

A model based meta-analysis of the placebo response for EASI and pruritus NRS scores in moderate to severe atopic dermatitis

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Introduction

- AD is a long-term inflammatory skin disorder mainly characterized by eczematous lesions and pruritus [1, 2].
- The assessment of disease severity and efficacy is based on various scoring tools including physician's assessment such as EASI and patient-reported outcomes e.g. pNRS [1].
- The course of the disease is heterogeneous, and the treatment response varies, potentially affecting the magnitude of the placebo response in AD studies [1, 3].
- The limited availability of longitudinal placebo data coupled with the small sample size in early phase studies makes the optimal treatment decision in late phase studies more challenging.

Methods

- Certara's Atopic Dermatitis Clinical Outcomes Database released in December 2022 was used in the current MBMA [4].
- 38 studies (3179 participants) with EASI score data and 28 studies (3060 participants) with pNRS score data were analysed.
- A moderate to severe AD population was considered in this analysis which was defined as follows:
 - age ≥ 18 yrs
 - baseline EASI score ≥16
 - IGA≥3
 - BSA involvement ≥10%
 - randomised drug: placebo
 - no topical corticosteroids, topical calcineurin inhibitor and antihistamines as background therapy in placebo arms of selected studies
- The analysis was conducted using R (version 3.2.5) on a validated GSK modelling platform.
- A two-stage approach was employed. The first step was to model the sd of the average placebo response. The second step was to model the placebo response.
- Logistic transformation was applied to absolute EASI and pNRS scores [5] and the propagation error function associated with the transformation was derived as shown below.

$EASI_{transf.} = -(\ln(72-EASI) - \ln(72+EASI))$	$sd_{transf.} = (sd/36)/(1-(EASI/72)^2)$
$pNRS_{transf.} = -(\ln(10-pNRS) - \ln(10+pNRS))$	$sd_{transf.} = (sd/5)/(1-(pNRS/10)^2)$
- A global estimate for all transformed sd values was obtained using a regression-based approach.
- Model development included the investigation of random effects and plausible covariates (i.e., study phase, study arm, baseline) on relevant parameters.
- Overall model GoF was assessed graphically and by statistical tests.

Results

- A three-parameter model was found to best describe the transformed sd values for EASI and pNRS scores (Table 1) whereas an exponential response model could adequately characterise the placebo response over time for transformed EASI and pNRS scores (Table 1, Figure 2).
- The transformed sd of EASI and pNRS scores was found dependent on time.
- No significant covariate effects could be identified.

Table 1: Summary of model parameter estimates

Model	Parameter (Unit)	EASI		pNRS	
		Value	se	Value	se
$\ln(sd) = \ln(sdbl + \exp(\alpha_0 + \alpha_1 * \ln(time/12)))$	sdbl	0.296	0.0248	0.571	0.0515
	α_0	-1.950	0.1852	-1.346	0.1514
	α_1	0.767	0.2768	1.008	0.2147
placebo = $\theta_{eo,i} + \theta_{eom,i} * (1 - \exp(-\exp(\theta_{ln(kt,i)} * time)))$	eo	0.8984	0.00524	1.81	0.0097
	eom	-0.3086	0.02041	-0.53	0.0646
	$\ln(kt)$ (1/wk)	-1.0305	0.15261	-1.58	0.2014
	kt (1/wk)	0.3570	NA	0.206	NA
	t½ (wk)	1.94	NA	3.37	NA

α_0 , natural log of sd increment from baseline to Week 12; α_1 , slope of relationship between $\ln(time/12)$ and $\ln(sd-sdbl)$; eo, intercept reflecting the immediate placebo response at time=0; eom, maximal placebo response reflecting the steady state placebo response; kt, rate constant reflecting the rate of change of placebo response over time; $\ln(kt)$, natural log of kt; sdbl, sd at baseline; t½, half-life of placebo response calculated as $\ln(2)/\exp(kt)$.

Abbreviations

AD, Atopic Dermatitis; BSA, Body Surface Area; GoF, Goodness of Fit; EASI, Eczema Area and Severity Index.; IGA, Investigator's Global Assessment Scale; MBMA, Model Based Meta-Analysis; Ph, Phase; pNRS, pruritus Numerical Rating Scale; sd, standard deviation; se, standard error; NA, not applicable

References

- Bieber T. *Nat Rev Drug Discov.* 2022;21:21-40
- Penton H et al. *Dermatol Ther (Heidelb).* 2023;13:2549-2571
- Lee HH et al. *J Am Acad Dermatol.* 2020;82(1):62-71

Conclusions

- An exponential model could adequately describe the time course of the placebo response for transformed EASI and pNRS scores.
- No significant covariate effects could be identified.
- Based on an exploratory graphical analysis, Ph2 studies seem to have a wider range in baseline EASI and pNRS score values compared to Ph3 studies.
- The proposed placebo models could be used as priors to support design characteristics and analyses in late phase AD studies.

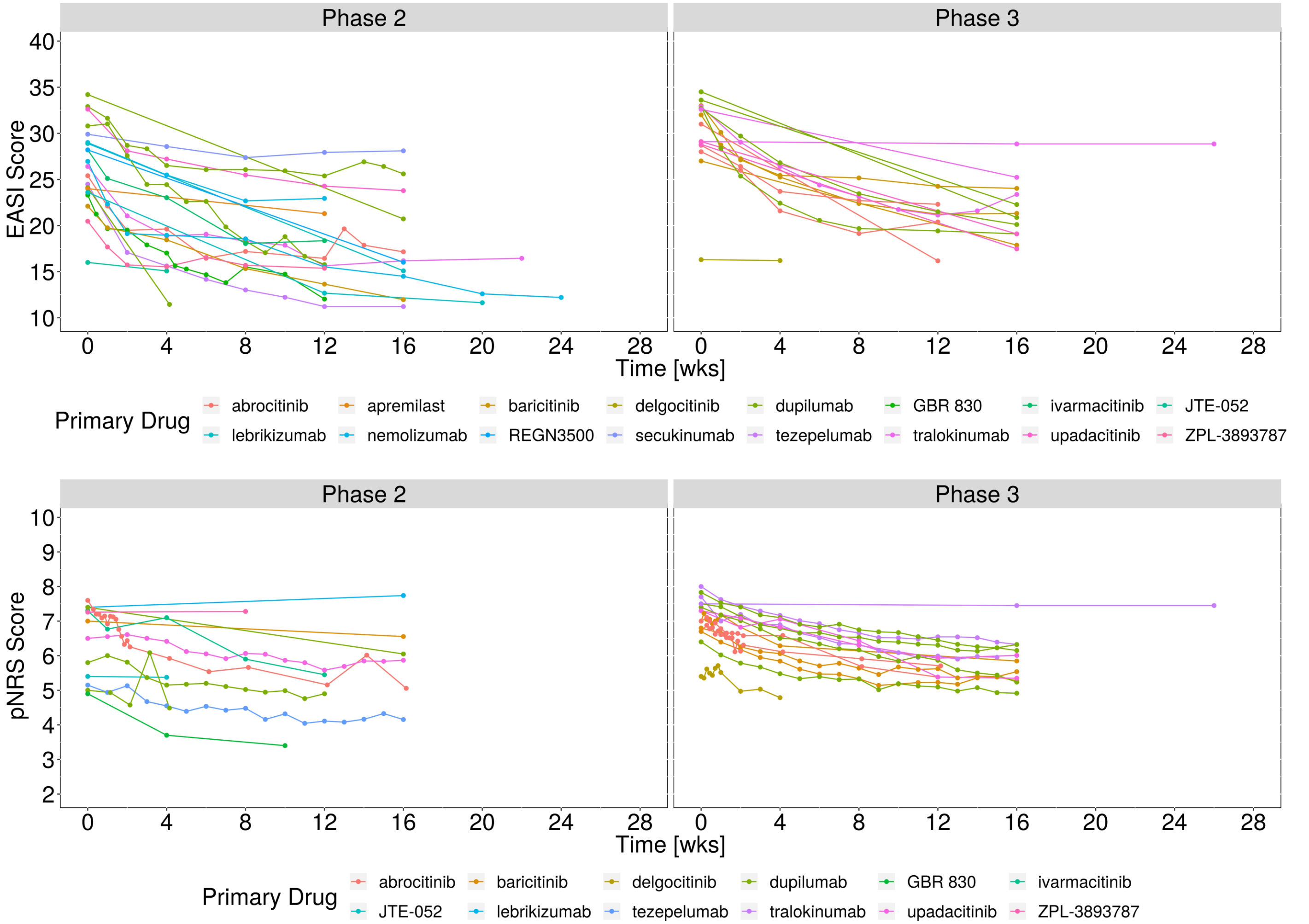
Objectives

- A MBMA was performed utilising publicly available efficacy data with the following objectives:
- to characterise the time course of placebo response, as assessed by EASI and pNRS scores, in patients with moderate to severe AD
 - to support design characteristics and provide higher confidence in dose-response analyses in late phase studies.

Results (cont'd)

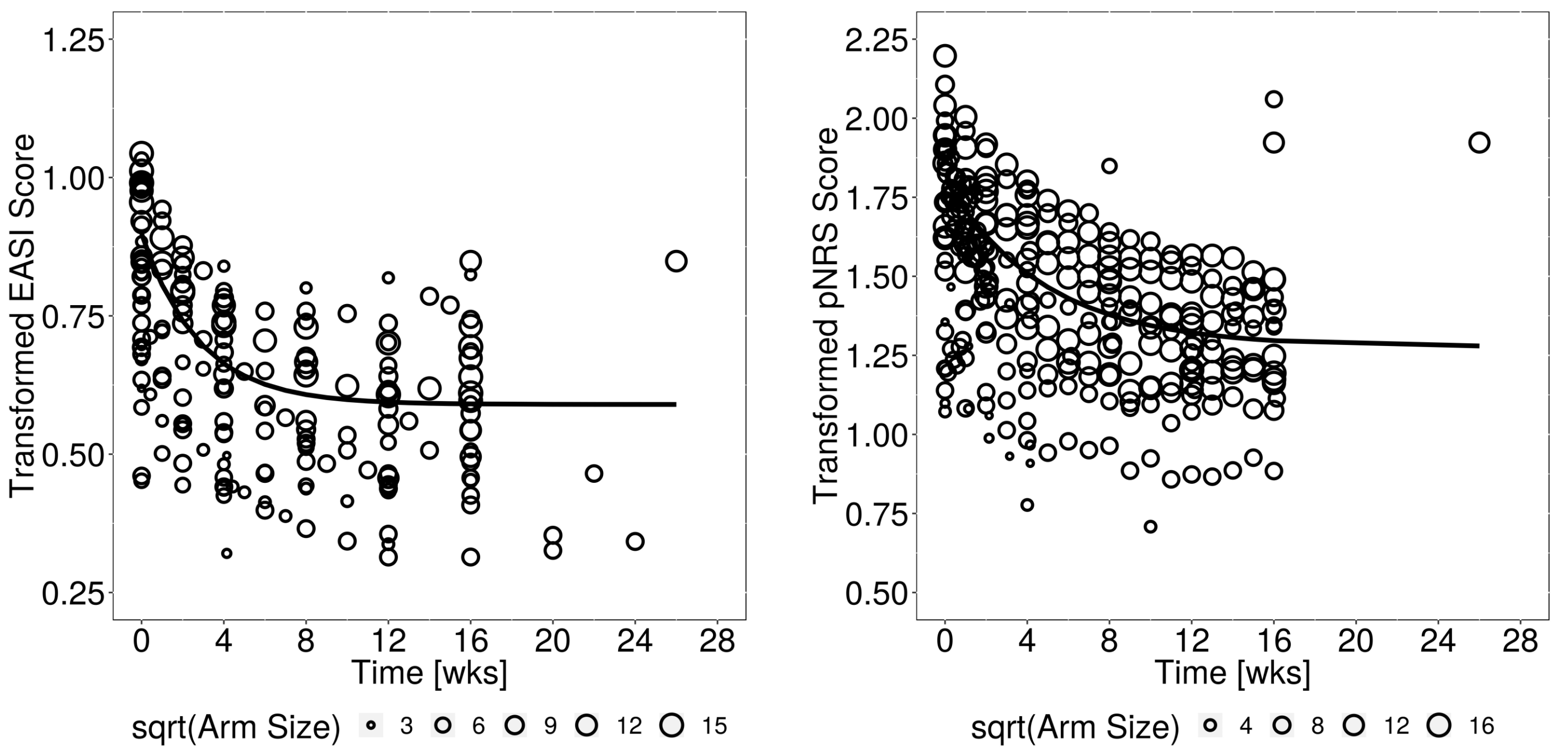
- Ph2 studies seem to have a wider range in baseline EASI and pNRS values compared to Ph3 studies (Figure 1).
- The sd of pNRS score seems to increase over time in Ph3 studies whereas in Ph2 studies, there is a tendency to decrease up to Week 3 and start stabilising beyond that timepoint. Of note, the Ph2 studies had a higher sd of pNRS score at baseline compared to the Ph3 studies.
- A faster half-life of placebo response was predicted for the transformed EASI score (1.94 wks) compared to the transformed pNRS score (3.37 wks).

Figure 1: Observed time course of EASI and pNRS placebo response by study phase and primary drug



Notes:
Phase 2a, Phase 2b, and Phase 2 studies have been pooled together and are shown as Phase 2. The absolute EASI and pNRS score values for baricitinib Phase 2 studies were missing from the source database and have been imputed as baseline*(1 + percent change/100).

Figure 2: Model-predicted and observed time course of the transformed EASI and pNRS placebo response



Notes:
Solid line shows the model-predicted time course of transformed EASI and pNRS placebo response. Open circles show the observed values of transformed EASI and pNRS placebo response.

Disclosures

EP, NBB, MS are employees of, and shareholders in, GSK.