Translational Modeling of Tanezumab Pharmacokinetics (PK) and Tanezumab-NGF Relationship to Predict Free NGF Concentrations in Nonhuman Primates (NHP) and Humans

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Purpose

Tanezumab is an anti-NGF mAb that is currently being tested in Phase 3 studies to treat moderate-to-severe osteoarthritis (OA) patients for chronic pain. A PK-NGF model was developed to predict the NGF suppression in OA patients. The model was used to predict unobserved NGF suppression in NHP that were investigated for neuronal safety at high tanezumab exposure levels.

Methods

The database consisted of plasma tanezumab concentrations (n=2330) and total NGF concentrations (n=3222) collected in two Phase 3 Studies from OA patients (n=737) who received 2.5 mg, 5 mg, or 10 mg doses of tanezumab subcutaneously Q8W. For NHP predictions, tanezumab concentrations (n=1076) were available in 33 NHPs with dosing of 1.2 mg/kg/Q8W subcutaneously over a 6 month period. The population PK and PK-NGF analyses were conducted via nonlinear mixed-effects using NONMEM 7.3.0. A sequential approach was used for the modeling of the clinical data with fixed population PK parameters in the PK-NGF binding model utilizing a quasi-steady-state (QSS) approximation of the target-mediated drug disposition (TMDD) model to predict drug, target concentrations and target inhibition (1).

Results

The human SC PK was described by a two-compartment model with first-order absorption and parallel linear and non-linear elimination. In the PK-NGF binding model, the Kss (quasi-steady-state constant) and NGF elimination rate were estimated with good precision and were similar to vitro Kd and nonclinical estimates respectively. The NHP PK was described by a linear two-compartment model with first order SC absorption. Supported by in vitro (2) and in vivo (3) data, NGF related parameters (Kint: internalization rate constant of the NGF-tanezumab complex; Ksyn: zero-order NGF production rate; Kss: quasi-steady-state constant; baseline NGF) were assumed to be equivalent to the clinical estimates in the NHP PK-NGF model. In humans, comparison of predicted free NGF concentrations with observed markers of pain relief indicated that exposure predicted to result in partial suppression of NGF (~25%) is associated with clinical benefits while 20-fold higher exposure in NHPs predicted to result in >90% NGF suppression is not associated with adverse events (4).

Conclusion

Translational PK-NGF modeling was shown to be a useful tool to bridge between species target-driven effects and helped with interpreting exposure margins across clinical and nonclinical studies.

References:

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