Title: A Mechanism-based Population Model of Vildagliptin Pharmacokinetics and Dipeptidyl Peptidase IV Inhibition

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Objectives: Vildagliptin is a novel antidiabetic agent that acts by inhibiting dipeptidyl peptidase IV (DPP-4). The objective of this modeling was to 1) assess the PK of vildagliptin at different dose levels by population PK modeling, 2) build a mechanism-based population model that simultaneously describes the PK of vildagliptin and its effects on DPP-4 activity at different dose levels based on the underlying physiology.

Methods: Thirteen patients with type 2 diabetes mellitus received oral doses of vildagliptin 10 mg, 25 mg, 100 mg and placebo twice daily for 28 days in a double-blind crossover study [1]. Vildagliptin concentrations, DPP-4 activity, active glucagon-like peptide-1, active glucose-dependent insulinotropic peptide, glucose, insulin, and glucagon were measured on day 28 of each period. All data on PK and DPP-4 activity were co-modeled in NONMEM VI with the method FOCE with interaction.

Results: A model for target-mediated drug disposition (TMDD, [2]) that accounts for the high-affinity binding of vildagliptin to its target DPP-4 in plasma and tissues could well describe the PK and DPP-4 activity data simultaneously. The binding of vildagliptin to DPP-4 can be described by capacity-limited kinetics. Most vildagliptin molecules dissociate from the receptor by a slow first-order process. A smaller fraction of the bound drug is hydrolyzed by DPP-4 which results in an inactive metabolite. Data are population mean (inter-individual coefficient of variation). The total non-saturable clearance was 33 L/h (22%), the central volume of distribution was 42 L (24%), and absorption half-life was 0.88 h (27%). The parameter estimates for vildagliptin binding to DPP-4 were 105 nM for the association constant Kd (51%), 0.48 l/h for the first-order dissociation rate constant koff (19%), and 0.11 l/h for the first-order rate constant for hydrolyzation of vildagliptin by DPP-4, kmetVilda (43%). The apparent amount of DPP-4 in the tissue compartment was estimated to be about 2000 times higher than the amount in the central compartment. Due to the limited amount of DPP-4 in plasma and tissues, vildagliptin concentrations increase slightly more than proportional with increasing doses. The estimates for the binding parameters are in the range of the values reported from in vitro studies in the literature. This model had highly sufficient predictive performance.

Conclusions: Population PK modeling of the data from three different doses indicated the presence of a small saturable elimination pathway for vildagliptin. The PK and DPP-4 activity could be described simultaneously by a model including saturable binding of vildagliptin to DPP-4 in plasma and tissues and partial hydrolyzation of vildagliptin by DPP-4. Therefore, vildagliptin is unique in the characteristics of being both an inhibitor and a substrate for DPP-4. By utilizing the TMDD approach, information on the mechanism of DPP-4 inhibition by vildagliptin from published in vitro studies could be integrated in the PK model. This model can be used to predict the effects of other dosage regimen on DPP-4 inhibition and will be expanded to incorporate the effects of vildagliptin on other biomarkers.

References:
Figure 1: Model diagram

$\frac{K_a}{t_{lag}} \xrightarrow{\uparrow} \text{CL}

\text{Vildagliptin} \quad \text{central cmt.} \quad A_P \quad V_P

\text{Free DPP-4} \quad \text{central cmt.} \quad (R_{maxP} - DR_P)

\text{Vildagliptin} \quad \text{peripheral cmt.} \quad A_T \quad V_T

\text{Free DPP-4} \quad \text{periph. cmt.} \quad (R_{maxT} - DR_T)

V_{maxP} = (R_{maxP} - DR_P) \cdot k_2

V_{maxT} = (R_{maxT} - DR_T) \cdot k_2

\text{DPP-4 activity} = (R_{maxP} - DR_P) \cdot \text{factor}

Figure 2: Visual predictive checks for the 10 mg and the 100 mg dose on Day 28