

# Characterising the onset of response using public domain data and MBMA: application cases in Atopic Dermatitis and Psoriatic Arthritis



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## Background

Immune-mediated inflammatory diseases (IMIDs) comprise a group of conditions sharing common immune pathways and are often treated with similar drugs and drug classes [1]. Public domain data is instrumental in addressing strategic clinical questions in drug-development. Model-Based Meta Analysis (MBMA) provides a quantitative framework to leverage public and proprietary information within and across different diseases. MBMA has been applied in immunology to support dose-bridging across different diseases, such as between rheumatoid arthritis (RA) and axial spondyloarthritis (AxSpA) [2] and between inflammatory bowel diseases (IBDs) and other immune-related inflammatory diseases [3]. Also an MBMA characterising the onset of the response in AxSpA [4] was recently conducted. In fact, characterising the onset of response across drug classes and understanding whether and when the plateau has been reached are clinical questions with a direct impact on study design and primary timepoint definition for clinical endpoints.

## Objectives

The aims of this work were:

- To conduct exploratory analyses of the onset of mean EASI score in atopic dermatitis (AD) and onset of ACR20 response in psoriatic arthritis (PSA).
- To perform a full MBMA analysis based on longitudinal ACR20 response data in PSA to support a study futility analysis planning for an asset currently in clinical development at GSK.

## Methods

- Database:** Certara's clinical trial outcome databases for AD and PSA [5] were used as data sources in the analysis (supported by GSK).
- Exploratory analyses:** Two exploratory analyses focusing on mean EASI score and on ACR20 score data up to week 16 were performed. Placebo-corrected responses were normalised to the response at week 16 and analysed using nonlinear regression for binary endpoints, implemented in the generalised nonlinear least squares (gnls) routine in R (4.0.2). An exponential time-course of the onset of response was assumed.
- Full MBMA:** For ACR20, a full MBMA assuming a drug-class-independent unstructured model for the description of onset of effect was performed based on the following equations:

$$N_{ijt} \sim \text{binomial}(N_{ijt}, P(\text{ACR20})_{ijt})$$

- Number of patients with ACR20 response in treatment arm  $j$  of trial  $i$  at time  $t$  ( $N_{ijt}$ ) was assumed to follow a binomial distribution with probability of response  $P(\text{ACR20})_{ijt}$  and sample size  $N_{ijt}$ .

$$P(\text{ACR20})_{ijt} = E_{o_{acr20,it}} + E_{drug} \cdot E_{onset} \cdot E_{cov}$$

- Probability of response  $P(\text{ACR20})_{ijt}$  was described as the sum of an unstructured placebo response in trial  $i$  at time  $t$  ( $E_{o_{acr20,it}}$ ) and a fixed effect for every drug ( $E_{drug}$ , accounting for dose response where applicable) multiplied by a function describing time course of onset relative to week 16 and a function  $covEff$  describing covariates effect

$$E_{onset} = 1 + k_1 \cdot (t = 1) + k_2 \cdot (t = 2) + k_4 \cdot (t = 4) + k_8 \cdot (t = 8) + k_{12} \cdot (t = 12)$$

- Where  $t=1, t=2, t=4, t=8,$  and  $t=12$  indicate data corresponding to 1, 2, 4, 8, or 12 week time bins. Onset of response is described by  $k_1, k_2, k_4, k_8,$  and  $k_{12}$  relative to the response at week 16

$$E_{cov} = 1 + b_{cov} \cdot (cov - med(cov))$$

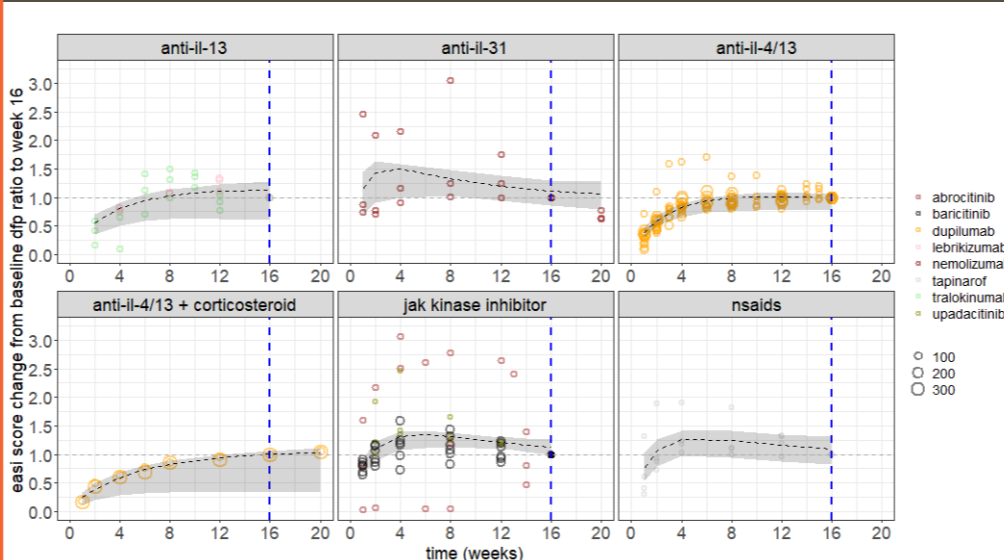
- Linear covariate effect centred around the median

- As the focus of this analysis was on the dynamics of the response, constant effect across treatment regimens (doses, dosing intervals) was assumed for most of the drugs beside the ones showing clear dose-response relationships. The effects of covariates such as the use of methotrexate as background therapy and the prior use of biologics were evaluated. Based on the modelling framework, the fractional treatment effect relative to week 16 was simulated.

## Results

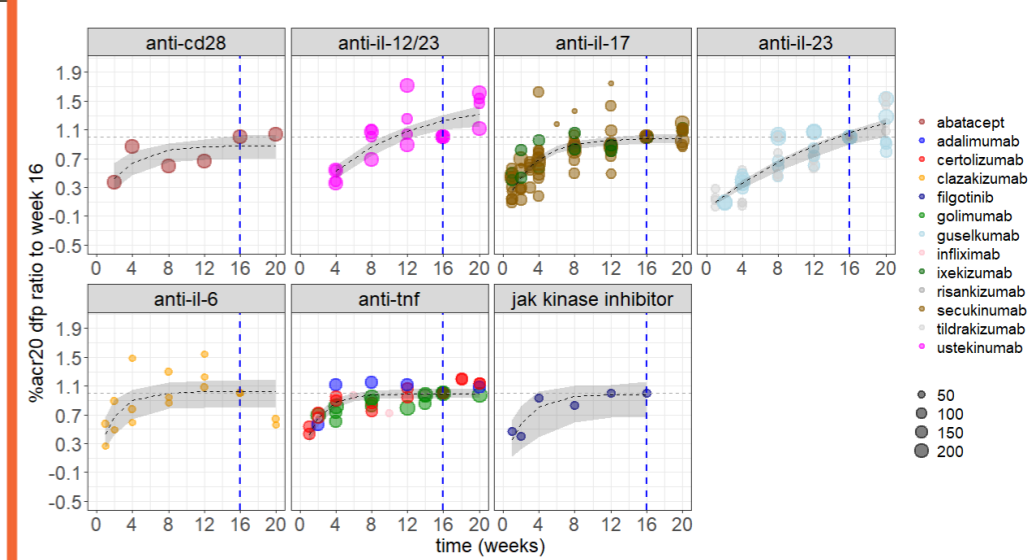
- Exploratory analyses:** mean EASI score at week 16 was reported in 18 studies of drugs belonging to the following drug classes: anti-IL-13, anti-il-31, anti-IL-4/13, anti-IL-4/13 in combination with corticosteroid, Janus kinase (JAK) inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs). ACR20 responses at week 16 were reported in 31 studies of drugs belonging to the following drug classes: anti-CD28, anti-IL-12/23, anti-IL-17, anti-IL-23, anti-IL-6, and JAK inhibitor drugs. The exploratory analyses showed that a model assuming exponential onset and power function offset for mean EASI score (Figure 1) or exponential onset for ACR20 response (Figure 2) could adequately describe the observed ACR20 and EASI data. For both analyses, most of the drug classes were found to reach the plateau of the response at around 8 weeks.

Figure 1. EASI score in AD: exponential onset and power function offset model results



Symbol: reported EASI change from baseline and difference from placebo (dfp) ratio to 16; Dashed Line: fitted exponential onset and power function offset model; Gray area: 95% confidence interval based on the variance-covariance matrix of the estimate

Figure 2. ACR20 score in PSA: exponential onset model results



Symbol: reported ACR20 scores difference from placebo (dfp) ratio to 16; Dashed Line: fitted exponential onset model; Gray area: 95% confidence interval based on the variance-covariance matrix of the estimate

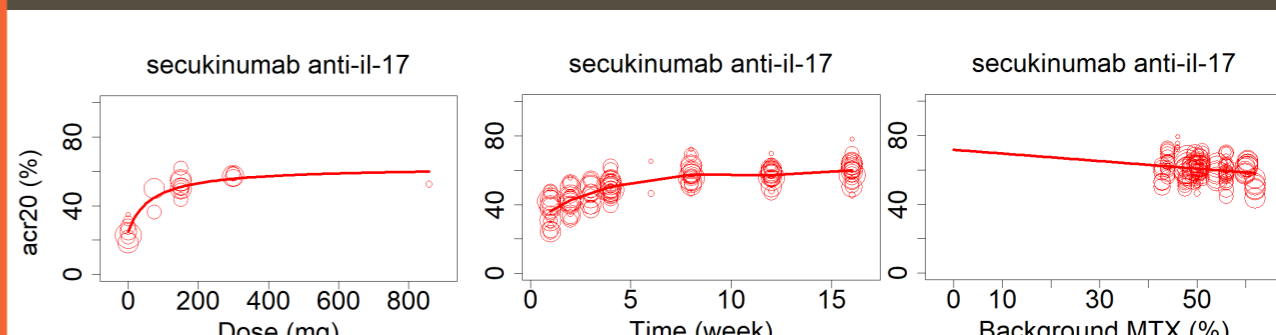
- Full MBMA of ACR20 response:** A model describing a constant treatment effect was estimated for all drugs except for secukinumab where a dose-response relationship was identified. Onset of response was estimated within time bins across classes. Use of background methotrexate was found to be a significant covariate suggesting a negative correlation between the percent of patients on methotrexate treatment and ACR20 response. The model was able to accurately describe available data. Model parameters were estimated with good precision. Partial residual plots for secukinumab, are shown in Figure 3, a subset of parameter estimates related to the onset of response and dose-response of secukinumab are shown in Table 1.

Table 1. Parameter estimates of full MBMA model

Parameter	Estimates	RSE
b_bck.mtx	-0.006	40%
Ed50_sec	67.15	7%
E_sec	0.377	10%
k <sub>1</sub>	0.5086	6%
k <sub>2</sub>	0.6077	8%
k <sub>4</sub>	0.7641	15%
k <sub>8</sub>	0.9315	73%
k <sub>12</sub>	0.9277	68%

Reference time point: week 16; bck.mtx associated with p-value < 0.0001 based on the likelihood ratio test; E\_sec: maximum effect for secukinumab; RSE: relative standard error; MTX: methotrexate; Only parameter estimates related to secukinumab and onset of effect are shown.

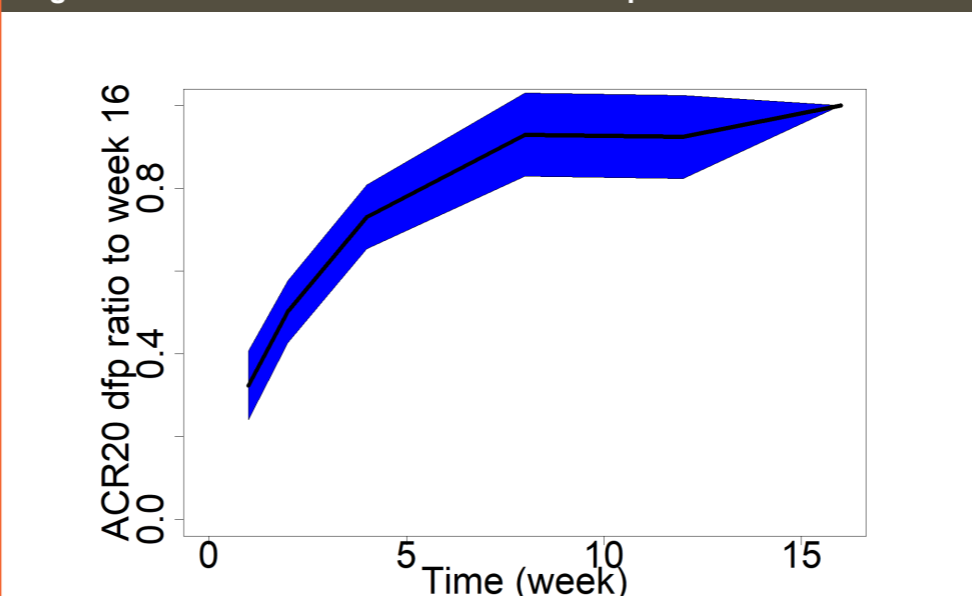
Figure 3. Partial residual plots for secukinumab vs dose, time and % of background MTX.



Observations (symbols) and predictions (solid line) were adjusted to the typical placebo response = 0.25, median background MTX = 54, reference time point = week 16, and maximum secukinumab dose = 857 mg

- Simulations of ACR20 response:** Simulated treatment effect relative to week 16 (Figure 4 and Table 2) indicated that approximately 90% of the ACR20 response at week 16 was reached at around week 8. Analogous results based on exploratory analysis are shown in Table 3, for comparison.

Figure 4. Simulated ACR20 difference from placebo ratio to week 16



Solid line: Model prediction based in maximum likelihood model parameter estimates. Shaded area: 95% CI based on 10000 simulated parameter estimates from the variance-covariance matrix

Table 2. ACR20 dfp ratio to week 16 based on full MBMA

Week	Fractional treatment effect relative to week (95% CI)
4	0.73 [0.65, 0.81]
8	0.93 [0.83, 1.03]
12	0.92 [0.82, 1.03]

ML full MBMA model predictions [95% CI]; CI: confidence interval; ML: maximum likelihood

Table 3. ACR20 dfp ratio to week 16 based on exploratory analysis

Drug class	Fractional treatment effect at week 8 relative to week 16 [95% CI]
anti-cd28	0.73 [0.55, 0.85]
anti-il-12/23	0.73 [0.6, 0.81]
anti-il-17	0.81 [0.75, 0.86]
anti-il-23	0.52 [0.43, 0.58]
anti-il-6	1.04 [0.77, 1.18]
anti-tnf	0.93 [0.87, 0.98]
jak kinase inhibitor	0.91 [0.62, 1.04]

95% CI based on 10000 simulated parameter estimates from the variance-covariance matrix

## Conclusions

- Exploratory and model-based meta-analysis methodology was successfully applied across different immune diseases.
- For both exploratory analyses of mean EASI score in AD and ACR20 response in PSA, onset of response was found to reach the plateau at approximately 8 weeks.
- These results were confirmed also in the full MBMA analysis where an unstructured onset model was assumed.

## References

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