Usefulness of physiology-based PK to mitigate risk in early clinical drug development?

May 18th 2017

An Van den Bergh

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

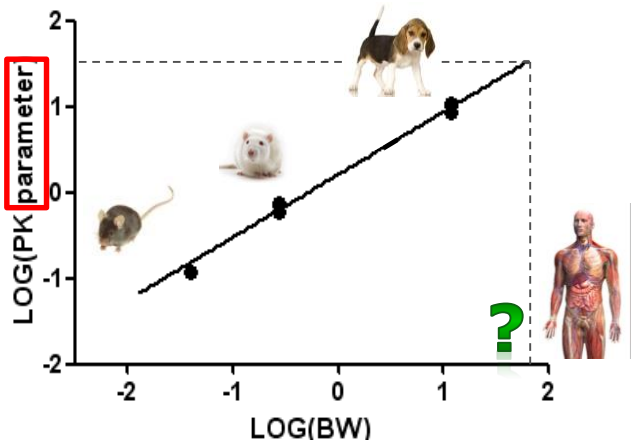
Strategic questions as foundation for early PBPK

- Will the predicted PK profile meet the clinical needs?
- Likelihood or understanding of dose (dis) proportionality?
- Accumulation during repeated dosing as expected?
- Drug-Drug Interactions in Patients?
- Among a set of potential candidates, which one has the most favourable PK profile?
- Can we anticipate a PK difference between healthy volunteers and patients?

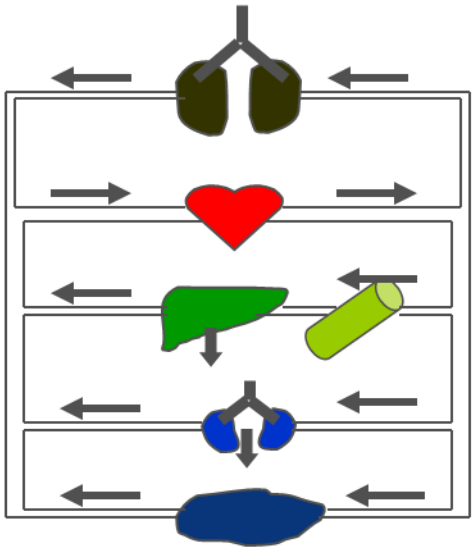
Understand components governing PK drug behaviour

FIH modeling approaches

Allometry (empirical)



Physiology Based PK (PBPK) (mechanistic)

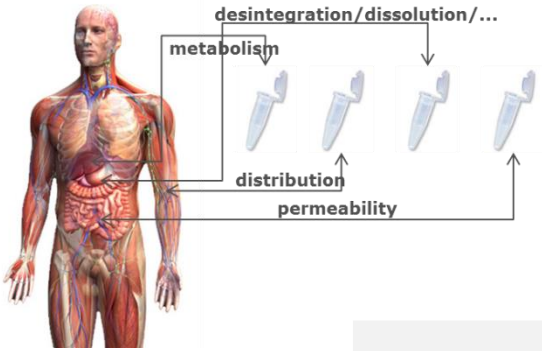


Extrapolation of isolated PK parameters (CL & Vd)

Predict time profile of drug concentration

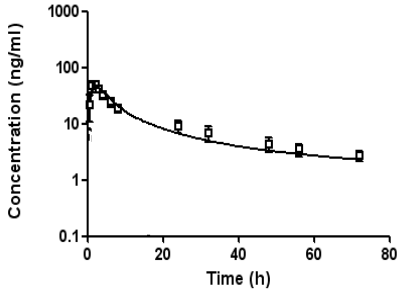
PBPK modeling

Integration of multiple sources of individual data into the physiological context

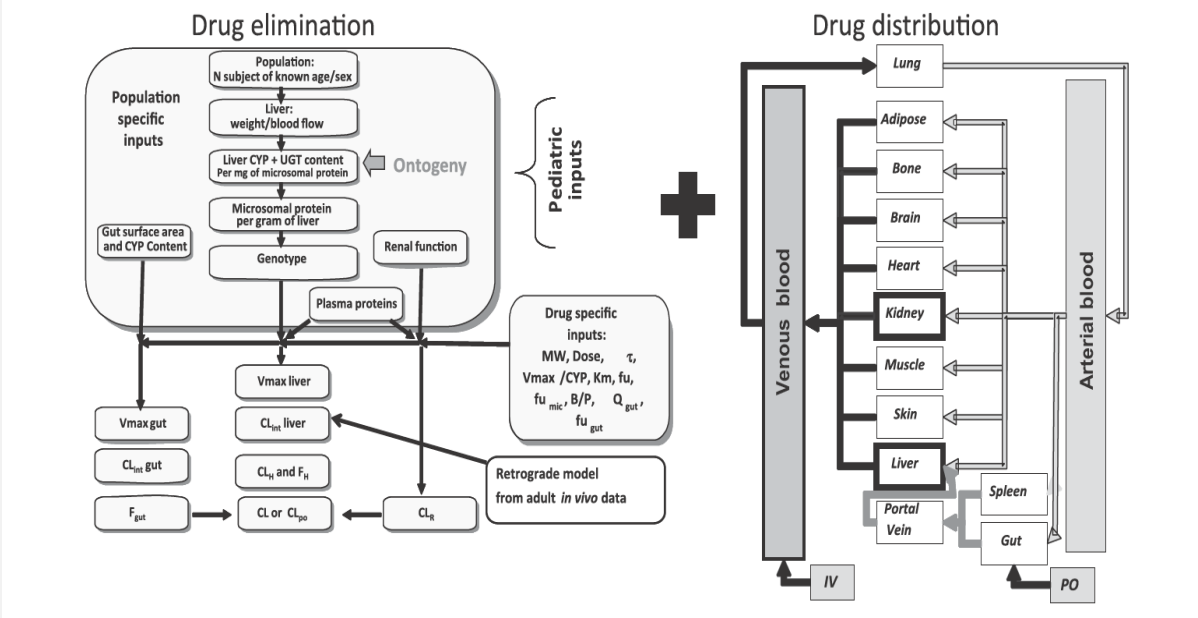


?

Predicting human PK .. and have a prepared mind



-virtual physiology
-compound specific parameters
-differential equations



TN Johnson and A Rostami-Hodjegan, Pediatric Anesthesia, 2010

PBPK modeling throughout development

----------In vivo PK and Biopharmaceutics----------

Prioritization of cmpds

Human PK and efficacious dose (dosing regimen)

Food effect

Solid dose formulation

Predicting drug exposure for design of Tox/TK studies

Dose-exposure relationship -> FIH

----------Predict DDI liability----------

Alert potential DDI liability

Build up mechanistic model:

- CL pathways (metabolic enzymes & transporters involved)
- Mechanism of inhibition potential (MBI, rev. Inhibition)
- Absorption
- Metabolites

Eliminate unneccesary/refine design of clinical trials/ adapt dose when drugs are coadministered

------Special populations-----

----------Target organ distribution----------

Renal/Hepatic impairment/target population

Children/elderly

Target organ time profile

Ethnicity

Linked to PD

DDI in ….

Target organ time profile in…

PBPK modeling and mitigating risks

----------In vivo PK and Biopharmaceutics----------

Prioritization of cmpds

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Risk = spending many resources for development of compound with suboptimal PK (e.g. necessity to dose t.i.d.)

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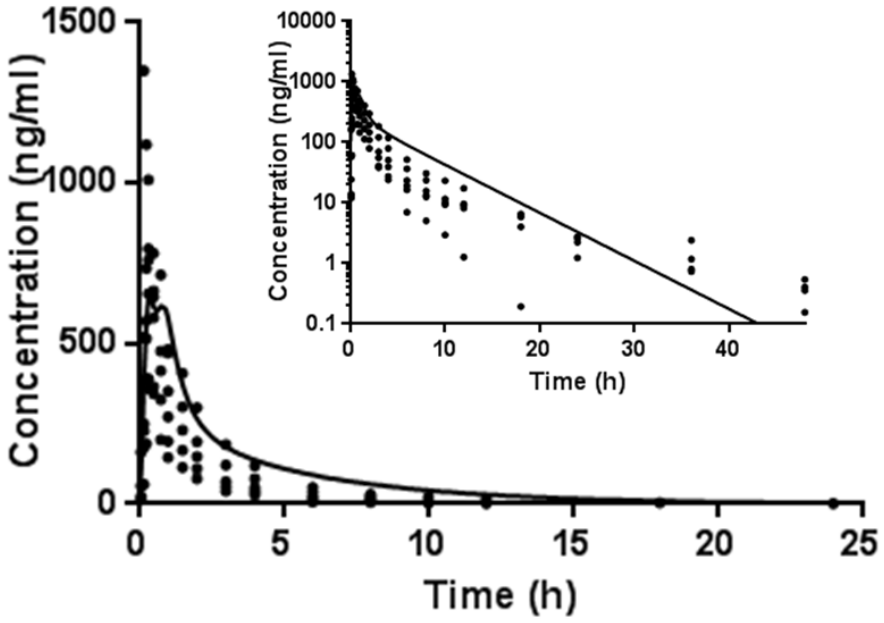
Drug candidate differentiation with limited information

Background: PK of lead cmpd is not optimal (half life short; high fluctuation peak trough)
→ evaluate potential of 2 back-ups, integrating preclinical ADME and human microdose study data prior to SAD study without need for extensive TOX support

	JNJ-X
MW	✓
Lipophilicity (logP)	✓
Ionization constant (pKa)	✓
Solubility (mg/mL)	✓
Human effective permeability (cm/s)	✓
Blood to plasma ratio	✓
Plasma unbound fraction	✓
Microsomal unbound fraction	✓
Intrinsic clearance hepatocytes	✓
Volume of distribution (tissue partitioning)	✓

All necessary information available for lead compound



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	JNJ-X	JNJ-Y	JNJ-Z
MW	✓	✓	✓
Lipophilicity (logP)	✓	✓	✓
Ionization constant (pKa)	✓	✓	✓
Solubility (mg/mL)	✓	✓	✗
Human effective permeability (cm/s)	✓	✗	✗
Blood to plasma ratio	✓	✓	✗
Plasma unbound fraction	✓	✓	✓
Microsomal unbound fraction	✓	✗	✗
Intrinsic clearance hepatocytes	✓	✓ ✗	✓ ✗
Volume of distribution (tissue partitioning)	✓	✓	✗

Limited information available for back-up compounds
→ assumptions to be taken

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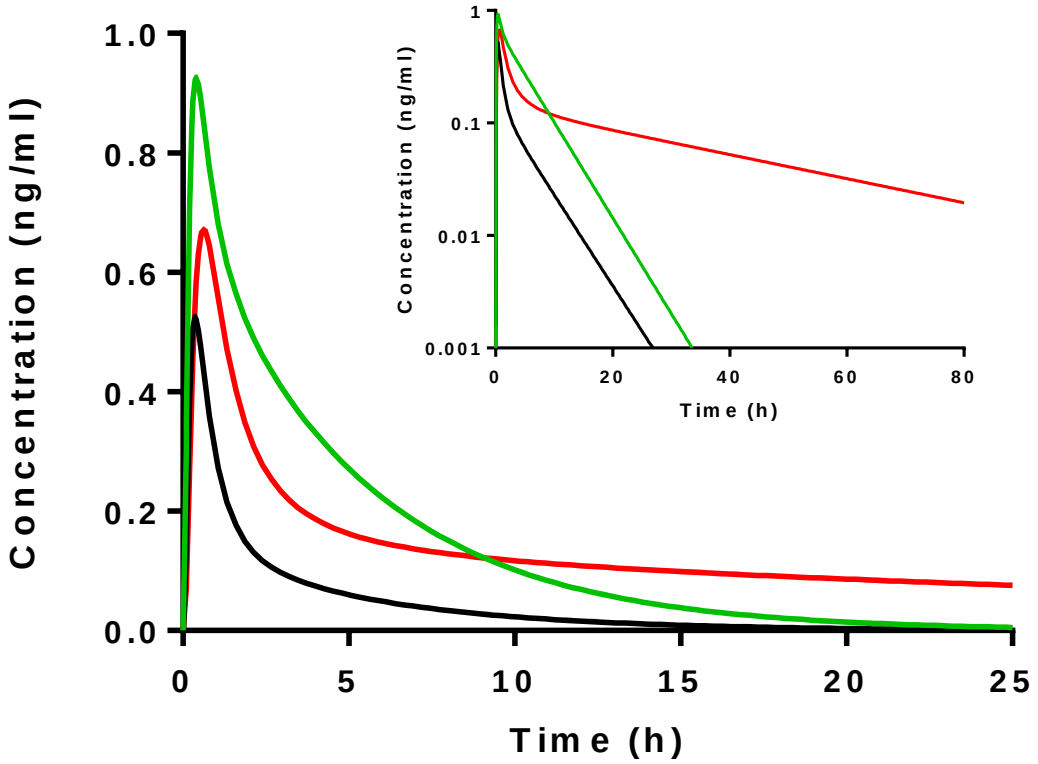
Results microdose study

100ug JNJ-X
100ug JNJ-Y
100ug JNJ-Z



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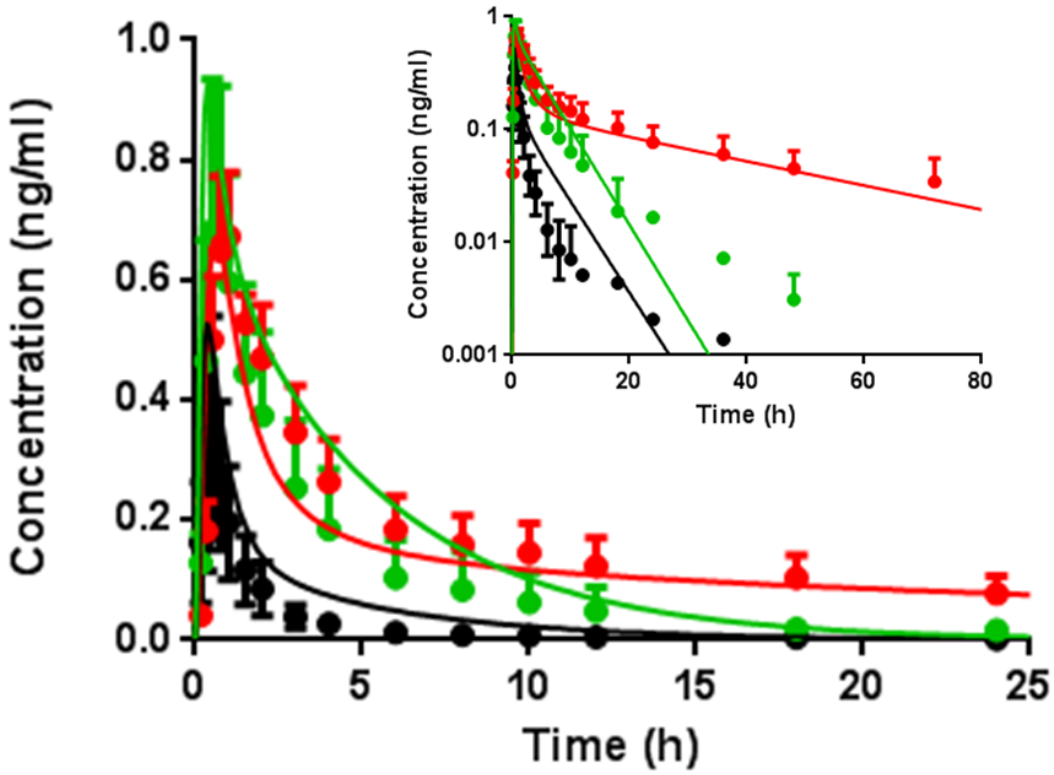

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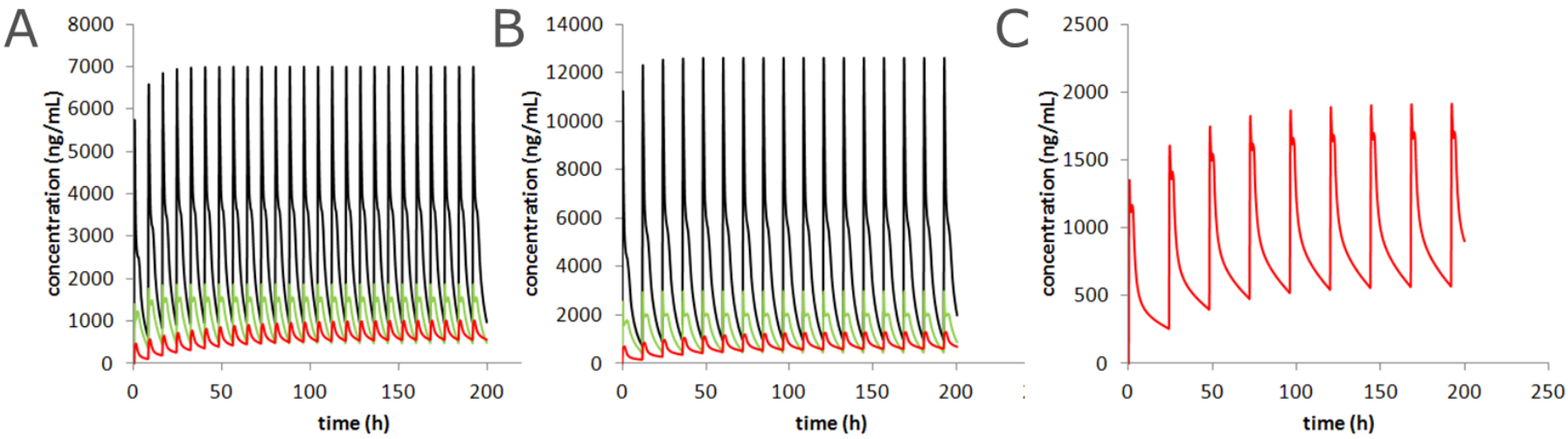
Predictions to reach efficacious concentrations

Efficacious concentrations:
1000ng/mL for JNJ-X
570ng/mL for JNJ-Y
450ng/mL for JNJ-Z

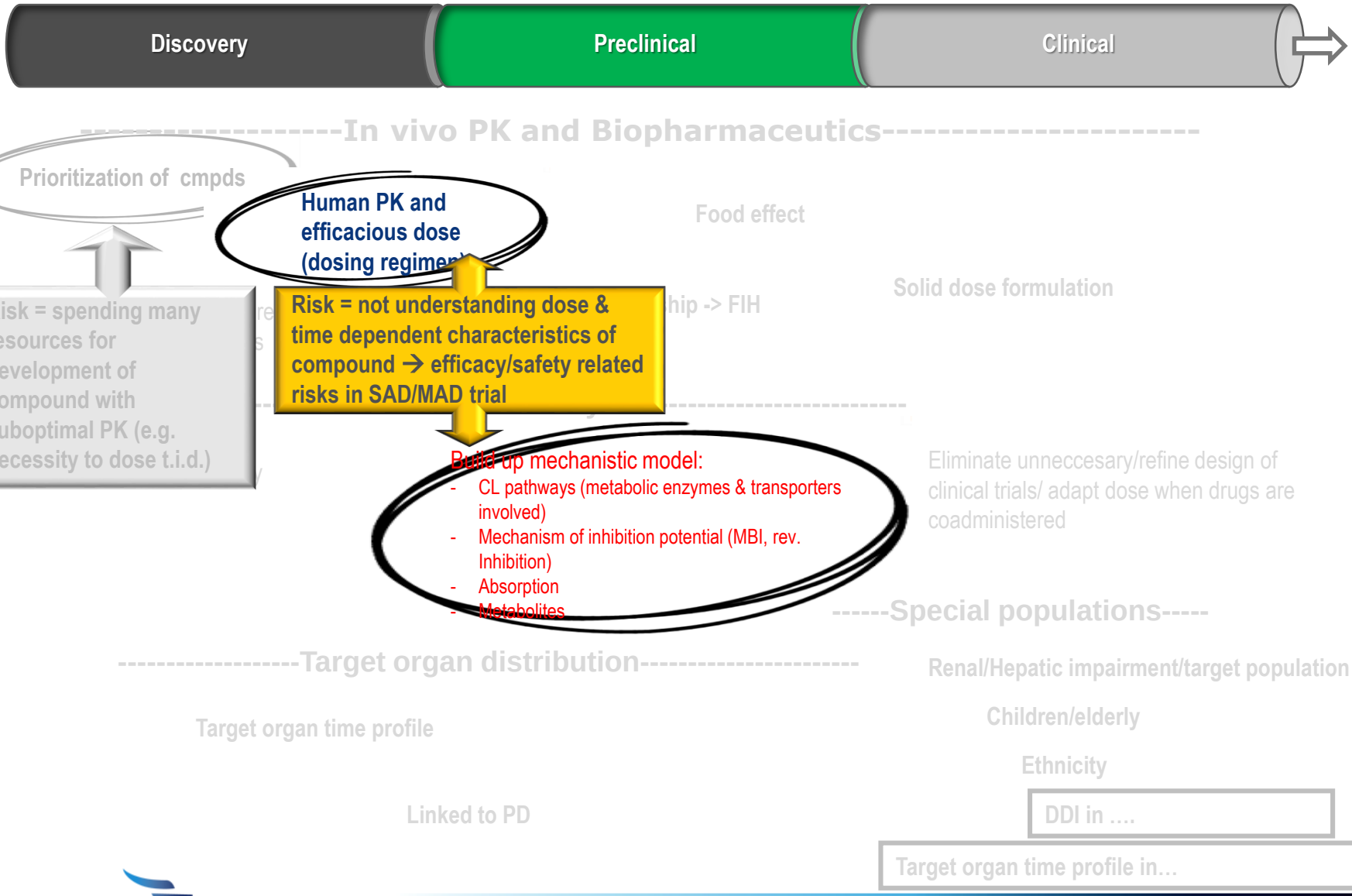


825mg t.i.d. JNJ-X
85mg t.i.d. JNJ-Y
225mg t.i.d. JNJ-Z

1500mg b.i.d. JNJ-X
150mg b.i.d. JNJ-Y
420mg b.i.d. JNJ-Z

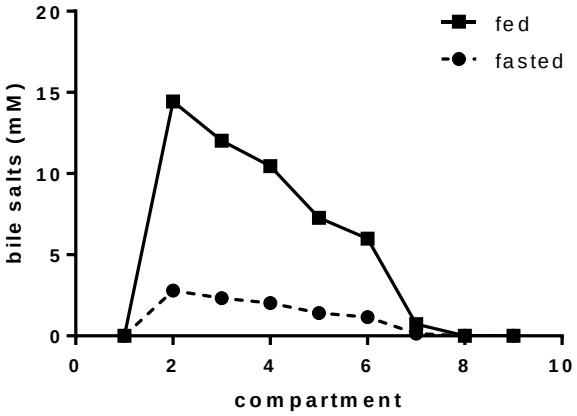
>1000mg q.d. JNJ-X
325mg q.d. JNJ-Y
>1000mg q.d. JNJ-Z

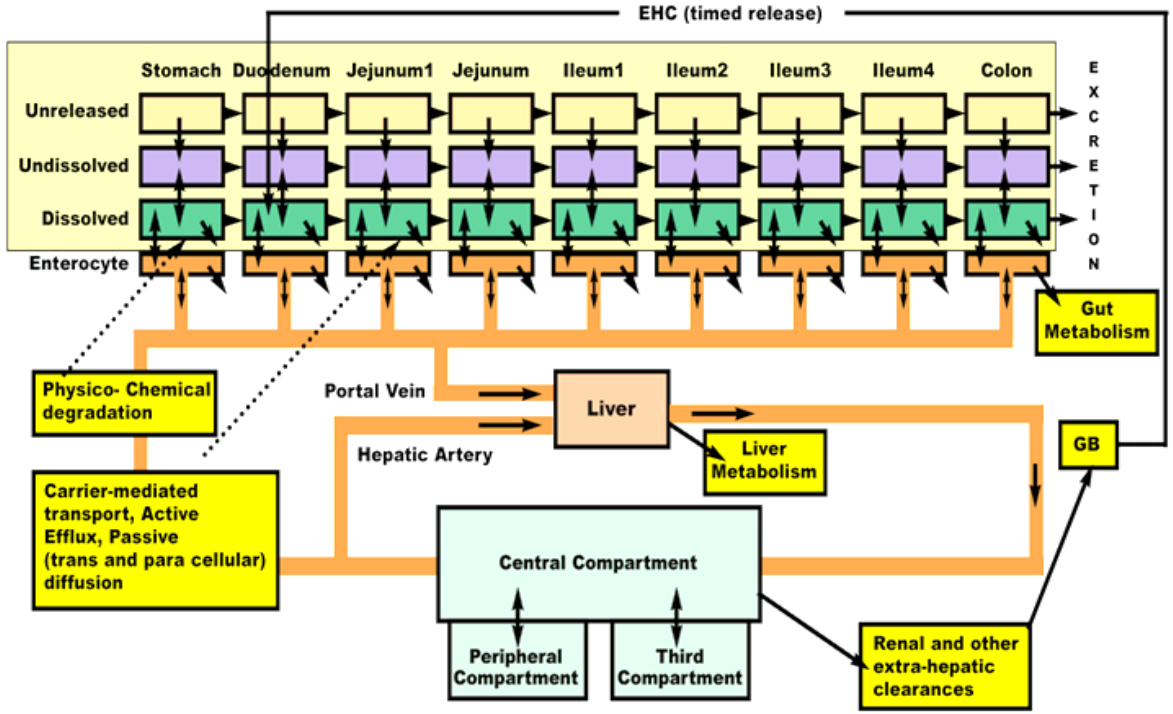
PBPK modeling and mitigating risks



Anticipate less than dose proportional absorption in SAD

Background: JNJ-X has a high permeability and a low solubility (0.0003mg/mL @ pH7 – note: pKa_{base}<2)
Large effect of bile salts due to high lipophilicity (Fassif 0.005 mg/mL; Fessif 0.011mg/mL)
Metabolized by CYP3A4 (95%)
→ will enough exposure be reached in SAD and/or from which dose onwards will nonlinearity kick in?





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Dose (mg)	Cmax (ng/ml)	AUC inf (ng.hrs/ml)	F (bioavailability) (%)
5	14-38	36-154	41-73
20	58-102	312-513	37-61
75	105-243	556-1384	22-44
225	311-722	1105-3405	17-33
500	690-916	2140-4188	15-19
1000	1380-1830	4032-7895	14-18
1500	2069-2744	5294-11600	14-18

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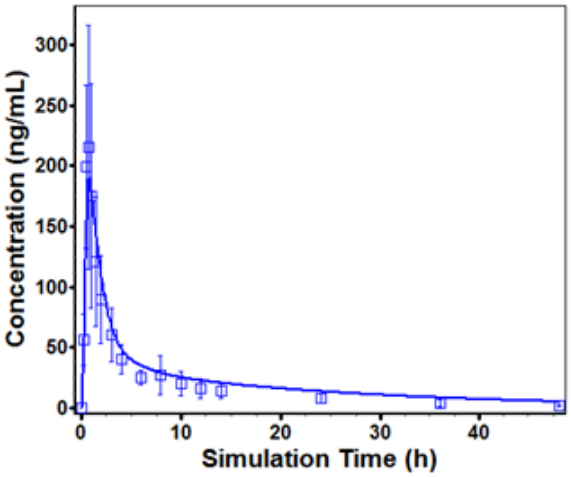
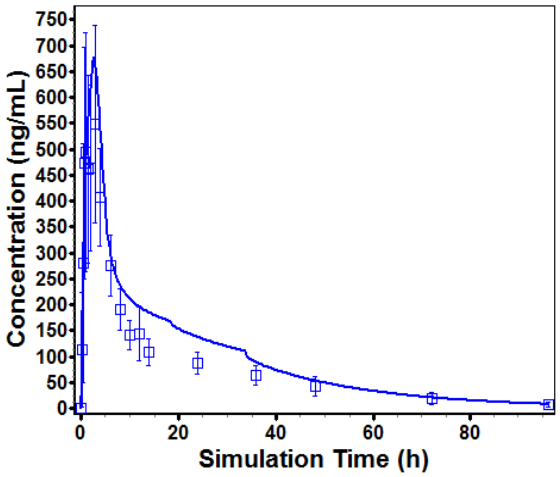
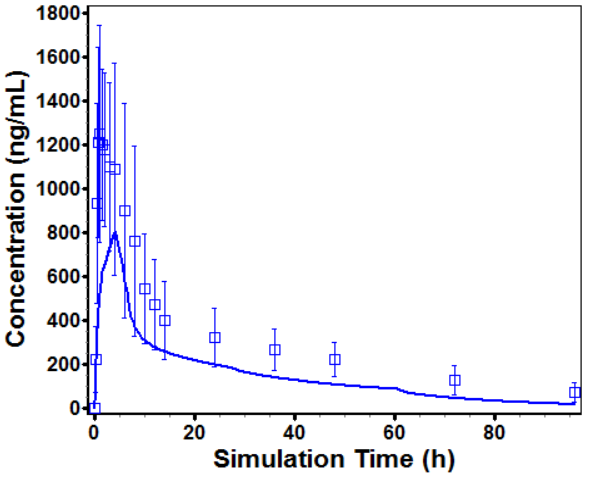
20 mg
F pred 72%



225 mg
F pred 52%



1000 mg
F pred 18%



Understand more than dose proportionality in SAD?

Background: JNJ-X is planned to go FIH
Preclinically more than dose proportional PK is observed
What will be the predicted human PK profile? What should be the starting dose? And which dosing steps should be taken in the SAD trial?

Dog p.o. data	5 mg/kg
F (%)	178
Cmax (ng/ml)	1980
Tmax (h)	2-4
AUC 0-inf (ng.h/ml)	12200

Due to saturation in metabolic pathways?
(i.v. study in the dog @ 0.2 mg/kg: moderate clearance)

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Dog p.o. data	5 mg/kg	1 mg/kg	0.1 mg/kg
F (%)	178	69	61
Cmax (ng/ml)	1980	290	17.1
Tmax (h)	2-4	0.5-2	0.5-2
AUC 0-inf (ng.h/ml)	12200	1420	125

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Lower doses tested in the dog
→ Saturation kicks in already between 1 and 5mg/kg

Saturation tested in human hepatocytes.
Also there, saturation to be expected from low doses onwards

- Risk of very fast clearance at starting dose, hence very low concentrations → detection limit??
- Escalating doses should be carefully chosen

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PBPK model can guide those decisions →

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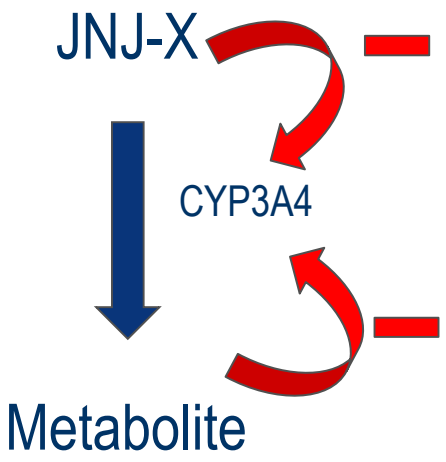
Anticipating exposure during MD? Auto-inhibition case

Background: JNJ-X is a high clearance compound; mainly metabolized by CYP3A4
It is also a reversible and time-dependent inhibitor of CYP3A4
→ it may inhibit its own metabolism
→ from which concentration onwards will nonlinearity kick in in the MAD study?



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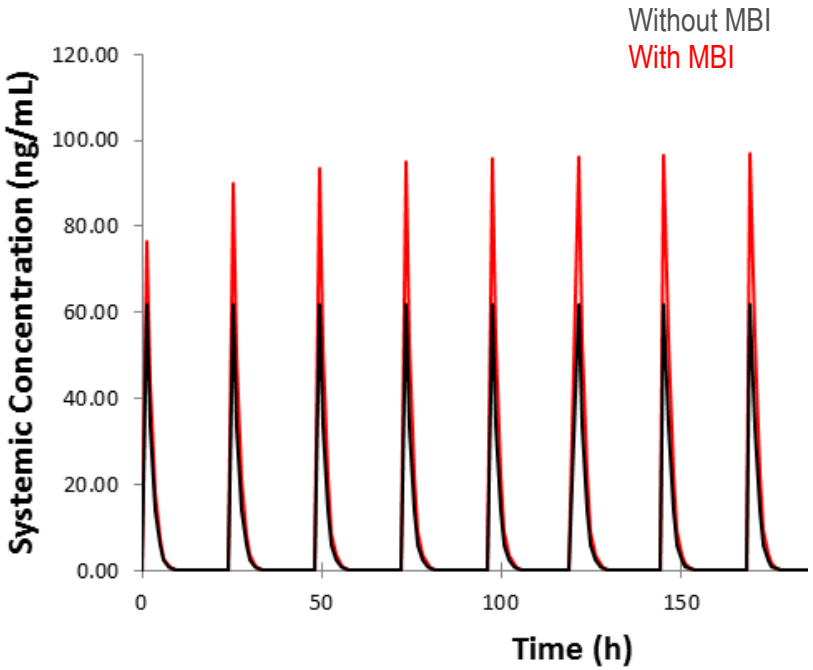
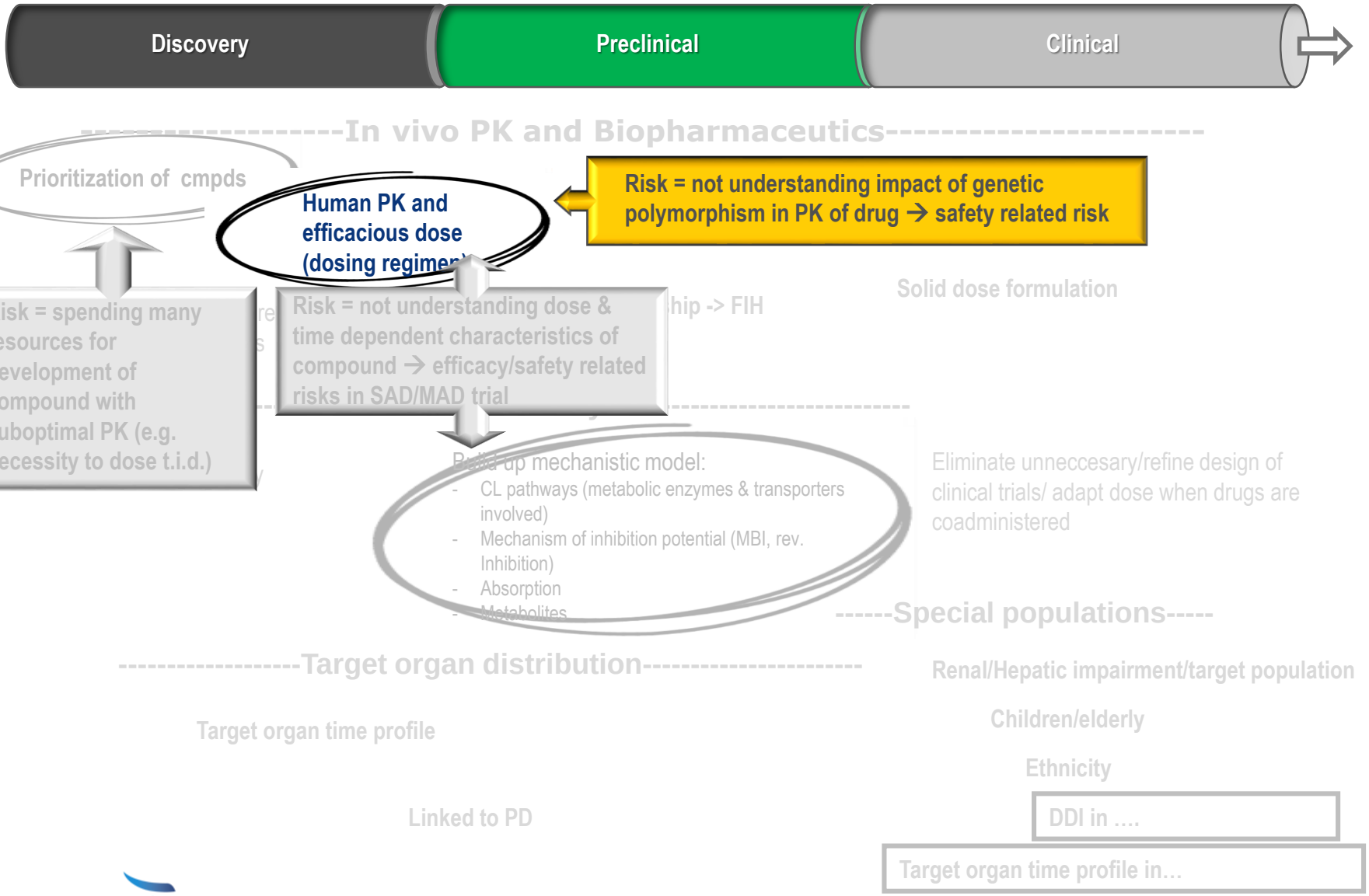


PBPK modeling and mitigating risks



Anticipate impact of genetic polymorphism in PK profile

Background: Clopidogrel is a prodrug that is metabolized by an esterase-dependent pathway leading to an inactive metabolite and a CYP450 dependent pathway leading to its active metabolite mediated mainly by CYP2C19
Polymorphisms of CYP2C19 affect the PK (and PD) of clopidogrel
Can impact of different CYP2C19 activ. (poor, intermediate, extensive, ultrarapid metabolizers) be anticipated?

1521-009X/43/4/510–522$25.00
DRUG METABOLISM AND DISPOSITION

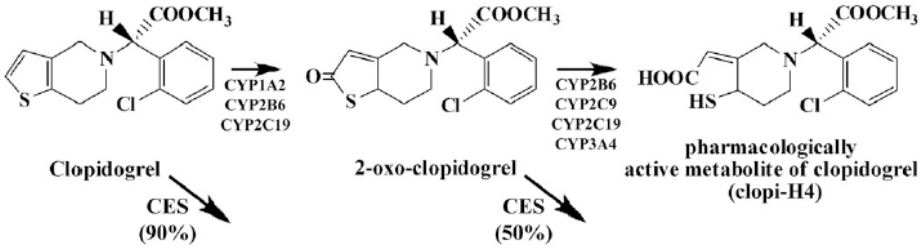
http://dx.doi.org/10.1124/dmd.114.062596
Drug Metab Dispos 43:510–522, April 2015

Physiologically Based Pharmacokinetic Modeling for Sequential Metabolism: Effect of CYP2C19 Genetic Polymorphism on Clopidogrel and Clopidogrel Active Metabolite Pharmacokinetics

Nassim Djebli, David Fabre, Xavier Boulenc, Gérard Fabre, Eric Sultan, and Fabrice Hurbin

Sanofi R&D, Drug Disposition, Disposition Safety and Animal Research, Montpellier, France

Received December 9, 2014; accepted January 21, 2015



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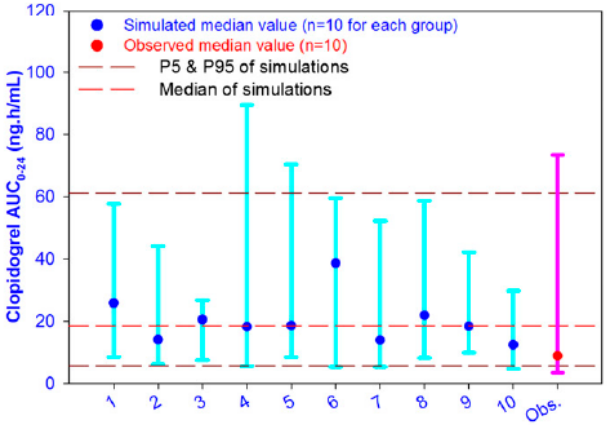
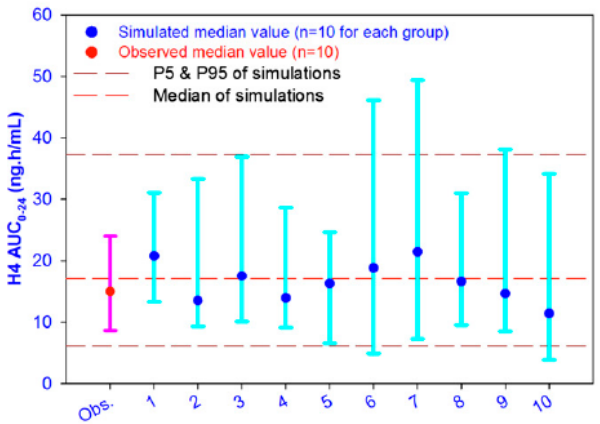
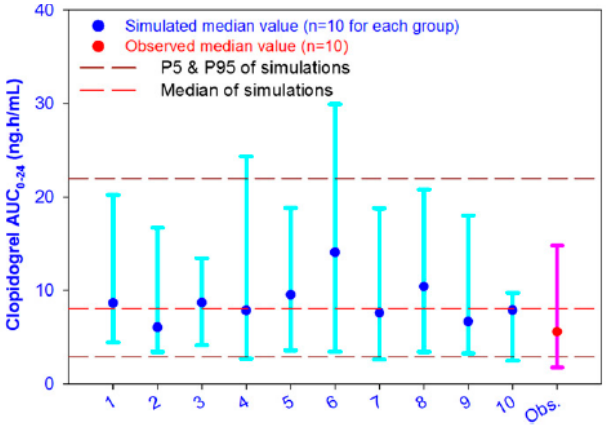
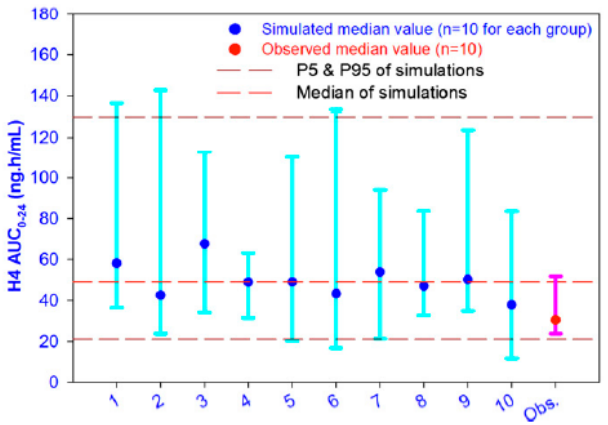
	Clopidogrel prodrug	Active metabolite
Poor metabolizers		
Ultrarapid metabolizers		

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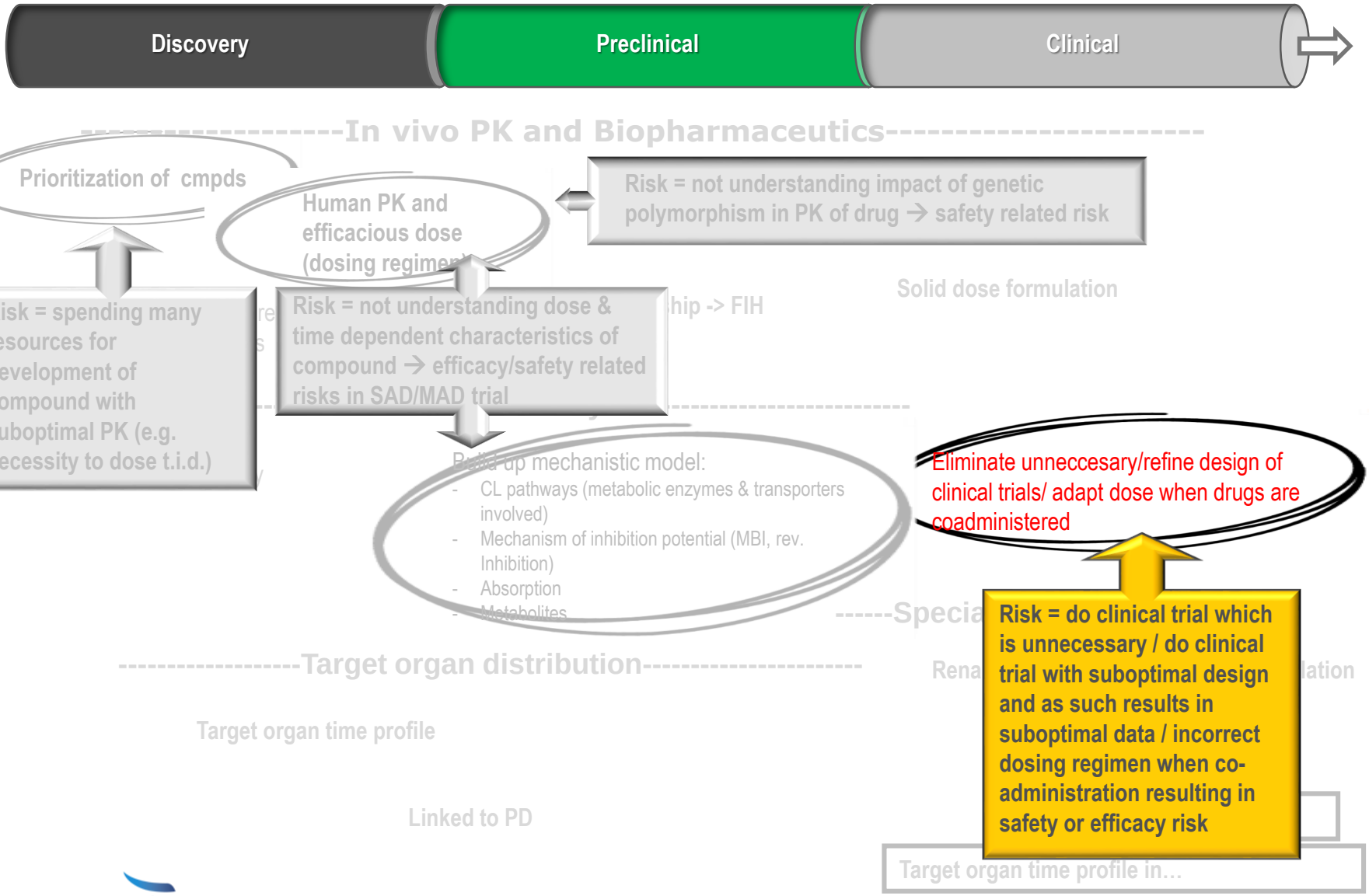
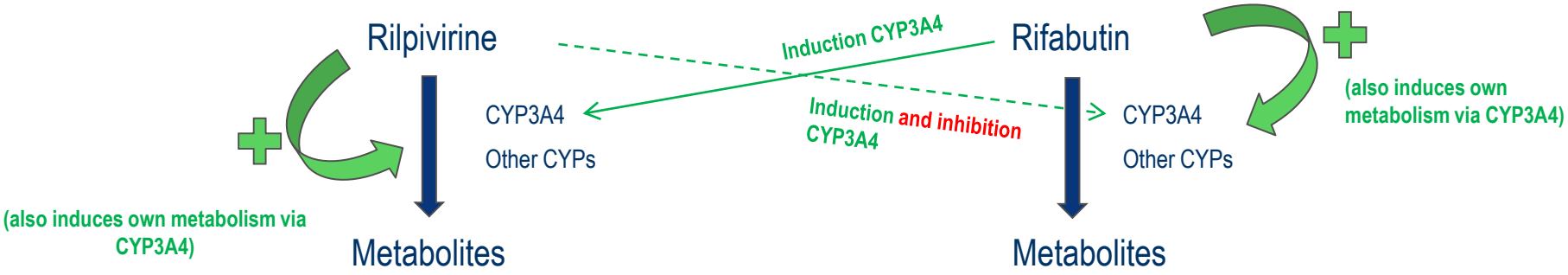


Adapting dose in case of induction by rifabutin ?

Background: Rifabutin lowers the concentrations of rilpivirine.

→ dose of rilpivirine x 2 to overcome the decrease in exposure upon coadministration

→ what to do after stopping rifabutin? (when rifabutin is stopped an ongoing inducing is expected for a few more days)



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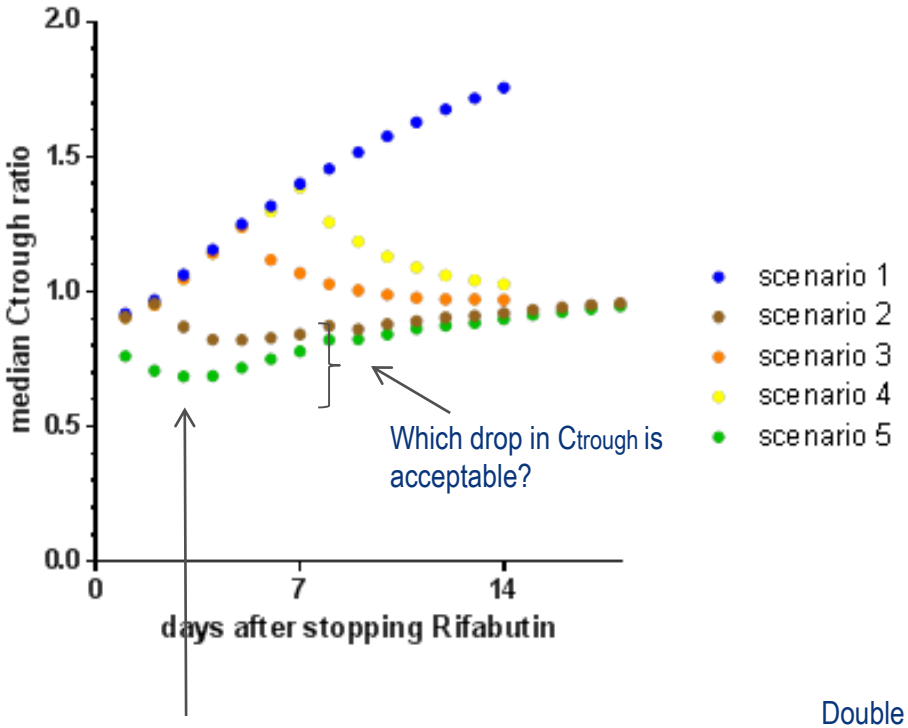
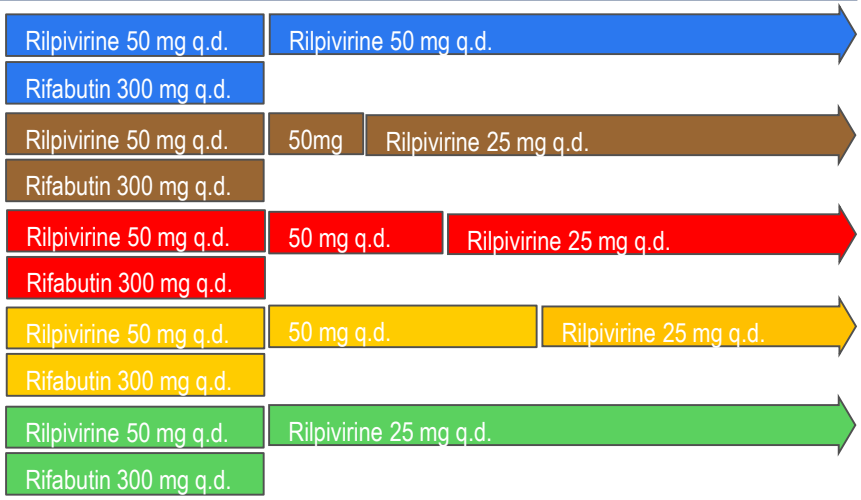


When Rifabutin is stopped, an ongoing inducing is to be expected for a few more days.



Double dose rilpivirine to overcome the decrease in exposure upon coadministration

Stop of rifabutin

Several scenario's tested with different dosing regimen of rilpivirine

Summary

Value of PBPK in Risk Mitigation in Early Studies.

- Predict time profile of drug concentrations based upon in vitro ADME data and plausible biology
- Confirm mechanisms governing the (nonlinear) PK during dose escalation in the first human SAD & MAD studies
- Anticipate impact of genetic polymorphism in PK profile
- Anticipate drug interactions in First-in-Patient studies
- Differentiate drug candidates

" The Prepared Mind" (Dr. Paul Janssen, 1983)

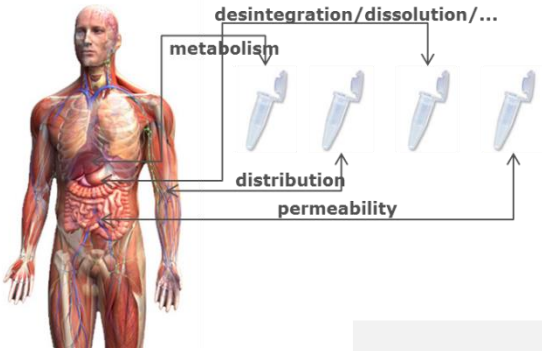
Acknowledgments

- Achiel Van Peer
- Loeckie De Zwart
- Jan Snoeys
- Marieke Voets
- Mario Monshouwer

Back-ups

PBPK modeling

Integration of multiple sources of individual data into the physiological context



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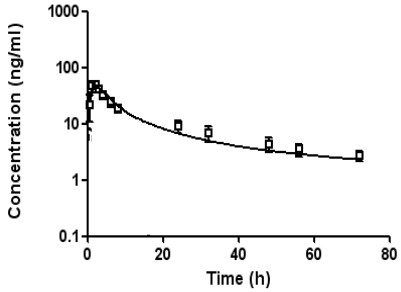
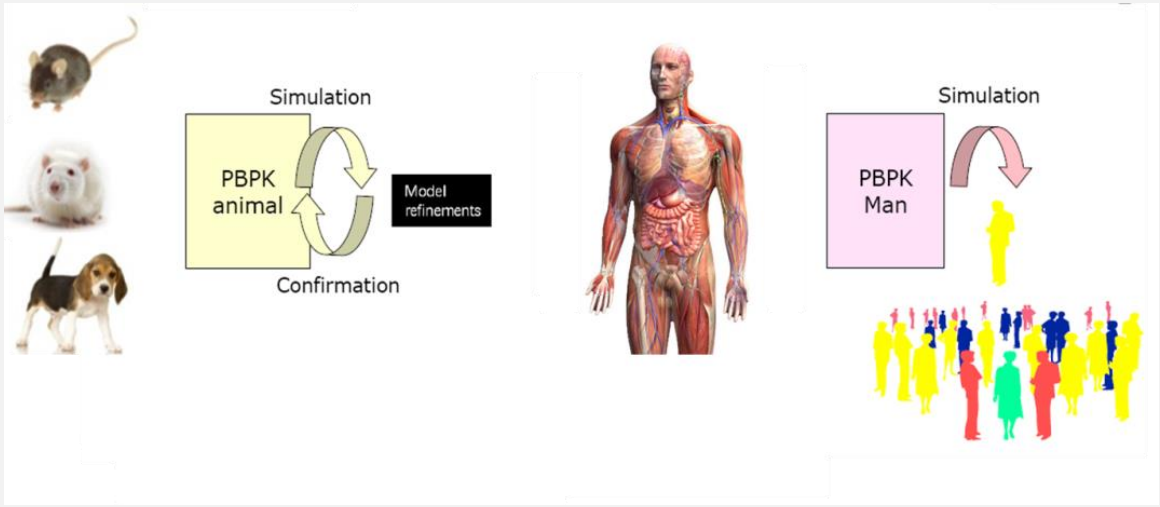
Predicting human PK
.. and have a prepared mind





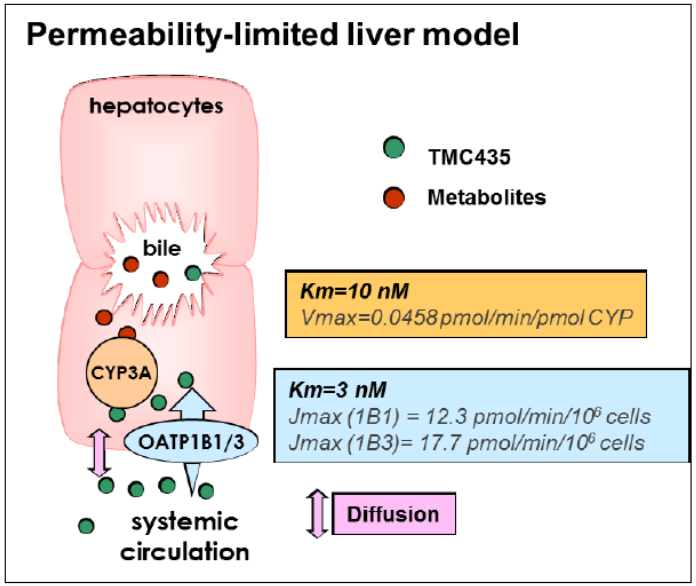
Understand more than dose proportionality in SAD?

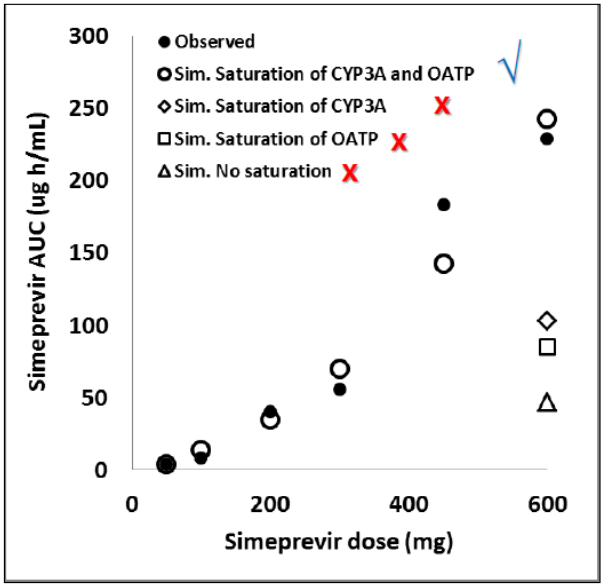
Background:

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Case Study: FDA Review of Simeprevir

Can saturation mechanisms explain nonlinear pharmacokinetics of simeprevir?

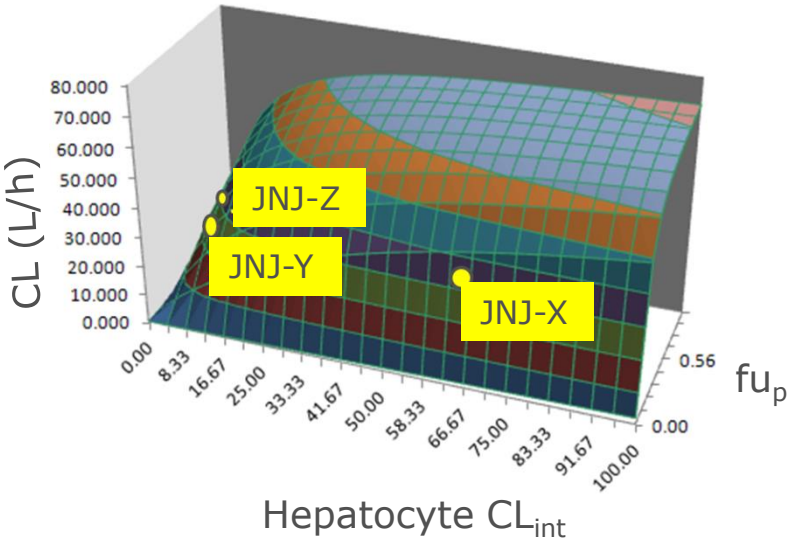


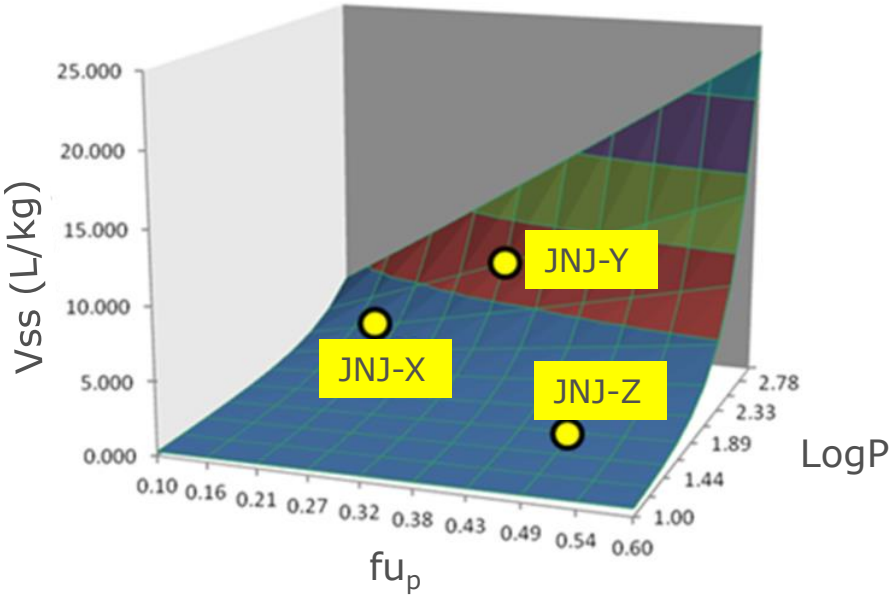


http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205123Orig1s000ClinPharmR.pdf 3

Discovery: candidate differentiation

Aim: PK of lead cmpd is not optimal (half life short; high fluctuation peak trough)
→ evaluate potential of 2 back-ups, integrating preclinical ADME and human microdose study data prior to SAD study without need for extensive TOX support





Even though hepatocyte Clint is 7-8 fold lower for JNJ-Y and JNJ-Z
→ Clearance is only ~2 fold lower for JNJ-Y and JNJ-Z

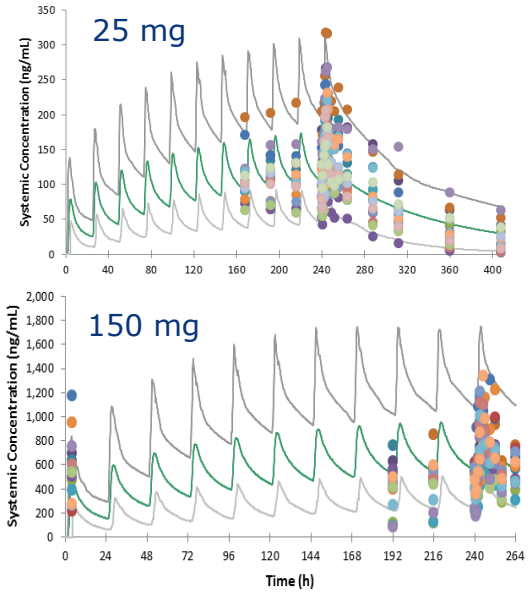
Higher lipophilicity (logP) of JNJ-Y
→ Higher volume of distribution of JNJ-Y

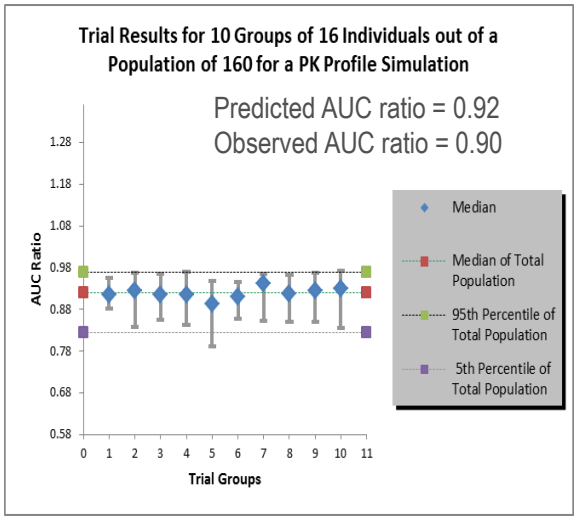
Terminal half-life reasonably longer for JNJ-Y compared to the 2 other compounds (related to a higher volume of distribution)
→ JNJ-Y seemed to be most valuable with regard to a multiple dosing regimen.

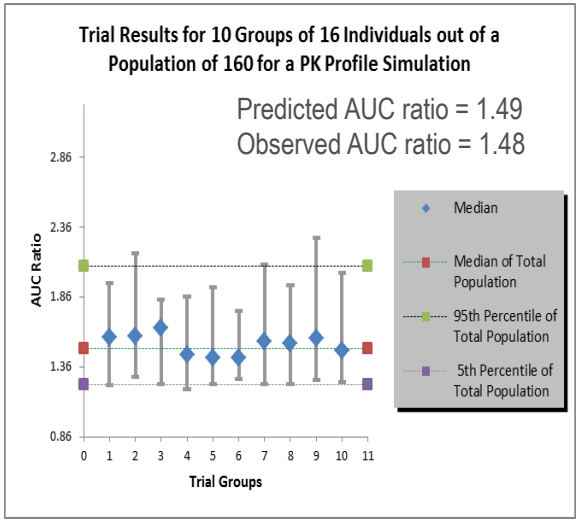
Clinical: eliminate unnecessary trial

Aim: Rifabutin lowers the concentrations of rilpivirine.
→ dose of rilpivirine x 2 to overcome the decrease in exposure upon coadministr.
→ what to do after stopping rifabutin? (when rifabutin is stopped an ongoing inducing is expected for a few more days)

Multiple ascending dose study	50mg sildenafil + 75mg qd rilpivirine	150mg qd rilpivirine+400mg qd keto







VERFICATION RILPIVIRINE MODEL

Verification of CYP3A4 contribution?

- Clinical study data with CYP3A4 inhibitor ketoconazole
- Multiple ascending dose study (auto-induction)

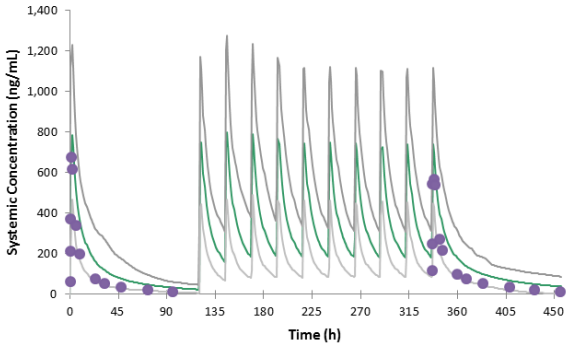
Verification of inhibition and induction effects on CYP3A4?

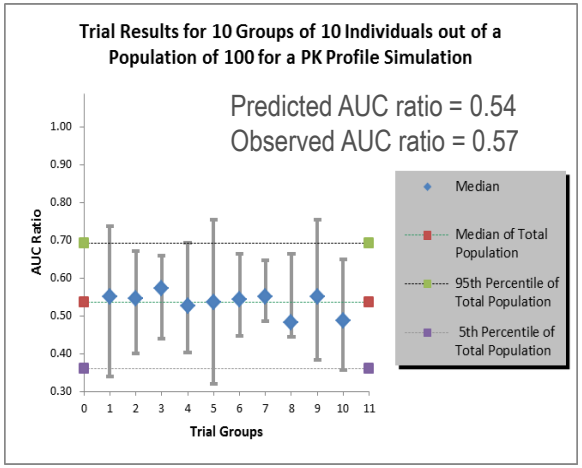
- Clinical study data with CYP3A4 substrate sildenafil

Clinical: eliminate unnecessary trial

Aim: Rifabutin lowers the concentrations of rilpivirine.
→ dose of rilpivirine x 2 to overcome the decrease in exposure upon coadministr.
→ what to do after stopping rifabutin? (when rifabutin is stopped an ongoing inducing is expected for a few more days)

Multiple ascending dose study	25mg rilpivirine + 300mg qd rifabutin





VERIFICATION RIFABUTIN MODEL

Verification of induction effects on CYP3A4?
- Clinical study data with rifabutin

Verification of inducing concentrations at steady state?
- Multiple ascending dose study

Abstract

The transition from preclinical development to clinical studies is a major milestone in a drug development project. During this transition the selection of the most suitable starting dose and dosing regimen of the first-in-man study is one of the primary expectations. The starting dose and dosing regimen should be sufficiently low to avoid toxicity (i.e. safety related risk) and sufficiently high to avoid unnecessary human trials (i.e. efficacy related risk). A consolidation of all available preclinical information is essential to provide estimates for these doses. Several approaches are being used in this regard, from very simple (minimum anticipated biological effect level (MABEL), allometry, Dedrick approach) to more complex (physiology based PK modeling (PBPK)). Unlike the simple approaches, PBPK modelling integrates preclinical in vitro and in vivo data into a mechanistic framework to predict plasma and tissue concentration-time profiles, and to address mechanistic issues that are relevant to pharmacokinetics (e.g. saturable metabolism and/or absorption, interspecies differences, expression levels and activity of metabolizing enzymes and transporters). Such mechanistic models result in a prepared mind once the first human volunteer/patient is being dosed. Several case examples are shown where mechanistic models helped mitigating potential issues (compound selection during drug discovery, setting the dose, the escalation steps, and the regimen of first-in-man studies (thereby taking into consideration saturation and time-dependent processes), and setting the dose for drug-drug interaction studies).