EMA EFPIA workshop
Break-out session no. 2

Case Study Title: M&S for dose adjustment in renally impaired patients

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BOS2: Position statement

- "Dosing recommendations for situations which cannot be tested (e.g. because no specific inhibitor is available) or should be avoided to be tested (e.g. inhibition of transporters and CYPs in an old female patient), can be given based on M&S"

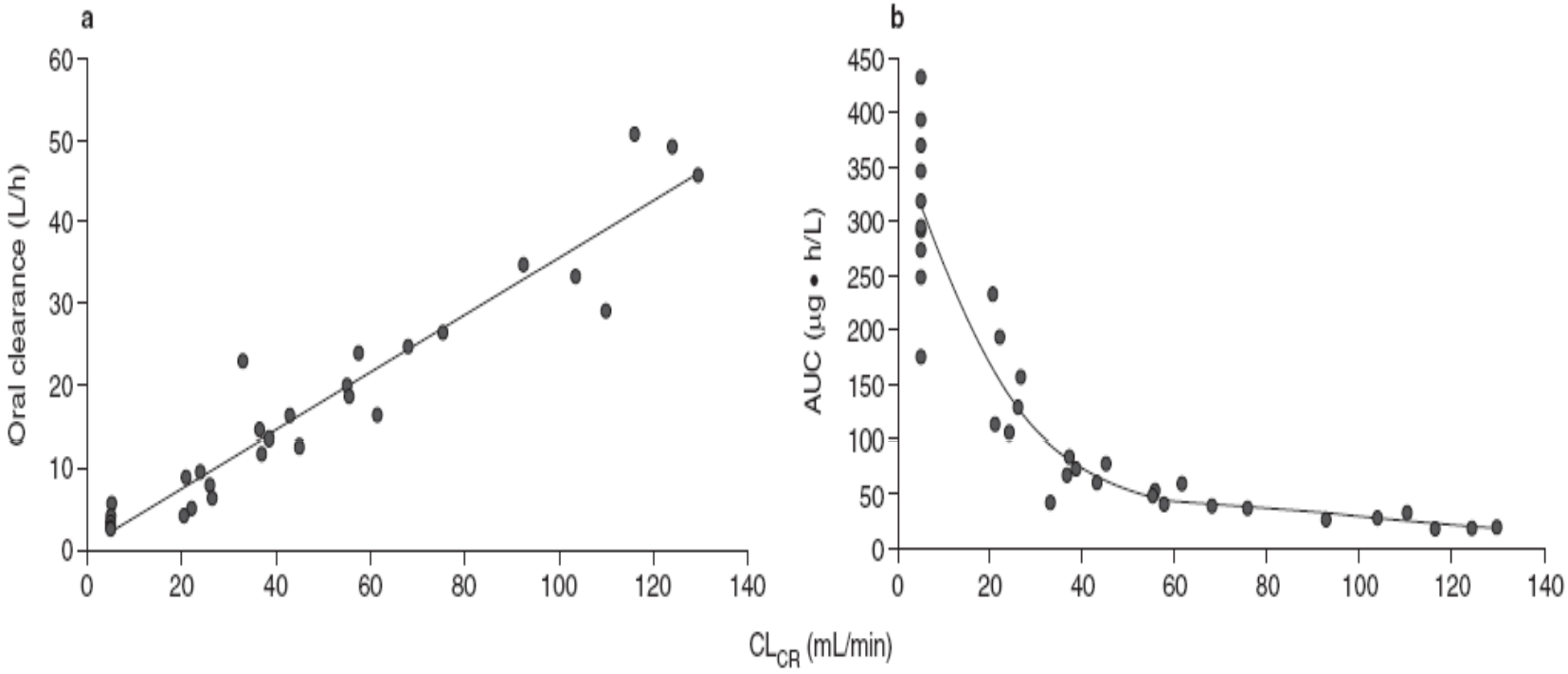
Background & Rationale

- NCE
- Mainly renal elimination
- PK study in renal impairment
  - 34 subjects with varying degree of renal function
    - normal RF, mild, moderate, severe RI, dialysis
- M&S used to support dosing recommendations in patients with renal impairment

Influence of renal function on PK

CL vs renal function

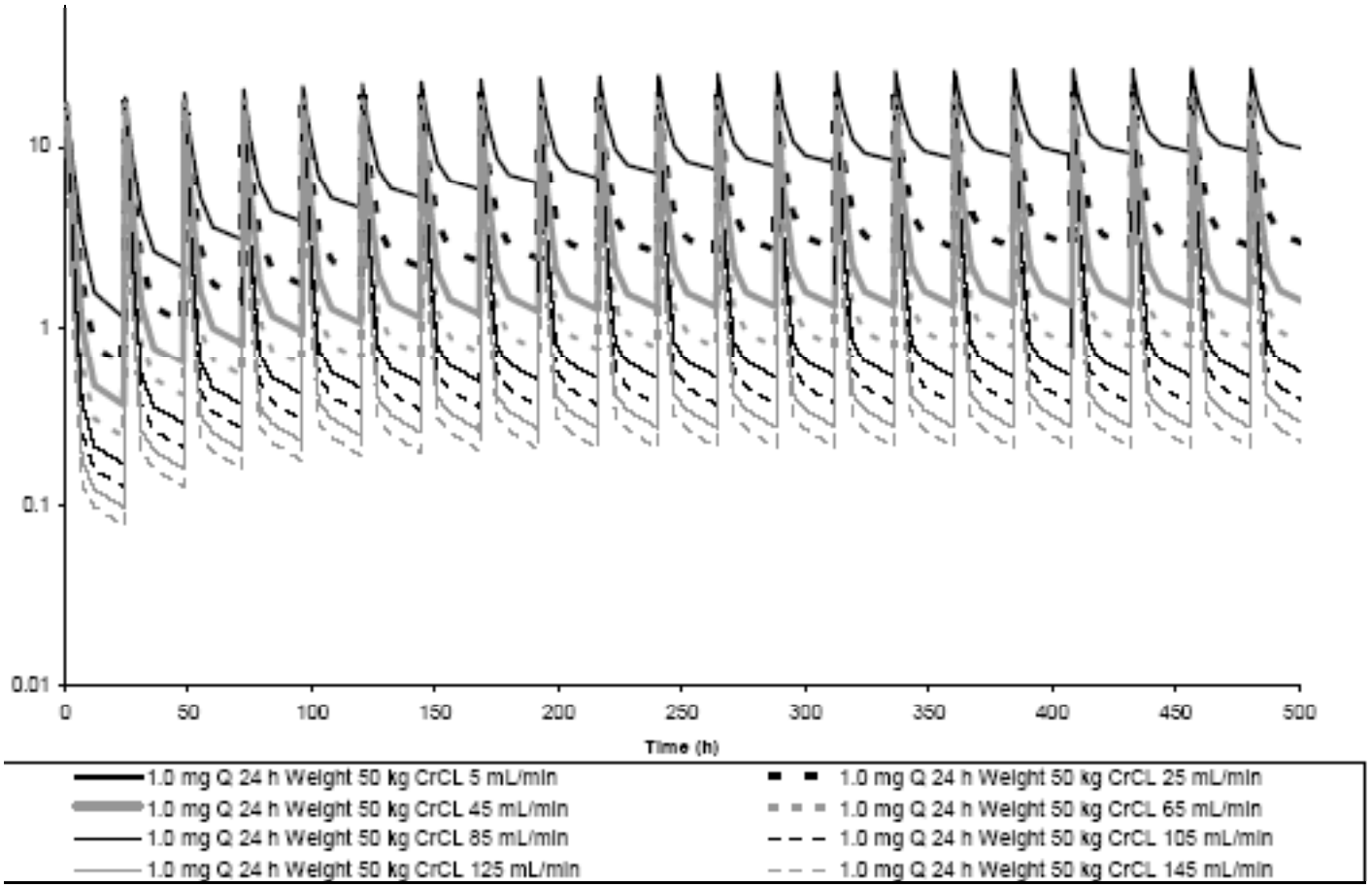
AUC vs renal function



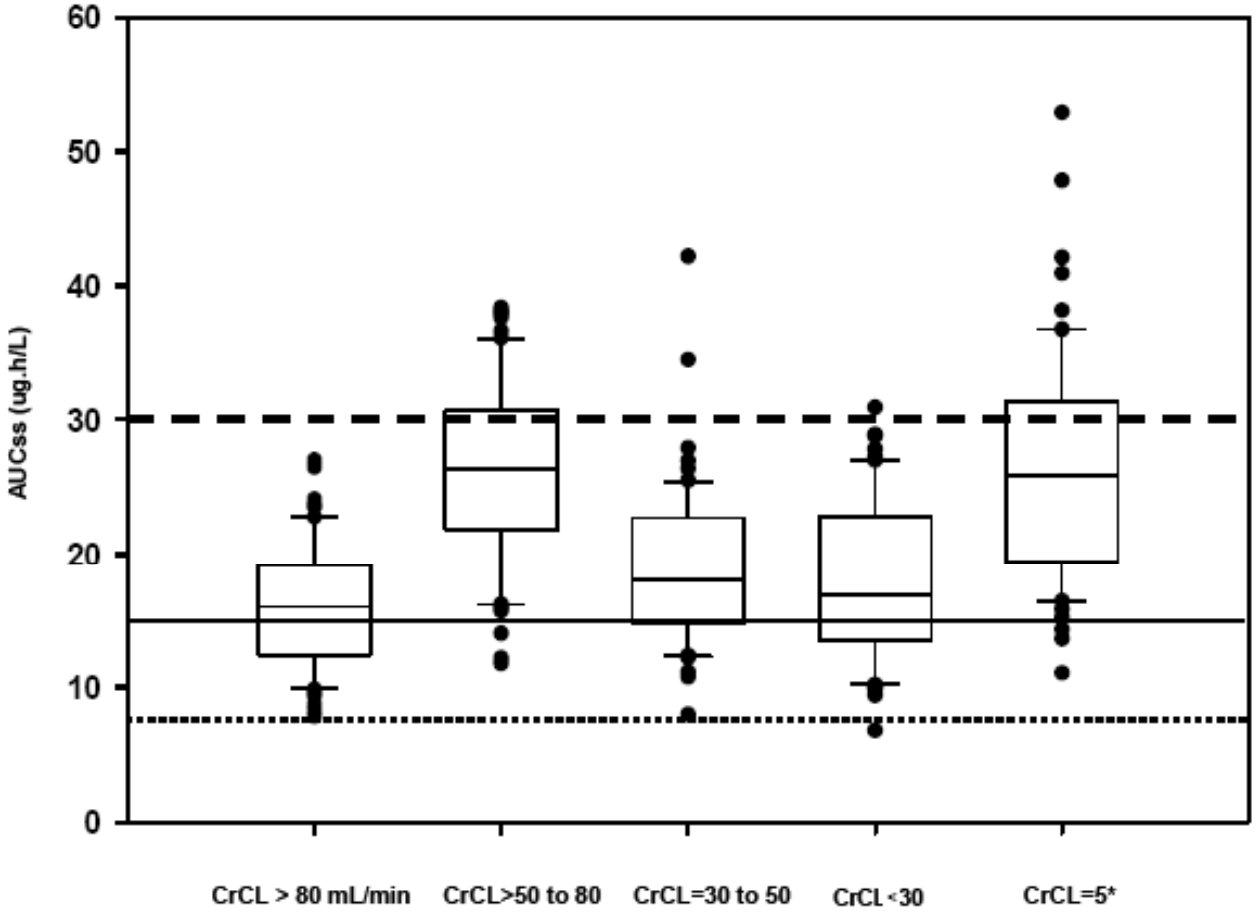
Proposed dosage recommendations

- Renal impairment: Dose reduced to
  - 50% in moderate RI (CLcr 30-50 ml/min)
  - 30% in severe RI (CLcr 10-30 ml/min)
  - 20% in ESRD (CLcr <10 ml/min)
- Based on
  - population PK analysis of renal impairment study
  - simulations
    - steady state concentration time profile at different dose levels
    - exposure with proposed dosing recommendations
  - target criteria for AUC:
    - AUC should be within a range from the lower limit of AUC in the group with normal renal function up to an upper value representing an AUC 2 times the geometric mean AUC of the normal renal function group

Simulated steady state concentration time profile with no dose adjustment



Simulated exposure for proposed dosage regimen



Assessor's comments

- PopPK analysis considered robust
  - model described observed data well
  - good prediction of parameter estimates
  - suitable for simulations
- Defined target AUC range was questioned
  - not based on exposure response relationship for efficacy and safety
- More details on simulations requested
  - unclear how many subjects in each group were simulated and from which distribution of renal function these subjects were chosen
  - A plot over individual predicted AUCs with the proposed dosage regimen vs. renal function (CLcr) as a continuous variable with appropriate AUC target limits visible was requested

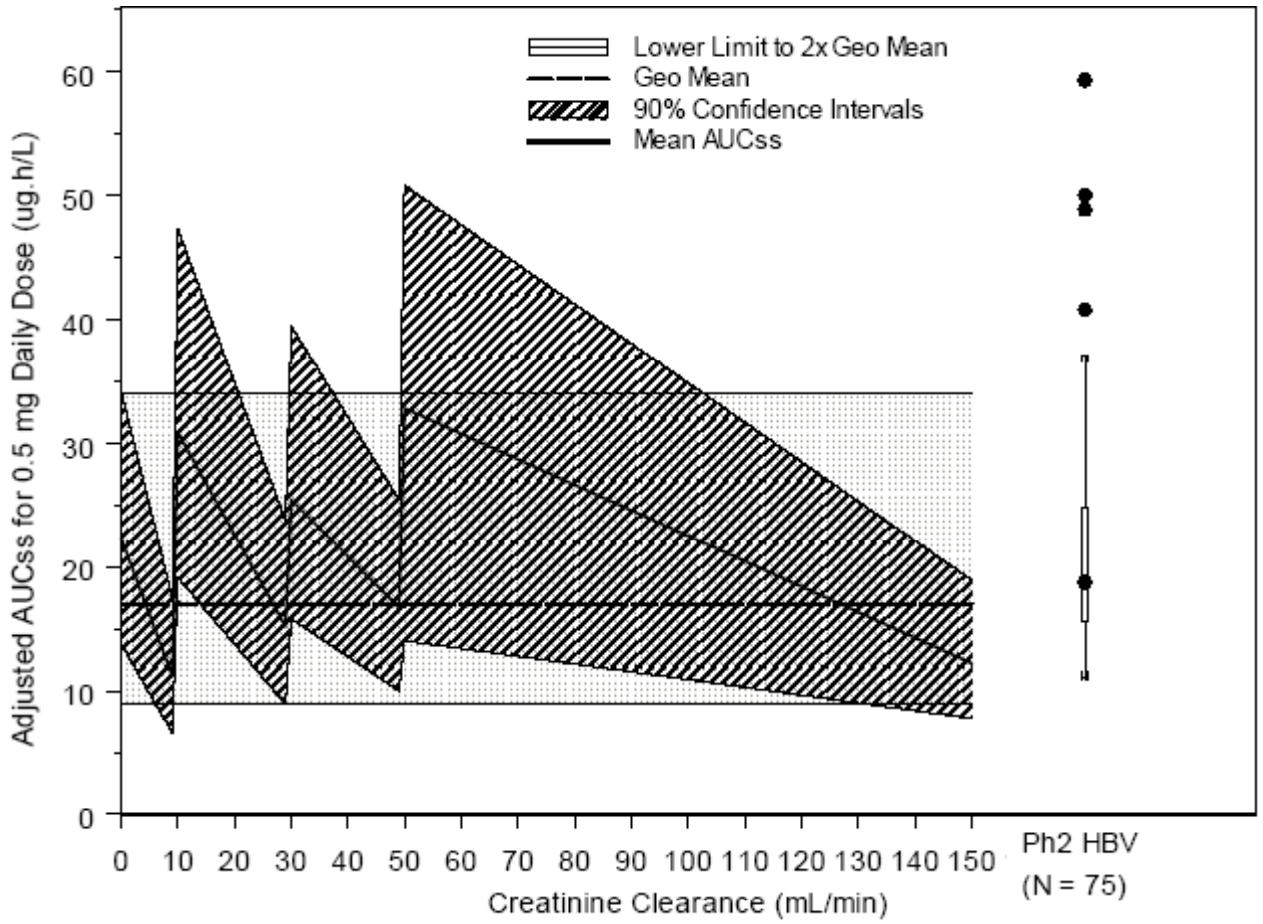
Company response

- Target critria explained
  - empirical approach was initially used
  - intended exposure range was established using exposure values from subjects with normal renal function
    - lower limit of the reference range exposure was selected based on the lower limit of the simulated AUC_{ss} values in subjects with normal renal function
    - upper limits of the range was defined as an exposure that was 2-times the geometric mean exposure in subjects with normal renal function
  - claimed to result in exposures within the range of the Phase 2 and 3 populations

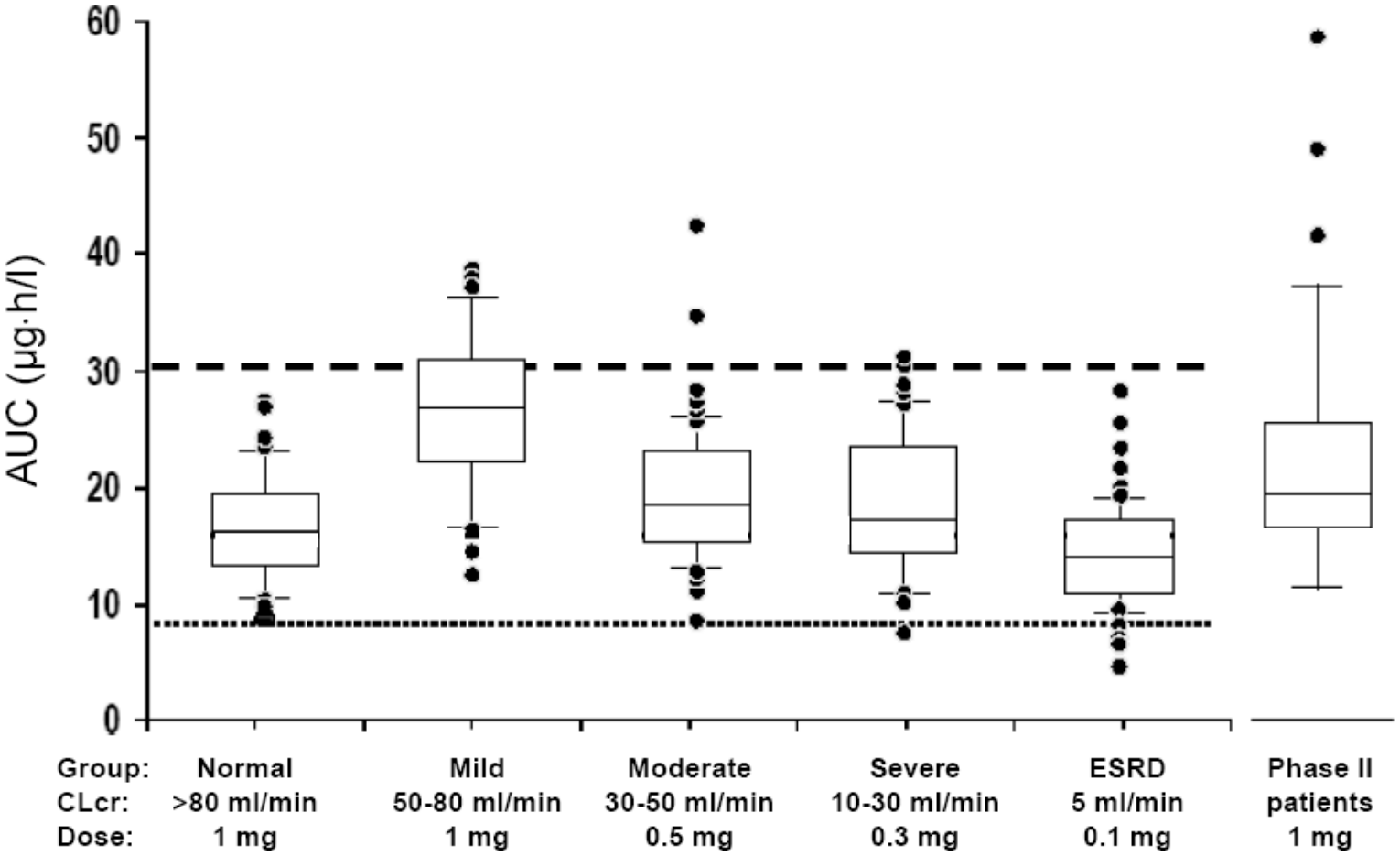
Company response

- Clarification of conducted simulation
  - 300 replicates of the 30 subjects in the renal impairment study simulated
  - severe renal impairment group
    - CLcr values varied from 20.5 to 26.5 mL/min.
    - *"the range of CLcr used for the simulation in the severe renal impairment group was within the range of 10-<30 mL/min, therefore, the simulation was performed within the appropriate CLcr range"*
- New simulation
  - to illustrate AUCs vs renal function as continuous variable
    - Subjects were simulated with CLcrs at the low and high end of each dose adjustment group.
    - 1000 replicates were simulated
    - Geometric mean and 90% prediction interval illustrated

Simulated exposure with renal function as continuous variable



Simulated exposure with adjusted doses in reduced renal function



Assessor's comments

- Defined target AUC discussed
  - company rationale (not basing this on exposure response relationship for efficacy and safety) criticised
- Simulation
  - Severe renal impairment group not representative
    - simulated subjects with CLcr 20-27 ml/min does not cover whole range 10-30 ml/min
  - New simulation provides useful information
- Dosing recommendations
  - assessed taking into account also PK/PD relationship (provided in response to other questions) and information on safety at increased exposure

Conclusions

- Modelling and simulation of dose adjustment in renal impairment in line with the guideline on pharmacokinetic studies in renal impairment
- Limitations of the initially submitted simulations solved by additional simulations
- Issues related to target exposure range not satisfactorily addressed but proposed dosage recommendations supported by other information provided

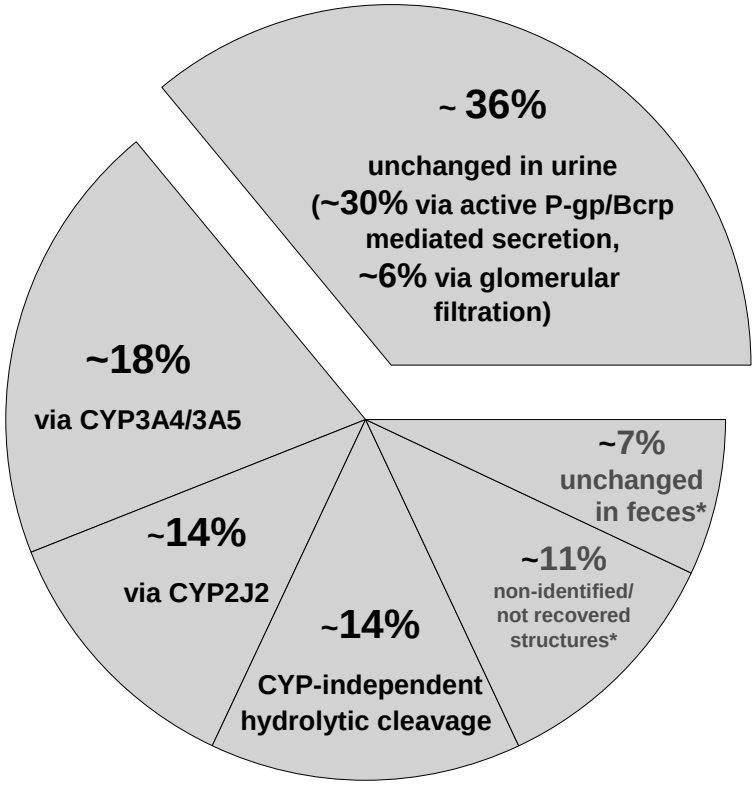
- The M&S was useful in the assessment and provided more confidence in the proposed dose recommendations in renal impairment

Case Study Title:

Modelling of drug interaction mechanism and estimation of drug interaction in patients with renal impairment

- NCE
- Modelling was used to explain mechanism of interactions
- "Simulations" used to predict exposure in populations with several risk factors

Elimination pathways



Interaction studies

	AUC
• Ketoconazole	↑ 2.6-fold
• Ritonavir	↑ 2.5-fold
• Erythromycin	↑ 1.3-fold
• Clarithromycin	↑ 1.5-fold

- AUC, C_{max}, renal excretion, renal function, fu measured in all studies
- Effect on CL/F, CL_R, CL_{RF}, CL_{RS} calculated
- Mechanistic modelling
  - inhibitor effects on CL_{NR} and CL_{RS} estimated

CL_R: renal clearance, CL_{RF}: renal filtration clearance, CL_{RS}: renal secretion clearance, CL_{NR}: non-renal clearance

Estimated effects

	NCA		Modelling	
	CL/F	CL_{RS}	CL_{NR}	CL_{RS}
Ketoconazole	61%↓	44%↓	66%↓	30%↓
Ritonavir	60%↓	82%↓	61%↓	74%↓
Erythromycin	25%↓	7%↑	27%↓	-
Clarithromycin	36%↓	10%↓		

Interaction studies – conclusions regarding interaction mechanism

	AUC	
• Ketoconazole	↑ 2.6-fold	Inhibition of CYP3A4 and P-gp/BCRP
• Ritonavir	↑ 2.5-fold	
• Erythromycin	↑ 1.3-fold	Inhibition of CYP3A4
• Clarithromycin	↑ 1.5-fold	Mainly inhibition of CYP3A4

➢Drug interaction potential discussed based on potency in inhibition of CYP3A4 and P-gp/BCRP
→ relevant recommendations in labelling

"Simulation" of CYP3A4 inhibition and renal impairment

- Effects on total clearance calculated from
  - partial clearance via CYP3A4
    - with no, 30, 50 or 90% decrease reflecting no, mild, moderate or severe CYP3A4 inhibition
  - data from renal impairment study
    - normal renal function, mild, moderate, severe renal impairment
- $\Rightarrow$ estimated exposure in patients with different degree of renal impairment and concomitant administration of no, mild, moderate or severe CYP3A4 inhibitors

Estimated mean impact of renal impairment and concomitant use of a CYP3A4 inhibitor on AUC of drug X

x-fold increase in AUC vs Normal Renal Function

Impact on CYP3A4 clearance	Normal renal function ≥ 80 mL/min	Mild renal impairment 50-79 mL/min	Moderate renal impairment 30-49 mL/min	Severe renal impairment < 30 mL/min
No inhibition[a]	1.00	1.49	1.66	1.79
30% inhibition	1.09	1.64	1.84	1.99
50% inhibition[b]	1.15	1.75	1.98	2.15
90% inhibition[c]	1.32	2.04	2.35	2.57

a reflecting the effect of pure renal impairment according to study data 11002
b reflecting the concomitant use of a moderate CYP3A4 inhibitor like erythromycin
c reflecting the concomitant use of a strong CYP3A4 inhibitor like clarithroymcin
Note: CYP3A4/3A5 clearance = actual + 1/3 of non-recovered (= 23.3% of total CL or 38% of CL_H)

Used to discuss recommendations in patients with renal impairment and concomitant administration of CYP3A4 inhibitors (restrictions, caution…)

Conclusions

- Modelling interaction mechanism
  - used for mechanistic understanding of studied interaction and for developing labelling for various inhibitors
    - modelling estimates were mainly used qualitatively
- Estimation of impact of CYP3A4 inhibition in renal impairment
  - calculation/estimation rather than simulation
  - provided added information on potential exposure in patients with several risk factors
- Assessment
  - assessment was based both on study results and modelling/estimations
  - resulted in warning statements in SPC
  - Note: possibly PBPK simulation could provide additional information

Comments on position statement

Position statement:

"Dosing recommendations for situations which cannot be tested (e.g. because no specific inhibitor is available) or should be avoided to be tested (e.g. inhibition of transporters and CYPs in an old female patient), can be given based on M&S"

Case study 1 (renal impairment):

Specific dosing recommendations were based on M&S

Case study 2 (interactions and renal impairment):

Treatment recommendations were based on M&S

- warning (use not recommended), caution

Comments on position statement

- M&S can be used to provide treatment recommendations (contraindication, warning (e.g. use not recommended), caution,…) for situations which cannot be tested or should be avoided to be tested
- Dosing recommendations
  - Requires high confidence in M&S
    - to base specific dose adjustment on M&S alone would require very robust models, very good model qualification, well justified assumptions, limitations of the model clearly discussed etc.
  - Could be acceptable for
    - adjustment of dose e.g. in renal impairment, based on M&S of PK data in subjects with renal impairment
    - interpolation of well characterized pharmacokinetic processes (eg. between subjects with normal and severe renal impairment, between poor and extensive metabolisers)
    - more easily accepted if therapeutic window is wide
  - Extrapolation outside studied range generally not accepted

Comments on position statement (cont)

- Difficult to provide generalised recommendations
- Scientific unknowns cannot be solved by M&S
- Case by case decision depending on other supporting data
- Uncertainties in M&S will be part of benefit/risk
  - A higher risk regarding uncertain M&S could potentially be accepted if benefit is high so benefit/risk balance remains positive
- Consider Scientific advice