Tanezumab is a humanized monoclonal IgG2 antibody that binds to human nerve growth factor (NGF) with high affinity and specificity.

Tanezumab is currently in development for the treatment of osteoarthritis, chronic low back pain, and other chronic pain conditions.

**OBJECTIVE**

- To characterize the exposure-response (overall daily pain score (DPS)) relationship vs. time for tanezumab.

**METHODS**

**Study Design**

- Four hundred and forty-four osteoarthritis (OA) patients were treated in one of the following dose groups: placebo or 10, 25, 50, 100, or 200 μg/kg tanezumab administered as a 10-minute intravenous (IV) infusion on 2 occasions, 55 days apart (Day 1 and Day 56).
- Blood samples for the determination of tanezumab plasma concentrations were collected before and 1 and 2 hours after both doses of tanezumab (Days 1 and 56) as well as on Days 14, 28, 70, 84, 112, 136, and 182.
- DPS was recorded every evening on a visual analog scale (VAS) describing average pain over the past 24 hours from 0 (no pain) to 100 (worst pain possible).

**Modeling Strategy**

- The PK of tanezumab was well described by a 2-compartment model. The plots of VPC indicate that the observed mean DPS (with 90% confidence intervals) was well predicted by the model (Figure 5).
- The PK/PD model developed for the average weekly pain score (WPS) dose response, showing the largest and smallest effects for dosing intervals of 6, 8, and 12 weeks, demonstrates that efficacy is maintained across an 8-week dosing interval (Figure 4).

**RESULTS**

- The PK of tanezumab was well described by a 2-compartment model.
- Body weight was found to be a significant predictor of clearance and volume.
- Incorporating an auto-correlation strategy and dose regimen.
- The naive pooled approach was employed.
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- The model used here was limited by the assumption that each DPS observation was independent, which was not the case. The model can be improved by:
  - Incorporating an auto-correlation
  - Investigating the random effects model and improving the skewness of inter-individual variability.
  - Incorporating a mechanistic component of the biology of NGF to describe the observed attenuation of DPS.
- Extending work to other clinical pain states.

**DISCUSSION**

- The model used here was limited by the assumption that each DPS observation was independent, which was not the case. The model can be improved by:
  - Incorporating an auto-correlation
  - Investigating the random effects model and improving the skewness of inter-individual variability.
  - Incorporating a mechanistic component of the biology of NGF to describe the observed attenuation of DPS.
  - Extending work to other clinical pain states.

**CONCLUSIONS**

- The DPS data were adequately described by the proposed semi-mechanistic PK/PD model.
- Subsequent simulations using the PK/PD model support the use of an 8-week dosing regimen with fixed doses of 2.5, 5, and 10 mg tanezumab in Phase 3 studies in OA patients.