Population PKPD Analysis of CD4 and ACR Response after SC Administration of Tregalizumab to Patients with Rheumatoid Arthritis

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Objectives

To develop population pharmacokinetic-pharmacodynamic (PKPD) models that describe the relationship between tregalizumab exposure, or dose, and the response in modulation of cell surface cluster of differentiation 4 (CD4) expression, as well as in clinical efficacy endpoints (American College of Rheumatology [ACR]).

Background

- Tregalizumab (BT-061) is a non-depleting anti-CD4 antibody with antagonist effect on effector T cells and agonist effect on regulatory T cells.
- Biotest has tested intravenous (IV) and subcutaneous (SC) formulations of tregalizumab in healthy volunteers (studies 961 and 985), rheumatoid arthritis (RA) patients (studies 962, 971 and 979), psoriasis patients (studies 967 and 973) and has just completed a Phase IIb study with SC administration in combination with methotrexate (MTX) in the treatment of subjects with active RA who have an inadequate response to MTX alone (study 986).
- To establish the full dose-response, Study 986 proposed a broad dosage range from 25 to 200 mg. Upon completion of this study 986, a population PKPD modeling analysis was performed.

Conclusion

The tregalizumab dose-CD4 relationship, as well as the tregalizumab dose-ACR relationship, in studies 962, 971, 979, and 986 were well captured by the developed PKPD models. The models predicted that at the highest dose level studied, 200 mg, the maximal effect in CD4 was not reached whilst minor ACR improvements were achieved.

Data and Methods

- The population PKPD analysis was based on data from the study 986 as well as 3 other Phase II clinical trials (studies 962, 971, and 979) with tregalizumab in RA patients.
- The PK properties of tregalizumab following single and multiple IV and SC administrations were first characterized using data from 4 other Phase I and Phase II studies in healthy volunteers and psoriasis patients (studies 961, 967, 973 and 985).
- The PK model was based on 697 samples from 159 subjects. The model was used to derive individual PK profiles for all subjects in studies 962, 971, 979 and 986.
- The data set used in the population PKPD analysis consisted of 3848 measurements of CD4 (CD4 mean fluorescence intensity [CD4MFI] observations) from 489 subjects, and 3726 ACR measurements from 530 subjects.

Results

In a preceding step, a population PK model describing the PK characteristics of tregalizumab was developed via simultaneous analysis of IV and SC data. The established PK model was in good agreement with the tregalizumab plasma concentrations observed in studies 962, 971, 979 and 986 (results not shown). Individual plasma concentration predictions at the time points of PD measurements in studies 962, 971, 979 and 986 were generated from the model.

Population PKPD models were developed to characterize the relationship between tregalizumab exposure, or dose, and the PD biomarker CD4MFI as well as the clinical efficacy endpoints ACR. Several dose and concentration dependent models were assessed and it was concluded that dose was a better predictor of the responses than the individual plasma concentration predictions.

The final CD4MFI model was a direct effect model (i.e. no delay between the BT-061 treatment and the CD4MFI response), where an maximum effect (E_{max}) function described the relationship between the BT-061 dose and the inhibitory effect on CD4MFI. E_{max} and ED_{50} were estimated to 0.677 and 58.6 mg, respectively. The typical CD4MFI reduction was estimated to 52% in the 200 mg dose group which was the highest dose level studied.

The final ACR model was a direct study-specific effect model between tregalizumab dose and the discrete probabilities of transition from a responder Markov state to another amongst: non-responder, ACR20, ACR50 or ACR70. The structure of the ACR model is depicted in Figure 1. In comparison to the control arm (MTX only) at 12 weeks, the 200 mg dose in study 986 was predicted to lead to an 11% (absolute) reduction in the transitions from ACR20 to non-responder and an increase in the transitions from ACR20 to ACR20, ACR50 and ACR70, of 6%, 5% and 0.5%, respectively.

The performances of the CD4MFI and ACR models were assessed by visual predictive checks (VPC) which showed good descriptions of the BT-061-CD4MFI and BT-061-ACR relationships, as illustrated in Figures 2 and 3.

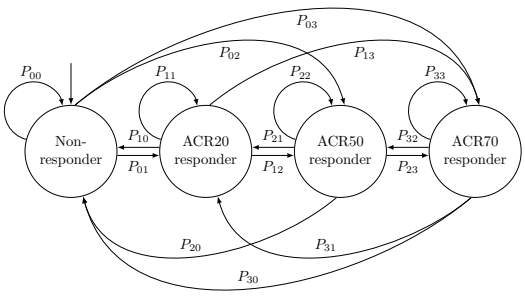

Figure 1. *Illustration of the four-state Markov model used in the ACR model. ACR: American College of Rheumatology*

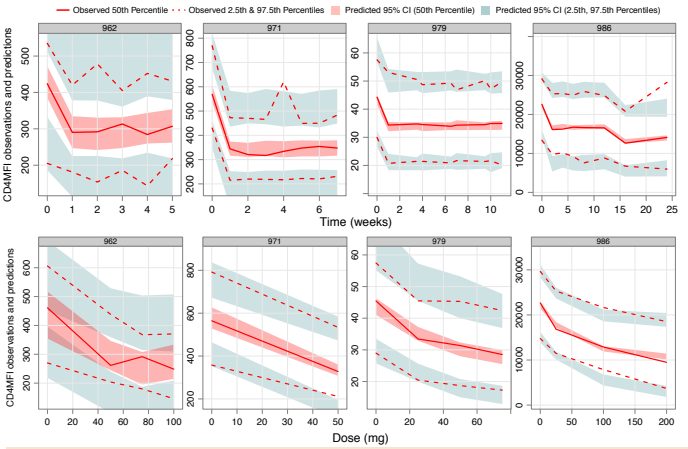

Figure 2. *Prediction corrected VPC of the final CD4MFI model versus time (top panels) and versus dose (bottom panels), stratified by study. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles predicted by the model. CD4MFI: CD4 mean fluorescence intensity; VPC: visual predictive check*

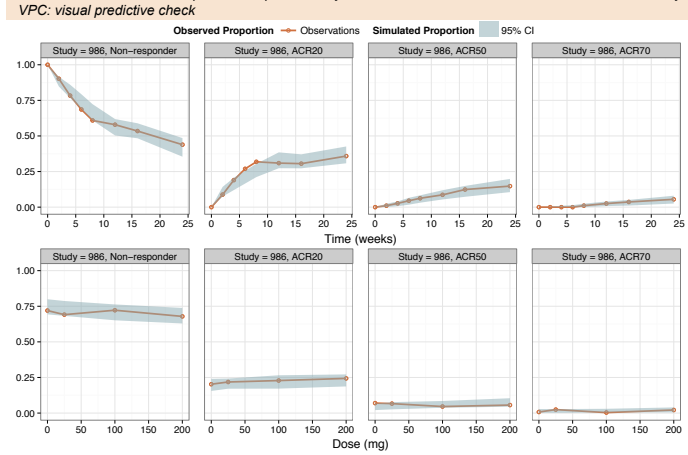

Figure 3. *Categorical VPC of the final ACR model representing the cumulative ACR response proportions versus time (top panels) and versus dose (bottom panels) for study 986. The solid lines represent the observations; the shaded blue areas represent the 95% confidence interval of the predictions from the model. ACR: American College of Rheumatology; VPC: visual predictive check.*