Population Pharmacokinetics of a Monoclonal Antibody Tanezumab in Chronic Pelvic Pain Conditions
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Background
Nerve Growth Factor (NGF) is involved in the transmission and sensation of inflammatory and neuropathic pain signalling1-2. Tanezumab, a humanized monoclonal IgG2 antibody that binds NGF with high affinity and specificity and effectively blocks NGF activity3, reduces pain and improves function patients with moderate to severe pain from Osteoarthritis (OA) of the knee and hip and chronic lower back pain4. Tanezumab is currently being investigated for the treatment of pain in subjects with Chronic Pelvic Pain Conditions, such as Inestinal Cystitus (IC), Chronic Prostatitus (CP) and Endometriosis (ENDO). The goal of this exploratory population pharmacokinetic (PK) analysis was to assess the PK of Tanezumab in patients with Chronic Pelvic Pain Conditions and osteoarthritis and specifically:
- to explore demographic covariates that may be predictive of Tanezumab exposure
- to compare the exposure in subjects with OA and Chronic Pelvic Pain conditions

Methods
This analysis included a total of 3239 PK measurements from 303 patients across the 4 populations. All studies were parallel group, randomized, placebo-controlled, double-blind studies, to document efficacy, safety and PK. Serial blood samples were collected over a period of 16 – 24 weeks after IV infusion over 10 min. Of the number of subjects included in the PK analysis, 75 OA subjects received a single dose of either 25, 100, 200 or 330 µg/kg, 33 IC subjects 200 µg/kg, 30 CP subjects 20 mg and 22 ENDO subjects 15 mg. 143 OA subjects received two doses of either 100 or 200 µg/kg separated by 8 weeks. The demographic parameters across the treatments are summarized in table 1.

Model development was performed using non-linear mixed effects modelling with a proportional odds model (NONMEM 7.2 using ADVAN 4 TRANS4 from the PREDDD library). The test for inclusion of an individual covariate was to be performed at a significance level of 0.05, during the forward step model development.

Results
An IV infusion, 2-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination pathways adequately describes the population PK of tanezumab across all indications. The final model was described using two additive sigma’s, and a mixture model. The shrinkage estimates are summarised in table 2 and figure 1. Across all single covariates candidate models, only models with bodyweight on Cl, V1 and V2 separated by 8 weeks. The demographic parameters across the treatments are summarized in table 1.

Figure 1: Typical Individual (Patient) Tanezumab Concentration Time Profile by Indication

Figure 2: Comparison of Conditional Weighted Residuals for the Final Tanezumab PK model indicating a General Lack of Model Specification.

Figure 3: Histogram of Tanezumab Population PK Final model Individual Random Effect Parameters illustrating the Between Subject Variability Parameter Distributions.

Conclusions
The Pharmacokinetics of Tanezumab was well described by a 2-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination pathways.
Pharmacokinetics of Tanezumab in patients with Chronic Pelvic Conditions appear to be similar to those in Osteoarthritis.

REFERENCES