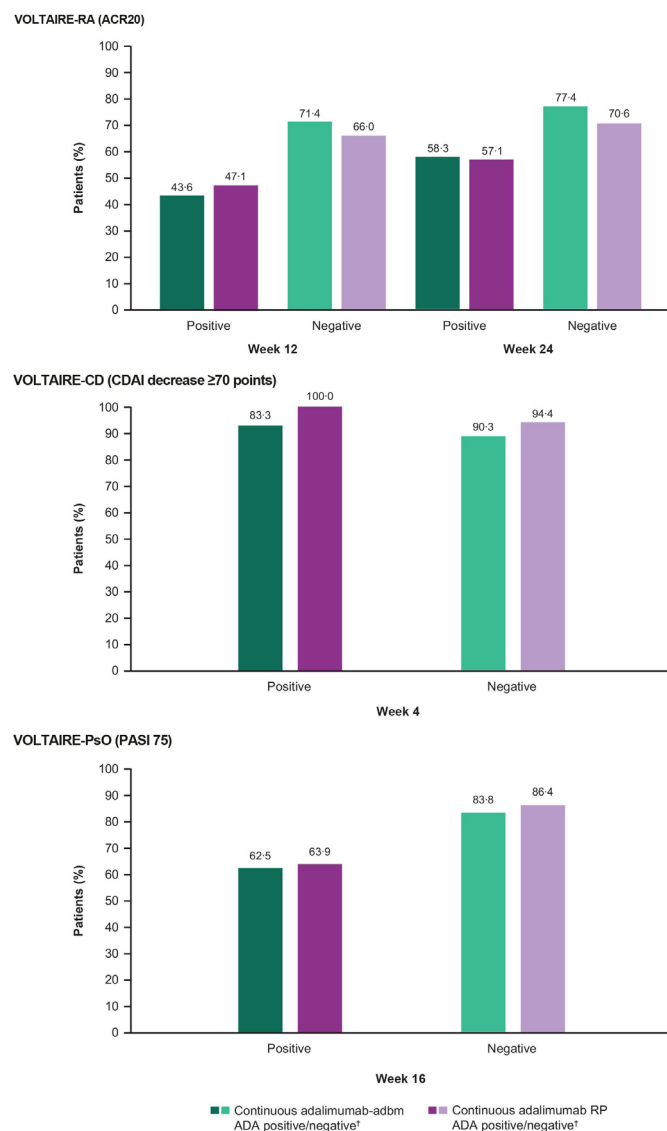


Figure 4 Frequency of patients meeting primary clinical response criteria per treatment arm stratified by nAb titre positivity (safety analysis sets) for VOLTAIRE-RA, VOLTAIRE-CD and VOLTAIRE-PsO RCTs. ACR20, American College of Rheumatology 20% response criteria; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; nAb, neutralising antibody; PASI, Psoriasis Area and Severity Index; PASI 50 / PASI 75, 50% or 75% reduction in PASI, respectively; RCT, randomised controlled trial; RA, rheumatoid arthritis; RCT, randomised controlled trial; RP, reference product.

arm and 16.8 (3.9) mg/week in the adalimumab RP arm. In VOLTAIRE-CD, stable doses of azathioprine, 6-mercaptopurine or methotrexate were received by 36% of patients.

Immunogenicity

Although patients in all three trials were excluded for prior adalimumab use, positive ADA titres were detected at baseline in all VOLTAIRE treatment arms except the adalimumab RP group in VOLTAIRE-CD (table 3). ADA titres increased over time in all VOLTAIRE treatment arms, with evidence of a plateau at week 24 in

VOLTAIRE-RA and VOLTAIRE-CD (figure 1). Incidence of ADAs was lowest in VOLTAIRE-RA and highest in VOLTAIRE-PsO. In VOLTAIRE-RA, incidence of ADAs was similar in the adalimumab-adbm and adalimumab RP arms to week 24 and after rerandomisation to week 48. Incidence of ADAs was also similar in both treatment arms in VOLTAIRE-PsO, but higher in the adalimumab-adbm arm than the adalimumab RP arm of VOLTAIRE-CD.

nAbs were detected at baseline in both treatment arms of VOLTAIRE-RA and VOLTAIRE-PsO and at week 4 in both treatment arms of VOLTAIRE-CD (table 3). The trajectory of nAb incidence was similar to that of ADA incidence (figure 2). nAb development was lowest in VOLTAIRE-RA and VOLTAIRE-CD and highest in VOLTAIRE-PsO. nAb development was similar in the adalimumab-adbm and adalimumab RP arms at all time points in VOLTAIRE-RA and VOLTAIRE-PsO and appeared higher in the adalimumab-adbm arm in VOLTAIRE-CD.

Across treatment arms in VOLTAIRE-RA and VOLTAIRE-PsO, attainment of the primary efficacy endpoint was less frequent among patients with positive ADA and nAb titres (figures 3 and 4), although ADA and nAb development appeared to have no effect on the primary endpoint in VOLTAIRE-CD. There was no difference between adalimumab-adbm and adalimumab RP with respect to the primary endpoints in VOLTAIRE-PsO, and efficacy outcomes were not affected by positive ADA or nAb titres.

The proportion of ADA-positive and nAb-positive patients at baseline and throughout in VOLTAIRE-RA and VOLTAIRE-PsO RCTs did not differ by patient sex (online supplemental tables S1–S3). In contrast, in VOLTAIRE-CD approximately two times as many women than men developed ADA-positive and nAb-positive titres in the adalimumab RP arm, though this difference was not seen in the adalimumab-adbm arm.

DISCUSSION

The immunogenicity data for adalimumab-adbm has been well characterised across the VOLTAIRE trials, providing information on the experience with adalimumab-adbm relative to adalimumab RP across different immune-mediated inflammatory diseases and by sex. These analyses confirm the biosimilarity of adalimumab-adbm with adalimumab RP in adult patients with RA, CD and PsO. ADA and nAb development were similar in the two treatment arms in VOLTAIRE-RA and VOLTAIRE-PsO, appearing higher in the adalimumab-adbm arm of VOLTAIRE-CD. However, the presence of ADAs and nAbs had no bearing on the primary efficacy outcomes in any of the trials.

Treatments, sample timings and analysis methods were consistent across the different VOLTAIRE trials. However, there remain important differences between the patient populations and consequentially, in the background medications and that were included in each trial. Patients with RA and CD regularly receive glucocorticoid prescriptions,

both oral and parenteral. However, glucocorticoids do not abrogate or decrease ADA responses; agents that do mitigate these responses are antiproliferative agents, specifically methotrexate, azathioprine, leflunomide and mycophenolate mofetil, if given with the first dose of the biologic therapy. Patients in the VOLTAIRE-RA trial received methotrexate as background therapy, while stable doses of azathioprine, 6-mercaptopurine or methotrexate were being given in 36% of patients in VOLTAIRE-CD, contrasting with an absence of these background therapies in VOLTAIRE-PsO. Higher rates of ADA development occurred in VOLTAIRE-PsO than VOLTAIRE-RA and VOLTAIRE-CD, likely owing to this lack of background therapy in the VOLTAIRE-PsO trial. ADAs and nAb titres after exposure to adalimumab-adbm and adalimumab RP were comparable in male and female patients across the VOLTAIRE trials, aligning with results of a multicentre retrospective cohort study.²⁰ In addition to limitations resulting from differences in visit schedules, making any comparisons to immunogenicity data from historical RP is complicated by the increased sensitivity and stringency demonstrated by current immunogenicity assays used for biosimilars.²¹ Acid dissociation followed by the more sensitive ECLIA for detection of ADAs, as used in this study programme, is not dependent on serum drug concentrations. The positive ADA titres detected at baseline may have been due to false positives. While some patients had been exposed to other biologics prior to these studies, previous immunogenicity studies have shown no indication of cross-reactivity to other biologic agents including other TNF inhibitors.²¹ Finally, it should be noted that the data presented here are from patients with PsO, RA or CD and may not be applicable to other indications (eg, ankylosing spondylitis) for which adalimumab-adbm has also been approved.¹

ADA titres, ADAs and nAbs were first measurable at day 1 in small numbers and increased over time. Immunogenicity parameters were similar between the RP and biosimilar throughout the period covered in each RCT, and the presence of ADAs or nAbs had no apparent effect on efficacy. These analyses further confirm the biosimilarity of adalimumab-adbm with adalimumab RP in adult patients with RA, CD and PsO.

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Competing interests VS reports consulting for AbbVie, Amgen, Aria, AstraZeneca, Bayer, Bioventus, BlackRock, BMS, Boehringer Ingelheim, Celltrion, ChemoCentryx, Equillium, Gilead, Genentech/Roche, Glenmark, GSK, Horizon, Inmedix, Janssen, Kiniksa, Kypha, Lilly, Merck, MiMedx, Novartis, Pfizer, Priovant, Regeneron, Rheos, R-Pharma, Samsung, Sandoz, Sanofi, Scipher, Setpoint, Sorrento, Spherix and Tonix. SB reports previous employment by Boehringer Ingelheim Pharmaceuticals. DM reports previous employment by Boehringer Ingelheim Pharmaceuticals.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The protocol was approved by the applicable independent ethics committee or institutional review board at each participating site (see individual study publications for details),^{6–8} and the study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, providing regulatory activities are complete and other criteria are met. Researchers should use the <https://vivli.org/> link to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

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<SUPPLEMENTAL MATERIAL>

Table S1 Antibody development in the men and women of VOLTAIRE-RA

Status	Adalimumab-adbm (n=324)		Adalimumab RP (n=321)	
	Men (n=57)	Women (n=267)	Men (n=52)	Women (n=269)
Antibody first detectable				
ADA	Week 1	Baseline	Baseline	Baseline
nAb	Week 2	Baseline	Baseline	Baseline
ADA titre at primary endpoint, mean (SD) [median: Q1,Q3]	27.7 (37.0) at W12	58.0 (98.7) at W12	503.3 (1922.6) at W12	322.8 (1084.6) at W12
	[8: 4, 32]	[16: 4, 64]	[6: 6,64]	[16: 4, 64]
	122.8 (250.0) at W24	168.4 (804.2) at W24	195.4 (339.4) at W24	315.6 (1704.3) at W24
	[32: 4, 64]	[32: 8, 128]	[64: 16, 64]	[32: 8, 128]
Proportion of patients with antibodies over time*				
ADA positive				
Baseline	0% (0/57)	4.1% (11/266)	11.5% (6/52)	5.6% (15/269)
Week 1	1.9% (1/53)	6.4% (17/264)	15.7% (8/51)	8.1% (21/260)
Week 2	3.8% (2/53)	11.3% (30/265)	13.7% (7/51)	16.5% (44/267)
Week 4	12.7% (7/55)	21.6% (57/264)	23.5% (12/51)	19.2% (51/265)
Week 12	24.5% (13/53)	34.0% (88/259)	38.3% (18/47)	34.2% (88/257)
Week 24	38.0% (19/50)	44.7% (110/246)	53.2% (25/47)	46.9% (119/254)
Week 40	37.0% (17/46)	42.5% (102/240)	52.3% (23/44)	43.4% (105/242)
Week 48	37.5% (18/48)	42.8% (101/236)	51.2% (22/43)	41.0% (98/239)
nAb positive				
Baseline	0% (0/57)	3.4% (9/266)	9.6% (5/52)	4.1% (11/269)
Week 1	0% (0/53)	3.4% (9/264)	5.9% (3/51)	4.2% (11/260)
Week 2	1.9% (1/53)	3.4% (9/265)	13.7% (7/51)	6.7% (18/267)
Week 4	3.6% (2/55)	7.2% (19/264)	9.8% (5/51)	7.2% (19/265)
Week 12	7.5% (4/53)	13.5% (35/259)	21.3% (10/47)	16.0% (41/257)
Week 24	14.0% (7/50)	16.7% (41/246)	25.5% (12/47)	20.1% (51/254)
Week 40	6.5% (3/46)	14.2% (34/240)	20.5% (9/44)	16.1% (39/242)
Week 48	14.6% (7/48)	20.3% (48/236)	25.6% (11/43)	16.3% (39/239)

*Reported in the randomised population at baseline.

ADA, anti-drug antibody; nAb, neutralising antibody; RA, rheumatoid arthritis; RP, reference product; SD, standard deviation; W, week.

Table S2 Antibody development in the men and women of VOLTAIRE-CD

Status	Adalimumab-adbm (n=72)		Adalimumab RP (n=75)	
	Men (n=39)	Women (n=33)	Men (n =44)	Women (n=31)
Antibody first detectable				
ADA	Baseline	Baseline	Week 4	Week 4
nAb	Week 4	Week 4	Week 24	Week 4
ADA titre at primary endpoint, mean (SD) [median: Q1, Q3]	1095.0 (2873.0) at W4 [10: 1.5, 272]	51.7 (100.3) at W4 [16: 4, 16]	32.5 (44.6) at W4 [32.5: 1, 64]	2.5 (2.1) at W4 [10: 3, 16]
Proportion of patients with antibodies over time				
ADA positive				
Baseline	5.4% (2/37)	3.1% (1/32)	0% (0/43)	0% (0/31)
Week 4	21.6% (8/37)	19.4% (6/31)	4.8% (2/42)	6.5% (2/31)
Week 24	65.6% (21/32)	74.1% (20/27)	32.4% (11/34)	63.0% (17/27)
Week 48	64.3% (18/28)	62.5% (15/24)	37.5% (12/32)	70.8% (17/24)
nAb positive				
Baseline	0% (0/37)	0% (0/32)	0% (0/43)	0% (0/31)
Week 4	10.8% (4/37)	6.5% (2/31)	0% (0/42)	6.5% (2/31)
Week 24	31.3% (10/32)	40.7% (11/27)	14.7% (5/34)	33.3% (9/27)
Week 48	25.0% (7/28)	25.0% (6/24)	15.6% (5/32)	25.0% (6/24)

ADA, anti-drug antibody; CD, Crohn’s disease; nAb, neutralising antibody; RP, reference product; SD, standard deviation; W, week.

Table S3. Antibody development in the men and women of VOLTAIRE-PsO.

Status	Adalimumab-adbm (n=159)		Adalimumab RP (n=158)	
	Men (n=101)	Women (n=58)	Men (n=102)	Women (n=56)
Antibody first detectable				
ADA	Baseline	Baseline	Baseline	Baseline
nAb	Baseline	Week 16	Baseline	Baseline
ADA titre at primary endpoint, median (range) [Q1, Q3]	32 (1–16,384) at W16 [16, 128]	48 (1–1024) at W16 [32, 128]	32 (2–2048) at W16 [16, 128]	32 (2–16,384) at W16 [16, 64]
Proportion of patients with antibodies over time				
ADA positive				
Baseline	12.9% (13/101)	6.9% (4/58)	12.7% (13/102)	7.1% (4/56)
Week 16	69.9% (65/93)	65.5% (36/55)	68.0% (96/97)	78.8% (41/52)
Week 24	76.8% (73/95)	72.7% (40/55)	76.1% (70/92)	81.1% (43/53)
nAb positive				
Baseline	1.0% (1/101)	0% (0/58)	2.0% (2/102)	1.8% (1/56)
Week 16	54.8% (51/93)	52.7% (29/55)	50.5% (49/97)	65.4% (34/52)
Week 24	54.7% (52/95)	49.1% (27/55)	52.2% (48/92)	66.0% (35/53)

ADA, anti-drug antibody; nAb, neutralising antibody; PsO, chronic plaque psoriasis; RP, reference product; W, week.