Scientific strategies necessary to resolve FDA clinical hold on anti-nerve growth factor inhibitors: The story of tanezumab

Patrice BÉLANGER1, Mark BUTT2, Paul BUTLER1, Siddhartha BHATT3, Stephen FOOTE3, Dave SHELTON4, Mark EVANS1, Rosalin ARENDS3, Susan HURST3, Carlin OKERBERG3, Tom CUMMINGS3, David POTTER3, Jill STEIDL-NICHOLS3, Mark ZORBAS1

1Pfizer Inc, San Diego, USA, 2Tox Path Specialists, LLC, USA, 3Pfizer, Inc., Groton, USA, 4Pfizer, Inc., South San Francisco, USA

Tanezumab is a monoclonal antibody (mAb) that binds to and inhibits the actions of nerve growth factor (NGF). Tanezumab is under clinical investigation for the treatment of pain associated with osteoarthritis, chronic low back pain, and cancer pain. On 14 December 2012, the U.S. Food and Drug (FDA) placed all anti-NGF mAb development programs on partial clinical hold due to adverse changes in the sympathetic nervous system of mature animals. The FDA indicated that to resume clinical studies, Pfizer must submit rigorous scientific data which characterize the sympathetic nervous system response to tanezumab and provide evidence that tanezumab may be used safely for the duration of the proposed clinical studies. Since the issuance of the partial clinical hold, Pfizer completed three studies in nonhuman primates to examine further the effects of tanezumab on the sympathetic nervous system. The results from these studies characterized the sympathetic nervous system response to tanezumab and clearly established that tanezumab does not cause neuronal cell death. In addition, these results show that exposure to tanezumab in non-human primates is associated with stereological changes in sympathetic ganglia, including smaller ganglion volume, smaller average neuron size/area, and lower estimated total neuron counts. These effects do not progress over time, are fully reversible, and are not associated with any adverse functional consequences. These data were submitted to the FDA in February 2015. In March 2015, FDA lifted the partial clinical hold on the tanezumab development program, allowing osteoarthritis and chronic low back pain studies with tanezumab to proceed.