# Application of PBPK modeling to support labelling initiatives: Janssen case study

**Jan Snoeys**

Janssen | 18.11.2019

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A New York city native living with schizophrenia, Michelle uses her talents to reduce stigma and start conversations about mental health.

# PBPK in regulatory discussions (2011 – 2019)

| NDA | Generic name | Brand name | Approval date | Specific question(s) addressed using PBPK | Informed prescription drug labeling? |
|---|---|---|---|---|---|
| 022406 | Rivaroxaban | XARELTO | 07/01/2011 | • Assess a complex and multiple interaction scenario: subjects with renal impairment and co-administered a combined P-gp and CYP3A4 inhibitor | Yes |
| 202022 | Rilpivirine | EDURANT | 05/20/2011 | • Predict optimal rilpivirine dosing regimen during rifabutin coadministration and after rifabutin dosing is stopped. | Yes |
| 204042 | Canagliflozin | INVOKANA | 3/29/2013 | • Confirm the lack of DDI in vivo using simvastatin (CYP3A substrate), ethinyl estradiol (CYP3A substrate), and S-warfarin (CYP2C9 substrate) as substrates<br>• NDA on particle engineering<br>• Post-approval on potential presence of low levels of a new polymorph in commercial production | Yes<br><br>Accepted<br>Accepted |
| 204410 | Macitentan | OPSUMIT | 10/18/2013 | • Predict the effect of a strong CYP3A inhibitor on macitentan PK | Yes |
| 205552 | Ibrutinib | IMBRUVICA | 11/13/2013 | • Predict the effect of a moderate CYP3A inhibitor or inducer on ibrutinib PK | Yes |
| 205123 | Simeprevir | OLYSIO | 11/22/2013 | • Assessing the significance of a transporter (OATP1B1/3) on simeprevir disposition<br>• Change of dissolution specs | Yes<br>Accepted |
| 205879 | Canagliflozin Metformin | Invokamet XR | 09/20/2016 | • Clinically relevant dissolution specification (canagliflozin) | Accepted |
| 210951 | Apalutamide | ERLEADA | 02/14/2018 | • Predict the effect of CYP3A or CYP2C8 inhibitors/inducers on apalutamide exposure<br>• Predict the effect of apalutamide on OAT3 or OCT2/MATE substrates<br>• Clinically relevant dissolution specification<br>• Clinically relevant specification for polymorphic purity | Yes<br><br>No<br>Accepted<br>Accepted<br>(except EMA) |
| 211243 | Esketamine | SPRAVATO | 03/05/2019 | • Predict the effect of esketamine (intranasal) on midazolam and ethinyl estradiol<br>• Predict effect of CYP2B6 inhibition on esketamine exposure after intranasal administration | Possible<br>No |
| 212018 | Erdafitinib | BALVERSA | 04/11/2019 | • Predict the exposure of erdafitinib in CYP2C9*3/*3 subjects<br>• Predict the effect of CYP3A or CYP2C9 inhibitors in CYP2C9*3/*3 subjects<br>• Predict the effect of potent CYP3A/2C9 inducer on erdafitinib<br>• Predict the effect of erdafitinib on Pgp substrates and dose staggering strategy<br><br>• Predict the effect of erdafitinib on midazolam<br>• Predict the effect of erdafinitib on OCT2 substrates | Yes<br>Yes<br>No<br>Partial (staggering accepted)<br>No<br>No |

# Take home messages:

1. Clearly defined objective/purpose of the PBPK M&S

2. Deep scientific insight on limitations/opportunities of the models used to generate compound specific input data, model structures and physiology parameters

3. Verify drug independent system components/virtual populations with variety of compounds with broad range of physicochemical properties

4. Make sure to verify compound specific PBPK model with all relevant (linked to M&S objective) observed clinical datasets for a specific defined purpose/question

5. Fully understand the consequence/impact of model optimisation
   - Experimental testing of the hypothesis to optimise specific input parameter
   - How sensitive is the model outcome to a change in this parameter?
   - If parameter cannot be experimentally determined can it reliably be estimated from a clinical study

6. Be mindful of how accurate simulations of unknown clinical scenarios have to be to allow important decision making.
   - Risk/benefit ratio of drug of interest
   - Complexity (including ethical aspect) of an eventual real clinical trial scenario
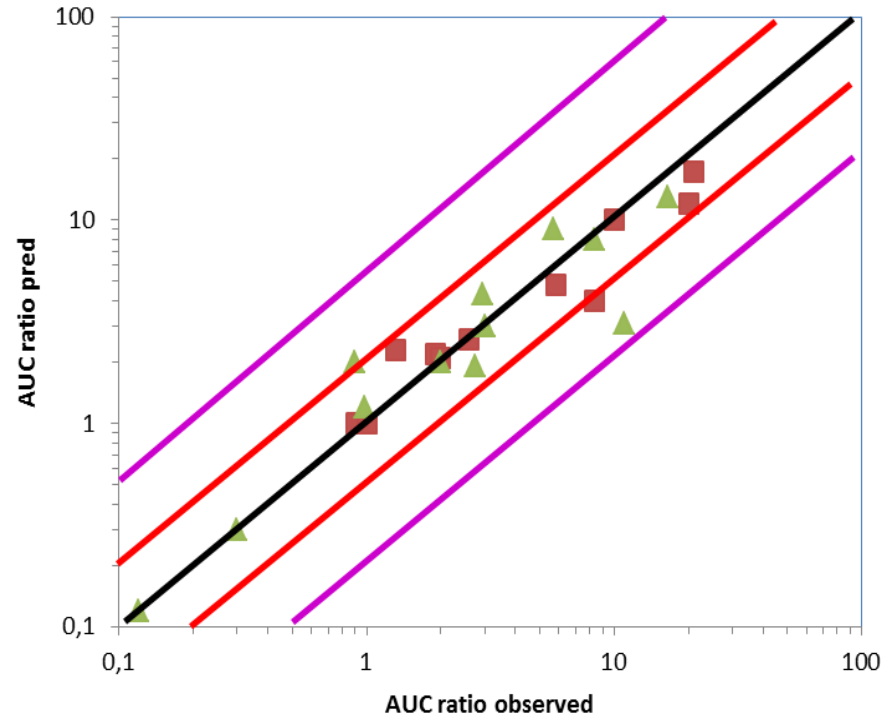
# Ibrutinib

- Ibrutinib approved in more than 100 countries with at least one indication since 2013. USPI Feb 2018:
  - Mantle cell lymphoma who have received at least one prior therapy (breakthrough therapy designation - BTD)
  - Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL)
  - CLL/SLL with 17p deletion (BTD)
  - Waldenström's macroglobulinemia (BTD)
  - Marginal zone lymphoma who require systemic therapy and have received at least one prior anti-CD20-based therapy
  - Chronic graft versus host disease after failure of one or more lines of systemic therapy (BTD)

- High clearance compound
  - IV clearance close to hepatic blood flow -> clearance sensitive to hepatic blood flow. Oral clearance >20x hepatic blood flow (low bioavailability due to extensive first pass extraction)

- Elimination pathway
  - Metabolism only; CYP3A (96% of metabolic clearance)

- Complete absorption

- High inter-subject variability

# PBPK M&S to address key questions

1) Can we predict the effect of mild, moderate and strong CYP3A inhibitors on ibrutinib PK in fasted subjects given the availability of a ketoconazole DDI study in fasted subjects?

2) Can we predict the effect of moderate CYP3A inducers on ibrutinib PK in fasted subjects given the availability of a rifampicin DDI study in fasted subjects?

3) Can we predict the effect of CYP3A inhibitors or CYP3A inducers on ibrutinib PK in non-fasted subjects given the mechanistic understanding of the difference in PK in fasted versus non-fasted subjects?

4) Can we predict the effect of mild, moderate and severe hepatic impairment on ibrutinib PK?
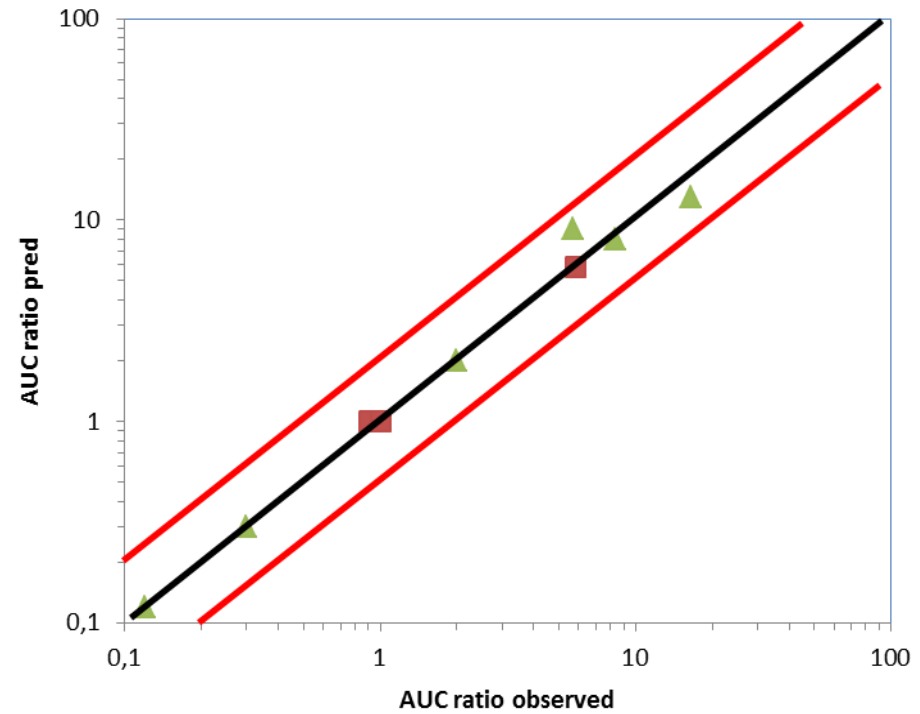
# PBPK DDI predictions: KPIs (2007-2012)

No verification with clinical DDI



- 70% within 1.3-fold
- 96% within 2-fold
- 100% within 5-fold

■ Reversible CYP inhibition

▲ MBI, transporters and induction

Verification with 1 clinical DDI



- 93% within 1.3-fold
- 100% within 2-fold

High confidence in 2012 that for ibrutinib in fasted subjects we can predict DDI with mild, moderate and strong CYP3A inhibitors or inducers

# Ibrutinib DDI prediction in non-fasted subjects

Hypothesis: food effect for ibrutinib (max 2-fold increase) is not linked to increase in fraction absorbed but to decrease in first pass extraction due to higher liver blood flow in fed subjects

- If food effect is linked to change in fraction absorbed => no effect on the extent of DDI with CYP3A inhibitors
- If ibrutinib food effect is linked to reduced first pass extraction => reduced extent of DDI to be expected with CYP3A inhibitors
- Development of non-fasted ibrutinib PBPK model to predict the effect of CYP3A inhibitors or inducers. Benchmark versus relevant reference compounds (eg budenoside)
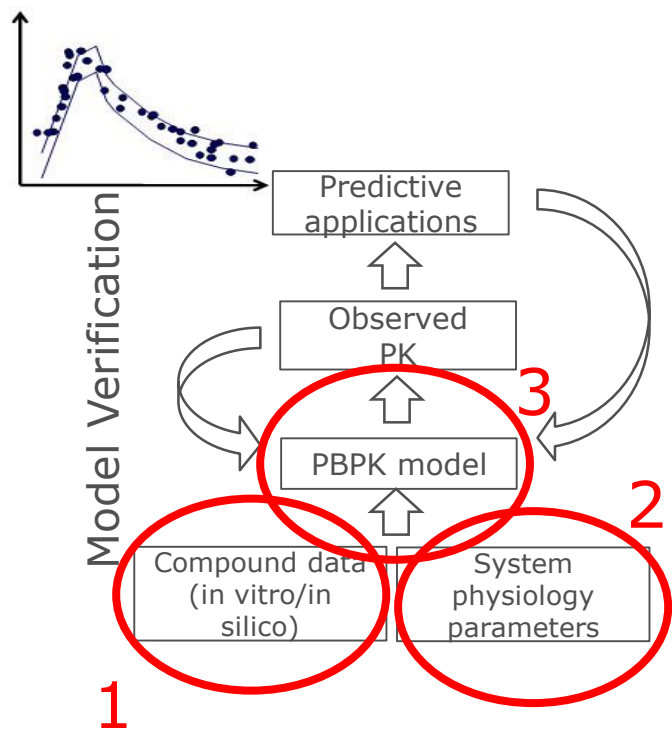
# Hepatic Insufficiency (2007-2012)
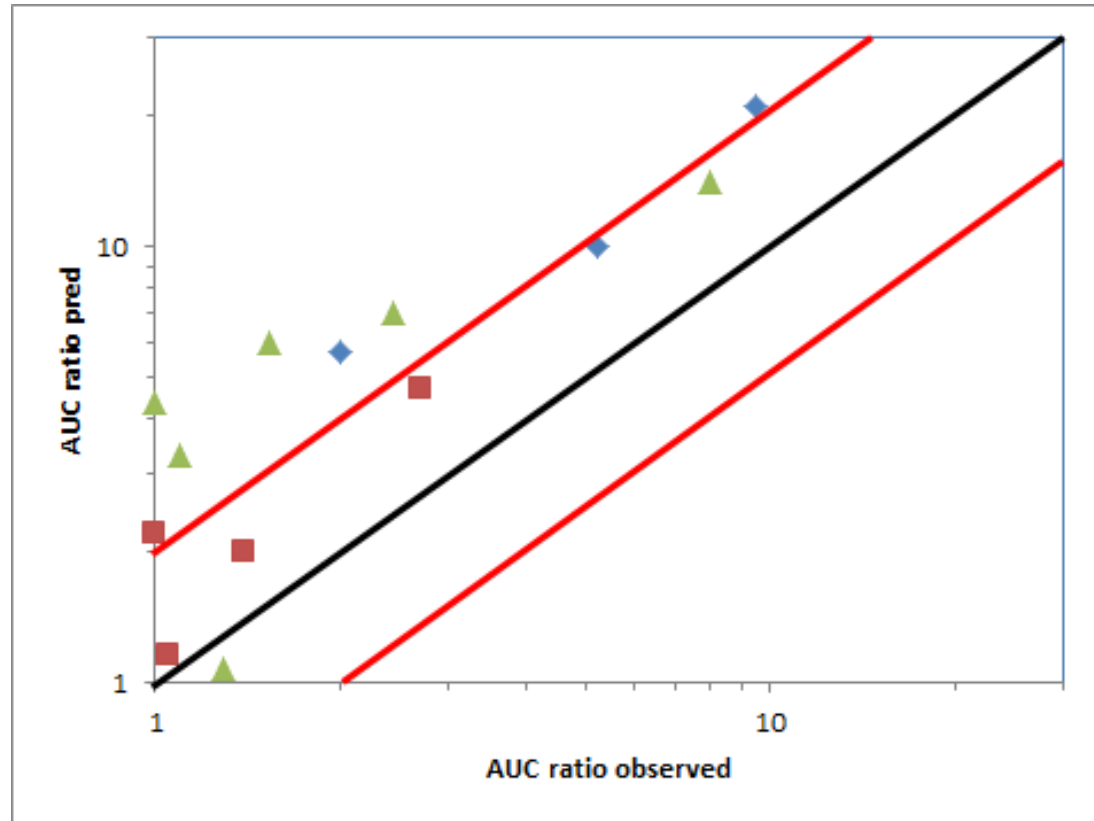


Low confidence in 2012 that for ibrutinib we could accurately simulate the effect of mild, moderate and severe hepatic impairment
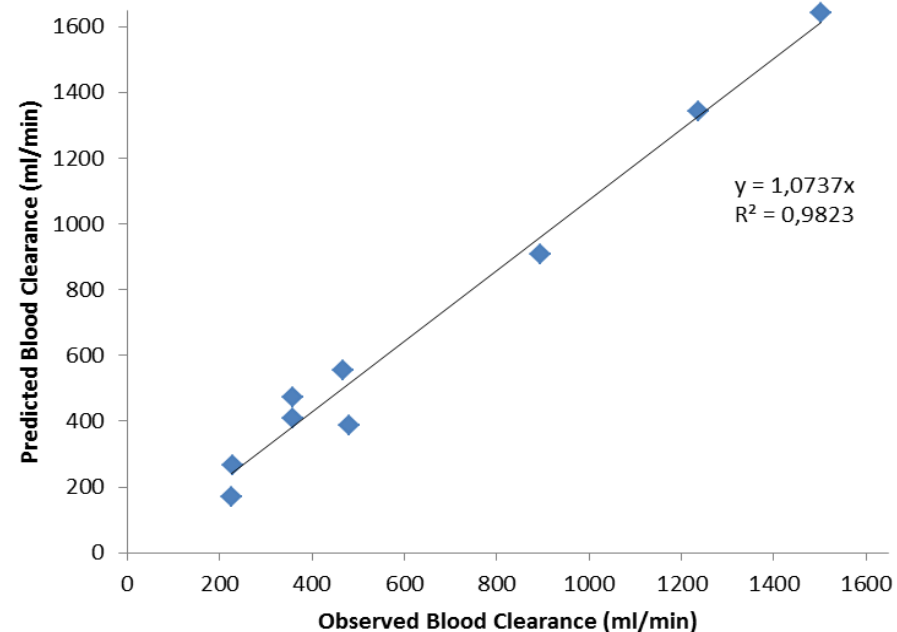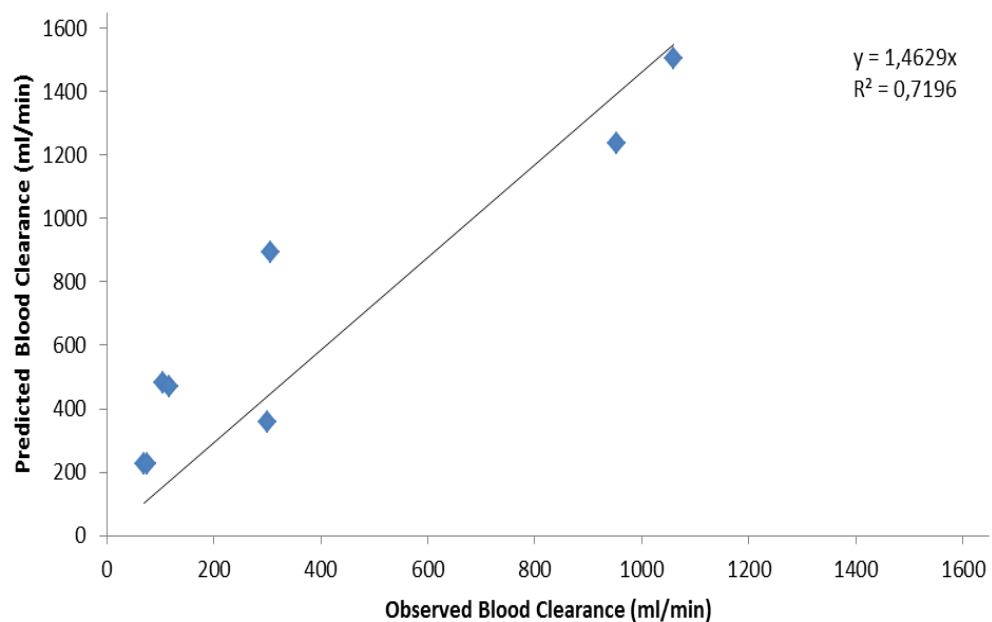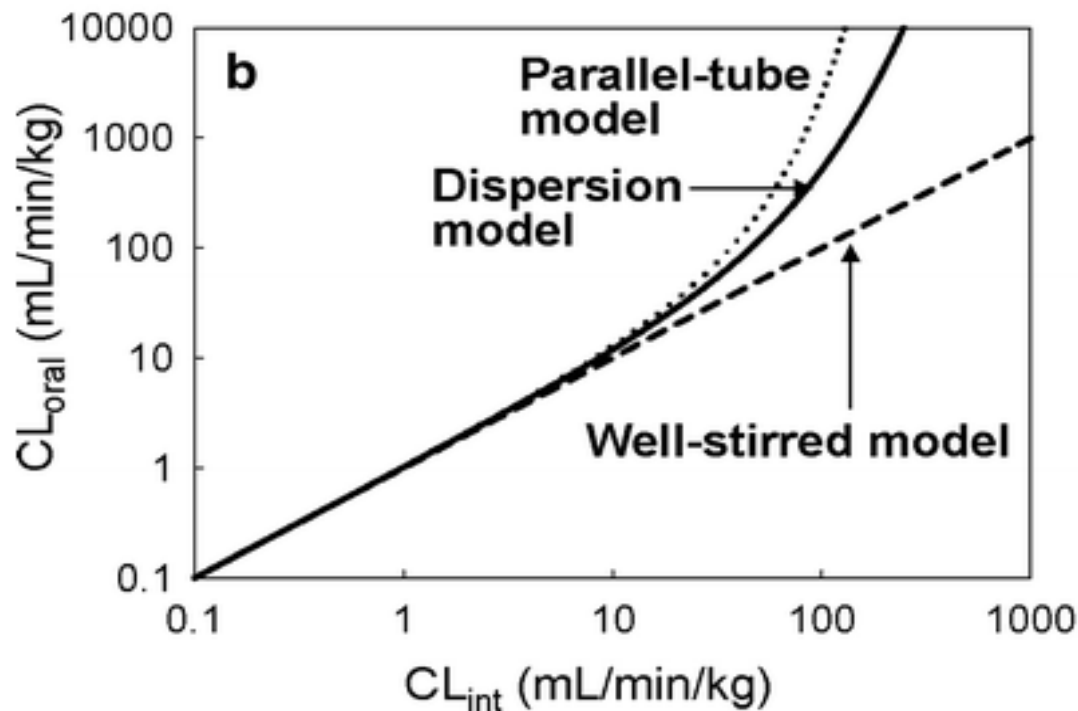
# PBPK model verification crucial



- Verification needed at 3 levels
  1. Predictive power highly dependent on high quality input data (compound dependent)
  2. System physiology parameters
  3. Model structure

# Input data verification

## Hepatocyte intrinsic clearance for BCSI/II compounds
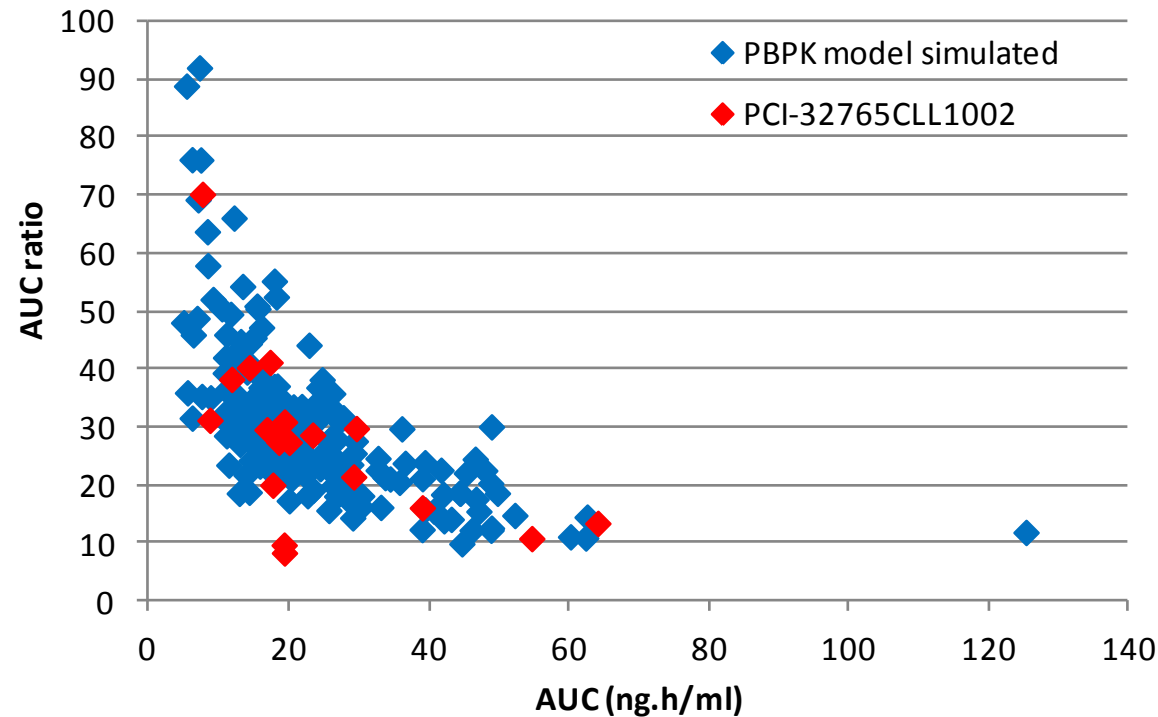
# Model structure verification



Chiba M et al. AAPS J, 2009

- Use $CL_{int,u\ in\ vivo}$ to calculate blood clearance ($CL_b$) with parallel tube equation   $CL_b = Qh * (1- e^{-(CL_{int,\ in\ vivo}*fu/BP)})$

- Calculate $CL_{int,u\ in\ vivo}$ with the well-stirred equation $CL_b = Qh * (CL_{int,\ in\ vivo} * f_u/BP) / (Qh + (CL_{int,\ in\ vivo} * f_u/BP))$

# Ibrutinib PBPK model verification for DDI simulations with CYP3A perpetrators



- Prospective simulation of DDI of ibrutinib with ketoconazole indicated large interaction (20-30-fold). Lower dose from 140 mg to 40 mg in keto-arm

- DDI of 40 mg ibrutinib + 400 mg qd ketoconazole in fasted healthy subjects well captured; including observed variability.

# PBPK report simulating DDIs with ibrutinib in fasted healthy subjects included in FDA submission (2013)
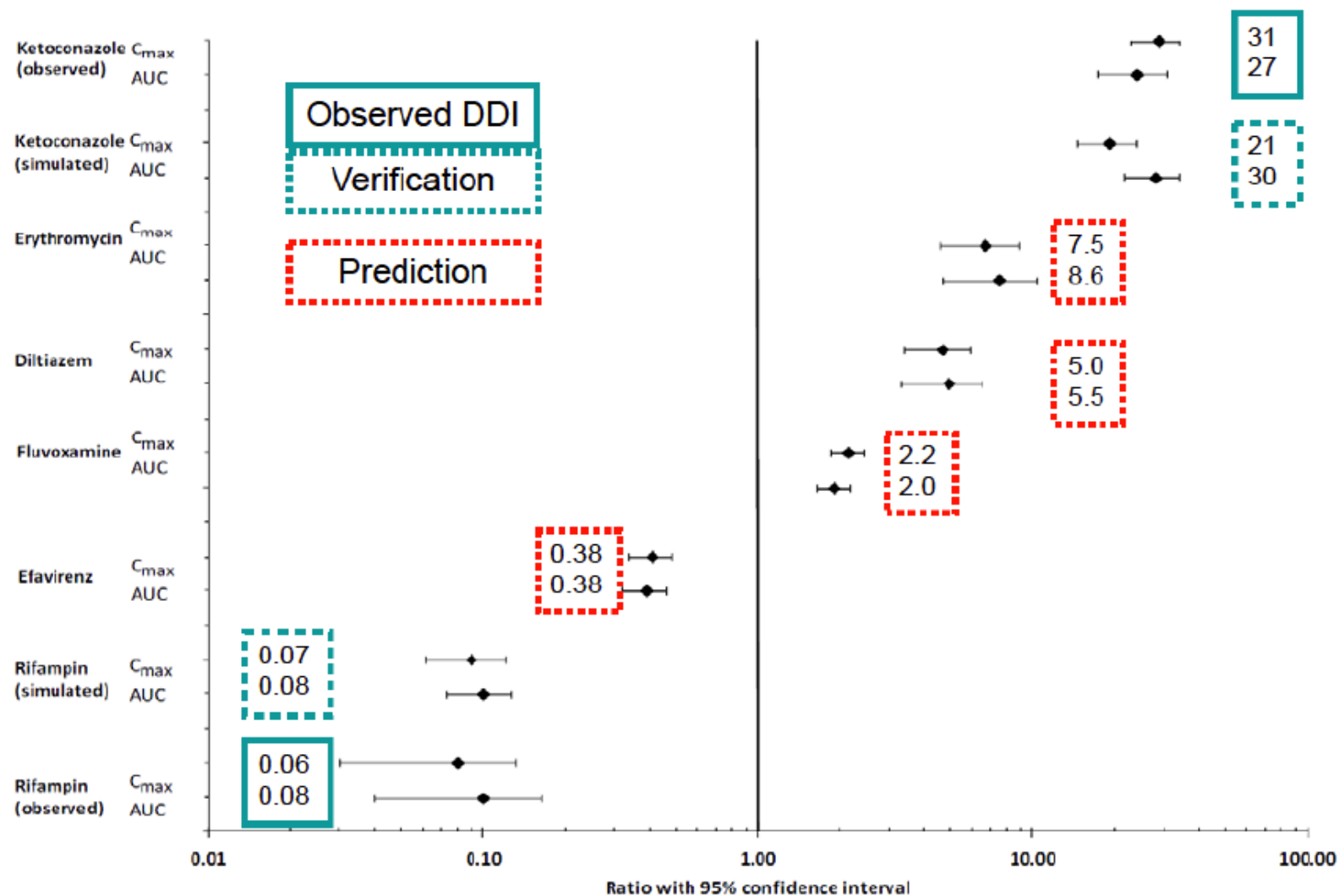


http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

# Ibrutinib DDI simulations in non-fasted subjects
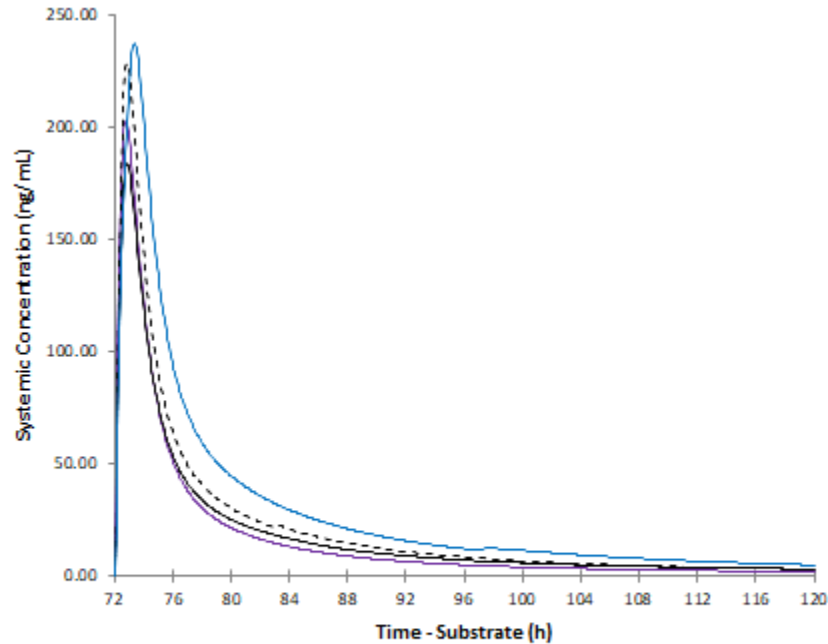


| CYP3A inhibitor | Ibrutib $C_{max}$ ratio | Ibrutinib AUC ratio |
|---|---|---|
| 200 mg qd itraconazole (strong) | 6.2 | 10.7 |
| 200 mg bid voriconazole (moderate strong) | 5.9 | 6.4 |
| 500 mg tid erythromycin (moderate) | 4.6 | 5.1 |

- 400 mg qd ketoconazole as strong CYP3A inhibitor resulted in 27x ibrutinib $C_{max}$ increase and 24x ibrutinib AUC increase in <u>fasted</u> subjects.

# Regulatory interactions FDA:
## FDA response to ibrutinib PBPK report (2013)

**Answer regarding special populations**

- Regarding difference between healthy subjects and patient population
  - "It was explained that differences were most likely due to food effect"
  - Based on mechanistic PK knowledge of ibrutinib it was speculated that the DDI potential in fed subjects would be less than in fasted subjects

- Regarding hepatic impaired populations
  - "It was emphasized that the available hepatic impaired populations in the Simcyp software are not accurately predicting the exposure and based on internal experience generally overestimate the observed exposure in these populations."

# Initial USPI* for treatment of Mantle Cell Lymphoma with Imbruvica (Ibrutinib) dose of 560 mg qd (Nov 2013)

**Coadministration of Ibrutinib with CYP3A Inhibitors**

In a sequential design trial of 18 healthy volunteers, a single dose of 120 mg of IMBRUVICA was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 - 9). Ketoconazole increased ibrutinib dose-normalized $C_{max}$ and AUC 29-fold and 24-fold, respectively. Simulations using physiologically based pharmacokinetic (PBPK) models suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6- to 9-fold in fasted condition.

…Concomitant use of strong CYP3A inhibitors not recommended…

…Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used…

**Coadministration of Ibrutinib with CYP3A Inducers**

Preliminary PK data from an ongoing dedicated drug interaction trial and simulations using PBPK indicate that rifampin (a strong CYP3A inducer) can decrease ibrutinib $C_{max}$ and AUC by more than 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib up to 3-fold.
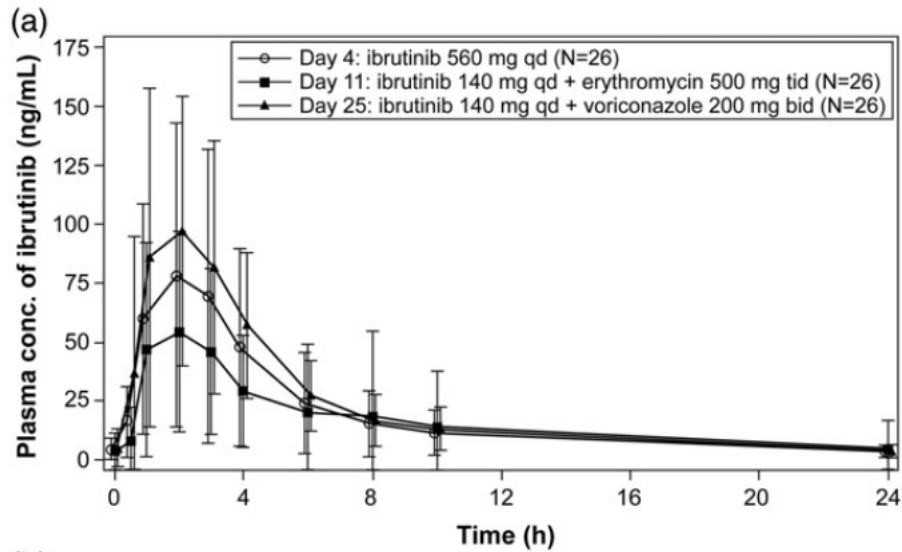
…Avoid concomitant use of strong CYP3A inducers….

**Hepatic insufficiency**

….There is insufficient data to recommend a dose of IMBRUVICA in patients with baseline hepatic insufficiency….

\* Language is no longer included in the current USPI

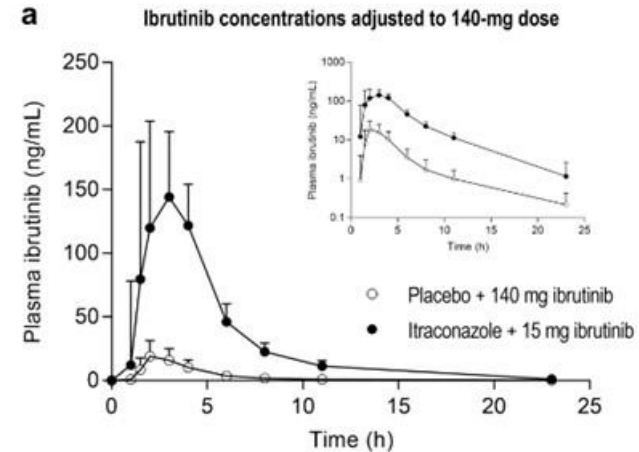# DDI with voriconazole, erythromycin and itraconazole in non-fasted subjects (2018-2019)



(a)

Legend:
- Day 4: ibrutinib 560 mg qd (N=26)
- Day 11: ibrutinib 140 mg qd + erythromycin 500 mg tid (N=26)
- Day 25: ibrutinib 140 mg qd + voriconazole 200 mg bid (N=26)

**Table 2.** Summary of pharmacokinetic parameters of ibrutinib and PCI-45227.

| Treatment | n | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $AUC_{0-24h}$ (ng·h/mL) |
|---|---|---|---|---|
| Ibrutinib parameters | | | | |
| Ibrutinib alone 560 mg | 26 | $89.4 \pm 67.1$ | 2.00 (0.50–4.92) | $470 \pm 350$ |
| Ibrutinib 140 mg + erythromycin | 26[a] | $75.5 \pm 47.9$ | 2.00 (1.00–8.00) | $397 \pm 420$ |
| Ibrutinib 140 mg + voriconazole | 26 | $129 \pm 63.4$ | 2.00 (0.53–4.67) | $559 \pm 251$ |

The results of this study demonstrate that 140 mg ibrutinib administered with voriconazole or erythromycin provides exposures generally within the clinical range observed in patients with B-cell malignancies receiving a 560 mg dose

de Jong et al. Leukemia and Lymphoma 2018



a — Ibrutinib concentrations adjusted to 140-mg dose
- Placebo + 140 mg ibrutinib
- Itraconazole + 15 mg ibrutinib

b — Unadjusted ibrutinib concentrations
- Placebo + 140 mg ibrutinib
- Itraconazole + 15 mg ibrutinib

ibrutinib $C_{max}$: 9x
ibrutinib AUC: 10 x
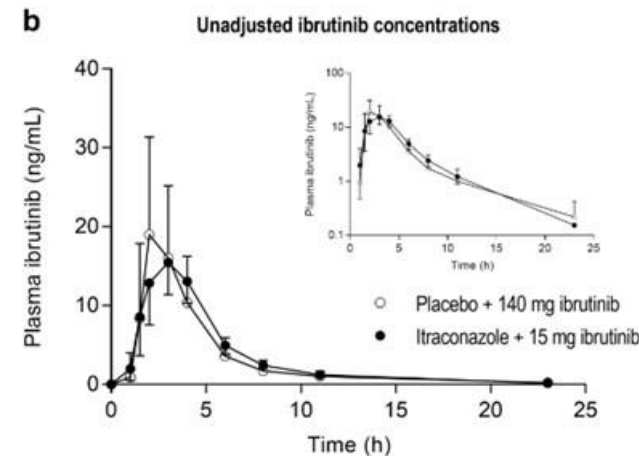
Tapaninen et al. Clin Transl Sci Oct 2019

# Simulations vs observed ibrutinib 140 mg single dose PK data in hepatic impaired subjects (2013)

| | | Observed* | | | | Predicted | | | | Ratio Pred/Obs |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | GeoMean | SD | Ratio* | N | GeoMean | SD | Ratio* | |
| **Cmax (ng/ml)** | Healthy | 6 | 6.22 | 8.29 | | 100 | 25 | 15 | | |
| | CP-A | 6 | 32.1 | 36.2 | 5.2 | 100 | 108 | 48 | 4.3 | 0.83 |
| | CP-B | 10 | 54.5 | 37.8 | 8.8 | 100 | 241 | 83 | 9.6 | 1.1 |
| | CP-C | 8 | 43.3 | 37.8 | 7.0 | 100 | 388 | 94 | 16 | 2.3 |
| **AUCinf (ng/ml.h)** | Healthy | 6 | 63.6 | 33.3 | | 100 | 83 | 51 | | |
| | CP-A | 6 | 169 | 372 | 2.7 | 100 | 394 | 144 | 4.8 | 1.8 |
| | CP-B | 10 | 506 | 236 | 8.0 | 100 | 1135 | 319 | 14 | 1.8 |
| | CP-C | 8 | 602 | 162 | 9.5 | 100 | 1702 | 446 | 21 | 2.2 |
| **fu,p (%)** | Healthy | 6 | 3.11 | 1.23 | | 100 | 2.6 | 0.26 | | |
| | CP-A | 6 | 2.99 | 0.515 | 0.96 | 100 | 3.1 | 0.42 | 1.2 | 1.3 |
| | CP-B | 10 | 3.75 | 0.634 | 1.2 | 100 | 3.9 | 0.63 | 1.5 | 1.3 |
| | CP-C | 8 | 4.96 | 0.878 | 1.6 | 100 | 5.2 | 0.85 | 2.0 | 1.3 |
| **AUCinf,u** | Healthy | 6 | 1.98 | 2.24 | | 100 | 2.16 | 1.5 | | |
| | CP-A | 6 | 5.09 | 12.9 | 2.6 | 100 | 12.2 | 4.46 | 5.7 | 2.2 |
| | CP-B | 10 | 19.0 | 9.96 | 9.6 | 100 | 44.3 | 12.4 | 21 | 2.2 |
| | CP-C | 8 | 28.2 | 8.17 | 14 | 100 | 88.5 | 23.2 | 41 | 2.9 |

**Extent of exposure increase (AUC) in mild, moderate and severe hepatic impairment overpredicted(predicted/observed ratio 1.8-2.2)**
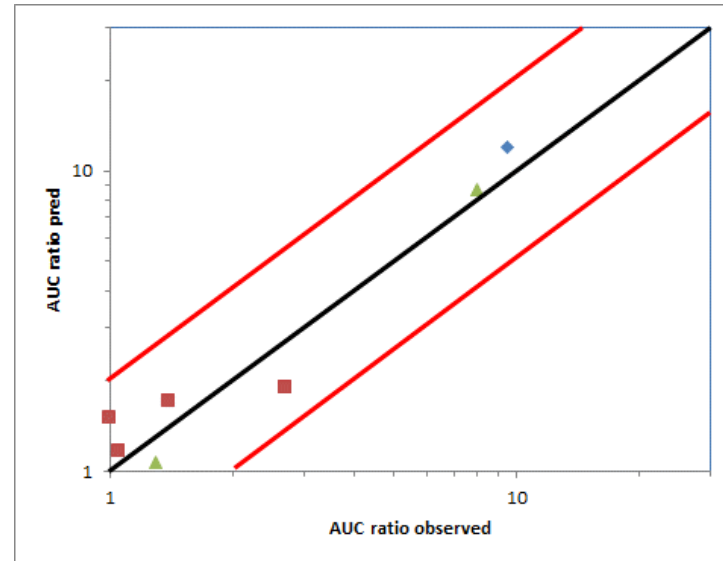
*de Jong et al. Leukemia and Lymphoma 2017

# Hepatic Insufficiency (verification of physiology parameters)
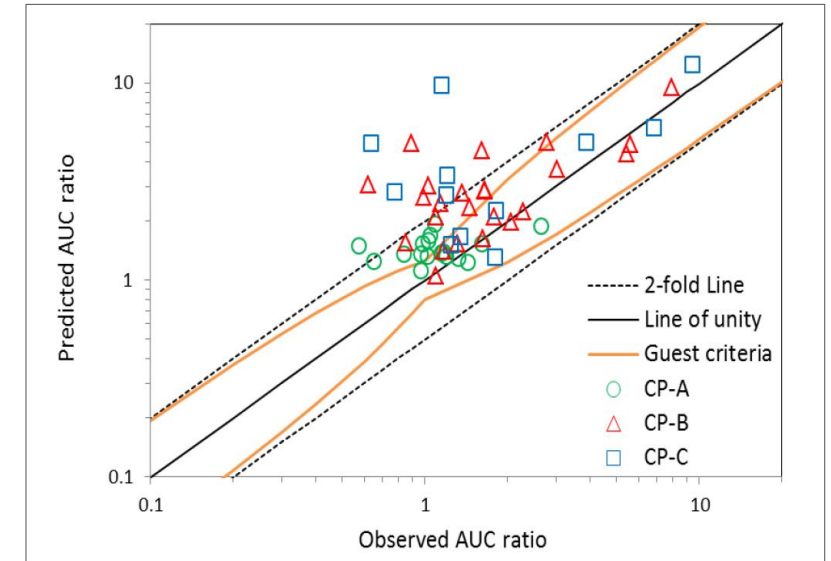
Hepatic Insufficiency
(Janssen 2007-2012)
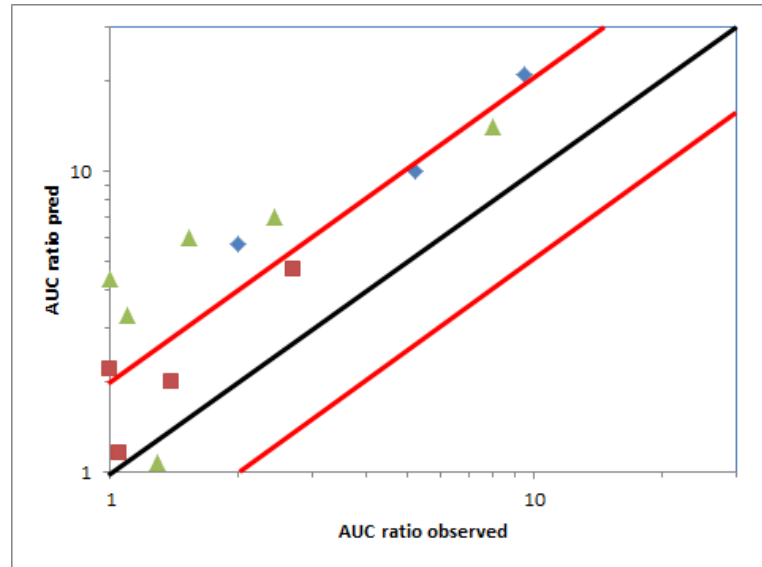
Hepatic Insufficiency
(Janssen 2016 – 2019)

Hepatic Insufficiency
(IQ 2019)



■ CP-A   ▲ CP-B   ◆ CP-C

Unpublished data

- IQ PBPK Renal and Hepatic Organ impairment working group
- Improved understanding since 2012 of impact of hepatic insuffiency on CYP activity, PPB and portacaval shunting (the latter very important for high clearance compounds)

# Predictions vs observed ibrutinib PK data in hepatic impaired subjects (2018)

| | | Observed | | | | Predicted | | | | Ratio Pred/Obs |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | GeoMean | SD | Ratio* | N | GeoMean | SD | Ratio* | |
| **Cmax (ng/ml)** | Healthy | 6 | 6.22 | 8.29 | | 100 | 26.5 | 21.1 | | |
| | CP-A | 6 | 32.1 | 36.2 | 5.2 | 100 | 41.6 | 28.1 | 1.6 | 0.30 |
| | CP-B | 10 | 54.5 | 37.8 | 8.8 | 100 | 150 | 64.9 | 5.7 | 0.70 |
| | CP-C | 8 | 43.3 | 37.8 | 7.0 | 100 | 202 | 80.4 | 7.6 | 1.1 |
| **AUCinf (ng/ml.h)** | Healthy | 6 | 63.6 | 33.3 | | 100 | 72.7 | 56.1 | | |
| | CP-A | 6 | 169 | 372 | 2.7 | 100 | 137 | 88.2 | 1.9 | 0.71 |
| | CP-B | 10 | 506 | 236 | 8.0 | 100 | 635 | 272 | 8.7 | 1.1 |
| | CP-C | 8 | 602 | 162 | 9.5 | 100 | 904 | 368 | 12 | 1.3 |
| **fu,p (%)** | Healthy | 6 | 3.11 | 1.23 | | 100 | 2.67 | 0.254 | | |
| | CP-A | 6 | 2.99 | 0.515 | 0.96 | 100 | 2.92 | 0.499 | 1.1 | 1.2 |
| | CP-B | 10 | 3.75 | 0.634 | 1.2 | 100 | 3.62 | 0.749 | 1.4 | 1.2 |
| | CP-C | 8 | 4.96 | 0.878 | 1.6 | 100 | 4.81 | 0.959 | 1.8 | 1.1 |
| **AUCinf,u** | Healthy | 6 | 1.98 | 2.24 | | 100 | 1.94 | 1.37 | | |
| | CP-A | 6 | 5.09 | 12.9 | 2.6 | 100 | 3.99 | 2.56 | 2.1 | 0.81 |
| | CP-B | 10 | 19.0 | 9.96 | 9.6 | 100 | 23.0 | 9.63 | 12 | 1.3 |
| | CP-C | 8 | 28.2 | 8.17 | 14 | 100 | 43.5 | 16.7 | 22 | 1.6 |

- Increase in plasma fraction unbound accurately simulated (Ibrutinib mainly albumin bound)

- Extent of exposure increase (AUC) in mild, moderate and severe hepatic impairment accurately simulated (predicted/observed ratio 0.71-1.3)
  - Indicative that reduction in intestinal/hepatic CYP3A abundance in PBPK software is realistic
  - Indicative that extent of portacaval shunting in hepatic impaired subjects is realistically simulated

# Conclusions case example Ibrutinib

1. Ibrutinib approved for MCL indication by FDA in 2013

   - PBPK model verification crucial at 3 levels: input data (compound specific), model structure (model dependent) and physiology parameters (system dependent)

   - PBPK model informed dosing regimen with CYP3A perpetrators based on simulations in fasted subjects and clinical DDI study in fasted subjects with ketoconazole (DDI: 29x Cmax and 24x AUC)

   - Simulations in non-fasted subjects (patients) and lower extent of interaction not referenced in label

   - Simulations for hepatic impairment not used for labelling due to concern on overprediction but used to select the 140 mg ibrutinib dose for the clinical hepatic impairment study

2. Clinical DDI studies with strong or moderate CYP3A inhibitors conducted post approval

   - Verified the dosing recommendations of the initial label in 2013

   - Showed that interaction potential in non-fasted subjects is less pronounced

3. Hepatic impairment simulations not used in 2013 to inform the label due to concerns on overprediction

   - Retrospective analysis based on observed hepatic impairment data shows an overprediction of 1.8-2.9x on ibrutinib $AUC_{(u)}$

   - Based on improvements in virtual hepatic impairment populations, overprediction is largely reduced in current PBPK software package

# Acknowledgements

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- Jan de Jong

- An Van Den Bergh, Marie-emilie Willemin, Christophe Tistaert

- Janssen DMPK *in vitro* lab

- PBPK commercial software science teams

- IQ PBPK Renal and Hepatic Organ impairment working group

- Health Authorities