EMEA EFPIA Workshop 19Dec08

Integrating PGx Early into Drug Development:

PK as a working example

EMEA/EFPIA PGx in PK Workshop

Case 3: PGx Data Submission to Biomarker Scientific Advice

Task: What does the team do next?

Case 3 – Setting the stage

Situation:
Project team has (genotype) data from five Phase I & one phase IIa studies

Goal: To pool PGx data from different sources to increase power

Objectives of the Team:
• Use PGx data as a decision criteria in upcoming pivotal clinical trial
• Assessment on whether (or not) to submit PGx data to EMEA, and what / how to submit these data.

Given:

- PGx study was conducted under tight turnaround timeline to meet development decision for submission to Biomarker Scientific Advice

- Study designs varied in terms of:
  - Demographic representation
  - Phenotype prediction (dependent on PK parameters and cut-off)
  - PGx Assay format
  - Data format

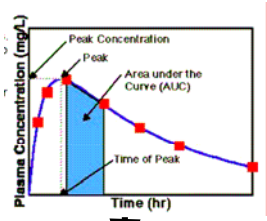
Different Formats and Analytic Processes for PGx Data

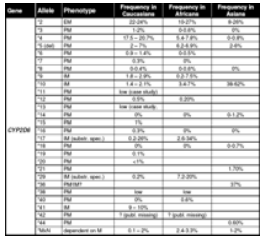
Raw Data

PK

Reference Data

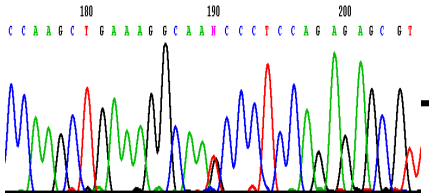
Microarrays





Polymorphism data for different demographic groups

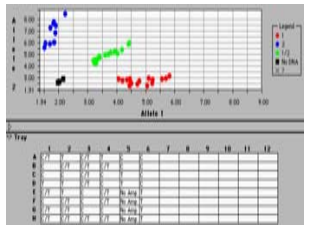
Sequencing

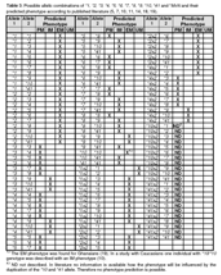


Data Processing

Haplotype data (star allele nomenclature)

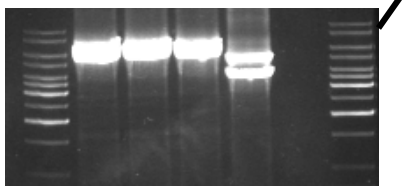
TaqMan





Predicted ADME phenotypes based on literature data for known drugs

Fragment analysis



Genotyping Results per sample

SNP genotypes (SNP1: A/A, SNP2: A/B, etc)
Haplotypes / Alleles (*1/*X, *X/*X, etc)
Predicted ADME Phenotype (EM, PM, etc)

Assay formats to generate raw data

Study Report

What type of genotyping results to be included?
What type of data formats and standards to be used?

Interpretation of raw data

Team considers….

- How do you report PGx data?
- Is it different depending on which clinical decision is being made from the dataset?
- What are the format and standards?
- What standards and steps are to be considered to accept a genomic biomarker for clinical use?

Team Output on Data Submission to EMEA Scientific Advice

WHAT is reported ?

What is reported > **Dataset:**	Do not report	Report individual study results of QA-controlled studies only	Report only individual study results (of all studies)	Report meta-analysis results	Other (eg scientific publication)
Data from QA-controlled GT study (Scenario 1 hypothesis driven)					
Data from exploratory study (Scenario 2 hypothesis driven / generation)					
Data from exploratory studies (Scenario 3 Affy chip; hypothesis generation)					
Combined data from QA-controlled and exploratory studies (Scenario 4)					

Team Output on Data Submission to EMEA Scientific Advice

HOW are data reported ?

Meta analysis

How is reported> **Dataset:**	Do not report	Report as Genotyping Data	Report as predicted phenotype (EM, PM)	Weighted contribution of individual studies	Perform / include multiple testing correction	Combine data from different ethnicities
Data from QA-controlled GT study (Scenario 1 hypothesis driven)						
Data from exploratory study (Scenario 2 hypothesis driven / generation)						
Data from exploratory studies (Scenario 3 Affy chip; hypothesis generation)						
Combined data from QA-controlled and exploratory studies (Scenario 4)						

Scenario 1

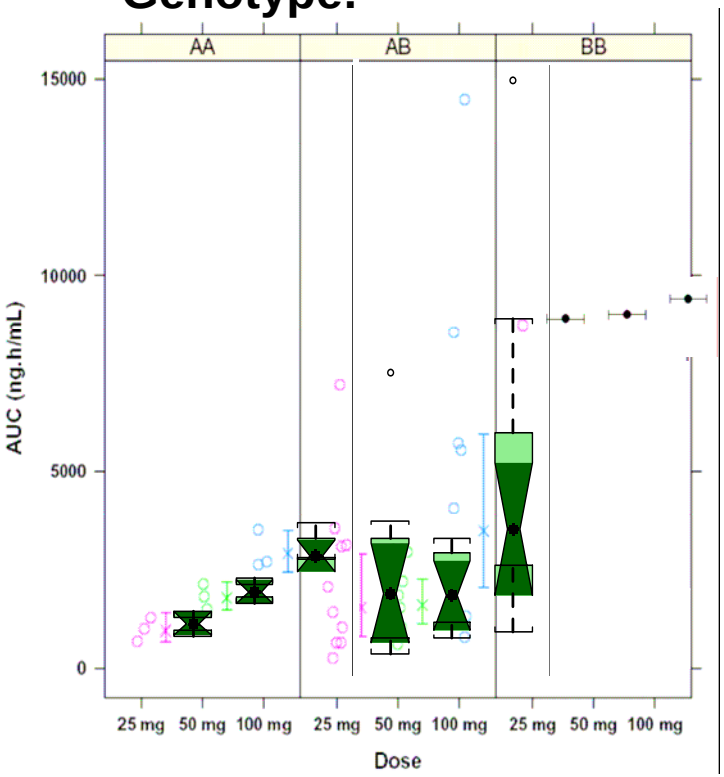
Hypothesis driven

Three Phase 1 studies available with PGx data

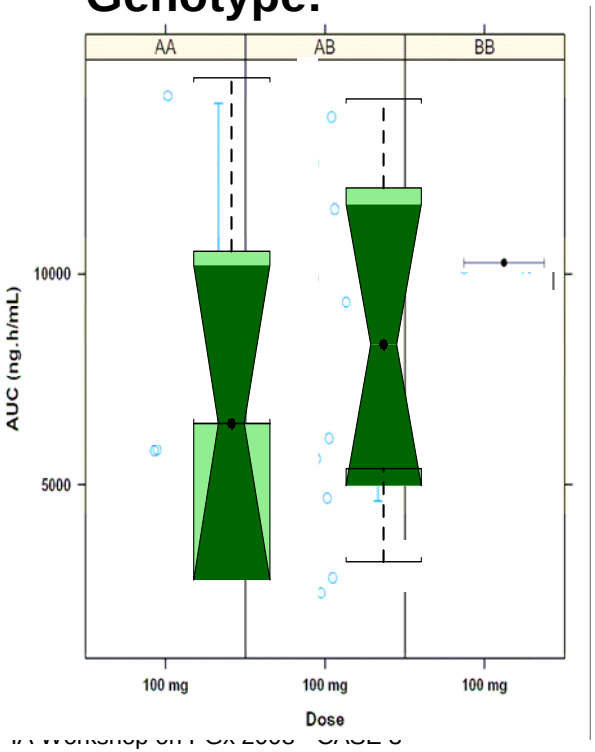
Genotyping:

- CYP2C8 pre-defined in the protocol, as there was preclinical evidence
- Gel-based assays for specific CYP2C8 alleles:
- All alleles (no selection for geographical selective alleles)
- Genotyping studies performed with Quality Management defined procedure

Genotype:



Genotype:



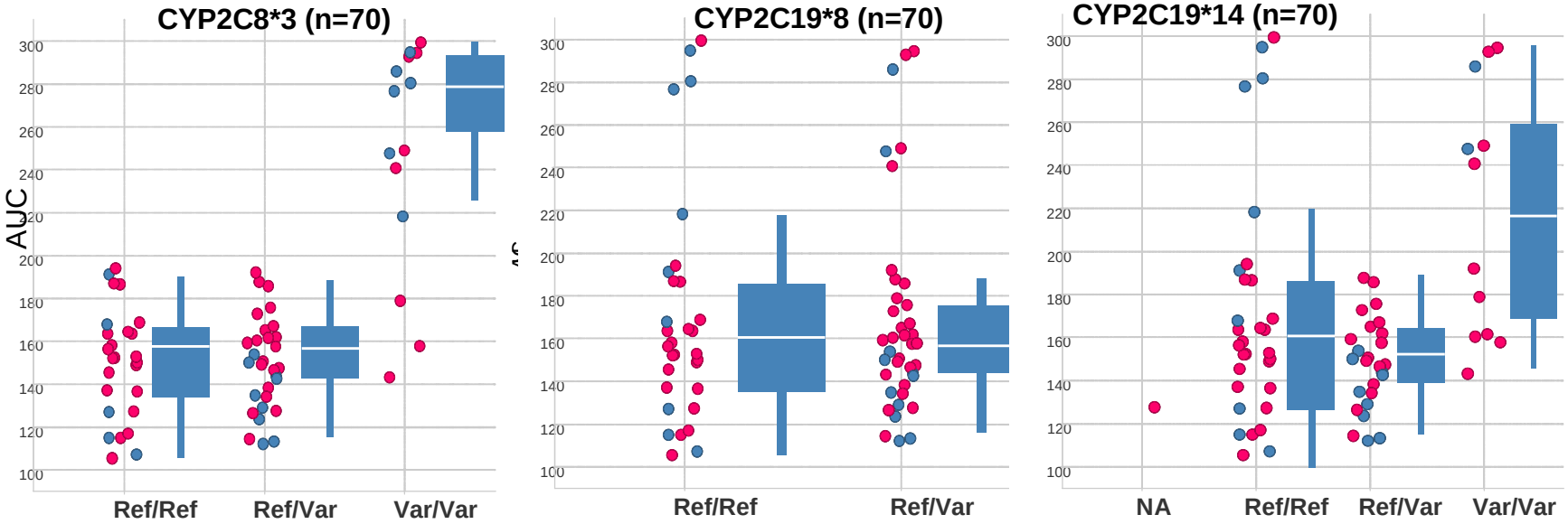
Scenario 2

Hypothesis driven / generation

Two Phase 1 studies available with PGx data

Genotyping:

- Several CYP450 genes genotyped, including CYP2C8 (as there was preclinical evidence)
- Commercially available assays used (internal research) – mixed platforms (TaqMan [red dots] and primer extension [blue dots] assays)
- All described alleles genotyped, including rare alleles (of all different ethnicities)
- Genotyping studies performed as exploratory research (without formal Quality Management defined procedure)



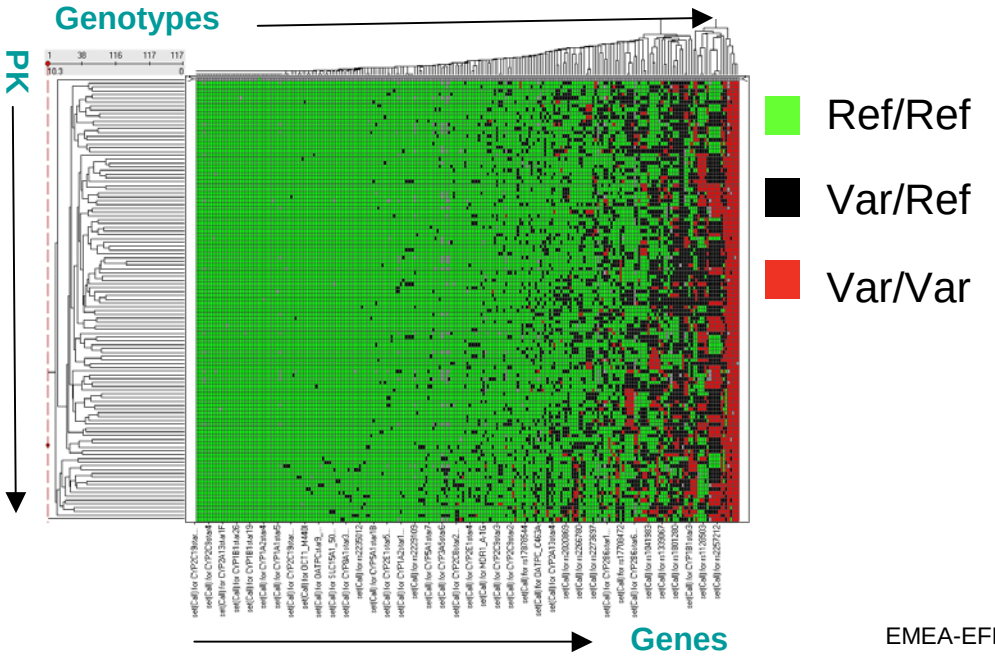
Scenario 3

Hypothesis generation

One Phase 2 study available with PGx data
(reason: explore PK and PD; test emerging technologies:DMET)

Genotyping:

- Affymetrix DMET chip
- Aim = Hypothesis generation
- Assays performed with Vendor
- Genotyping studies performed as exploratory research (without formal Quality Management defined procedure)
- Association with CYP2C8 and transporter gene



Chi-square test with Correction for multiple testing (Bonferroni)
Significance at P<=0.05

Gene name	haplotype	Ref/ Ref	Ref/Var	Var/ Var	G p-value*
CYP2C8	**CYP2C8star3**	**199**	**58**	**20**	**0.00004***
SLCO1B1	**OATPCstar10_A 1964G**	**187**	**63**	**25**	**0.0001***
CYP3A4	**CYP3A4star19_I VS10+12GA**	161	88	27	0.0007
CYP1A2	CYP1A2star1C	245	28	3	0.003
CYP2E1	rs2515641	179	76	22	0.003
FMO2	rs6671692	268	6	1	0.004
CYP3A43	rs800667	200	63	12	0.004
CYP2D6	CYP2D6star17_2 850CT	127	104	46	0.005
ABCB1	rs2032588	248	26	3	0.006
PTGIS	rs5626	271	5	0	0.007
CYP2D6	CYP2D6star17_1 023CT	254	14	8	0.007
CYP2A13	CYP2A13star1H_ 6432CT	224	46	7	0.007

Scenario 4 **Combined data from different studies**

Multiple clinical studies with PGx data available

Genotyping:

- CYP2C8 data available from **3 phase I** studies (QM-defined procedure) **(Scenario 1)**
- Data from **2 phase I** studies (exploratory research) **(Scenario 2)**
- Data from **1 phase II** study (ADME chip) **(Scenario 3)**
- Aim = Hypothesis driven (CYP2C8 + transporter) => Analysis / reporting with focus on CYP2C8 / transporter data only (pooling of PGx data in order to increase power)
- Assays performed on different platforms (See previous scenarios)

Scenario 1 : studies 1	(n=30) and 2 (n=38)	N=416
Scenario 2 : studies 3	(n=50) and 4 (n=20)	
Scenario 3 : study 5	(n=278)	

What were the issues for the Team?

Team Task:

1. What is reported for clinical analysis?
2. What is standard and format for team submission to EMEA Biomarker Scientific Advice?

- Expansion of haplotypes in different populations
- Predicted Phenotype (metaboliser genotype status)

- Scientist on team wanted Raw SNP data, allele, genotypes,
- Clinical pharmacologist only wanted predicted phenotype (no alleles)

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Different Formats and Analytic Processes for PGx Data

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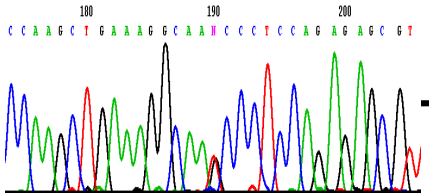

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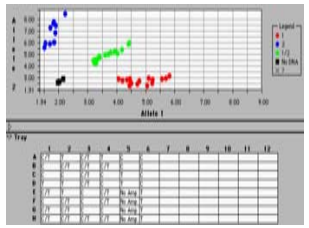

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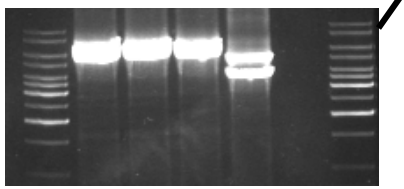
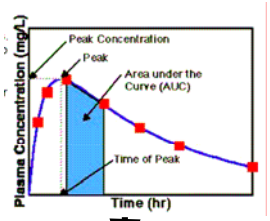


PK



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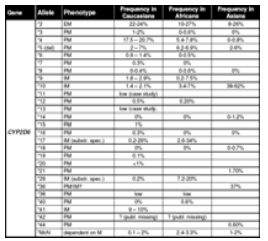
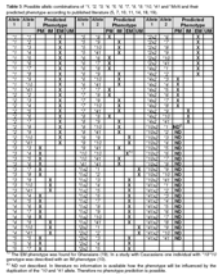


Polymorphism data for different demographic groups

Haplotype data (star allele nomenclature)



Predicted ADME phenotypes based on literature data for known drugs

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Predicted ADME Phenotype (EM, PM, etc)

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What type of data formats and standards to be used?

Assay formats to generate raw data

Interpretation of raw data

Backup Slides

Reporting issues

- **Criteria for selection of polymorphisms / alleles to be analysed**
  - Sample size
  - Frequency depending on ethnic composition / age / gender of study population
  - Functional effect
- **Polymorphism genotype data**
  - Which nomenclature / reference system?
- **Haplotype / Allele definition**
  - Which nomenclature / reference system?
- **Phenotype prediction**
  - *1 accuracy, alleles analysed (high / low frequency)
  - Prediction based on literature data for known drugs
- **Method / assay**
  - Definition of criteria for assay validation eg minimal requirements rather than imposing specific quality standard
- **Clinical endpoint**
- **Definition of PK parameters**
  - **AUC, C-Max etc. What is the cut-off being used to de designate metabolizing or responder status**

Data formats issues

- **Table embedded into report**
- **Submission of a separate table**
  - in a company specific format
  - in a format which will be compatible with many different database formats so that sharing of data with outside parties is possible
  - SAS datasets
- **Formats have to be compatible if data from different sources will be combined or downloaded into different databases**
  - Integration of genotype data into database with clinical information
  - Different types of data are stored in separate databases
    - Eg, Database for exploratory research containing full set of data and database for clinical research containing only predicted phenotype data if available

Meta Analysis Issues

- Results from different platforms comparable?
- Predictive significance (qualification)
- Different data formats from different studies?
- Weighted contribution of different studies?
- Allele definition (SNP ID, “star” nomenclature, WT vs mutant allele, genotype, predicted phenotype)?
- *1 (Wild Type) prediction as different alleles are determined

– Statistical Analysis platform (SAS vs. S^+, R, Homebrew, etc)
– Population substructure

Meta analyses issues

- *NOTE:*
- Different options: 1. reanalyze genotypes of cyp4502C8*3 and OATPC*10:
- score significance @ P<0.05)
- 2. analyze subset (train) and use the rest as a test set to
- demonstrate significance
- 3….

PK report (?)

Team plans the following submission to EMEA:

a) Typical EMEA PK Study Report includes: <give example>

b) What is different for PGx?

- Method Description as per established PK assays
- Analytical validation as per established PK assays

<u>Pgx Specific Discussion</u>:

- Predicted Phenotype Description of Alleles (FDA Metabolite status designation)
- Data analysis
- Statistics: Power Calculation (FDA)
- Ethnicities and alleles per major demographic (ethnic) groups

With GN…and if included why, level of details under each heading

Assay formats

- **Gel based assays for CYP450 with preclinical evidence** (With Quality Management defined procedure)
  - most frequent alleles (cut-off for allele selection = allele frequency >1%)
  - Focused on “Caucasian” alleles
- **Commercially available assays for several cyp450’s** (Internal study)
  - All described alleles including rare alleles
  - No restriction on ethnicity
- **Affymetrix DMET chip** (With vendor)
  - Additional association with transporter allele identified
  - Hypothesis generation

Items that are under GCP

As per other established clinical lab practices, no need to describe:

- Blood Collection
- Blood Storage pending DNA use
- Shipping
- DNA Extraction
- DNA storage
- DNA qualification as indicated

Not part of submission

- Specimen collection most likely blood but sometimes other specimens (buccal swab, sputum, etc…) are collected
- Specimen storage
- Specimen shipment
- DNA extraction from specimen
- DNA dilution
- DNA storage
- Genotyping using a specific method / assay
- Genotype calling
- Reporting of genotypes

Team consults….

- Is there a Standard rating procedure to increase confidence towards confirming genomic biomarker?
- SNP nomenclature, NCBI (or not)
- (We'll need to invite SDO expert on this case to share their learnings… eg Standards Development Organizations (SDOs) such as ISO, CEN, HL7, and CDISC)