CLINICAL SCIENCE

Abatacept and non-melanoma skin cancer in patients with rheumatoid arthritis: a comprehensive evaluation of randomised controlled trials and observational studies

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ABSTRACT

Objectives: This study aims to evaluate non-melanoma skin cancer (NMSC) risk associated with abatacept treatment for rheumatoid arthritis (RA).

Methods: This evaluation included 16 abatacept RA clinical trials and 6 observational studies. NMSC incidence rates (IRs)/1000 patient-years (p-y) of exposure were compared between patients treated with abatacept versus placebo, conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs) and other biological/targeted synthetic (b/ts)DMARDs. For observational studies, a random-effects model was used to pool rate ratios (RRs).

Results: 49,000 patients receiving abatacept were analysed from clinical trials (~7000) and observational studies (~42,000). In randomised trials (n=4138; median abatacept exposure, 12 (range 2–30) months), NMSC IRs (95% CIs) were not significantly different for abatacept (6.0 (3.3 to 10.0)) and placebo (4.0 (1.3 to 9.3)) and remained stable throughout the long-term, open-label period (median cumulative exposure, 28 (range 2–130 months); 21,335 p-y of exposure (7044 patients over 3 years)). For registry databases, NMSC IRs/1000 p-y were 5–12 (abatacept), 1.6–10 (csDMARDs) and 3–8 (other b/tsDMARDs). Claims database IRs were 19–22 (abatacept), 15–18 (csDMARDs) and 14–17 (other b/tsDMARDs). Pooled RRs (95% CIs) from observational studies for NMSC in patients receiving abatacept were 1.84 (1.00 to 3.37) vs csDMARDs and 1.11 (0.98 to 1.26) vs other b/tsDMARDs.

Conclusions: Consistent with the warnings and precautions of the abatacept label, this analysis suggests a potential increase in NMSC risk with abatacept use compared with csDMARDs. No significant increase was observed compared with b/tsDMARDs, but the lower limit of the 95% CI was close to unity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with rheumatoid arthritis (RA) may be at increased risk of non-melanoma skin cancer (NMSC) due to immunological changes associated with the condition and some of its treatments.

⇒ Across nine randomised, double-blind clinical trials in >2500 patients with RA, the incidence rate of NMSC in patients treated with abatacept was not significantly higher than that reported with placebo.

WHAT THIS STUDY ADDS

⇒ Observational data from registries and claims databases are used for an ongoing assessment of the risk of NMSC in patients exposed to abatacept. The observed results are consistent with the warnings and precautions of the immunosuppression section of the abatacept label.

⇒ This analysis shows an increase in the risk of NMSC with abatacept use compared with conventional synthetic disease-modifying antirheumatic drugs (DMARDs). The rate ratios for other biological/targeted synthetic DMARDs compared with abatacept was not significant; however, the lower bound of the 95% CI was close to 1.0.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Consistent with treatment guidelines, healthcare providers should continue to perform routine dermatological screening for early detection of NMSC. This practice is recommended in patients with RA regardless of the type of DMARD used.

INTRODUCTION

Compared with the general population, patients with rheumatoid arthritis (RA) are at an increased risk for certain malignancies, including non-melanoma skin cancer (NMSC), basal cell carcinoma (BCC) and squamous cell carcinoma, due to immunological changes associated with RA, shared risk factors (eg, smoking) and some available RA treatments.1–7 For drugs routinely used to treat RA, there is some, although weak, evidence that their use is associated with an increased risk of NMSC.8–10 Glucocorticoids may increase the risk of basal cell and squamous cell carcinoma,8,9 and conventional synthetic disease-modifying antirheumatic drugs...
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cumulative effects of immunosuppressive biological therapy on the occurrence of malignancies including NMSC are challenging to determine and have not been fully elucidated. 3 5 11–13

Abatacept is a selective costimulation modulator that blocks the interaction between CD80/CD86 on antigen-presenting cells and CD28 on T cells, disrupting the continuous cycle of T-cell activation that characterises RA. 14-17 Abatacept has demonstrated efficacy in established 18-24 and early RA, 25 26 and is effective in treating juvenile idiopathic arthritis and psoriatic arthritis. 27-30
Since its initial approval in 2005, and as verified by results from data, July 2023). 31–33

randomised, double-blind, placebo-controlled trials with seven open-label extensions. The data are presented from the double-blind treatment periods (randomised, placebo-controlled) and long-term, open-label treatment periods (online supplemental table S1). All safety evaluations were conducted and reported according to Good Clinical Practice guidelines.

Postmarketing observational studies

The observational data sources included in this analysis were part of a 10-year post-marketing commitment and comprised of three patient disease registries that collect data prospectively on inflammatory arthritis and/or biological treatment—the Anti-Rheumatic Therapy in Sweden (ARTIS) registry in Sweden, The National Databank for Rheumatic Diseases (FORWARD) in the USA and the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) registry in Germany—and three healthcare claims databases—Truven MarketScan Commercial and Supplemental Medicare (MarketScan), IMS PharMetrics (PharMetrics) and Optum Clinformatics Data Mart (Optum). Patients with an RA diagnosis who were treated with abatacept, csDMARDs or other bs/DMARDs were included (characteristics and statistical models of the individual data sources are provided in online supplemental table S2).

The observational/epidemiological study data were analysed in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, applicable regulatory requirements and the Declaration of Helsinki.

Study populations

Abatacept RA CDP

All study participants who received at least one dose of abatacept (either subcutaneously or intravenously) or placebo in the double-blind and cumulative periods (double-blind and open-label) were included.

Observational studies

Per the postmarketing commitment studies, investigators from each registry identified patients with RA who initiated abatacept treatment and compared them with patients within the same registry who were treated with csDMARDs or other bs/DMARDs. Patients treated with csDMARDs in ARTIS were bs/DMARD-naive. Therapies included csDMARDs (aurorhthio-glucoside, auranofin, azathioprine, cyclosporine, gold sodium thiomalate, hydroxychloroquine, leflunomide, methotrexate, penicillamine, sulfasalazine and tacrolimus) and other bs/DMARDs (adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib). The distribution of the treatments within the comparison groups within each data source may have changed over the 10-year period as new treatments became available.

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.

Study assessments

Abatacept RA CDP

Investigators assessed the overall rate and distribution between different NMSC histological types in the CDP during the double-blind and cumulative periods. Frequency (number and percentage of patients with NMSC) and incidence rates (IRs) of NMSC per 1000 patient-years (p-y) of exposure were calculated for patients receiving abatacept and placebo. At study integration, events were classified using the Medical Dictionary for Regulatory Activities (V.19.0).

Observational studies

The overall NMSC risk was evaluated from the six observational studies. To address heterogeneity and the probability of causality, consistent with previous observations, 34 the prescribing label for abatacept mentions reports of skin cancer in patients receiving the drug; 34 therefore, periodic skin examinations are recommended for all patients treated with abatacept. Previous epidemiological analyses have been inconsistent: while some have identified an increased NMSC risk associated with abatacept compared with csDMARDs and other biological/targeted synthetic (bs/DMARDs), others have not. 35

This study aimed to use all available data to evaluate the risk of NMSC associated with abatacept treatment for RA. NMSC incidence was a prespecified outcome of interest in the 10-year postmarketing epidemiology studies (observational studies). Here, we present a comprehensive review of those data that includes our previously published integrated safety data from the randomised, double-blind trials in RA 34 and the results from the cumulative open-label extension periods from the abatacept clinical development programme (CDP) plus additional open-label studies. In summary, this study evaluated data from the cumulative CDP and six observational studies that were part of a 10-year postmarketing commitment.

METHODS

In this post hoc analysis, all available data within Bristol Myers Squibb were considered for inclusion. Following review, it was determined that the best level of evidence was the clinical trial data and the postmarketing epidemiology studies designed to evaluate NMSC as an outcome.

Study design

Randomised trials (double-blind and open-label studies) and postmarketing observational studies were used to evaluate the incidence of NMSC in patients with RA treated with abatacept.

Data sources

Abatacept RA CDP

The CDP included data from 16 studies sponsored by Bristol Myers Squibb on patients with RA who received at least one abatacept treatment. The analysis used data from nine randomised, double-blind, placebo-controlled trials with seven open-label extensions. The data are presented from the double-blind treatment periods (randomised, placebo-controlled) and long-term, open-label treatment periods (online supplemental table S1). All safety evaluations were conducted and reported according to Good Clinical Practice guidelines.
the first day of treatment with the RA drug was considered the index date, and a 180-day latency period was applied to all data sources (except FORWARD, which performed an intention-to-treat analysis) given that the risk is expected to begin beyond the immediate period of initial treatment exposure. Details on the specific criteria and verification of the NMSC event are listed below:

1. In ARTIS, incident cases of NMSC were identified through linkage to the Swedish cancer registry. (2) FOR FORWARD, NMSC outcomes were reported through patient questionnaires and coded using International Classifications of Diseases, Ninth Revision (ICD-9) diagnosis codes. (3) In RABBIT, malignancy data were reported by rheumatologists as AEs at every study clinical visit, by relatives if rheumatological care was terminated (with cases confirmed by medical charts, discharge letters or physician reports), or by health authorities in cases of patient death.

NMSC outcomes after the index date in the three healthcare claims databases were identified with ICD-9 diagnosis codes. Exposure is presented as p-y, and computed from 180 days after treatment initiation (index date) until NMSC detection, end of enrolment in the database, or end of data collection, whichever occurred first.

Statistical analyses
Abatacept RA CDP
NMSC frequency was calculated from the number of patients with one or multiple events. Patients with multiple occurrences of the same NMSC AE were only counted once for that AE.

Duration of exposure was defined as days from treatment initiation to the end of the treatment period. For patients who discontinued treatment, this was defined from treatment initiation to the day of treatment cessation in the short-term, double-blind period or the long-term, open-label period plus 56 or 60 days, respectively (approximately four half-lives of abatacept in humans).

The IRs of NMSC with 95% CIs were calculated as the number of patients with at least one event per 1000 p-y of exposure; p-y of exposure were censored at the time of first event occurrence or end of the treatment period if no AE was reported.

Events were assumed to follow a Poisson distribution.

Summary statistics are presented by treatment group (abatacept or placebo); data for all patients treated with abatacept were combined, regardless of study, dose level and formulation.

Observational studies
Within each data source, baseline demographic and clinical characteristics were compared between abatacept, csDMARDs or other b/tsDMARDs groups. Crude (unadjusted) IRs per 1000 p-y of exposure with 95% CIs for NMSC events were calculated. The first NMSC occurrence during follow-up was counted as the incident event. Multivariate models estimated adjusted rate ratios (RRs) and 95% CIs, adjusting for different baseline variables, to compare abatacept with each comparator group. Most registries adjusted for demographics and disease characteristics, including age and prior therapy. However, each registry may have collected additional characteristics that were then included in the fully adjusted model. Other differences that could not be included in a model were data collection methods, reporting criteria and validation of event procedures. Therefore, differences exist within each registry’s calculated RR. Details are described in the individual postmarketing commitment registry protocols, including details of the comparison cohort(s) within that registry. For example, adjusted RR was not calculated for csDMARDs in the healthcare claims databases or for b/tsDMARDs in the RABBIT database. To account for heterogeneity, a random-effects model was used to pool the RRs. The model assumes that the different data sources do not necessarily estimate the same magnitude of treatment effect. Rather, they estimate treatment effects that follow similar distributions across studies, allowing for the incorporation of clinical, methodological or statistical heterogeneity. In addition to covariates included in the summary statistics, there were differences in the definition of comparators. Thus, only data sources with similarly defined comparators were included in this meta-analysis. Similarly adjusted data models were included for calculating the pooled RR for overall malignancy. To incorporate a latency time window, the primary analysis was performed 180 days after treatment initiation. In addition, a sensitivity analysis was performed without a latency time window.

RESULTS
Patient characteristics and exposure
Abatacept RA CDP
Overall, nine randomised studies with seven open-label extensions were included. The population characteristics between the double-blind and cumulative periods were largely similar. Baseline demographics and disease characteristics for the patients in the double-blind, placebo-controlled treatment period of the randomised controlled trials (RCTs) are published elsewhere; baseline characteristics and the exact sample size for the open-label (cumulative) period are shown in online supplemental table S3. In the double-blind period, 2633 patients received abatacept and 1485 received placebo. The mean (SD) duration of exposure to abatacept and placebo was 10.8 (3.3) and 10.3 (3.5) months, median exposure to abatacept and placebo was 12 (range, 2–30) and 12 (range, 0–27) months, and total exposure was 2357 and 1254 p-y, respectively. In the cumulative period, 7044 patients received intravenous or subcutaneous abatacept. The mean (SD) duration of exposure to abatacept was 37 (26) months, median exposure was 28 (range, 2–130) months and total exposure for all nine clinical studies was 21 335 p-y.

Observational studies
Demographics and baseline characteristics for patients receiving abatacept, csDMARDs and other b/tsDMARDs are shown in online supplemental table S4. Briefly, a total of 4545 patients receiving abatacept were included in the postmarketing epidemiologic analyses. In the ARTIS, FORWARD and RABBIT registries, the cumulative p-y of exposure for abatacept, csDMARDs and other b/tsDMARDs were 2502–4444, 366–7064 and 9658–56 098, respectively. In the MarketScan, PharMetrics and Optum databases, ~37 000 patients initiating abatacept and ~110 000 patients initiating other b/tsDMARDs were identified. Two studies were eligible for inclusion in the pooled comparison against csDMARDs; a fully adjusted point estimate was not available from ARTIS, and the MarketScan, PharMetrics, and Optum databases did not run RRs for this comparison. In the claims databases, the p-y of exposure to abatacept and b/tsDMARDs by NMSC occurrence were 27 756 and 88 569 for MarketScan, 22 043 and 77 738 for PharMetrics, and 6384 and 23 588 for Optum, respectively.
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**Table 1** IRs for NMSC AEs during the double-blind, placebo-controlled treatment period of the abatacept clinical development programme

<table>
<thead>
<tr>
<th></th>
<th>Abatacept (n=2653; 2357 p-y)</th>
<th>Placebo (n=1485; 1254 p-y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with event, * n (%)</td>
<td>IR/1000 p-y</td>
</tr>
<tr>
<td>NMSC combined</td>
<td>14 (0.5)</td>
<td>6.0</td>
</tr>
<tr>
<td>BCC†</td>
<td>12 (0.5)</td>
<td>5.1</td>
</tr>
<tr>
<td>SCC‡§</td>
<td>5 (0.2)</td>
<td>2.1</td>
</tr>
<tr>
<td>SCC of the skin</td>
<td>1 (&lt;0.1)</td>
<td>0.4</td>
</tr>
<tr>
<td>Bowen’s disease</td>
<td>1 (&lt;0.1)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Includes data up to 56 or 60 days (intravenous phase 2 studies only) after last dose in the short-term, double-blind period or up to the start of the long-term period, whichever occurred first.

Missing values indicate data not reported.

Data shown exclude events with missing preferred term.

*Patients may experience more than 1 type of event.
†All patients experienced only 1 BCC event.
‡Sixty-nine patients experienced 1 SCC event; 2 patients experienced 2–3 SCC events.
§All the events reported with the preferred term of SCC were referred to SCC of the skin by evaluating individual AE reports or AE terms reported by investigators.

**Incidence of NMSC**

**Abatacept RA CDP**

As previously reported, 14 (0.5%) patients treated with abatacept and 5 (0.3%) patients receiving placebo experienced at least one NMSC event in the double-blind, placebo-controlled treatment period (table 1). The IR per 1000 p-y for combined NMSC histological types was similar between abatacept (6.0 (95% CI 3.3 to 10.0)) and placebo (4.0 (95% CI 1.3 to 9.3)); BCC was the most frequently reported NMSC type (table 1).4

In the cumulative period, 106 (1.5%) abatacept-treated patients reported at least one NMSC event; the IR for NMSC in the cumulative period (5.0 (95% CI 4.1 to 6.1)) was similar to that reported in the double-blind period (tables 1 and 2). BCC continued to be the most common NMSC type (n=84 (1.2%), IR 4.0).

**Observational studies**

In the three registries, IRs ranged from 4.7 to 11.5 for abatacept, 1.6 to 10.2 for csDMARDs and 2.7 to 8.4 for other b/tsDMARDs (tables 3 and 4).4 As previously reported, in the three healthcare claims databases, IRs ranged from 18.7 to 22.3 for abatacept,14.5 to 17.9 for csDMARDs and 14.2 to 17.2 for other b/tsDMARDs (tables 3 and 4).4

Among patients treated with abatacept compared with csDMARDs, the RR for NMSC was 0.90 (95% CI 0.20 to 4.13) in the FORWARD registry, 2.10 (95% CI 1.09 to 4.05) in the RABBIT registry and 1.84 (95% CI 1.00 to 3.37) when pooled from both registries (figure 1). Based on the pooled RRs from ARTIS, FORWARD, MarketScan, PharMetrics and Optum, the RR was 1.11 (95% CI 0.98 to 1.26) when abatacept was compared with other b/tsDMARDs (figure 2).

**Table 2** IRs for NMSC AEs during the cumulative period of the abatacept clinical development programme

<table>
<thead>
<tr>
<th></th>
<th>Abatacept (n=7044; 21 335 p-y)</th>
<th>Placebo (n=2653; 23 571 p-y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with event, * n (%)</td>
<td>IR/1000 p-y</td>
</tr>
</tbody>
</table>
| NMSC combined  | 106 (1.5)                   | 5.0          | 4.1 to 6.1 | 4 patients experienced 1 SCC event and 1 patient experienced 2–3 SCC events. In the placebo-treated group, all patients experienced only 1 BCC event.

**Table 3** IRs and RRs of NMSC for abatacept versus csDMARDs across studies

<table>
<thead>
<tr>
<th></th>
<th>Abatacept IR/1000 p-y (95% CI)</th>
<th>csDMARD IR/1000 p-y (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTIS</td>
<td>11.5 (9.1 to 14.3)</td>
<td>10.2 (9.9 to 10.5)†</td>
<td>1.60 (1.27 to 2.00)‡</td>
</tr>
<tr>
<td>FORWARD</td>
<td>5.5 (4.0 to 7.3)</td>
<td>7.1 (4.3 to 11.0)</td>
<td>0.90 (0.20 to 4.13)</td>
</tr>
<tr>
<td>RABBIT</td>
<td>4.7 (3.0 to 7.2)</td>
<td>1.6 (0.8 to 2.8)</td>
<td>2.10 (1.09 to 4.05)</td>
</tr>
<tr>
<td>US administrative healthcare claims databases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MarketScan</td>
<td>22.3 (20.6 to 24.2)</td>
<td>17.9 (17.4 to 18.3)</td>
<td>–</td>
</tr>
<tr>
<td>PharMetrics</td>
<td>18.7 (17.0 to 20.6)</td>
<td>14.5 (14.1 to 14.9)</td>
<td>–</td>
</tr>
<tr>
<td>Optum</td>
<td>19.3 (16.0 to 23.0)</td>
<td>14.8 (14.0 to 15.6)</td>
<td>–</td>
</tr>
</tbody>
</table>

Missing values indicate data not reported (study objective highlighted that the csDMARD group was not the best comparator).

*IRs and RRs presented in these tables reflect the data presented in the respective study reports. The collection of the data and the statistical analysis differed in each study.
†Biological-naive patients (most of whom would have been receiving csDMARDs).
‡Adjusted RR is not a fully adjusted model (age, sex and comorbidities only).
§All patients experienced only 1 BCC event.
**DISCUSSION**

This comprehensive analysis of NMSC in abatacept-treated patients includes both clinical trial data and observational epidemiological data from 48,550 patients treated with abatacept. Our findings are consistent with the abatacept label and previous reports. The clinical trial data for the double-blind period in the abatacept CDP (n=4138) showed similar NMSC IRs, with overlapping CIs, in patients receiving abatacept (IR 6.0 (95% CI 3.3 to 10.0)) and placebo (IR 4.0 (95% CI 1.3 to 9.3)). These IRs remained stable throughout the long-term, open-label period (cumulative =70444; IR 5.0 (95% CI 4.1 to 6.1)).

The real-world, long-term observational epidemiological studies showed variability across different data sources included in this study when comparing abatacept with csDMARDs or other b/tsDMARDs. Overall, the pooled analyses suggest an increase in the risk of NMSC with abatacept use compared with csDMARDs (RR 1.84 (95% CI 1.00 to 3.37)), and a possible small but not significant increase in the risk (RR 1.11 (95% CI 0.98 to 1.26)) when compared with other b/tsDMARDs. Differences in IRs were observed between the data sources (clinical trials vs observational studies), and there were observed differences in the incidence of NMSC between the data sources, with the Swedish registry (ARTIS) and US claims databases having higher IRs of NMSC and the US registry (FORWARD) having lower IRs of NMSC.

As observed, the IRs are higher in the healthcare claims databases compared with the IRs reported in the registries. This can possibly be explained by over-reporting NMSC in the former, unlike the registries, use a single diagnostic code with no link to a biopsy-confirming diagnosis. Database IRs reported here ranged from 14 to 22 per 1000 p-y and were consistent with the literature. IRs for NMSC in patients receiving a bDMARD ranged from 1 to 36/1000 p-y depending on the source in the literature.12 These differences highlight the challenges and need for continual assessments across multiple robust data sources containing diverse populations to broaden the scope of the findings.

Within the observational studies presented here, abatacept IRs were numerically higher than those for csDMARDs and other b/tsDMARDs, which could be because patients treated with abatacept were slightly older and more likely to be exposed to one or more b/tsDMARDs before abatacept initiation. A recent meta-analysis of the MarketScan, PharMetrics and Optum databases found a small but non-significant increase in NMSC for abatacept versus other b/tsDMARDs (RR 1.1 (95% CI 0.9 to 1.3)).11 Within the literature, earlier analyses of observational data provided inconsistent results; some studies identified a higher NMSC risk with abatacept, while others did not.4 12 35 36 38

An increased NMSC risk (squamous cell carcinoma) with abatacept versus csDMARDs was reported in an earlier observational analysis of the ARTIS registry (RR 2.2 (95% CI 1.3 to 3.5)).12 Similarly, an increased NMSC risk was reported for abatacept versus methotrexate in another observational study of patients with RA followed from 2004 to 2010 (RR 15.3 (95% CI 2.1 to 114.0)).13 A MarketScan database analysis of ~4000 patients receiving abatacept as initial RA treatment and ~60,000 receiving other b/tsDMARDs found that abatacept was associated with a significantly increased NMSC incidence compared with other b/tsDMARDs (adjusted RR 1.2 (95% CI 1.0 to 1.4)).14 Another recent systematic review and meta-analysis showed that any kind of biological therapy increased the NMSC risk in patients with RA and those with psoriasis compared with patients not receiving biological therapy.15 Conversely, a publication of FORWARD patients found IRs for NMSC comparable and low in patients receiving abatacept, csDMARDs and other b/tsDMARDs; HRs for NMSC risk between abatacept and csDMARDs and other b/tsDMARDs were not statistically different.

**Table 4** IRs and RRs of NMSC for abatacept versus other b/tsDMARDs across studies*†

<table>
<thead>
<tr>
<th></th>
<th>Abatacept IR/1000</th>
<th>Other b/tsDMARD IR/1000</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTIS</td>
<td>11.5 (9.1 to 14.3)</td>
<td>8.4 (7.9 to 9.1)</td>
<td>1.24 (0.94 to 1.64)</td>
</tr>
<tr>
<td>FORWARD</td>
<td>5.5 (4.0 to 7.3)</td>
<td>4.6 (3.0 to 6.8)</td>
<td>0.98 (0.47 to 2.06)</td>
</tr>
<tr>
<td>RABBIT</td>
<td>4.7 (3.0 to 7.2)</td>
<td>2.7 (2.1 to 3.4)</td>
<td>–</td>
</tr>
<tr>
<td>US administrative healthcare claims databases†</td>
<td>MarketScan 22.3 (20.6 to 24.2)</td>
<td>17.2 (16.4 to 18.1)</td>
<td>1.00 (0.82 to 1.22)</td>
</tr>
<tr>
<td>PharMetrics 18.7 (17.0 to 20.6)</td>
<td>15.1 (14.3 to 16.0)</td>
<td>1.0 (0.88 to 1.37)</td>
<td></td>
</tr>
<tr>
<td>Optum 19.3 (16.0 to 23.0)</td>
<td>14.2 (12.7 to 15.8)</td>
<td>1.50 (0.99 to 2.17)</td>
<td></td>
</tr>
</tbody>
</table>

Missing values indicated data not reported.

*IRs and RRs presented in these tables reflect the data presented in the respective study reports. The collection of the data and the statistical analysis differed in each study.
†Adjusted RR is propensity score matched. See Simon et al. for further details of propensity matching.

**Figure 1** Pooled analysis of NMSC RRs for abatacept versus other b/tsDMARDs. RABBIT did not run RRs for this comparison. A random-effects model was used to address heterogeneity. The RRs were calculated separately in each database and a pooled estimate was conducted. ARTIS, Anti-Rheumatic Therapy in Sweden; csDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; FORWARD, The National Databank for Rheumatic Diseases; MarketScan, Truven MarketScan Commercial and Supplemental Medicare; NMSC, non-melanoma skin cancer; Optum, Optum Clininformatics Data Mart; PharMetrics, IMS PharMetrics; p-y, patient-years; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy; RR, rate ratio.

**Figure 2** Pooled analysis of NMSC RRs for abatacept versus other b/tsDMARDs. RABBIT did not run RRs for this comparison. A random-effects model was used to address heterogeneity. The RRs were calculated separately in each database and a pooled estimate was conducted. ARTIS, Anti-Rheumatic Therapy in Sweden; b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drug; FORWARD, The National Databank for Rheumatic Diseases; MarketScan, Truven MarketScan Commercial and Supplemental Medicare; NMSC, non-melanoma skin cancer; Optum, Optum Clininformatics Data Mart; PharMetrics, IMS PharMetrics; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy; RR, rate ratio.
tsDMARDs groups were not significantly different (adjusted HR 1.1 (95% CI 0.2 to 5.0) and 1.1 (95% CI 0.6 to 2.1) for abatacept vs csDMARDs and other b/tsDMARDs, respectively). Further, in two large US database cohort studies of patients with RA, the published NMSC IRs ranged from ~13 to ~19 per 1000 p-y. This variability in findings could reflect biases inadvertently introduced by local prescription preferences (eg, age and prior DMARD exposure) and patient populations included, indicating the need for a wider range of data sources for a more definitive conclusion.

A notable study strength is the use of data from multiple clinical trials and databases across Europe and the USA, representing a large and geographically diverse group of patients and clinical practices. The epidemiological studies provided large, diverse populations for evaluation: abatacept (n=41 506), csDMARDs (n=5 27 539) and other b/tsDMARDs (n=1 42 597). However, this also introduces heterogeneity in population NMSC risk.

Limitations of clinical trial data include short treatment periods and lack of a comparator group in the cumulative period. The RCT data presentation may be limited in interpretation but is similar to other biologics. When compared indirectly to published data, our IRs are within the range observed, and clinical trials are not designed or powered to detect rare events. Our postmarketing programme analysis also had insufficient power to detect small differences in the relatively rare event of NMSC. The postmarketing epidemiology studies were, by design, powered to detect an increase in the risk of NMSC. With a 2:1 non-bDMARD-to-abatacept design, a minimum detectable relative risk of approximately 1.6 can be detected with 4500 cumulative p-y of abatacept exposure (data not shown). In the medical claims data with 37 000 p-y of abatacept exposure, we could detect a minimum detectable relative risk of ~1.26 with some precision. According to the minimum detectable relative risk, at least 10 000 p-y of abatacept exposure would be required to detect a relative risk of 1.37 for abatacept vs comparator groups; at least 20 000 p-y of abatacept exposure would be required to detect a relative risk of 1.27. Although the CDP constitutes the most robust possible dataset currently available, due to the rarity of NMSC events, the CDP did not have the required p-y to detect such small relative risks for abatacept versus comparators. Furthermore, RCTs do not collect all variables associated with NMSC risk. Comparisons between results of trials and observational studies should be interpreted with caution because of population differences resulting from more stringent eligibility criteria in clinical trials than real-world cohort studies, particularly for comorbidities and prior history of malignancies. There were also methodological differences in diagnosing/identifying NMSC between data sources used for this study; while the CDP separated BCC and squamous cell carcinoma NMSC types, the databases and registries, except ARTIS, did not. Further limitations due to heterogeneity between the observational/epidemiological studies include differences in data collection methods, reporting criteria, validation of event processes and relative risk calculation. Regarding the pooled analysis comparing abatacept with csDMARDs, only two of six epidemiological studies (from FORWARD and RABBIT) reported RRs. As the three registries did not collect data separately for bDMARDs and tsDMARDs, we were unable to present these data as separate groups in this evaluation. Finally, interpretation is hampered by the complexity of the therapeutic space with numerous csDMARDs and b/tsDMARDs and local prescribing rules influencing the order and patients in which these diverse agents can be used. In summary, the results of our analysis are consistent with the warnings and precautions of the abatacept prescribing label.

CONCLUSIONS

This evaluation of clinical trial and observational data on NMSC risk in patients with RA shows an increased NMSC risk for patients receiving abatacept compared with csDMARDs, but it also corroborates previous findings of insufficient evidence to suggest causation, or an increased NMSC risk compared with other b/tsDMARDs. The known elevation in NMSC risk in patients with RA indicates that routine dermatological screening for early detection is warranted regardless of the DMARD used.

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Contributors

TS, KM, MB, JA and MAM provided substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. TS, MB and MAM drafted the work or revised it critically for important intellectual content. All authors provided final approval of the version published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TS and LD: affiliation at the time of analysis. MAM is the guarantor for this work.

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Competing interests

TS was an employee of and shareholder in Bristol Myers Squibb (at the time of the analysis; former employee at present). LD, VK, AD and MAM are employees of and shareholders in Bristol Myers Squibb. JS reports advisory board involvement, speaker fees and grant/research support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, and Novartis. KM reports grant/research support from Rheumatology Research Foundation. MH is an employee of the University of Maryland School of Medicine (full time) and US Department of Veterans Affairs (part time); reports consultancy fees and advisory board involvement from Bristol Myers Squibb, Eli Lilly, Kolon TissueGene, Inc, Novartis, Pfizer, Samumed and Theragene. A member of the Data Safety Monitoring Committee for Galapagos, Roche, and IQVIA; reports royalties from Elsevier and UpToDate; reports stock ownership in BriOri Biotech and Theragene; and is president of Rheumcon. MB reports consultancy fees from Novartis. JA reports grant/research support from AbbVie, Bristol Myers Squibb, Eli Lilly, Galapagos, Merck, Pfizer, Roche, Samsung Bioepis, Sanofi and UCB for ARTIS. AS reports speaker fees from AbbVie, Bristol Myers Squibb, Celltrion, Lilly, Merck, Pfizer and Roche.

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.

Provenance and peer review

Not commissioned; externally peer reviewed.
Rheumatoid arthritis

Data availability statement Bristol Myers Squibb’s policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-process.html. Data are available on reasonable request.

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Abbreviations
ABA, abatacept
AGREE, Abatacept study to Gauge Remission and joint damage progression in methotrexate-naive patients with Early Erosive rheumatoid arthritis
AIM, Abatacept in Inadequate responders to MTX
ARTIS, Anti-Rheumatic Therapy in Sweden
ASSURE, Abatacept Study of Safety in Use with other RA thErapiEs
ATTAIN, Abatacept Trial in Treatment of Anti-TNF INadequate responders
ATTEST, Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating RA
AVERT, Assessing Very Early Rheumatoid arthritis Treatment
b, biologic
bg, background
BMI, body mass index
CCP2, cyclic citrullinated peptide 2
CHF, congestive heart failure
CKD, chronic kidney disease
COPD, chronic obstructive pulmonary disease
CRP, C-reactive protein
cs, conventional synthetic
DAS-28, Disease Activity Score in 28 joints
DI, Disability Index
DMARD, disease-modifying antirheumatic drug
ESR, erythrocyte sedimentation rate

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FORWARD, The National Databank for Rheumatic Diseases
HAQ, Health Assessment Questionnaire
HR, hazard ratio
hs, high-sensitivity
ICD-9, International Classification of Diseases, Ninth Revision
IFX, infliximab
IV, intravenous
MarketScan, Truven MarketScan® Commercial and Supplemental Medicare
MI, myocardial infarction
MTX, methotrexate
NMSC, non-melanoma skin cancer
NPR, National Patient Registry
NSAID, non-steroidal anti-inflammatory drug
Optum, Optum® Clinformatics® Data Mart
PAD, peripheral artery disease
PBO, placebo
PharMetrics, IMS PharMetrics
RA, rheumatoid arthritis
RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy
RF, rheumatoid factor
SC, subcutaneous
SD, standard deviation
TNF, tumour necrosis factor
ts, targeted synthetic
VAS, visual analogue scale
Potential confounders included in the models

**ARTIS:** Age at treatment start; sex; seropositive disease (RF+/RF− status); RA disease duration (<5, 5+ years); calendar year of entry into cohort; DAS-28; HAQ; tender joint count; swollen joint count; patient’s VAS global health; ESR; CRP; VAS pain; concomitant MTX, csDMARD, oral steroids or NSAIDs at the time point of cohort entry (Y/N); history of hospitalisation listing infection, last 5 years (Y/N); history of malignancy or lymphoma, ever before (Y/N); history of knee/hip joint replacement surgery, hypertension, diabetes, heart failure, ischaemic heart disease, COPD/interstitial lung disease, and chronic kidney failure, last 5 years (Y/N); total number of days spent in hospital, last 5 years.

**FORWARD:** Age; sex; educational level; ethnic origin; RA duration; Rheumatic Disease Comorbidity Index; history of cancer; HAQ disability; BMI; smoking habits; being employed at total income (103 US dollars); VAS scales such as pain, global severity, fatigue, HAQ II, quality of life; individual comorbidities at baseline: hypertension, diabetes, hospitalised due to infections, CHF, history of lymphoma, MI, coronary heart disease, chronic liver disease, COPD, CKD, leukopenia, neutropenia and PAD (individual comorbidities used descriptively); treatment variables: lifetime DMARD, biological or DMARD and biological use, IV antibiotics, use of MTX, use of DMARDs other than MTX, use of hydroxychloroquine, use of prednisone, dose of prednisone, use of NSAIDs, and number of prior biologicals taken.

**RABBIT:** Age; sex; treatment line at enrolment (first/second line versus ≥ third line); smoking (never versus ever/unknown); and averaged DAS-28 values over the complete follow-up time.

**MarketScan, PharMetrics, Optum:** Sex; age at index date; year of index date; any bDMARDs; csDMARDs; MTX; IV antibiotics; corticosteroids; NSAIDs; hypertension; diabetes; hospitalised infections; malignancy; lymphoma; COPD; asthma; CKD; leukopenia; neutropenia; PAD; hyperlipidaemia; cardiovascular disease; autoimmune disease (excluding RA).
**Supplemental Table S1  Randomised, double-blind trials of abatacept in patients with RA in the analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population (all adults with active RA)</th>
<th>Intervention</th>
<th>Duration of double-blinded period (months)*</th>
<th>Patients, n</th>
<th>Long-term, open-label period</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Abatacept</td>
<td>Placebo</td>
<td></td>
<td>Abatacept from Day 1</td>
<td>Placebo</td>
</tr>
<tr>
<td>AGREE</td>
<td>Early†, erosive, MTX-naive</td>
<td>IV ABA or PBO + bg MTX</td>
<td>12</td>
<td>256</td>
<td>256</td>
<td>After Day 365+: 227</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ABA: 116</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ABA + MTX: 116</td>
<td></td>
</tr>
<tr>
<td>AVERT</td>
<td>Early†, erosive, MTX- and biologic-naive</td>
<td>SC ABA, SC ABA + MTX or PBO + MTX</td>
<td>12</td>
<td>116</td>
<td>116</td>
<td>From Day 365+: 43†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ABA: 116</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ABA + MTX: 119</td>
<td></td>
</tr>
<tr>
<td>ATTEST§</td>
<td>Inadequate response to MTX</td>
<td>IV ABA, IFX or PBO + bg MTX</td>
<td>6</td>
<td>156</td>
<td>110</td>
<td>After Day 169+: 107</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IFX after Day 365+: 136</td>
<td></td>
</tr>
<tr>
<td>AIM</td>
<td>Inadequate response to MTX</td>
<td>IV ABA or PBO + bg MTX</td>
<td>12</td>
<td>433</td>
<td>219</td>
<td>After Day 365+: 161</td>
</tr>
<tr>
<td>IM101100</td>
<td>Inadequate response to MTX</td>
<td>IV ABA or PBO + bg MTX</td>
<td>12</td>
<td>220</td>
<td>119</td>
<td>After Day 360+: 67</td>
</tr>
<tr>
<td>IM101063</td>
<td>With bg DMARD</td>
<td>SC ABA or PBO + bg DMARD</td>
<td>3</td>
<td>51</td>
<td>17</td>
<td>From 12 weeks+: 17</td>
</tr>
<tr>
<td>ATTAIN</td>
<td>Inadequate response to MTX</td>
<td>IV ABA or PBO + bg DMARD</td>
<td>6</td>
<td>258</td>
<td>133</td>
<td>After Day 169+: 99</td>
</tr>
<tr>
<td>ASSURE</td>
<td>With bg DMARDs and/or biologics</td>
<td>IV ABA or PBO + bg RA therapy</td>
<td>12</td>
<td>959</td>
<td>482</td>
<td>After Day 360+: 384</td>
</tr>
<tr>
<td>IM101101</td>
<td>Inadequate response to etanercept</td>
<td>IV ABA or PBO + bg etanercept</td>
<td>12</td>
<td>85</td>
<td>36</td>
<td>After Day 360+: 22</td>
</tr>
</tbody>
</table>
*The start of the double-blind study period for a participant was defined as the day of the first study therapy; the stop was either 56 days or 60 days (IV phase 2 trials only) after the first dose or start of the long-term period, whichever occurred first.
†Early RA: disease duration ≤2 years, DAS-28 (CRP) ≥3.2 at study entry; anti-CCP2 positive.
‡From Day 365+ (i.e., 6 months of re-treatment after at least 3 months in the 12-month withdrawal period).
§Patients treated with IFX were not included in this analysis (n=165).
### Supplemental Table S2  Characteristics of and statistical methods used in data sources included in the post-marketing abatacept study

<table>
<thead>
<tr>
<th>Country</th>
<th>ARTIS</th>
<th>RABBIT</th>
<th>FORWARD</th>
<th>MarketScan</th>
<th>PharMetrics</th>
<th>Optum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study period</td>
<td>1 Jan 2007 to 31 Dec 2016</td>
<td>1 Jan 2007 to 30 Apr 2017</td>
<td>1 Jul 2005 to 31 Dec 2105</td>
<td>From 2006</td>
<td>From 2007</td>
<td>From 2002</td>
</tr>
<tr>
<td>Data type</td>
<td>National biological registries</td>
<td>National disease registry</td>
<td>Healthcare claims database</td>
<td>Healthcare claims database</td>
<td>Healthcare claims database</td>
<td></td>
</tr>
<tr>
<td>Mean follow-up, years</td>
<td>3.5</td>
<td>3.7</td>
<td>3.2</td>
<td>2.0</td>
<td>2.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Abatacept</td>
<td>6.2*</td>
<td>3.1</td>
<td>2.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>csDMARDs</td>
<td>4.7</td>
<td>3.8</td>
<td>3.1</td>
<td>2.2</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Sample size, n</td>
<td>2434</td>
<td>615</td>
<td>1496</td>
<td>19 170</td>
<td>13 590</td>
<td>4201</td>
</tr>
<tr>
<td>csDMARDs</td>
<td>67 762</td>
<td>3199</td>
<td>1520</td>
<td>210 830</td>
<td>186 866</td>
<td>57 362</td>
</tr>
<tr>
<td>b/tsDMARDs</td>
<td>22 439</td>
<td>6810</td>
<td>3490</td>
<td>55 261</td>
<td>40 751</td>
<td>13 846</td>
</tr>
<tr>
<td>NMSC identification/ICD diagnosis code</td>
<td>NPR or cancer register</td>
<td>Physician report</td>
<td>Self-report with physicians/record validation</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-9</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>Cox proportional hazards regression analysis comparing abatacept with each comparator group</td>
<td>Cox proportional hazard models comparing</td>
<td>Marginal structural models comparing abatacept to each of the comparator cohorts; inverse</td>
<td>A meta-analysis across the data sources was performed to determine the HRs of the outcome in abatacept initiators compared with the other sources</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Missing values indicate data not reported.

*bDMARD-naive patients (most of whom had been receiving csDMARDs).
Supplemental Table S3  Baseline demographics and disease characteristics of patients treated with abatacept in the cumulative period

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Abatacept (n=7044)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52 (13)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74 (19)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5675 (81)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>5940 (84)</td>
</tr>
<tr>
<td>Duration of exposure, person-years</td>
<td>21 335</td>
</tr>
<tr>
<td>Months of exposure</td>
<td>37 (26)</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>8.1 (9)</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>24.8 (30)</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>28.9 (14)</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>19.8 (10)</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>1.6 (1)</td>
</tr>
<tr>
<td>Patient pain, 0–100 VAS</td>
<td>64.3 (21)</td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td></td>
</tr>
<tr>
<td>NSAIDs, n (%)</td>
<td>5380 (76)</td>
</tr>
<tr>
<td>Oral glucocorticoids, n (%)</td>
<td>3959 (56)</td>
</tr>
<tr>
<td>Oral dose of glucocorticoids, mg</td>
<td>7.1 (4)</td>
</tr>
<tr>
<td>Methotrexate, n (%)</td>
<td>5418 (77)</td>
</tr>
<tr>
<td>Anti-TNF, n (%)</td>
<td>271 (4)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise indicated.
### Supplemental Table S4  Baseline patient demographics and disease characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ARTIS</th>
<th>FORWARD</th>
<th>RABBIT</th>
<th>MarketScan</th>
<th>PharMetrics</th>
<th>Optum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABA</td>
<td>cs†</td>
<td>b/ts</td>
<td>ABA</td>
<td>cs†</td>
<td>b/ts</td>
</tr>
<tr>
<td>N</td>
<td>2434</td>
<td>67 762</td>
<td>22 439</td>
<td>1496</td>
<td>1520 3490</td>
<td>615 3199</td>
</tr>
<tr>
<td>Age, years, mean</td>
<td>59</td>
<td>63</td>
<td>57</td>
<td>62</td>
<td>63 61</td>
<td>58</td>
</tr>
<tr>
<td>Female, %</td>
<td>80</td>
<td>71</td>
<td>86</td>
<td>81</td>
<td>75 74</td>
<td>75</td>
</tr>
<tr>
<td>Duration of RA, years</td>
<td>14</td>
<td>–</td>
<td>12</td>
<td>17</td>
<td>15 17</td>
<td>12</td>
</tr>
<tr>
<td>History of malignancy, %</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>27</td>
<td>28 26</td>
<td>4</td>
</tr>
<tr>
<td>History of prior biologic use, %</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>– 4</td>
<td>49</td>
</tr>
<tr>
<td>Mean number of prior biologics used</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>– 0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>0</td>
<td>16</td>
<td>0</td>
<td>56</td>
<td>0</td>
<td>71 42</td>
<td>29</td>
</tr>
<tr>
<td>1</td>
<td>27</td>
<td>0</td>
<td>29</td>
<td>15</td>
<td>18 47</td>
<td>27</td>
</tr>
<tr>
<td>≥2</td>
<td>57</td>
<td>0</td>
<td>15</td>
<td>85</td>
<td>11 11</td>
<td>44</td>
</tr>
<tr>
<td>Cumulative patient-years of exposure</td>
<td>4444</td>
<td>366</td>
<td>56 098</td>
<td>2502</td>
<td>4340 9658</td>
<td>2588 7064</td>
</tr>
</tbody>
</table>

Missing values indicate data not reported.

b, cs, and ts all refer to DMARDs.

**Baseline period varies depending on the data source; generally, claims-based data applied as baseline and registries used cohort entry as the baseline period.**

†**Biologic-naive patients (most of whom would have been receiving csDMARDs).**

‡n=1392 (n=615 enrolled at start of abatacept, plus n=777 who switched to abatacept); demographics are provided for the 615 enrolled in the abatacept group at the start.