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

**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 Ia): 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).

- **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 (%) ≤4% for all fixed effect parameters (Table 1). Goodness of fit plots showed a good ability of the model to predict observed concentrations (Fig.2).

- **IR Models** could be used to characterize changes in FPG and HbA1c over 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**
