# Case 1:
# PGx-Design in Phase I based on *In vitro* Data

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# Objective of Session

Understanding the pre-clinical drivers that determine the incorporation of PGx in phase I studies.

# Format of Session

- This workshop is designing the phase I programme for a NCE
- When phase I studies are being designed, information from pre-clinical studies that is relevant to PK issues (e.g. *in vitro* metabolism, metabolites in pre-clinical species etc.) is available.
- Data from transporters may also be available

Workshop task:
Recommendations on the most appropriate phase I strategy for different scenarios

# PGx Options in Phase I

- Depending on the in vitro/in vivo pre-clinical data, there are a number of options for PGx in phase I studies:
  - Do nothing
  - Collect DNA for future analysis should phenotypes (e.g. PK outliers) emerge that warrant PGx study
  - Genotype participants in phase I studies at specific genes
  - Enriched study in participants with defined genotype as an entry criterion
  - Exclude particular genotype groups (e.g. poor metabolizers) from initial - or all - phase I studies

# Key Points to Consider

- CHMP Reflection Paper on PG in PK Evaluation:

> If human *in vitro* data suggest major involvement of a protein known to be subject to functionally important genetic polymorphism, inclusion of genotyping directed to the candidate gene is warranted in early phase I studies.

> Involvement of transporters …presently the knowledge of this field is not mature enough for early genotyping to be required only on the basis of *in vitro* data.

> It is recommended that samples from early phase I studies are stored to allow retrospective analysis ...

- *In vitro* metabolism data are not necessarily predictive of human drug metabolism, quantitatively or even qualitatively
- For many ADME genes, the link between genotype and phenotype is unclear
- Generating genetic data that is not used for progressing drug development is inappropriate

# Compound under Development

- The company is developing a new chemical entity (drug A) for a serious, chronic disease, Diabetes Mellitus Type 2
- Drug A shows no major toxicities in animals at exposures expected to provide >80% receptor occupancy.
- The limiting toxicity is elevated body temperature in dogs.
- Extrapolating to human exposure, it is expected that there will be a safety margin of ~10x at a therapeutic dose.

# Core Case Summary

**Drug A for Diabetes type 2 (**2nd in class) has:

| | |
|---|---|
| Predicted Therapeutic Margin | **narrow** |
| Proposed Therapeutic Level | **need high receptor occupancy** |
| Exposure:Response Curve | **unknown location on curve** |
| In-vitro ADME Phenotyping | **see data** |
| Observed Clinical Exposures | **see data** |

# Core Metabolism Data Set

- The data below show results from a in-vitro ADME phenotype study
  - Compound is incubated with human liver microsomes
  - Preclinical Data indicates Oxidative Metabolism is the major clearance route for Drug A
  - Effect of CYP isoform inhibitors is determined
- For the core data set and each variation, the CYP sub-type inhibition is given, plus other relevant comments
- For each scenario, the preferred PGx approach in phase I is to be identified

# Discussion to Design Phase 1 Programme

| Dataset | Do Nothing | Collect DNA only | Prospective Phase I Genotyping | Specific Enriched Study | Exclude e.g. PMs | Other |
|---|---|---|---|---|---|---|
| Core set: CYP2D6 signal | | | | | | |
| Variation 1: CYP3A4 signal | | | | | | |
| Variation 2: CYP2C8 signal | | | | | | |
| Variation 3: No metabolites | | | | | | |
| Variation 4: low CYP2D6 signal | | | | | | |
| OATP Transporter Signal | | | | | | |

# Core Data Set – CYP2D6 Metabolism

- Oxidised metabolites seen in pre-clinical species

| Inhibitor | Target CYP Isoform | CLint (µL/min/mg protein) | % Inhibition |
|---|---|---|---|
| Control | | 12.5 | - |
| Furafylline | **1A2** | 12.9 | **0** |
| Sulfaphenoxazole | **2C9** | 11.9 | **4** |
| Omeprazole | **2C19** | 11.7 | **6** |
| Quinidine | **2D6** | 6.9 | **45** |
| Ketoconazole | **3A4/5** | 10.6 | **15** |
| Trimethoprim | **2C8** | 11.5 | **8** |

# Variation 1 – CYP3A4/5 Metabolism

- As per core set, but metabolism is via CYP3A4

| Inhibitor | Target CYP Isoform | CLint (µL/min/mg protein) | % Inhibition |
|---|---|---|---|
| Control | | 12.5 | - |
| Furafylline | **1A2** | 12.9 | **0** |
| Sulfaphenoxazole | **2C9** | 11.9 | **4** |
| Omeprazole | **2C19** | 11.7 | **6** |
| Quinidine | **2D6** | 10.6 | **15** |
| Ketoconazole | **3A4/5** | 6.9 | **45** |
| Trimethoprim | **2C8** | 11.5 | **8** |

# Variation 2 – CYP2C8 Metabolism

- As per core set, but metabolism is via 2C8

| Inhibitor | Target CYP Isoform | CLint (µL/min/mg protein) | % Inhibition |
|---|---|---|---|
| Control | | 12.5 | - |
| Furafylline | **1A2** | 12.9 | **0** |
| Sulfaphenoxazole | **2C9** | 11.9 | **4** |
| Omeprazole | **2C19** | 11.7 | **6** |
| Quinidine | **2D6** | 10.6 | **15** |
| Ketoconazole | **3A4/5** | 10.5 | **15** |
| Trimethoprim | **2C8** | 5.6 | **55** |

# Variation 3 – No Oxidised Metabolites

- As per core dataset, but no oxidative metabolites seen in pre-clinical species – compound excreted unchanged in faeces

| Inhibitor | Target CYP Isoform | CLint (µL/min/mg protein) | % Inhibition |
|---|---|---|---|
| Control | | 12.5 | - |
| Furafylline | **1A2** | 12.9 | **0** |
| Sulfaphenoxazole | **2C9** | 11.9 | **4** |
| Omeprazole | **2C19** | 11.7 | **6** |
| Quinidine | **2D6** | 6.9 | **45** |
| Ketoconazole | **3A4/5** | 10.6 | **15** |
| Trimethoprim | **2C8** | 11.5 | **8** |

# Variation 4 – Reduced CYP2D6 Metabolism

- As per core set, except that CYP2D6 specific metabolism is 22% (as opposed to 40%).

| Inhibitor | Target CYP Isoform | CLint (µL/min/mg protein) | % Inhibition |
|---|---|---|---|
| Control | | 12.5 | - |
| Furafylline | **1A2** | 12.9 | **0** |
| Sulfaphenoxazole | **2C9** | 11.9 | **4** |
| Omeprazole | **2C19** | 11.7 | **6** |
| Quinidine | **2D6** | 9.8 | **22** |
| Ketoconazole | **3A4/5** | 11.8 | **5** |
| Trimethoprim | **2C8** | 11.5 | **8** |

# Transporter Studies

- Increasingly, transporters implicated in drug disposition, efficacy and safety
- Compound A (target organ – liver) tested for uptake in cells transfected with human OATP receptors, including known polymorphisms
  - Data for OATP sub-types expressed as rate of uptake into transfected cells
  - Data for OATP1B1 variants expressed as percentage activity of ‘wild-type’ transporter

# OATP Transport Data

| OATP Sub-type | Rate of Uptake | OATP1B1 Variant | Frequency | Rate of Uptake |
|---|---|---|---|---|
| **Vehicle** | 0.8 | *1a | 0.56 | 12.5 |
| **1A2** | 4.5 | *1b | 0.26 | 10.2 |
| **1B1** | 12.5 | *5 | 0.02 | 1.5 |
| **1B3** | 6.2 | *15 | 0.16 | 4.5 |
| **2B1** | 3.5 | | | |

- The data show significant uptake by OATP1B1, which is greatly reduced in known human variants
- Some uptake is seen with other OATP sub-types

# Discussion to Design Phase 1 Programme

| Dataset | Do Nothing | Collect DNA only | Prospective Phase I Genotyping | Specific Enriched Study | Exclude e.g. PMs | Other |
|---|---|---|---|---|---|---|
| Core set: CYP2D6 signal | | | | | | |
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| Variation 2: CYP2C8 signal | | | | | | |
| Variation 3: No metabolites | | | | | | |
| Variation 4: low CYP2D6 signal | | | | | | |
| OATP Transporter Signal | | | | | | |