

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 K_d (51%), 0.48 1/h for the first-order dissociation rate constant k_{off} (19%), and 0.11 1/h for the first-order rate constant for hydrolyzation of vildagliptin by DPP-4, $k_{metVilda}$ (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 regimens on DPP-4 inhibition and will be expanded to incorporate the effects of vildagliptin on other biomarkers.

References:

[1] He Y-L et al. (2007) Clin Pharmacokinet; 46: 577-588.

[2] Mager DE and Jusko WJ. (2001) J Pharmacokinet Pharmacodyn; 28: 507-532.

Figure 1: Model diagram

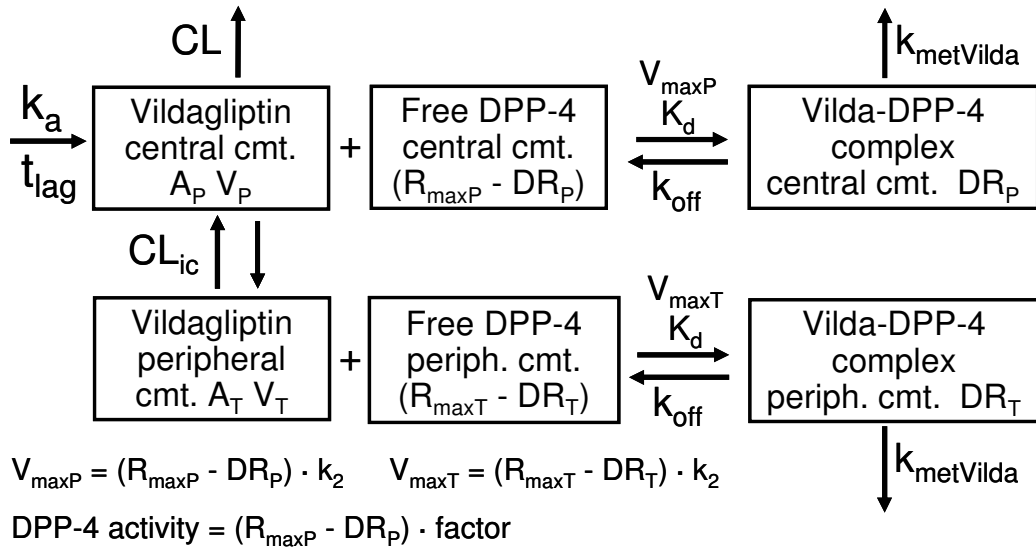


Figure 2: Visual predictive checks for the 10 mg and the 100 mg dose on Day 28

