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 signalling[1,2]
Tanezumab, a humanized monoclonal IgG2 antibody that binds NGF with high affinity and specificity and effectively blocks NGF activity[3], reduces pain and improves function patients with moderate to severe pain from Osteoarthritis (OA) of the knee and hip and chronic lower back pain[4].
Tanezumab is currently been investigated for the treatment of pain in subjects with Chronic Pelvic Pain Conditions, such as Institual 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 300 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.**

Table 1 Baseline Demographics

	Osteoarthritis	Institual Cystitus	Chronic Prostatitus	Endometriosis
Gender n (%)				
Female	123 (56)	30 (91)	0	22 (100)
Male	95 (44)	3 (9)	30 (100)	0
Age, y, mean (SD)	56.5 (7.8)	43.2 (14.0)	50.5 (11.9)	29.9 (6.7)
range	35 - 78	21 - 74	28 - 72	19 - 42
BWT, kg, mean (SD)	90.5 (18.9)	77.0 (17.9)	88.7 (14.2)	69.2 (14.7)
range	42 - 139	52 - 136	60 - 132	48 - 94

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 described the population PK of tanezumab across all indications. The residual error was described using two additive sigma's, and a mixture model. The shrinkage was low for Cl, V_1 and V_2, 5 – 16%, but large for Vm 50%. The final model estimates are summarised in **table 2 and figure 1.** Across all single covariates candidate models, only models with bodyweight on Cl, V1 and V2 decreased the OFV by 54 points.

Table 2 Summary of Population PK Parameters

Parameter	Estimate	RSE (%)	Parameter	Estimate	RSE (%)
Cl (L/day)	0.178	3.2	low RSV (%)	9.3	23.6
V1 (L)	3.35	2.5	high RSV (%)	33.8	20.5
V2(L)	2.85	2.7			
Q (L/day)	0.851	2.6	IIV CL (%) eta1	35.8	28.6
Vmax (µg/day)	5.08	23.6	IIV V1 (%) eta2	30.7	26.9
Km (µg/L)	15.8	52.5	IIV V2 (%) eta3	28.6	34.1
Weight on Cl	0.867	12.6	IIV Vmax (%) eta4	48.8	14.9
Weight on V1	0.689	15.1	corr Cl-V1	0.09	7.8
Weight on V2	0.696	11.8	corr Cl-V2	0.07	9.5
Mix Prob. Low RSV	0.769	3.6	corr V1-V2	0.07	8.1

Plots of conditional weighted residuals and histograms of between subject random-effects illustrate general lack of model misspecification (**Figure 2 and 3**) and illustrate homogeneity of between subject variance.

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

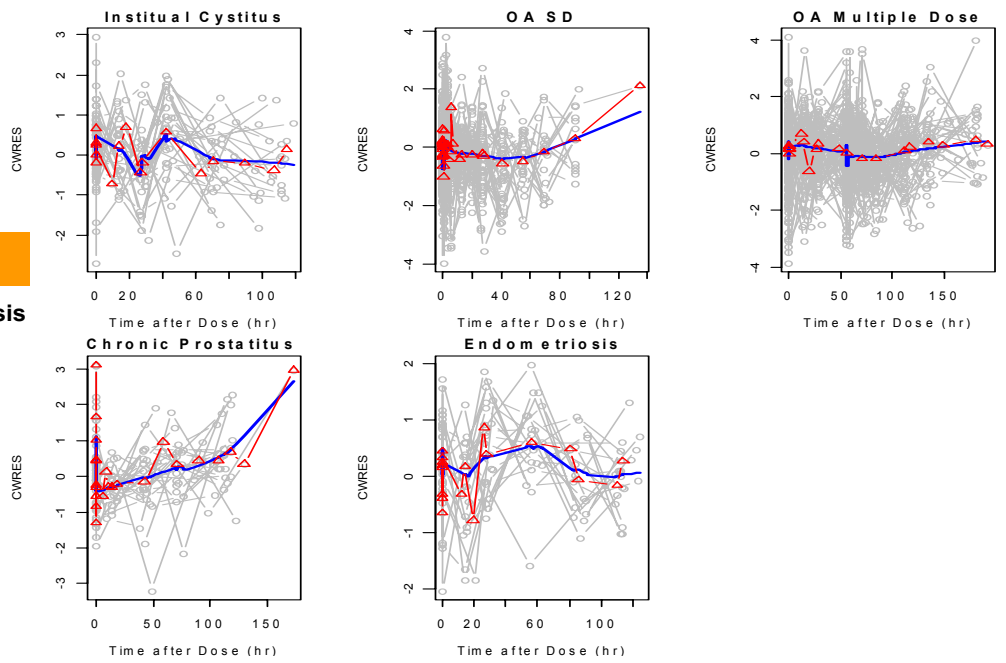


Figure 3: Histogram of Tanezumab Population PK Final model Individual Random Effect Parameters illustrating the Between Subject Variablity Parameter Distributions.

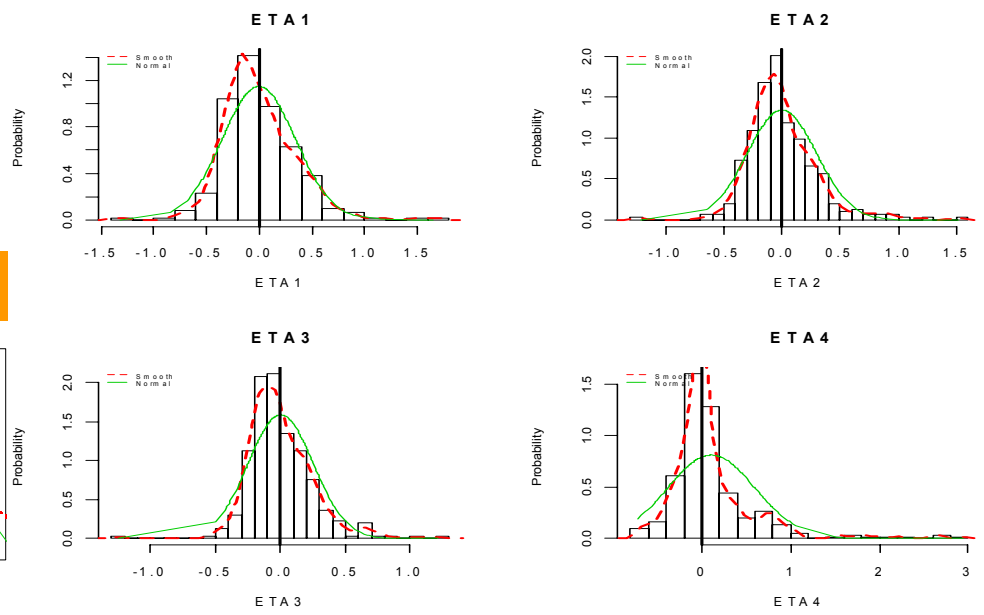
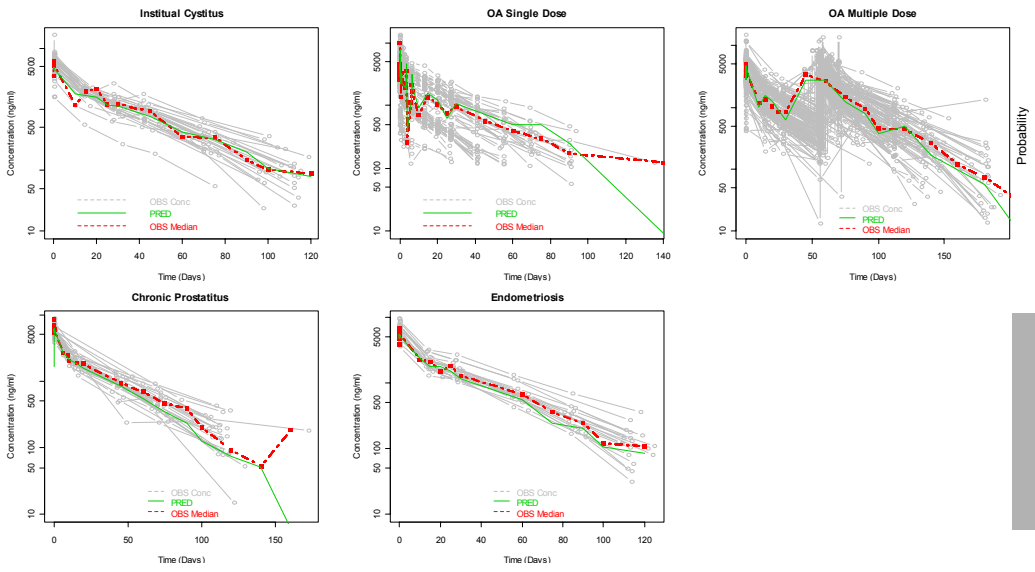


Figure 1: Typical Individual (PRED) Tanezumab Concentration Time Profile by Indication



Conclusions

The Pharmacokinetics of Tanezumab was well described by a 2-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination pathways.

Pharmacokinetics of Tanezumeb in patients with Chronic Pelvic Conditions appear to be similar to those in Osteoarthritis.

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