Model-Based Meta-Analysis Compares DAS28 Rheumatoid Arthritis Treatment Effects and Suggests an Expedited Trial Design for Early Clinical Development

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A nonlinear mixed effects modeling approach was used to conduct a model-based meta-analysis (MBMA) of longitudinal, summary-level, baseline-corrected 28-joint Disease Activity Score (ΔDAS28) clinical trial data from seven approved rheumatoid arthritis (RA) drugs (abatacept, adalimumab, certolizumab, etanercept, rituximab, tocilizumab, and tofacitinib), representing 130 randomized clinical trials in 27,355 patients. All of the drugs except tocilizumab were found to have relatively similar ΔDAS28 time courses and efficacy (baseline-corrected and placebo-corrected) at 24 weeks and beyond of approximately 0.87–1.3 units in the typical RA patient population. Tocilizumab was estimated to have a differentially greater response of 1.99 at 24 weeks, likely due to its disproportionate effect on the acute-phase cytokine interleukin-6. Baseline DAS28, disease duration, percentage of male participants, and the year of conduct of the trial were found to have statistically significant effects on the timing and/or magnitude of ΔDAS28 in the control arms. Clinical trial simulations using the present MBMA indicated that abatacept, certolizumab, etanercept, tocilizumab, and tofacitinib would be expected to have a greater than 70% probability of showing a statistically significant difference vs. control at Week 6 with a sample size of ~ 30 patients per arm. In future RA clinical trials, an interim analysis conducted as early as 6 weeks after treatment initiation, with relatively small sample sizes, should be sufficient to detect the ΔDAS28 treatment effect vs. placebo.

Study Highlights

What is the current knowledge on the topic?

☑️ This is the first model-based meta-analysis of 28-joint Disease Activity Score (DAS28) in rheumatoid arthritis (RA). Prior model-based meta-analyses in RA have focused on American College of Rheumatology score.

What question did this study address?

☑️ Is DAS28–erythrocyte sedimentation rate highly related with DAS28–C-reactive protein across RA therapies with different mechanisms of action? Can historical data on the time-course of DAS28 be used to estimate the comparative efficacy of RA therapies? Can a model-based meta-analysis (MBMA) of DAS28 across numerous RA therapies be used to determine the minimum time and sample size to conduct an interim analysis?

What does this study add to our knowledge?

☑️ This analysis provides a robust comparative efficacy of numerous RA therapies using DAS28. It also uses clinical trial simulation to propose an optimal time and sample size for conducting an interim analysis of efficacy.

How might this change clinical pharmacology or translational science?

☑️ This analysis demonstrates the utility of MBMAs in integrating data across therapies and clinical trials, and then utilizing the data for decision making in clinical drug development. The work provides the methodology and framework for how this can be implemented.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation, autoantibody production, and progressive joint damage.1 Multiple clinical indexes are available to evaluate RA disease activity, including the 28-joint Disease Activity Score (DAS28).2 DAS28 is a continuous measure of disease activity and typically exhibits a normal distribution in populations with RA.3 DAS28 integrates measures of physical examination (tender and swollen joint counts), acute-phase reactants (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)), and patient self-assessed global health; the combination of these variables

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1At the time of analysis

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into a single score may more comprehensively capture disease severity than the individual variables. Two additional advantages of the DAS28 include (i) its clinical diagnostic utility, meaning that scores can be readily interpreted to reflect disease activity categories (i.e., remission (< 2.6) and low (≥ 2.6 to < 3.2), moderate (≥ 3.2 to ≤ 5.1), or high (> 5.1) disease activity), and (ii) its high sensitivity to detect small changes in disease severity. Such high sensitivity to changes in disease activity has led to increased adoption of DAS28 in clinical practice and for regulatory agencies to assess its efficacy over the dichotomous American College of Rheumatology (ACR) score. The high sensitivity of DAS28 makes it particularly useful in the design of smaller clinical trials, typically early in development, where large sample sizes are less feasible.

In addition to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate, a range of biologic agents and small molecules are approved for the treatment of RA, encompassing a variety of mechanisms of action (MoAs). Existing clinical practice recommendations in the United States and Europe provide evidence-based algorithms for the treatment of RA. The competitive nature of drug development in RA necessitates informed decision making as early as possible based on the efficacy of investigational treatments relative to that of approved drugs. Additionally, early decision making in clinical development will reduce the risk that patients with RA undergo prolonged exposure to ineffective drugs. In early-stage clinical trials in RA, efficacy is typically assessed over a period of ≥ 12 weeks. Considering the abundance of DAS28 data that have been reported for approved therapies, this analysis sought to determine whether evaluation of DAS28 at a timepoint prior to 12 weeks can be predictive of longer-term efficacy, and whether historical DAS28 data for approved RA treatments can be used to evaluate the comparative efficacy of novel RA treatments in early development.

Model-based meta-analysis (MBMA) is an approach to meta-analysis that explicitly incorporates model-based regression of longitudinal response and/or dose response in the analysis of summary-level data. As in traditional meta-analysis, MBMA allows for the estimation of the mean trial outcome and its variability. The additional benefit of this approach is its ability to quantify the impact of population/trial design characteristics. Thus, the inclusion of a model to characterize longitudinal treatment responses and/or the dose response allows for MBMA to predict/simulate new clinical scenarios through clinical trial simulation. MBMA approaches are increasingly being used to leverage existing publicly available data and to inform the development of new drugs in a range of diseases. Previous longitudinal MBMAs established the framework for indirectly comparing the magnitude of treatment response and time course in RA, using ACR scores. Based on these previous MBMAs, it is reasonable to hypothesize that the existing MBMA framework can be extended to other efficacy measures (e.g., DAS28).

Here, we describe the application of an MBMA to characterize baseline-corrected DAS28 (ΔDAS28) time-course profiles for RA treatments with different MoAs to determine whether this analysis can guide early decision making for the development of RA treatments. In particular, whether early efficacy assessment (< 12 weeks) could be indicative of efficacy at 12 weeks and beyond, and whether historical ΔDAS28 data could be used for assessment of comparative efficacy of new vs. approved RA treatments.

**METHODS**

**Data sources**

The data analyzed in this report were derived from the Quantify RA Clinical Outcomes Database (version 03/08/2018; Certara, Princeton, NJ, USA), a comprehensive database of RA clinical trials published from 1994 to 2018, named “RA database” hereafter. It includes efficacy and safety information on all biologics and newer synthetic DMARDs currently approved or in development for the treatment of RA. The RA database contains information for 266 clinical trials, representing 884 treatment arms and ~ 94,609 patients from 507 references (see Supplementary Materials). An earlier version of the RA database, including publications up to 2009, was described by Mandema et al. in 2011.

**Assessment of the DAS28-CRP vs. DAS28-ESR relationship**

Most of the trials in the RA database reported either DAS28-ESR or DAS28-CRP, with only a small number (~ 10%) reporting both. Separate modeling of each end point was not feasible because of the limited number of records for some of the drugs. To examine whether it was reasonable to pool records of the two DAS28 end points, an analysis of the linear relationship between the two end points was conducted.

Time-matched DAS28-ESR and DAS28-CRP records were extracted from the RA database. Records with missing DAS28-ESR and/or DAS28-CRP values were excluded, and duplications due to multiple reports of the same trial outcome were removed. The data set consisted of 323 paired records of DAS28-ESR and DAS28-CRP representing 17 drugs with six distinct MoAs (anti–cluster of differentiation 20 (CD20), T-cell costimulation modulation, interleukin (IL)-17 inhibition, anti–IL-6R, anti-tumor necrosis factor (TNF), and Janus kinase inhibition). (Table 1) and trial durations of up to 52 weeks (Table S1). The linear relationship between DAS28-ESR and DAS28-CRP was assessed using linear mixed-effects (LME) regression (Eq. 1) with weighting by sample size in R (v.3.4.3; Bristol-Myers Squibb, Princeton, NJ, USA):

\[
\text{DAS28}_\text{CRP}_{ij,k} = b + a \times \text{DAS28}_\text{ESR}_{ijk} + \eta_{ij}^{\text{trial}} + \eta_{ij}^{\text{arm}} + \left( N_{ij} \right)^{-0.5} \epsilon_{ijk}
\]  

where the DAS28-CRP (DAS28 CRP in Eq. 1) in study i, arm j, observation k, was estimated based on the linear relationship with the DAS28-ESR (DAS28 ESR in Eq. 1) measurement in study i, arm j, observation k, with an intercept of b and a slope of a. Interstudy (\( \eta_{ij}^{\text{trial}} \)) and interarm (\( \eta_{ij}^{\text{arm}} \)) random effects were estimated, with the residual random effects weighted by the square root of the sample size in each study arm \((N_{ij})^{-0.5} \) for Baseline DAS28, drug class, and duration of treatment were evaluated as covariates with Akaike information criterion used for model selection. The performance of this model (Eq. 1) was also examined using diagnostic plots.

To ascertain the degree to which the marginal DAS28-CRP predictions could be inaccurate, absolute percentage error (APE; Eq. 2), and mean APE (MAPE; Eq. 3) were calculated. The APE provides individual relative prediction errors, and the 95th percentile of the APE can serve as a worst-case measure of the inaccuracy of predictions. The MAPE provides the average of all individual relative prediction errors.

\[
\text{APE} = \left| \frac{\text{Pred} - \text{Obs}}{\text{Obs}} \right| \times 100\%
\]  

\[
\text{MAPE} = \left[ \frac{\sum_{i=1}^{n} \left| \frac{\text{Pred} - \text{Obs}}{\text{Obs}} \right|}{n} \right] \times \frac{1}{n} \times 100\%
\]
Assessment of the CRP vs. ESR relationship

The DAS28-CRP vs. DAS28-ESR relationship could not be assessed for tocilizumab as none of the 14 trials of tocilizumab in the RA database reported both DAS28-ESR and DAS28-CRP. Because it was desirable to include tocilizumab in the DMMA, we sought to determine whether the DAS28 data for tocilizumab could be pooled into the analysis set based on the DAS28-CRP vs. DAS28-ESR relationship described above. As such, it was necessary to demonstrate that this relationship would be applicable to tocilizumab. As the only difference between the calculation of DAS28-CRP and DAS28-ESR is the CRP/ESR measurement, any relationship that may exist between DAS28-CRP and DAS28-ESR should be reflected in the relationship between CRP and ESR. A data set extracted from the RA data set containing time-matched pairs of CRP and ESR was used to conduct an LME regression similar to that described above. As such, it was necessary to demonstrate that this relationship was described with the following equation (Eq. 4):

\[
\text{CRP}_{ij,k} = b + a \times \text{ESR}_{ij,k} + \eta_{\text{study}}^{\text{ESR}} + \eta_{\text{arm}}^{\text{ESR}} + \left( N_i^{\text{ESR}} \right)^{-0.5} \epsilon_{ij,k}^{\text{ESR}}
\]

where the CRP in study \(i\), arm \(j\), observation \(k\), was estimated based on the linear relationship with the ESR measurement in study \(i\), arm \(j\), observation \(k\) with an intercept of \(b\) and a slope of \(a\). Interstudy (\(\eta_{\text{study}}^{\text{ESR}}\)) and interarm (\(\eta_{\text{arm}}^{\text{ESR}}\)) random effects were estimated, with the residual random effects weighted by the square root of sample size in each study arm (\(N_i^{\text{ESR}}\))−0.5.

MBMA of the ΔDAS28 time course

ΔDAS28 time-course data for randomized treatment (either placebo or active drug on a stable background of csDMARDs) were extracted from the RA database for the following therapies representing diverse MoAs: abatacept, adalimumab, certolizumab, etanercept, rituximab, and tofacitinib. Eligible trials included all patients with active RA; trial arms in which patients received concomitant RA treatment (other than csDMARDs and the investigational drug being evaluated) were excluded. Trials in which patients received prior biologic therapy were eligible for inclusion. Records with baseline or all post-baseline DAS28 values missing were excluded; duplications were removed. Active treatment arms were included in the MBMA for the regulatory-approved doses in adults with moderate-to-severe RA. ΔDAS28-ESR and ΔDAS28-CRP were pooled for the MBMA by converting ΔDAS28-ESR to ΔDAS28-CRP using the relationship described in Eq. 1. The MBMA data set consisted of 994 longitudinal ΔDAS28 summary-level data records, representing data from 27,355 patients evaluated in 130 randomized, controlled clinical trials (197 trial arms) of seven approved RA drugs with five distinct MoAs. The data set included 106 background DMARD treatment arms, many of which came from trials that met the overall criteria for inclusion, but with active arms that did not meet the criteria for inclusion. This allowed for a more robust estimate of the time course of ΔDAS28 in placebo and the associated between-trial covariate effects. The key characteristics of the trials and patient populations included in the meta-analysis are provided in Table 2.

A non-linear mixed-effects modeling approach was implemented to characterize the mean ΔDAS28 vs. time and inter-trial variability using the methodology previously described by Ahn and French in 2010.\(^a\) Two different models of ΔDAS28 vs. time were evaluated, one with an exponential function (Eq. 5) and the other with a Hill function (Eq. 6). In both models, the ΔDAS28 at time \(t\), \(\Delta\text{DAS28}(t)\) for a given study \(i\), arm \(j\), was the sum of placebo and drug effects, both on top of background therapies.

\[
\Delta\text{DAS28}_{ij}(t) = -E_{\text{max},\text{placebo}} \times \left[ 1 - e^{-R_t,\text{placebo}} \right] \times -E_{\text{max},\text{drug}} \times \left[ 1 - e^{-R_t,\text{drug}} \right] \times \epsilon_{ij}(t)
\]

\[
\Delta\text{DAS28}_{ij}(t) = \left[ \frac{E_{\text{max},\text{placebo}} \times e^{-R_{t,\text{placebo}}} + E_{\text{max},\text{drug}} \times e^{R_{t,\text{drug}}}}{E_{\text{50},\text{placebo}}^{\text{ET}} + E_{\text{50},\text{drug}}^{\text{ET}}} \right] \times \epsilon_{ij}(t)
\]

where \(E_{\text{max},\text{placebo}}\) is the maximum ΔDAS28 in the placebo arm for study \(i\), \(E_{\text{max},\text{drug}}\) is the maximum ΔDAS28 treatment effect in the active treatment arm for each drug in study \(i\), arm \(j\); \(R_{t,\text{placebo}}\) and \(R_{t,\text{drug}}\) represent the rate of change vs. time in ΔDAS28 for placebo and each drug in study \(i\); \(y\) is the Hill coefficient that governs the shape of the ΔDAS28 vs. time relationship in the Hill function; \(N_i\) is the mean sample in the study \(i\), arm \(j\); and \(\epsilon_{ij}(t)\) is the within-arm residual error estimated with an additive normal distribution. Inter-trial variability for the model parameters was estimated using additive normal (\(E_{\text{max}}\); Eq. 7) or proportional log-normal (\(R_t\) and \(E_{50}\); Eq. 8) distributions.

\[
P_i = P_{TV} \times \left( \frac{N_i^{\text{ESR}}}{100} \right)^{-0.5}
\]

\[
P_i = P_{TV} + \eta_i \times \left( \frac{N_i^{\text{ESR}}}{100} \right)^{-0.5}
\]

where \(P_i\) is the parameter estimate for an individual trial, \(P_{TV}\) is the estimated typical value of the parameter, \(\eta_i\) is the random effect for inter-trial variability, and \(N_i\) is the mean sample size per arm for the trial. Both the interarm and within-arm residual random effects were weighted using the square root of the sample size normalized to 100 participants.\(^a\)
Covariate selection for testing was based on clinical plausibility and focused on baseline variables. Tested covariates included mean baseline DAS28, mean age, percentage of male participants in a given trial arm (binary; < 18.5%), mean disease duration (years), percentage of participants who failed methotrexate (binary; < 100%), percentage of participants on background csDMARDs (binary; < 50%), and the year of trial conduct (Table 2). Covariates were incorporated in the model additively with continuous covariates being log transformed and normalized to the median value in the data set (Eq. 9), and binary categorical covariate effects estimated only for the particular category selected (Eq. 10). The median of the covariate values was used as the cutoff for binary (%) variables, thus converting a continuous % scale to yes/no binary (%) variables, thus converting a continuous % scale to yes/no binary (%).

RA clinical trial simulation

The longitudinal ΔDAS28 model was used to conduct a simulation of hypothetical RA clinical trials to determine the optimal timing of an interim analysis of efficacy. Baseline characteristics of the simulated RA population were based on the median values across the trials in the meta-analysis data set.

All patients were on stable background therapies, predominantly methotrexate. CD20, cluster of differentiation 20; DAS28, 28-joint disease activity score; IL-6R, interleukin-6 receptor; JAK, Janus kinase; MBMA, model-based meta-analysis; RA database, Quantify RA Clinical Outcomes Database; TNF, tumor necrosis factor.

Values are mean (min–max) of the reported mean values for the studies, converted to DAS28-CRP using the LME (linear mixed-effects) model. Means are weighted by the square root of sample size for each trial. Placebo refers to background therapy in the control arm of the various studies included in the analysis.

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Table 2 Characteristics of studies extracted from the RA database used in an MBMA of change from baseline in DAS28 over time

| Mechanism                      | Drug             | Number of trials | Number of patients | Baseline DAS28<sup>a</sup> | Age (years)<sup>a</sup> | % male<sup>a</sup> | Disease duration (years)<sup>a</sup> |
|--------------------------------|------------------|------------------|--------------------|-----------------------------|--------------------------|-----------------|---------------------------------|
| T-cell costimulation modulator | Abatacept        | 16               | 3478               | 5.9 (4.0–6.4)               | 51 (45–56)               | 20 (12–41)      | 6.6 (0.5–12)                   |
| Anti-TNF                       | Adalimumab       | 15               | 2802               | 5.8 (5.5–6.4)               | 53 (48–56)               | 21 (15–28)      | 5.3 (0.3–11)                   |
| Anti-TNF                       | Certolizumab     | 10               | 2654               | 5.5 (3.9–6)                 | 53 (50–56)               | 21 (16–28)      | 5.6 (0.24–8.7)                |
| Anti-TNF                       | Etanercept       | 8                | 1747               | 4.9 (3.8–5.7)               | 52 (48–60)               | 18 (12–29)      | 7.7 (6.2–9.3)                 |
| Anti-CD20                      | Rituimab         | 14               | 1336               | 5.8 (5.3–6.2)               | 53 (51–58)               | 21 (9.8–33)     | 9.9 (4.9–13)                  |
| Anti–IL-6R                     | Tocilizumab      | 18               | 3724               | 5.5 (4.4–6)                 | 53 (50–57)               | 19 (9.8–27)     | 7.8 (2.2–11)                  |
| JAK inhibitor                  | Tofacitinib      | 10               | 1611               | 5.6 (5–5.8)                 | 53 (50–55)               | 17 (12–28)      | 8.3 (2.9–13)                  |
| Placebo<sup>a</sup>            | Placebo          | 106              | 10003              | 5.7 (3.7–6.5)               | 53 (46–61)               | 19 (0–45)       | 8.2 (0.57–14)                 |

All patients were on stable background therapies, predominantly methotrexate. CD20, cluster of differentiation 20; DAS28, 28-joint disease activity score; IL-6R, interleukin-6 receptor; JAK, Janus kinase; MBMA, model-based meta-analysis; RA database, Quantify RA Clinical Outcomes Database; TNF, tumor necrosis factor.

Values are mean (min–max) of the reported mean values for the studies, converted to DAS28-CRP using the LME (linear mixed-effects) model. Means are weighted by the square root of sample size for each trial. Placebo refers to background therapy in the control arm of the various studies included in the analysis.

RA clinical trial simulation

The longitudinal ΔDAS28 model was used to conduct a simulation of hypothetical RA clinical trials to determine the optimal timing of an interim analysis of efficacy. Baseline characteristics of the simulated RA population were based on the median values across the trials in the meta-analysis data set.

As the MBMA could predict only the mean ΔDAS28(τ), an LME model was developed using the MBMA data set to estimate the within-arm intersubject variance so that clinical trial simulation could be performed. The model was based on the relationship between the pooled (i.e., sum of variances of all sources) and sample variance (i.e., within-arm interpatient variance) as described in Furukawa et al. (Eq. 11).

V'<sub>τ</sub>(τ) = β<sub>0τ</sub> + β<sub>1τ</sub> × (τ/τ<sub>med</sub>) + β<sub>2τ</sub> × ΔDAS28(τ) + η<sub>τ</sub> + ε<sub>τ</sub>(τ) (11)

where V'<sub>τ</sub>(τ) is the variance of study i as a function of time, normalized to sample size (N = 1); β<sub>0τ</sub> is the estimated variance at t = 0 in study i; β<sub>1τ</sub> is the estimate for the effect of time (normalized to the median time τ<sub>med</sub>); β<sub>2τ</sub> is the estimate for the effect of ΔDAS28(τ); and η<sub>τ</sub> and ε<sub>τ</sub>(τ) are the between-trial and within-trial random effects, respectively.

Two sets of clinical trial simulations were conducted, the first in which the sample size was held constant at N = 50 per arm but the timing of the interim analysis varied between 0 and 12 weeks; the other in which the timing of the interim analysis was held constant at 6 weeks but the sample size varied between N = 2 and 300 per arm. Ten thousand trials were simulated to determine the probability of detecting a statistically significant difference (asymptotic normal 90% confidence intervals do not overlap) between the treatment and placebo arms for each scenario. The simulations were conducted using R (v:3.5.2).

RESULTS

Assessment of the DAS28-CRP vs. DAS28-ESR relationship

A strong linear relationship between DAS28-CRP and DAS28-ESR that was independent of drug class, baseline DAS28, and time since start of treatment was demonstrated by the model in Eq. 1 (Figure 1). The slope (a) and intercept (b) parameters were
estimated to be $0.899 \pm 0.00568$ and $-0.194 \pm 0.0484$, respectively, indicating a linear relationship with a constant difference of 0.2 units. The inter-trial and interarm standard deviations (SDs) were 0.183 and 0.084, respectively, indicating a low variance relative to the range of DAS28 measurements. The marginal predictions of DAS28-CRP were reasonably accurate with a 95th percentile of the APE of 13% and a MAPE of 4.2%. These results provide confidence in pooling the $\Delta$DAS28-ESR and $\Delta$DAS28-CRP data in the subsequently described MBMA.

### Assessment of the CRP vs. ESR relationship
CRP and ESR were found to have a strong linear relationship that was not dependent on drug MoA (Figure S2), indicating that the DAS28-CRP vs. DAS28-ESR relationship established above was applicable to tocilizumab.

### MBMA of the $\Delta$DAS28 time course
Prior to conducting the MBMA, $\Delta$DAS28-ESR values from studies that did not report DAS28-CRP were converted to $\Delta$DAS28-CRP using the aforementioned LME model. This provided summary-level $\Delta$DAS28-CRP data from 197 trial arms from 130 randomized controlled trials of seven different approved RA therapies to conduct the MBMA (Table 2). Funnel plots of the $\Delta$DAS28-CRP data relative to the weights for the observations indicate that the meta-analysis data were not biased with respect to the sampling variance for any of the drugs included in the MBMA (data not shown). Of the two models evaluated, based on a comparison of the Akaike information criterion ($E_{\text{max}}: -1587$, exponential: $-1412$), the $E_{\text{max}}$ model provided a better fit to the $\Delta$DAS28 vs. time data compared with the exponential model. A term for progression of $\Delta$DAS28-CRP over time was added, in
addition to the drug and placebo effects, because it improved the fit of the data (ΔOFV ~ 108):

$$\Delta \text{DAS28} (t) = -\left[ \frac{E_{\text{max,placebo}} \cdot t^{r_{\text{placebo}}}}{ET_{50,\text{placebo}}} + \frac{E_{\text{max,drug}} \cdot t^{r_{\text{drug}}}}{ET_{50,\text{drug}}} + \gamma \right]^{100}$$

$$\text{PROG} \times t + \left( \frac{N}{100} \right)^{0.5}$$

(12)

where PROG is the increase in ΔDAS28-CRP over time (i.e., worsening of disease symptoms), and was estimated to be 0.105 units per year. This final model provided a good fit to the mean ΔDAS28 time course data for all treatments and trials (Figure 2).

The model-estimated parameters for treatment and covariate effects are provided in Table S3. Of the covariate-parameter combinations evaluated, several significant trial-level covariate effects were estimated for the placebo ΔDAS28 response ($E_{\text{max,placebo}} \sim$ baseline DAS28; $E_{\text{max,placebo}} \sim$ disease duration; $ET_{50,\text{placebo}} \sim$ baseline DAS28; $\gamma_{\text{placebo}} \sim$ (male participants < 18.5%)) and one for the slope of ΔDAS28 progression (PROG ~ trial year; Table S3). The estimated ΔDAS28 treatment effects at 4, 12, 24, and 48 weeks in a typical RA population for the seven drugs in the meta-analysis are provided in Table 3. Similarly, Figure 3a shows the 24-week ΔDAS28 for all seven therapies and placebo in the same population, while Figure 3b shows the 24-week time course of ΔDAS28 treatment effects (i.e., placebo-subtracted ΔDAS28). All of the drugs except for tocilizumab are estimated to have similar ΔDAS28 responses at 24 weeks and beyond in the typical RA patient population. Tocilizumab is estimated to be associated with a greater ΔDAS28 response with a 48-week response of 2.15. Rituximab had a relatively slower onset of action compared with the other drugs (Figure 3b and Table 3).

**RA clinical trial simulation**

Estimation of ΔDAS28 SD. Intersubject variability of ΔDAS28, expressed as SD, was estimated using the LME model, as shown in Eq. 11. The SD was estimated to be 1.10 ± 0.0414 and was found to increase slightly with time (0.0043/week) and magnitude of ΔDAS28 (0.0798 per unit of ΔDAS28). This LME model enabled conversion of arm-level ΔDAS28 predictions to individual-level predictions. The marginal
patients per arm (compared with placebo at Week 6, with a sample size of ~ 30 patients per arm) would be expected to have a greater than 70% probability of showing a statistically significant difference compared with placebo. Tocilizumab is estimated to have a greater 24-week DAS28 response of 1.99. However, it appears that the degree of difference for tocilizumab is greater in DAS28 than in ACR scores. This is likely due to the disproportionate effect of IL-6R inhibition on acute-phase inflammation, resulting in a much greater effect on either ESR or CRP. A similar differentiation between these compounds was seen in those reaching 20% reduction in ACR criteria. In a Bayesian network meta-analysis, tocilizumab had greater efficacy compared with rituximab, abatacept, and tofacitinib. Another network meta-analysis demonstrated that tocilizumab had greater efficacy using ACR scores vs. rituximab and abatacept. However, despite a high degree of heterogeneity in baseline variables and treatments in this analysis. While tocilizumab was not included in this analysis due to the lack of relevant data, the strong relationship between CRP and ESR across a variety of MoAs suggested that the LME model for predicting DAS28-CRP based on DAS28-ESR would be applicable to tocilizumab. This CRP vs. ESR relationship was found to be independent of time and MoA, suggesting that anti–IL-6R drugs may not affect CRP differently than ESR, a finding that has been reported previously. Together, these findings justified the pooling of baseline-corrected DAS28-CRP in the MBMA, whether they were directly reported or derived from DAS28-ESR using the established relationship, and support tracking only one of these two end points in future RA clinical trials. The combination of both DAS28-ESR and DAS28-CRP data enabled a more robust MBMA, using as much of the available clinical trial data as possible.

While this is the first longitudinal meta-analysis of DAS28 in RA that we are aware of, these findings are consistent with prior meta-analyses using ACR scores. In an MBMA of all of these drugs (except tofacitinib) using ACR scores, a slightly better efficacy for the 8 mg/kg tocilizumab dose compared with the other drugs evaluated was seen. A similar differentiation between these compounds was seen in those reaching 20% reduction in ACR criteria. In a Bayesian network meta-analysis, tocilizumab had greater efficacy compared with rituximab, abatacept, and tofacitinib. Another network meta-analysis demonstrated that tocilizumab had greater efficacy using ACR scores vs. rituximab and abatacept. However, despite a high degree of heterogeneity in baseline variables and treatments in this analysis. While tocilizumab was not included in this analysis due to the lack of relevant data, the strong relationship between CRP and ESR across a variety of MoAs suggested that the LME model for predicting DAS28-CRP based on DAS28-ESR would be applicable to tocilizumab. This CRP vs. ESR relationship was found to be independent of time and MoA, suggesting that anti–IL-6R drugs may not affect CRP differently than ESR, a finding that has been reported previously. Together, these findings justified the pooling of baseline-corrected DAS28-CRP in the MBMA, whether they were directly reported or derived from DAS28-ESR using the established relationship, and support tracking only one of these two end points in future RA clinical trials. The combination of both DAS28-ESR and DAS28-CRP data enabled a more robust MBMA, using as much of the available clinical trial data as possible.

**DISCUSSION**

The MBMA reported here allows a comparison of the ΔDAS28 time course for seven approved RA therapies, with normalization for trial-level covariates. The MBMA permits the prediction of the treatment-specific effects for each of these drugs in a typical RA population. Patients in most of the trial arms in the MBMA had an inadequate response to methotrexate and were rheumatoid factor seropositive with longstanding RA. Some of the arms in the analysis included patients who were previously exposed to biologic agents, primarily anti-TNFs; most of these patients experienced anti-TNF failure. Abatacept, adalimumab, certolizumab, etanercept, rituximab, and tofacitinib were estimated to be associated with relatively similar placebo-corrected ΔDAS28 responses at 24 weeks and beyond of ~ 0.87–1.26 units in the typical RA patient population. Tocilizumab is estimated to have a greater 24-week ΔDAS28 response of 1.99.

Previous analyses based on cross-sectional individual patient data identified a strong linear relationship between DAS28-CRP and DAS28-ESR. In the current analysis, a similar relationship was also seen between arm-level mean DAS28-ESR and DAS28-CRP, which was independent of time and drug MoA. This was still true despite a high degree of heterogeneity in baseline variables and treatments in this analysis. While tocilizumab was not included in this analysis due to the lack of relevant data, the strong relationship between CRP and ESR across a variety of MoAs suggested that the LME model for predicting DAS28-CRP based on DAS28-ESR would be applicable to tocilizumab. This CRP vs. ESR relationship was found to be independent of time and MoA, suggesting that anti–IL-6R drugs may not affect CRP differently than ESR, a finding that has been reported previously. Together, these findings justified the pooling of baseline-corrected DAS28-CRP in the MBMA, whether they were directly reported or derived from DAS28-ESR using the established relationship, and support tracking only one of these two end points in future RA clinical trials. The combination of both DAS28-ESR and DAS28-CRP data enabled a more robust MBMA, using as much of the available clinical trial data as possible.

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**Table 3** Estimated DAS28 baseline normalized placebo and treatment effects at different timepoints in patients who failed methotrexate on a background DMARD

| Drug              | Maintenance treatment regimen | 4 weeks | 12 weeks | 24 weeks | 48 weeks |
|-------------------|-------------------------------|---------|----------|----------|----------|
| Abatacept         | 10 mg/kg IV q.4wk or 125 mg q.wk SC | 0.715 (0.571–0.896) | 1.02 (0.852–1.19) | 1.14 (0.96–1.32) | 1.22 (1.02–1.41) |
| Adalimumab        | 40 mg SC q.2wk                | 0.607 (0.459–0.788) | 0.801 (0.637–0.977) | 0.871 (0.701–1.05) | 0.911 (0.735–1.1) |
| Certolizumab      | 200 mg SC q.2wk or 400 mg SC q.4wk | 0.802 (0.643–0.993) | 1.04 (0.853–1.24) | 1.13 (0.921–1.34) | 1.18 (0.956–1.39) |
| Etanercept        | 50 mg SC q.wk                 | 0.794 (0.56–1.14) | 1.06 (0.833–1.31) | 1.17 (0.921–1.41) | 1.23 (0.965–1.49) |
| Rituximab         | 1,000 mg INF x 2/year         | 0.368 (0.295–0.456) | 0.75 (0.609–0.897) | 1.02 (0.816–1.21) | 1.24 (0.976–1.49) |
| Tocilizumab       | 8 mg/kg IV q.4wk              | 1.14 (1.01–1.28) | 1.73 (1.58–1.88) | 1.99 (1.82–2.16) | 2.15 (1.96–2.33) |
| Tofacitinib       | 5 mg PO b.i.d.                | 0.756 (0.603–0.916) | 0.949 (0.766–1.13) | 1.01 (0.817–1.21) | 1.05 (0.844–1.25) |
| Placebo           | NA                            | 0.576 (0.496–0.658) | 0.872 (0.794–0.948) | 1.07 (0.984–1.15) | 1.25 (1.12–1.36) |

b.i.d., twice daily; CI, confidence interval; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying anti-rheumatic drug; IL-6R, Interleukin-6 receptor; INF, infusion; IV, intravenous; JAK, Janus kinase; NA, not applicable; PO, oral; q.wk, weekly; q.2wk, every 2 weeks; q.4wk, every 4 weeks; SC, subcutaneous. a95% confidence interval represents the variability in the posterior distribution of parameters and inter-trial variability. bEstimated mean DAS28 response in a trial with 19% male participants, with an mean age of 53 years, a disease duration of 8.2 years, and a mean baseline DAS28 of 6.2. Placebo is only corrected for baseline DAS28, while the drug effects are corrected for baseline and placebo.
Of the covariates evaluated on the study level, the effect of background treatment vs. time, the effects of baseline DAS28, disease duration, and the percentage of male participants (< 18.5%) could be estimated (Table S3). Baseline DAS28 also had an impact on the progression of DAS28 over time. No covariate effects could be estimated on the drug treatment effects. Higher baseline DAS28 was associated with a slightly greater maximum placebo response (~ 0.7% per DAS28 unit) and a longer time to maximum placebo response (~ 24% per DAS28 unit). Both of these effects are likely due to an intrinsic relationship between baseline DAS28 and the DAS28 change over time. Longer disease duration was associated with a reduced placebo response (~ 0.8% per 5 years), consistent with the known effect of disease duration on clinical responses in RA.\(^{41}\) This analysis included clinical trials from 1994 to 2018. Earlier trials tended to have a greater background DAS28 progression compared with more recent ones (~ 0.31 DAS28 units/year in 2000 vs. ~ 0.0025 DAS28 units/year in 2016). This is likely associated with an improvement in the background DMARD therapies and their administration/compliance over the years. A reduction in baseline disease activity as measured by DAS28 has been observed in clinical trials conducted from 2000 to 2010.\(^{42}\)

Figure 3 Change from baseline in (a) mean DAS28 and (b) placebo-corrected. Treatment regimens: abatacept: 10 mg/kg IV q.4wk or 125 mg SC q.wk; adalimumab: 40 mg SC q.2wk; certolizumab: 200 or 400 mg SC q.2wk; etanercept: 50 mg SC q.wk; rituximab: 1,000 mg INF × 2/year; tocilizumab: 8 mg/kg SC q.4wk; tofacitinib: 5 mg PO b.i.d. DAS28 response in a population that failed methotrexate, is on a background of DMARD and that is 19% male, with a mean age of 53 years, a disease duration of 8.2 years, and a mean baseline DAS28 of 6.2. b.i.d., twice daily; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying anti-rheumatic drug; INF, infusion; IV, intravenous; PO, oral; q.wk, weekly; q.2wk, every 2 weeks; q.4wk, every 4 weeks; SC, subcutaneous.
variety of efficacy end points.\textsuperscript{43–47} The simulations conducted with this MBMA model suggest that a decision based upon efficacy is feasible even sooner than 12 weeks after initiation of treatment. This would reduce the exposure of patients with RA to potentially ineffective therapies, and permit redeployment of resources toward more promising drug candidates.

Clinical trial simulation of all seven RA drugs included in the MBMA with a typical design demonstrates that nearly all of the approved RA drugs would have a high probability of demonstrating efficacy vs. placebo after only 4–6 weeks of treatment (Figure 4). The only exception is rituximab due to its apparently slower onset of treatment effect. Tocilizumab shows the greatest separation from placebo at the earliest time, and with the smallest sample size, due to its estimated higher treatment effect. What we can derive from these clinical simulations is that we would expect nearly all drugs that are efficacious in RA to demonstrate a statistically significant separation from placebo by Week 6 with as few as 30 patients. Given the highly competitive nature of the treatment landscape in RA, the few drugs with a slower onset of action that do not display efficacy by Week 6 may not be desirable for further clinical development. Based on the MBMA and clinical trial simulations, it appears reasonable to include a decision-making step on efficacy at the 6-week timepoint, with relatively small sample sizes. This would enable an early evaluation of efficacy with limited resource commitment, notwithstanding any potential safety/tolerability issues.

Figure 4 Clinical trial simulation to evaluate the effect of timing and sample size on the utility of DAS28 to demonstrate a treatment effect for different RA therapies. (a) Probability of detecting a treatment effect vs. placebo as a function of time with a constant sample size of \( N = 50 \) per arm. (b) Probability of detecting a treatment effect vs. placebo as a function of sample size (per arm) after 6 weeks of treatment. Treatment regimens: abatacept: 10 mg/kg IV or 125 mg SC; adalimumab: 40 mg SC q.2wk; certolizumab: 200 or 400 mg SC q.2wk; etanercept: 50 mg SC q.wk; rituximab: 1,000 mg INF × 2/year; tocilizumab: 8 mg/kg SC q.4wk; tofacitinib: 5 mg PO b.i.d. Dotted lines represent the interim analysis time of (a) 6 weeks or (b) the sample size of \( N = 50 \). \( \Delta \)DAS28, change from baseline in 28-joint Disease Activity Score; b.i.d., twice daily; DAS28, 28-joint Disease Activity Score; INF, infusion; IV, intravenous; PO, oral; q.wk, weekly; q.2wk, every 2 weeks; q.4wk, every 4 weeks; RA, rheumatoid arthritis; SC, subcutaneous.
The MBMA reported here permits comparison of emerging DAS28 data from a new compound with historical data from the seven drugs included in the analysis. The comparison would be able to account for differences in study design and execution, allowing for a decision to be made on the potential competitiveness of the new investigational drug with these prior-approved therapies. As additional therapies are approved, they can also be included in the MBMA to make the scope more comprehensive.

**SUPPORTING INFORMATION**
Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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**CONFLICTS OF INTEREST**
All authors are employees of Bristol Myers Squibb and hold company stock.

**AUTHOR CONTRIBUTIONS**
T.L. and Y.L. wrote the manuscript. T.L., Y.L., R.W., and M.N. designed the research. T.L., Y.L., and M.B.-P. performed the research. T.L., Y.L., and M.B.-P. analyzed the data. T.L. and M.B.-P. contributed new reagents / analytical tools.

**DATA AVAILABILITY STATEMENT**
Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners临床 trials and research disclosure-commitment.html.

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