UF College of Pharmacy
UNIVERSITY of FLORIDA

Application of a PBPK model to support dose selection in special populations - Bilastine as a case example

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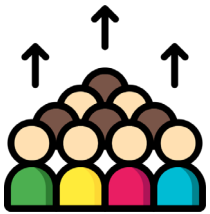
Global perspective population aging

727 M persons 65 years or over in **2020**

65 years or over is expected to increase from **9.3 %** in **2020** to around **16.0 %** in **2050**

Projected # of older persons worldwide over **1.5 B** in **2050**



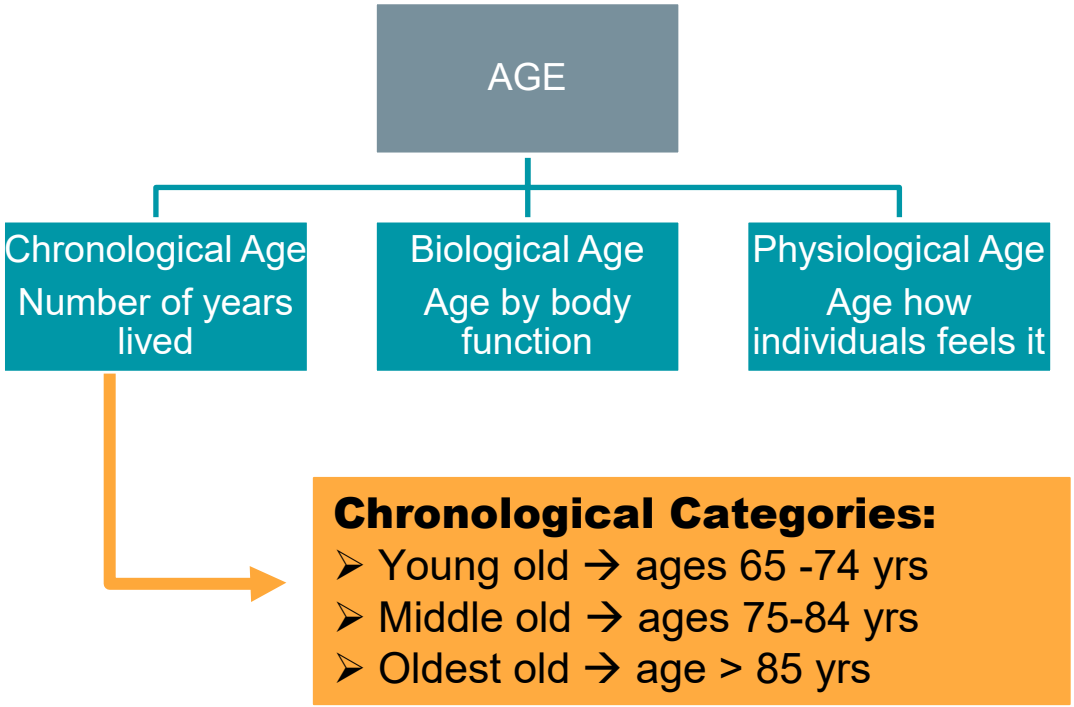
Unprecedented pressure on the healthcare systems!

What can we do?

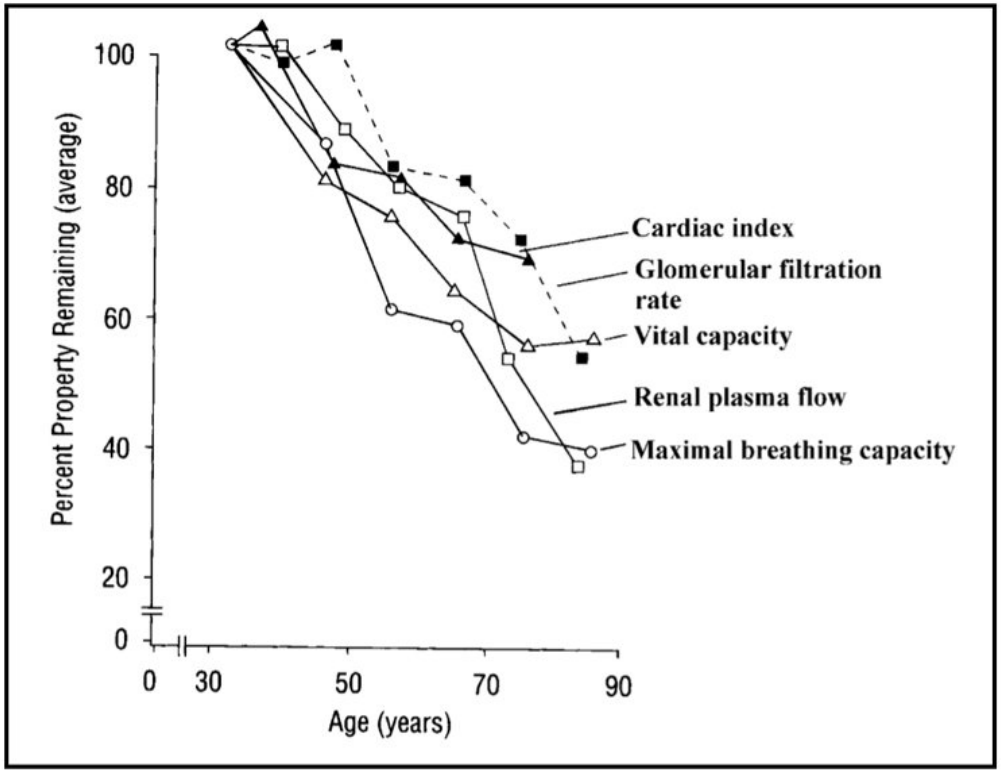
Science of aging
Effect of aging on PK/PD

United Nations Department of Economic and Social Affairs, Population Division (2020). World Population Ageing 2020 Highlights: Living arrangements of older persons (ST/ESA/SER.A/451).

Age clasification older adults

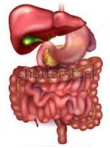


Physiological functions and age



Rowland & Tozer, 1995

Effect of physiological changes on PK processes in the elderly



Absorption

-Increase gastric pH

- Delayed gastric emptying

- Decreased splanchnic blood flow

- Decreased intestinal motility

- First pass effect usually reduced

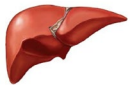
Metabolism

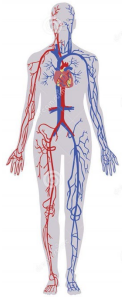
- Decreased liver mass

Decreased hepatic blow flow

Decreased Phase I oxidative metabolism

- Unaltered phase II metabolism (Conjugation & Acetylation)





Distribution

- Increased body fat

- Decreased TBW

Decreased serum albumin

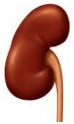
Increased α1-glycoprotein

Renal Elimination

- Decreased creatinine clearance

- Decreased GFR

- Decreased tubular filtration



Challenges in drug development for older adults

Need of dedicated formulations

Possible dose adjustments needed due to PK/PD/response/AE changes in older adults

Possible dose adjustments needed due to DDI

Possible dose adjustments needed due to comorbities/D-disease interactions

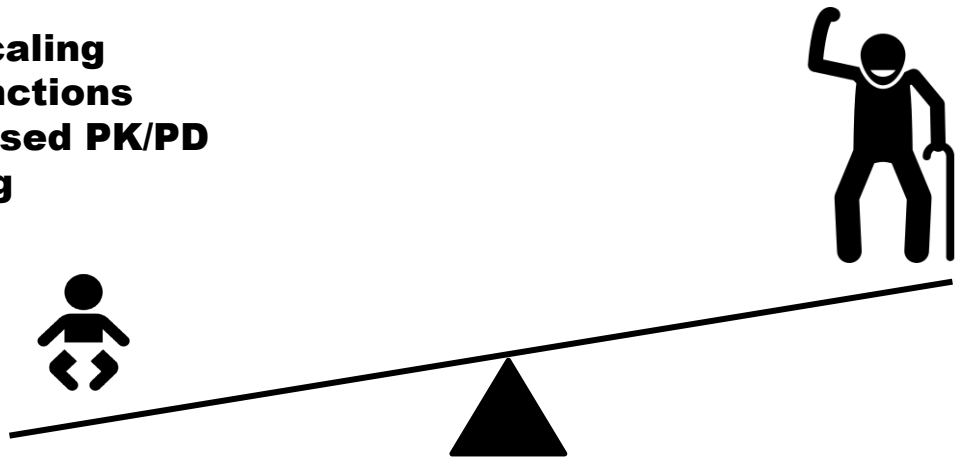
Heterogenous population

Under-representation in CT

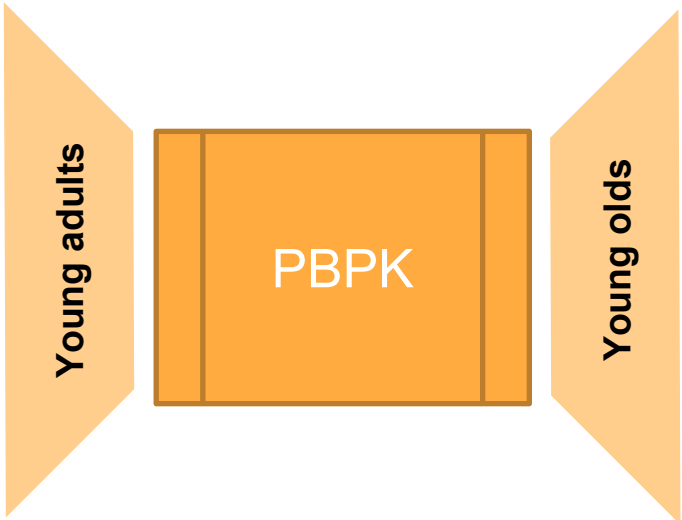
Pediatric vs Geriatrics Pharmacology

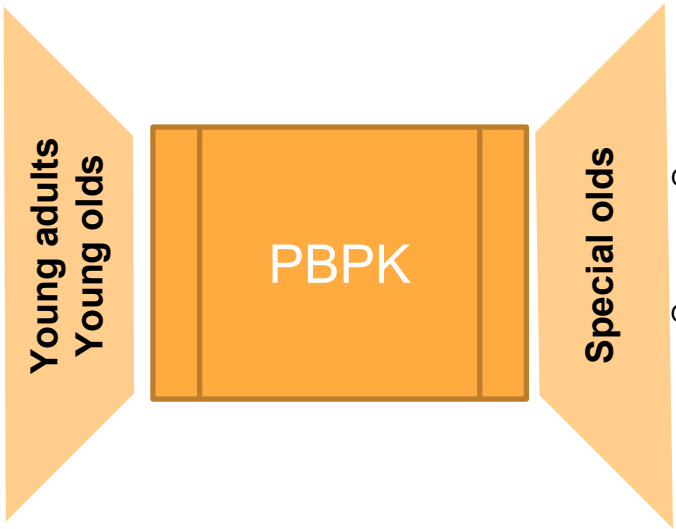
Aging functions??
Physiologically based PK/PD modeling

Allometric scaling
Maturation functions
Physiologically based PK/PD modeling



PBPK modeling can support DD for older adults





Identical twins

Geriatrics with comorbidity1

Geriatrics with comorbidity2

Geriatrics with comedication1

Geriatrics with comorbidity 1+ comedication2

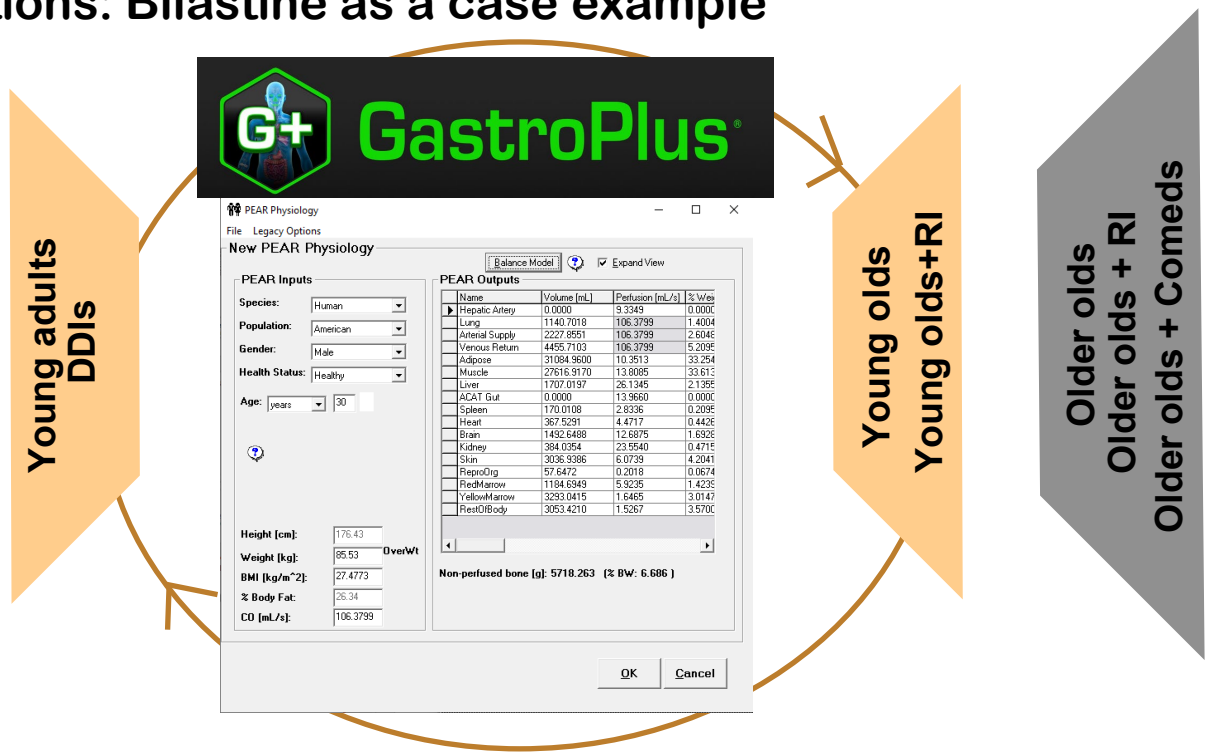
...

Generate information to support dosing information in under-studied groups in CT

Unrealistic to study all possible scenarios in CT

Bilastine case example

Application of a PBPK model to support dose selection in special populations: Bilastine as a case example



Background

Bilastine is an **antihistamine drug** used world widely

Bilastine

Non-sedating **antihistamine drug**

Using in more than **200 countries**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pmda

Dosing info

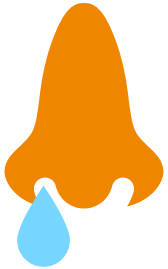
20mg QD

Adults

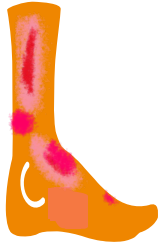
10mg QD

Children

Indications



Allergic rhinitis



Chronic urticaria

Background

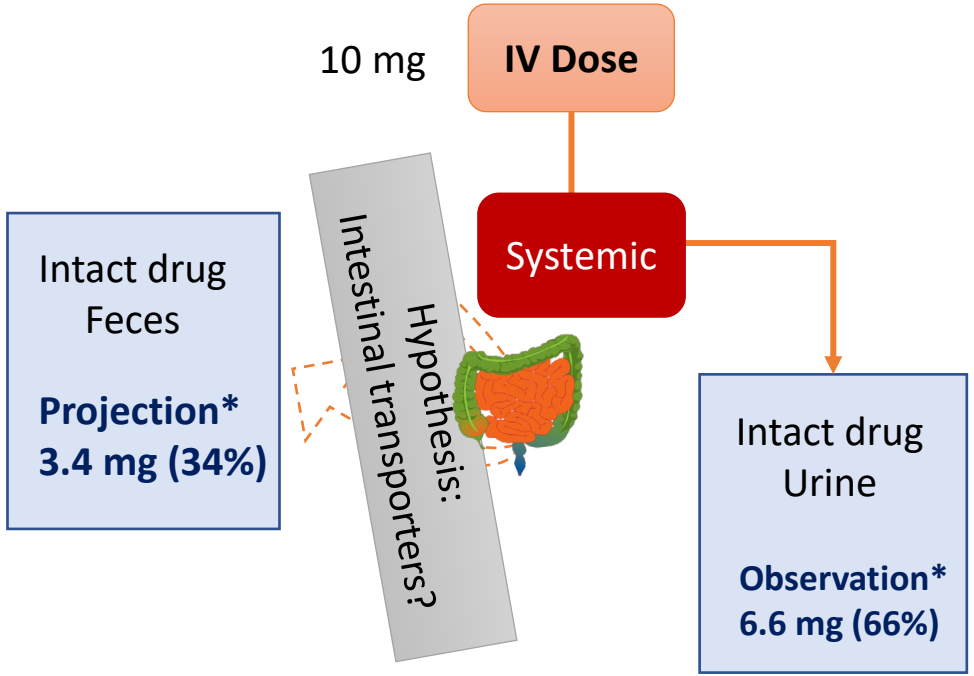
Bilastine shows **unique pharmacokinetic (PK)** properties

Absorption & Distribution

- Known interaction with P-gp
- Less likely to cross blood brain barrier → less sedation

Metabolism & Elimination

- Not significantly metabolized → excreted unchanged form
- No accumulation
- Neither hepatic enzyme inducer nor inhibitor

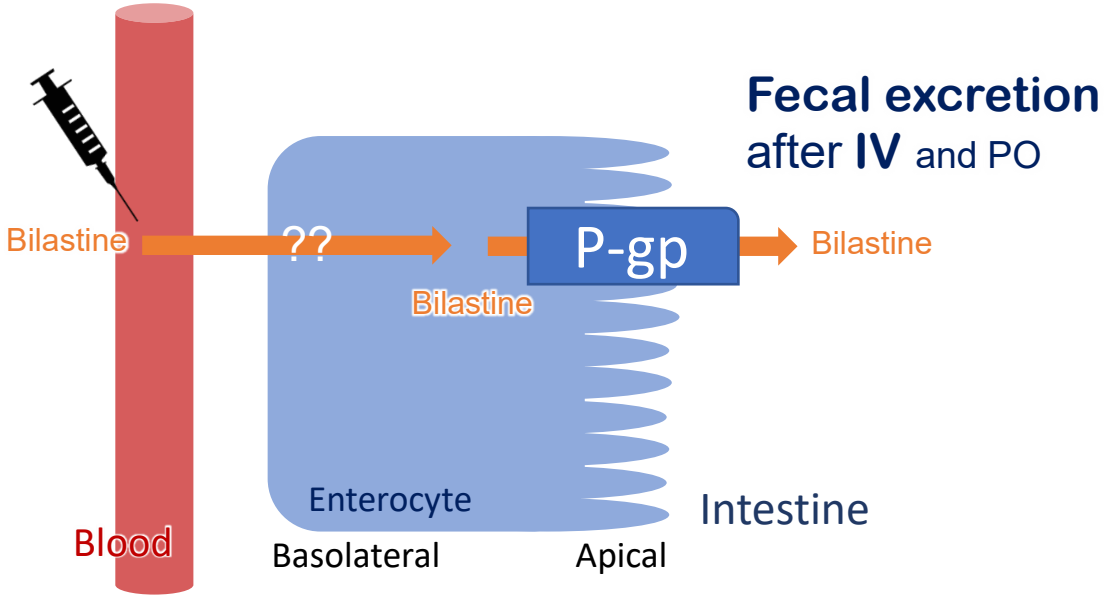


* Oral bioavailability study : urine excretion collected

Sadaba et al. Clin Drug Investig 2013; 33:375-381
Kim and Lo Re et al. CPT PSP 2021; 10(9):1006-1017

Unmet need

Insufficient mechanistical understanding of **intestinal transporter's role on bilastine's PK**

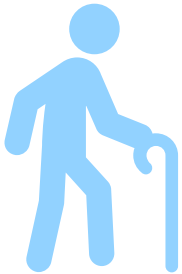


Need to evaluate the impact of **intestinal transporters** on **bilastine's pharmacokinetics**

Unmet need

What is an **appropriate dose** for **geriatrics?**

Why important?



Geriatrics

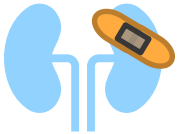
Non-sedating feature and **reduced risk of DDI** may be more **beneficial/appealing** to geriatrics

Challenges

Under-represented in **clinical trials**

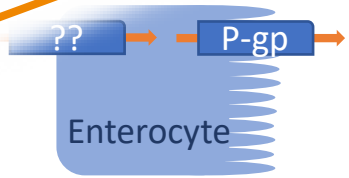
data

Hard to use conventional PopPK approach



co-morbidities

co-medications

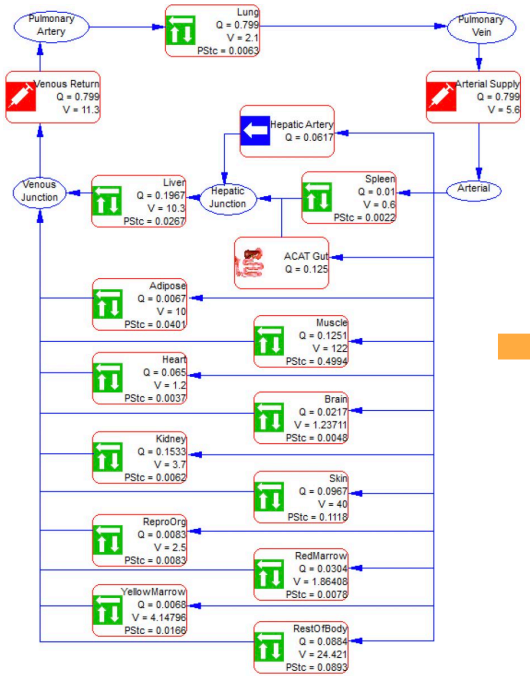


Insufficient mechanistical **understanding of transporter**'s role **on PK**

How to solve

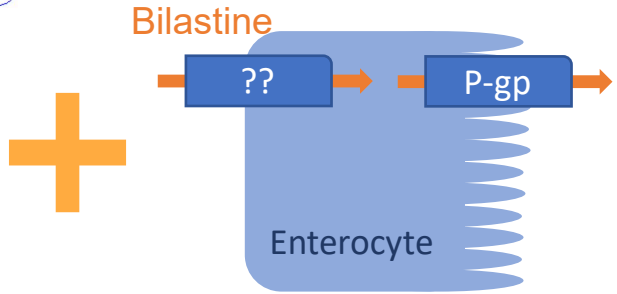
Developing full PBPK model considering intestinal transporters

Full PBPK



Software: GastroPlus 9.6

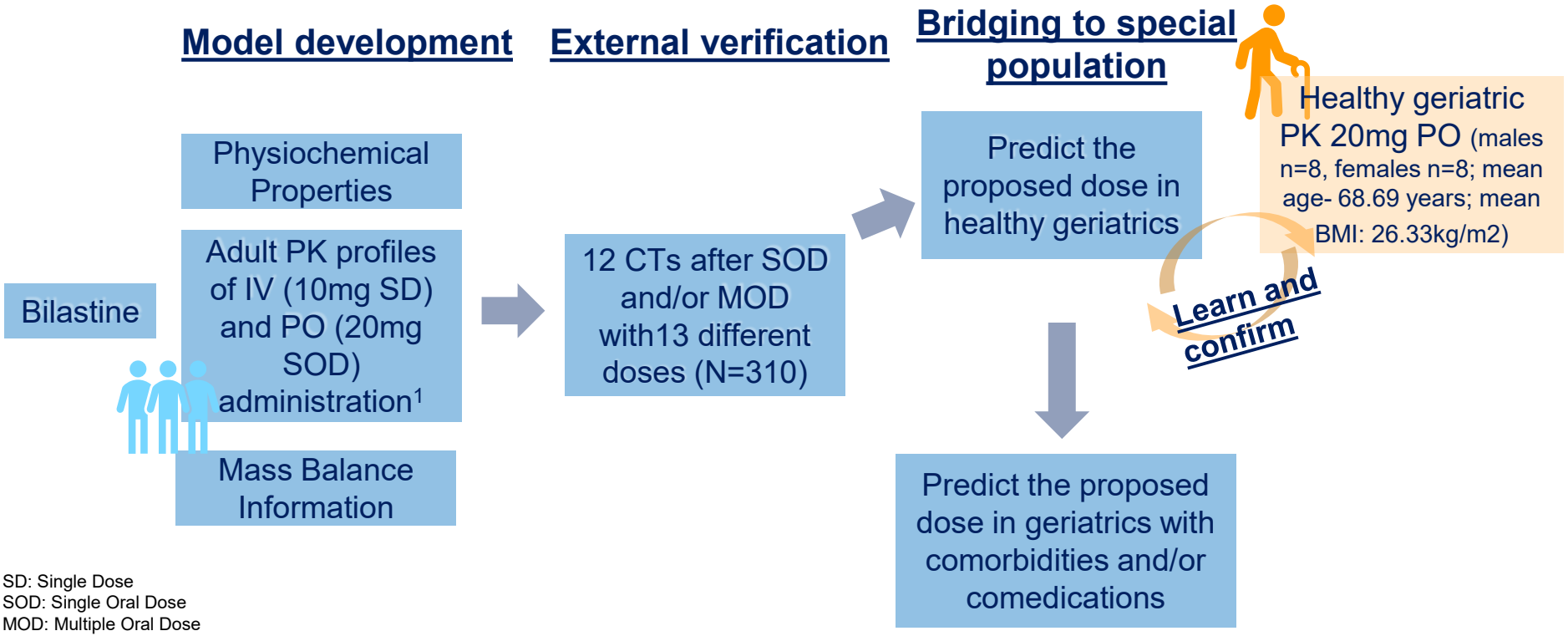
Develop the model in healthy adults



Add instestinal transporters

How to solve

Developing full PBPK model in **healthy** geriatrics - Workflow



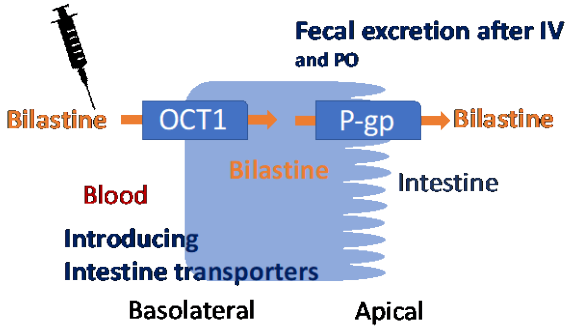
SD: Single Dose
SOD: Single Oral Dose
MOD: Multiple Oral Dose
CT: Clinical Trial

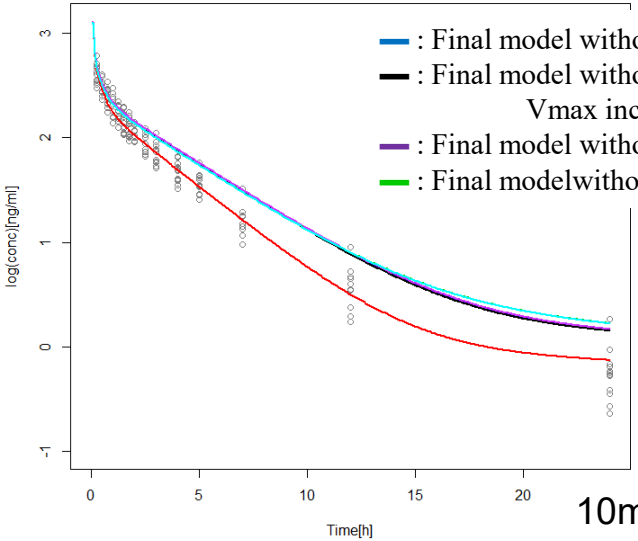
1. Sadaba et al. (2013) Clin Drug Investig 33:375–381

Results

Bilastine PBPK model in healthy young adults - Need both apical and basolateral transpoerters

Introducing intestinal transporters into PBPK model





Learning

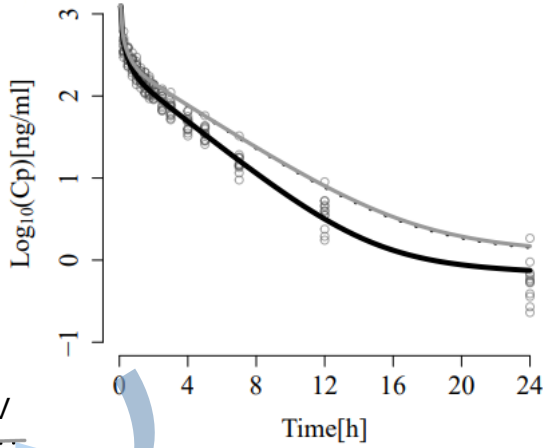
Need both Apical efflux and basolateral influx transporters

Apical efflux transporter alone **cannot** explain fecal excretion; The presence of a **basolateral influx** transporter(s) in the intestine is needed to see the effect of P-gp after IV administration

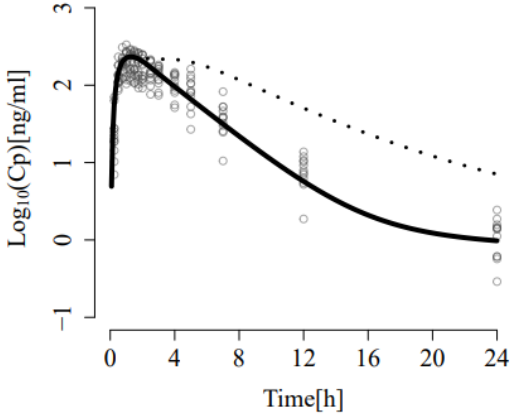
Bilastine PBPK model in healthy young adults - Final model

Final model
- Black bold line

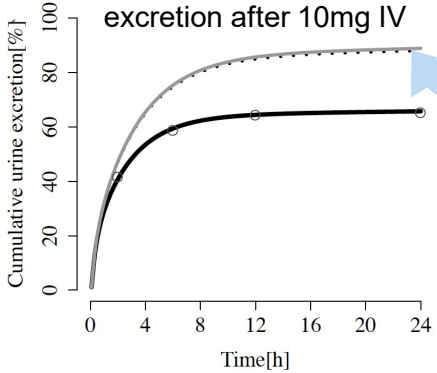
10mg IV



20mg PO



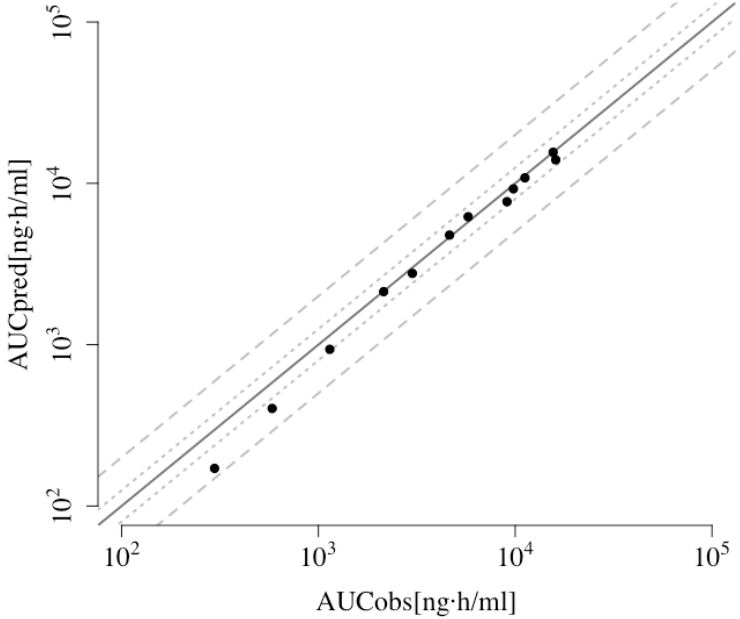
Cumulative urine excretion after 10mg IV

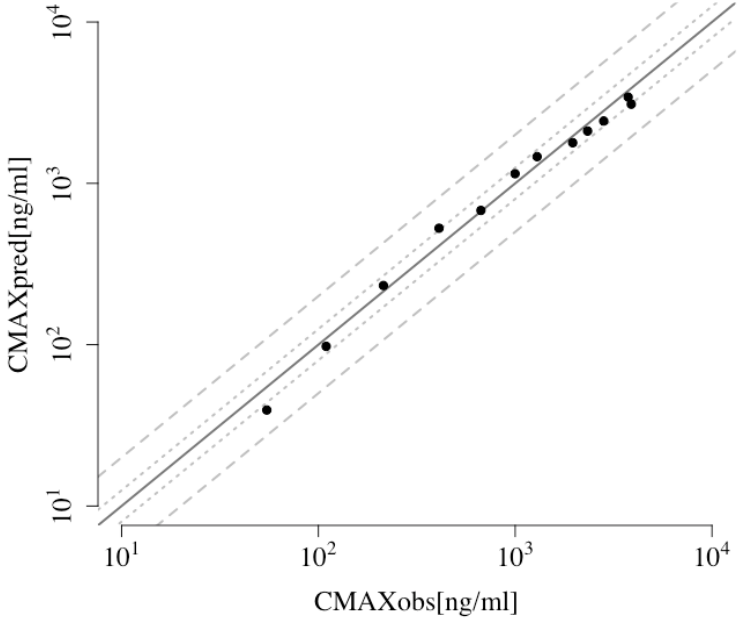


The developed model fits well for both IV and PO in healthy young adults

Results

Bilastine PBPK model in healthy young adults - Verification with different dose

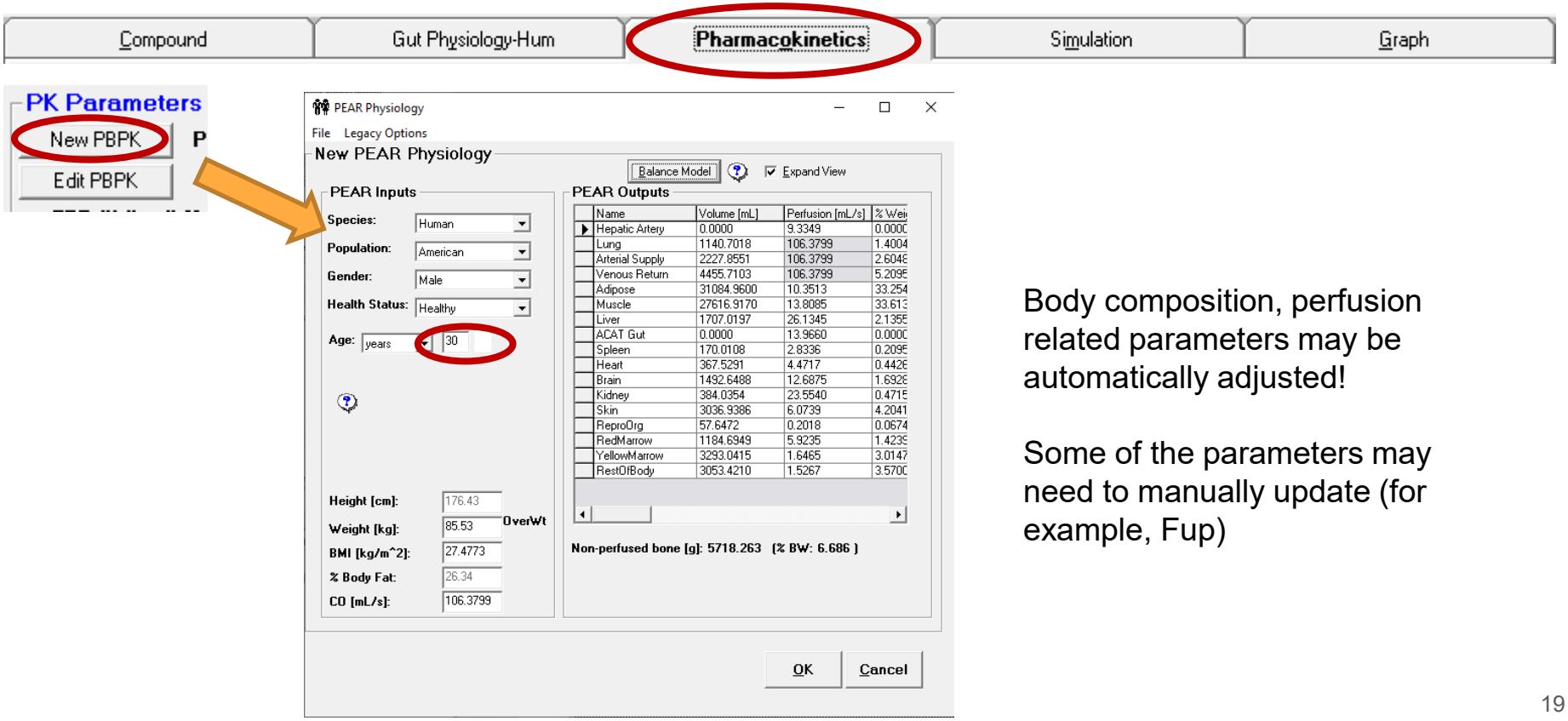




5mg 10mg, 20mg, 40mg, 50mg, 80mg, 100mg, 120mg, 140mg, 160mg, 200mg, 220mg; dotted line-1.25 fold range; dashed line- 2 fold range
Note- 5mg was different formulation

Results

Create geriatric virtual subject using PEAR physiology



Body composition, perfusion related parameters may be automatically adjusted!

Some of the parameters may need to manually update (for example, Fup)

Results

Healthy geriatrics need no dose adjustment – go with 20mg QD

Models' PK prediction for 20mg QD dose

	Cmax (ng/ml)	AUC (ng·h/ml)
Young adults PopPK (N=5000)	223.29 [74.88 - 478.12]	1103.88 [370.03 - 2311.15]
Geriatric PopPK (N=1500)	176.02 [133.04 - 227.98]	1129.40 [588.65 - 1891.86]
Senescence at 70 (N=16)	204.06 [170.91 - 258.51]*	1478.14 [1222.83 - 2010.15]*
PBPK at 70 (N=1500)	213.39 [62.10 - 425.26]	1176.82 [280.17 - 2464.71]
PBPK at 80 (N=1500)	233.63 [60.62 - 445.22]	1307.59 [278.66 - 2813.93]

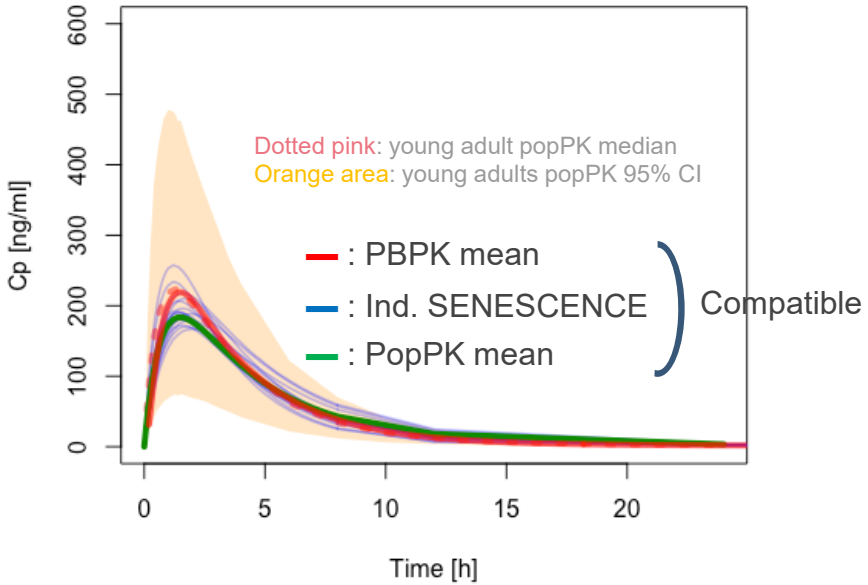
Young adults AUC from the observation : mean=1160 ng h/ml; range: 481-2528 ng h/ml

Young adults Cmax from the observation : mean=260 ng h/ml; range: 63-924 ng/ml

* Due to sparse N size, minimum value and maximum value are presented

Virtual subjects

At mean age of 68 (from CTs)



Similar exposure with young adults

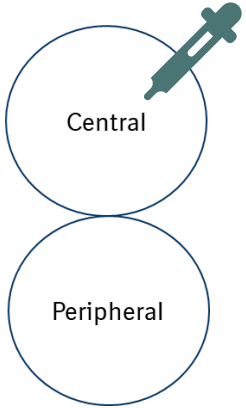
Learning

No need of dose adjustment in geriatrics

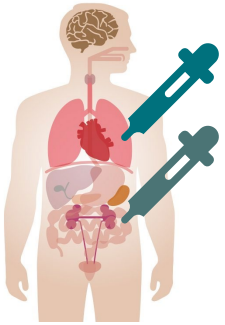
CTs: clinical trials

Advantages

PBPK has various advantages



Classical PK modeling	PBPK model
Data Driven	Mechanism centric
Simple structure, less computational burden	Complicated structure Require high computational power
Mostly systemic exposure only	Systemic + organ specific exposure
Limited extrapolation	**Various extrapolation**
Test hypothesis	Test + generate hypothesis
	Integrating drug related properties



CTs: clinical trials

Ongoing works
DDI, renal impairments

Extrapolation

Dose for geriatrics with comorbidities?

Labeling information of bilastine in renal impairment:

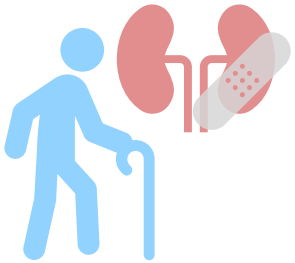
- **Studies conducted in adults in special risk groups (renally impaired patients) indicate that it is not necessary to adjust the dose of bilastine in adults.**

In a study in subjects with renal impairment the mean (SD) AUC0-∞ increased from 737.4 (± 260.8) ng x hr/mL in subjects without impairment (GFR: > 80 mL/min/1.73 m2) to: 967.4 (± 140.2) ng x hr/mL in subjects with mild impairment (GFR: 50-80 mL/min/1.73 m2), 1384.2 (± 263.23) ng x hr/mL in subjects with moderate impairment (GFR: 30 - <50 mL/min/1.73 m2), and 1708.5 (± 699.0) ng x hr/mL in subjects with severe impairment (GFR: < 30 mL/min/1.73 m2). Mean (SD) half-life of bilastine was 9.3 h (± 2.8) in subjects without impairment, 15.1 h (± 7.7) in subjects with mild impairment, 10.5 h (± 2.3) in subjects with moderate impairment and 18.4 h (± 11.4) in subjects with severe impairment. Urinary excretion of bilastine was essentially complete after 48 -72 h in all subjects. These pharmacokinetic changes are not expected to have a clinically relevant influence on the safety of bilastine, since bilastine plasma levels in patients with renal impairment are still within the safety range of bilastine.

What this study adds

1) Identification of those physiological processes playing a more important role in bilastine plasma exposure in patients with renal impairment
2) Confirm that no dose adjustments are needed in patients with RI in order to verify the predictive capacity of the model and the validity of the physiologically based assumptions

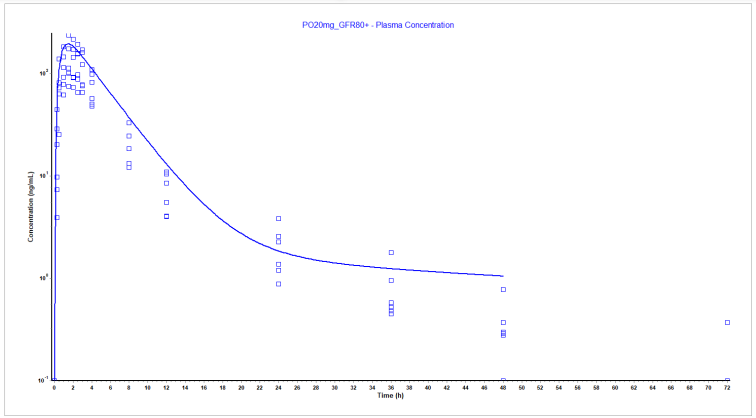
Study Design and Population

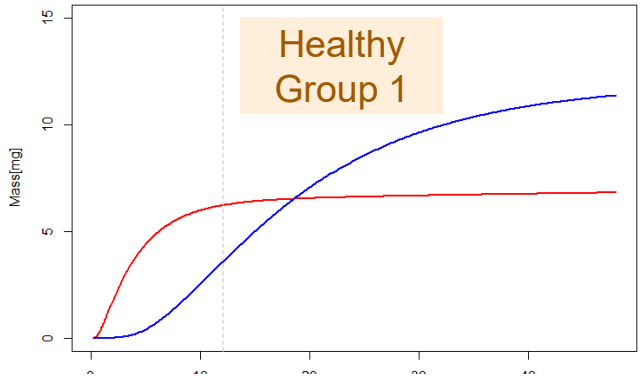


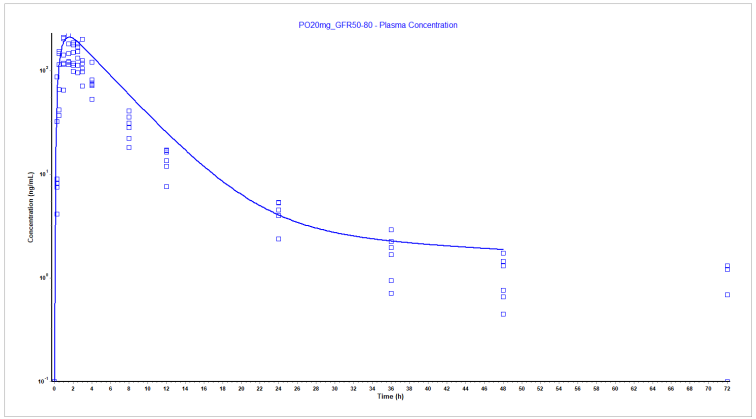
Baseline characteristics	Group 1 Healthy	Group 2 Mild	Group 3 Moderate	Group 4 Severe
N	N=6	N=6	N=6	N=6
GFR (ml/min); Mean±SD	110.0±13.08	63.33±7.84	32.17±6.80	20.00±6.69
Age (years)	65.7±1.97	71.2±5.42	71.3±4.63	65.0±14.63
Sex				
Male	5	5	5	4
Female	1	1	1	2

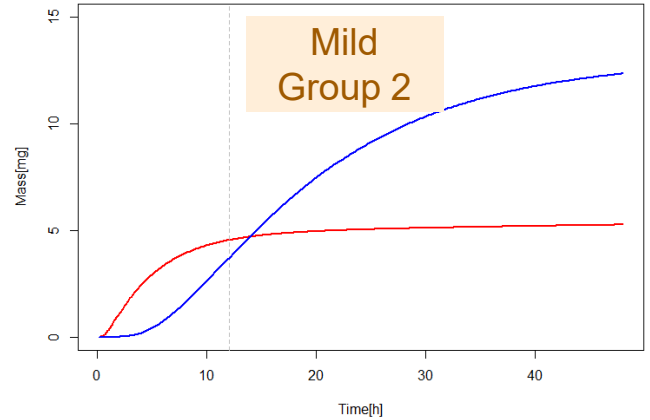
Preliminary results

PK prediction for geriatrics with different kidney impairment level



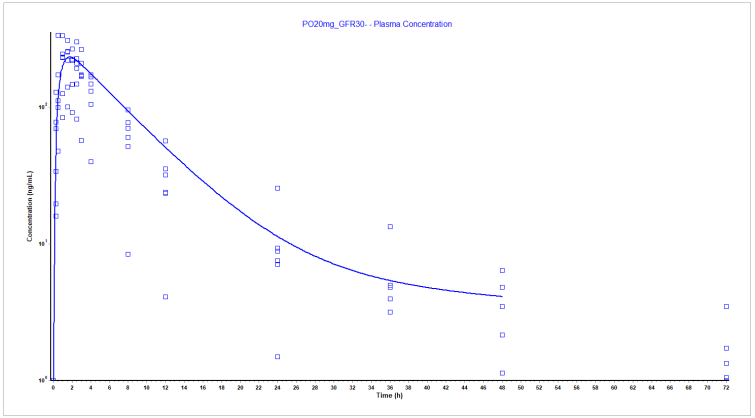


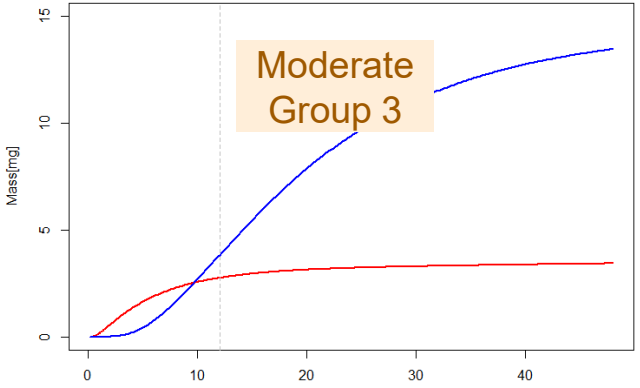


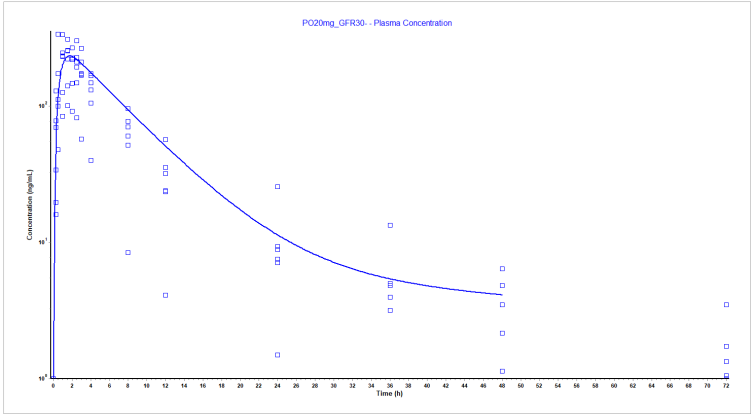


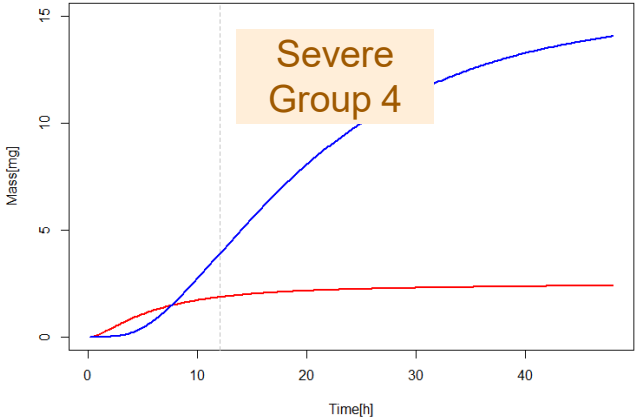
Preliminary results

PK prediction for geriatrics with different kidney impairment level



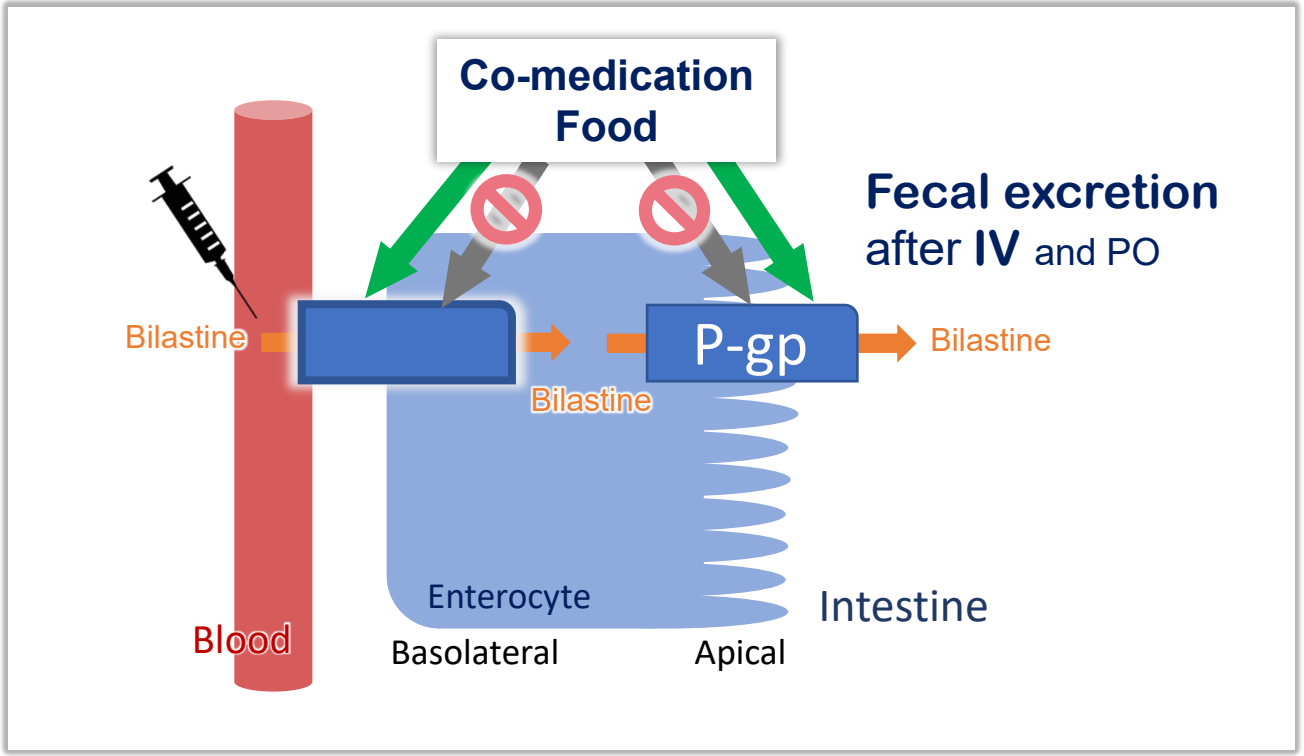


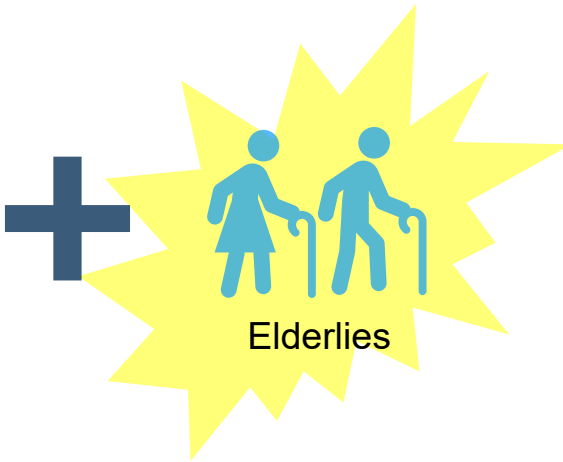




Future directions

Eveluate drug-drug interactions in geriatrics

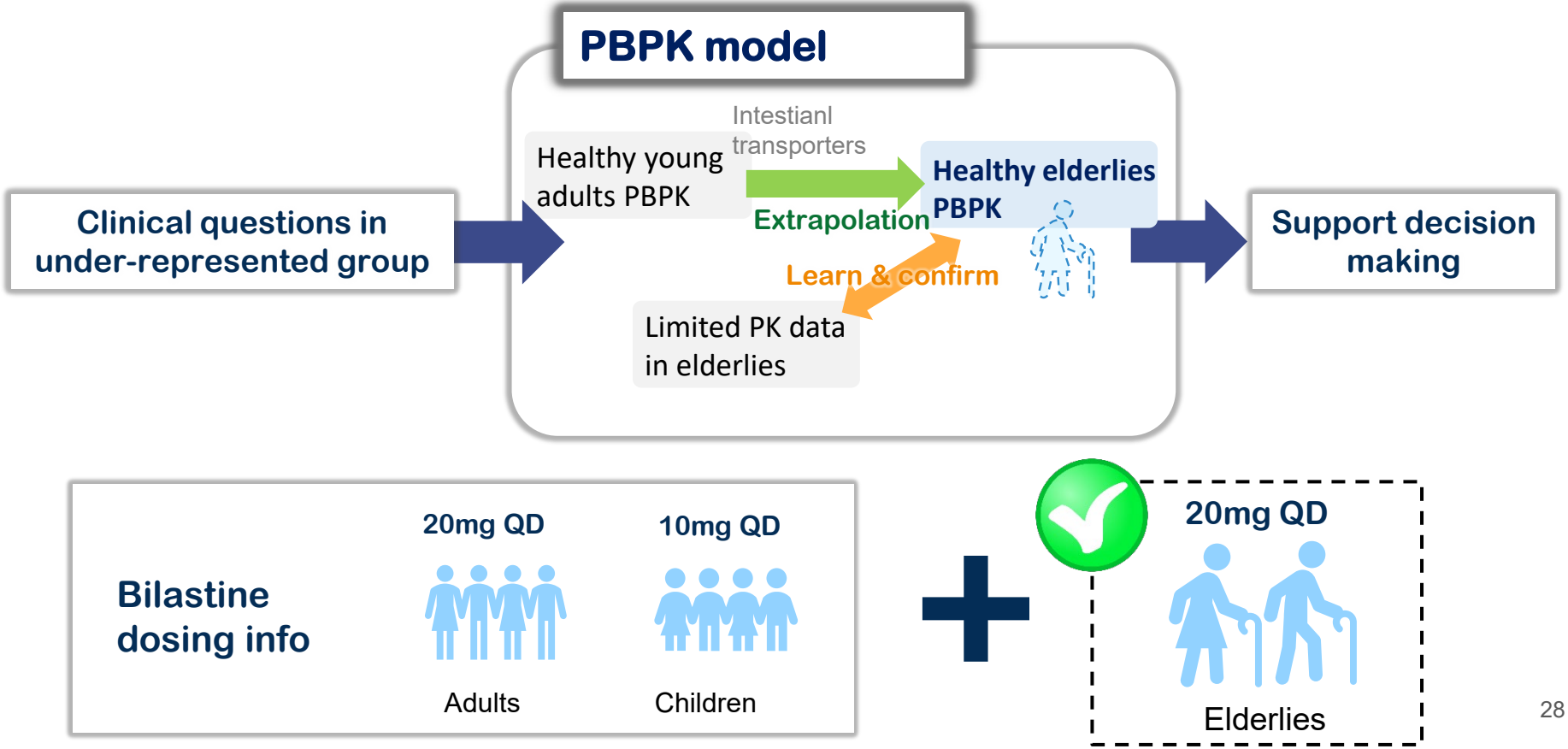




Develop PBPK model using GastroPlus 9.6

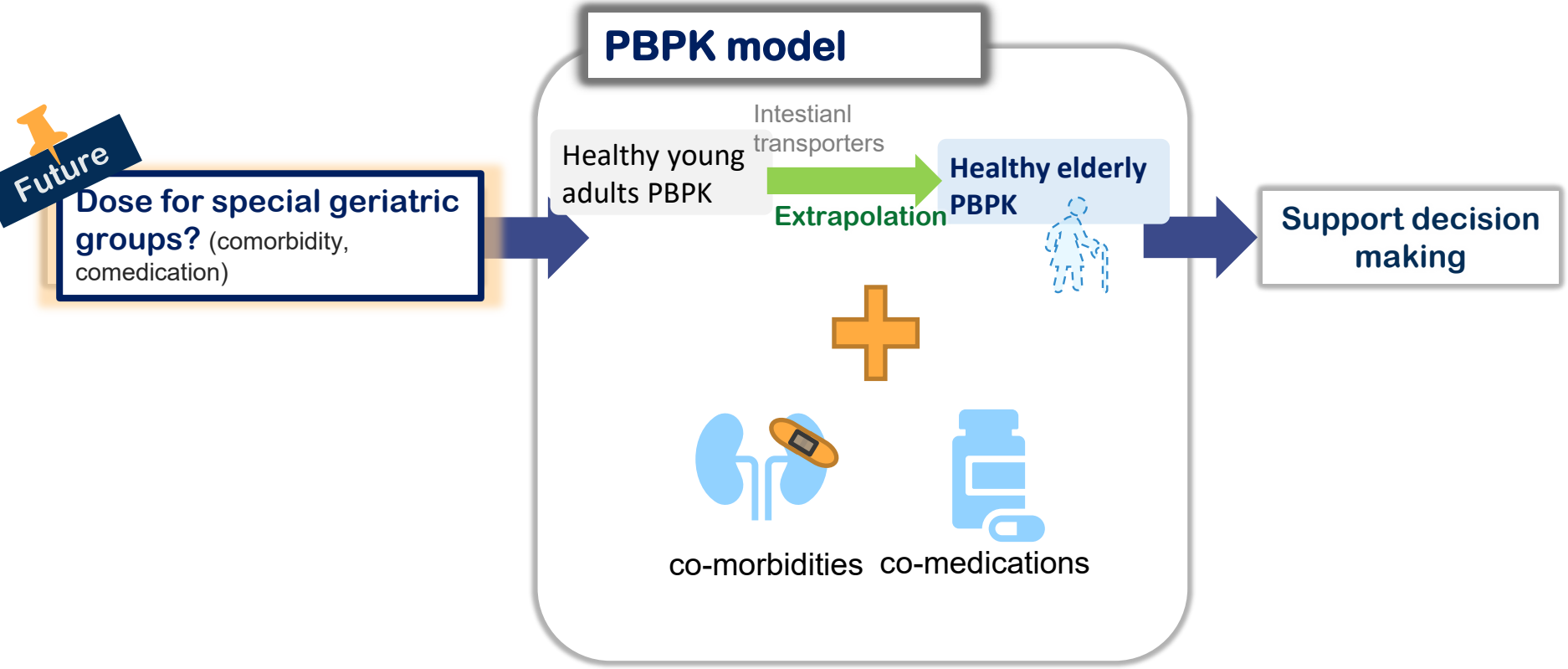
Conclusion

PBPK model confirmed that there is no need of dose adjustment for healthy elderies



Next steps

Expand the PBPK model for other special populations



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Stephan Schmidt
Chaejin Kim

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BACKUP

Bilastine PBPK model assumptions

Senescence			
Main assumptions	Justification	Approach to assess the impact	Conclusion
Changes in the PK as a consequence of aging related changes in albumin, GFR, CO, TBW and TBF F mean in young subjects similar to that in older adults	Known processes involved in bilastine's PK that was also successfully used previously for pediatrics	Comparison of individual parameters predicted with the senescence model compared to EBE from a PopPK model	Individual predictions within the two-fold and less than 30% prediction error in the case of mean parameters (Senescence vs. geriatric popPK). The equation used to predict bilastine CL successfully tested CLr in patients with renal dysfunction [22]. Miss-predictions on CL/F attributable to 1) use of mean F from young adults, and 2) possible changes in F with aging not considered in the model.
PBPK			
Main assumptions	Justification	Approach to assess the impact	Conclusion
Apical and basolateral transporters involved in bilastine secretion and absorption Renal CL main route of elimination of bilastine No impact of aging on drug transporters	Only 66% of the drug recovered in urine after iv but CLr is the main elimination pathway[19]. Amount recovered in urine after oral: ~42%[19] DDI and in vitro studies evidenced the influence of transporters at an intestinal level Mass balance study[19,20] Not enough evidence to inform possible changes	Compare predictions and observations before and after the inclusion of transporters for iv and oral. Comparison with the mass balance results. Comparison of urine recovery in the mass balance studies with the PBPK mass balance Application of the model to predict the PK in older subjects and comparison with observations	Apical and basolateral transporters needed to predict bilastine PK profile after iv and po administration After iv administration, only 74 % of the drug predicted to be systemically available (in line with observed 66% recovery in urine) and the rest secreted to the GI track by active transporters. After po, only about 42.3% predicted to be systemically available; and 40% recovered in urine. This is in line with drug's renal CL and amount recovered in urine in the BA study (42%)[19]. These results are also in line with the radio-labelled mass balance study[20]. Bilastine is eliminated by renal filtration in the kidneys Decrease in renal CL in subjects with renal impairment was proportional to the decrease in the GFR Bilastine plasma concentrations were well predicted in geriatric subjects without the inclusion of aging related changes on drug transporters

Use of a PBPK Model to Enhance the Mechanistic Understanding of Bilastine's PK in special population

What is known/background

- **Bilastine** is an antihistamine drug approved in EU, Canada and Asia in patients ≥ 12 years for the treatment of allergic disorders such as rhinoconjunctivitis and urticaria.
- In Europe, it is also approved for patients who are ≥ 6 years of age.
- Bilastine PK has been widely studied. However, the **influence** of efflux and influx **transporters** on Bilastine's PK is still **under-investigated**.

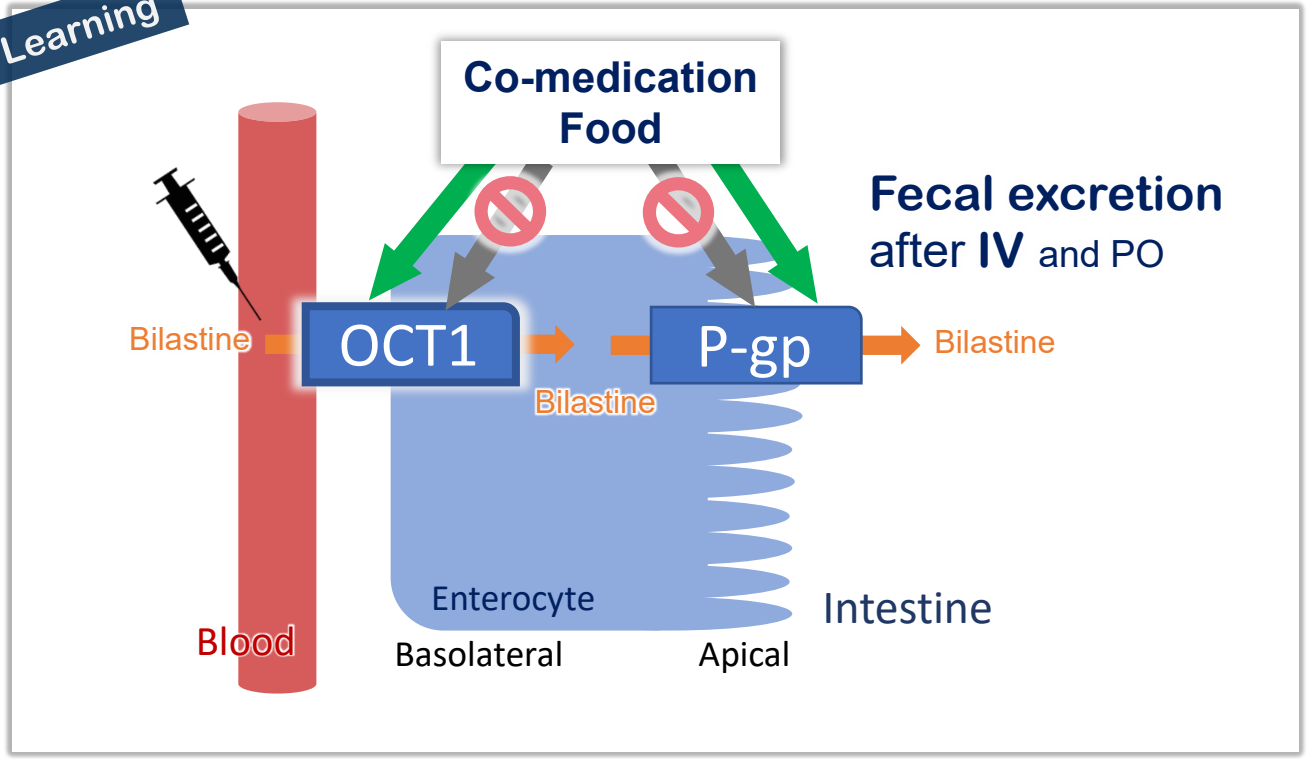
What is unmet need/What will this study add

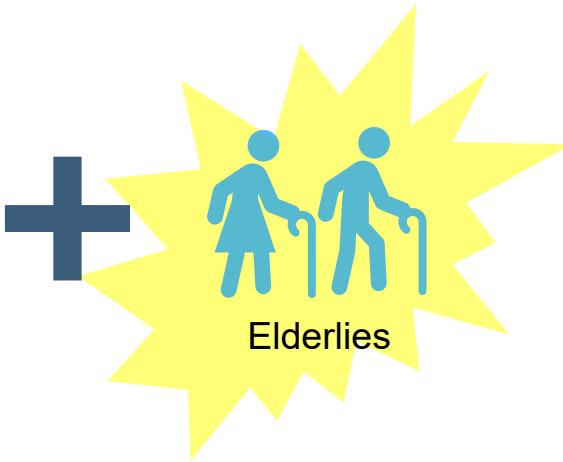
- To provide a enhanced **mechanistic understanding** of the balance between influx and efflux **transporters** that play a role in **Bilastine absorption/elimination** through the use of **PBPK model**.
- To use the model to **bridge the PK knowledge to special populations:**
  - **Children** (2 to <12 years): 1) Children ≥ 6 years, where information exists from the pediatric indication and then 2) **Extrapolate** to children down to 2 years.
  - **Elderlies** (≥ 65 years) and patients with **renal impairment** (mild to severe)

Learning from PBPK

Transporters are involved on **PK**
– support evaluation of **DDIs** (e.g. grapefruit juice)

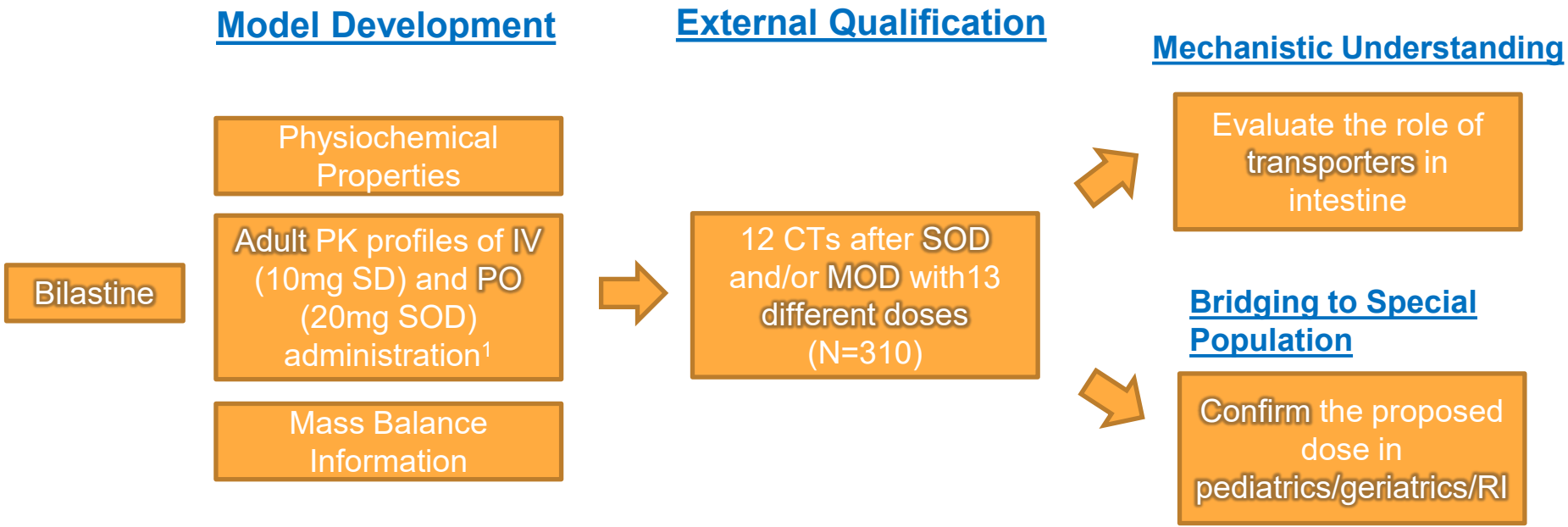
Learning





Develop PBPK model using GastroPlus 9.6

PBPK Model Development Working Flow



SD: Single Dose
SOD: Single Oral Dose
MOD: Multiple Oral Dose
CT: Clinical Trial

1. Sadaba et al. (2013) Clin Drug Investig 33:375–381

Model Development

Model Development -IV

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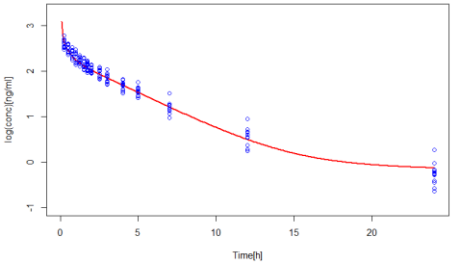
Plasma Concentration



	Obs	Calc
Simulation Time Elapsed (h):		24
Fa %:	0	73.732
FDp %:	0	73.731
F %:	0	73.743
Cmax (ng/mL):	410.94	1245.3
TMax (h):	0.25	0.0833
AUC 0-inf (ng-h/mL):	763.52	621.56
AUC 0-t (ng-h/mL):	749.3	793.45
CMax Liver (ng/mL):		222.83

442.927(ng/ml) at t=0.25

Model Development -PO

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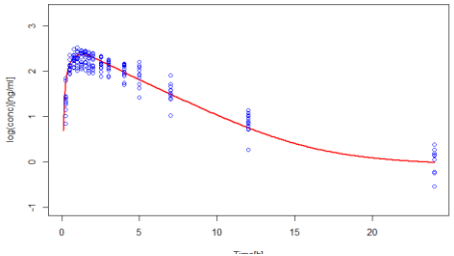
Plasma Concentration



	Obs	Calc
Simulation Time Elapsed (h):		24
Fa %:	0	42.422
FDp %:	0	42.421
F %:	0	42.402
Cmax (ng/mL):	219.67	232.71
TMax (h):	1	1.28
AUC 0-inf (ng-h/mL):	984.11	936.05
AUC 0-t (ng-h/mL):	975.96	910.77
CMax Liver (ng/mL):		69.762

Model Development -IV

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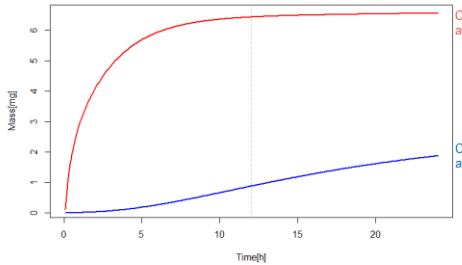
Urine(red) and Fecal (blue) Excretion



Cumulative Urine Excretion at 24h: 6.571mg(65.71%)

Observed: 66%

Cumulative Fecal Excretion at 24h: 1.874mg(18.74%)

Model Development -PO

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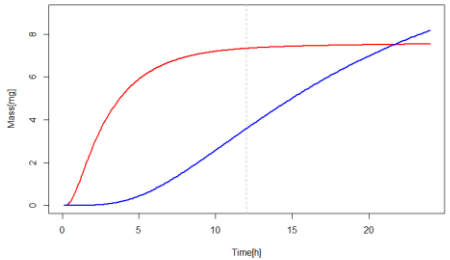
Urine(red) and Fecal (blue) Excretion



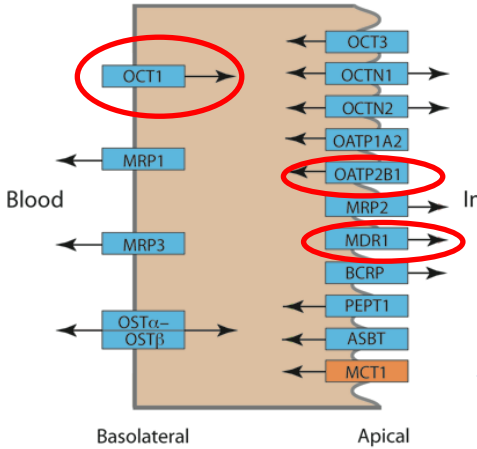
Cumulative Fecal Excretion at 24h: 8.173mg(40.87%)

Cumulative Urine Excretion at 24h: 7.543mg(37.72%)

Observed: 40%

Question 1: How can we explain large fecal excretion in IV?

- IV administration, only 66% of drug was recovered in urine.
- Considering the facts that no accumulation and no metabolism, rest of drug may be excreted through fecal route.
- Most probable explanation is P-gp pump out the drug.
- **Can P-gp pump out the drug without any transporter's role in basolateral side?**

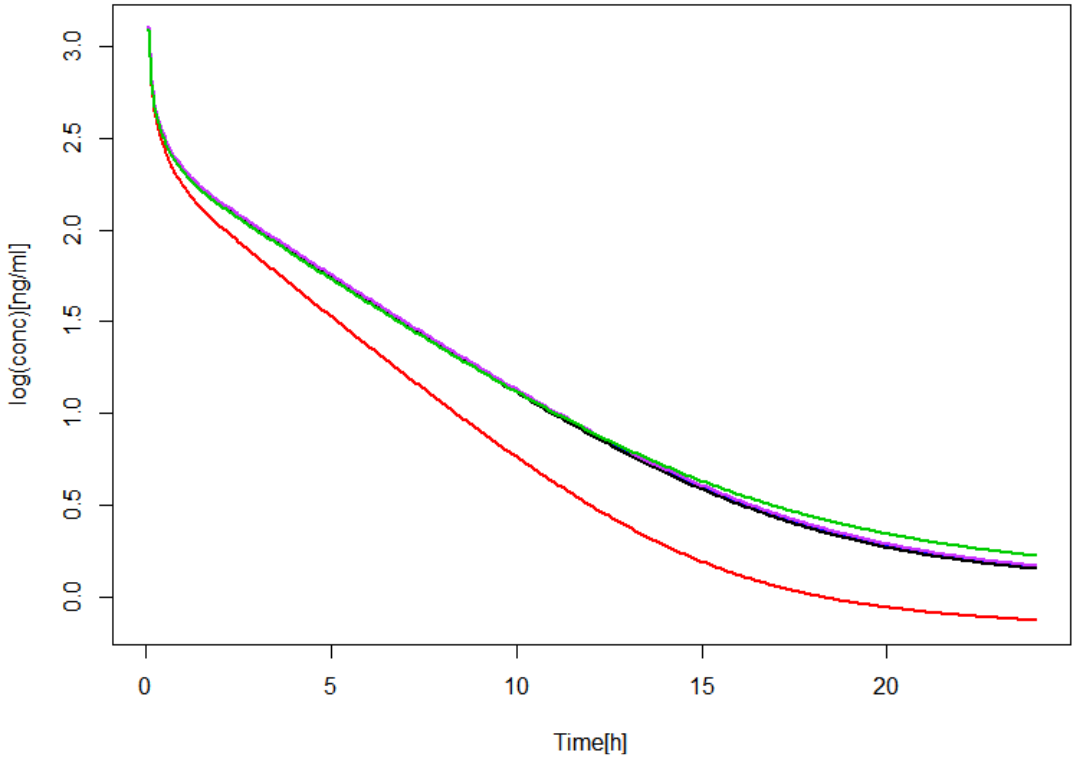


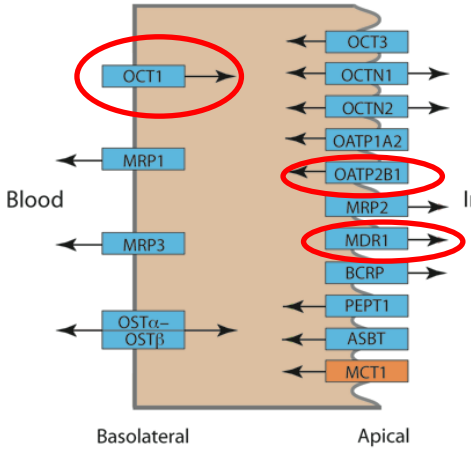
Only little amount of Drug exist for IV

http://transportal.compbio.ucsf.edu/organs/small-intestine/

Effect of OCT1 and P-gp on Bilastine Elimination

Plasma Concentration





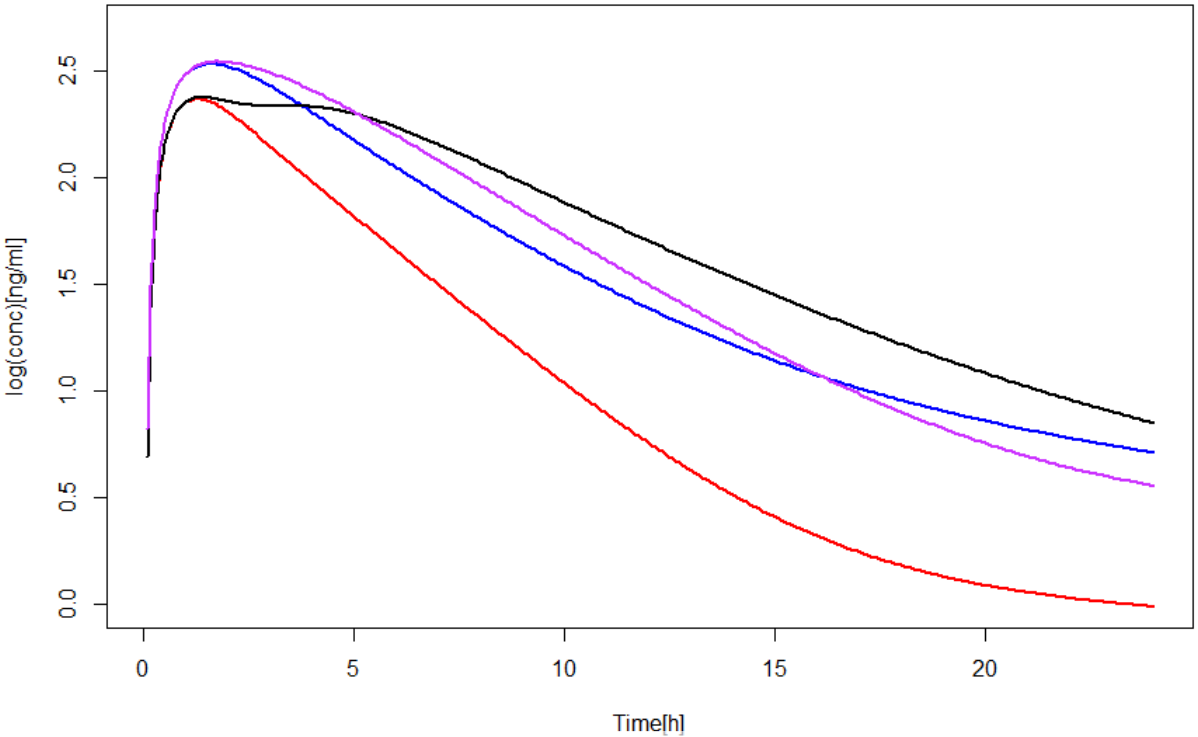
Only little amount of Drug exist for IV

- (red) : Final PBPK Model(FM)
- (blue) : FM without OCT1
- (black) : FM without OCT1 but 10 fold Vmax increase(0.01mg/s) of P-gp in gut
- (purple): FM without OCT1 and P-gp in gut
- (green) : FM without P-gp in gut

http://transportal.compbio.ucsf.edu/organs/small-intestine/

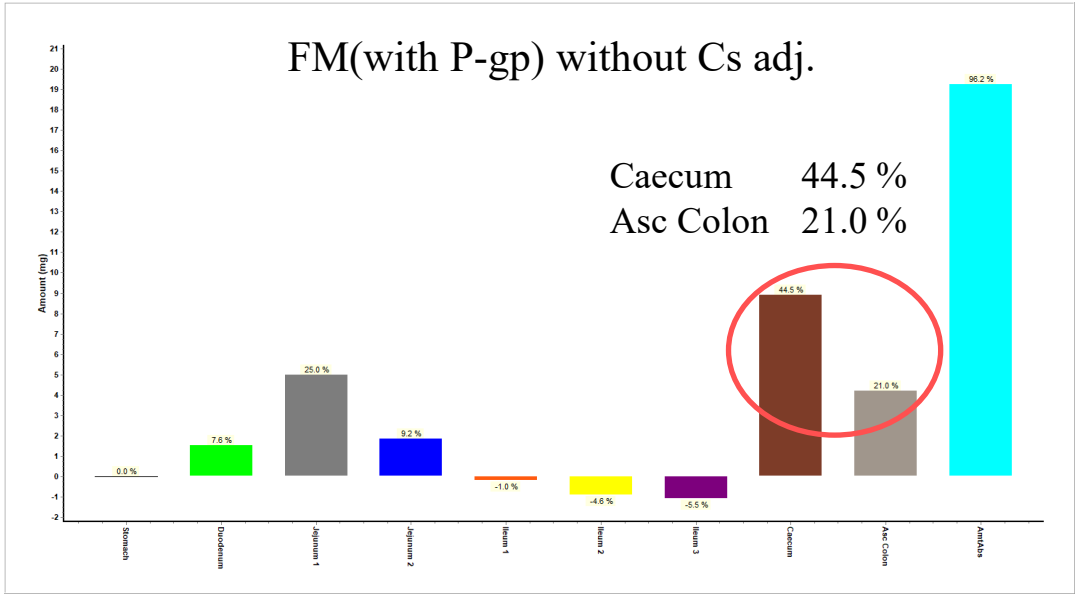
Question 1-1: What is the role of P-gp in absorption of bilastine?

Plasma Concentration



(red) : Final PBPK Model(FM)
(blue) : FM without P-gp in gut
(black) : FM without Cs adjustment
(purple): FM without P-gp in gut and Cs adjustment

Effect of P-gp in gut and Cs on PO PK profile

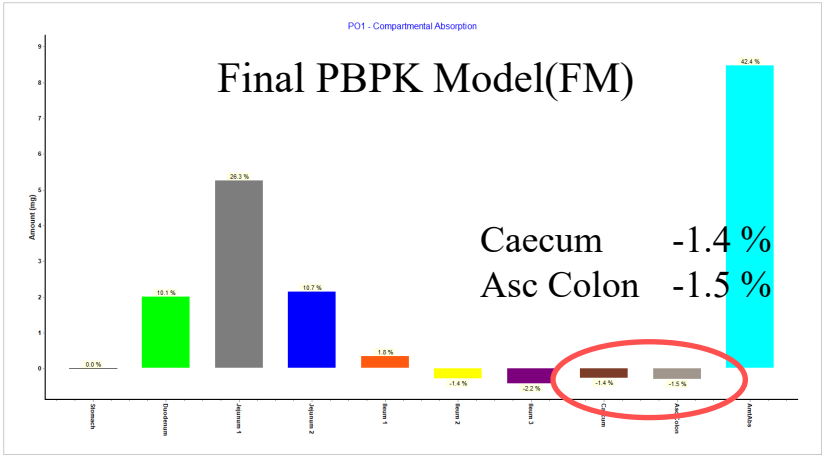


Is such a high large intestine absorption reasonable?

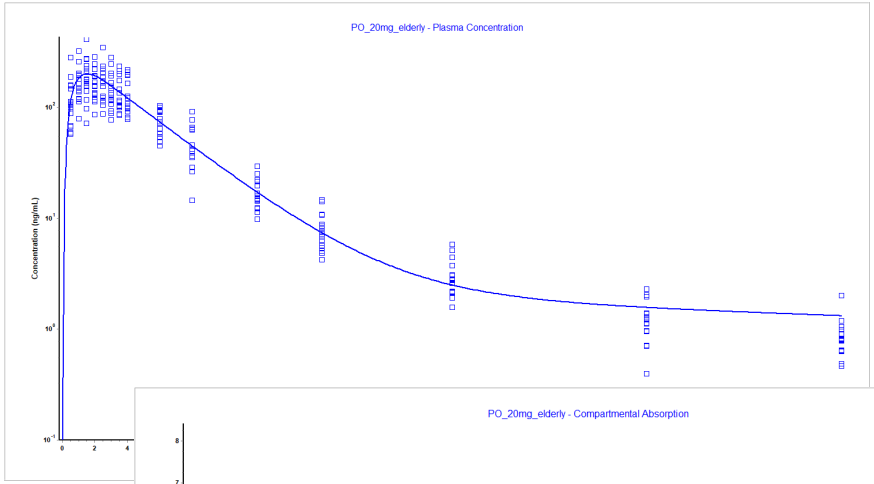
Efflux Capacity of P-gp in the Large Intestine

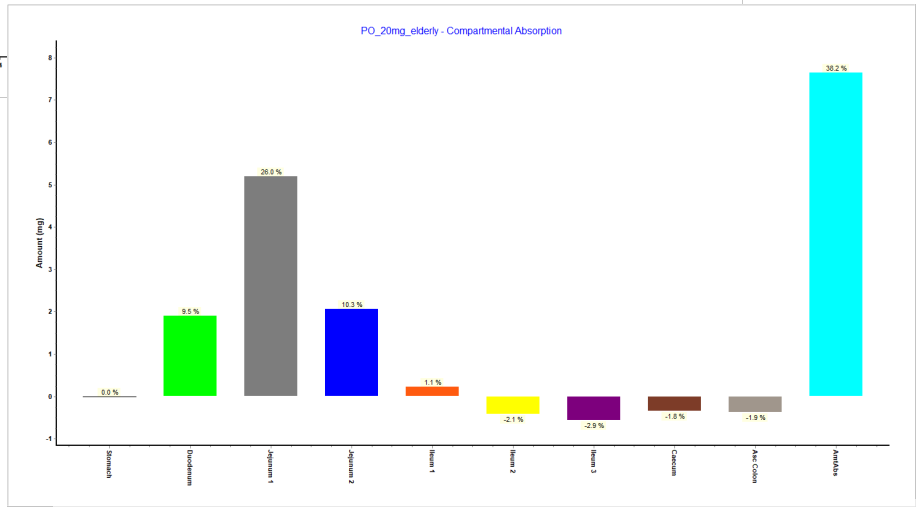
- Kagan et al. (2010) reported that P-gp's efflux capacity in rat differ by its location in the intestine.
- Talinolol was used in the study since talinolol is P-gp substrate but not a substrate for CYPs, which is the same as bilastine.
- Talinolol showed almost negligible absorption from the large intestine (< 1%) in rat
- Gramatte et al. (1996) reported that absorption capabilities of talinolol decrease along the small intestine

efflux capacity of P-gp in the large intestine is higher than small intestine.



20mg PO on Elderly





PK model

Age: 68

Weight: 86.19kg

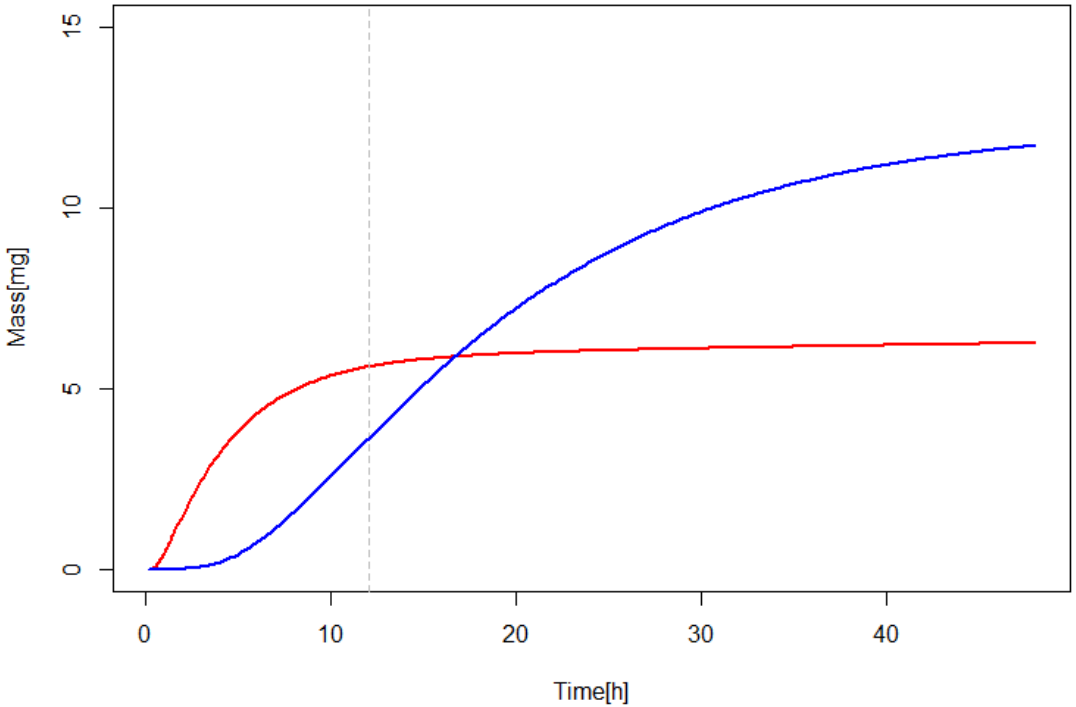
Sex: Male

GFR: 5.4022 L/h

Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	38.21
FDp %:	0	38.209
F %:	0	38.188
Cmax (ng/mL):	210.61	201.89
TMax (h):	1.5	1.5
AUC 0-inf (ng-h/mL):	1224.4	1265.4
AUC 0-t (ng-h/mL):	1187.8	1157.7
CMax Liver (ng/mL):		123.94

20mg PO on Elderly- elimination

Urine(red) and Fecal (blue) Excretion



Cumulative Fecal Excretion
at 24h: 8.519mg(42.59%)

Cumulative Urine Excretion
at 24h: 6.041mg(30.21%)

Learning from the Model

- **Basolateral side influx transporters** are needed in order to explain bilastine's large portion of fecal excretion in IV
- **Very low large intestine absorption**
    1) Supported by literature (Talinolol)
    2) **Efflux capacity of P-gp varies** depending on the region of intestine

Limitations

- Transporter kinetics are **too arbitrary** as not *in vitro* information available
- The model is **not predictive** at **low doses** (≤10 mg)

Future Study Direction

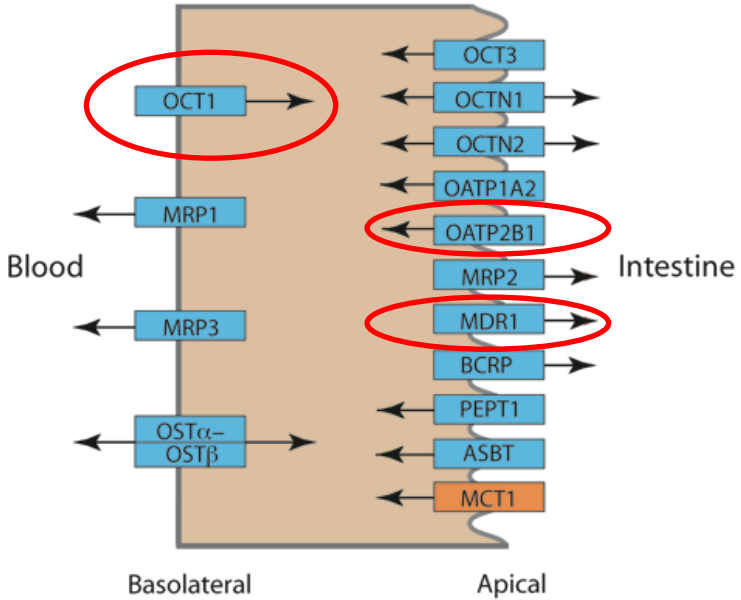
- Refine the pediatric/geriatric model
- Explore renal impairment patients
- Identify key physiological processes (and ontogeny) influencing the PK in special population

Role of Transporters in Bilastine's Absorption and Elimination

- IV administration, only 66% of drug was recovered in urine.
- Considering the facts that no accumulation and no metabolism, rest of drug may be excreted through fecal route.

- Some affinity with **P-gp** (apical-efflux), **OATP** (apical-influx) and **OCT1** (basolateral-influx) but at very high concentration

- Renal elimination: 8.3 L/h



Input Parameters

Input Parameters: Drug Specific

Drug-specific Parameters for Bilastine				
Parameter	Input Value	Parameter Value	Experimental?	Source
LogP	2.8	2.3~5/3.2	Predicted	DrugBank/GastroPlus
Fraction Unbound	0.13	0.10-0.16	Experimental	Vozmediano et al. 2018
Molecular Weight	463.62 (g/mol)			DrugBank
pKa	8.78 (base)/ 4.4 (acid)			Vozmediano et al. 2018
Solubility	0.5 (at pH=6.41)	0.00203 vs 0.13 vs 0.5(mg/mL)	Experimental(0.5)	*In Vitro*/GastroPlus/Pharmaceutics Proprietary information
Peff	1.9x10^6(cm/s)		Experimental	Proprietary information (Selected ABSCa option)
B/P Conc. Ratio	0.65		Predicted	GastroPlus prediction

Input Parameters: Biological System Specific

Drug related Parameters for Bilastine			
Parameter	Parameter Value	Literature Range	Note
Renal Clearance (L/h)	8.27 (IV), 9.20 (PO)		Sadaba, 2013
Tissue model	Permeability limited model (SpecPStc:0.0001)		Manually optimized
Kp calculation method	Lukacova (Rodgers: Single)		Not significant differences between methods

PBPK Model: 20yr old American Health Male 66kg

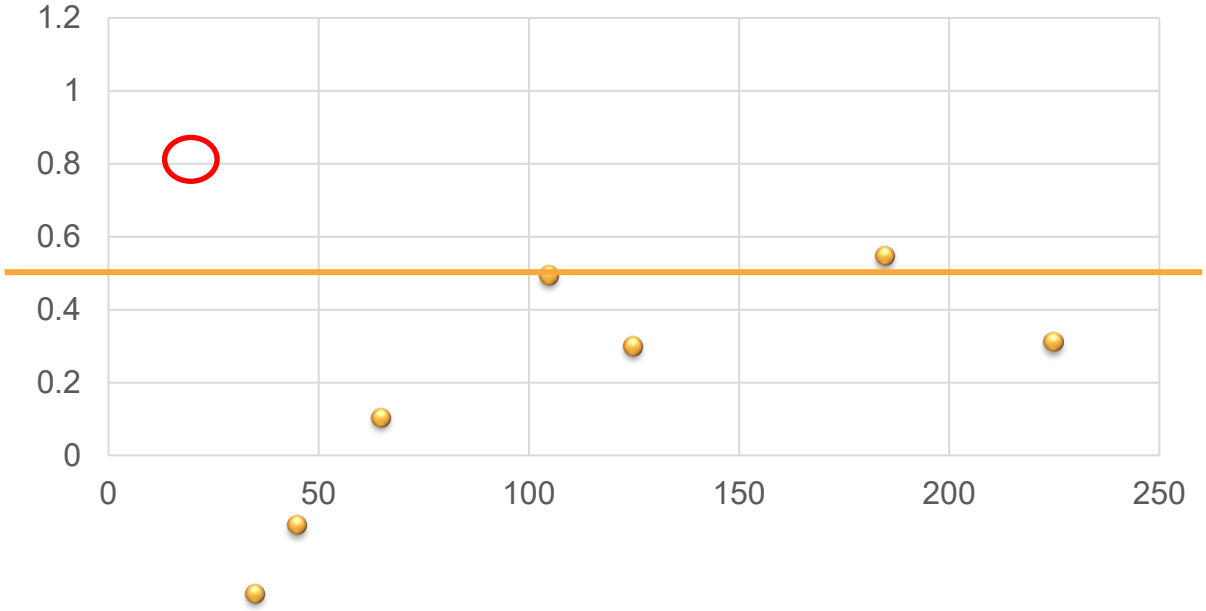
Input Parameters: Missing Information

PBPK Parameters for Bilastine		
Parameter	How to overcome	Note
Vmax and Km of Transporters	Manually optimized	OATP(gut, Apical, Influx): Vmax-0.00001(mg/s)/Km-1000(mg/L) OCTN(gut, Basolateral, Influx): Vmax-0.5(mg/s)/Km-250(mg/L) Pgp(gut, Apical, Efflux): Vmax-0.001(mg/s)/Km-1(mg/L) Pgp(Brain&Liver): Vmax-1(mg/s)/Km-1(mg/L)
Colon absorption?	Manually optimize C3, C4 values	C3: 0.05, C4: 0

Use of a PBPK Model to Enhance the Mechanistic Understanding of Bilastine's PK

Model Qualification

-AUCpred/AUCobs ratio; Single Simulation



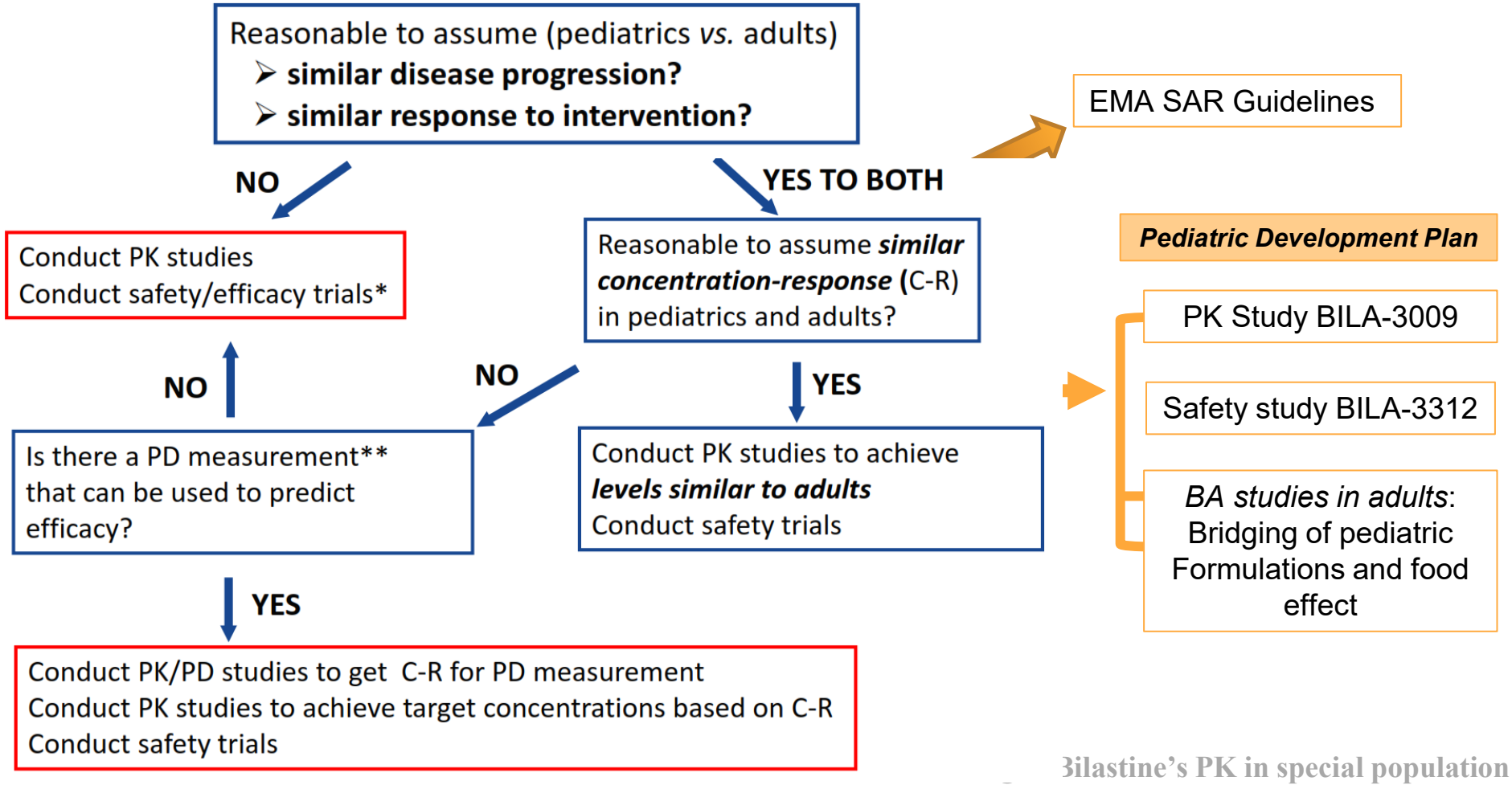
Question 2: Confirm pediatric approval dose

- Labeled Indication(s) (EU): symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticari for 12 years (6 years) of age and over

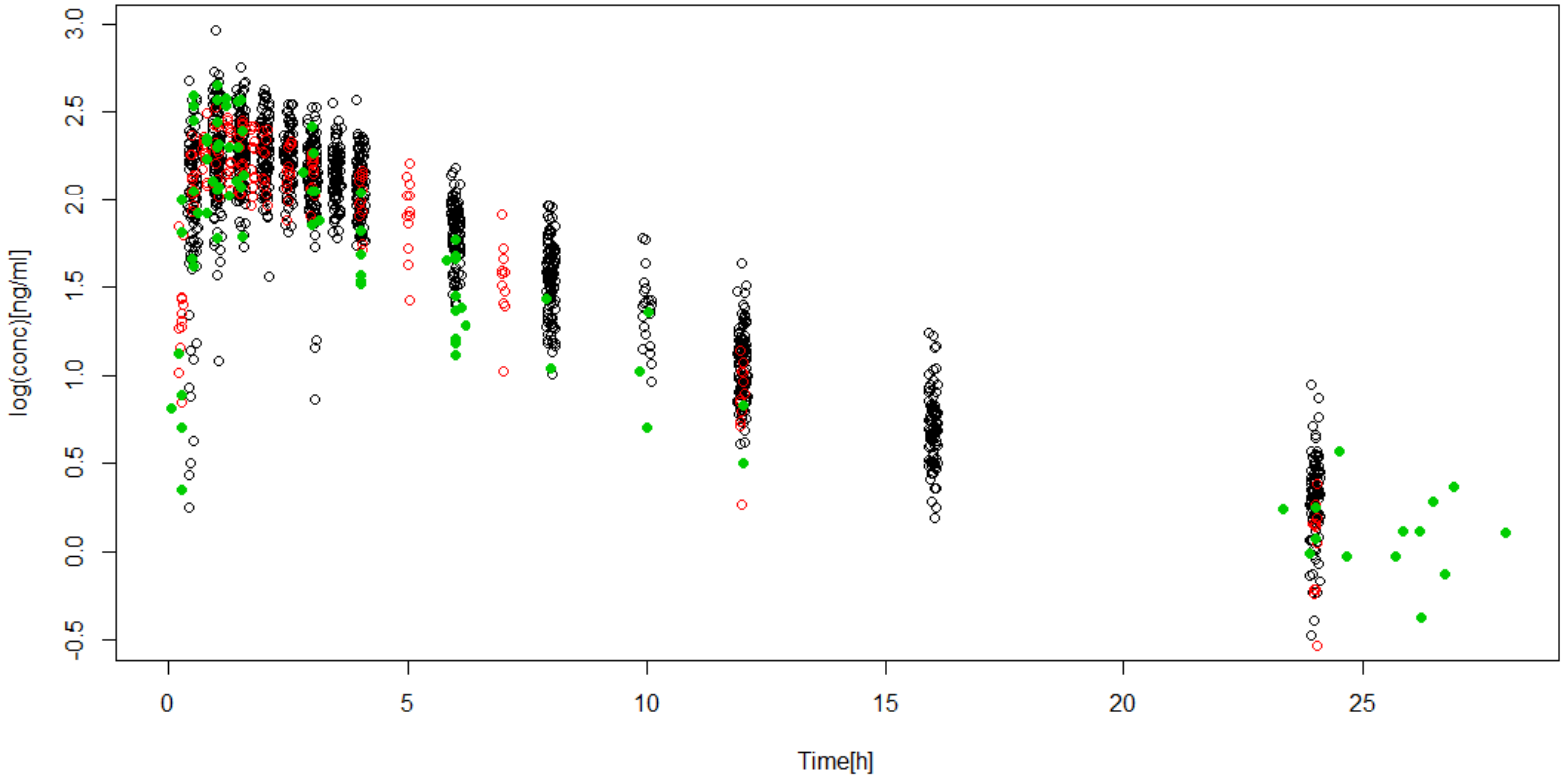
- Administration : 20 mg QD PO (adult)
- Recently, 10mg QD PO in 6~11 yrs is approved in EU

- Let's apply the model to the pediatric approval dose!

Pediatric Development Decision Tree Bilastine



Observations of Bilastine Concentration in Adult 20mg and Peds(6~11yrs) 10mg

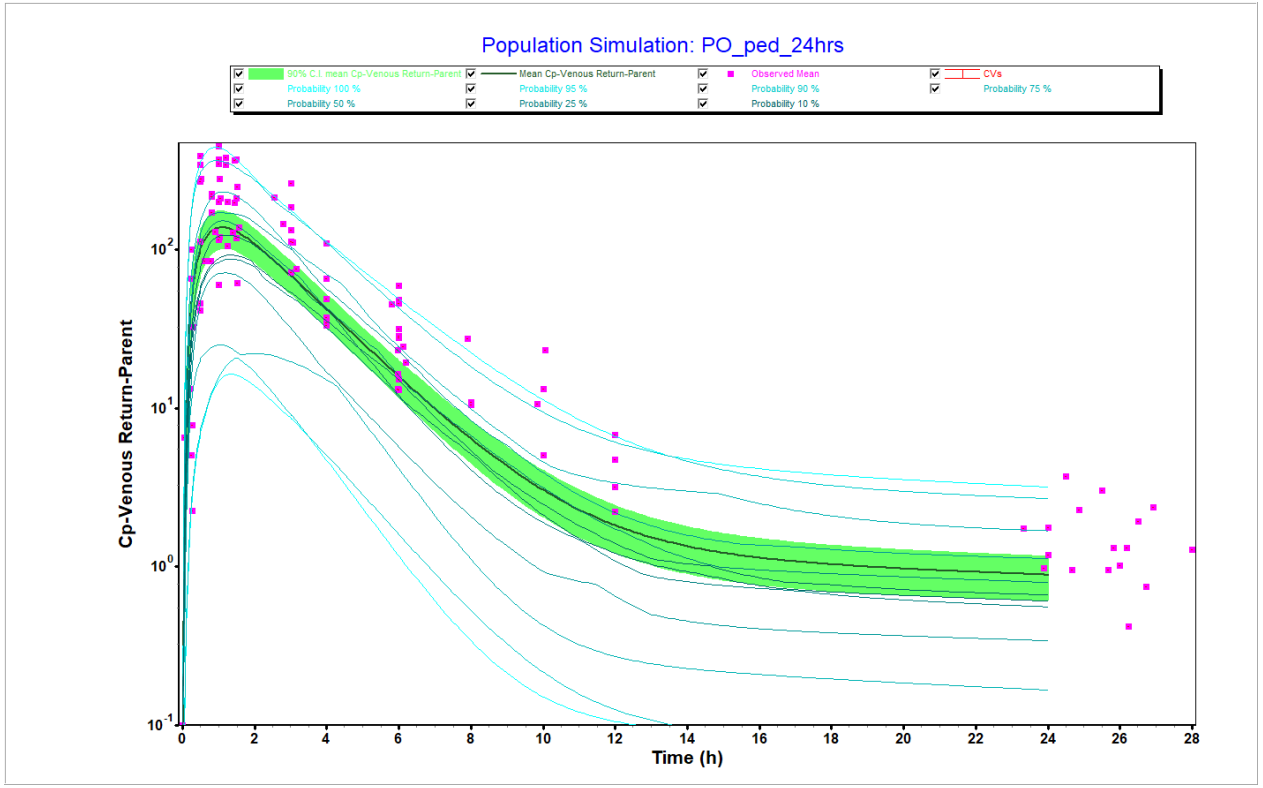


○ : 20mg Adult

○ : 20 mg Adult (Sadaba's)

● : 10mg Peds (6~11yrs)

10mg PO on Pediatrics

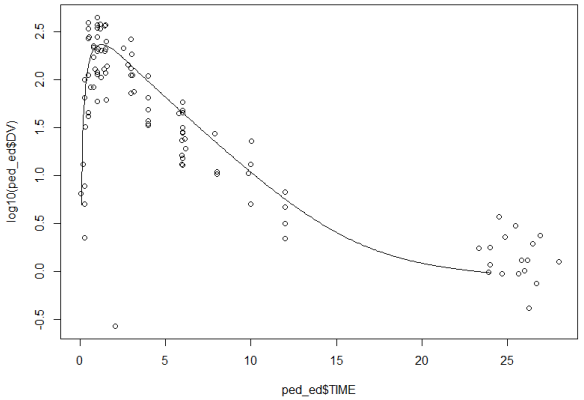


Population Simulation

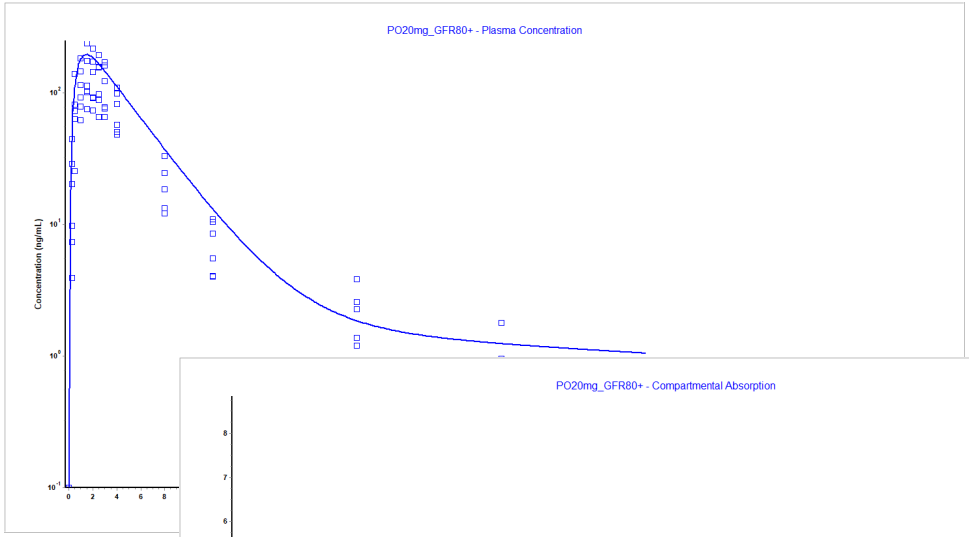
Age: 6~11

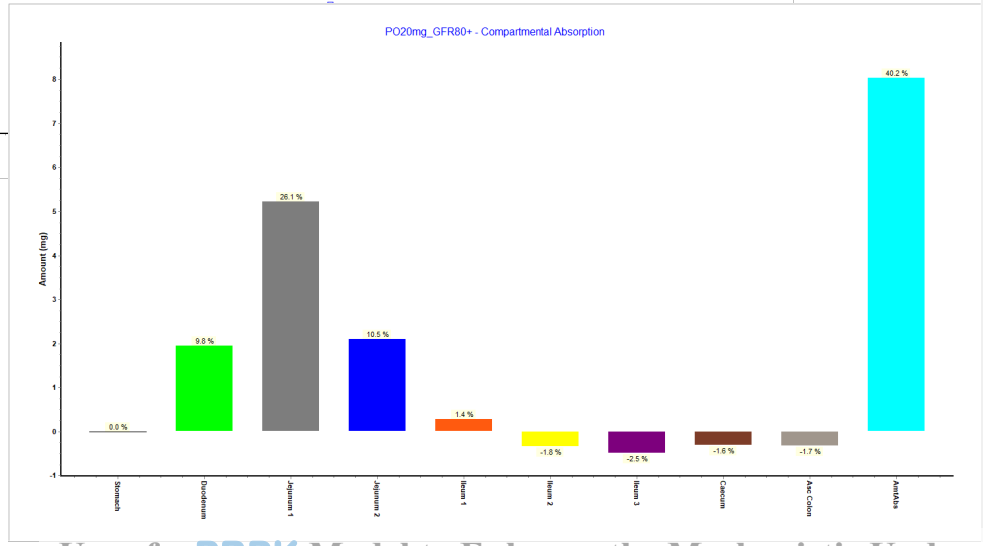
Weight: 23.6~42kg

BMI: 14.86~19.29



20mg PO on Group1 Healthy GFR





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PK model

Age: 68

Weight: 86.19kg

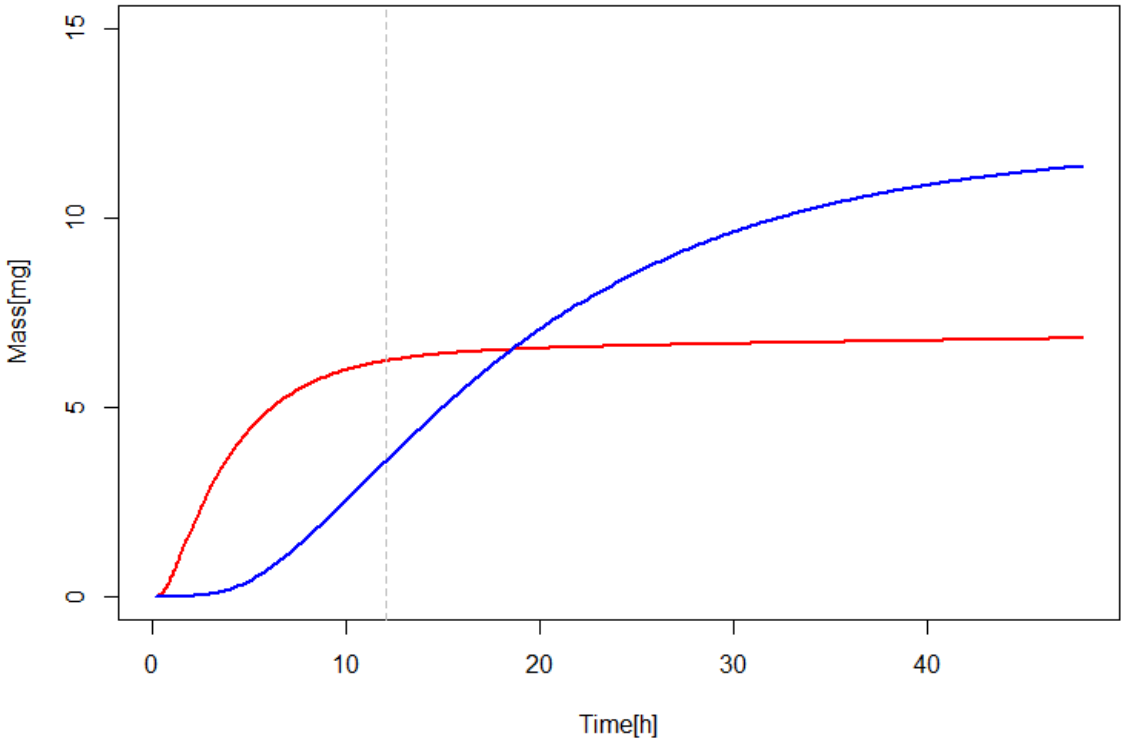
Sex: Male

GFR: 6.6 L/h

Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	40.212
FDp %:	0	40.212
F %:	0	40.19
Cmax (ng/mL):	144	194.6
TMax (h):	1.5	1.5
AUC 0-inf (ng-h/mL):	737.73	1117.3
AUC 0-t (ng-h/mL):	735.74	1032.5
CMax Liver (ng/mL):		122.22

20mg PO on Group1 Healthy GFR- elimination

Urine(red) and Fecal (blue) Excretion



Cumulative Fecal Excretion
at 24h: 8.314mg(41.57%)

Cumulative Urine Excretion
at 24h: 6.612mg(33.06%)

20mg PO on Group2 Mild GFR

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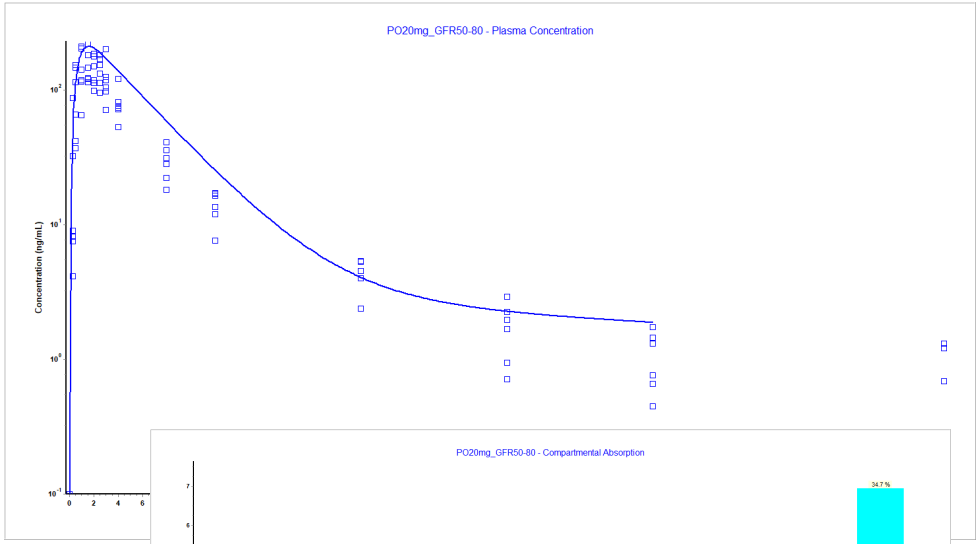
PK model

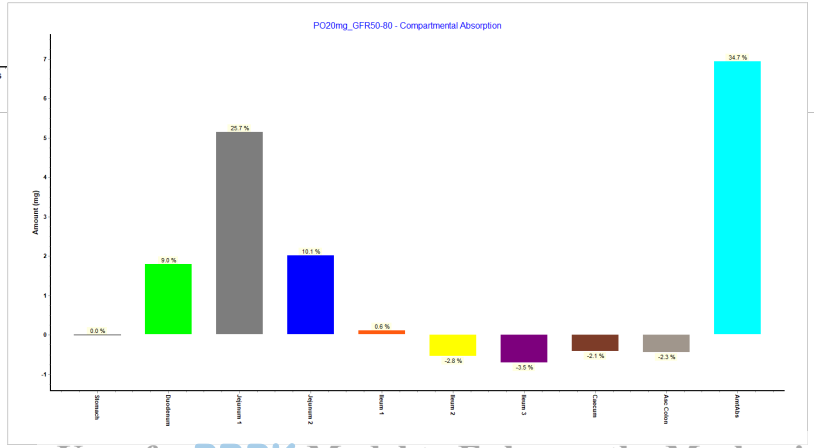
Age: 68

Weight: 86.19kg

Sex: Male

GFR: 3.8196 L/h

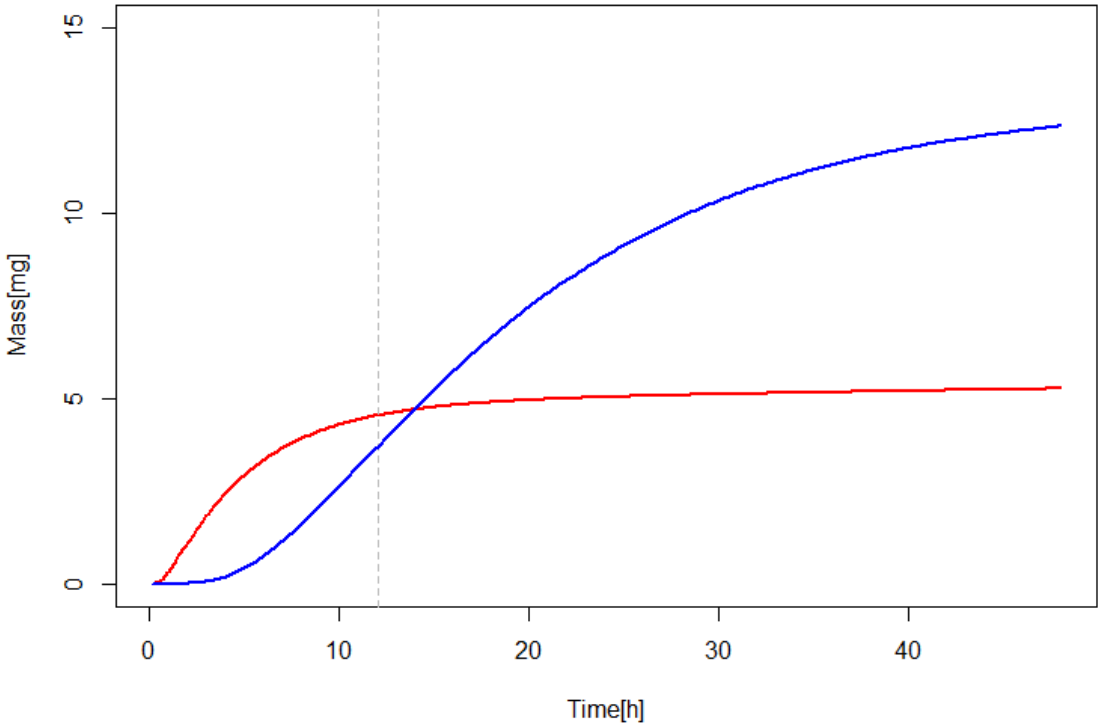




Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	34.675
FDp %:	0	34.674
F %:	0	34.655
Cmax (ng/mL):	172.11	212.82
TMax (h):	1.5	1.6
AUC 0-inf (ng-h/mL):	972.45	1529.1
AUC 0-t (ng-h/mL):	950.67	1377.4
CMax Liver (ng/mL):		126.35

20mg PO on Group2 Mild GFR- elimination

Urine(red) and Fecal (blue) Excretion



Cumulative Fecal Excretion at 24h: 8.856mg(44.28%)

Cumulative Urine Excretion at 24h: 5.038mg(25.19%)

20mg PO on Group3 Moderate GFR

UF UNIVERSITY of FLORIDA

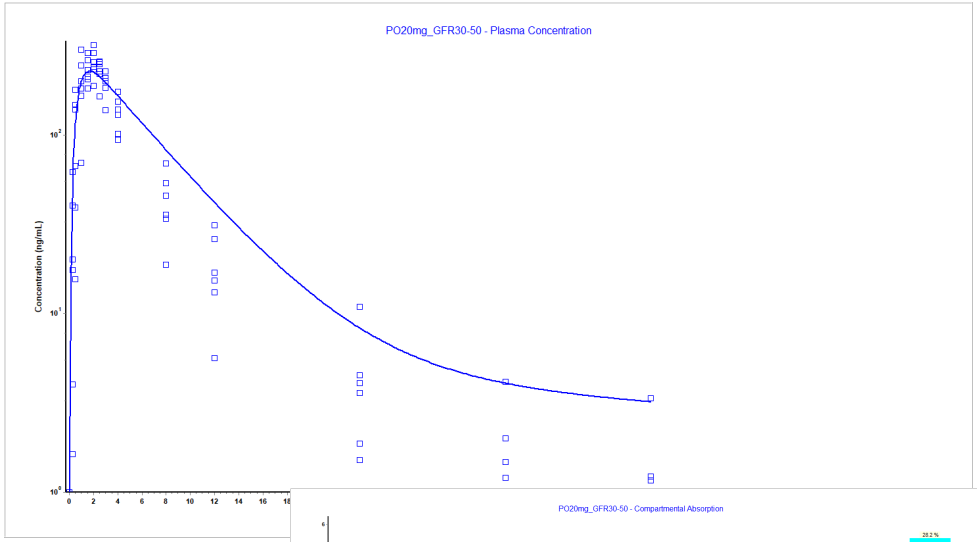
PK model

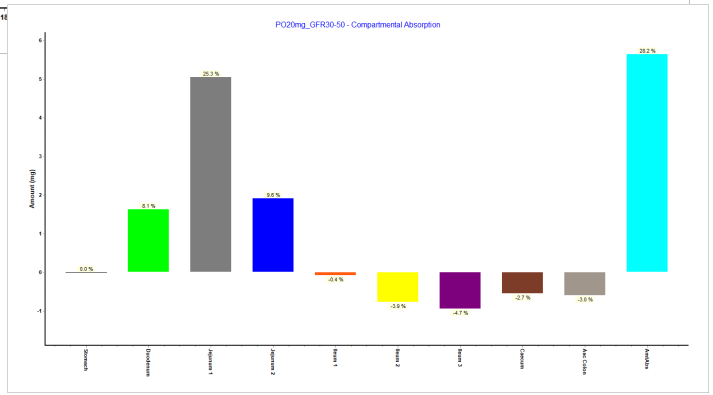
Age: 68

Weight: 86.19kg

Sex: Male

GFR: 1.9302 L/h

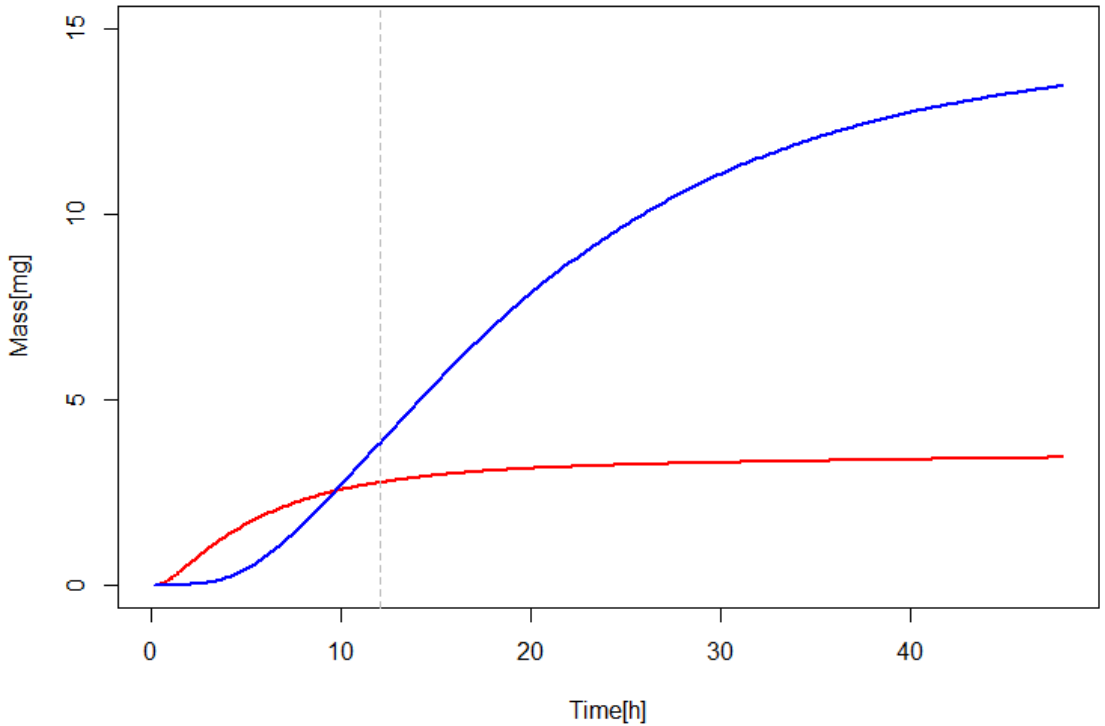




Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	28.213
FDp %:	0	28.211
F %:	0	28.196
Cmax (ng/mL):	271.09	227.67
TMax (h):	2	1.7
AUC 0-inf (ng-h/mL):	1382.4	2010
AUC 0-t (ng-h/mL):	1380	1776.3
CMax Liver (ng/mL):		129.56

20mg PO on Group3 Moderate GFR- elimination

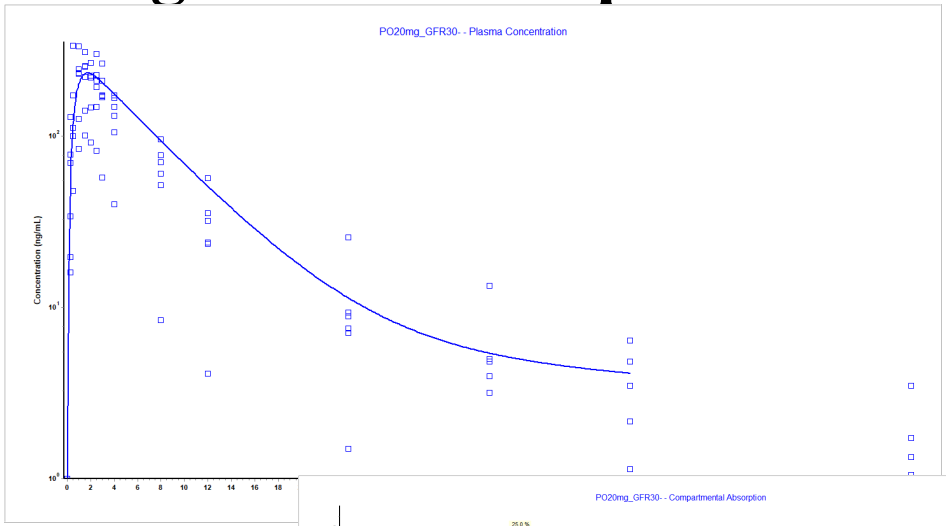
Urine(red) and Fecal (blue) Excretion

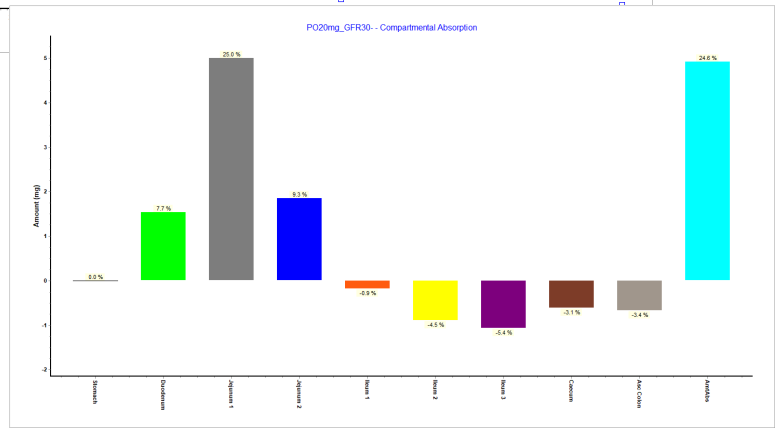


Cumulative Fecal Excretion at 24h: 9.405mg(47.03%)

Cumulative Urine Excretion at 24h: 3.222mg(16.11%)

20mg PO on Group4 Severe GFR





PK model

Age: 68

Weight: 86.19kg

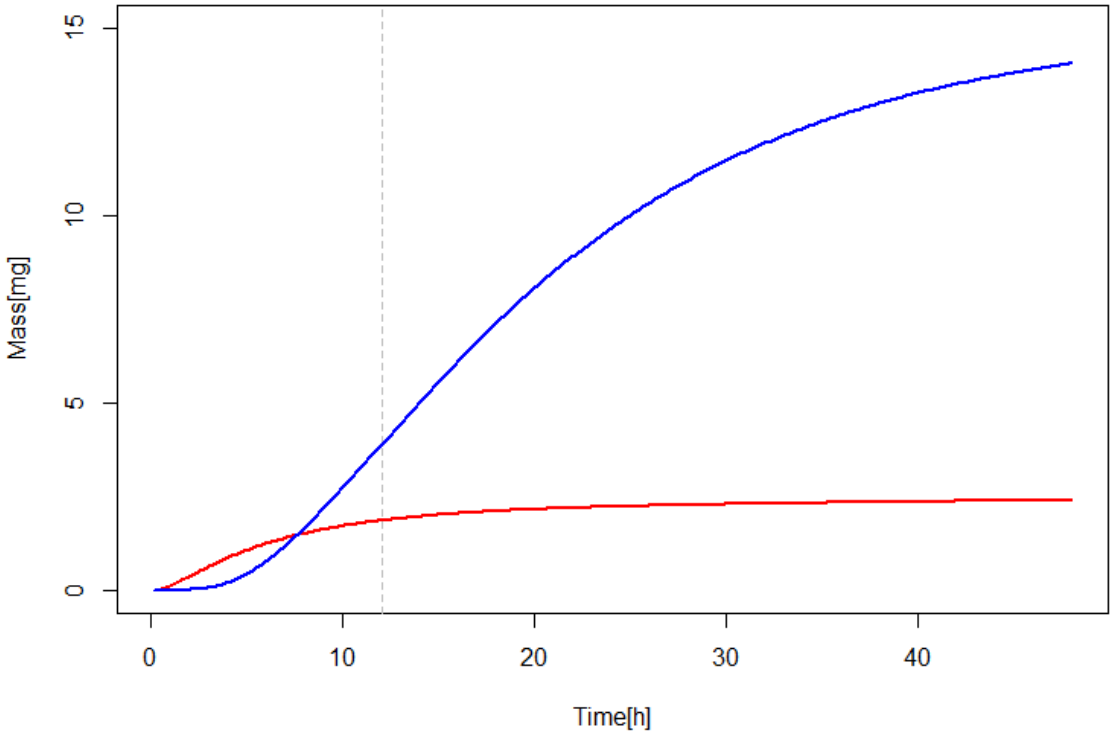
Sex: Male

GFR: 1.2 L/h

Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	24.612
FDp %:	0	24.609
F %:	0	24.596
Cmax (ng/mL):	228.79	234.1
TMax (h):	0.5	1.76
AUC 0-inf (ng-h/mL):	1723.9	2274.8
AUC 0-t (ng-h/mL):	1657.7	1997.5
CMax Liver (ng/mL):		130.97

20mg PO on Group4 Severe GFR- elimination

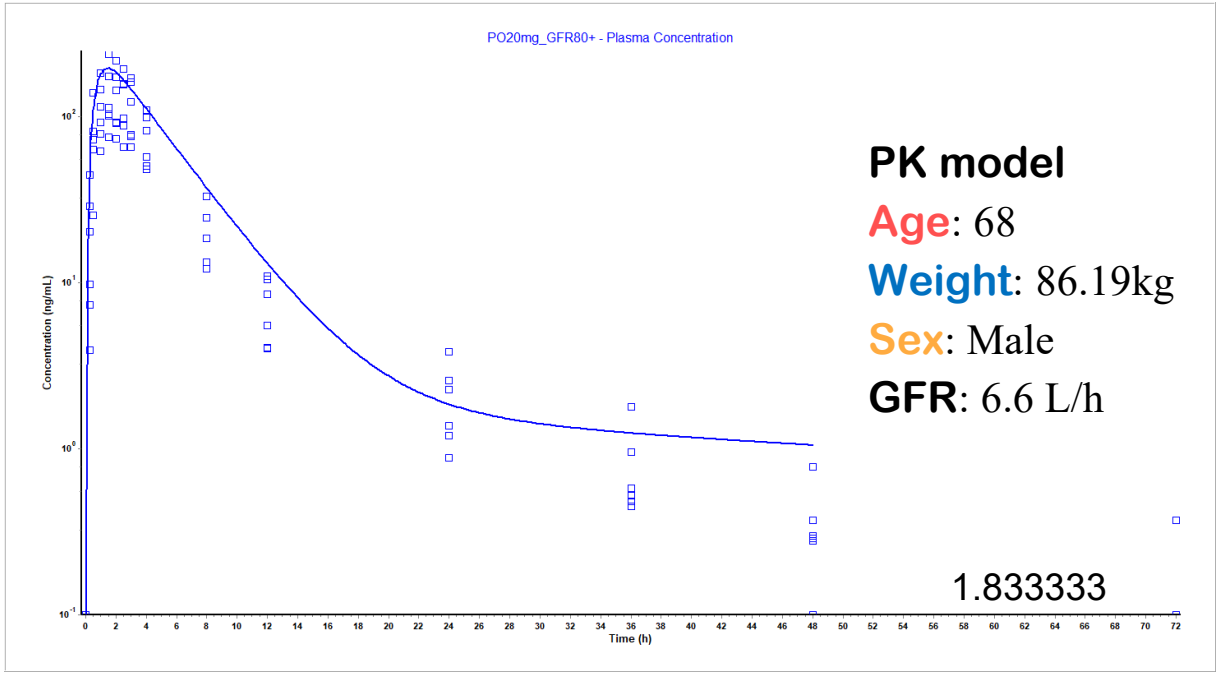
Urine(red) and Fecal (blue) Excretion



Cumulative Fecal Excretion at 24h: 9.678mg(48.39%)

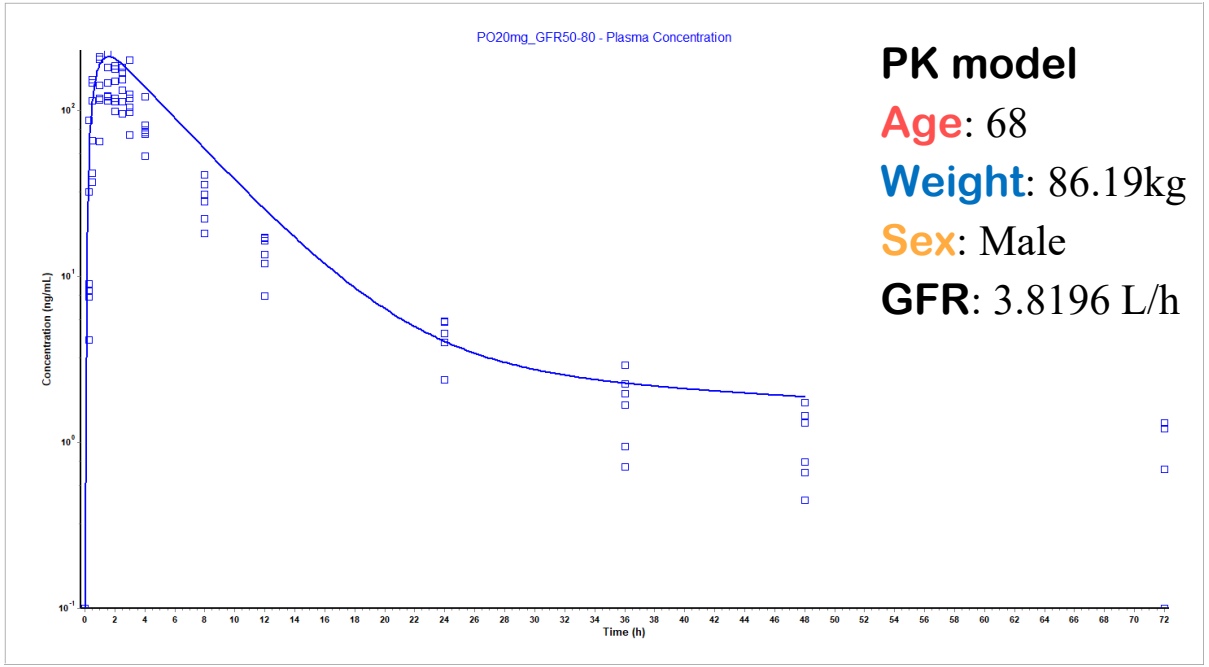
Cumulative Urine Excretion at 24h: 2.227mg(11.35%)

20mg PO on Group1 Healthy GFR



Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	40.212
FDp %:	0	40.212
F %:	0	40.19
Cmax (ng/mL):	144	194.6
TMax (h):	1.5	1.5
AUC 0-inf (ng-h/mL):	737.73	1117.3
AUC 0-t (ng-h/mL):	735.74	1032.5
CMax Liver (ng/mL):		122.22

20mg PO on Group2 Mild GFR



PK model

Age: 68

Weight: 86.19kg

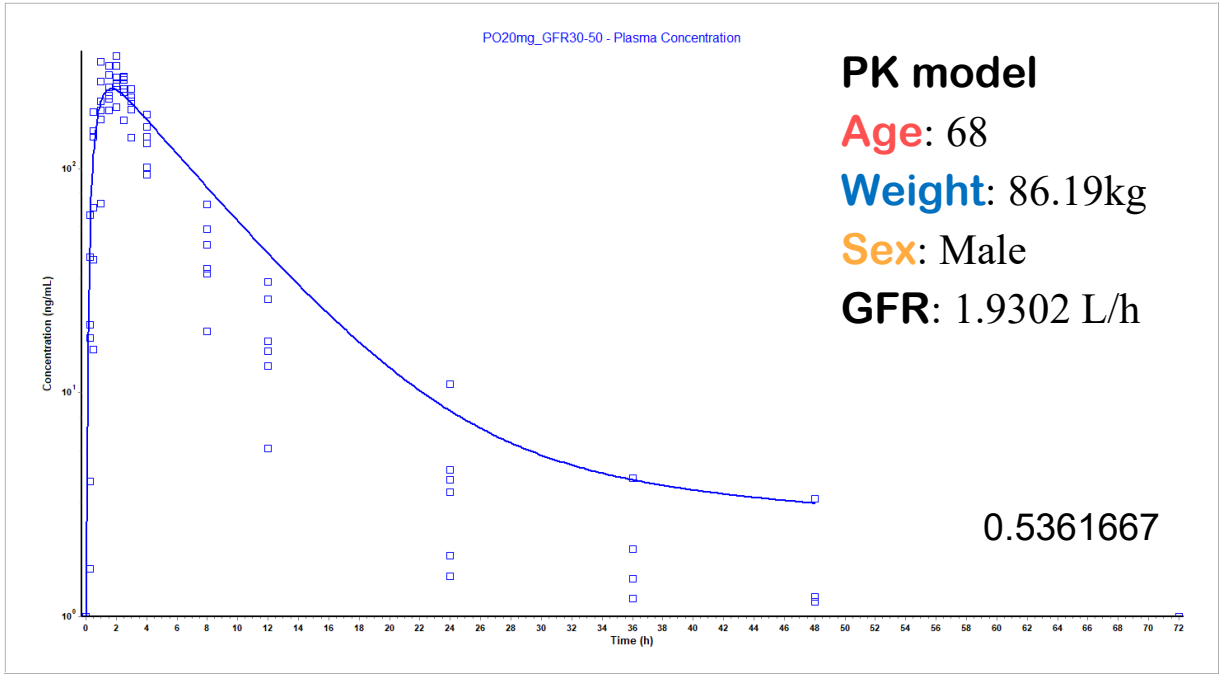
Sex: Male

GFR: 3.8196 L/h

Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	34.675
FDp %:	0	34.674
F %:	0	34.655
Cmax (ng/mL):	172.11	212.82
TMax (h):	1.5	1.6
AUC 0-inf (ng-h/mL):	972.45	1529.1
AUC 0-t (ng-h/mL):	950.67	1377.4
CMax Liver (ng/mL):		126.35

1.0555

20mg PO on Group3 Moderate GFR



PK model

Age: 68

Weight: 86.19kg

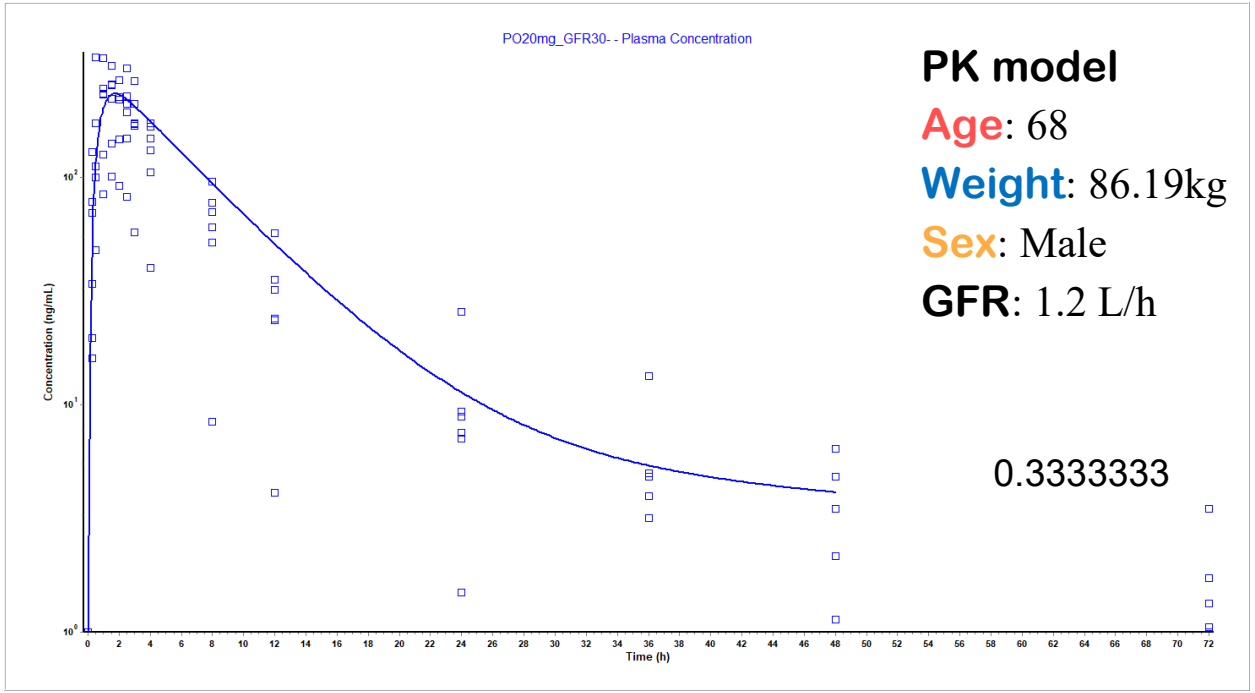
Sex: Male

GFR: 1.9302 L/h

0.5361667

Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	28.213
FDp %:	0	28.211
F %:	0	28.196
Cmax (ng/mL):	271.09	227.67
TMax (h):	2	1.7
AUC 0-inf (ng-h/mL):	1382.4	2010
AUC 0-t (ng-h/mL):	1380	1776.3
CMax Liver (ng/mL):		129.56

20mg PO on Group4 Severe GFR



PK model

Age: 68

Weight: 86.19kg

Sex: Male

GFR: 1.2 L/h

0.3333333

Simulation Time Elapsed (h):		48.
	Obs	Calc
Fa %:	0	24.612
FDp %:	0	24.609
F %:	0	24.596
Cmax (ng/mL):	228.79	234.1
TMax (h):	0.5	1.76
AUC 0-inf (ng-h/mL):	1723.9	2274.8
AUC 0-t (ng-h/mL):	1657.7	1997.5
CMax Liver (ng/mL):		130.97

20mg PO by GFR- elimination summary

Baseline characteristics	Group 1 Healthy	Group 2 Mild	Group 3 Moderate	Group 4 Severe
N	N=6	N=6	N=6	N=6
GFR (ml/min); Mean±SD	110.0±13.08	63.33±7.84	32.17±6.80	20.00±6.69
Age (years)	65.7±1.97	71.2±5.42	71.3±4.63	65.0±14.63
Sex				
Male	5	5	5	4
Female	1	1	1	2
Urine excretion at 24h	6.612mg (33.06%)	5.038mg (25.19%)	3.222mg (16.11%)	2.227mg (11.35%)
Fecal excretion at 24h	8.314mg (41.57%)	8.856mg (44.28%)	9.405mg (47.03%)	9.678mg (48.39%)

Study 459_05
Demographic characteristics

GROUP 3_MALE

ID	AGE (years)	SEX	WEIGHT (kg)	HEIGHT (cm)
17	73	male	68.7	177
18	67	male	79.9	174
19	66	male	73.2	179
20	65	male	63.4	168
21	83	male	73.9	167
22	73	male	83.7	170
23	66	male	77	160
24	65	male	80.5	173
Average	69.75	male	75.0375	171

Study 459_05
Demographic characteristics

GROUP 4_FEMALE

ID	AGE (years)	SEX	WEIGHT (kg)	HEIGHT (cm)
25	69	female	48.4	150
26	65	female	82.1	169
27	65	female	64.4	161
28	67	female	78	164
29	77	female	70.2	160
30	65	female	85.1	168
31	65	female	72.4	161
32	68	female	68	163
Average	67.625	female	71.075	162