Modelling and Simulation in Type 2 Diabetes: Development of a general drug-disease model based on a meta analysis of over 40 studies investigating 5 $PPAR_{\gamma}$ / $PPAR_{\alpha\gamma}$ drugs

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Introduction

- Outline of the goals of the project
- Data used
- Model development
- Model qualification
- Simulation results
- Sensitivity analyses
- Conclusions

The goals of the M&S work were defined at the start of the project

- Develop a robust model to describe the PPAR pharmacotherapeutic 'landscape'
- Incorporate the results from a (4 month) Phase 2 study for a new investigational drug (drug X) into the model
- Estimate/predict the dose response for drug X in longer durations studies (6 month) *versus*:
  - Placebo
  - Potential comparators in Phase 3
- Simulate/evaluate potential phase 3 designs
- Assess robustness of results
- (also, multiple secondary goals, e.g. how best to design combination studies)

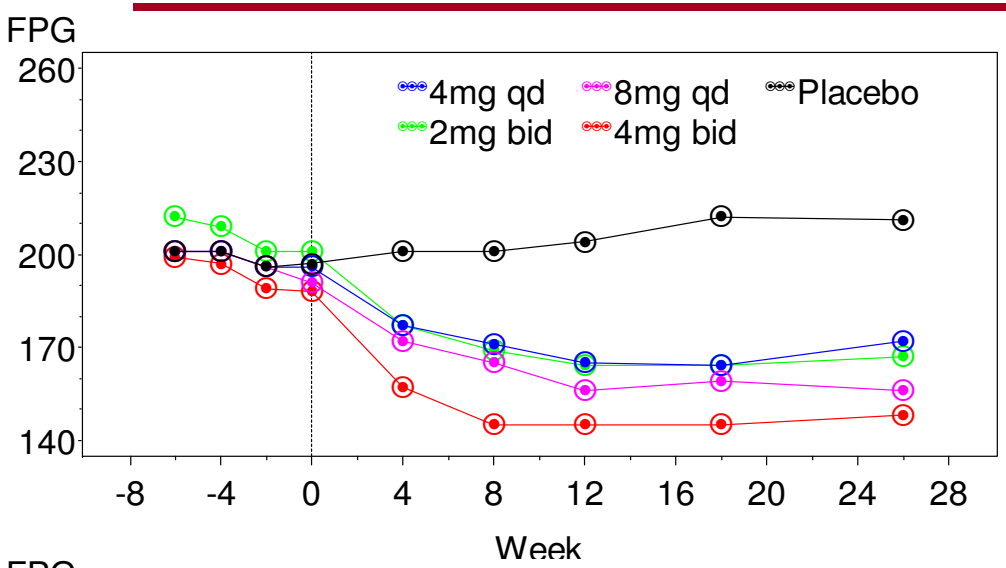
The goal of the data aggregation was to include most (if not all) RCT's for this therapeutic area

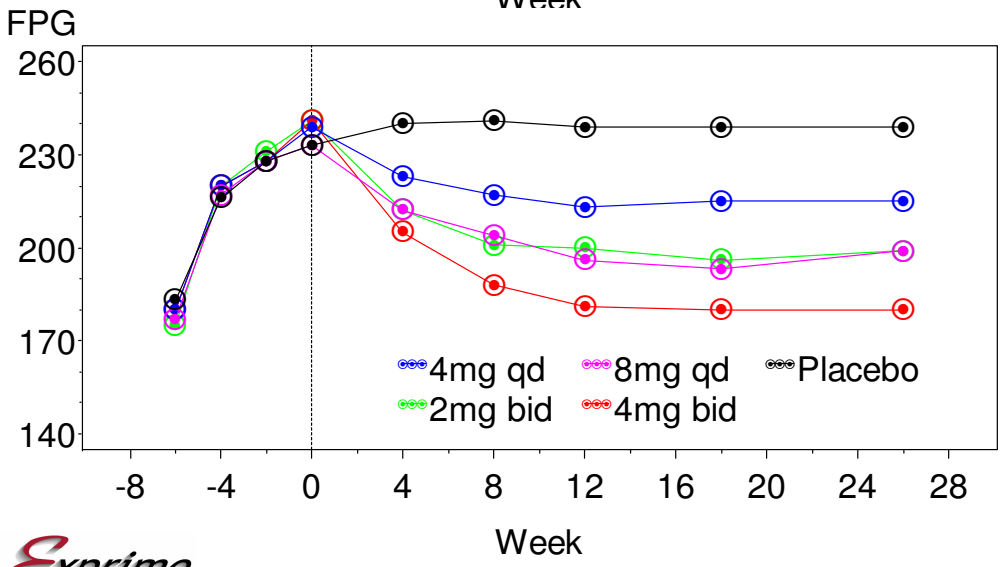
- Good data = good inference. EMEA guidelines - Strongest evidence of treatment effect is… "a meta analysis of RCT's".
- Type 2 diabetes – Glycosylated Haemoglobin (HbA1c) and Fasting Plasma Glucose (FPG)

		Studies
Rezulin	(Troglitazone)	11
Avandia	(Rosiglitazone)	11
Actos	(Pioglitazone)	15
Ragaglitazar/GI262570		4
Drug X		1

- Data for both HbA1c and FPG. Split by previous treatment (drug naïve, previously treated). 42 studies, 139 treatment arms, 298 longitudinal (mean) profiles, total N > 16000.

Model Development – FPG changes as a function of drug, dose, duration and patient population





Avandia – SBA study 24

Phillips et al., Diabetes Care. 2001 Feb;24(2):308-15

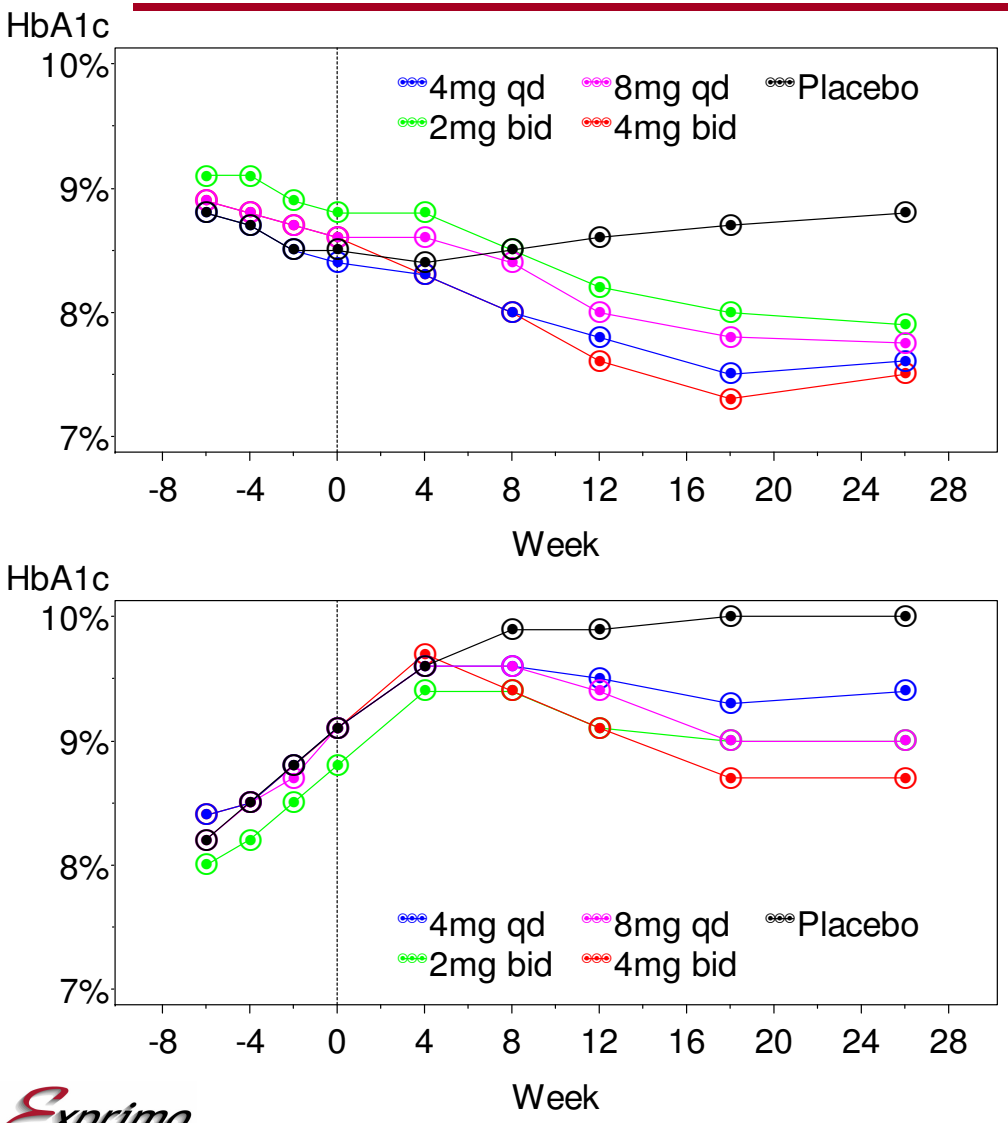
Top: Drug naive patients
Bottom: Previously treated patients
- 6 weeks = placebo run in.

Placebo profile
Dose response
Delay in full effect

Model
Disease
Drug#
Delay##

= drug/regimen
= drug offset/drug onset

HbA1c changes as a function of drug, dose, duration and patient population



Avandia – SBA study 24

Phillips et al., Diabetes Care. 2001 Feb;24(2):308-15

Top: Drug naive patients

Bottom: Previously treated patients

- 6 weeks = placebo run in

Note:
HbA1c changes slower than FPG

The model captured the main features of the changing efficacy responses– disease/drug/delay

Effect

$$effect = plac\_eff \,.\, (1 - drug\_eff)$$

Disease/Placebo effect

$$plac\_eff = intercept \,.\, (1 + fr \,.\, slope1 \,.\, time + (1 - fr) \,.\, oad\_eff \,.\, time\_delay))$$

where $time\_delay = 1 - \exp(-k1 \,.\, time_2)$

fr = fraction of patients in 'drug naive' group

Drug/Delay

$$drug\_eff = \frac{E_{max} \cdot Dose^{\gamma}}{ED_{50j}^{\gamma} + Dose^{\gamma}} \,.\, (1 - \exp(-k2 \,.\, time))$$

where

k2 is the delay in reaching full PD effect

γ is the hill coefficient

Emax = maximal effect

ED50 = dose which gives 50% of Emax

j = 1,2,3,4,5,6 (tro, pio, ros od, ros bid, 570, rag)

Here FPG

Similar structure for HbA1c (with some shared parameters), but the delay in effect modelled differently

(HbA1c changing more slowly)

Model had 38 parameters, including 6 random effects

Before looking to simulate new studies, a key Posterior Prediction Check (PPC) was defined

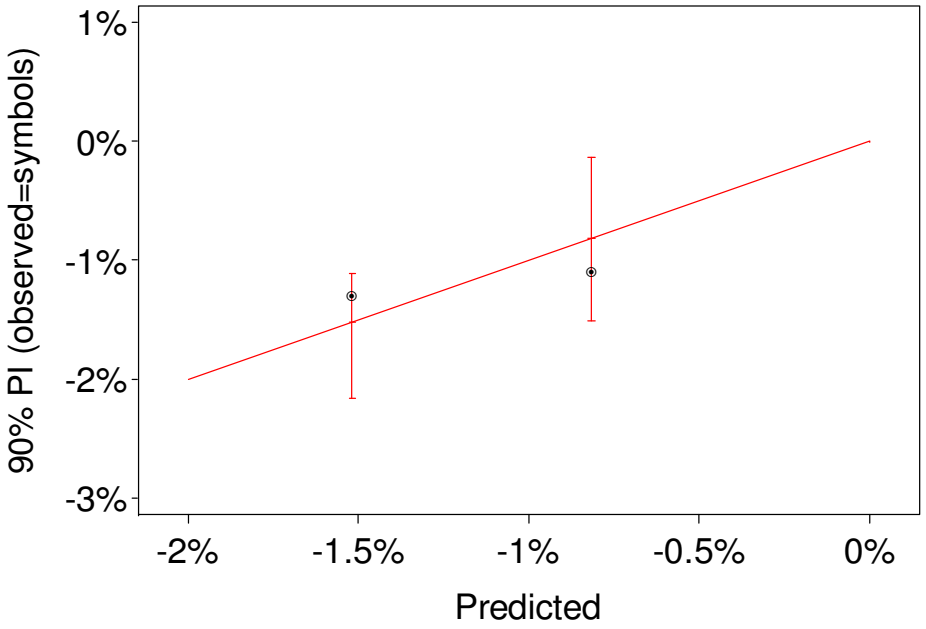
For every placebo controlled study, a difference from placebo (delta) at endpoint (last visit) was observed. 157 deltas in total in database.

Using only baseline information (e.g. patient population, baseline response, treatment duration, drug, dose, regimen, sample size), each study was simulated 100 times. The observed delta was compared to the 90% prediction interval from the 100 identical simulated studies.

For example, the Phillips 2001 (Avandia, 26 weeks) study included:

	N	Observed delta	Median (90% PI)
4mg bid, previously treated	135	-1.3%	-1.5% (-1.1%, -2.2%)
4mg qd, drug naïve,	40	-1.2%	-0.8% (-0.1%, -1.5%)

For these two treatment arms, the observed result can be compared graphically to the prediction



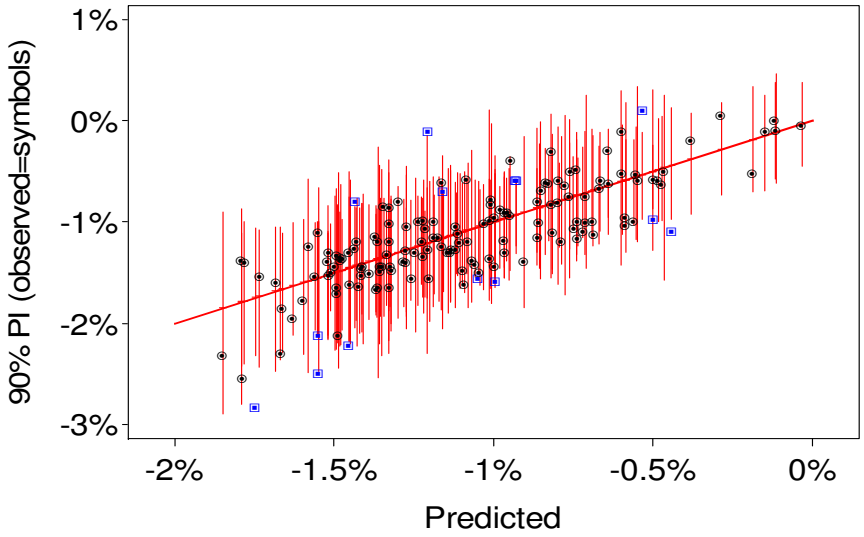
Red vertical lines are the 90% prediction interval for each of these two treatment arms.

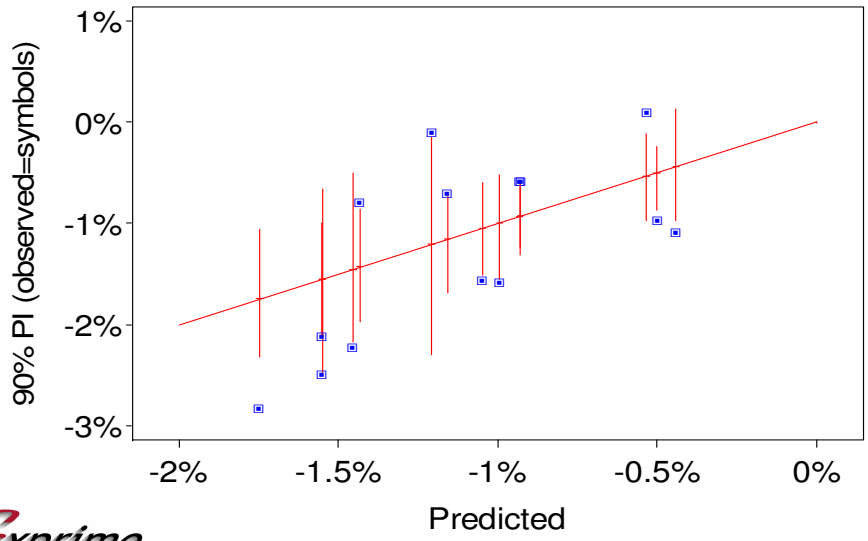
If observed = predicted, the observed result (black circles) would fall on line of identity (model predicted).

For a 90% prediction interval, expect 90% of observed results to fall within their own prediction interval.

Here, both treatment arms are within their own prediction interval.

The PPC showed that the model/simulations was fit for the purpose for which it was developed





Top: All 157 results (observed, and 90% PI)

143/157 (91%) observed results were within the 90% prediction interval.

Bottom: The 14 observed deltas that were not within the 90% PI.

8/6 are under/over predicted.
3/4/7 for Actos/Avandia/Rezulin.
9/5 for mono/combination studies.
Low and high doses, and small and big sample sizes, are represented.

=> NO SYSTEMATIC BIASES

A brief outline of how the simulations were performed

- Uncertainty simulations: (the true effect)

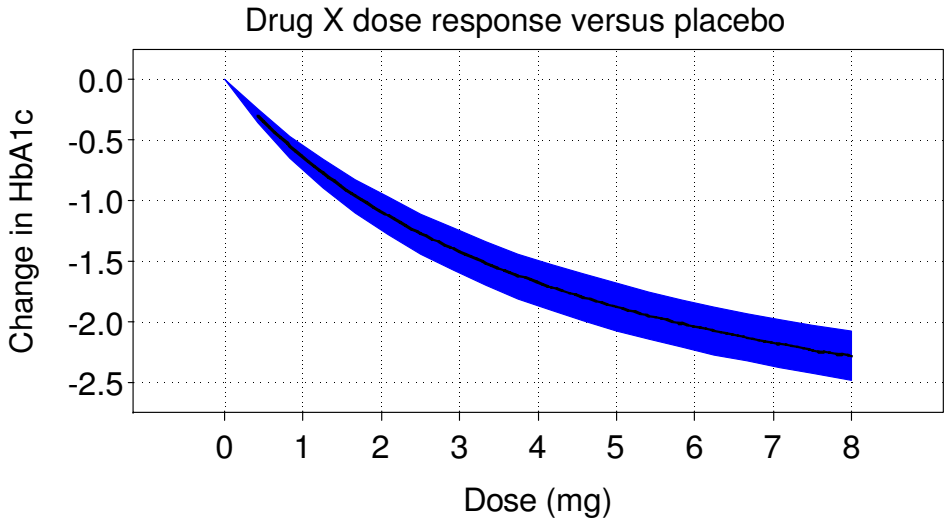
  (resampling from estimated parameters using multivariate normal (MVN) distribution based on estimates and variance-covariance matrix – 1000 simulations)

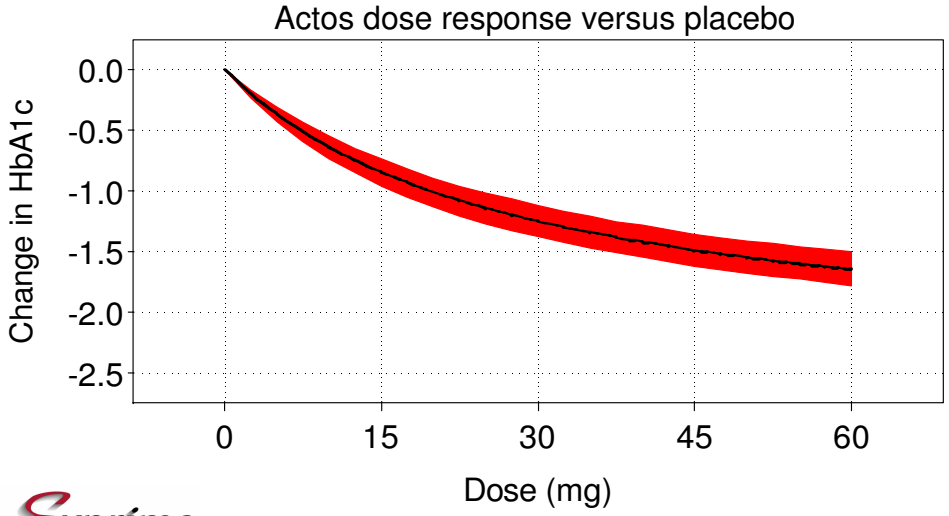
- Study level simulations (as above, but now 'adding in' between patient variability from using finite sample size)

  key metric:

  - Likelihood of achieving superiority/non-inferiority in a given active control phase 3 design.
  - Superiority = success = lower 95% CI above 0.

The predicted difference from placebo for both Drug X and Actos across the dose ranges





Change in HbA1c for a given duration, population etc., across the dose range.

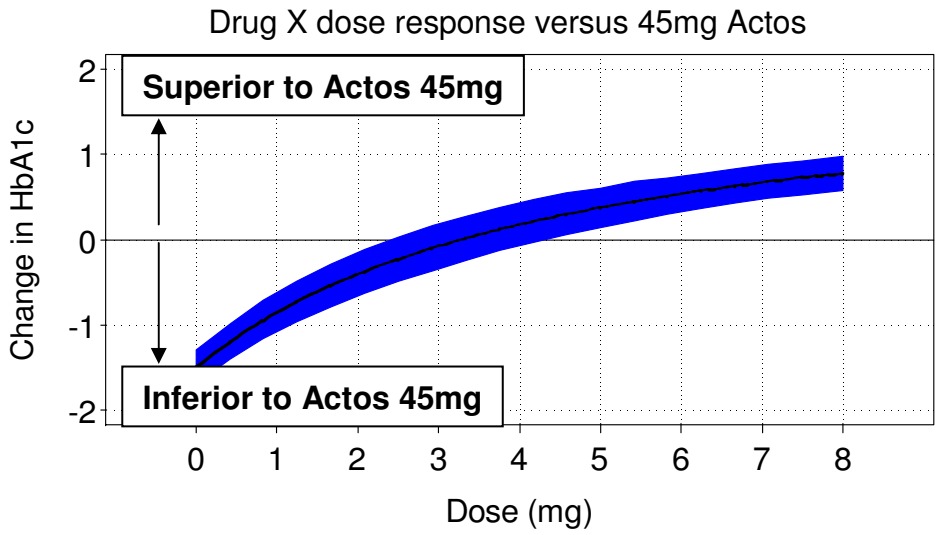
Top: Drug X dose response
Bottom: Actos dose response

Black line = Median prediction
Band = 90% Prediction Interval

Results could be determined for any dose level of any drug (i.e. all potential comparators).

Note: Greater uncertainty on Drug X relative to Actos.

The predicted Drug X dose response *versus* 45mg Actos was also determined

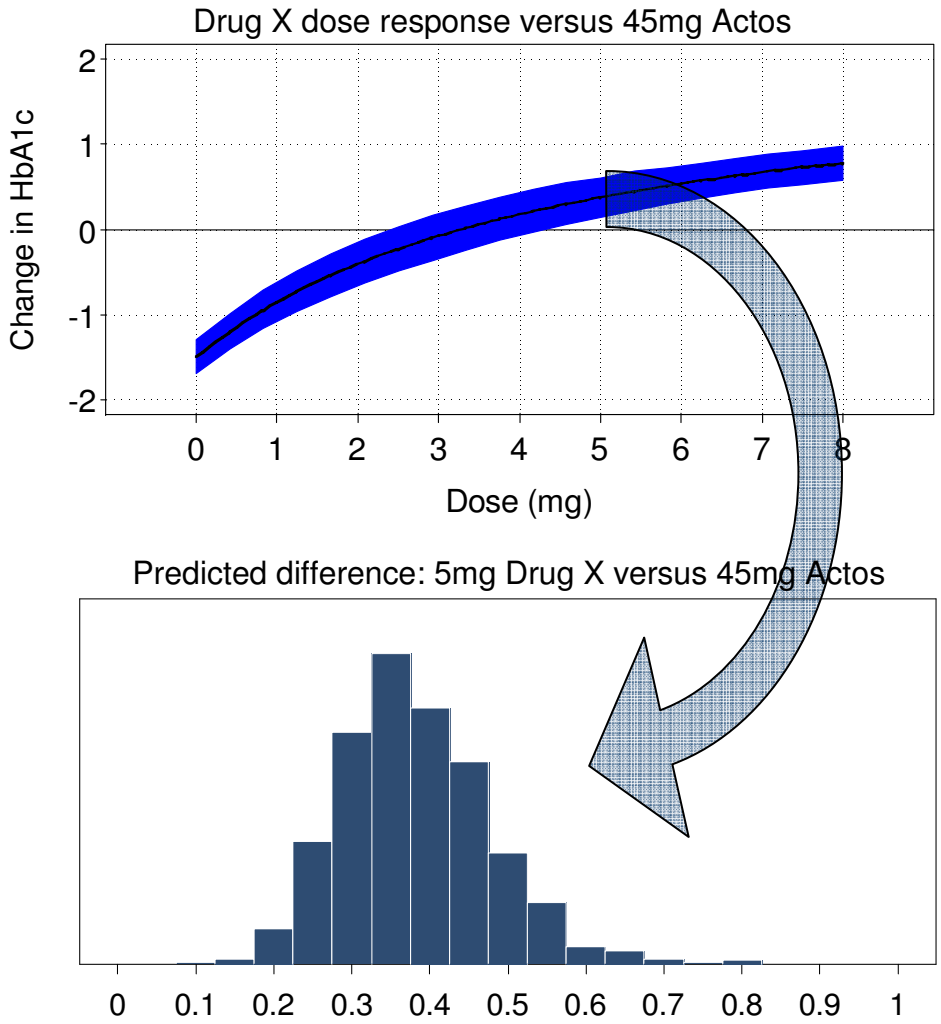


Change in HbA1c for a given duration, population etc, across Drug X dose range, but now relative to 45mg Actos.

At Drug X = 0mg (placebo), same as previous slide.

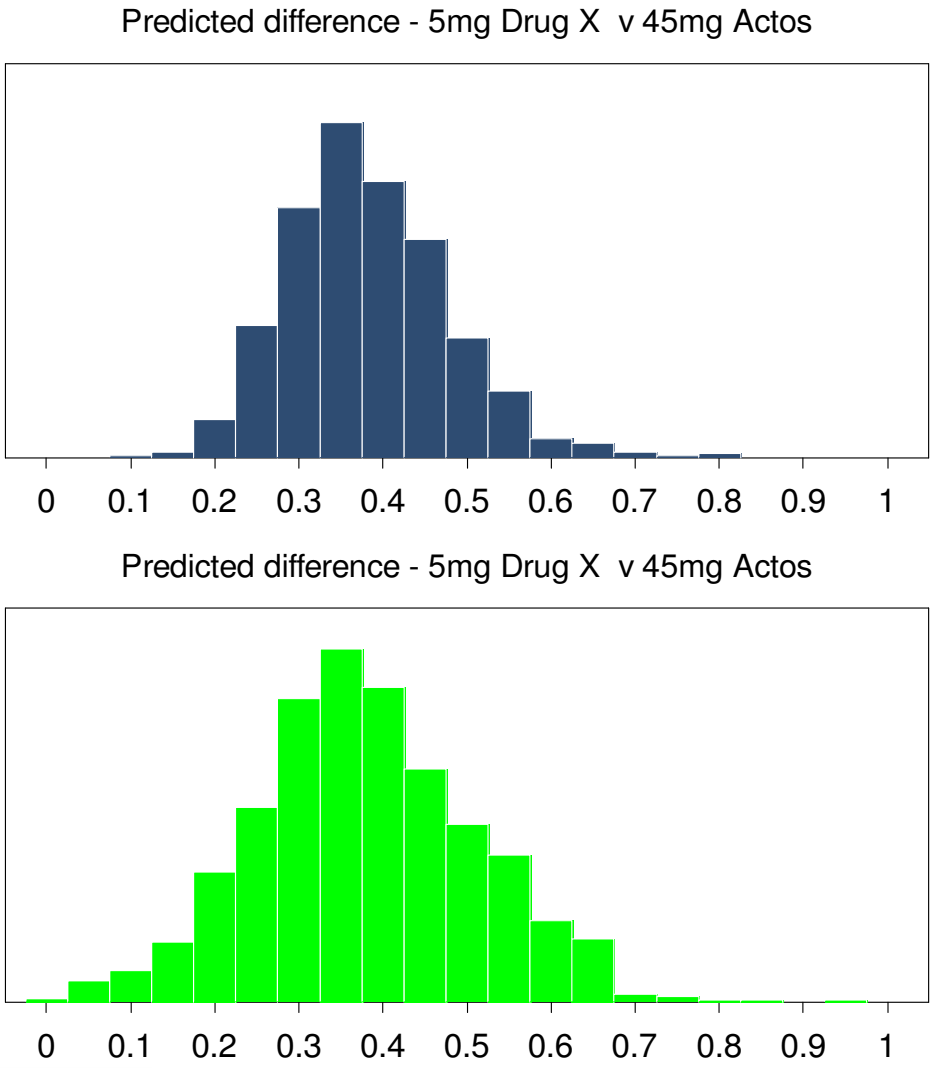
Clearly, at doses lower than 3mg, drug X is inferior to 45mg Actos, whereas at 5mg and above, it is superior.

The predicted difference from 45mg Actos can be shown for any particular dose of Drug X



Predicted difference between 5mg Drug X and 45mg Actos. This represents our best estimate of the 'true' difference between these treatments

Including between patient variability, the estimated treatment effects become naturally flatter

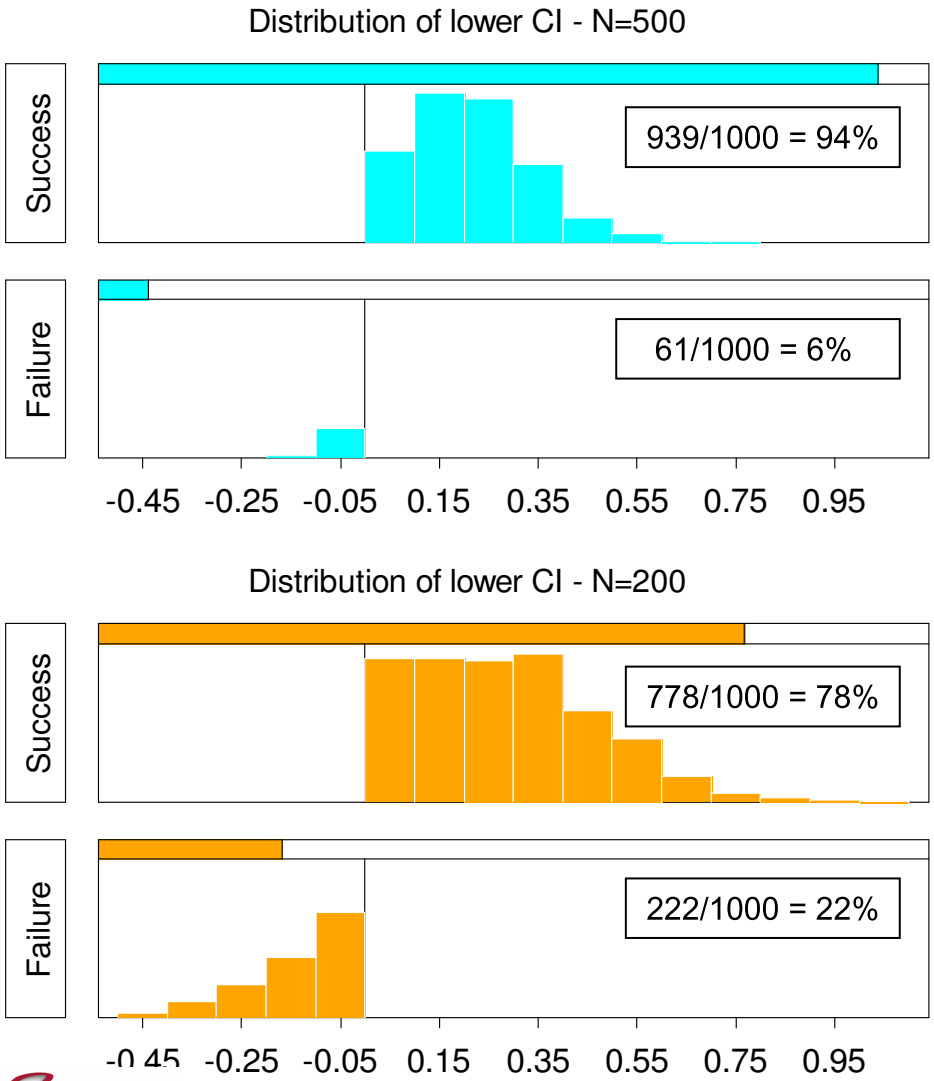


Distribution of predicted differences between 5mg Drug X and 45mg Actos across 1000 simulations.

Top: As before. No study level variability (between patient variability).

Bottom: Now with N=500 per arm (500 patients on 5mg Drug X, 500 patients on 45mg Actos).

The likelihood of success was determined for different sample sizes in Phase 3



<u>5mg Drug X *versus* 45mg Actos</u>

Now have 'added in' variability from using finite sample size.

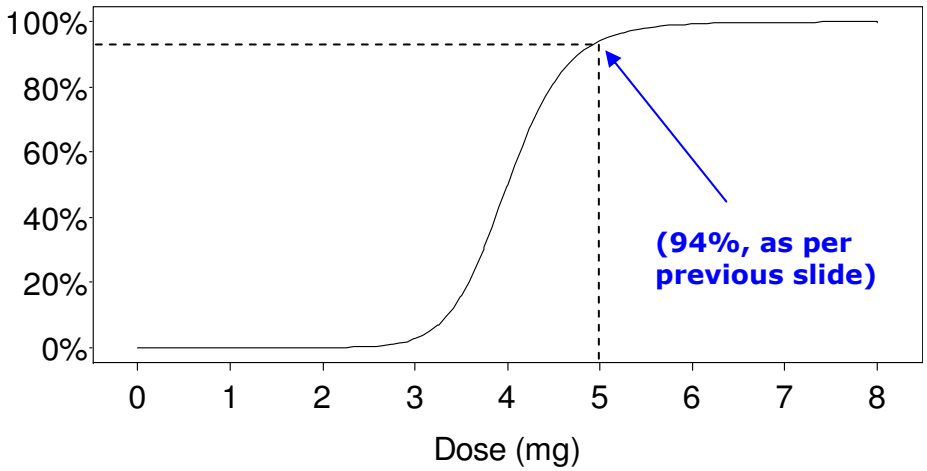
1000 simulated studies.

Figures show the distribution of the lower 95% CI. If lower 95% CI > 0, then have shown superiority (=success).

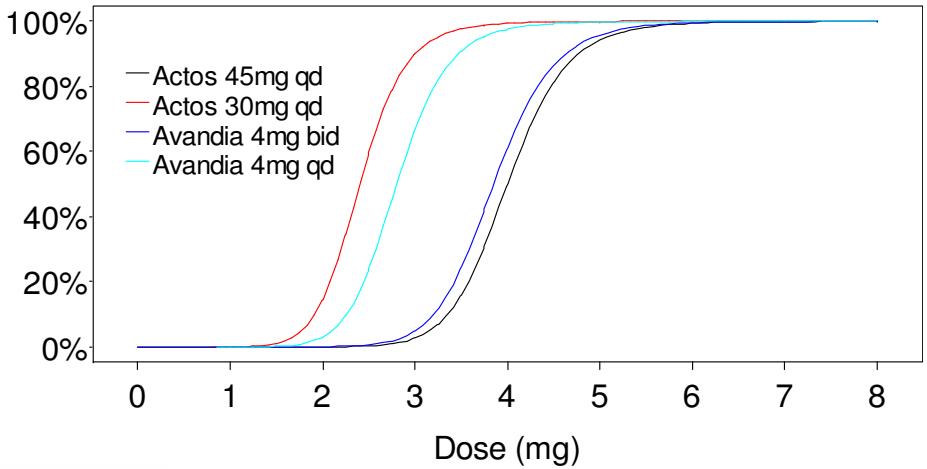
Chance of success = 94% for N=500, and 78% for N=200.

The likelihood of success was determined for different comparators over the Drug X dose range

Likelihood of success versus Actos 45mg



Likelihood of success versus other comparators



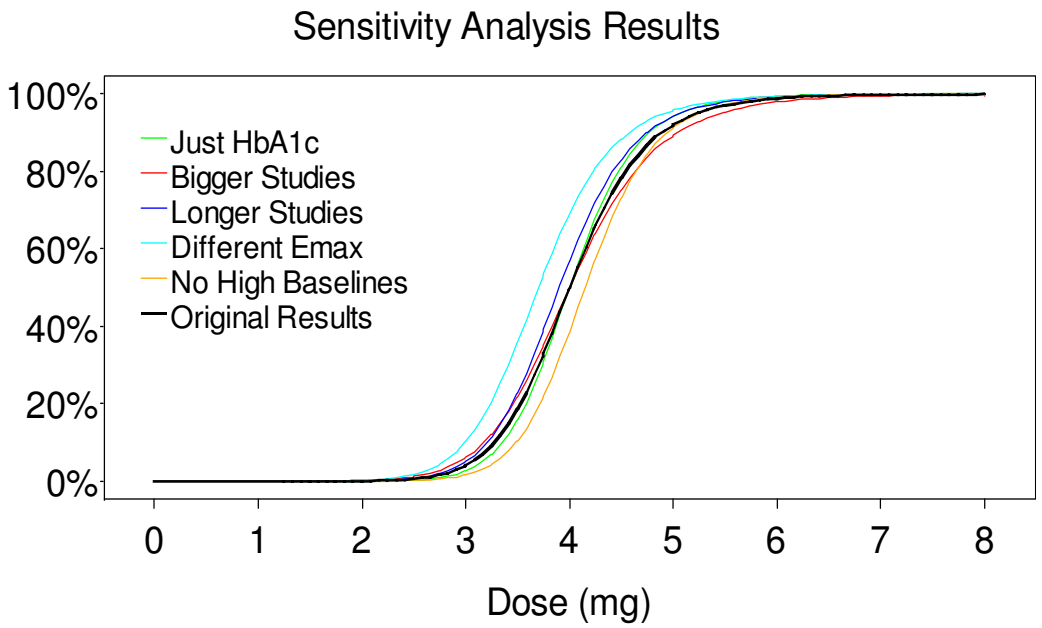
For N=500 per arm

Y-axis = % of simulations that are successful (lower 95% CI >0 = superiority claim)
X-axis = Dose of Drug X

Bottom Figure:
Likelihood of success *versus* different comparators

Note:
importance of comparator (e.g. at 3mg)

An extensive sensitivity analyses showed that the results were generally robust



1) Only HbA1c data
2) Only bigger studies (N>50)
3) Only longer studies (>16 weeks)
4) Different Emax for Drug X
5) No 'high baseline' studies

After discussion with the project team, five sensitivity analyses were undertaken.

Here, the results of the sensitivity analysis for the comparison against 45mg Actos.

At below 3mg and above 5mg, all results are similar. At 4mg, some judgement is required.

Conclusions

- Developed a robust therapeutic model that described the pharmacotherapeutic area – a lot of data/information used!
- Prospectively evaluated key phase 3 designs
- Can be applied to future compounds in the type 2 diabetes portfolio
- Multiple additional applications (e.g. combining with PoC studies on FPG to predict HbA1c)
- Planning (1 year) prior to Phase 2 results enabled model to be in place and evaluated beforehand

- This is only a start! Many areas yet to be explored
- A nice project to work on!

Questions

HbA1c

Model Fits for HbA1c

FPG

Model Fits for FPG

Questions

HbA1c

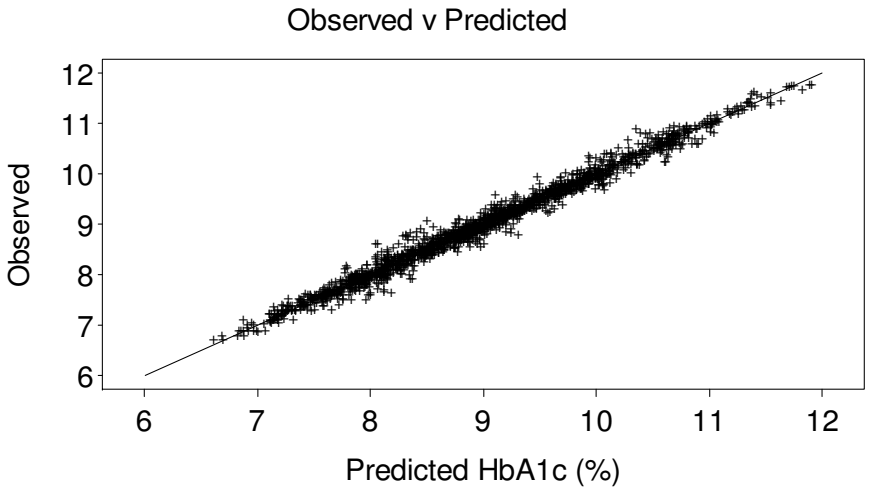
Model Fits for HbA1c

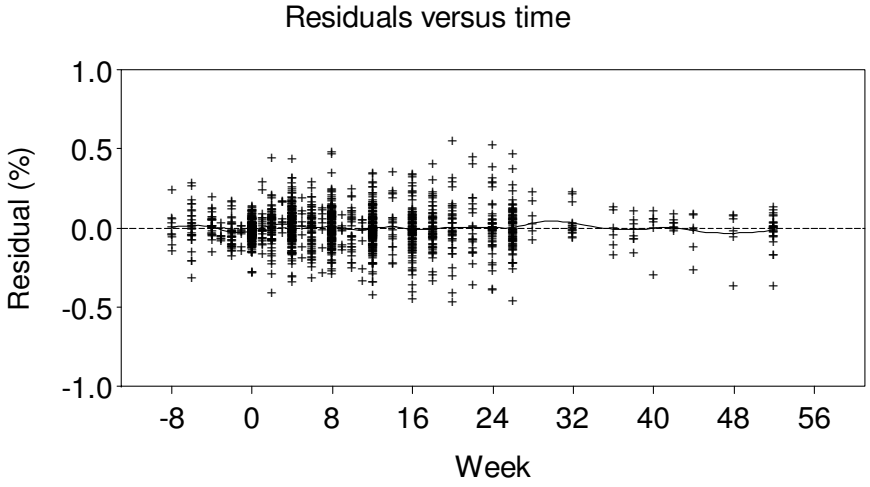
FPG

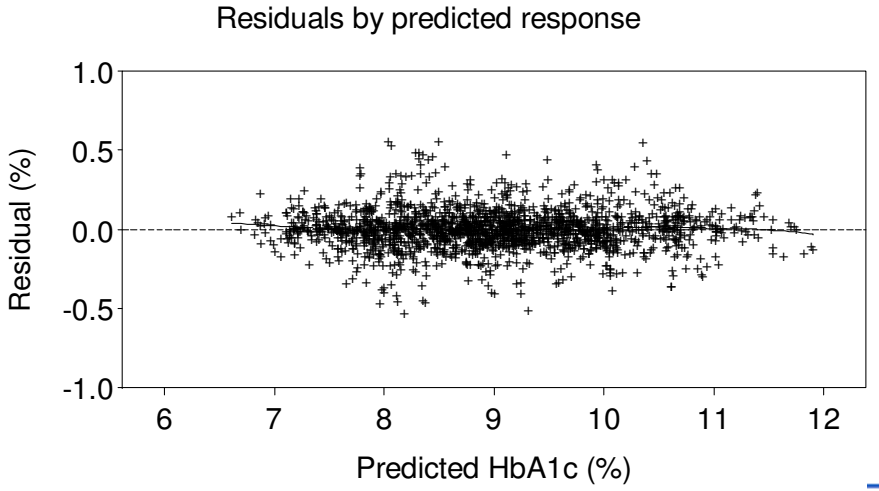
Model Fits for FPG

Backup slides

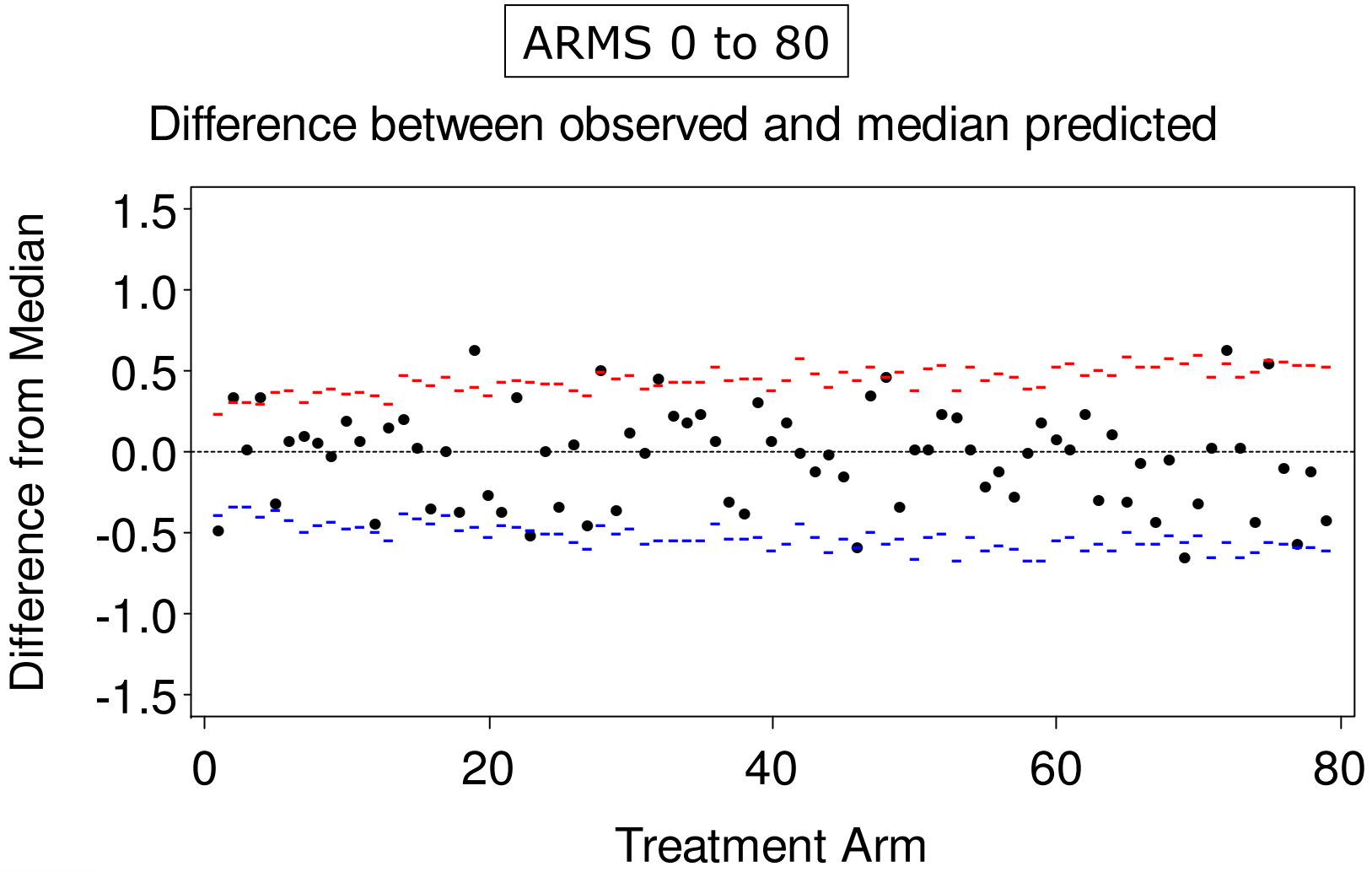
A selection of the goodness of fit plots





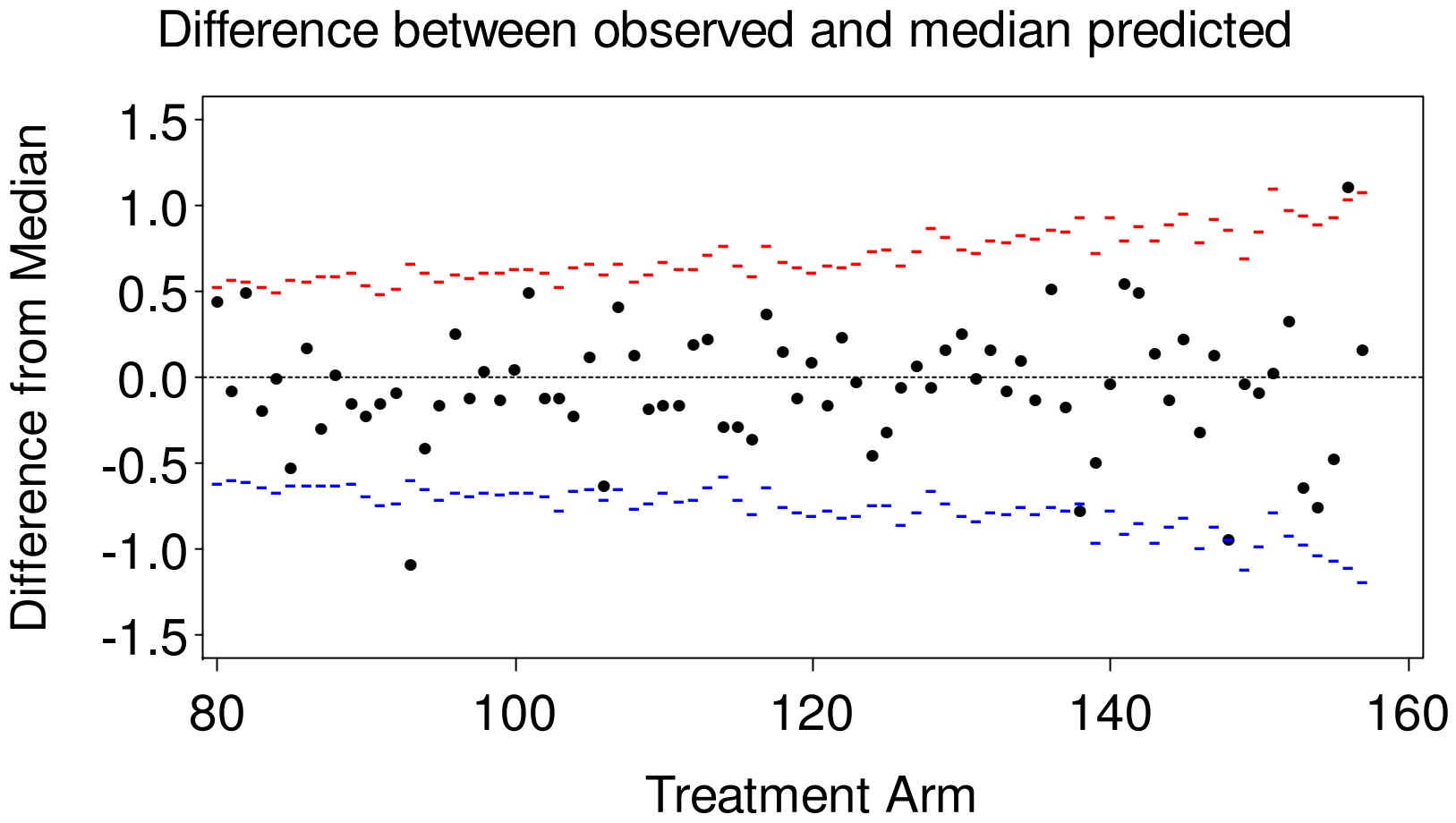


PPC – by treatment arm (ordered from smallest PI (largest studies) to biggest (smaller studies))



PPC – by treatment arm (ordered from smallest PI (largest studies) to biggest (smaller studies))

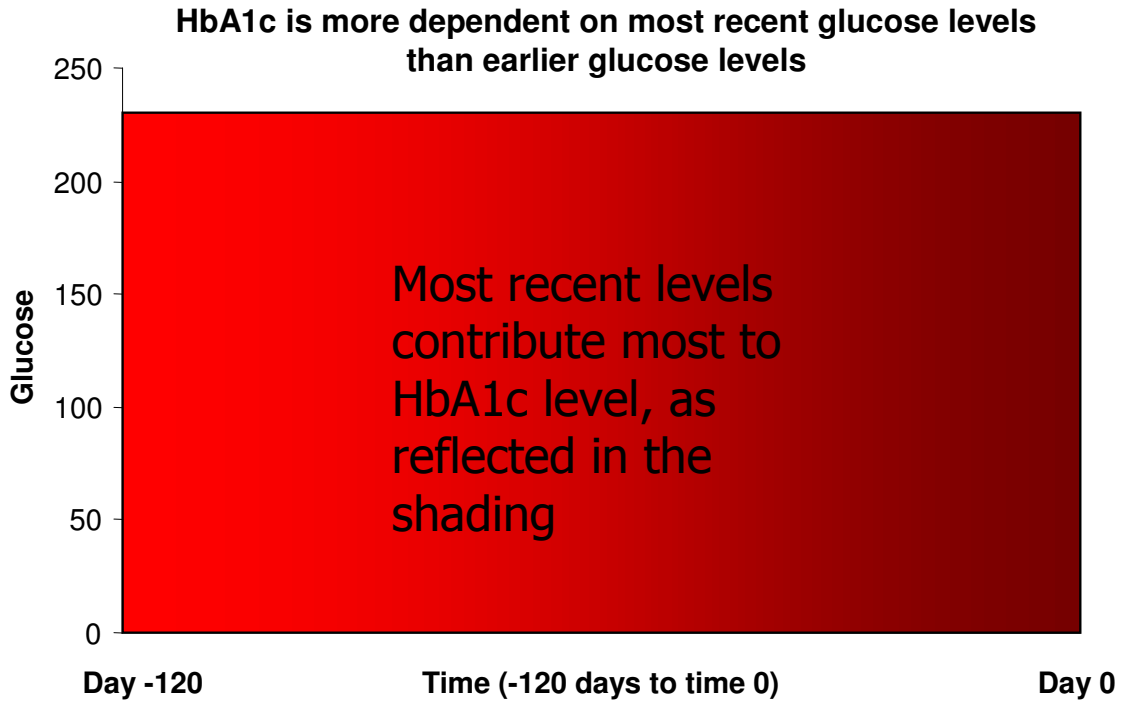
ARMS 80 to 157



Other model components

- Population differences (drug naïve, previously treated)
- Duration of run in
- Duration of treatment
- QD versus BID
- Onset/offset of drug effect, maximal effects.
- Role of baseline FPG/HbA1c
- Concomitant metformin, sulfonylureas (e.g. glyburide)
- Differential effects for drug X
- Six random effects at the study (not treatment arm) level

HbA1c is essentially a (complex) weighted average of glucose control over the last 120 days or so



120 days used as ball park figure for RBC lifespan

The additional 'noise' due to using a finite sample size

- Have some opinion of true value of between patient variance (σ^2).
- Study will estimate σ^2 with $\hat{s}^2$, which is based on χ^2 distribution (with df based on n).
- Difference between means (in addition to true difference) will be approximately normal with variance equal to $2\hat{s}^2/n$.

  That is, for each replicate i:

$$\bar{x}_{1i} - \bar{x}_{2i} = \text{True}_i + N\left(0, \frac{2\hat{s}_i^2}{n}\right)$$

PPARs

- **peroxisome proliferator activated receptor gamma** (PPARγ) agonists belongs to the thiazolidinedione family.
- In type 2 diabetic patients, insulin resistance is usually initially compensated by an increase in insulin production and ultimately followed by insulin deficiency, resulting from a progressive pancreatic beta-cell failure.
- PPARγ are nuclear receptors predominantly present in human liver, muscle and adipocytes, the major sites of insulin actions. Their activation regulates the transcription of several genes, involved in glucose and lipid metabolism. The effect of PPARγ activation on gene expression finally leads to an improvement of glucose metabolism.

Future applications

- Integration and development of similar models for PPAR related safety (edema, weight gain)
- Extrapolating short duration studies (e.g. PoC FPG/Phase 2 studies to phase 3)
- Integrate with subject level models
- Relate to oral glucose tolerance test (OGTT) results
- Investigate and describe (in a semi-mechanistic fashion) the relationship between the rate parameters for FPG (or derived MPG) and the rate parameters for HbA1c
- Position new diabetic drugs (with different mechanism of action) to the PPAR's (e.g. evaluate possible head-to-head comparisons).