Aggregate data model-based meta-analysis is a regression approach to compare the dose–response and/or time-course across different treatments by using data from the literature. Literature search and systematic review following the Cochrane approach yielded 912 sources for investigational and approved treatments for psoriasis. In addition, data for tofacitinib were obtained from an internal database. Tofacitinib is an oral Janus kinase inhibitor. Two mathematical models were developed for Psoriasis Area and Severity Index (PASI) response in moderate to severe psoriasis patients to quantify the time to maximum effect for PASI75 and to evaluate the dose–response relationship for PASI responders (PASI50, PASI75, PASI90, PASI100) at Week 12. Body weight exhibited an inverse effect on the placebo component of both models, suggesting that body weight affects the overall PASI response regardless of drug. This analysis provides a quantitative framework for efficacy comparisons across psoriasis treatments.

Psoriasis is a common chronic skin disorder typically characterized by erythematous papules and plaques with a silver scale, although other clinical presentations also occur. Management of psoriasis may involve topical and systemic medications, phototherapy, stress reduction, climatotherapy, and various adjuncts based on individual patients’ clinical situations.

Aggregate data (study-level) model-based meta-analysis is a regression approach to compare the dose–response and/or time-course across different treatments by using data from the literature. As more drugs become available to treat patients, the compilation of clinical responses across drugs provides a better understanding of whether newer agents offer greater pharmacological benefit compared with existing ones, including faster onset of action, increased efficacy, and/or better safety profiles.

In this analysis, data from the literature on Psoriasis Area and Severity Index (PASI) response in patients with moderate to severe psoriasis were collected for both investigational and marketed drugs. Data for tofacitinib were obtained from an internal Pfizer database (all tofacitinib studies used in this analysis have been published). Tofacitinib is an oral Janus kinase (JAK) inhibitor. An oral tablet of tofacitinib dosed as 5 mg or 10 mg twice daily (b.i.d.) was demonstrated to be efficacious for the treatment of moderate to severe psoriasis in four phase III clinical studies.

To evaluate the magnitude and onset of the drug effect, two mathematical models were developed: 1) a longitudinal model to quantify the time course of PASI75 (primary clinical endpoint representing the proportion of patients achieving ≥75%
reduction in PASI score from baseline), and 2) a landmark model to quantify the dose–response relationship for PASI responders (PASI50, PASI75, PASI90, PASI100) at Week 12 (primary efficacy timepoint in the majority of studies; primary efficacy timepoints ranged from 10–24 weeks across all studies). The impact of body weight was tested in both models. The results from the two models were compared, and the predictive performance for PASI response was assessed. This analysis allows a quantitative understanding of treatment options for patients with psoriasis by providing a framework for efficacy comparisons across systemic agents.

RESULTS
Available data
The literature search yielded 912 abstracts, of which 151 studies were identified for potential inclusion in the analyses. Following application of additional inclusion/exclusion criteria, the final analysis included 71 studies for landmark and 57 studies for longitudinal analyses (Figure 1: Supplementary Material).

The final database included interleukin (IL)-12/23 inhibitors (ustekinumab, briakinumab), tumor necrosis factor (TNF)-α inhibitors (adalimumab, etanercept, certolizumab, infliximab), IL-17 inhibitors (secukinumab, ixekizumab, brodalumab), T-lymphocyte (CD2) antagonist (alefacept), phosphodiesterase-4 (PDE4) inhibitor (apremilast), JAK inhibitors (tofacitinib, baricitinib), and traditional oral agents (methotrexate, cyclosporine, acitretin). All drugs were included in the landmark model; however, the longitudinal model did not include cyclosporine, acitretin, or baricitinib due to insufficient longitudinal data.

Longitudinal model
The temporal relationship between dose and PASI75 response was adequately described by the longitudinal model. PASI75 response increased toward a maximum that eventually plateaued over time for most treatments. The PASI75 time course curves for the model-predicted PASI75 were overlaid with the observed data for each drug (Figure 2).

ET50 and ET90 (the time to reach 50% and 90% of the maximal treatment effect (Emax)) were estimated from the model (Table 1). Emax was achieved by Week 12 for the majority of drugs except alefacept (estimated ET50 for alefacept was 11.1 weeks; ET90 was not able to be estimated from available data). The mean (standard deviation (SD)) ET50 across all drugs was 6.48 (2.06) weeks, and ranged from 3.7–9.2 weeks, with the exception of alefacept (Table 1; Figure 2). The mean (SD) ET90 across all drugs, excluding alefacept, was 12.6 (2.92) weeks. A trend between ET50 and Emax was detected, such that drugs with higher Emax tended to have a shorter ET50 than those with lower

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Figure 1  Search strategy flow diagram. Details of studies included in the final database are listed in the Supplementary Appendix. PASI75, ≥75% reduction from baseline Psoriasis Area and Severity Index score.
For example, the IL-17 inhibitors were predicted to achieve ET₅₀ following ~4 weeks of treatment. Correspondingly, the predicted PASI75 response for IL-17 inhibitors ranged from 22–49% at 4 weeks and reached ~80% at 12 weeks. In contrast, other systemic agents with longer ET₅₀, such as methotrexate and alefacept, had lower PASI75 responses (less than 30% at 12 weeks).
Treatment effect was well-characterized by an E\textsubscript{max} model with a different E\textsubscript{max} and potency (ED\textsubscript{50}; dose achieving 50% of maximal response) for each drug within each class. Body weight was shown to have an inverse relationship with both the placebo response (B) and the rate constant of drug effect (k\textsubscript{drug}), in which the rate constant describes the time-course component in the model. The median body weight effect estimates (95% confidence interval) in the final model for the maximal placebo effect and the rate constant of drug effect were -0.193 [-0.277, -0.119] and -0.867 [-1.32, -0.496], respectively (from nonparametric bootstrap; N = 1,000); both excluded 0. The final parameter estimates for the longitudinal model are presented in Supplementary Table 1.

Landmark model

Dose–response for PASI endpoints (PASI50, 75, 90, and 100) was well characterized by a sigmoidal E\textsubscript{max} function with a different E\textsubscript{max} for each drug class and different ED\textsubscript{50} for every drug within each class. The final parameter estimates for the landmark model are presented in Supplementary Table 2.

### Table 1 Longitudinal model-predicted percentage of PASI75 responders for systemic treatment in patients with moderate to severe psoriasis at 4 and 12 weeks

| Drug | Clinical dose | ET\textsubscript{50} (Week) | ET\textsubscript{90} (Week) | PASI75 (%) |
|------|---------------|-----------------------------|-----------------------------|------------|
| **TNF-\(\alpha\) inhibitor** | | | | |
| Adalimumab | 40 mg Q2W | 6.0 (4.6, 7.8) | 11.7 (8.5, 16.1) | 15.6 (5.15, 30.2) | 65.9 (53.6, 76.8) |
| Certolizumab\(^a\) | 200 mg Q2W | 4.2 (2.8, 6.0) | 9.9 (6.5, 14.3) | 38.8 (21.7, 59.4) | 74.5 (62.2, 84.1) |
| Etanercept | 25 mg BIW | 8.2 (6.3, 10.8) | 16.4 (12.3, 20.8) | 4.64 (0.00, 10.7) | 32.0 (20.7, 44.0) |
| Etanercept | 50 mg BIW | 7.7 (6.1, 9.9) | 14.6 (11.8, 19.0) | 6.87 (1.08, 15.7) | 48.7 (34.2, 60.6) |
| Infliximab | 5 mg/kg Q8W | 4.7 (3.5, 6.2) | 10.0 (6.8, 14.2) | 32.7 (16.0, 51.5) | 75.3 (62.6, 85.8) |
| **IL-17 inhibitor** | | | | |
| Brodalumab\(^b\) | 210 mg Q2W | 3.9 (2.8, 5.3) | 9.2 (6.1, 13.1) | 46.9 (27.1, 66.7) | 80.2 (69.0, 89.2) |
| Ixekizumab | 80 mg Q4W | 3.7 (2.6, 5.3) | 8.9 (5.7, 13.1) | 48.8 (29.4, 68.6) | 81.7 (71.7, 90.7) |
| Secukinumab | 150 mg QM | 5.5 (4.1, 7.1) | 11.0 (7.7, 15.3) | 21.5 (8.86, 37.7) | 69.2 (57.0, 79.5) |
| **IL-12/23 inhibitor** | | | | |
| Briakinumab\(^d\) | 100 mg Q4W | 5.8 (4.7, 7.0) | 10.9 (8.8, 13.6) | 19.0 (7.13, 34.8) | 78.4 (67.2, 87.9) |
| Ustekinumab | 45 mg Q12W | 7.1 (5.8, 8.7) | 13.3 (11.1, 16.7) | 10.2 (3.01, 21.6) | 65.2 (51.9, 76.4) |
| **Dihydrofolate reductase inhibitor** | | | | |
| Methotrexate | 18 mg QW | 9.2 (7.3, 11.5) | 18.7 (15.3, 21.6) | 3.38 (0.000, 8.61) | 28.5 (17.0, 40.0) |
| **JAK inhibitor** | | | | |
| Tofacitinib\(^a\) | 5 mg BID | 6.9 (5.0, 9.6) | 14.3 (9.4, 20.1) | 9.21 (1.85, 19.4) | 40.8 (28.2, 52.5) |
| Tofacitinib\(^a\) | 10 mg BID | 6.0 (4.5, 8.1) | 12.2 (8.4, 17.5) | 16.9 (6.23, 32.8) | 60.7 (48.1, 72.5) |
| Baricitinib\(^a\) | 10 mg QD | NA | NA | NA | NA |
| **Vitamin A analog** | | | | |
| Acitretin | 30 mg QD | NA | NA | NA | NA |
| **CD2 antagonist** | | | | |
| Alefacept | 10 mg QW | 11.1 (9.0, 13.9) | >24\(^c\) (23.5, NA) | 1.99 (0.000, 6.20) | 15.6 (7.09, 24.1) |
| **PDE4 inhibitor** | | | | |
| Apremilast | 30 mg BID | 7.4 (5.4, 10.2) | 15.1 (10.2, 20.7) | 5.66 (0.345, 12.7) | 28.5 (17.9, 39.8) |
| **Calcineurin Inhibitor** | | | | |
| Ciclosporin | 2.5–5 mg/kg/d | NA | NA | NA | NA |

Values presented are mean (90% confidence intervals) and were generated assuming a typical weight of 90 kg.

\(^a\)Investigational. \(^b\)Discontinued. All other drugs are approved. \(^c\)Alefacept data only reported up to 24 weeks; ET\textsubscript{50} is estimated to occur sometime beyond the time period for which there were reported data. BID, twice daily; BIW, twice weekly; CD2, T lymphocyte; ET\textsubscript{50}, time to reach 50% of the maximal treatment effect; ET\textsubscript{90}, time to reach 90% of the maximal treatment effect; IL, interleukin; JAK, Janus kinase; NA, not available; PASI75, > 75% reduction from baseline Psoriasis Area and Severity Index score; PDE4, phosphodiesterase 4; QD, once daily; QM, once monthly; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; Q12W, once every 12 weeks; TNF, tumor necrosis factor.
response relationship for the model-predicted PASI response overlaid with the observed data for each drug is presented in Figure 3. The model-predicted PASI responses for a typical patient for each drug are summarized in Table 2. There was close agreement between the estimates from the longitudinal model and the landmark model, although the confidence intervals were generally wider for the values generated from the longitudinal model.

The effect of body weight on PASI response was also tested in the landmark model on placebo effect and/or drug effect terms. There was no significant improvement in the model fit when the weight effect was applied to any of the drug effect terms (E_{max}, E_{D50}), while it was significant for the placebo effect term. Therefore, the presented predictions are based on a model in which body weight was retained for the placebo effect term alone. Although the effect was small, weight was shown to have a statistically significant negative effect on the placebo response (i.e., heavier patients showed a lesser response compared with lighter patients).

Among injectable/infusible agents, IL-17 inhibitors were the most efficacious, with ixekizumab (80 mg) demonstrating the highest placebo-adjusted response rate (88.2% [86.8, 89.5] and 71.7% [69.1, 74.6] for PASI75 and PASI90, respectively) at Week 12. Within the oral systemic treatments, tofacitinib 10 mg b.i.d. and cyclosporine 5 mg/kg/d had comparable response rates.
of 53.8% (47.0, 58.7) and 46.7% (36.9, 56.5) for PASI75 and 27.5% (22.1, 31.8) and 22.1% (16.0, 29.6) for PASI90, respectively. Acitretin 30 mg q.d. and apremilast 30 mg b.i.d. showed the lowest efficacy among the oral systemic agents (25.0% [16.1, 36.7] and 26.8% [23.2, 31.8] for PASI75, and 9.57% [5.55, 15.7] and 10.3% [8.52, 12.8] for PASI90, respectively).

External validation (predicting longitudinal PASI90)
The final longitudinal model, developed from the time-course PASI75 dataset (test dataset), was used to predict the time-course of PASI90 response (validation dataset). When scaling factors obtained from the landmark model were incorporated into the longitudinal model, predictions of PASI response were consistent with the observed data, with the majority of reported PASI90 responses falling within the 90% prediction interval (Figure 5).

| Drug                  | Clinical dose | Landmark model-predicted PASI responders (%) | Landmark model-predicted difference from placebo (%) |
|-----------------------|---------------|---------------------------------------------|------------------------------------------------------|
|                       |               | PASI75 | PASI90 | PASI75 | PASI90 |
| **TNF-α inhibitor**   |               |        |        |        |        |
| Adalimumab            | 40 mg Q2W     | 64.9   | 37.9   | 59.5   | 36.3   |
| Certolizumab<sup>a</sup> | 200 mg Q2W  | 73.5   | 48.2   | 68.0   | 46.5   |
| Etanercept            | 25 mg BIW     | 37.4   | 16.1   | 31.9   | 14.3   |
| Etanercept            | 50 mg BIW     | 54.0   | 27.6   | 48.4   | 26.0   |
| Infliximab            | 5 mg/kg Q8W   | 77.0   | 53.0   | 71.6   | 51.3   |
| **IL-17 inhibitor**   |               |        |        |        |        |
| Brodalumab<sup>b</sup> | 210 mg Q2W  | 81.2   | 59.3   | 75.8   | 57.7   |
| Ixekizumab            | 80 mg Q4W     | 88.2   | 71.7   | 82.7   | 70.0   |
| Secukinumab           | 150 mg QM     | 75.7   | 51.1   | 70.2   | 49.4   |
| **IL-12/23 inhibitor**|               |        |        |        |        |
| Briakinumab<sup>b</sup> | 100 mg Q4W  | 80.8   | 58.4   | 75.2   | 56.8   |
| Ustekinumab           | 45 mg Q12W    | 70.3   | 43.6   | 64.9   | 41.9   |
| **Dihydrofolate reductase inhibitor** |             |        |        |        |        |
| Methotrexate          | 18 mg QW      | 36.4   | 15.5   | 31.0   | 13.8   |
| **JAK inhibitor**     |               |        |        |        |        |
| Tofacitinib<sup>a</sup> | 5 mg BID     | 35.2   | 14.8   | 29.7   | 13.1   |
| Tofacitinib<sup>a</sup> | 10 mg BID    | 53.8   | 27.5   | 48.2   | 25.8   |
| Baricitinib<sup>a</sup> | 10 mg QD     | 33.2   | 13.6   | 27.5   | 11.9   |
| **Vitamin A analog**  |               |        |        |        |        |
| Acitretin             | 30 mg QD      | 25.0   | 9.57   | 19.6   | 7.92   |
| **CD2 antagonist**    |               |        |        |        |        |
| Alefacept             | 10 mg QW      | 22.7   | 8.39   | 17.2   | 6.61   |
| **PDE4 inhibitor**    |               |        |        |        |        |
| Apremilast            | 30 mg BID     | 26.8   | 10.3   | 21.3   | 8.60   |
| **Calcineurin inhibitor** |           |        |        |        |        |
| Ciclosporin           | 2.5–5 mg/kg/d | 46.7   | 22.1   | 41.2   | 20.4   |

Values presented are mean (90% confidence intervals) and were generated assuming a typical weight of 90 kg.

<sup>a</sup>Investigational. <sup>b</sup>Discontinued. All other drugs are approved. BID, twice daily; BIW, twice weekly; CD2, T lymphocyte; IL, interleukin; JAK, Janus kinase; PASI75/90, > 75% or > 90% reduction from baseline Psoriasis Area and Severity Index score; PDE4, phosphodiesterase 4; QD, once daily; QM, once monthly; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Q8W, once every 8 weeks; Q12W, once every 12 weeks; TNF, tumor necrosis factor.
for these compounds, confirming that the models were reasonably describing the data.

**DISCUSSION**

Aggregate level landmark and longitudinal models were used to evaluate the dose–response (magnitude) and time-course (onset of drug effect) of PASI response in patients receiving systemic agents for the treatment of moderate to severe psoriasis. Both models adequately described the data, suggesting that the dose–response relationships are well-captured using sigmoidal $E_{\text{max}}$ function structures, and that the maximum drug effect is achieved within 12 weeks across most of the drugs included in this analysis. Moreover, both models suggest that drugs with the same mechanism of action demonstrate a consistent dose–response.

One of the benefits of the longitudinal model is that it enables the comparison of the rate of onset among drugs. In this analysis, ET$\text{50}$ was estimated from the predicted time-course of PASI75 responses. Generally, drugs with the highest efficacy had the fastest onset of action. For example, the highest efficacy was observed with the IL-17 inhibitors ixekizumab and brodalumab (PASI75 response $\approx$80%) at the primary evaluation timepoint (12 weeks), with ET$\text{50}$ of 3.7 and 3.9 weeks, respectively. In comparison, the lowest efficacy was observed for alefacept (PASI75 response 16%) with an ET$\text{50}$ of $\approx$11 weeks. The average ET$\text{50}$ across all drugs in this analysis was 6.5 weeks. Understanding differences in ET$\text{50}$ allows studies to be modified to provide an appropriate time-frame to compare drug efficacy. Early assessments (after 4–6 weeks of treatment) may be sufficient for drugs with shorter ET$\text{50}$ and highly efficacious drugs (e.g., ixekizumab and brodalumab), whereas a longer sampling duration may be required to allow patients to achieve maximum benefit for drugs with longer ET$\text{50}$ (e.g., etanercept, methotrexate, or apremilast).

The relationship between body weight and PASI response was of clinical interest, and an inverse relationship was detected in this meta-analysis. In both longitudinal and landmark analyses, body weight was identified as exhibiting an inverse effect on...
the placebo component of the model, suggesting that body weight affects the overall PASI response regardless of drug. The body weight effect was also significant on the temporal component of drug effect ($k_{drug}$) in the longitudinal model. These data suggest that heavier patients tend to achieve lower efficacy and may also experience slower onset of effect compared with lighter patients. The significance of the weight effect on the placebo component of the models should not be interpreted in a mechanistic context, as the models were developed based on summary level, and not patient level, data. The important finding was that, despite this attribution, body weight demonstrated an effect on the absolute difference in the percentage of responders between active and control groups. Therefore, increasing drug dose may be particularly beneficial for heavier patients if they fail to show a meaningful clinical response at lower doses. Such a decision to escalate the dose in heavier patients can be achieved by evaluating the dose–response characteristics of each drug and assessing the location of the clinical dose relative to the drug’s ED50.

However, caution is required in interpreting covariate effects with aggregate-level data. In general, meta-analyses using data from the literature report covariates (age, body weight, sex, race, etc.) as summary statistics (mean or median % of the trial dataset), which results in reduced power to detect clinically relevant interactions. In an analysis conducted by Lambert et al., it was demonstrated that even moderately strong interactions may not be adequately detected in the meta-analytic setting. Furthermore, there is also a risk that introduction of aggregate-level covariates may result in underestimation of exposure–response effects. Therefore, although both meta-analytic models reported here suggested that increasing body weight has an inverse effect on PASI response, the true magnitude of this interaction may not have been captured in this setting. Instead, the use of individual level data may provide better estimates of the magnitude of this effect and may enhance the understanding of this relationship on a mechanistic level.

As with any meta-analysis, the utility of the results depends, in part, on the studies that provided the information for analysis. We therefore investigated heterogeneity in the aggregated pooled dataset. During study selection, only predefined inclusion and exclusion criteria were applied to control for possible heterogeneity across the pooled studies. The parameterization of the
landmark model therefore incorporated a study-specific placebo effect ($E_0$) for each trial. In this manner, study-related differences were accounted for by allowing the placebo effect of the PASI response to shift across different studies. In contrast, the drug effect was assumed to be constant across studies, i.e., all of the differences in response for a given drug at a given dose were assumed to be related to differences between studies and not to the drug itself.

When predicted placebo effects ($E_0$) from the landmark model were plotted for each study ($N = 71$), they were shown to be normally distributed around a single value (data not shown). However, the $I^2$ statistic of placebo effects (which describes the percentage of variance that is related to between-study differences) was estimated to be 82%, suggesting that the parameterization for study-specific placebo effect in the landmark model may have helped to adequately control for any potential study-related heterogeneity in the dataset. A similar approach (estimating study-specific placebo effects) was also attempted in the longitudinal model, but the results were inconclusive due to overparameterization. Instead, a placebo component was modeled as a population mean response with between-study variability as a random effect. The estimated random effects in the longitudinal model were nearly normally distributed, suggesting that the parsimonious model (without estimating study-specific placebo effects) is a reasonable alternative to describe the data.

Due to the advancement of antipsoriatic therapies, PASI90 may eventually replace PASI75 as the key indicator of efficacy in investigational trials. New psoriasis therapies with targeted mechanisms (e.g., secukinumab, ixekizumab, and brodalumab) have shown much higher levels of improvement in clinical studies, and therefore the emphasis from clinicians, regulators, and drug developers is shifting to higher threshold endpoints, such as PASI90. The external validation of predicted PASI90 response in the longitudinal setting shows high agreement with the scalability employed in the landmark setting, and both PASI75 and PASI90 results tended to plateau at $\sim$12 weeks. This suggests that a simple scaling factor can be used to link PASI75 and responses, especially in the period following attainment of $E_{max}$. It is worth noting that the external validation was performed by bridging the models, i.e., the longitudinal model for PASI75 was used to predict PASI90 by incorporating the estimated relationship between PASI75 and PASI90 from the landmark model. This represents a much higher hurdle for model validation than applying the same model on a different dataset.

The magnitude of treatment effects for systemic agents was visualized with predicted PASI responses. Consistent with previous reports, IL-17 inhibitors appeared to be the most efficacious injectable/infusible psoriasis treatments, followed by other classes of drugs. Infliximab (5 mg/kg) and ixekizumab (80 mg) had the highest responses among TNF-α inhibitors and IL-17 inhibitors, respectively. Among the oral agents, tofacitinib 10 mg b.i.d. and cyclosporine 5 mg/kg/d appeared to have comparable efficacy, which was higher than other approved or investigational systemic oral treatments. Acitretin 30 mg q.d. and apremilast 30 mg b.i.d. showed the lowest efficacy among the oral systemic treatments.

In summary, two mathematical models were developed to describe the time-course and dose–response from the data across all systemic treatments for patients with psoriasis. The simulation results also suggest that the model could be useful to predict the time-course of other PASI subscales such as PASI90. These models provide a quantitative framework to understand the current treatment options and a potential use of models in drug development, either alone or bridging together, to predict the time-course for endpoints of interest with investigational drugs.

METHODS

Database development

The data for the analysis originated from two sources: data from the literature for approved and investigational psoriasis treatments from 1998 through 2015, and summary level data for tofacitinib phase II and III clinical studies. Although the results from tofacitinib clinical studies are published, the corresponding summary data for this analysis were obtained from a Pfizer internal database to maintain numerical accuracy.

Literature search and data selection. Following the search and selection strategy proposed by the Cochrane group, the Ovid Medline search engine, US-based and European regulatory documents such as Summary Basis of Approvals and European Public Assessment Reports were searched from 1964 to 2015 for reports of PASI responders in clinical trials for the pharmaceutical treatment of psoriasis. The search strategy focused on moderate to severe plaque psoriasis, randomized placebo or active-controlled trials of IL-12/23 inhibitors, TNF-α inhibitors, IL-17 inhibitors, CD2 antagonists, PDE4 inhibitors, JAK inhibitors, and traditional oral agents. The primary efficacy endpoint PASI75 and other PASI scores (PASI50, PASI90, and PASI100) were captured in the database.

Abstracts of potential records were screened by qualified personnel to determine the relevance to the research objectives; the study designs, treatment regimens, and patient populations were scrutinized to ensure that all studies represented data that supported pooling. PASI response data that passed the screening process were extracted from published articles, relevant conference posters, and/or abstracts. The data from selected sources were captured or digitized, then data curation (e.g., unit standardization, normalization of different dose regimens) was performed.

Although a single database was generated to support both the longitudinal and landmark analysis, three separate datasets were created as required by the modeling objectives. In the longitudinal analysis, all repeated measures of PASI75 response (test dataset) were used for model building, and all repeated measures of PAS90 response (validation dataset) were used for the external validation. The third dataset was for the landmark analysis; PASI responses (PASI50, 75, 90, 100) at the primary efficacy measurement time (majority of studies were 12 weeks; range, 10–24 weeks) were included.

Model development

Longitudinal model. The longitudinal model structure consisted of placebo and drug effects that were exponential vs. time describing the longitudinal aspect of the effect. The response value was transformed into the logit scale to restrict the estimated probability values between 0 and 1 as shown in the following equations:

\[ Pr(PASI75) = g \left( f_0 + f_{\text{drug}} \right) \]  
\[ g = \frac{1}{1 + e^{-\left( f_0 + f_{\text{drug}} \right)}} \]  
\[ f_0 = A + B \cdot \left( 1 - e^{-k_{\text{bdr}}} \times \text{time}(\eta) \right) \]


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where \(Pr\) is the probability, \(g\) is the inverse logit function to transform the treatment effect, which is the sum of placebo (\(g_0\)) and drug effect (\(g_d\)) to the probability scale. The parameter \(k_{\text{pr}}\) and \(k_{\text{d}}\) are rate constants describing onset of placebo and drug effects, respectively, with a modeled unique estimate for each drug.

The dose–response component of the model was described by a sigmoidal \(Emax\) function. The model estimated the parameters for \(A\) (intercept), \(B\) (asymptote on placebo model), \(E\) (asymptote on drug model), \(ED_{50}\) (dose achieving 50% of maximal response), for each drug. The normalized dose by the regulatory approved dose regimen, or, normalized dose by the most frequently reported dose regimen (for nonapproved drugs) was used to account for different doses or unique titration schemes for each drug during clinical studies. The Hill coefficient \(\gamma\) was also tested in the model. However, the parameter(s) were not estimated for rate constant or dose–response terms if there was not sufficient longitudinal or dose–response information available for a certain drug. The between-study variability was described by \(\xi\), having a normal probability distribution with mean 0 and variance \(\sigma^2\).

**Landmark model.** A joint analysis of the efficacy endpoints (PASI50, 75, 90, and 100) was performed to estimate differences in relative effect for each endpoint by treatment. The response variable was the percentage of patients achieving PASI50, 75, 90, and 100 at each trial endpoint, typically 12 weeks post-first dose administration.

The structure for the joint meta-regression model of PASI50, PASI75, PASI90, and PASI100 responses is summarized in Equations 5 through 8. The final model was structured as follows:

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where \(P(\text{event})_{ijk}\) represents the probability (%) of a patient having an event for the \(i\)th endpoint in the \(j\)th treatment arm of the \(k\)th trial and \(g\) was the inverse logit function to transform the treatment effect to the probability scale.

\(E_0\) captures the estimated placebo response in PASI75 scores for a patient with body weight 90 kg (approximate median of the dataset) in the \(\ell\)th trial as defined in Equation 6. A different placebo response was estimated for every trial with a constant fixed shift between PASI levels.

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where \(\text{trial}_{\ell}\) is a baseline placebo response for the \(\ell\)th trial; \(I_1\), \(I_2\), and \(I_3\) are coefficients for PASI50, PASI90, or PASI100 relative to PASI75 scores.

\(E_{\text{drug}}\) represents the drug-response with drug-specific model parameters, such as maximum response for each drug (\(em_d\)) and an effective dose for each individual drug (\(ED_{50d}\)). For the traditional oral systemic treatments (methotrexate, cyclosporine, and acitretin), the optimal PASI response was achieved in practice by flexible dose adjustment for each patient, based on safety and efficacy. Therefore, there were insufficient data in the literature to fully describe the dose–response relationship for these drugs. As such, the maximum responses for traditional oral systemic agents were modeled as single-step offsets (Equation 7).

For TNF-\(\alpha\) inhibitor, IL-12/23 inhibitor, IL-17 inhibitor, CD2 antagonist, PDE4 inhibitor, and JAK inhibitor, a sigmoidal \(Emax\) function was used to describe the relationship between dose and PASI response for each drug (Equation 7). As with \(E_0\), a scaling factor was applied to the estimated \(Emax\) to account for differences in PASI75, PASI50, PASI90, and PASI100 scores (Equation 8).

If drug is traditional systemic agent : \(em = em_d\),

All other drugs : \(em = \frac{em_d + DOSE_{d}^{wd}}{exp(ED_{50,d})^{wd} + DOSE_{d}^{wd}}\)

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\text{\[7\]}
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In the above equations, \(em_d\) represented the drug-specific maximum effect; \(\gamma_d\) was the Hill coefficient; \(ED_{50d}\) was the estimated dose of half of the maximum effect and \(I_2\), \(I_6\), and \(I_7\) were scaling factors applied to PASI50, PASI90, and PASI100 scores, respectively. In this analysis, a single Hill coefficient was applied to all drug classes except for IL-17 inhibitors. The dose–response curve for IL-17 inhibitors was sufficiently different from other drugs of interest that an individual offset was required to more appropriately describe the dose–response relationship.

The random effect \(\eta_d\) on overall drug response (\(E_0 + E_{\text{drug}}\)) was defined as having a mean 0 and variance \(\sigma^2\). The model included terms to account for the correlation between different PASI scores (i.e., PASI50, PASI75, PASI90, or PASI100) within the same study and to account for the correlation between PASI scores among different arms within the same study.

**Covariate model.** Based on previous knowledge, body weight was an important determinant of efficacy in patients with psoriasis. Therefore, body weight was tested as a covariate in the longitudinal model and in the landmark model if body weight data were available in the literature (aggregated level, either by study arm or stratified by body weight), as described in Equations 9 and 10, respectively:

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If body weight data were not reported (10–15% of studies in the literature), \(WEIG\) was set to 90 so that there was no influence on the covariate estimation. The weight effect was tested on the treatment effect of the drug (\(Emax\), \(ED_{50}\), or \(k_{\text{drug}}\)), as well as on the placebo effect (\(E_0\)).

**Residual error model.** In both the longitudinal and landmark analyses, the predicted PASI responses represented the probability of \(\geq 50\%, \geq 75\%, \geq 90\%,\) or 100% improvement in PASI scores. The residual error component \(\epsilon\) had a normal probability distribution with mean 0 and variance \(\sigma^2\). Weight based on standard errors of fitted values (see Equations 11 and 12) was noted as \(W\), and the number of subjects for each arm within each study to account for the effect on parameter estimation due to the size of each trial was noted as \(N\). Because studies were weighted by inverse of standard errors, larger studies had more influence on estimating the parameter means.

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Additionally, due to the longitudinal nature of the data and correlation within timepoint measurements of the same group of patients, a third level of variability (with mean 0 and variance \(\sigma^2_{\text{CORR}}\)) was also incorporated into the longitudinal model as shown below:

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The standard model diagnostics (e.g., goodness-of-fit plots, precisions of the parameter estimates) were performed for both models to assess the model adequacy and any residual error model misspecifications.

Simulations. Simulations were performed using the final model parameter estimates. The results were overlaid with observed data for both time course (longitudinal) and dose–response at 12 weeks (landmark) data by drug (and dose) to visually compare the results and confirm the model performance. Predicted PASI75 responses generated from the longitudinal model were compared to predicted PASI75 responses from the landmark model to demonstrate consistency between the models. ET$_{50}$ and ET$_{90}$ (the time to reach 50% and 90% of the maximal treatment effect) were also calculated from the longitudinal model.

The final landmark model was used to simulate PASI75 or PASI90 responses at Week 12 for a typical patient with moderate to severe psoriasis for each drug at clinically recommended doses. Placebo-adjusted treatment effect (effect size) for each drug was summarized in a forest plot.

External validation. External validation was performed for PASI90 time-course response (using the validation dataset), in which the final model for longitudinal PASI75 was used to simulate ($N = 1,000$) the PASI90 time-course by incorporating the scaling factor between PASI75 and PASI90 obtained from the landmark model, then overlaid with the observed PASI90 time-course data.

Modeling software. Longitudinal data analyses were conducted using Nonlinear Mixed Effect Modeling software NONMEM (v. 7.3) using the first-order conditional expectation method. A nonlinear mixed-effects routine in S-PLUS 8.0.4 for Windows (Insightful, Seattle, WA) was used for the landmark analysis. The input datasets and model outputs were manipulated and all graphical displays were generated using R (v. 3.0.2) and Rstudio (v. 0.99.879). Bootstrap was performed using PsN (v. 3.5.4).

Additional Supporting Information may be found in the online version of this article.

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CONFLICTS OF INTEREST
K.I., S.A., P.G, R.W, H.V., H.T., S.K., and A.T. are employees and shareholders of Pfizer Inc. T.C., and M.K. were employees of Pfizer Inc at the time of the analysis. J.M. has acted as a consultant for Pfizer Inc. L.P. has received consultancy/speaker’s honoraria from AbbVie, Almirall, Amgen, Biogen, Boehringer, Celgene, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, MSD, Novartis, Pfizer Inc, and Sandoz. L.P. has participated in a company-sponsored speaker’s bureau for Celgene, Janssen, MSD, Novartis, and Pfizer Inc.

AUTHOR CONTRIBUTIONS
K.I., T.C., S.A., P.G., J.W.M., L.P., R.W., H.V., H.T., S.K., A.T., and M.K. designed the research; K.I., T.C., and S.A. analyzed the data.

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