

Population Pharmacokinetic Analysis of Tanezumab, a Novel Monoclonal Antibody to Nerve Growth Factor, Following Intravenous or Subcutaneous Administration to Patients With Osteoarthritis or Chronic Low Back Pain in Phase 2b and Phase 3 Studies

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INTRODUCTION

- Tanezumab is a monoclonal antibody that binds to and inhibits the actions of nerve growth factor (NGF).
- The NGF inhibitor class may offer an important breakthrough in the treatment of chronic pain and is under clinical investigation for the treatment of pain associated with osteoarthritis (OA) or other chronic pain conditions.
- Model-informed drug development (MIDD) approach including population pharmacokinetics (PK), PK/pharmacodynamics and target-mediated drug disposition modelling analyses have been incorporated across the drug development programme.¹⁻⁵
- This analysis describes an integrated population PK analysis of intravenous (IV) and subcutaneous (SC) data from patients with OA and chronic low back pain (CLBP) in pivotal phase 2b and phase 3 studies.
- The main objectives were:
 - Create IV/SC joint PK model across the phase 2b and phase 3 studies, conditioning on prior characterisation of factors impacting drug disposition.
 - Evaluate the factors impacting the absorption characteristics of tanezumab following SC administration across emerging phase 3 SC OA and CLBP studies.
 - Investigate the impact of baseline NGF and treatment-emergent anti-drug antibodies (TE ADA) patient status on tanezumab PK.

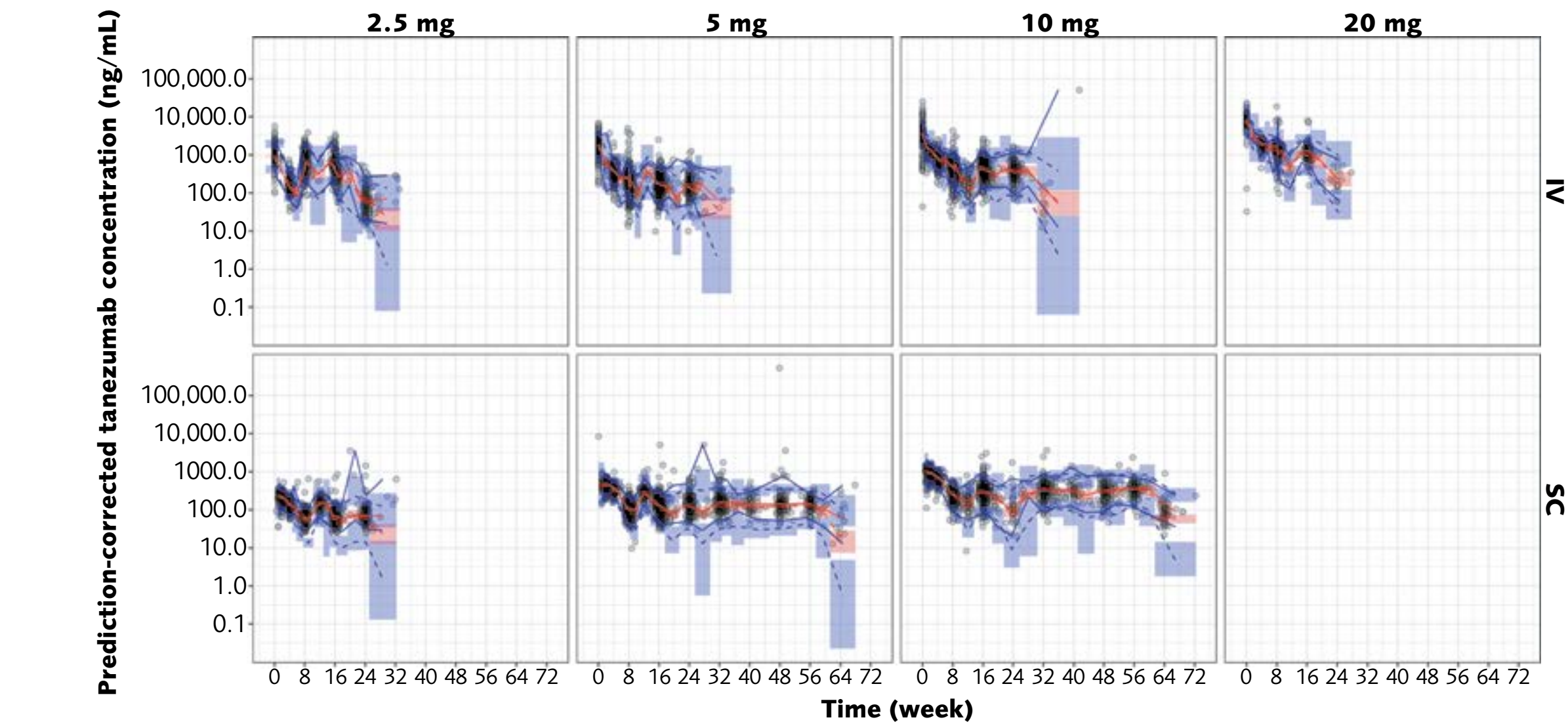
METHODS

- The model building was conducted based on the following 2-step strategy:
 - Analysis following both IV and SC administration based on a previous analysis of IV OA studies.⁵
 - Inclusion of the more recent phase 3 SC OA and CLBP studies into the model from 1.
- The potential impact of NGF levels, TE ADA and ADA titre was assessed by incorporating the covariate effect into the final model. These analyses used the non-linear mixed-effects modelling approach.
- The software packages NONMEM (v7.3) and Perl-speaks-NONMEM (eg, VPC, SCM, and SIR) and R software were also used.

RESULTS

- A 2-compartment model with parallel linear and non-linear eliminations and first-order absorption adequately described the plasma tanezumab concentration vs time data following tanezumab IV and SC administration across 4646 patients over 18,000 concentration measurements.
- Prediction-corrected concentration–time profiles were generally consistent with the observed profiles (**Figure 1**).

FIGURE 1: Prediction-corrected visual predictive check plot for tanezumab concentrations stratified by dose and administration route

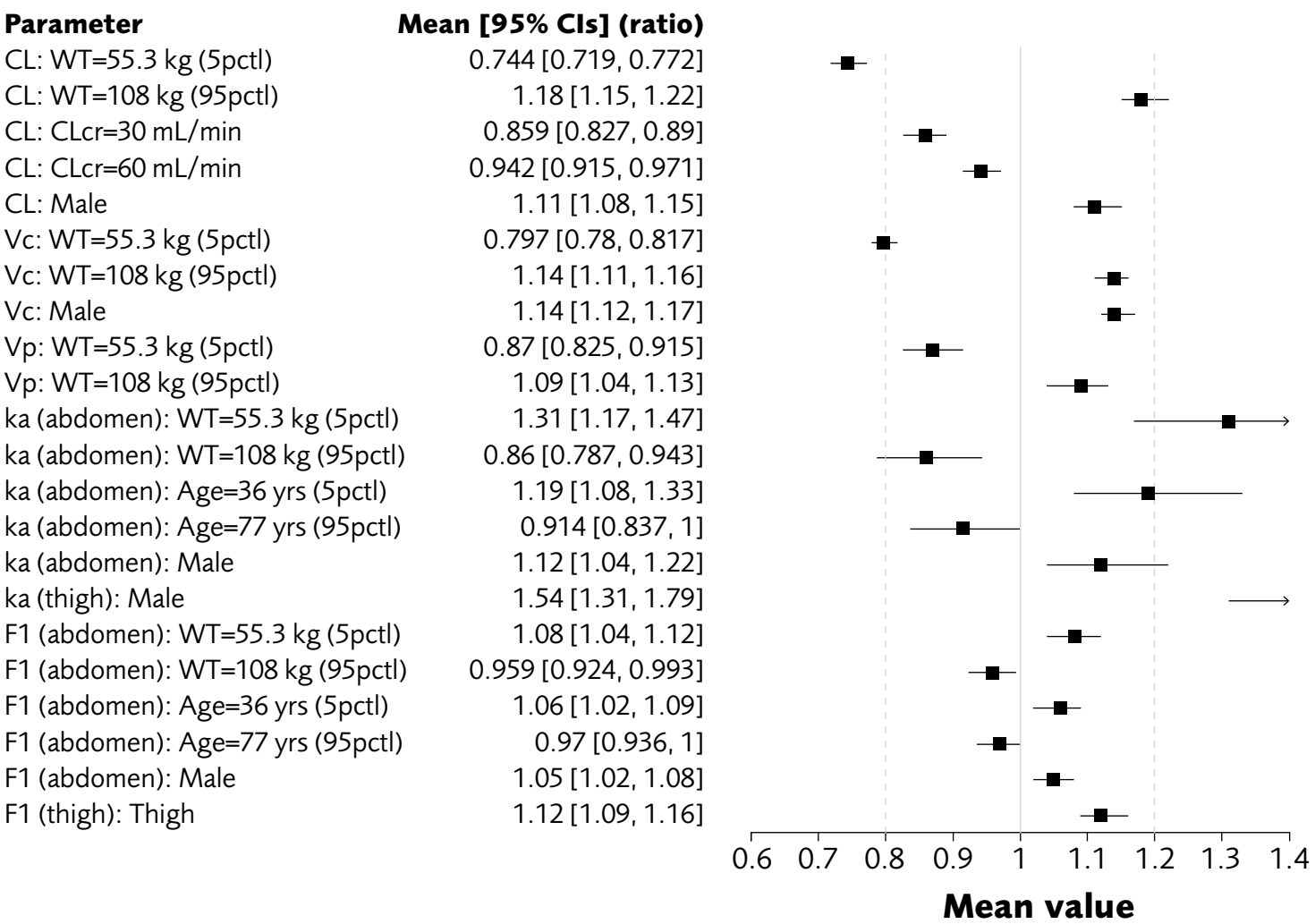


Red line (blue lines): observed median (2.5th and 97.5th percentiles). Red dashed line (blue dashed lines): model-predicted median (2.5th and 97.5th percentiles). Red areas (blue areas): model-predicted 95% CI of median (2.5th and 97.5th percentiles). Closed circle: observed tanezumab concentration–time data. IV, intravenous; SC, subcutaneous.

- The estimated disposition parameters clearance (CL), volume of central distribution (Vc), volume of peripheral distribution (Vp) and concentration at half maximum elimination capacity (Km) (relative standard error %) were 0.133 (0.961) L/day, 2.6 (0.733) L, 1.77 (1.26) L and 31.2 (24.1) µg/L.
- The bioavailability (F1) following SC administration into the abdomen for the more intensively sampled study was estimated to be 73% and 76% compared with 62% and 65% in the more sparsely sampled studies for females and males, respectively.
- Steady-state simulations for the every 8 weeks regimen indicated that despite the lower F1 and maximum concentration, tanezumab concentrations measured from Week 4 post-dose within a dosing interval were similar for the IV and SC routes of administration.
- The final model included effects of body weight (WT), dose, creatinine clearance (CLcr) and sex on CL; WT and sex on Vc; and WT on Vp.

- In addition, injection site (abdomen or thigh), age, sex and WT were estimated to impact F1, whereas age, sex and WT were also estimated to impact the rate of absorption (ka) following SC administration.
- WT was the only factor to influence CL and Vc with a greater than ±20% change across the WT distribution. A small 14% decrease in CL was observed with CLcr down to the 30 mL/min. In terms of ka, WT and sex led to a greater than ±20% change, whereas WT, age, sex and injection site also have a limited impact on F1 (**Figure 2**).
- Baseline NGF had a minimal but statistically significant effect on maximum elimination capacity (VM).
- The TE ADA status was associated with a 7% increase in CL. A model with ADA titre predicted a 6% increase in CL at the median of ADA titre levels.

FIGURE 2: Impact of individual covariates on population mean PK parameters as a ratio (95% CI) to reference covariate values



Each black box (horizontal lines) shows median (2.5th to 97.5th percentiles) for the corresponding population mean PK parameter as a ratio to reference covariate value. Vertical solid and dashed lines indicate ratio to reference 100% and ±20%, respectively. Arrows indicate that the limit exceeds range of the figure. Reference covariates values: WT = 84.7 kg, age = 59 years, CLcr = 93.5 mL/min, dose = 2.5 mg, route = SC administration (abdomen), sex = female, study = post-2015 SC studies. CL, clearance; CLcr, creatinine clearance; F1, bioavailability; ka, rate of absorption; pctl, percentile; PK, pharmacokinetic; SC, subcutaneous; Vc, volume of central distribution; Vp, volume of peripheral distribution; WT, weight.

CONCLUSIONS

- This IV/SC joint PK model adequately described the plasma tanezumab concentration vs time data following tanezumab IV and SC administration in patients with OA or CLBP.
- WT was the most important covariate. This is consistent with the original IV OA population PK estimation where WT was also the only covariate to significantly impact inter-individual variability (IIV), reducing it from 35% to 27% with other covariates only reducing IIV by another 1%.⁵
- This analysis supports the conclusions from prior analyses that there was no need to adjust the dose of tanezumab across the range of demographics (WT, sex, age, race, renal function) or choice of injection site.
- Baseline NGF had a minimal effect on VM. The TE ADA status was associated with a slightly higher clearance of tanezumab, but there was no evidence of a clinically meaningful difference.



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