Feasibility assessment of PBPK modelling for Endogenous Compounds: Baseline levels of endogenous compounds in the Caucasian population

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BACKGROUND

- There is increasing interest in the potential utility of Endogenous Compounds (EC's) as biomarkers for assessment of drug-induced enzyme level/activity changes of (a) CYP3A or (b) UGT1A1 following chronic dosing of the drug of interest.
- In July 2013, Consortium Members were asked to identify a series of EC's for further evaluation, with a view to implementation within the Simcyp Simulator.
- The two top ranked compounds and their proposed utility as biomarkers are given in Table 1.

Table 1: The top 2 ranked endogenous compounds and their utility

Biomarker	Utility
4-β-OH Cholesterol (4bOH-C)	Induction of CYP3A enzyme
Bilirubin; -conjugates	Induction and inhibition of UGT1A1, OATP2B1 and MRP2

AIMS

To evaluate the feasibility of developing the most popular EC's (Table 1).

METHODS:

- A systematic literature search using representative key words in PubMed and the internet for the two EC's was performed.
- Discussions were held with Consortium Members (*e.g.*, webinar 1st August 2013) on their experiences with these biomarkers and potential data sharing opportunities.
- Key areas identified for investigation were baseline plasma levels of each biomarker in a Healthy Volunteer population and routes of biotransformation.

RESULTS

- 4-β-Hydroxycholesterol

A biomarker for CYP3A4 as decreased levels could indicate need for a clinical DDI study - a mitigation strategy.

Challenges

- Complex metabolism. Contribution of **CYP7A1** (CYP27A1, CYP46A1, and CYP11A1) to the metabolism of Cholesterol and 4bOH-C (Figure 1). The **half-life** before and after induction of CYP3A is reported to be 60 h and 400 h, respectively.
- [4bOH-C] reflects **average** changes in hepatic CYP3A levels, thus only clinically relevant following chronic dosing.
- Will not reflect **gut** CYP3A levels
- **Transporter** involvement is unknown

RESULTS (cont)

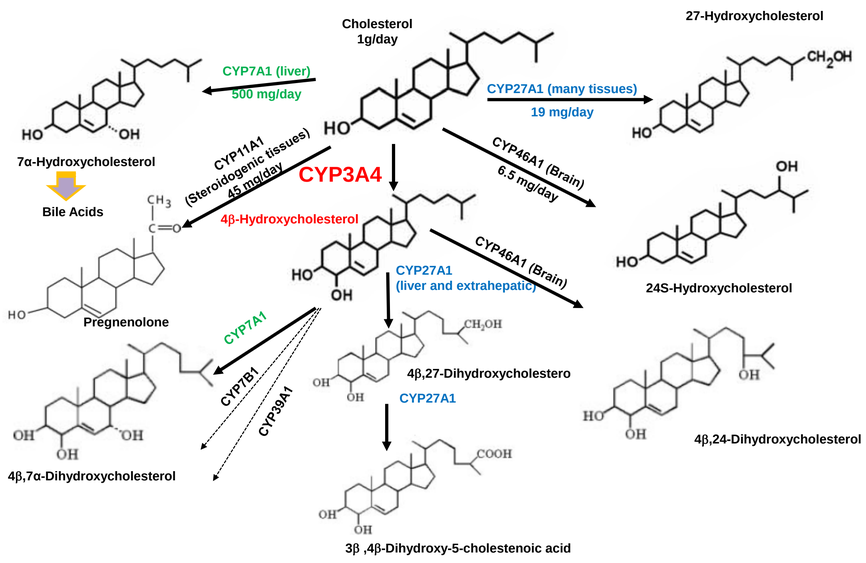

Figure 1 – Cholesterol metabolism

Baseline Population values

- The mean plasma level of 4bOH-C in Caucasians is 34 ng/mL (CV = 51%, n=374), which is higher than that reported for a Korean population (Figure 2).

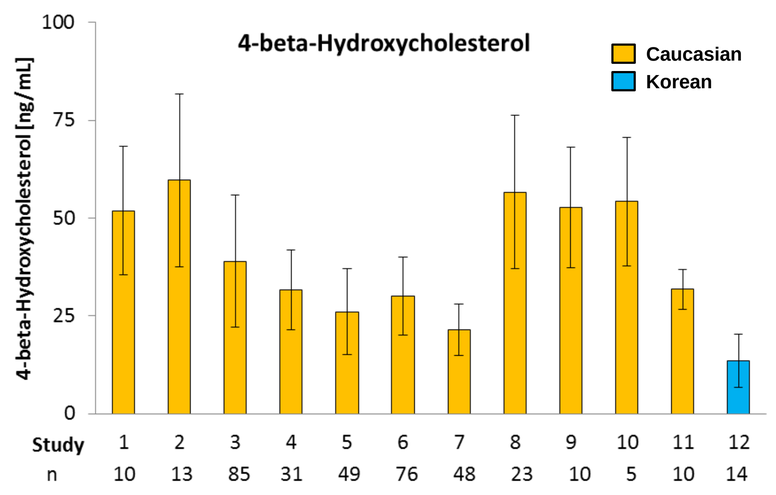

Figure 2 – Baseline population levels for plasma [4bOH-C] (Mean ± SD) in Healthy Volunteers.

- It should be noted that there is a high degree of inter-individual variability (Figure 3), and therefore, it may be more appropriate to represent [4bOH-C] levels relative to [cholesterol] levels. These ratios in the Caucasian population range between 0.06 and 0.26, n= 74 (2 references).

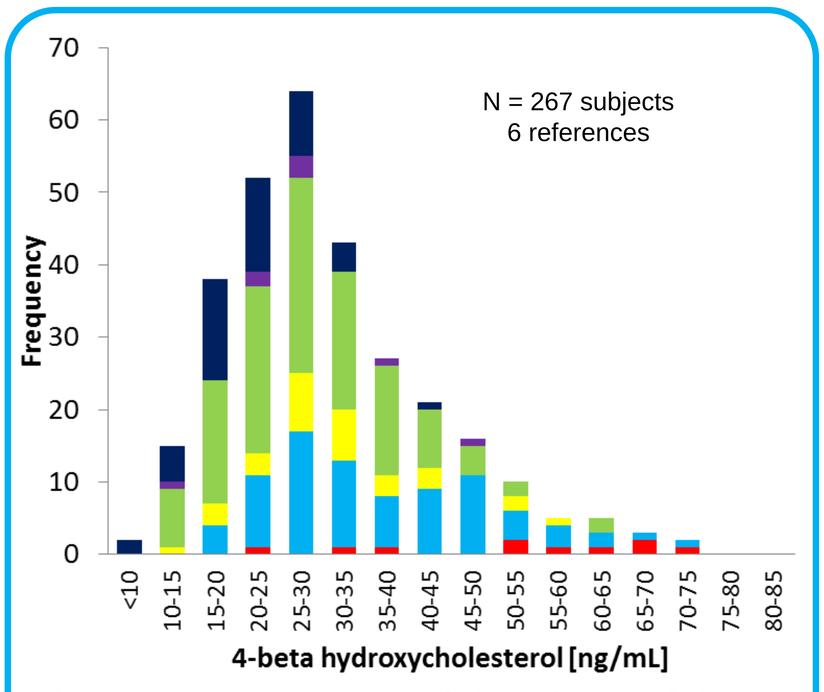

Figure 3 – Frequency of the plasma [4bOH-C] in Caucasians. Each colour represents one reference.

RESULTS (cont)

- Bilirubin and glucuronides

A schematic of the formation and breakdown of bilirubin is shown in Figure 4. Total serum bilirubin (bilirubin + bilirubin glucuronide), conjugated and unconjugated plasma levels reflect protein changes differently.

- *Biliverdin reductase* reduces Biliverdin to *unconjugated*, water-insoluble **Bilirubin**, which is carried in blood bound to serum albumin
- Bilirubin is *conjugated* to glucoronic acids by uridinediphosphateglucoronyl transferase (UGT1A1) and conjugated bilirubin (water-soluble) is transported into bile canaliculi by MRP2
- Intestinal bacteria deconjugate and breakdown bilirubin into colourless urobilinogens, which are primarily excreted in faeces

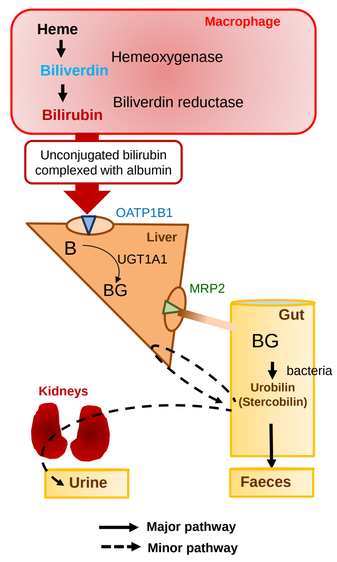

Figure 4 – Bilirubin metabolism and elimination

- Elevated conjugated, unconjugated and total serum bilirubin level (TSBL) are a marker for intrahepatic **jaundice.**
- In prehepatic jaundice the conjugated bilirubin and urinary bilirubin are absent. In post-hepatic jaundice, conjugated and total bilirubin levels are elevated.
- Baseline TSBL are given in Figure 5.

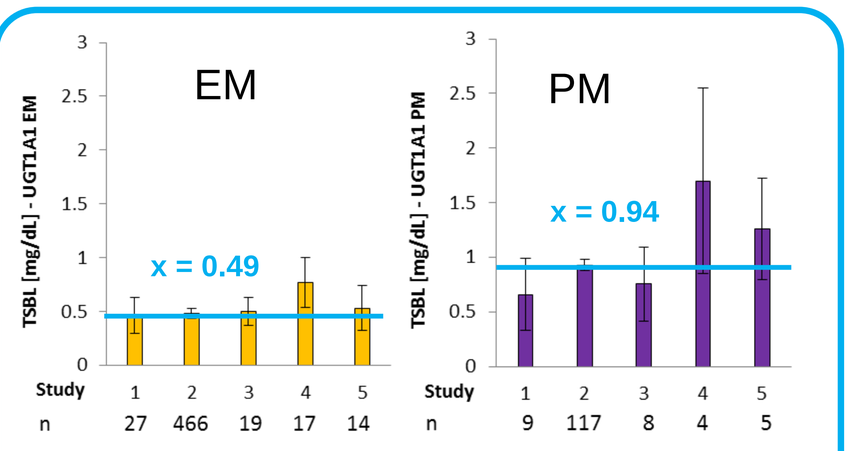

Figure 5 – Baseline levels for total serum bilirubin in healthy Caucasians for UGT1A1 extensive and poor metabolisers (not separated by OATP1B1 phenotypes).

Challenges

- More information on the impact of **OATP1B1** on levels of conjugated and unconjugated bilirubin is required.
- An induction model for **UGT1A1** is needed, therefore turnover numbers for UGT1A1 are required.

Dear Consortium Member,

Initial baseline levels and the routes of biotransformation for the top 2 endogenous compounds have been collated. We would like to collate further data.

Please contact us, if you would like to contribute and discuss.