

Prediction of Free Target Suppression Following Subcutaneous Administration of Tanezumab Based on Target-Mediated Drug Disposition Approximation Model

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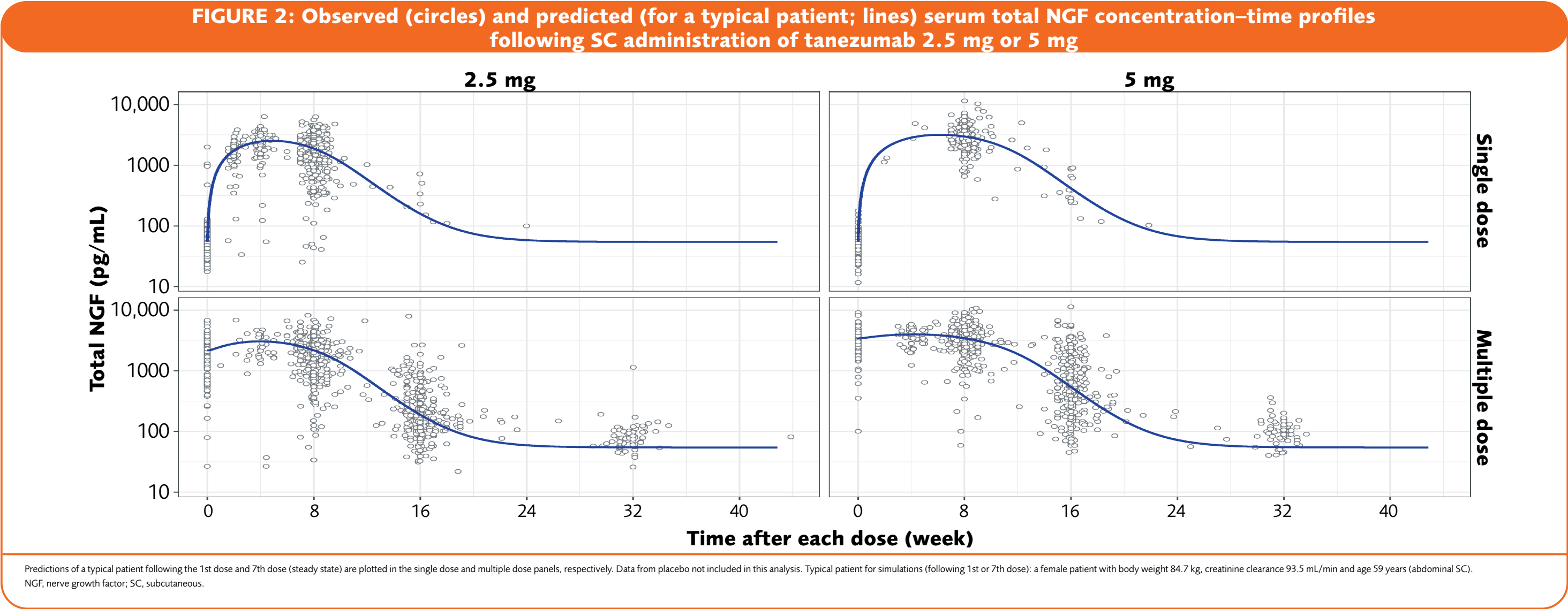
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INTRODUCTION

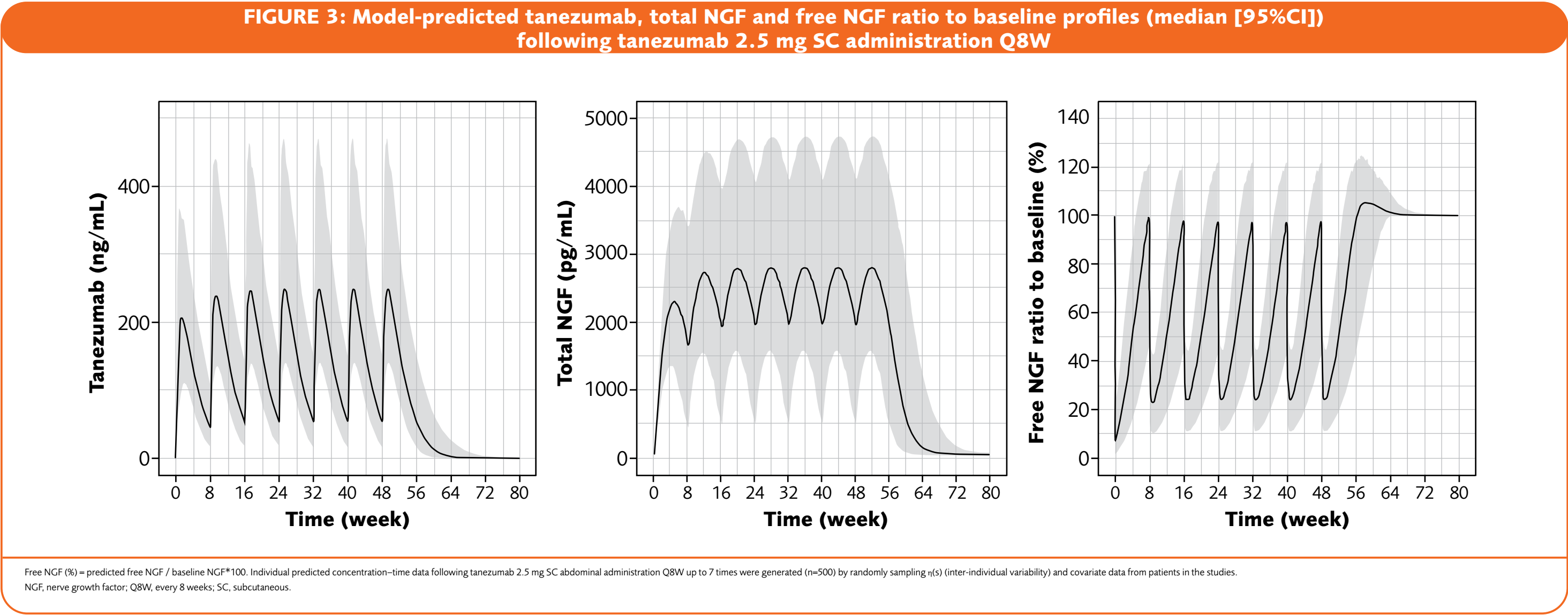
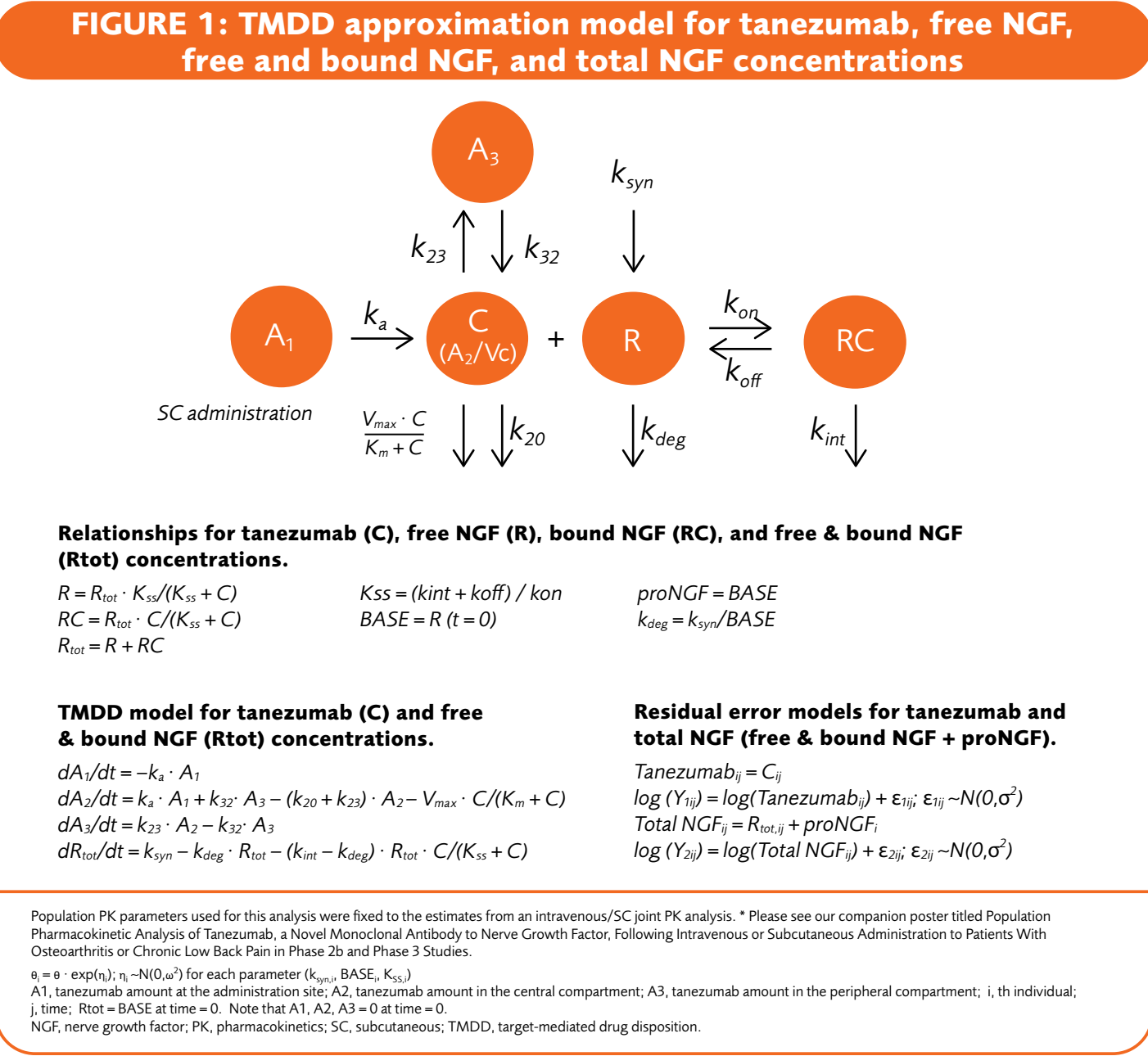
- Tanezumab, a novel monoclonal antibody against nerve growth factor (NGF), is being developed to treat pain from moderate to severe osteoarthritis (OA).
- NGF plays a role in the modulation of nociception, which has led to NGF becoming a novel and attractive therapeutic target for painful conditions.¹
- Target-mediated drug disposition (TMDD) approximation models were investigated to predict unobserved free systemic NGF concentration following tanezumab administration.^{2,3}
- Objective of this study was to predict free systemic NGF suppression following subcutaneous (SC) administration every 8 weeks (Q8W) of tanezumab in patients with OA based on a TMDD model updated from the previous investigation³ using available data from 3 pivotal phase 3 studies.

METHODS

- A TMDD approximation model; indirect response model interpretation of the Michaelis-Menten approximation to full TMDD model^{4,5} was fitted to plasma tanezumab and serum NGF (free and bound NGF, and proNGF) concentration–time data following SC administration of tanezumab 2.5 mg or 5 mg Q8W in patients with OA across 3 phase 3 studies (**Figure 1**).



Predictions of a typical patient following the 1st dose and 7th dose (steady state) are plotted in the single dose and multiple dose panels, respectively. Data from placebo not included in this analysis. Typical patient for simulations (following 1st or 7th dose): a female patient with body weight 84.7 kg, creatinine clearance 93.5 mL/min and age 59 years (abdominal SC). NGF, nerve growth factor; SC, subcutaneous.



Free NGF (%) = predicted free NGF / baseline NGF*100. Individual predicted concentration–time data following tanezumab 2.5 mg SC abdominal administration Q8W up to 7 times were generated (n=500) by randomly sampling η (s) (inter-individual variability) and covariate data from patients in the studies. NGF, nerve growth factor; Q8W, every 8 weeks; SC, subcutaneous.

- Population pharmacokinetic (PK) parameters used for this analysis were fixed to the estimates from an intravenous/SC joint PK analysis, which was separately conducted using data from phase 2/3 studies. In the studies, sparse PK data for plasma tanezumab were collected, whereas serum NGF data were collected in a subset of the population.
- These analyses used the non-linear mixed-effects modelling approach. The software packages NONMEM (non-linear mixed-effects modelling, version 7.3.0 with the parallel processing system) and Perl-speaks-NONMEM (a Perl module for NONMEM-related programming, version 4.7.9), and R software (a language and environment for statistical computing, versions 3.2.2, 3.4.1 and 3.6.1) were also used.

RESULTS

- The number of samples for plasma tanezumab concentration and serum total NGF concentration was 7856 (2542 patients) and 3490 (790 patients), respectively, which was used for the TMDD modelling. Of these patients, 706 patients had samples for both tanezumab and total NGF.
- The pharmacodynamic parameter estimates (relative standard error) for NGF production rate constant (ksyn), baseline NGF concentration (BASE), internalisation rate constant (elimination rate of tanezumab-NGF complex, kint) and steady-state constant (Kss) were 174 pg/mL/day (5.96%), 27.3 pg/mL (1.51%), 0.0309 1/day (8.21%) and 0.728 ng/mL (4.30%), respectively. Inter-individual variability for ksyn, BASE and Kss (CV) were estimated to be 22.0%, 20.2% and 48.3%, respectively. **Figure 2** shows observed and predicted (for a typical patient) total NGF concentrations.
- Predictions from the PK-NGF model indicate that 2.5 mg by SC administration Q8W would suppress free NGF concentration in the systemic circulation by approximately 75% near the peak of tanezumab concentration, and by <5% at the trough (**Figure 3**).
- Another simulation considering inter-individual variability indicated that free NGF concentration was predicted to return to the baseline level at approximately 8 weeks (95% prediction interval: 5 to 16 weeks) after the last SC dose of tanezumab 2.5 mg (**Figure 3**).

CONCLUSIONS

- A prior TMDD approximation model has been applied to data following tanezumab SC administration Q8W to provide a prediction of unobservable free systemic NGF suppression, in support of the understanding of the pharmacology of tanezumab.



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