



## ***Mechanistic Models to Simulate Dose Response of IgE Suppression Following Dosing of Anti-IgE Monoclonal Antibodies***

**Conducted by Pascal Chanu, PharmD., Pharsight - A Certara Company**

**Your moderator will be Linh Nguyen, Exelixis**

**Thursday, August 5, 2010 from 12:30 pm to 2:00 pm EDT**

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### **About the Webinar:**

The purpose of this webinar is to provide an overview of biomarkers, highlighting critical concepts such as: the characteristics of target versus mechanism biomarkers, biomarker assay issues, and the role of constructing and validating mechanistic PK-PD models for translational research.

**Objectives:** The aim of this study was to use mechanistic models to simulate dose response of IgE suppression for anti-IgE monoclonal antibodies such as omalizumab vs. higher affinity antibodies.

**Methods:** A previously published instantaneous equilibrium (IE) drug-IgE binding model for omalizumab [1,2] was used to perform simulations of expected IgE suppression for anti-IgE monoclonal antibodies. The equilibrium assumption being only valid for limited ranges of drug affinity and dose, the IE model was extended to a full target-mediated disposition (TMD) model [3]. The models were implemented in Pharsight® Trial Simulator™ to perform simulations. Model implementation was evaluated by simulating multiple replicates of the data in the original papers and comparing with published plots and results. The TMD model was then used to simulate dose response (proportion of patients with IgE suppression below threshold levels, e.g. 50 ng/mL) in specific regions of the omalizumab dosing table including patients non-treatable by omalizumab (Xolair package insert) for omalizumab, and other more potent anti-IgE antibodies (10-to 30-fold increase in affinity) to characterize the affinity-potency relationship of such antibodies.

**Results:** Both the IE and TMD models reproduced well the data in the original papers. The IE model however, predicted continuous increase in in-vivo potency with increasing IgE affinity whereas the TMD model predicted a maximum 2.4 to 3-fold increase in potency with a 10-fold increased affinity and no difference between 10-fold and 30-fold increase in affinity. The latter is consistent with clinical data [4]. Simulations demonstrated that a 10-fold more potent drug would suppress free IgE below 50 ng/mL in 95% of the patients (a suppression associated with clinical efficacy in asthma) at 225 mg every 2 weeks in the most challenging patient subgroup (i.e. patients with high IgE and large body weight).

**Conclusions:** A fully mechanistic TMD model is required for PKPD translation across anti-IgE antibodies and should be pursued in the clinical setting wherever possible. There is potential to treat a larger patient population with a more convenient dosing paradigm and a higher potency anti-IgE antibody.

## About the Presenter:



At the end of his Pharm D, Pascal Chanu started Modeling during hospital residency, performing therapeutic drug monitoring in children and also his first runs with NONMEM. He joined Roche (Basel) in 2003 for six years as pharmacometrician and as Disease Area Modeling & Simulation expert in CNS. He is now based in Lyon, working for Pharsight since November 2008 within the European Strategic Consulting Group. He dealt with various therapeutic areas, among them Virology, CNS, Anemia, Cardiology, Diabetes.

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