PK PD Modelling and simulation in early development

When and how does it make sense

Eliane fuseau

17-18 March 2004, Strasbourg

Club Phase I, AGAH
PK PD in early development

Law
Health authorities
Guidances …

Ethics
Useless exposure
Risk/benefit ratio

Drug development

Modelling
Formulation, PK, PD, ER
Bridging formulations, populations

Money
Development costs
Errors costs
Attrition
**PK PD modelling in early development: scope**

- **Regulatory drive:**
  - Need to improve efficiency of DD and of application review
  - ER, in discovery and development (pre-clinical to clinical pharmacology and to patients)

- **Money/time/ethics**
  - Bioavailability, PK, PD, bridging (formulations, populations, regions)
  - ↓↓ development of 2nd in class, of line extensions

- **Label/profile/money/ethics**
  - Understanding the variability in response between subjects
  - Manage the individual risk/benefit ratio
Exposure-Response Relationships-
Guidance for Industry
FDA Expectations:
Where we are, Where we’d like to be

Brian Booth
FDA/CDER/OCPB/DPE
Boothb@cder.fda.gov
Purpose of the Guidance

To describe the role(s) of E-R relationships in drug development and the types of data and approaches that can be used to determine these relationships.
Measuring Response

1. Clinical Endpoints
   survival, cure, etc

2. Surrogate Endpoints
   Blood Pressure, Progression Free Survival,

3. *Biomarkers*
   prostate specific antigen,
Clinical Drug Development

1. Discovery & Development
   • linking pre-clinical to human
   • proof of concept
   • guidance for future trials

2. Safety and Effectiveness
   • contribute 1° safety and effectiveness
   • support for 1° effectiveness
   • support for new populations, sub-populations, dosage forms, routes, regimens

End of Phase 2a
- PK/PD, M&S, CTS
1. Discovery & Development
(pre-clinical & phase 1) proof of concept, guidance for future trials

![Graph showing change in imaging vs. drug concentration with symbols for biomarker and patient response lines.]

- **Line:** Biomarker Response
- **Symbols:** Patient Response

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EMF Consulting
Proposal for End-of-Phase 2A (EOP2A) Meetings

Advisory Committee for Pharmaceutical Sciences
Clinical Pharmacology Subcommittee
November 17-18, 2003

Lawrence J. Lesko, Ph.D., FCP
Office of Clinical Pharmacology and Biopharmaceutics, CDER, FDA
Guidances Driving Hypothesis


Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998)

Dose-Response Information to Support Drug Registration (1995)
Timing of Meeting

- Pre-IND
- EOP1
- EOP2A
- EOP2
- Pre-NDA
- Labeling

- Preclinical
- Phase 1
- Phase 2A
- Phase 2B
- Phase 3
- Phase 4

- NDA Submission
- Action Letter

Phase 1
Rationale for Meeting Time

• Complete information on preclinical pharmacology and E-R
• Complete dose-tolerance (safety) data in healthy volunteers
• Initial efficacy (proof-of-concept) and safety data in patients
• Prior to so-called “registration or label studies” on special populations, drug interactions and food studies
• Discuss study designs using emerging technologies such as pharmacogenetics
Opportunity to Apply Mechanistic and Quantitative Methods

- Modeling and simulation to analyze all E-R data and explore dose choices
- Design of studies using computer-assisted clinical trial simulation
- Design of PPK studies to efficiently identify co-variates affecting E-R
- Discuss therapeutic equivalence boundaries based on E-R to interpret special population studies
Which Drug Development Programs Would Benefit the Most?

Limited resources

- first-in-class or significant therapeutic advancement
- well-understood pathophysiology and pharmacology
- completeness of EOP2A background package
- experience of sponsor in drug development
Summary: Goals of EOP2A Meeting

• Decrease uncertainty in further drug development, e.g., phase 3
• Quantitative analysis of E-R data to suggest dose ranges for clinical study
• Identify missing or discuss necessary information prior to submission
• Improve informational quality and minimize delays in NDA review
PK and PD modelling & simulation Phase 1

PK

- Animal to man, FTIM, single dose PK, metabolic, PD (markers, surrogates).
- Formulation, absorption, absolute bioavailability, repeat-dose PK, dose-proportionality, time effect, dose effect.
- Demography, drug, food or disease interactions

PD

- Maximum tolerated dose in healthy, exposure
- Demography, drug, disease interactions
- Biomarkers, clinical endpoints
- ER estimation in healthy, in patients target population
PD evaluations: determination of ER

- Pre-clinical or human
- Needed: dose, time, repeated administration, disease on PK & PD
  - 3 or more dose levels (PK), large conc range (PD), optimise measures for PK and PD separately
  - SD vs. MD, wash-out followed by new SD
  - Complete profile for shape of model, sparse for pop estimates
  - PD should be all effects observed: wanted or adverse
  - Look for tolerance or sensitization
  - Look for PK and PD Drug-drug interactions
  - Consider variability: BSV, BOV, residual
- Estimate onset, duration and offset of effect
- Evaluate time effect on the disease: positive and/or negative control
Examples

- PhD thesis, Dr Vibeke Hatorpe, DTC (Denmark)
  - M&S across a “complete” development program in diabetes, partially *a posteriori*
- Absorption/formulation example (EMF)
  - High permeability, low solubility drug
  - Particle size problem
Diabetes and role of PPAR $\alpha$ & $\gamma$

Key regulators of intra- and extra cellular lipid and lipoprotein metabolism.

- Triglyceride production and metabolism
- HDL cholesterol production and the reverse cholesterol transport pathway
- FFA metabolism
- Adipocyte differentiation
- Glucose metabolism: PPAR$\gamma$ in glucose homeostasis is still debating
Blood Glucose Homeostasis

**HEPATIC GLUCOSE PRODUCTION**

**GLUCOSE UPTAKE**

**GLYCOGEN SYNTHESIS**

**GLYCOGENOLYSIS**

**GLUCONEOGENESIS**

**CARBOHYDRATES**

**DIET**

**INTESTINE**

**MUSCLE**

**LIVER**

**LIPOLYSIS**

**FFA**

**ADIPOSE TISSUE**

**PANCREAS**

**INSULIN**

**GLUCOSE UPTAKE**

**GLYCOGEN SYNTHESIS**
Lipid and Lipoprotein metabolism

**Nascent HDL**
- CHYLCROMNS
- B-48, E, C
- FFA+MG
- LPLIPASE
- ADIPOSE TISSUE
- CHOLESTEROL + TRIGLYCERIDES
- B-100, E, C

**Remnants**
- CHOLESTEROL + TRIGLYCERIDES
- B-48, E
- FFA+MG
- LPLIPASE
- MUSCLE

**VLDL**
- CHOLESTEROL + TRIGLYCERIDES
- B-100, E, C
- FFA+MG
- LPLIPASE
- MUSCLE

**IDL**
- CHOLESTEROL + TRIGLYCERIDES
- B-100, E
- FFA+MG
- LPLIPASE
- MUSCLE

**LDL**
- CHOLESTEROL + TRIGLYCERIDES
- B-100
- FFA+MG
- LPLIPASE
- MUSCLE

**HDL**
- CHOLESTEROL + TRIGLYCERIDES
- PL, APO A, E
- NASCENT HDL

**DIET**
- CHOLESTEROL + TRIGLYCERIDES
- PL, APO A, E

**Liver**
- BILE SALT
- CHOLESTEROL + TRIGLYCERIDES
- B-100, E, C

**Adipose tissue**
- CHOLESTEROL
- CHOLESTERYL ESTER
- B-48, E
- FFA+MG

**Muscle**
- CHOLESTEROL
- CHOLESTERYL ESTER
- B-48, E
- FFA+MG

**Peripheral tissue**
- CHOLESTEROL
- CHOLESTERYL ESTER
- B-48, E
- FFA+MG

**Endogenous pathway**
- LIVER
- ADIPOSE TISSUE
- PERIPHERAL TISSUE

**Exogenous pathway**
- INTESTINE
PKPD modelling & simulation in the early phases of the development, from non-clinical to phase I and from phase I to phase II, development of

- Allometric interspecies model from non-clinical PK to predict human PK.
- PK model for healthy subjects and patients with type 2 diabetes.
- PD model for the effects on glucose and lipid homeostasis in early clinical development (phase I) and in later phase clinical development (phase II).
- Influence of demographics, baseline characteristics and disease state.
- PD model for unwanted clinical outcomes and compare to the PD models for desirable clinical effects to assess the risk/benefit ratio.
- Evaluate the predictive value of the models
NNC 61-0029 In vitro & in vivo data

Transactivation assays

- PPARγ: NNC 61-0029 ~ Rosiglitazone
- PPARα: NNC 61-0029 ~ WY 14643

In type 2 diabetic db/db male mice

- ↓ fasting blood glucose, ↓ insulin, ↓ triglycerides

Pre-clinical PK

- Up to 4-week in rat (0, 0.1, 1, 5, 10, 25, 50 mg/kg),
- 4-week toxicity in dog (0, 0.2, 1, and 5 mg/kg)
- PK in mini-pig (SD 0.5 mg/kg)
- PK in monkey (SD 14 mg/kg)

Plasma protein binding; intrinsic clearance $C_{\text{int}}$ (incubation with hepatocytes).
**NNC 61-0029 human data**

- **Phase 1 HS:**
  - DB, placebo-controlled, dose escalation (6 dose levels: 1mg to 90 mg), oral SD for safety, tolerability and the PK in 48 healthy males

- **Phase 1b HS + Patients:**
  - DB, placebo-controlled, //, MD (3 dose levels), 7 days in 24 HS, 21 days in 15 males with type 2 diabetes
  - Fasting lipids and blood glucose at baseline and end of study
  - Fasting lipids, fructosamine, insulin, C-peptide and FPG weekly prior to dose
Phase 2a

- DB, 3-months, randomised, //, placebo-controlled, 200 patients with type 2 diabetes, 4-week WO, treated for at least 3 months, six groups: maintenance dose, 0.1 mg to 7mg.

- Trough levels at all visits

- Efficacy: HbA$_{1c}$, lipids, apolipoprotein A-I, and total apolipoprotein B, FPG, insulin, C-peptide, fructosamine, 6 hour lipid and glucose profile after a standard meal.
Interspecies allometric Scaling

Since low clearance (CYP450 mediated), use Boxenbaum two-terms power function:

\[ P = a \cdot WGT^b \cdot BW^y \quad \text{or} \quad P = a \cdot WGT^b / MLP \]

with \( MLP = 10.839 \cdot BW^{0.636} \cdot WGT^{-0.225} \)

Intrinsic clearance correction

\[ P = a \cdot WGT^b \cdot \left( CL_{an(hepatocytes)} / CL_{h(hepatocytes)} \right) \]

Estimation of allometric coefficients by NONMEM

PK estimation by species, with NONMEM
### PK parameters in different animals after oral dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rat* (n=196; male=90 female=106)</th>
<th>Dog (n=24; male=12 female=12)</th>
<th>Minipig (n=4; female)</th>
<th>Monkey (n=2; female)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (%SE) IIV (%)</td>
<td>Estimate (%SE) IIV (%)</td>
<td>Estimate (%SE) IIV (%)</td>
<td>Estimate (%SE) IIV (%)</td>
</tr>
<tr>
<td>CL/F (ml/hr/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>180 (7.4) 21.1</td>
<td>71.9 (12.9) 32.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>108 (6.9) 21.1</td>
<td>54.7 (9.7) 32.4</td>
<td>290 (43.4) 20.0</td>
<td>(5.8)</td>
</tr>
<tr>
<td>Effect of Day</td>
<td>0.19 (48.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V/F (ml/kg)</td>
<td>1080 (6.9)</td>
<td>401 (9.7) 26.2</td>
<td>1370 (13.1) 69.2</td>
<td>20.4</td>
</tr>
<tr>
<td>Vss/F (ml/kg)</td>
<td>-</td>
<td>927 (13.1) 46.8</td>
<td>5580 (17.5) 1810 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Q (ml/hr/kg)</td>
<td>-</td>
<td>135 (25.5) 95.9</td>
<td>2280 (17.0) 29.8</td>
<td>20.5 24.3</td>
</tr>
<tr>
<td>ka (hr⁻¹)</td>
<td>0.893 (23.6) 68.4</td>
<td>4.52 (15.0)</td>
<td>2.38 (15.8) 0.404</td>
<td>(13.9)</td>
</tr>
<tr>
<td>Random residual variability</td>
<td>0.20 (11.9) 0.142 (16.5)</td>
<td>0.145 (18.2) (51.8)</td>
<td>0.0394 (19.8) CV</td>
<td></td>
</tr>
<tr>
<td>%CV</td>
<td>44.7%</td>
<td>37.7%</td>
<td>38.1%</td>
<td>19.8%</td>
</tr>
</tbody>
</table>

*CL/F,male=180*Day/(0.19+Day) and CL/F, female=108*Day/(0.19+Day)
PK Results

Rat, Male

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
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</table>

Rat, Female

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Concentration (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
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<td>15</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
</tbody>
</table>

Dog, Male

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Concentration (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
</tr>
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</table>

Dog, Female

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<thead>
<tr>
<th>Time (h)</th>
<th>Concentration (ng/ml)</th>
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<tbody>
<tr>
<td>0</td>
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<td>6</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
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Monkey

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<tr>
<th>Time (h)</th>
<th>Concentration (ng/ml)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<td>15</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
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</tbody>
</table>

Minipig

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
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<tr>
<td>4</td>
<td>5</td>
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<tr>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>
**Allometric prediction in human**

~ complete failure

<table>
<thead>
<tr>
<th>Model notation</th>
<th>Human parameters in a 70 kg person</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL/F (L/hr)</td>
</tr>
<tr>
<td>CL = f(WGT, SEX)</td>
<td>3.9</td>
</tr>
<tr>
<td>V and Vss = f(WGT)</td>
<td></td>
</tr>
<tr>
<td>CL = f(WGT, SEX, BW)</td>
<td>-</td>
</tr>
<tr>
<td>V and Vss = f(WGT)</td>
<td></td>
</tr>
<tr>
<td>CL · MLP = f(WGT, SEX)</td>
<td>1.9</td>
</tr>
<tr>
<td>V and Vss = f(WGT)</td>
<td></td>
</tr>
<tr>
<td>CL · (CL_{int,h}/CL_{int,an}) = f(WGT, SEX)</td>
<td>0.49</td>
</tr>
<tr>
<td>V and Vss = f(WGT)</td>
<td></td>
</tr>
<tr>
<td>Observed in a single dose study (clinical study I)</td>
<td>0.077</td>
</tr>
</tbody>
</table>
Human PK SD Healthy subjects

Data and pop PRED
Human PK, MD HS & patients

**HS**

- **Dose 0.5 mg**
  - Concentration vs. Time graph:
    - Time (h): 0, 100, 200, 300, 400
    - Concentration (ng/ml): 100, 200, 300, 400

- **Dose 4 mg**
  - Concentration vs. Time graph:
    - Time (h): 0, 100, 200, 300, 400
    - Concentration (ng/ml): 0, 200, 400

- **Dose 16 mg**
  - Concentration vs. Time graph:
    - Time (h): 0, 100, 200, 300, 400
    - Concentration (ng/ml): 0, 500, 1000

**Type 2 diabetes**

- **Dose 0.5 mg**
  - Concentration vs. Time graph:
    - Time (h): 0, 200, 400, 600, 800, 1000
    - Concentration (ng/ml): 0, 200, 400, 600

- **Dose 4 mg**
  - Concentration vs. Time graph:
    - Time (h): 0, 200, 400, 600, 800, 1000
    - Concentration (ng/ml): 0, 1000, 2000

- **Dose 16 mg**
  - Concentration vs. Time graph:
    - Time (h): 0, 200, 400, 600, 800, 1000
    - Concentration (ng/ml): 0, 10000, 20000

Data and pop PRED
Human PK, effect of time, of dose

Clearance vs Day

Clearance vs Dose
Pharmacodynamic Analyses

- **PD variables:**
  - Biological markers of the glucose lowering effect: FPG, fructosamine
  - Biological markers for the effect on the lipid profile: triglycerides, free fatty acids (FFA), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)
  - Safety variable: haemoglobin

- **Analysis methods**
  - Univariate analysis of each PD variable with PK marker: dose,
  - Graphical exploration of relationships between PD variables: AUC or Cmin-ss
  - Selected PD variables analysed with other PD variables as covariates, to evaluate if these variables were a better predictor
General PKPD models

Dose → \( C_p \)

\( C_p \) → \( C_e \) via \( k_{e0} \)

\( C_e \) has indirect inhibition or stimulation on \( R \) via \( k_{in} \)

\( R \) has indirect inhibition or stimulation on \( C_e \) via \( k_{out} \)
Endpoints and models

- FPG, triglycerides
  - Indirect response model with loss of stimulatory response
  - Effect compartment, to allow for the difference in time to reach PK and PD steady-state
- FPG, fructosamine, triglycerides, free fatty acids, HDL and LDL
  - Inhibitory or stimulatory sigmoid $E_{\text{max}}$, with or without effect of time and with dose, plasma concentration or AUC as independent variable
## Phase 1 data, HS and patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model parameters</th>
<th>Population Estimate</th>
<th>95% CI</th>
<th>Intersubject variability (±SD or %CV)</th>
<th>Residual variability (±SD or %CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRIG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$E = E_0 - \frac{E_{\text{max}} \cdot AUC_{\gamma}}{EAUC_{50}^\gamma + AUC_{\gamma}}$</td>
<td>1.8</td>
<td>[1.5 ; 2.1]</td>
<td>± 0.6</td>
<td></td>
</tr>
<tr>
<td>$E_0$ (mmol/L)</td>
<td></td>
<td>1.4</td>
<td>[0.8 ; 1.9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}}$ (mmol/L)</td>
<td></td>
<td>182</td>
<td>[0 ; 397.6]</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.65</td>
<td>[0.06 ; 1.24]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$E = \alpha \cdot \text{TRIG}^\beta$</td>
<td>1.29</td>
<td>[1.17 ; 1.41]</td>
<td>20.3</td>
<td></td>
</tr>
<tr>
<td>$\alpha$ (mmol/L)</td>
<td></td>
<td>-0.206</td>
<td>[-0.31 ; -0.1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$</td>
<td>3.07</td>
<td>[2.62 ; 3.52]</td>
<td></td>
<td>27.7</td>
<td></td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$E = \alpha \cdot \text{TRIG}^\beta$</td>
<td>3.07</td>
<td>[2.62 ; 3.52]</td>
<td>27.7</td>
<td></td>
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<tr>
<td>$\alpha$ (mmol/L)</td>
<td></td>
<td>0.27</td>
<td>[0.2 ; 0.34]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$</td>
<td>0.27</td>
<td>[0.2 ; 0.34]</td>
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<td>FFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$E = E_0 - \frac{E_{\text{max}} \cdot \text{Dose}}{ED_{50} + \text{Dose}}$</td>
<td>$E_0$ (mmol/L)</td>
<td>0.49</td>
<td>[0.41 ; 0.56]</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$E_{\text{max}}$ (mmol/L)</td>
<td>0.34</td>
<td>[0.27 ; 0.41]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$ED_{50}$ (mg)</td>
<td>1.33</td>
<td>[0 ; 3.05]</td>
<td>29.9</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$E = E_0 - \frac{E_{\text{max}} \cdot \text{Dose}^\gamma}{ED_{50}^\gamma + \text{Dose}^\gamma}$</td>
<td>$E_0$ (mmol/L)</td>
<td>10.9</td>
<td>[9.5 ; 12.2]</td>
<td>± 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$E_{\text{max}}$ (mmol/L)</td>
<td>1.44</td>
<td>[0.4 ; 2.5]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$ED_{50}$ (mg)</td>
<td>0.47</td>
<td>[0.3 ; 0.7]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\gamma$</td>
<td>5.4</td>
<td>[1.9 ; 8.8]</td>
<td>± 1.0</td>
</tr>
<tr>
<td>FRUC</td>
<td>$E = \alpha + \beta \cdot \text{FPG}$</td>
<td>$\alpha$ (mmol/L)</td>
<td>274</td>
<td>[219 ; 329]</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\beta$</td>
<td>5.9</td>
<td>[1.4 ; 10.4]</td>
<td></td>
</tr>
</tbody>
</table>
Dose selection for phase IIa

Monte Carlo simulations of 1000 patients, 24 weeks

Population distribution of reduction in FPG after 24 weeks of treatment
**Overall conclusion**

... the work provides considerable information on the pharmacokinetics and pharmacodynamics ... summarised as:

- IIV in the PK and PD of a PPAR$_\alpha$ and $\gamma$ activator and identification of covariates added valuable information in the characterisation of the compound.

- proved to be a useful tool in dose and dose range selection by population simulations.

- small population sample was predictive in a larger population sample.

- Mixed effects PK modelling during non-clinical phase and subsequent interspecies allometric scaling did not adequately predict human pharmacokinetic parameters. The value of using ... prospectively is questionable and should be considered on a case-by-case basis.

- Predictions of IIa were accurate

- A dead mouse killed NNC 61-0029
EMF example 1: chronic disease, CNS

Healthy subjects
Form 1: SD 0.05 - 21, MD 1 - 12
Form 2: SD 4, MD 4 - 72

Effect of dose on Cmax & AUC

Phase 2/3
Form 1: MD 1 - 16
Form 2: MD 4 - 32
Example 1

- High permeability; very low solubility, depends on particle size

- Bioavailability at SD:
  - ↑ with food,
  - ↑ when particle size ↓,
  - ↑ when body size ↑ (for same dose)
  - ↓ when dose ↑ (for same subject)

- Form 1 & 2 ~ BE at SD 4

- $C_{avss}$ in phase 2a&b, 3:
  - ↑ exposure with form 2 vs. 1, ↓ apparent Cl
**PK and ER modelling program**

- Model for $F_{rel}$ developed in healthy and patients
- Pooled all patient studies, all forms, all doses, all populations (age 2-80)
- Estimate PK in target population
- Derived exposure at each visit
- Estimate ER relationship for efficacy clinical endpoints
- Safety: exposure in subjects with typical AE vs. subjects without
Results of modelling and net profit

- Differences between HS studies explained by formulations, substance batches (particle size), dose per kg
- Complete bridging between formulations/doses: gap closed
- Complete bridging between populations: adults and children
- Very limited BSV on PK
- Food effect irrelevant during chronic treatment: no dosing recommendation
- Precise estimation of DDIs in target population:
  - effects of each concmed on drug X PK
  - effects of X, demography and other concmeds on usual medications
Efficacy ER not affected by formulation, study design (for identical endpoint), by concomitant medications

Differences in response between studies explained by:

- Relative bio between formulations
- Baseline disease severity
- Differences in placebo response between population: children, adolescent and adults
- Different concomitant medications with period of development, leading to diff drug-drug interactions

No need for other bridging data between form 1 & 2 (money, exposure of healthy subjects, time)

ER Model available for line extensions (paediatric formulation)

ER requirements satisfied (maybe…)
PKPD tools/skills to acquire

- Predictions of absorption, metabolism, disposition from structure and physico-chemical properties: SIMCYP, Gastroplus…
- PK analysis, PKPD, parameter estimation, design …WinNonlin, Kinetica
- Population PK, PKPD: NONMEM
- Simulations: WinNonlin, WinNonmix, Nonmem, SAS, TS2..
- Databases: clinical data, PK data…
Building the knowledge database with M&S

- Predict human PK:
  - from animal, from drug properties, IVIVC,
  - Microdosing and AMS/PET
- Build model for ER from pre-clinical, animal studies
- Select human dose based on pre-clinical ER and predicted PK
  - Optimise design of FTIM study

- Build PK and ER model with biomarkers from FTIM
  - To design best phase I and phase 2a package using/for modelling and simulation.

- Evaluate ER in target (EOP2a meeting):
  - revise phase II and III program/ label/ product profile