# PKPD Modeling of Imeglimin Phase IIa Monotherapy Studies in Type 2 Diabetes Mellitus (T2DM)

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## INTRODUCTION

Imeglimin is the first in a new, tetrahydrotriazine-containing class of oral antidiabetic agents (OADs), the Glimins, for the treatment of T2DM. Imeglimin is entering Phase IIb.

## OBJECTIVES

A PKPD framework was set up early on to assess the longer term efficacy of Imeglimin.
Models were based on a biomarker (fasting plasma glucose, FPG) and the clinical endpoint (glycosylated hemoglobin (HbA1c)) in T2DM.

## METHODS

- **Data in T2DM Subjects**
  - Study 1 (Phase IIa): Imeglimin 1000 mg BID or 2000 mg OD was administered for 4 weeks in 39 subjects. Trough drug concentrations were collected, and a 24 h PK profile taken on D28 after the evening dose.
  - Study 2 (Phase IIa): Placebo, Imeglimin 500, or Imeglimin 1500 mg BID was administered for 8 weeks in 92 subjects. Trough drug concentrations were collected, and a 6 h PK profile taken on D57 after the morning dose. FPG was measured prior to treatment, every two weeks during treatment, and one week after treatment. HbA1c was measured prior to treatment and on D57.

- **PopPK Model.** Data available from the two studies were used: 99 subjects (50 males, 49 females) for a total of 1321 time points. The dose effect on bioavailability (F) was explored.

- **PopPKPD FPG and HbA1c Models.** PKPD models were developed using Study 2 data, in 92 subjects (36 males, 56 females; 27 naive and 65 nonnaive to OADs) for 637 FPG and 177 HbA1c measurements. Indirect response models were developed sequentially, with Imeglimin inhibiting glucose production, and HbA1c being produced from FPG (Fig.1).

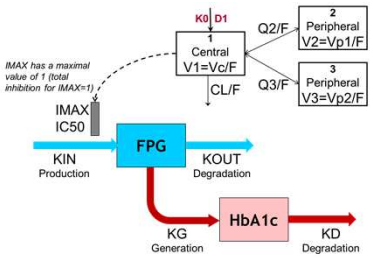


*Figure 1 - Diagram of PK & PKPD Models*

*CL/F=Apparent oral clearance (L/h); V1/F=Apparent volume of distribution of central compartment (L); V2/F and V3/F=Apparent volumes of distribution of peripheral compartments (L); Q2/F and Q3/F=Inter-compartmental apparent clearances (L/h); D1=Duration of zero-order absorption (h); F=Relative oral bioavailability; KIN=Zero-order glucose production rate constant (1/h); KOUT=First-order glucose removal rate constant (1/h); IMAX=Maximum possible inhibition of glucose production (≤1); IC50=Drug concentration in plasma required for 50% of maximal inhibition (ng/mL); KG=Pseudo first-order HbA1c production rate constant (1/h); KD=First-order HbA1c degradation rate constant (1/h)*

- **Model Development and Qualification.** Models developed in NONMEM 7.2 were qualified through Visual and Posterior Predictive Checks (VPC, PPC) in Trial Simulator v.2.2.1 (TS2).

## RESULTS

- **PopPK.** The final model was a three-compartment model with zero-order absorption and the influence of dose on F (fixed to 1 for the low dose). PK parameters were well estimated, with RSE (%) <34% for all fixed effect parameters (Table 1). Goodness of fit plots showed a good ability of the model to predict observed concentrations (Fig.2).

| PK Parameters | Population Estimates (RSE%) | IIV (%) (RSE%) |
|---|---|---|
| CL/F (L/h) | 60.2 (6.5%) | 30% (33%#) |
| V1/F (L) (Vc/F) | 197 (33.7%) | 66% (82%#) |
| V2/F (L) | 202 (29.2%) | 73% (62%#) |
| V3/F (L) | 183 (25.8%) | |
| Q2/F (L/h) | 159 (30.3%) | |
| Q3/F (L/h) | 4.26 (12.6%) | |
| D1 (h) | 4.97 (1.3%) | |
| Lag time (h) | 0.646 (24.5%) | |
| F at the 500mg dose | 1 fixed (reference) | |
| power function on F | -0.245 (24.9%) | |
| F at the 1000 mg dose | 0.84 | |
| F at the 1500 mg dose | 0.76 | |
| F at the 2000 mg dose | 0.71 | |

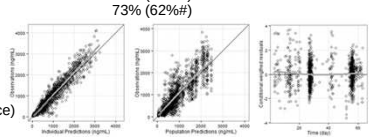

*Figure 2 – Diagnostic Plots for the PK Model of Imeglimin in T2DM*

*Table 1. Population PK Parameters of Imeglimin in T2DM*

## RESULTS

- **FPG PKPD Model.** Parameters were accurately estimated (RSE ≤27%) (Table 2).

| *PKPD Parameters* | *Population Estimates (RSE%)* | *IIV (%) (RSE%)* |
|---|---|---|
| KOUT (1/h) | 0.00204 (23%) | |
| $FPG_{SS}$ (mg/dL) | 173 (3%) | 15% (21%) |
| IC50 (ng/mL) | 8420 (27%) | |
| Effect of FPG baseline on $FPG_{SS}$ | 0.847 (11%) | |
| Proportional Residual Error (%) | 9% (9% ) | |
| *Derived* | | |
| KIN (1/h) | 0.380 (0.0037) | |

*Table 2. PopPKPD Parameters of the FPG Model following BID Administration of Imeglimin in T2DM*

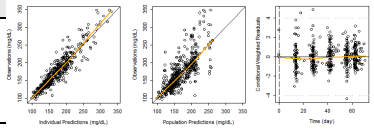

*Figure 3 – Diagnostic Plots for the FPG PKPD Model following Imeglimin Dosing in T2DM*

- **HbA1c PD Model.** Due to limited data, HbA1c degradation rate was fixed to a value estimated with denser data [1]. Other parameters were accurately estimated (RSE ≤20%) (Table 3).

| PD Parameters | Population Estimates (RSE%) | IIV (%) (RSE%) |
|---|---|---|
| KD (1/h) | 0.000664 fixed* | |
| $HbA1c_{SS}$ (%) | 8.00 (2%) | 17% (23%) |
| Effect of HbA1c baseline on $HbA1c_{SS}$ | 0.751 (20%) | |
| Proportional Residual Error (%) | 0.001 fixed** | |
| *Derived* | | |
| KG (1/h) | 2.97E-05 (2.59E-07) | |

*Table 3. PopPD Parameters of the HbA1c Model following BID Administration of Imeglimin in T2DM*

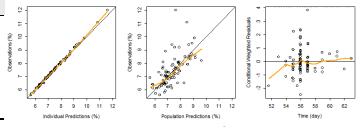

*Figure 4 – Diagnostic Plots for the HbA1c PD Model following Imeglimin Dosing in T2DM*

*$FPG_{SS}$=Fasting plasma glucose at steady-state; $HbA1c_{SS}$=HbA1c at steady-state (unmedicated); IC50=Concentration producing 50% of maximal effect; KD=First-order HbA1c degradation rate constant (1/h); KG=Pseudo first-order HbA1c production (generation) rate constant from FPG (1/h); KOUT=First-order glucose removal rate constant (1/h); RSE=Relative Standard Error; IIV=Inter-Individual Variability. # RSE of the variance; ¶ Mean (SE) of individual values calculated as KIN=KOUT.$FPG_{SS}$ or KG=KD.$HbA1c_{SS}$/$FPG_{SS}$; *Fixed to estimate of Rohatagi 2008; ** Fixed to a low value to allow convergence.*

- **Model Qualification.** Predictive checks indicated adequate performance of all models. Observations were within 90% prediction intervals.

❑ PK Model (Studies 1 and 2): Full PK profiles at end of treatment (EoT), after the evening dose for Study 1 and the morning dose for Study 2, were well predicted as shown in Fig.5.

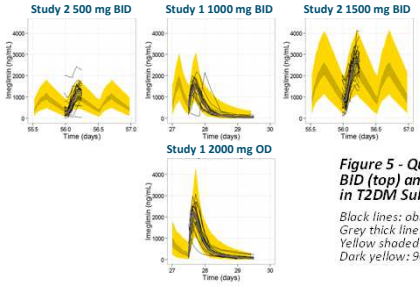


*Figure 5 - Qualification of the PK Model following BID (top) and OD (bottom) Imeglimin Dosing in T2DM Subjects (Studies 1 and 2)*

*Black lines: observed data.*
*Grey thick line: median of observations.*
*Yellow shaded area: 90% prediction interval.*
*Dark yellow: 90% prediction interval of the median.*

❑ FPG PKPD Model (Study 2): Median change from baseline (CFBL) at EoT in the placebo, 500 mg BID and 1500 mg BID groups was predicted respectively at 0.76 (5th, 95th percentiles: -0.01, 1.46), 0.03 (-0.64, 0.66) and -0.71 (-1.35, -0.08) mmol/L for FPG (vs. observed 0.55, 0.20 and -0.90 medians).

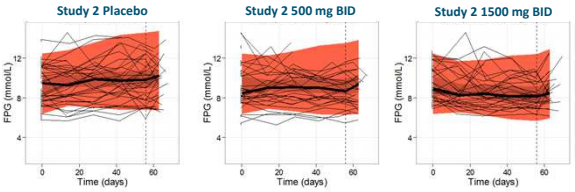


*Figure 6 - Qualification of the FPG PKPD Model following BID Imeglimin Dosing in T2DM Subjects (Study 2)*

*Black lines: observed data.*
*Grey thick line: median of observations.*
*Yellow shaded area: 90% prediction interval.*
*Dark yellow: 90% prediction interval of the median.*

❑ HbA1c Model (Study 2): Median CFBL at EoT in the placebo, 500 mg BID and 1500 mg BID groups was predicted respectively at 0.5 (5th, 95th percentiles: 0.0, 1.0), 0.2 (-0.2, 0.7) and -0.1 (-0.5, 0.4) % for HbA1c (vs. observed 0.2, 0.1 and -0.1 medians) after 8 weeks of treatment.

## CONCLUSION

- PK data from two Imeglimin monotherapy studies in T2DM subjects were combined. Data from Study 2 were limited (0-6 h profiles), and Study 1 with 24 h profiles was essential for the PK model development
- IR models could be used to characterize changes in FPG and HbA1c over 8 weeks of treatment
- Model development with early limited data should already prove useful in guiding biopharmaceutical development and the design of future Imeglimin studies.

## REFERENCES

[1] Rohatagi S et al. (2008). Model-based development of a PPARgamma agonist, rivoglitazone, to aid dose selection and optimize clinical trial designs. J Clin Pharmacol 48: 1420-9.
[2] Naik H et al. (2013). Pharmacometric approaches to guide dose selection of the novel GPR40 agonist TAK-875 in subjects with type 2 diabetes mellitus. CPT: Pharmacometrics & Systems Pharmacology 2, e22; doi:10.1038/psp.2012.23; advance online publication 9 January 2013

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