Item response theory-enabled translation between DAS28 and ACR – Key clinical endpoints within Rheumatoid Arthritis drug development

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Conclusions

- The IRT model predicted longitudinal response in individual components and composite scores (ACR, DAS28), including the phase3 ACR20 response.
- The model can be applied for clinical trial design, and for translation between phase2 and phase3 clinical endpoints.

Objectives

- Develop a longitudinal item-response theory (IRT) model, capable of predicting both **DAS28 response** and the proportion of **ACR20 responders**.
- Increase understanding of **response to otilimab across underlying ACR components**, and the importance of the C-reactive protein (CRP) component on ACR20 response.

Data

- Clinical data were available from **phase 2a (n=39) [1] and phase 2b (n=222)** [2] trials of subcutaneous otilimab in RA patients on a stable dose of methotrexate.
- Longitudinal data were available for **22.5, 45, 90, 135, or 180 mg, and placebo**.
- Data for modelling: Free otilimab concentration (drug exposure measure) and CRP in serum (inflammatory measure), and the standard ACR measures.
  (28 and 66/68 swollen and tender joint counts [SJC/TJC]), physician's and patient's global assessment of arthritis [PhGA, PtGA], patient's assessment of pain [PtPAIN] and disability [HAQ-DI]).

Methods

- **PK model:** A two-compartment model predicted the **individual otilimab concentration-time profiles**, which were used in the dose-exposure-response model.
- **Item model:** The independent occasion approach [3] was used to map data to the latent variable(s), via **binomial or graded response models** with increasing difficulty parameters (HAQ-DI). CRP was reduced into integers, and 66SJC and 68TJC were split into 28 SJC/TJC and 38 SJC and 40 TJC.
- **Longitudinal model:** Change in individual baseline latent variables ('RA disease') were described by an indirect response model with **a disease progression effect** (increasing or decreasing at the individual level) and **an inhibitory Emax drug effect** (linked to individual otilimab concentration-time profile), as given by:

$$\frac{d\mathrm{LV}}{dt} = R_{in} \cdot \left(\left(1 - \frac{1}{PRGM}\right) \cdot e^{-\frac{log(2)}{PRGT} \cdot t} + \frac{1}{PRGM}\right) \cdot \left(1 - \frac{Imax \cdot C_{free}}{IC_{50} + C_{free}}\right) - k_{out} \cdot \mathrm{LV}$$

Parameters: R_{in} (zero-order production rate); k_{out} (first-order degradation rate); *PRGM* (change in R_{in} due to disease progression); *PRGT* (time, *t*, where R_{in} achieves 50% of PRGM); *Imax* (maximum inhibition of R_{in}); *IC50* (drug concentration that achieves 50% of Imax).

Results

- The final IRT model described all underlying components well, including the composite score and primary endpoint in the phase 2b trial (DAS28, **Figure 1**).
- Strong correlation in individual model parameters were observed between the patient reported scores (PtGA, PtPAIN, HAQ-DI) and the physician reported scores (SJC, TJC, and PhGA), whereas CRP did not correlate with any other scores.
- Predicted ACR20 response at Week12 for phase3 programme ('contRAst') doses of 90 and 150 mg once weekly were 55 and 57%, respectively (**Figure 2**).
- This corresponded well with contRAst 1 results (55 and 51%, respectively), even though a higher placebo response of 43%, compared to 19%, was observed [4].
- PhGA, TJC, and SJC showed the highest response (with ~80% of individuals having a 20% decrease at Week12), with lower response rates for HAQ-DI (~55%), PtGA (~65%), PtPAIN (~66%) and CRP (~60%).
- Disease progression (which generally resulted in improvement), was also highest for PhGA, TJC, and SJC (~45% of individuals with a 20% decrease).
- Nullifying the drug effect on CRP did not have a major impact on the predicted ACR20 response rate (54 and 56%, respectively for the two doses) (**Figure 2**).

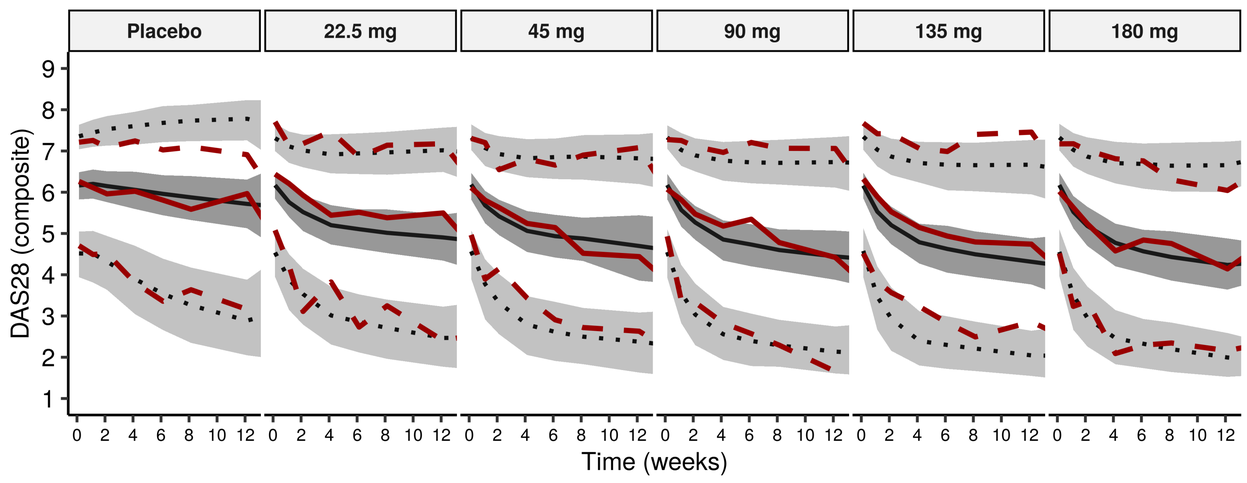

Figure 1: VPC for observed DAS28 response in the phase 2b trial. The median, 5th and 95th percentiles of the simulated data (black lines) are compared to the same statistics of the observed data (red lines).

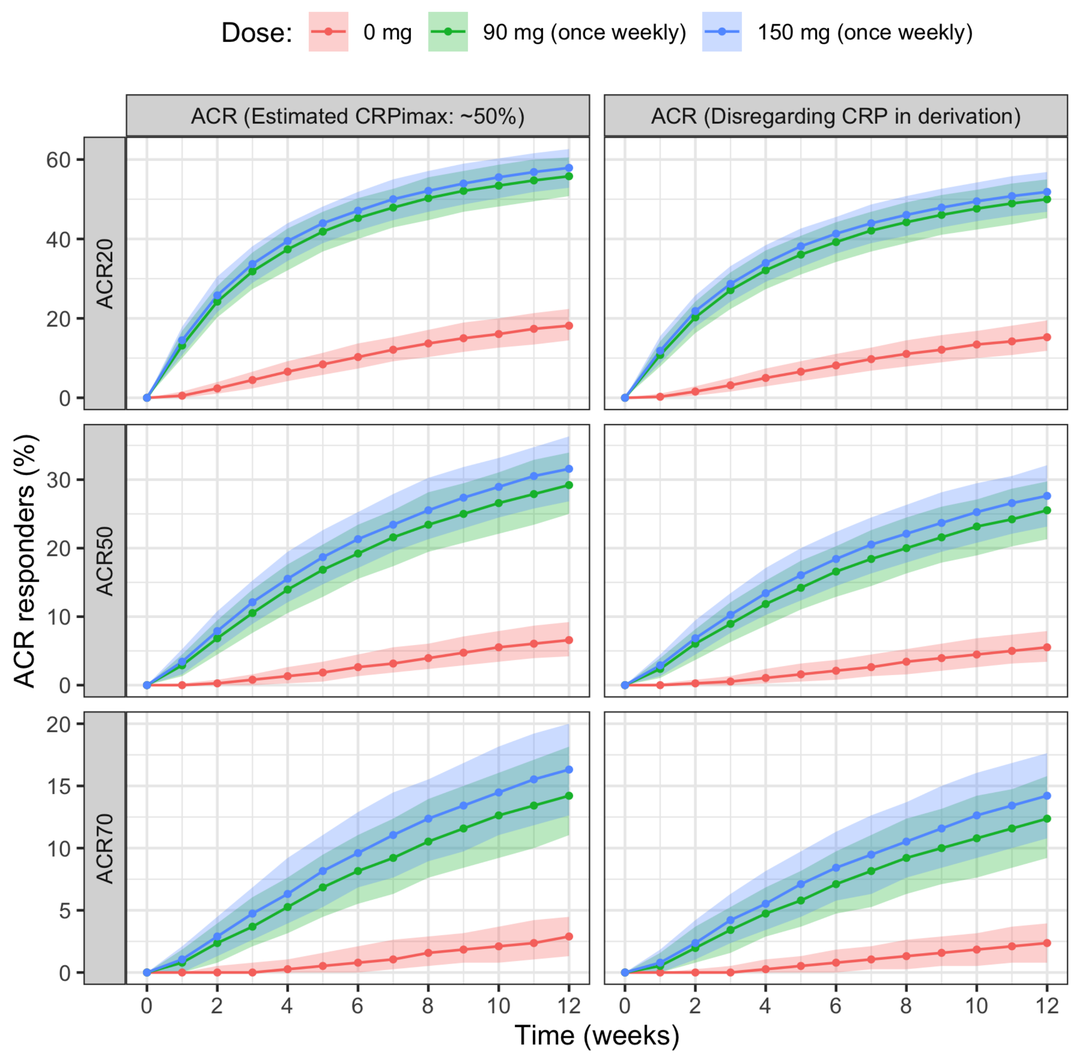

Figure 2: Simulations (n=500) mirroring the contRAst 1 protocol design, with ACR20/50/70 derived for the estimated effects (left) and for a case where CRP drug response is disregarded during derivation.

Background

- Otilimab, a high-affinity recombinant IgG1 antibody that binds to and inhibits GM-CSF, was developed for treatment of rheumatoid arthritis (RA).
- In RA, composite endpoints are used to measure disease activity and response to intervention. Most are based on a set of core disease activity measures established by the American College of Rheumatology (ACR).

References

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Disclosures

- Anders Thorsted's postdoctoral employment was financed by GSK through a research grant to Uppsala University.
- Anders Thorsted, Anubha Gupta, and Alienor Berges are employees of GSK and hold GSK shares.
- Mats O. Karlsson and Lena E. Friberg declare no competing financial interests.

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