Formulation-dependent Pediatric Physiologically based pharmacokinetic (PPBPK) modeling to aid drug development

Wen Lin, Tycho Heimbach, Handan He

DMPK, Novartis Institutes of Biological Research

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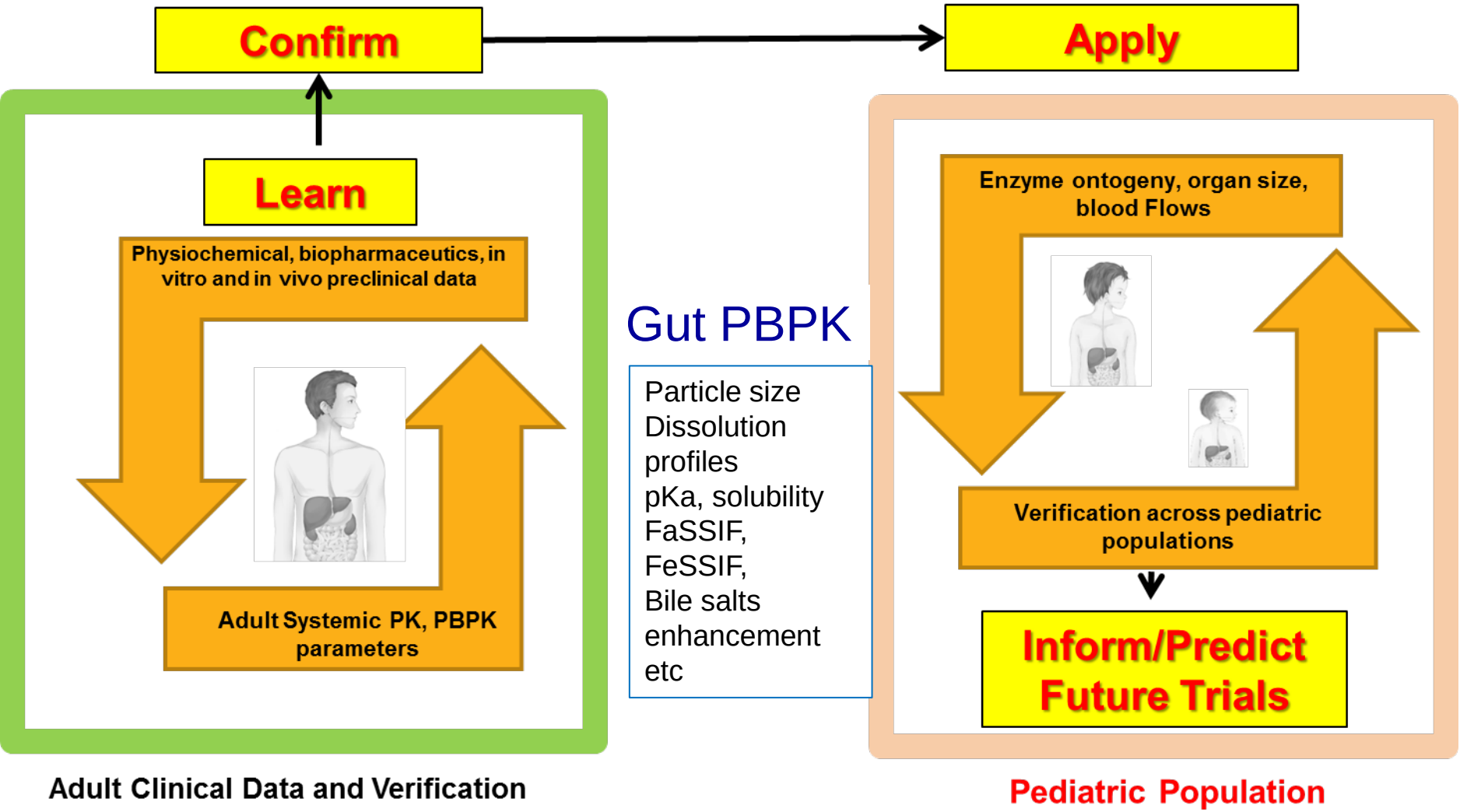
Outline

- Introduction
  - Formulation-dependent Pediatric Physiologically based pharmacokinetic (PPBPK) modeling
  - Common Challenges in PPBPK modeling
- Applied, Practical formulation-dependent pediatric PBPK Modeling
  - Case example 1: BCS IV drug
  - Case example 2: BCS II drug
- Summary/Recommendations

Workflow for formulation-dependent pediatric PBPK model

With adult human PK data



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Common Challenges in Pediatric PBPK modeling

Modeling tools: Simcyp® Paediatric Module, GastroPlus®

- Absorption: formulation dependent
  - Age and meal type affect gastric emptying (GE) time in premature neonates, full-term neonates, infants and children? (Bonner J, et al, 2015)
    - Age was not but meal type was
    - GE by aqueous solution: 48 min; GE by solid food: 98 min
  - Bile salt concentrations in premature neonates, full-term neonates, infants and children
    - For BCS II and IV compounds, age may impact bile salt enhancement on solubility and in vivo dissolution
    - Food effect in neonates and young infants
- Elimination
  - In vivo ontogeny profiles for drug metabolizing enzymes: UGTs, Carboxylesterase, etc
  - Much less is known about the ontogeny of transporters (BCS III and IV drugs)

Increased systemic exposures of artemether in infants < 5 kg with uncomplicated Plasmodium falciparum malaria treated with artemether-lumefantrine (Coartem®). Tiono AB, et al. Malar J 14:157.

Table 5 Pharmacokinetic exposure of artemether, dihydroartemisinin, and lumefantrine: comparison with historical data from older infants and children

Time point post-first dose	Current study		Historical data	
	Mean ± SD (CV %) [n]	Range	Mean ± SD (CV %) [n]	Range
	Artemether concentration (ng/mL)			
1 h	446 ± 321 (72%) [15]	19.7-1210	139 ± 160 (116%) [173]	0-932
2 h	380 ± 262 (68%) [18]	0-933	140 ± 122 (87%) [170]	0-776
	Dihydroartemisinin concentration (ng/mL)			
1 h	87.6 ± 58.9 (67%) [15]	7.2-202	46.0 ± 54.2 (118%) [177]	0-345
2 h	93.4 ± 67.0 (72%) [18]	0-252	57.4 ± 57.5 (100%) [178]	0-429
	Lumefantrine concentration (µg/mL)			
30 h	No sample taken		5.29 ± 4.28 (81%) [63]	0-23.7
54 h	6.50 ± 3.37 (52%) [17]	0.819-12.5	5.84 ± 4.28 (73%) [62]	0.524-21.4
66 h	6.04 ± 2.77 (45%) [17]	2.27-12.8	6.98 ± 5.29 (76%) [323]	0.069-42.0
84 h	3.40 ± 2.28 (67%) [17]	1.16-8.72	3.02 ± 2.08 (69%) [49]	0.010-7.80
168 h (Day 7)	0.815 ± 0.567 (70%) [16]	0.200-2.39	0.386 ± 0.326 (84%) [63]	0-1.71
336 h	No sample taken		0.541 ± 2.13 (394%) [65]	0-12.2

CV, coefficient of variation; h, hour; SD, standard deviation.

Coartem tablets are indicated for treatment of acute, uncomplicated malaria in patients of 5 kg and above

dispersible tablet (20 mg artemether/120 mg lumefantrine) following a regimen of one dispersible tablet twice daily for 3 days. The consumption of food or drink (mother's or formula milk) was recommended after dose to enhance lumefantrine absorption.

- **Lumefantrine**: Similar exposure in infants < 5 kg (< 3 months) as compared to infants > 5 kg

Artemether: 2-3 fold higher exposure in infants < 5 kg (< 3 months) as compared to infants > 5 kg

Physicochemical and Biopharmaceutical Properties of Lumefantrine

- MW 528.95
- Log P: 8.5 (G+ prediction)
- pKa: 8.3 (G+ prediction)

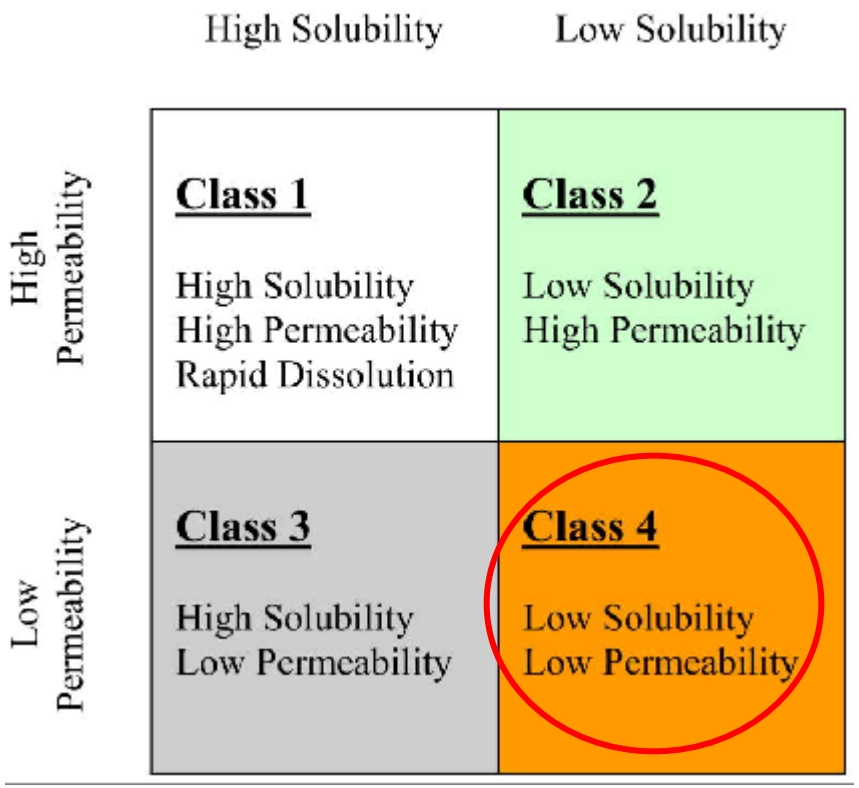
Solubility – Low

Medium	Solubility (mg/mL)
Fassif	<0.005
Fessif	< 0.05
0.1 N HCL	<0.1
water	<0.00005

Permeability – Low

- Caco2 Permeability : Low
- PAMPA Permeability : Low

- Delayed Tmax, long T1/2
- 16 fold food effect observed in HVs; F< 10% under fasting condition



➢ Lumefantrine can be categorized to pBCS IV (poor permeability, low solubility)

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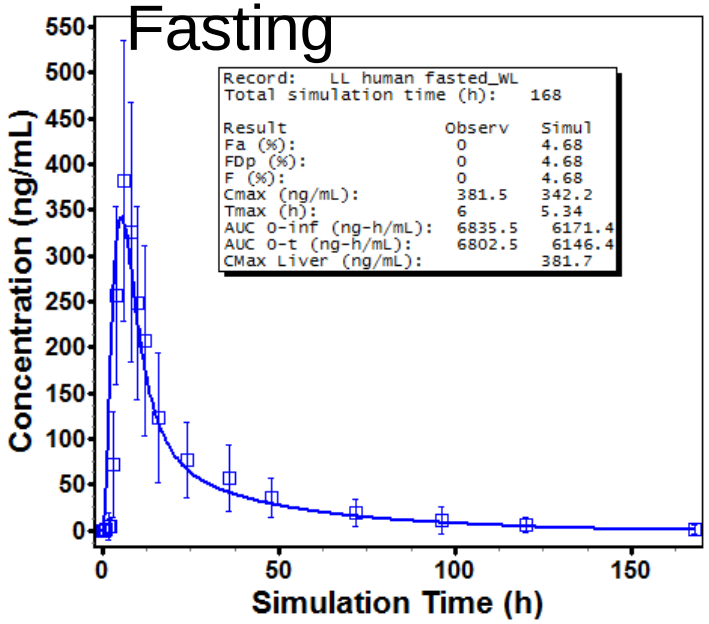
Adult ACAT model can well simulate ~16 fold positive food effect (FDA meal) in HVs

Formulation parameters included in the ACAT model

White *et al*. 1999

Fasting



Fed

- Model correctly predicted ~ 16 folds higher AUC
- Prediction error for Cmax and AUC < 20%
- Predicted vs. Observed Rsq = 0.9

PK parameters determined from IV study

Bile salt enhancement on solubility considered

Particle size, IR dissolution profile incorporated

Patients can't take Coartem with FDA meal

- Adult patients took minimal food to standard food
- Pediatric patients were recommended to consume some food (e.g. pancake) or drink (eg, breastmilk, broth, or sweetened condensed milk) (Abdulla S, et al 2008)

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Soya milk increases Lumefantrine exposure in HVs

Ashley et al, Tropical Medicine and International Health, 2007

- A single Lumefantrine dose, given with 0, 10, 40, 150, 500 mL of soya milk, corresponding to 0, 0.32, 1.28, 4.8 and 16 g fat, respectively
- Lumefantrine exposure increased up to ~ 6 fold by 500 mL Soya milk

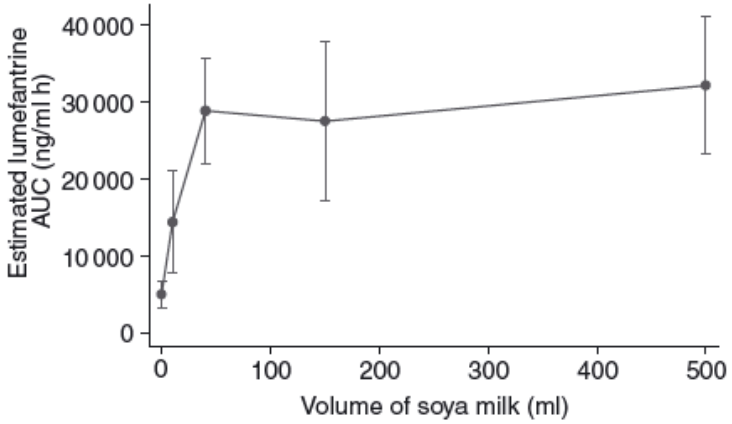

Figure 1 Relationship between estimated AUC and volume of milk taken; dots represent mean and bars represent 95% CI around mean.

- Bile salt concentrations in small intestine segments in Lumefantrine ACAT model modified
- 10 mL Soya milk/ACAT model predicted ~2 fold higher Lumefantrine AUC than fasting condition, comparable to the observed food effect

Compartment	Bile Salt (mM)
Stomach	0.0
Duodenum	7.000
Jejunum 1	6.000
Jejunum 2	5.000
Ileum 1	4.000
Ileum 2	2.000
Ileum 3	0.420
Caecum	0.0
Asc Colon	0.0

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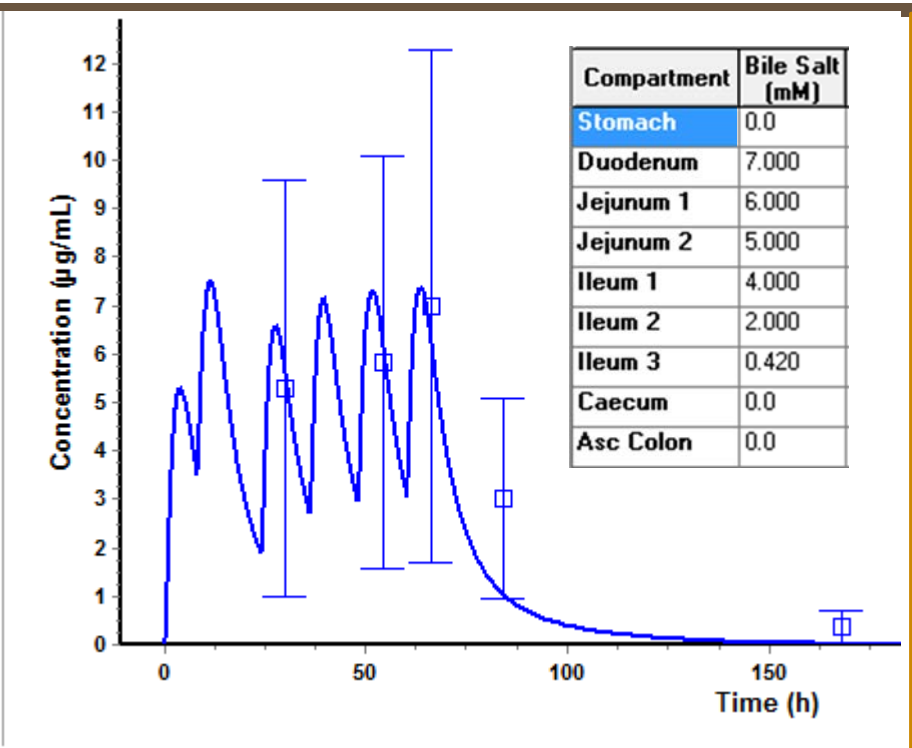
10 mL Soya milk/ACAT model can describe the Concentration-Time profile for Lumefantrine in infants with body weight = 5 -15 kg (> 3 months)



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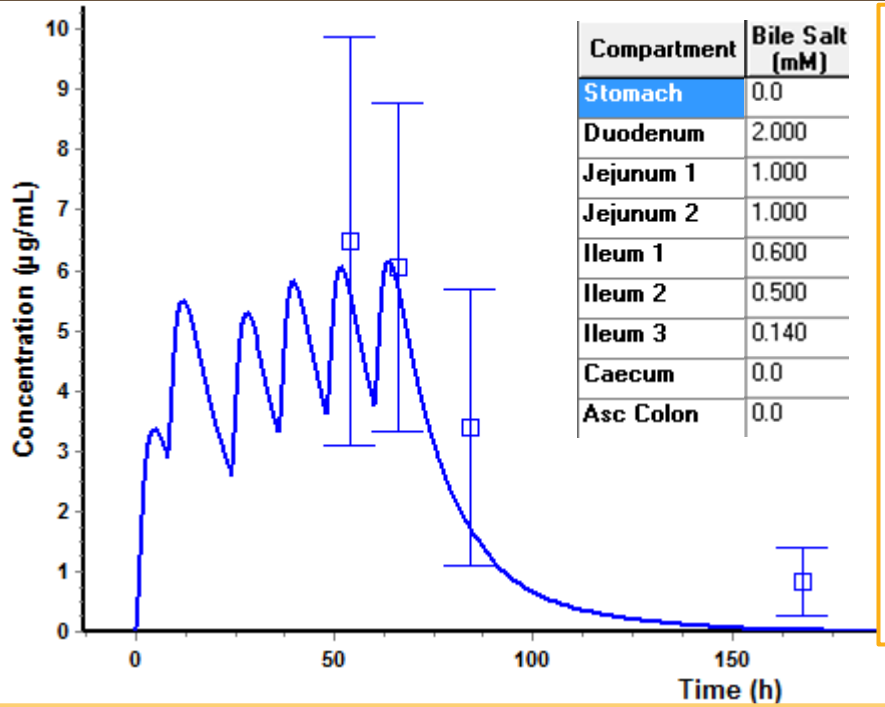
Ileum 2	2.000
Ileum 3	0.420
Caecum	0.0
Asc Colon	0.0

- Japanese female children population > 3 months
- in Gastroplus®
- 10 mL Soya milk/ACAT model
- GI transit time shortened
- Suspension formulation
- Pediatric PBPK model estimated CL
  - Ontogeny of CYP3A4 considered

- ACAT model predicted ~35% F in infants > 5 kg
- Japanese female infant/children population model selected: body weight similar to the tested patients from Africa
- Particle size changed: suspension (smaller particle size) not tablets

Neonates ACAT model could describe Lumefantrine PK profile in Infants (< 3 month) body weight < 5 kg

2 mM bile salts conc. in duodenum



Compartment	Bile Salt (mM)
Stomach	0.0
Duodenum	2.000
Jejunum 1	1.000
Jejunum 2	1.000
Ileum 1	0.600
Ileum 2	0.500
Ileum 3	0.140
Caecum	0.0
Asc Colon	0.0

- In neonates, the bile acid concentrations after a meal were about that required for the formation of micellar solutions and solubilization of fat (i.e. 2 mmol/L). Murphy and Singer, 1974
- CL in 1-3 months old infants estimated by PBPK model

- ACAT model predicted F < 10% in infants < 5 kg
- Simcyp pediatric model predicted ~3 fold lower CL in < 3 months old infants than > 3 month old infants
- ~3 folds lower absorption and ~ 3 fold lower CL in < 3 months old infants brought about the comparable Lumefantrine exposure to that in > 3 months old infants

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Physicochemical Properties of artemether

- MW 298
- Log P: ~3 (G+ prediction)
- pKa: None (neutral)

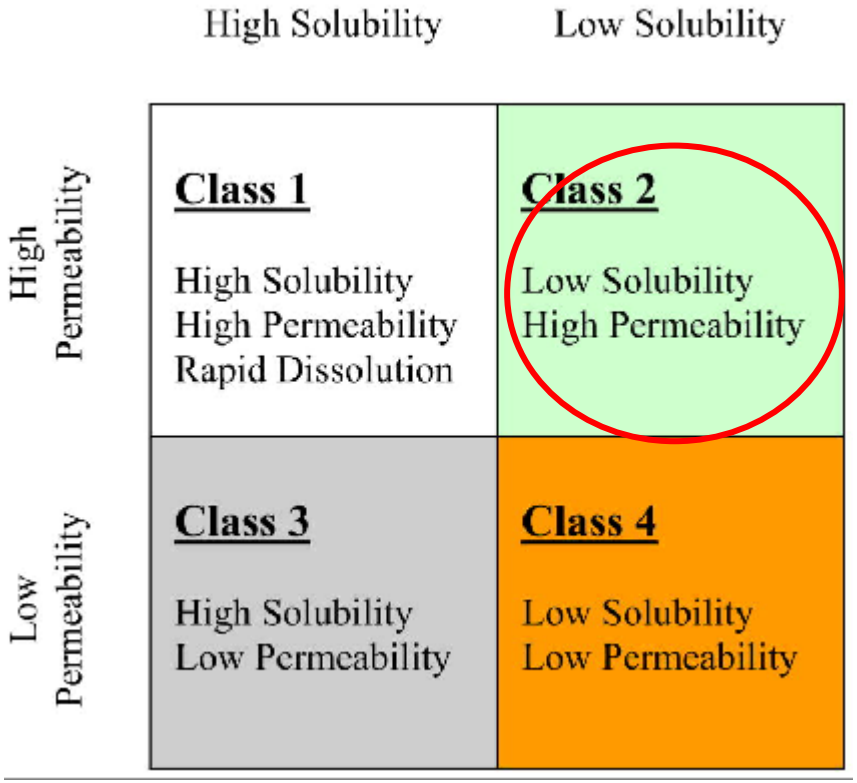
Solubility – Low

0.09 mg/mL (G+ prediction)

Permeability – high

- Caco2 Permeability : high
- PAMPA Permeability : high

~2 folds food effect observed in HVs



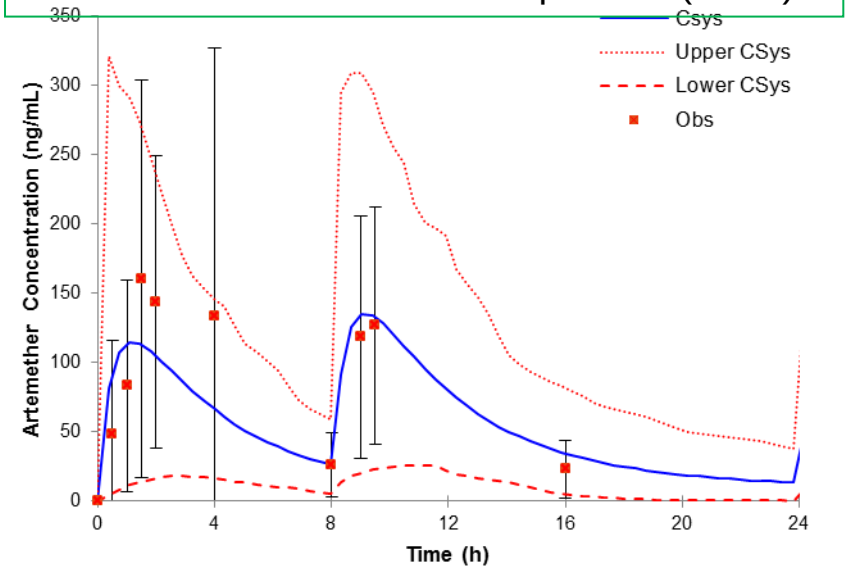
➢ Artemether can be categorized to pBCS II (poor permeability, low solubility)

➢ At low dose, artemether can be categorized to pBCS I. Clinical dose is 80 mg artemether in adult patients

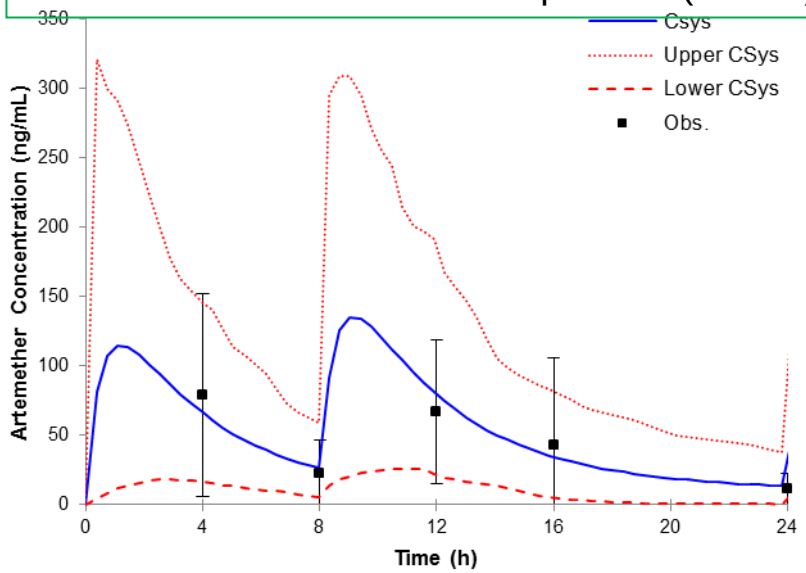
Simcyp adult PBPK model for artemether can well simulate the observed PK profile in adult patients

First-order absorption; minimal PBPK

Model construction: Observed artemether concentrations in adult malaria patients (N=12)

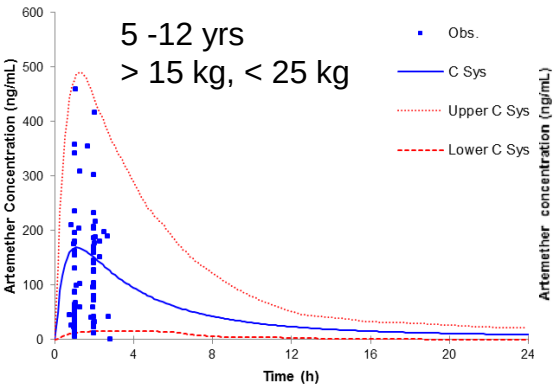


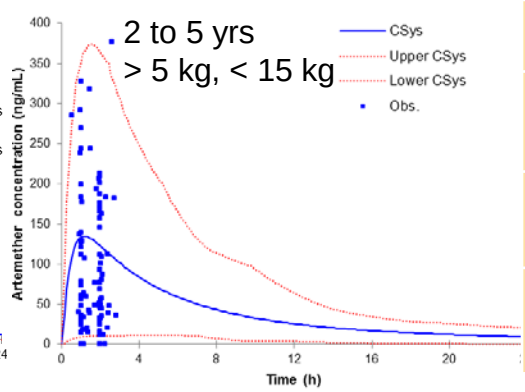
Model qualification: Observed artemether concentrations in adult malaria patients (N=218)



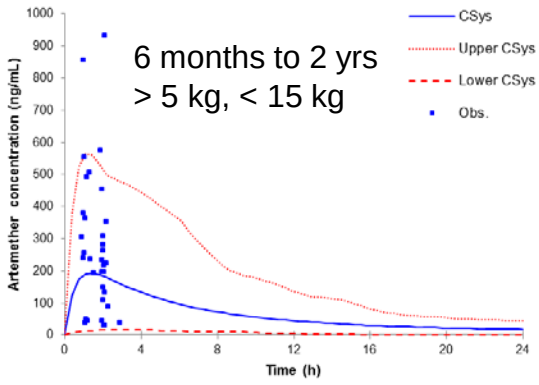
- Artemether PK: absorbed rapidly, Tmax ~ 2 h; significant first-pass effect
- 2 fold food effect with FDA meal in HVS: higher artemether Cmax in patients (minimal to standard food taken)
- PK parameters derived from the patients PK data
- Absorption for 80 mg artemether was estimated 100% by ACAT model in GastroPlus®

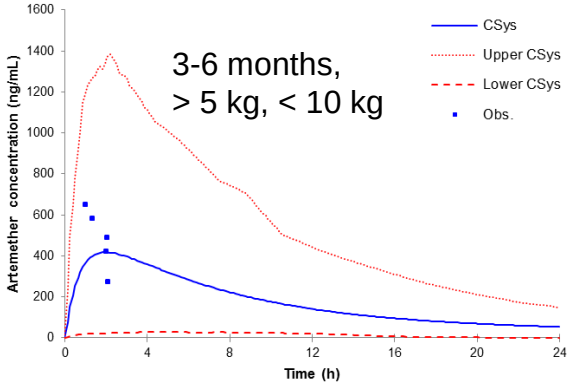
Simcyp Pediatric PBPK Model described well the concentration profiles for artemether in infants/children (1 month to 12 yrs): first-order absorption model

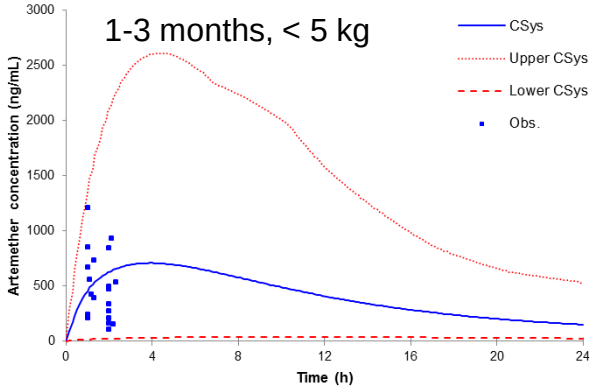




20 mg artemether	Cmax, ng/mL	AUC, ng·h/mL
3 to 6 months (≥5 to <10 kg)	453 [572 ± 81.3]	4303
1 to 3 months (≥5 to <10 kg)	714	7246
1 to 3 months (<5 kg)	755 [621 ± 299]	9828







- Exposure increased significantly in infants due to immature enzymes (1-3 mon. olds *vs.* 3-6 mon. olds) and lower body weight (> 5 kg *vs.* < 5 kg in 1-3 mon. olds)
- Mechanistic PBPK model can reliably simulate observed artemether PK in infant, children and adult

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Summary/Recommendation

- BCS II and IV drugs: food and bile salt may affect drug absorption in neonates and young infants.
  - Mechanism-based absorption mode required: ACAT in GastroPlus® or ADAM in Simcyp®
  - Maximize the food effect PK data in adult population to inform the pediatric absorption model
- BCS I drug: first-pass absorption model (ka) from adults to children
- BCS III drug
  - Negative food effect observed in adults, it may occur in neonates and young infants
  - Juvenile animal study to inform the absorption prediction in infants and children