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PBPK/PD Modeling and Simulations to Guide Dose Recommendation of Amlodipine with Viekirax or Viekira Pak

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Overview

- **Amlodipine is a commonly prescribed anti-hypertensive drug**
  - **Substrate for CYP3A4 and CYP3A5 (only 10% contribution from CYP3A5)**
- **Co-administration with Viekira Pak increases single-dose amlodipine C_{max} to 1.3 fold and AUC to 2.6 fold**
  - **Due to CYP3A4 inhibition by ritonavir (RTV), the PK booster in Viekira Pak**
- **Current recommendation for concomitant use with amlodipine is:**
  - **Viekira Pak USPI: "Decrease the dose of the calcium channel blocker. The dose of amlodipine should be decreased by at least 50%."**
  - **Viekirax SmPC: "Decrease amlodipine dose by 50% and monitor patients for clinical effects"**
  - **Viekirax JPI: "… caution should be exercised, such as use with reduced doses of calcium channel blockers …"**
- **PBPK Modeling was utilized to evaluate dosing adjustments**
  - **Amlodipine PBPK model is not available in the literature**
  - **RTV PBPK model was developed previously in Simcyp® (Shebley et al., Clinical Pharmacology & Therapeutics, 99, S1, 2016)**

Objectives

Model development

- Develop a PBPK model for amlodipine using data from literature
- Quantitatively capture the CYP3A contribution
- Apply “top-down” approach for model optimization:
- Link PBPK model to pharmacodynamic (PD) model to capture effect on systolic BP

Model validation

- Validate amlodipine PBPK model using published clinical data
- Validate model predicted DDI with RTV using clinical DDI data

Model application

- Simulate multiple-dose PK of amlodipine when co-administered with ritonavir-containing Viekira Pak
- Evaluate various amlodipine dosing scenarios after the last dose of Viekira Pak/Viekirax
- Analyze changes in systolic blood pressure due to various dosing strategies using pharmacodynamic (PD) model

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Amlodipine PBPK Model Development

Amlodipine physiochemical properties

Property	Value	References
Molecular weight	408.88	www.drugbank.ca
Fraction unbound in plasma	0.025	Norvasc labeling (Pfizer.com)
logP (n-octanol:water)	2.96	Caron et al., 2004
Solubility (mg/mL)	0.774	McDaid & Deasy, 1996
B:P	0.596	Simcyp® prediction toolbox
pKa (base)	9.1	Caron et al., 2004

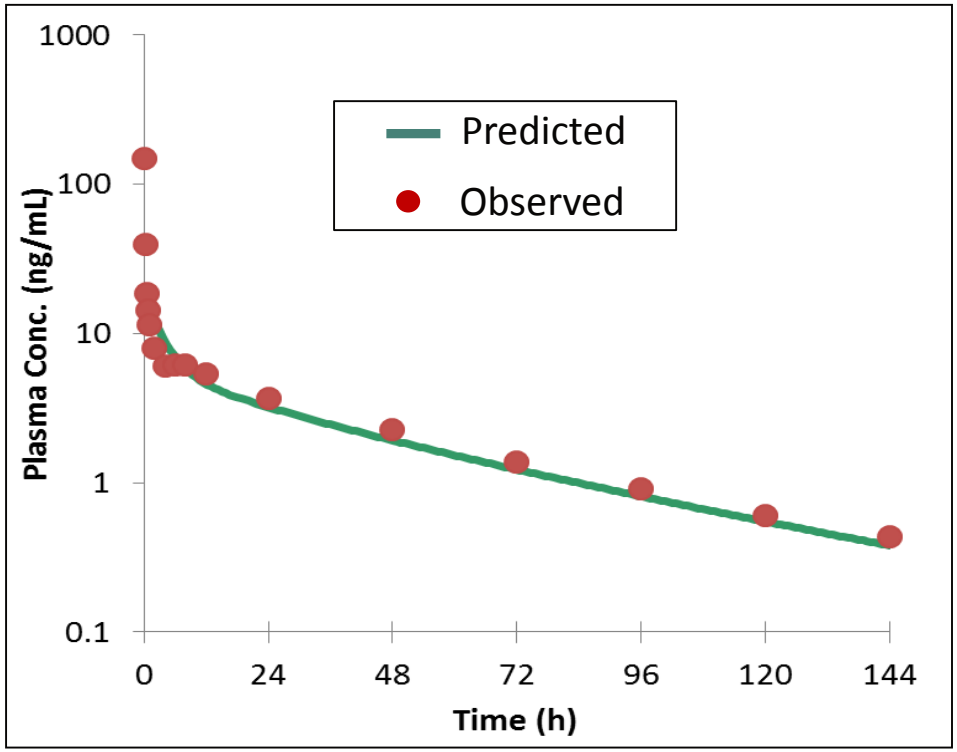
Amlodipine ADME/PK properties

Parameter	Value	Reference
Absorption	1.75×10^{-6} cm/s (Caco2, pH 6.5:7.4)	Rausl et al., 2006
Distribution	V_d (IV) = 21.4 L/kg	Faulkner et al., 1986
	V_{SAC} = 6.38 L/kg; Q_{SAC} = 102 L/h	Park et al., 2012
Metabolism	CYP3A4 (CYP3A5 10%)	Zhu et al., 2013
Elimination	6% renal clearance	Beresford et al., 1988
	33.9 L/h (IV clearance)	Faulkner et al., 1986
	Enterohepatic recirculation	Rausl et al., 2006

Summary of amlodipine clinical PK studies

Study	Population	Results	Source
IV and oral PK study	12 healthy subjects	PK parameters estimated	Faulkner et al., 1986
Renal insufficiency	27 renally impaired subjects	No significant changes	Laher et al., 1988
IV and oral ^{14}C study	2 healthy subjects	6% renal clearance	Beresford et al., 1988
DDI study with Indinavir + RTV	18 healthy HIV-negative subjects	AUC ratio = 1.8 Cmax ratio = 1.77	Glesby et al., 2005
SAD PK study with 2.5 mg, 5 mg, & 10 mg Amlodipine	12 healthy subjects	Time & dose proportional	Williams & Cubeddu, 1988
Food effect study with 10 mg dose of Amlodipine	6 healthy subjects	No food effect observed	Faulkner et al., 1989
DDI study with Viekira Pak	14 healthy subjects	AUC ratio = 2.57 Cmax ratio = 1.36	Menon et al., 2015

Verification of PBPK model for Amlodipine (IV dose)

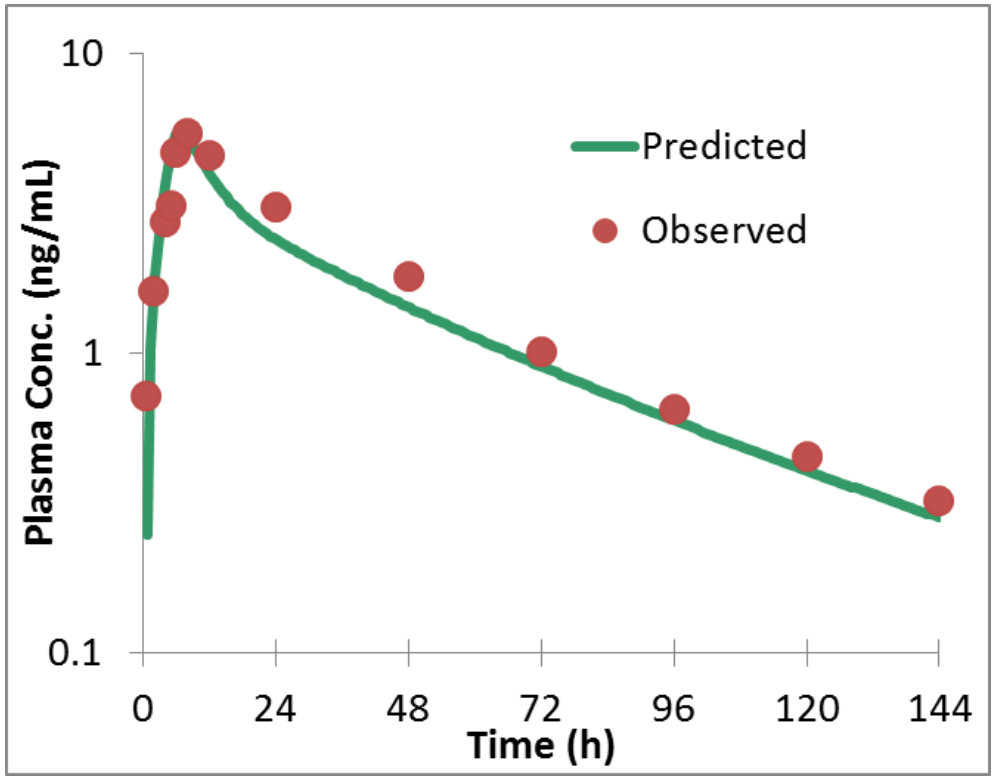


PK parameter	Pred	Obs.	Pred:Obs
AUC_{∞} (ng-h/mL)	319	371	0.86
$t_{1/2}$ (hr)	37.2	33.8	1.1

Simcyp® model predictions of plasma concentration agree reasonably well with clinical data for 10 mg IV infusion

(Clinical data and observed PK parameters from Faulkner et al., 1986; Mean of data from 12 healthy male volunteers)

Model optimization for Amlodipine oral dose

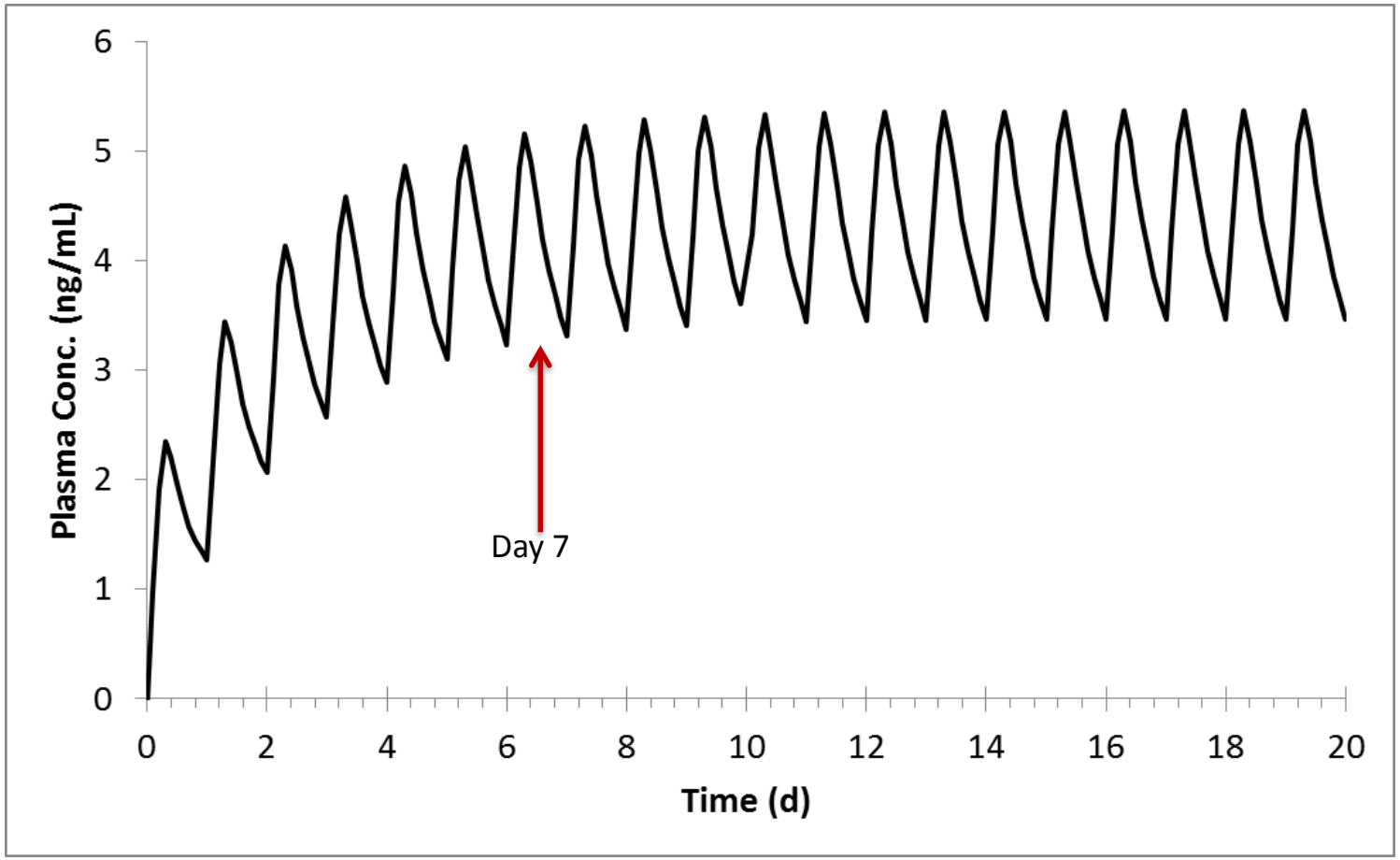


PK parameter	Pred.	Obs.	Pred:Obs
AUC_{∞} (ng-h/mL)	211	238	0.89
C_{max} (ng/mL)	5.5	5.9	0.93
T_{max} (hr)	6.82	7.6	0.9
$t_{1/2}$ (hr)	39.8	35.7	1.12
F	57	64	0.89

Simcyp model predictions of plasma concentration for 10 mg oral dose agree well with clinical data within prediction 12% error

(data points and observed PK parameters from Faulkner et al., 1986 for 12 subjects)

PBPK model simulation of 5 mg daily dosing of Amlodipine



Simcyp model predictions for amlodipine oral dosage of 5 mg QD over 20 days
Model predicted time to reach steady-state is consistent with reported observations (Meredith & Elliott, 1992)

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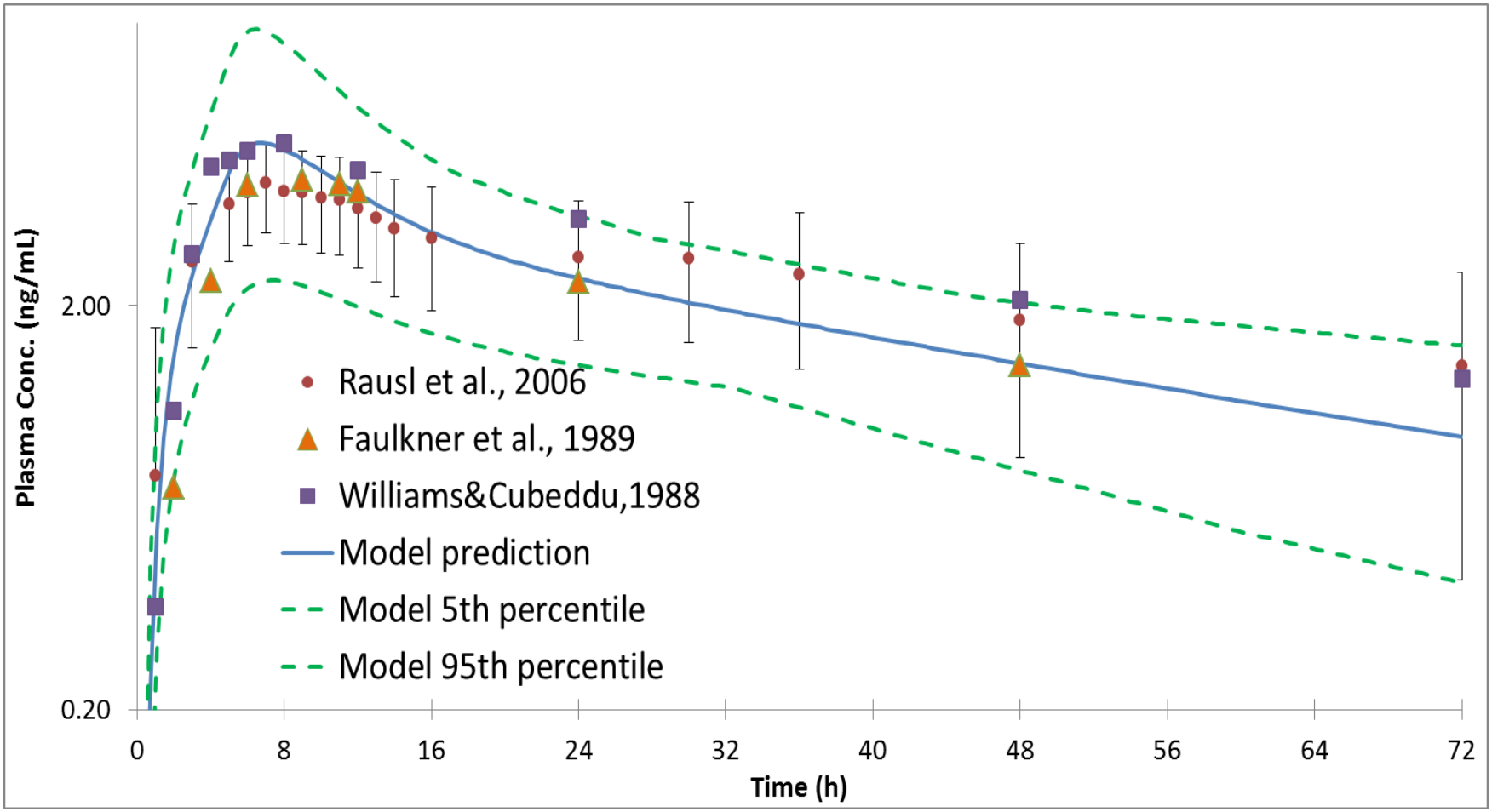
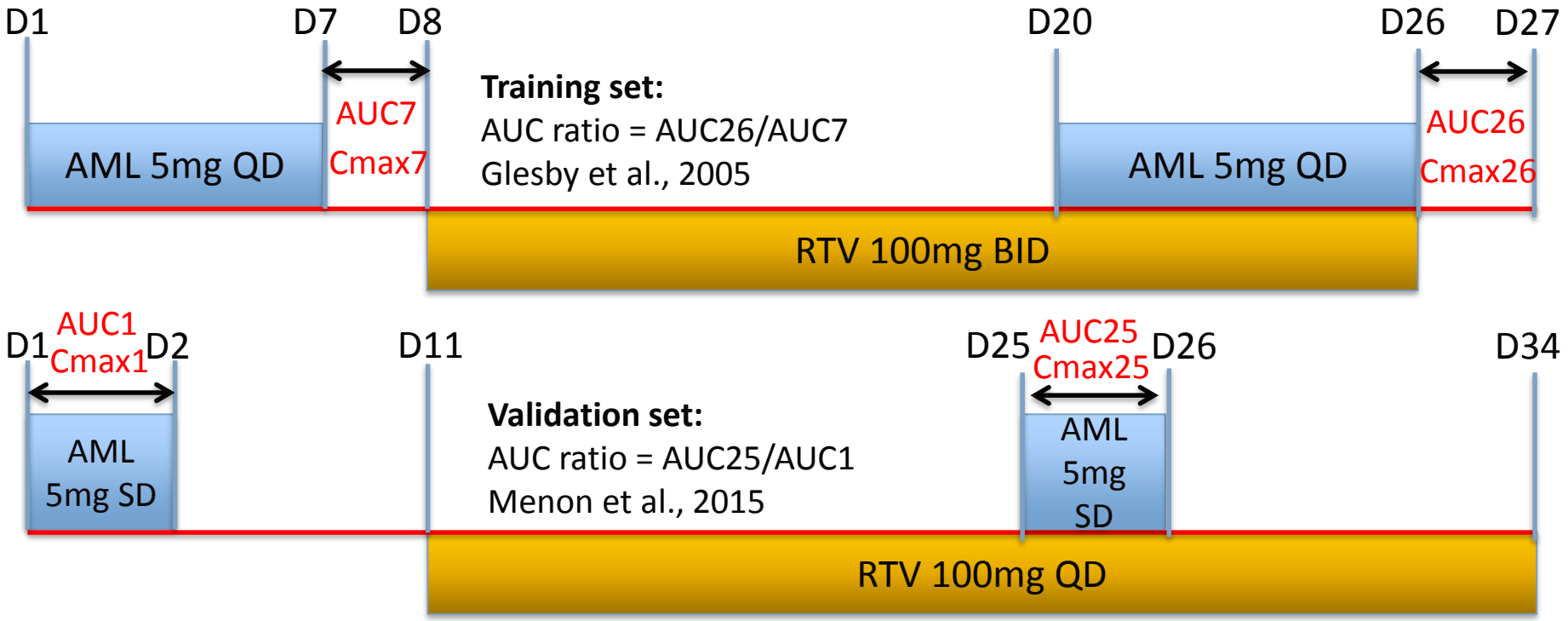
Amlodipine PBPK Model Validation

Model validation across multi-study clinical data



Clinical measurements across multiple studies fall within model predicted 5th and 95th percentile ranges

Clinical DDI studies design of Amlodipine (AML) with Ritonavir (RTV)



AML	Glesby et al., 2005[a]	Simcyp model	Menon et al., 2015[b]	Simcyp model
AUC ratio	1.89 (1.57-2.05)	1.97	2.57 (2.31-2.86)	2.65
C_{max} ratio	1.82 (1.55-2.02)	1.87	1.26 (1.11-1.44)	1.68

a: Indinavir/Ritonavir + Amlodipine
b: Ombitasvir/Paritaprevir/Ritonavir + Amlodipine

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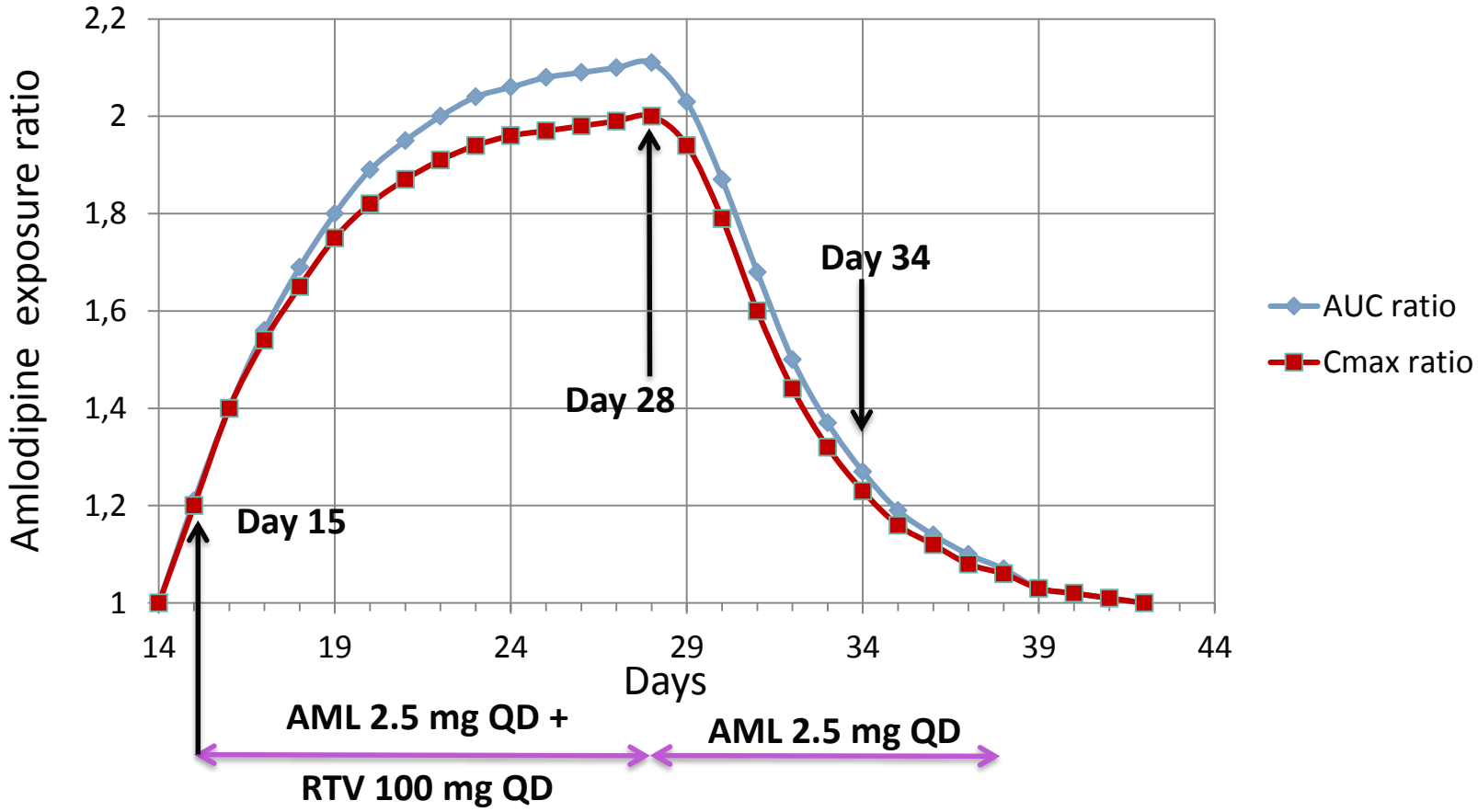
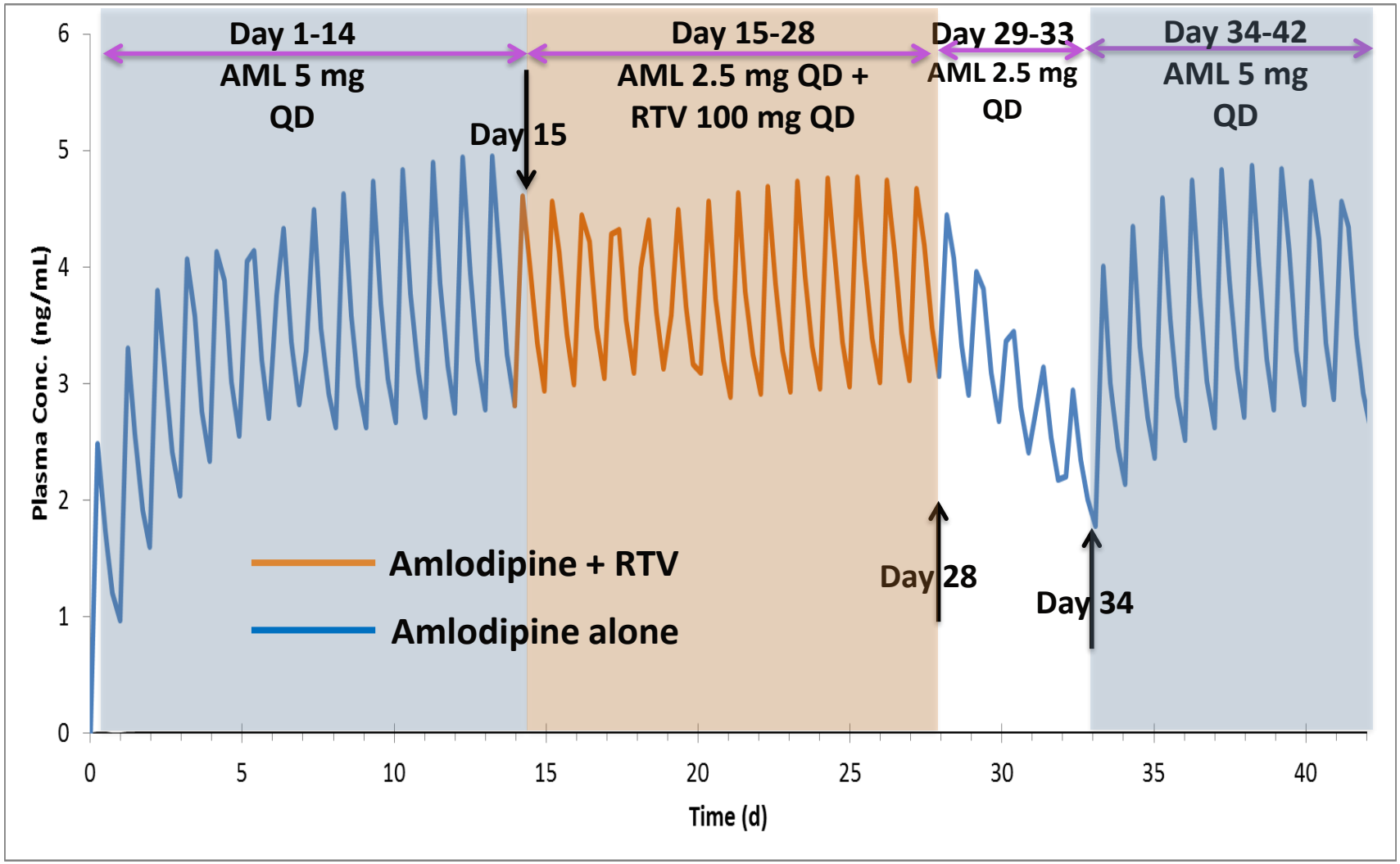
PBPK Model Simulation of Amlodipine with Viekira Pak/Viekirax Co-administration

Ritonavir time-based changes in DDI magnitude

Ritonavir effect on amlodipine exposure decreases to 20% with respect to baseline, 5 days after stopping ritonavir



Amlodipine steady-state PK with Ritonavir



Ritonavir effect on CYP3A4 persists for about 5 days after end of treatment

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Pharmacodynamic model for blood pressure regulation

Two different PD Models were evaluated

LINEAR MODEL

$$SBP = 134 + 4.85(SEX) - 1.22(C_{AVG})$$

SBP = Systolic Blood Pressure (in mmHg)

C_{AVG} = Average plasma conc. of AML (ng/mL)

SEX = 1 for males and 0 for females

FDA Clin. Pharm. Review, Norvasc, April 2002

NON-LINEAR MODEL

$$SBP = SBP_0 + mC\exp(-k_{eo}\ t)$$

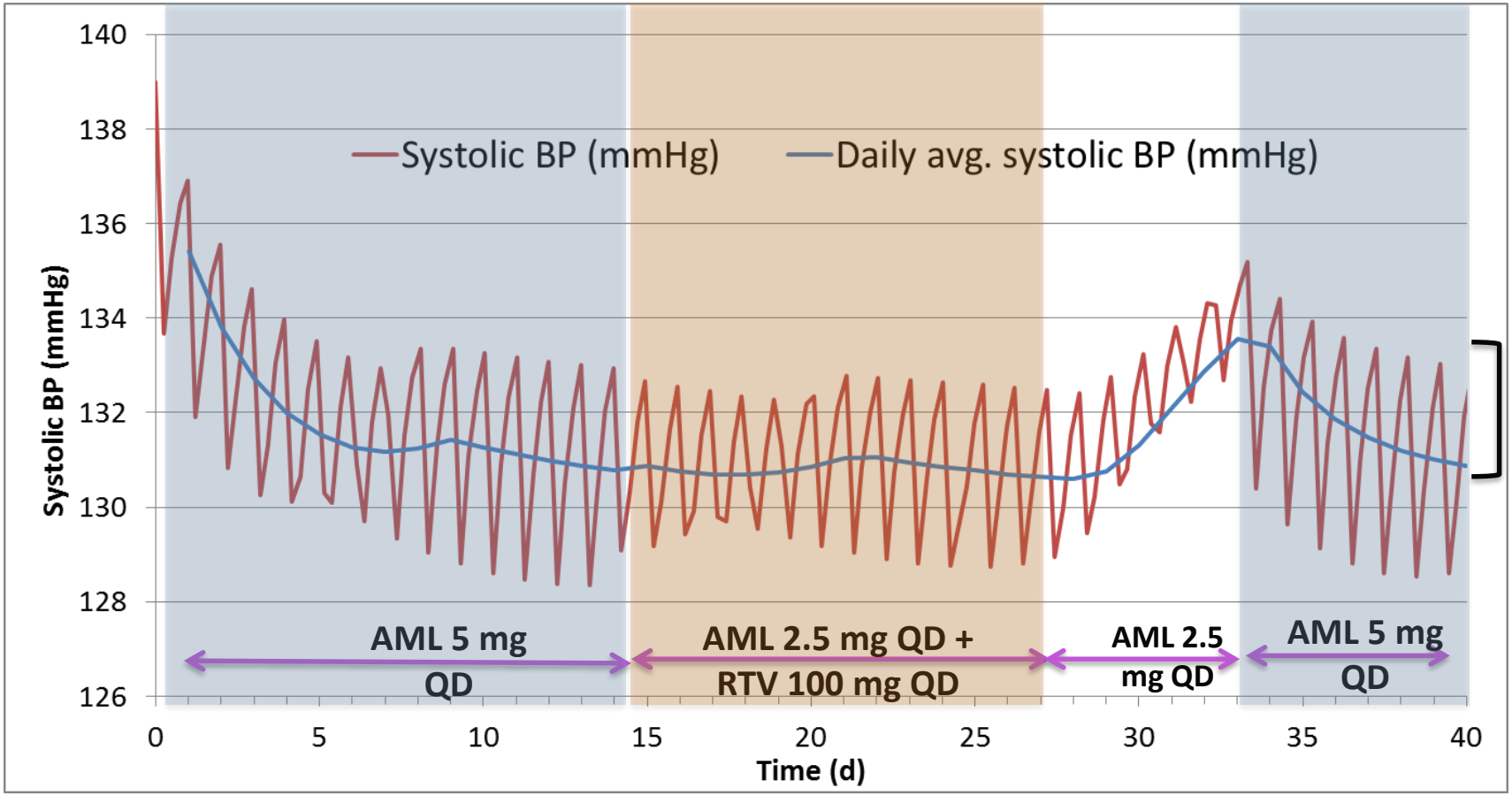
SBP = Systolic Blood Pressure (in mmHg)

C = Plasma conc. of AML (ng/mL)

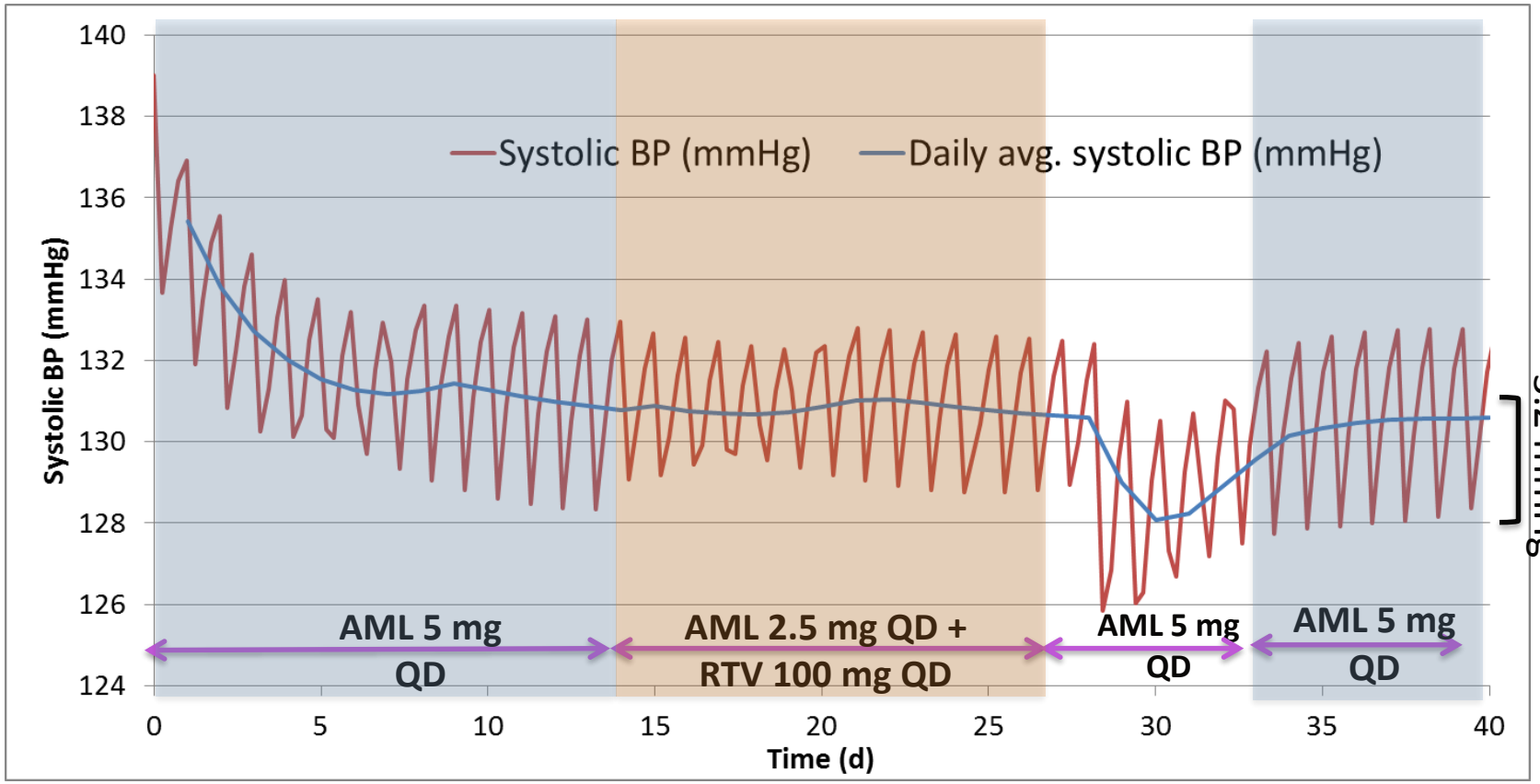
k_{eo} = elimination rate constant from effect compartment

Donnelly et al., Clin. Pharm. Therap. 1993

Amlodipine dose adjustment for 5 days post RTV stoppage



Amlodipine dose adjustment for 5 days post RTV stoppage



Switching back to the pre-ritonavir dose (5 mg) or keeping the dose at 2.5 mg for 5 days result in changes of about 3 mmHg in average systolic BP

SUMMARY

New PBPK model was developed for amlodipine oral dosage

- Incorporating CYP3A metabolism, parameters from literature
- Optimized and validated using published clinical DDI studies

Amlodipine oral dosage was simulated at steady-state along with Ritonavir co-administration

- Published RTV PBPK model was utilized, including CYP3A4 & CYP3A5 inhibition
- RTV effects on steady state amlodipine exposure was simulated

Amlodipine pharmacodynamics was modeled using previously published PK-PD relationship of AML exposure with systolic blood pressure

- Two different dose reduction schemes were analyzed for concomitant dosage of Viekira Pak and Amlodipine
- Based on the simulated effect on systolic BP, amlodipine at 50% reduced dose may be continued for 5 days after RTV is stopped, followed by a return to the full dose. Alternatively, the full dose of amlodipine may resume immediately the day after last dose of RTV