EMA EFPIA workshop
Break-out session no. 2

Case Study Title: Design of a model based dose-finding study in diabetes

Marie Sandström, Global Director Clinical Pharmacometrics, AstraZeneca
Sofia Friberg Hietala, Senior Pharmacometrician, AstraZeneca

AstraZeneca

Disclaimer

The view and opinions expressed in these slides are my own and do not necessarily represent the views of AstraZeneca

BOS2: Position statement

M&S analysis results together with prior knowledge (e.g. literature/other data) should be the the primary basis to decide on doses for phase II/III

AstraZeneca

Background & Rationale

- **The long term effect of an antidiabetic drug is best described through monitoring of glycosylated hemoglobin, HbA1c, which reflects the average glucose exposure during the last months prior to sampling.**
- **Given the slow turnover of HbA1c and the fact that the required change in HbA1c is quite small relative to its variability, dose-ranging studies based on traditional pair-wize comparisons need to be long (>3 months) and large (50 /group).**
- **We propose to use a model based approach in the assessment of the dose-response correlation based on:**
  - There is a well established model describing the glucose driven effect on HbA1c (Benincosa 2000, Rohatagi 2008)
  - With a model based approach all available data are used to evaluate the dose- response correlation, thus maximizing the use of the collected data
  - Models describing the time-course of the effect in individual patient allow for a better understanding of the sources of variability (inter- and intraindividual differences)

AstraZeneca

Objectives of the M&S work

To identify the dose-exposure-response and allow for the choice of optimal doses in Phase III

AstraZeneca

Available Data / Prior Models

Available models:

- Litterature model of FPG/HbA1c (Benincosa 2000, Rohatagi 2008)

Populating the model:

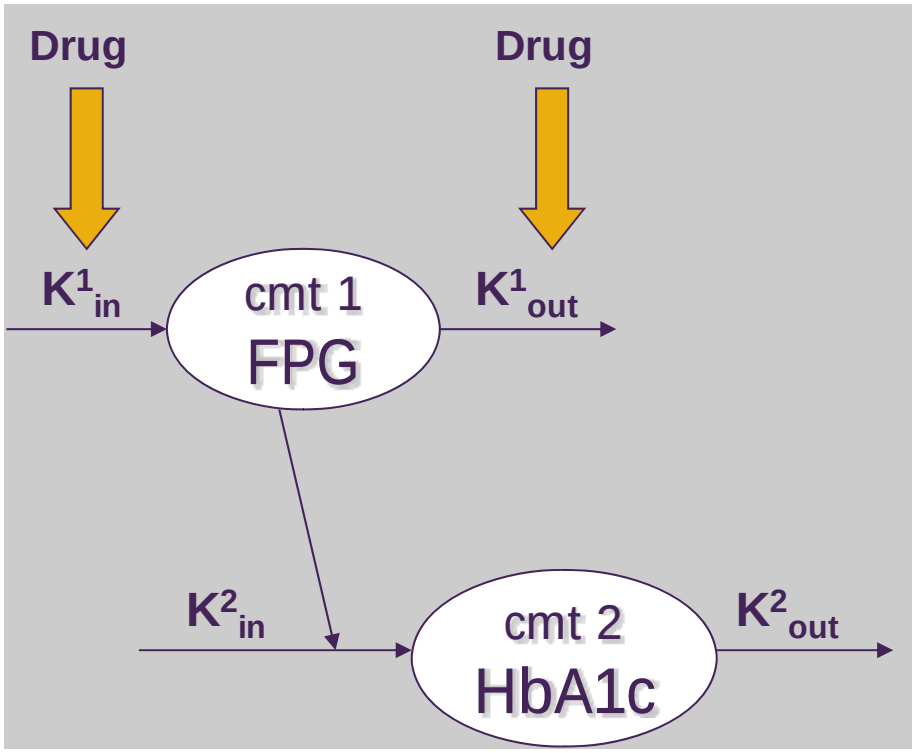
- Target specific data for a competitor compound describing the time-course of the effect

- In-house data from previous Phase II and Phase III studies in similar patient populations describing the variability in disease parameters (FPG, HbA1c)

AstraZeneca

M&S Assumptions:

The change in the primary variable, HbA1c, is driven by FPG



Diabetes model

$$\frac{dFPG}{dt} = K^1 in \times (1 - Eff1) - K^1 out \times (1 + Eff2) \times FPG$$

$$\frac{dHbA1c}{dt} = K^2 in \times FPG - K^2 out \times HbA1c$$

Drug effect

$$Eff = \frac{E\max \times Concentration}{EC_{50} \times Concentration}$$

AstraZeneca

Methods

Evaluation of study designs using simulation & estimation to determine:

- What is the power to detect a pre-specified, minimal relevant effect?
- What is the precision in parameter estimates (Emax, EC50)?
- What percentage of studies are likely to result in correct Go vs No Go depending on:
  - Study design
  - Prior assumptions

AstraZeneca

M&S Results

5 doses	Traditional design (t-test/ANCOVA)	Model based design
Information generated	Statistical significant dose	Statistical significant dose
		Allows prediction of efficacy/safety for •other duration •other doses and formulations •other populations Optimised Phase III study design
Sample size	270/140	115
Cost	12/6 million US$	5 million US$

AstraZeneca

Conclusions

- **With a model based approach all time points are used to evaluate the effect, adding strength to the analysis, and reducing the required sample size**
- **The model based analysis would allow for the prediction of efficacy/safety for:**
  - different treatment durations
  - different doses and formulations
  - other populations
- **The dose-exposure-response model would facilitate an optimised Phase III study design**
- **Potential draw-back:**
  - How should a reduced sample size in Phase II be addressed from the perspective of achieving an adequate number of exposed patients prior to entering Phase III?

AstraZeneca

Acknowledgements

AstraZeneca:
Catarina Nilsson, Clinical Pharmacology Scientists
Tore Persson, Statistical Science Director
Jan Eriksson, Medical Science Director
Johan Holmberg, Clinical Programme Director

Uppsala University:
Mats Karlsson, Professor
Martin Bergstrand, PhD

Back-up

AstraZeneca

M&S Pre-specification

The basic structural model was pre-specified, but all parameters would be reestimated using the study data.

AstraZeneca

Sensitivity to assumptions

Assumptions based on known Physiology and Pharmacology no sensitivity analysis conducted

AstraZeneca