Efficacy and prognostic factors of treatment retention with intravenous abatacept for rheumatoid arthritis: 24-month results from an international, prospective, real-world study

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Abstract

Objective

To evaluate retention of abatacept over 24 months in patients with rheumatoid arthritis (RA) in routine clinical practice across Europe and Canada.

Methods

ACTION (AbataCepT In rOutiNe clinical practice) was a prospective, observational, multicentre study of adult patients with moderate-to-severe RA who, at their physician's discretion, initiated treatment with intravenous abatacept. Enrolment occurred from May 2008 to December 2010, with up to 30 months of follow-up. The primary endpoint was the abatacept retention rate over 24 months. Crude abatacept retention rate was estimated using the Kaplan-Meier method. Prognostic factors of abatacept retention in patients with ≥1 prior biologic failure were derived from a Cox proportional hazards regression model, accounting for clustered data.

Results

A total of 1137 patients were enrolled (1573 patient-years on abatacept); most (89.2%) had experienced prior biologic failure. The overall crude abatacept retention rate at 24 months was 54.4% (95% confidence interval: 51.3, 57.4). Positivity for both rheumatoid factor and anti-cyclic citrullinated antibody, previous exposure to one or no anti-tumour necrosis factor agents, and cardiovascular comorbidity were prognostic of higher abatacept retention. Erythrocyte sedimentation rate ≥51 mm/hour and introduction of corticosteroid use at abatacept initiation were predictors of lower abatacept retention. Abatacept retention varied according to country. Abatacept was well tolerated without any unexpected safety signals.

Conclusion

In a real-world setting, intravenous abatacept treatment retention was more than 50% at 24 months. The identification of prognostic factors of abatacept retention could support individualised biologic treatment strategies in patients with moderate-to-severe RA.

Key words

abatacept, biological therapy, cohort studies, cyclic citrullinated peptide, rheumatoid arthritis, rheumatoid factor.

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Received on August 16, 2015; accepted in revised form on December 14, 2015.

Competing interests: see list on page 498.

Introduction

In rheumatoid arthritis (RA), treatment may be discontinued for different reasons including lack or loss of initial response and intolerance. Prognostic factors of treatment retention with biologic agents in a real-world setting may aid rheumatologists in making informed treatment decisions on the biologic agent of choice for individual patients.

Few studies have confirmed predictive factors of good clinical response to abatacept (1). Potential predictive/prognostic factors of response to abatacept vary among studies (2-4). As retention may depend on multiple factors, including efficacy and safety, prognostic factors of response may not be the same as those of retention. Consequently, it is important to assess retention rates and prognostic factors of abatacept retention in real-world studies, in which retention rates can be easily measured.

In the French Orencia and Rheumatoid Arthritis (ORA) Registry, anti-cyclic citrullinated peptide (CCP) antibody positivity was significantly more frequent in patients who continued abatacept treatment after 6 months compared with those patients who discontinued abatacept (2). Five-year abatacept retention was higher in patients who were biologic naïve compared with patients with previous exposure to biologic agents in the Swedish Quality Rheumatology Register (5). In a pan-European analysis of nine RA registries, rheumatoid factor (RF) positivity, anti-CCP antibody positivity and prior exposure to biologic agents influenced abatacept retention (6, 7). Additionally, lower abatacept retention was observed in countries with more *versus* less liberal access to biologic agents and higher *versus* lower gross domestic product (8).

The primary objective of ACTION (AbataCepT In rOutiNe clinical practice) is to evaluate long-term intravenous (IV) abatacept retention in adults with RA in clinical practice across Europe and Canada and, as a secondary objective, to identify prognostic factors of abatacept retention. Abatacept can be an effective treatment option both in patients who are biologic naïve and in those who have previously received other biologic agents (9, 10). In this analysis, we assessed prognostic factors of abatacept retention in patients with previous exposure to ≥1 biologic agent. The identification and confirmation of prognostic factors of abatacept retention may aid cost-effective, individualised treatment in patients with an inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or anti-tumour necrosis factors (TNFs).

Methods

Study design

Study design and ethics approvals for the ACTION study have been reported previously (11). ACTION was a non-interventional, multicentre, prospective, observational cohort study. The study setting was routine clinical practice across Europe (initially Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Italy and Netherlands) and Canada. Participating countries were required to have marketing authorisation of abatacept and a reimbursement policy. No product was provided to physicians or patients by the study sponsor.

Table I reflects the evolution of the abatacept product label to earlier use in the treatment paradigm. The 24-month results for patients enrolled in the cohort between May 2008 and December 2010 are reported here.

Follow-up was for up to 30 months or, if the patient discontinued abatacept treatment before the 24-month endpoint, for up to 6 months after abatacept discontinuation. Participating rheumatologists were randomly selected from a comprehensive list to ensure that investigators in each country were geographically well balanced and representative of rheumatologists who treat patients with biologic DMARDs.

Study population

Adults (≥18 years) with moderate-to-severe active RA (American Rheumatology Association 1987 definition (12)) and with available baseline characteristics who, at their physician's discretion, initiated IV abatacept (at time of, or within 3 months prior to, enrolment) in accordance with the Summary of Product Characteristics in Europe and the Product Monograph in Canada

Table I. Evolution of the abatacept product label in Europe and Canada.

Europe From marketing authorisation approval (21 May 2007) until 30 June 2010	Abatacept, in combination with methotrexate, is indicated for the treatment of moderate-to-severe active RA in adult patients who have had an insufficient response or intolerance to other DMARDs including at least one TNF-α inhibitor
Europe From 1 July 2010	Abatacept, in combination with methotrexate, is indicated for the treatment of moderate-to-severe active RA in adult patients who responded inadequately to previous therapy with one or more DMARDs including methotrexate or TNF-α inhibitor
Canada From marketing authorisation approval (29 June 2006)	Abatacept is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs and/or to TNF antagonists. Abatacept may be used as monotherapy or in combination with DMARD therapy

DMARD: disease-modifying anti-rheumatic drug; RA: rheumatoid arthritis; TNF-α: tumour necrosis factor-alpha.

were consecutively enrolled. Patients already participating in a randomised clinical trial in RA were excluded.

Assessments

The primary endpoint was the abatacept retention rate over 24 months. Retention was defined as consecutive time on treatment. Discontinuation from abatacept treatment was recorded by the physician at any follow-up visit. If patients discontinued abatacept, exposure to abatacept was defined as the time between the date of the first and last infusions plus 30 days.

Clinical efficacy was assessed by the European League Against Rheumatism (EULAR) response based on 28-joint Disease Activity Score (DAS28) (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) classified as good/moderate or no response (13); DAS28 (ESR or CRP)-defined remission (<2.6) and low disease activity (LDA; ≤3.2) rates, Clinical Disease Activity Index (CDAI) remission (≤2.8) and LDA (≤10) rates, and Boolean remission rate (14). Physical function was assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI). Improvements in HAQ-DI from baseline of ≥0.3 and ≥0.22 units were classified as a HAQ-DI response and clinically meaningful improvement, respectively (15).

The expected number of infusions for each patient was derived from their exposure to abatacept during the study period. To explore the possibility of dose escalation in overweight and obese patients, treatment adherence was assessed in patients who had previously received ≥1 biologic agent through the ratio of the number of infusions received to the number of infusions expected, by body mass index (BMI; underweight/normal [<25 kg/m^2], overweight [25–30 kg/m^2], obese class I [30–<35 kg/m^2] and obese class II/III [≥35 kg/m^2]) (16). Patients were considered adherent if they received 80–120% of the number of planned doses of abatacept.

Safety was evaluated in accordance with local regulations and registered with the drug manufacturer's global pharmacovigilance department. Related treatment-emergent adverse events (AEs) were assessed by the treating physician and reported to the pharmacovigilance department. The relationship between the study drug and any serious AEs (SAEs) was judged by the treating physician. An SAE was defined as an AE that was fatal or life-threatening, required or extended hospitalisation (except pregnancy), resulted in persistent or significant disability or incapacity, induced a congenital anomaly or birth defect, or was considered an important medical event. All deaths were reported whether or not they were treatment related. Safety was presented for the entire population, regardless of prior or concomitant treatment.

Statistical analyses

Descriptive analysis and crude retention rates were presented for all evaluable patients.

Baseline characteristics and demographics were reported using descriptive statistics including sample size, mean and standard deviation (SD) or proportions. Crude abatacept retention rate with corresponding 95% confidence intervals (CI) was estimated using the Kaplan-Meier method, stratified by anti-TNF exposure prior to abatacept (biologic naïve, 1 previous anti-TNF and ≥2 previous anti-TNFs). Right-censoring at the time of last information available was used for patients without reported abatacept discontinuation and with follow-up of <24 months. Crude retention rates (by number of previous anti-TNFs) were compared using a log-rank test.

Potential prognostic factors of abatacept retention, including socio-demographics, disease characteristics, previous and concomitant therapies at baseline and comorbidities at abatacept initiation, were assessed in patients with previous exposure to ≥1 biologic agent and who were enrolled in countries with a sufficient number of patients to allow between-country effects to be explored. For clinical outcomes, measures 'not done' or 'not available' were considered as specific categories and not as missing. Clinically relevant variables, known risk factors and prognostic factors with $p \leq 0.10$ in the univariate analysis were entered into a multivariate Cox proportional hazards regression model. A sandwich variance estimator was used to account for clustered data. Factors with $p \leq 0.10$ after backward selection in the initial multivariate model were retained in the final model. Co-linearity and interactions between potential prognostic factors were assessed. The aforementioned univariate analysis was re-run on the patient sample with non-missing data on variables included in the final multivariate model. Results are presented as hazard ratios (HRs) with corresponding 95% CI and *p*-values. Additional analyses were performed to assess the consistency of the prognostic factors identified. The first additional analysis accounted for missing data in covariates using multiple imputations by chained equations. In a second analysis, data reported as 'measure not done' or 'measure not

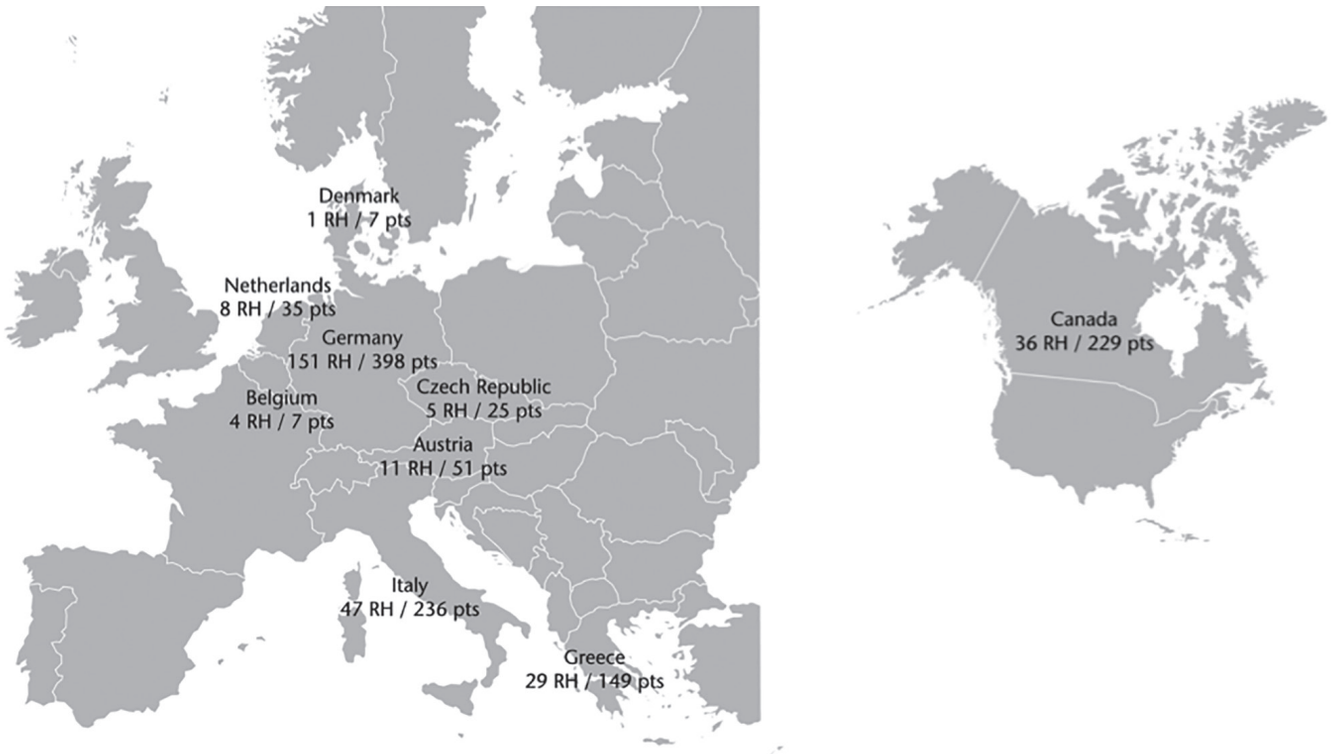


Fig. 1. Patient enrolment. RH: participating sites.

available' were considered missing and were imputed. In a third analysis, HR and 95% CI were adjusted for *a priori* covariates defined based on clinical experience and potential prognostic factors identified in the literature; missing data were imputed as in the first additional analysis. Detailed presentations of each analysis are provided in the supplementary materials, including the prognostic factors tested in the univariate analysis (Table S1), covariates in the third sensitivity analysis (Table S2) and a summary of the analyses conducted (Table S3).

Clinical outcomes were assessed in patients with relevant baseline data, *i.e.* clinical assessment performed no later than 8 days after first abatacept infusion, and are reported at 24 months in patients on treatment at that time point with data available, stratified by prior treatment. Clinical outcomes at 24 months, including EULAR response and HAQ-DI, were compared using Fisher's exact tests (three categories: biologic naïve, 1 previous anti-TNF and ≥2 previous anti-TNFs).

Changes in concomitant csDMARDs after 24 months were compared with baseline in patients with previous exposure to biologic agents who were retained on abatacept at 24 months.

Subgroup analyses were performed in patients with previous exposure to biologic agents; retention was stratified by treatment pattern at abatacept initiation (monotherapy or combination with csDMARDs [with or without methotrexate; MTX]) and BMI.

Results

Study population

Between May 2008 and December 2010, a total of 1137 patients were enrolled in the first cohort of the ACTION study (Cohort A) from 9 countries by 292 investigators (Fig. 1), representing 1573 patient-years on abatacept (last patient's last visit: 25 April 2013).

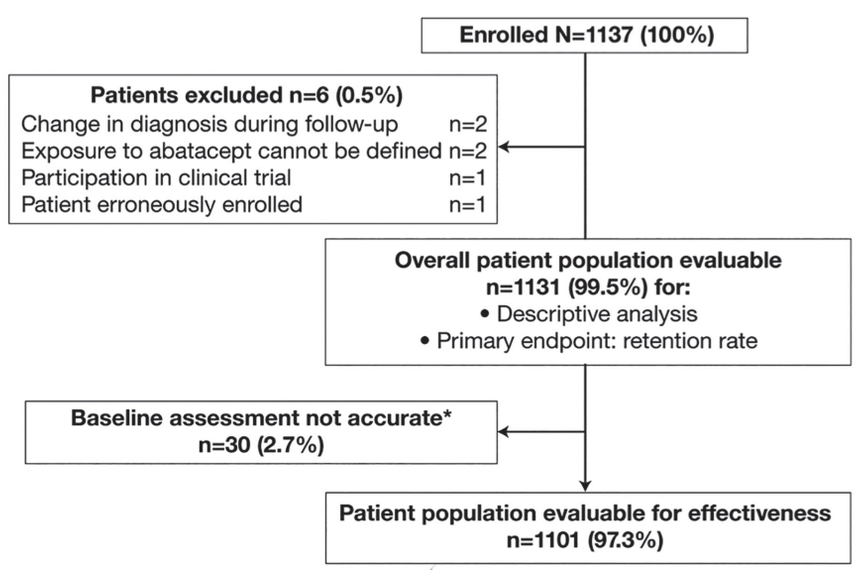


Fig. 2. Patient disposition. *Clinical assessment was performed no later than 8 days after the first infusion of abatacept.

Among 1131 evaluable patients (Fig. 2), 122/1131 (10.8%) were biologic naïve and 1009/1131 (89.2%) were previously exposed to ≥1 biologic agent: 487/1009 (48.3%) had received 1 anti-TNF, 504/1009 (50.0%) had received ≥2 anti-TNFs and 18/1009 (1.8%) had received only non-anti-TNF biologic agents. In patients who were previously exposed to a biologic agent, 237/1009 (23.5%) initiated abatacept as monotherapy and 772/1009 (76.5%) in combination with one or more csDMARDs (with MTX in 569/1009 [56.4%] and with non-MTX cs-DMARDs in 203/1009 [20.1%]). In the monotherapy group, 227/237 (95.8%) patients had previously received MTX (there were 295 individual MTX treatment courses among these 227 patients). The main reason for MTX discontinuation was intolerance/safety in 201/295 (68.1%) cases. Abatacept was initiated with concomitant corticosteroids in 734/1009 (72.7%) patients, at a median dose of 7.5 mg/day (n=692).

Overall, baseline demographics and clinical characteristics were similar for patients who were biologic naïve *versus* those with an inadequate response to previous biologic agents (Table II); however, mean disease duration was significantly shorter in patients who were biologic naïve ($p \leq 0.001$) and fewer patients had radiographic erosion ($p=0.014$). Among patients with previous exposure to biologic agents, those who initiated abatacept as monotherapy, rather than in combination with a DMARD, were significantly older (mean [SD] age: 59.1 [12.5] *vs*. 55.3 [12.2] years; $p \leq 0.001$), had longer disease duration (mean [SD]: 13.9 [10.6] *vs*. 11.2 [8.7] years; $p=0.001$), were more likely to have comorbidities (≥1 comorbidity: 77.2 *vs*. 70.6%; $p=0.047$) and had an inadequate response to a greater number of biologic agents (mean [SD]: 1.93 [0.91] *vs*. 1.77 [0.87]; $p=0.008$).

Abatacept retention

The overall crude retention rate (95% CI) estimated by Kaplan-Meier at 24 months was 54.4% (51.3, 57.4) (Fig. 3) and 53.4% (50.1, 56.6) in patients with ≥1 previous biologic failure. Crude re-

Table II. Baseline demographics and clinical characteristics at abatacept initiation by number of previous anti-TNFs.

	Biologic naïve (n=122)	Previously received a biologic agent* (n=1009)	1 previous anti-TNF (n=487)	2 or more previous anti-TNFs (n=504)
Baseline demographics at abatacept initiation				
Age, years	59.0 (13.9)	56.2 (12.4)	56.4 (12.3)	56.0 (12.5)
Female, n (%)	85 (69.7)	834 (82.7)	408 (83.8)	414 (82.1)
BMI, kg/m^2	27.4 (4.7), n=107	27.4 (5.7), n=950	27.4 (5.6), n=448	27.3 (5.7), n=486
Disease characteristics at abatacept initiation				
Disease duration at abatacept initiation, years	7.0 (7.8) n=120	11.8 (9.3) n=1004	10.2 (8.5) n=484	13.4 (9.7) n=502
Disease duration, years, n (%)				
<2	42 (35.0)	102 (10.2)	73 (15.1)	27 (5.4)
3–5	32 (26.7)	200 (19.9)	107 (22.1)	89 (17.7)
6–10	21 (17.5)	249 (24.8)	117 (24.2)	129 (25.7)
>10	25 (20.8) n=120	453 (45.1) n=1004	187 (38.6) n=484	257 (51.2) n=502
Tender joint count (28)	11.4 (7.3) n=109	11.5 (7.4) n=970	11.1 (7.2) n=468	11.7 (7.4) n=485
Swollen joint count (28)	9.5 (5.8) n=116	7.8 (5.8) n=979	7.6 (5.7) n=473	8.0 (6.0) n=489
Patient Global Assessment of disease activity, 100 mm VAS	61.4 (22.5) n=101	66.4 (20.1) n=928	66.3 (20.4) n=450	66.6 (19.8) n=462
Physician Global Assessment of disease activity, 100 mm VAS	63.0 (17.2) n=90	62.0 (19.3) n=871	61.9 (19.1) n=415	62.4 (19.3) n=440
Patient Global Assessment of pain, 100 mm VAS	60.0 (24.4) n=102	66.0 (20.6) n=916	65.8 (20.9) n=445	66.2 (20.4) n=455
Patients with erosions, n (%)	62 (58.5) n=106	601 (70.8) n=849	286 (69.1) n=414	304 (72.4) n=420
DAS28 (ESR) (calculated)	5.7 (1.2) n=90	5.7 (1.2) n=853	5.7 (1.2) n=414	5.7 (1.2) n=424
DAS28 (ESR) (collected)	5.5 (1.3) n=59	5.6 (1.2) n=711	5.6 (1.2) n=345	5.6 (1.3) n=357
DAS28 (CRP) (calculated)	5.2 (1.1) n=80	5.2 (1.1) n=829	5.1 (1.1) n=398	5.3 (1.1) n=416
DAS28 (CRP) (collected)	4.8 (1.1) n=11	5.2 (1.3) n=211	5.3 (1.3) n=93	5.2 (1.3) n=114
CDAI (calculated)	33.4 (13.0) n=88	31.8 (13.1) n=858	31.2 (12.9) n=410	32.3 (13.2) n=433
SDAI (calculated)	35.5 (13.8) n=74	34.0 (13.9) n=774	32.9 (13.5) n=369	34.9 (14.1) n=391
HAQ-DI	1.4 (0.6) n=111	1.6 (0.7) n=906	1.5 (0.7) n=444	1.6 (0.7) n=446
CRP, mg/dL	1.8 (3.2) n=95	2.4 (4.0) n=872	2.1 (3.4) n=422	2.7 (4.5) n=434
ESR, mm/h	31.3 (23.2) n=108	35.6 (24.6) n=903	36.3 (23.6) n=441	35.1 (25.5) n=447
Rheumatoid factor positive, n (%)	66 (67.3) n=98	562 (69.2) n=812	271 (69.8) n=388	282 (68.8) n=410
Anti-CCP positive, n (%)	41 (53.9) n=76	472 (65.1) n=725	233 (66.6) n=350	236 (64.5) n=366

All data are mean (SD) values unless otherwise indicated; clinical characteristics are presented in patients with baseline clinical assessment performed no later than 8 days after the first abatacept infusion. n represents the number of patients with available data. *18 patients received non-anti-TNF agents only. BMI: body mass index; CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; SD: standard deviation; SDAI: Simplified Disease Activity Index; TNF: tumour necrosis factor; VAS: visual analogue scale.

CI: confidence intervals; MTX: methotrexate; TNF: tumour necrosis factor.

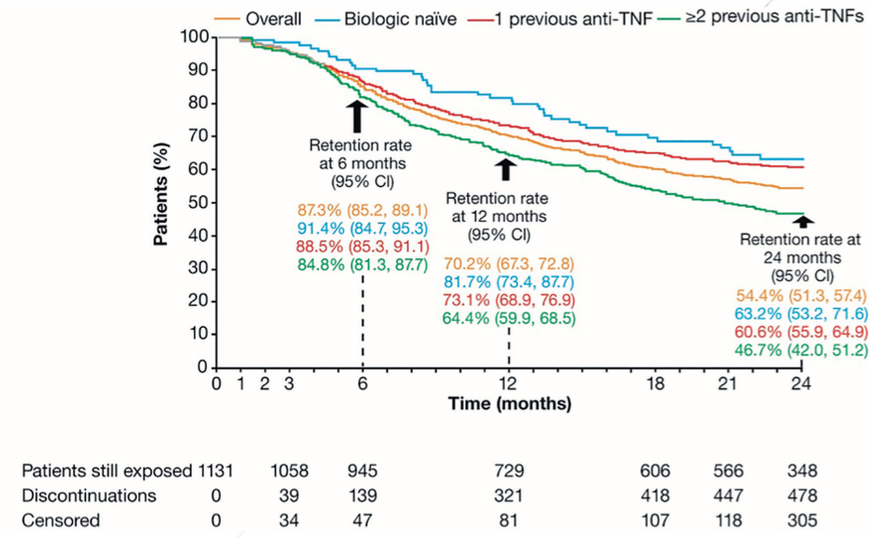


Fig. 3. Crude patient retention rates (95% CI) estimated by Kaplan-Meier over 24 months by prior exposure to anti-TNFs. If abatacept was discontinued, exposure to abatacept was defined as the time between the date of the first abatacept infusion and the date of the last abatacept infusion, plus 30 days. Censoring of patients not reporting discontinuation was performed using date of death, date of last contact or date of last follow-up visit. $p<0.001$ (log-rank).
CI: confidence intervals; MTX: methotrexate; TNF: tumour necrosis factor.

tention rates decreased with increasing number of previous anti-TNF failures (Fig. 3). Over 24 months, the most common reasons for abatacept discontinuation were inefficacy (34.4%) and intolerance (10.2%).

Overall, 995 of 1009 patients with previous exposure to biologic agents were included in the analysis of prognostic factors (seven patients each from Denmark and Belgium were excluded because the number of patients was insufficient to explore between-country differences). In total, 14 variables were retained from the univariate analysis and introduced in the multivariate model (supplementary material Fig. S1). Finally, seven variables were retained in the multivariate model, according to their statistical significance. In the multivariate model without imputation for missing data, patients had a significantly higher likelihood of abatacept retention if they had previous exposure to <2 anti-TNF agents, were positive for both RF and anti-CCP antibody or had cardiovascular comorbidity at abatacept initiation. Abatacept retention varied significantly by country, with higher retention in Greece and Italy *versus* Germany. A higher baseline ESR and the introduction of corticosteroid use at abatacept initiation were prognostic factors for lower abatacept retention (Fig. 4A). Use of a non-anti-TNF biologic agent before abatacept (last biologic agent: anakinra [n=14], ocrelizumab [n=3], rituximab [n=95] or tocilizumab [n=47]) showed borderline significance in the first model and was an additional prognostic factor of lower retention in the model with imputation of missing data (Fig. 4B). Disease duration, treatment pattern (monotherapy *vs.* combination) and BMI were not identified as prognostic factors of abatacept retention.

Efficacy

The proportion of patients in remission or with LDA after 6 months of abatacept treatment remained stable or increased over 24 months across multiple composite indices (Fig. S2). Overall, at 24 months, DAS28 (ESR), DAS28 (CRP), CDAI and Boolean remission were achieved in 28.5%, 37.0%, 22.5% and 14.1% of patients, respectively, and DAS28 (ESR), DAS28 (CRP) and CDAI LDA were achieved in 49.8%, 58.7% and 62.0% of patients, respectively. Improvements in HAQ-DI were similarly maintained (Fisher's exact test at 24 months: p=0.267; Fig. 5A). A good or moderate EULAR response at 24 months was achieved in 19/20 (95.0%) patients who were biologic naïve and in 227/283 (80.2%) patients who had ≥1 prior biologic agent failure (Fisher's exact test at 24 months: p=0.029; Fig. 5B).

Concomitant medication

Changes in concomitant medication were assessed in 407 patients on abatacept treatment at 24 months and who were previously exposed to ≥1 biologic agent; 88/407 (21.6%) patients initiated abatacept as monotherapy and 319/407 (78.4%) with concomitant csDMARDs. At 24 months, there was no change in treatment pattern compared with initiation in 348/407 (85.5%) patients; 21/407 (5.2%) patients had csDMARDs introduced and 38/407 (9.3%) had stopped all csDMARDs.

Subgroup analysis: abatacept retention by treatment pattern at initiation

Nearly 50% of patients who initiated abatacept monotherapy and 55% who initiated abatacept plus a csDMARD remained on abatacept treatment at 24 months (Fig. S3A). Using a multivariate Cox proportional hazards regression model adjusted for covariates, there was no statistically significant difference in the HR for abatacept discontinuation for combination therapies *versus* monotherapy (Fig. 4C).

Subgroup analysis: abatacept retention by BMI grouping

BMI did not impact crude abatacept retention rates in patients previously exposed to ≥1 previous biologic agent (Fig. S3B). Adjusted HRs show similar retention rates across all BMI groups (Fig. 4D). Increased BMI was not associated with an increased number of infusions and, at 24 months, a good or moderate EULAR response was achieved in a similar proportion of patients in each BMI subgroup (Supplementary material).

Safety

A total of 108 SAEs were reported in 61/1137 (5.4%) patients; 21 SAEs led to abatacept discontinuation (Table III).

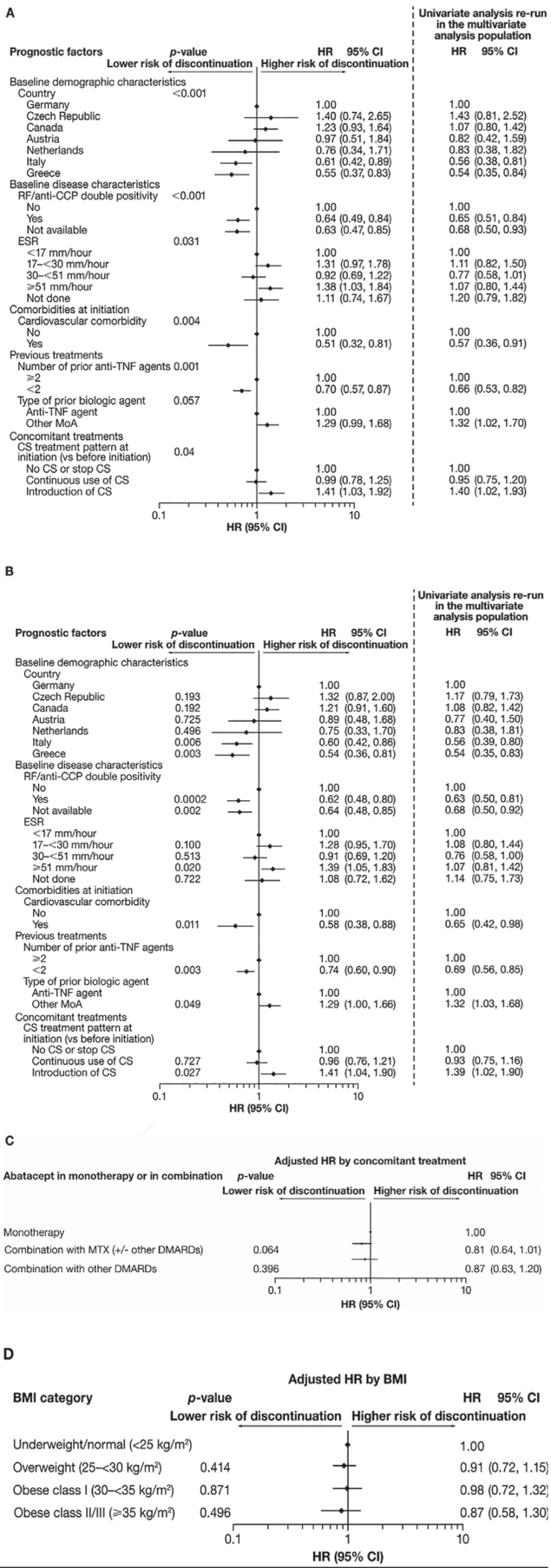
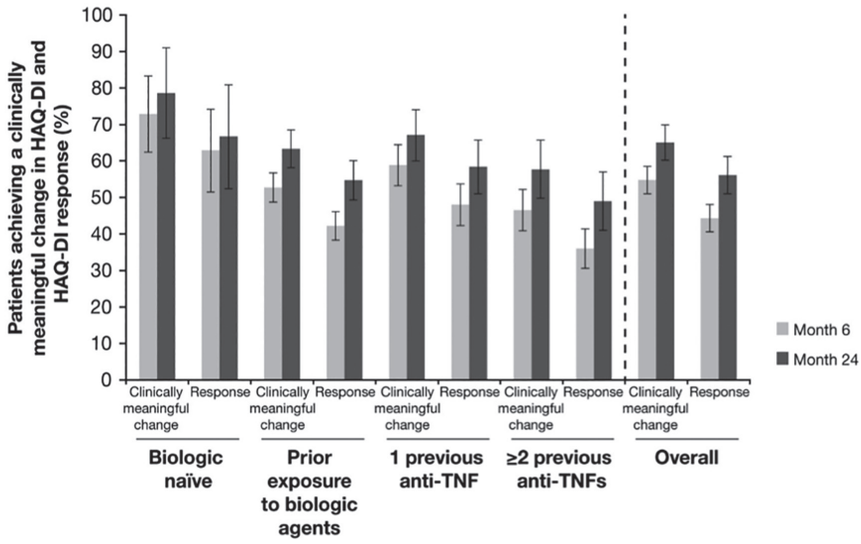


Fig. 4. Models of abatacept retention in patients with previous exposure to biologic agents:
A: Final multivariate model of abatacept retention without imputation of missing data (n=916);
B: Final multivariate model of abatacept retention with imputation of missing data (n=995);
C: Adjusted HR of abatacept retention for combination therapies *versus* monotherapy (n=995);
D: Adjusted HR of abatacept retention by baseline BMI group (n=995).
Analysis includes patients who enrolled in Austria, Canada, Czech Republic, Germany, Greece, Italy and Netherlands with previous exposure to ≥1 biologic agent. HRs and corresponding 95% CIs were estimated following a multivariate Cox proportional hazards regression model, with clustered data (sandwich method). An HR >1 indicates a higher likelihood of abatacept discontinuation, while an HR <1 indicates a lower likelihood of abatacept discontinuation. HRs are significant when the 95% CIs do not overlap 1.
Fig. 4A and **B**: following univariate analysis, prognostic factors were retained in the final multivariate model by backwards selection at the 10% threshold.
4B: missing data for covariates were imputed based on 2-stage conditional imputation of missing data performed using multiple imputations using chained equations.
4C: multivariate adjustments included demographic variables (country, age, sex, BMI), disease characteristics (RF, anti-citrullinated protein antibody status, DAS28 at baseline, disease duration), comorbidities at initiation (infections, COPD, diabetes, tobacco use, cardiac disorders) and treatment characteristics (number of prior anti-TNFs).
4D: multivariate adjustments included demographic variables (country, age, sex), disease characteristics (RF, anti-citrullinated protein antibody status, DAS28 at baseline, disease duration), comorbidities at initiation (infections, COPD, diabetes, tobacco use, cardiac disorders) and treatment characteristics (number of prior anti-TNFs, monotherapy/combination).
BMI: body mass index; CCP: cyclic citrullinated peptide; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CS: corticosteroid; DAS: Disease Activity Score; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; HR: hazard ratio; MoA: mode of action; MTX: methotrexate; RF: rheumatoid factor; TNF: tumour necrosis factor.

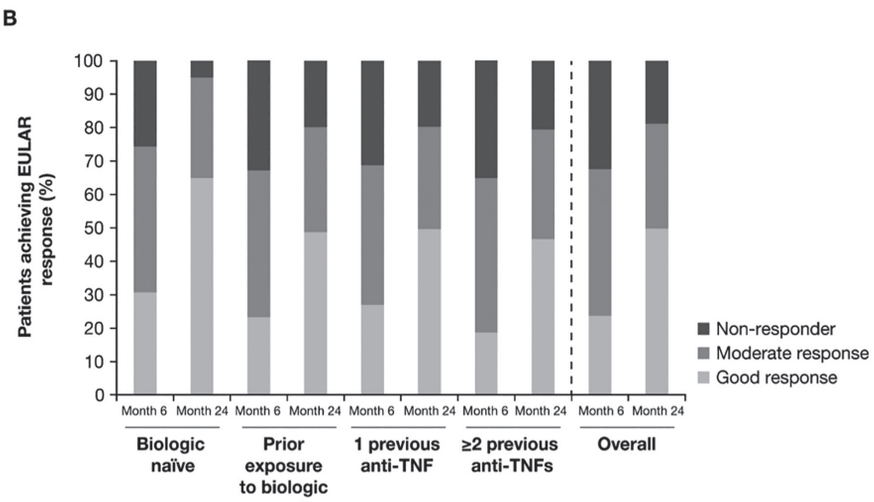
There were 12 deaths, of which none were considered related to abatacept treatment by the investigator or the drug manufacturer's pharmacovigilance department. Serious infection was reported in 25 patients; there were two opportunistic infections (*Cytomegalovirus* and *Pneumocystis jiroveci*); there were no cases of active tuberculosis. A total of 10 patients had malignancies (two of whom had pre-existing malignancies at baseline: brain tumour, Bowen's disease). Serious cardiac disorders occurred in five patients and serious hypersensitivity in two patients.

Discussion

ACTION is an international, prospective cohort study, designed to measure long-term retention rates and to identify prognostic factors of IV abatacept retention. Overall, more than 50% of patients remained on abatacept treatment over 24 months, and prognostic factors of abatacept retention were identified. Decreasing disease activity after 6 months of abatacept treatment continued to improve until 24 months. Real-world, long-term abatacept retention data in RA could serve as a surrogate measure of the benefit-to-harm ratio (17), supplementing the findings of randomised controlled trials with those from a more heterogeneous patient population who possess more varied characteristics, including comorbidities and levels of disease activity.
Abatacept retention rates at 24 months were higher in earlier *versus* later lines of treatment, consistent with the findings of other independent registries for abatacept (6, 8, 18) and other biologic agents (19, 20). Abatacept was well tolerated in a real-world RA population, many of whom were seropositive for RF or anti-CCP antibodies; the safety profile was consistent with previously published data and there were no new safety signals (21-23).
The prognostic factors identified in this analysis were consistent with different assumptions tested, and confirm those from a preliminary analysis of this ACTION cohort at 12 months (24). After 2 years of treatment, positivity for both RF and anti-CCP antibody was associated with a greater likelihood of



	Month 6 (n)	Month 24 (n)
Biologic naïve	70	42
Prior exposure to biologic agents	611	327
1 previous anti-TNF	296	173
≥2 previous anti-TNFs	303	149
Overall	681	369



	Month 6 (n)	Month 24 (n)
Biologic naïve	39	20
Prior exposure to biologic agents	529	283
1 previous anti-TNF	263	157
≥2 previous anti-TNFs	256	122
Overall	568	303

Fig. 5. Percentage of patients achieving various efficacy measures over 24 months: **A**: HAQ-DI*; **B**: EULAR response criteria†. n represents the number of patients with data available. *HAQ-DI response defined as an improvement from baseline of ≥0.3 units; p=0.029 (Fisher's exact text at 24 months). Clinically meaningful change in HAQ-DI defined as an improvement from baseline of ≥0.22 units. †EULAR response was based on DAS28 (ESR) or (CRP) (collected); p=0.267 (Fisher's exact test at 24 months) (13).
CRP: C-reactive protein; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; HAQ-DI: Health Assessment Questionnaire-Disability Index; TNF: tumour necrosis factor.

abatacept retention compared with single positivity or double negativity. An analysis across multiple European registries, geographically complementing those countries included in ACTION, found that RF and anti-CCP positivity were associated with greater likelihood of EULAR response and better abatacept retention than seronegativity (7). Abatacept is an effective treatment in patients with anti-citrullinated peptide antibody (ACPA) positivity in both clinical and real-world settings (25-27) and also in patients who are seronegative (28). The reasons underlying this association remain to be elucidated, but could be linked to the effect of abatacept on T cells and the subsequent impact on B-cell help and antibody production (29, 30). APCA and RF positivity were identified as predictors of both clinical response and maintenance of treatment with rituximab, a CD20-directed B cell-depleting agent, in analyses of European registry data (31-33). As noted for abatacept, predictors of rituximab retention include lower disability and fewer prior anti-TNF agents (34). In contrast with abatacept and rituximab, a recent meta-analysis failed to identify an association between RF and ACPA status and response to anti-TNF agents (35).
Cardiovascular comorbidity at initiation was prognostic of higher abatacept retention. In patients who have a history of cardiovascular comorbidities, options for switching RA treatment may be limited (36-40). We also found that abatacept retention varied by country despite unrestricted access to reimbursement as a key criterion for country participation. Between-country effects may be partially explained by genetic differences, environmental factors and differences in healthcare systems, including access to/uptake of biologic agents other than abatacept (41, 42). A trend to shorter abatacept maintenance in countries with relatively liberal access to biologic agents was identified in a pan-European study of RA registries (8, 43).
In subgroup analyses, the likelihood of remaining on abatacept monotherapy was similar to that for combination therapy when adjusted for covariates, although patients receiving mono-

Table III. Summary of serious adverse events.

	Patients enrolled n=1137
Deaths	12 (1.1)
SAEs reported	108 (9.5)
SAEs related* to study drug	61 (5.4)
Patients with SAE	61 (5.4)
Discontinuations due to SAE	21 (1.8)
Serious infections	31 (2.7)
Patients with serious infections	25 (2.2)
Malignancies†	11 (1.0)
Patients with malignancies	10 (0.9)
Patients with malignancies present at baseline	2 (0.2)
Serious cardiac disorders	7 (0.6)
Patients with cardiac disorders	5 (0.4)
Serious vascular disorders	4 (0.4)
Patients with serious vascular disorders	3 (0.3)
Hypersensitivity	2 (0.2)

Data are presented as n (%). Analysis presented as per pharmacovigilance database, based on total number of patients followed up in the first enrolment period (last patient's last visit: 25 April 2013).
*Considered related if at least the physician or the study sponsor assessed the event as related to abatacept.
†Bowen's disease (2 patients), Bowen's disease and basal cell carcinoma (1 patient), basal cell carcinoma (1 patient), malignant brain neoplasm (1 patient), malignant gastrointestinal cancer (1 patient), invasive ductal cell carcinoma (1 patient), malignant melanoma (1 patient), melanoma (1 patient), pelvic mass (1 patient) and non-Hodgkin's lymphoma (1 patient). SAE: serious adverse event.

therapy had more comorbidities and most were intolerant to MTX, supporting appropriate use of monotherapy in these patients. Similar findings were reported in a pan-European analysis of RA registries (44). IV abatacept was an effective treatment irrespective of BMI without the need for dose adjustment. In contrast, obesity may represent a risk factor for reduced efficacy of anti-TNFs in patients with longstanding RA, and dose escalation of anti-TNFs has been reported (45, 46).

ACTION did not interfere with routine practice and benefitted from a robust prospective study design with broad data collection that allowed the assessment of many covariates, including comorbidities and changes in treatment over 24 months; the random selection of participating study sites to ensure that these were representative of each country; and a narrow patient enrolment window for the analysis cohort to minimise calendar impact. ACTION reflects clinical practice by permitting the recording of measures 'not done'. Data were available for over 90% of patients for most variables captured, including abatacept exposure, age and sex. When ≥10% of data were missing (such as for composite indices, RF and anti-CCP status, Physician Global Assessment and CRP), the main reason was that these measures were not collected routinely in clinical practice, or were reported by the physician as 'not done' or 'not available'. Although quantitative data on missing measurements are not available, they do reveal some insight into patient management.

Study limitations inherent to real-world, non-randomised trials include: referral bias, channelling bias, lack of an active comparator and loss of patients to follow-up (attrition). In patients with an inadequate response to multiple biologic agents prior to abatacept treatment, physicians may have waited longer before deciding that a treatment was ineffective, potentially affecting the retention rate with subsequent abatacept. In ACTION, 149 (13.2%) patients had follow-up of less than 22.5 months, a finding in line with expectations for a real-world study design with a 24-month follow-up. Given the observational setting of the study, there was no obligation for the investigator to perform follow-up visits or clinical measurements; therefore, a substantial amount of clinical outcomes could be missing or not measured. Multiple imputation methods were not used for clinical outcomes at follow-up visits as this would require sequential imputations in the event of multiple missing measures over time and could introduce additional hazards at each step of imputation, reducing the benefit of such imputation.

Abatacept retention rates were highest in patients who received abatacept earlier in the treatment pathway and in patients with ACPA and RF double positivity; these prognostic factors have the potential to support individualised biologic agent treatment strategies in patients with moderate-to-severe RA.

Acknowledgements

The authors would like to thank all physicians and patients who participated in the ACTION study. The ACTION study was funded by Bristol-Myers Squibb, as study sponsor. Gilbert L'Italien (Executive Director, Worldwide Health Economics and Outcomes Research, Bristol-Myers Squibb at the time of the study) provided input into the design and interpretation of this study. Nathalie Schmidely (Research Scientist, Centre of Observational Research and Data Sciences, Bristol-Myers Squibb) provided input into the design and start-up activities of this study. Xavier Mariette (MD, Hôpital Bicêtre, Paris, France), David Evans (Director, Centre of Observational Research and Data Sciences, Bristol-Myers Squibb) and James Shaw (Associate Director, Worldwide Health Economics and Outcomes Research, Bristol-Myers Squibb) provided input into the design of the multivariate analyses. Dimitrios Boumpas (MD, University of Crete, Heraklion, Greece) contributed to data acquisition. Clinical research organisations involved in the ACTION study were Inventiv Health Clinical, Winicker Norimed, TFS Trial Form Support S.r.l., and Archemin BVBA, and statistical analyses support was provided by Florence Mercier (Stat Process) and Guillaume Desachy (Excelya). The first draft of the manuscript was prepared by academic and industry authors with professional medical writing and editorial assistance provided by Stephen Moore, PhD, of Caudex, and funded by Bristol-Myers Squibb. The academic authors vouch for the completeness and accuracy of the data and data analyses, and for the fidelity of the study to the protocol.

Disclosure statements

H.G. Nüßlein has received consulting fees and speaker honoraria from Bristol-Myers Squibb, Abbvie, Chugai, UCB, Pfizer, MSD, Novartis, and Roche.

R. Alten has received research grants and speaker honoraria from Bristol-Myers Squibb.

M. Galeazzi has nothing to disclose.

H.-M. Lorenz has received honoraria from Bristol-Myers Squibb, Abbvie, Chugai, UCB, Pfizer, MSD, Mundipharma, Novartis, Sanofi-Aventis, SOBI, Janssen-Cilag, and Roche for presentations and participation in advisory boards.

M.T. Nurmohamed has received consultancy fees from Abbott, Roche, Pfizer, MSD, UCB, SOBI, Bristol-Myers Squibb, and Janssen-Cilag; and has received payment for lectures from Abbott, Roche, Bristol-Myers Squibb, and Pfizer.

W.G. Bensen has attended advisory boards, presented data, and performed research for Bristol-Myers Squibb, Amgen, Abbott, UCB, Merck, Pfizer, Novartis, AstraZeneca, Roche, Janssen, Warner Chilcott, and Sanofi-Aventis.

G.R. Burmester has received consulting fees from Abbott Immunology Pharmaceuticals, Bristol-Myers Squibb, Roche, Merck, and Pfizer; research grants from Abbott Laboratories, Abbott Immunology Pharmaceuticals, Bristol-Myers Squibb, and Roche; and speaker honoraria from Abbott Immunology Pharmaceuticals, Bristol-Myers Squibb, and Roche.

H.-H. Peter has attended advisory boards for Pfizer Germany and is a scientific advisor for UCB.

P. Peichl has been a speaker for Bristol-Myers Squibb and Pfizer.

K. Pavelka has been a speaker for Pfizer, Amgen, MSD, Bristol-Myers Squibb, and Abbott.

M. Chartier is a consultant for Bristol-Myers Squibb.

C. Poncet is a consultant for Bristol-Myers Squibb.

C. Rauch is an employee of Bristol-Myers Squibb.

M. Le Bars is an employee of Bristol-Myers Squibb and holds stock options.

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