Case Study 2
Zurampic (lesinurad) immediate release tablet

Anders Lindahl
Quality Assessor
Swedish Medical Products Agency

Flora Musuamba Tshinanu
Pharmacometrician
Federal Agency for Medicines and Health Products, Belgium

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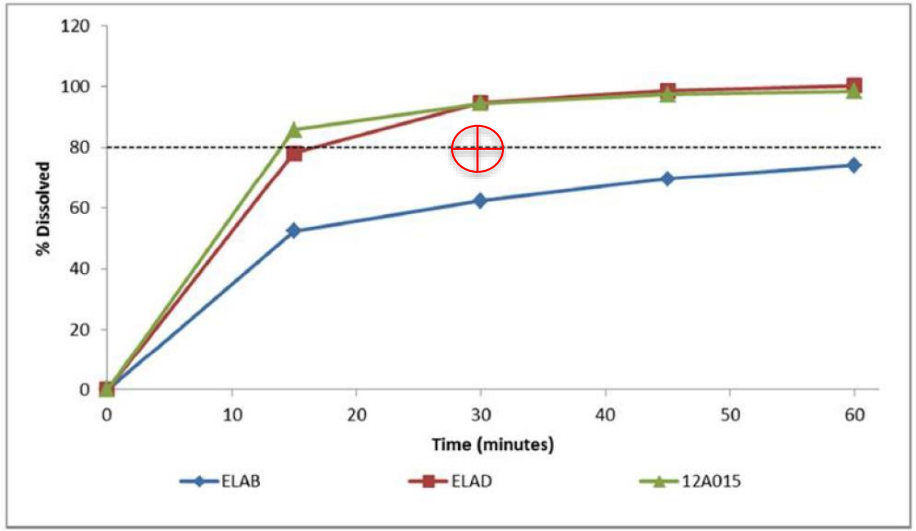
Overview

1. Purpose of the model and Regulatory impact
2. Modeling strategy
3. Model building
4. Evaluation of the predictive performance of the model
    a) Predicting the pivotal batch included in model building
    b) Predicting the non-bioequivalent batch ELAB
5. Parameter Sensitivity Analyses
6. Simulation of the intended scenario
7. Credibility matrix
8. Conclusions

1. Purpose of the model

- Justify that a dissolution specification of Q=80% at 30 min is acceptable for Zurampic (lesinurad) tablets (400 mg and 200 mg).



Paddle (USP II) 900 ml pH 4.5, 1% SLS, 75 rpm. Solub. 1.77 mg/ml
BCS 2 product, acid, high solubility @ intestinal pH

***In vitro* dissolution (QC) of batches included in study RDEA594-129:**

Pivotal batch 12A015

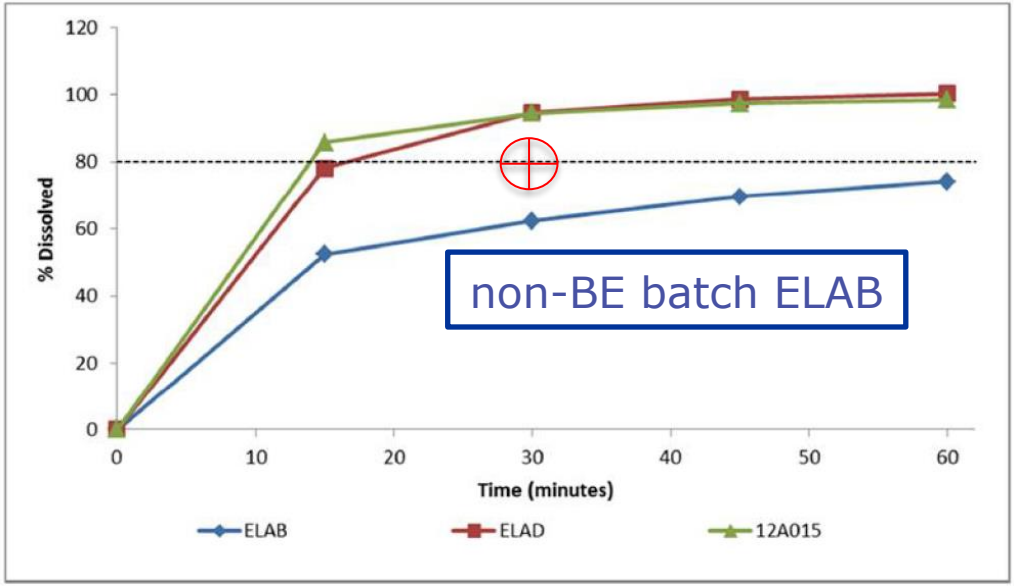
Batch ELAD was BE to batch 12A015
(both fasted and fed)

Batch ELAB was non-BE to batch 12A015
(both fasted and fed)

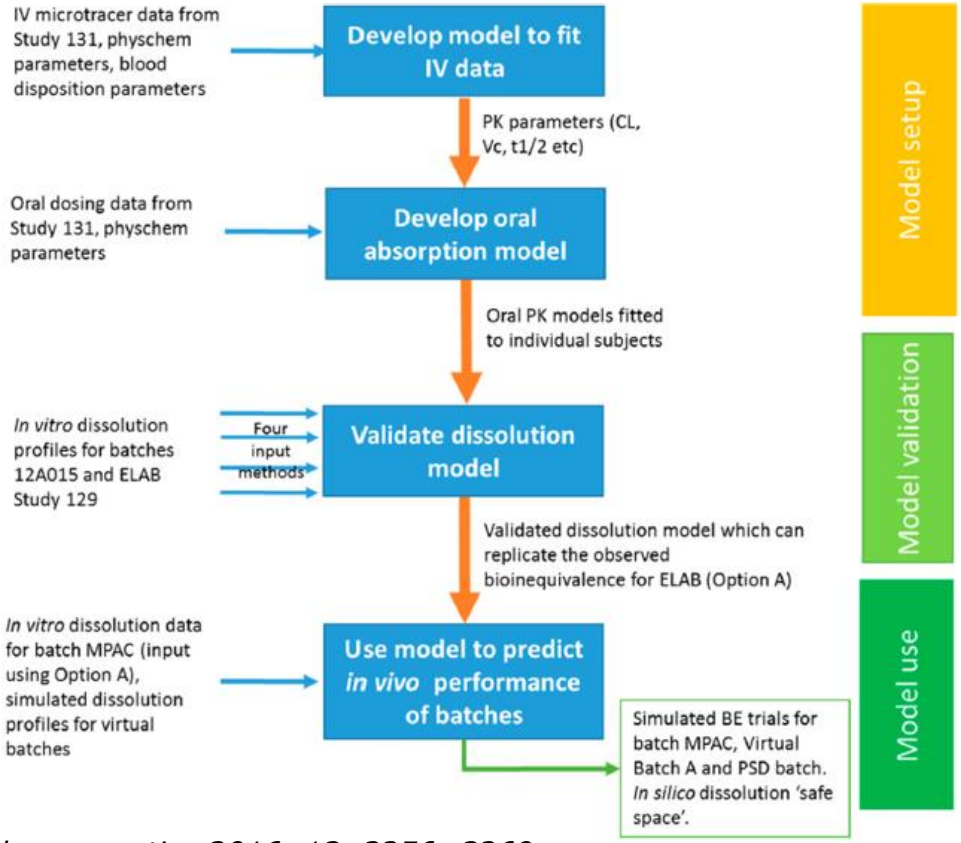
BE = Bioequivalent

Regulatory impact of the model is low

- EMA: the specification limit Q80% in 30 minutes was accepted based on the *in vitro* dissolution of the Phase 3 batches and two non-BE batches (over-granulated).
  - The PBBM model was not submitted to the EMA (only to the FDA)



2. Modeling strategy



- **iv microtracer data available**
- **Pivotal batch 12A015 400 mg**
  - Plasma profiles
    - *In vitro* dissolution
- **NON-BE batch ELAB 400 mg**
  - Plasma profiles
    - *In vitro* dissolution

Pepin et al. Mol. Pharmaceutics 2016, 13, 3256−3269

3. Model building

- ***Top-down data driven approach, individual models***
  - Individually extraction of PK parameters, 3-comp.
  - Individually fit Peff to observed oral plasma profile: Peff 1.7-5.4 x 10^{-4} cm/s
  - Individually fit of gastric emptying time to oral plasma profile.
- ***Uncertainties in gastric emptying, Peff and fluid volumes in GI tract.***
  - The % default values for standard volume occupation by water in the small intestine and colon (40% and 10%) respectively, were reduced to 7.5% and 2%*

**Schiller C. et al., Aliment Pharmacol Ther. 2005 Nov 15;22(10):971-979*

Model building, continued

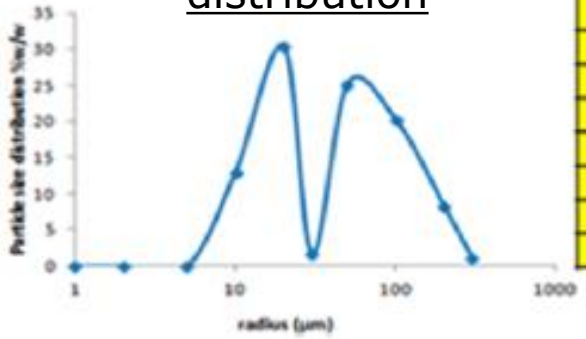
Theoretical Product-Particle Size Distribution (P-PSD) approach justified; influence of pH acceptable.

(if used to support setting of API particle size more data needed)

Uncertainties in formulation switch (no data shown).

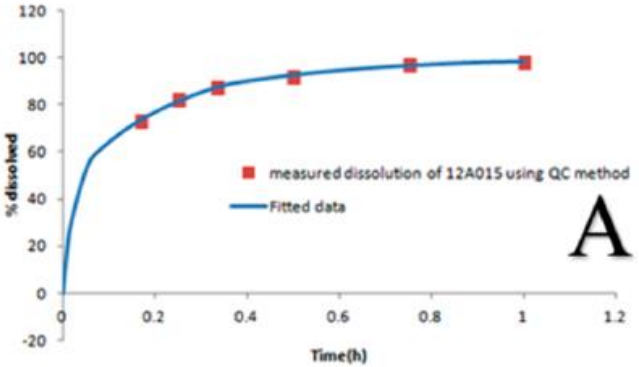
- **Input of *in vitro* dissolution data**: Fitting to a theoretical particle size distribution that would match observed *in vitro* dissolution for the batch.
- **Switch formulation** from immediate release tablet to delayed release enteric coated tablet to prevent release in the stomach.

Particle size distribution



Radius (um)	% w/w
10	13.05
20	30.36
30	1.67
50	25.22
100	20.26
200	8.36
300	1.09

In vitro dissolution (QC)



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Model building, continued

- Double peaks in three subjects: Mixed Multiple Dosing (MMD) used in G+ models.

subject	P_{eff} (cm/s $\times 10^{-4}$)	lag time first peak (h)	dose first peak (mg)	gastric residence time second peak (h)	dose second peak (mg)
S101	2.8121	3.17	400		
S102	2.4187	0.81	400		
S103	2.8765	1.73	400		
S106	2.9872	1.32	200	4.25	200
S112	3.7031	0.72			
S115	3.1256	0.09			
S116	2.7388	0.62			
S118	1.8112	0.01	150	2.01	250
S122	1.7419	1.37	200	5.37	200
S123	5.4409	0.54			

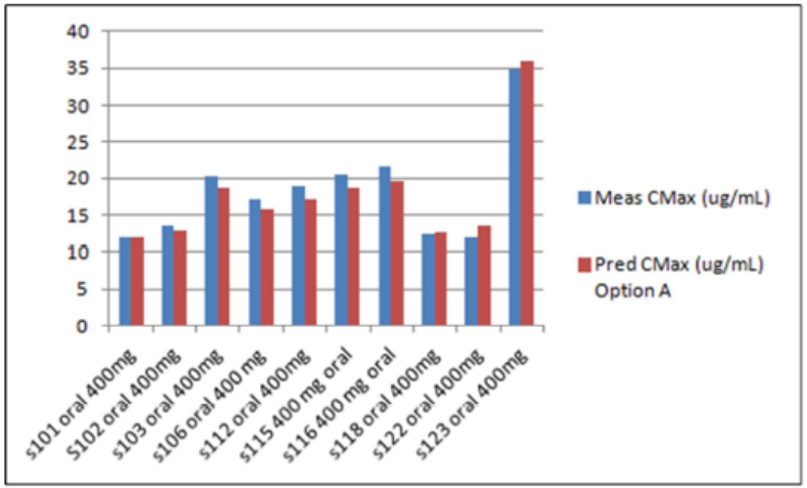
Individual models, uncertainties in gastric residence time. MMD questionable as input dose should be as in clinical study, i.e. 400 mg tablet at time zero in all subjects, long gastric residence time fasting needs justification

4. Evaluation of the predictive performance of the model

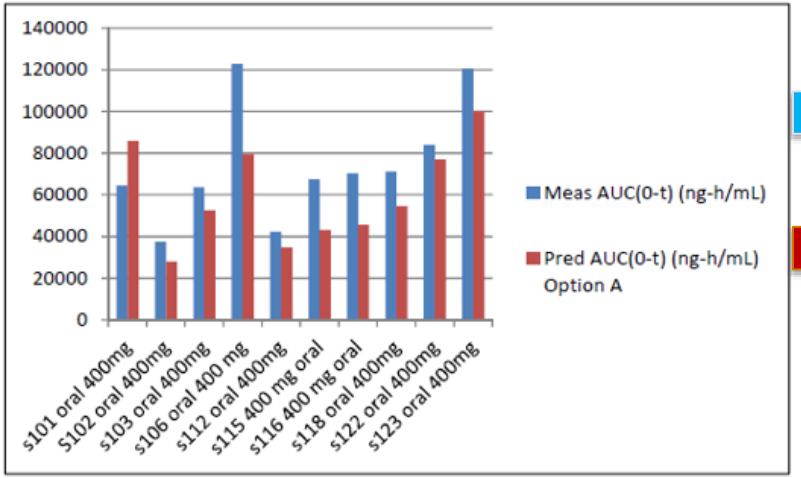
A. Prediction of **pivotal batch 12A015** (used in model building)

"Satisfactory prediction" according to the company. Model seems to underpredict, especially AUC. Would like to see summary statistics. What is the prediction error? What is an acceptable prediction error according to the company?

Cmax



AUC



Measured

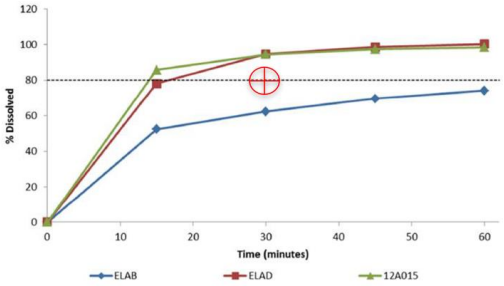
Predicted

4. Evaluation of the predictive performance of the model

B. Prediction of **non-BE batch ELAB**

"For batch ELAB it was necessary to **reduce the dose in the GastroPlus simulation** to compensate for the lower exposure (AUC ratio 0.88) obtained in the clinical study comparing batch ELAB to batch 12A015. The dose was reduced to 352 mg (0.88 x 400 mg)." "The model could adequately predict Cmax ratio between ELAB and 12A015"

The model input dose should be the clinical dose 400 mg, not 352 mg. This is not acceptable. Predicting ratio only is not a preferrable approach. The model can not predict the non-BE batch.



5. Parameter Sensitivity Analyses (PSA)

Figure 39 Parameter sensitivity analysis for batch 12A015

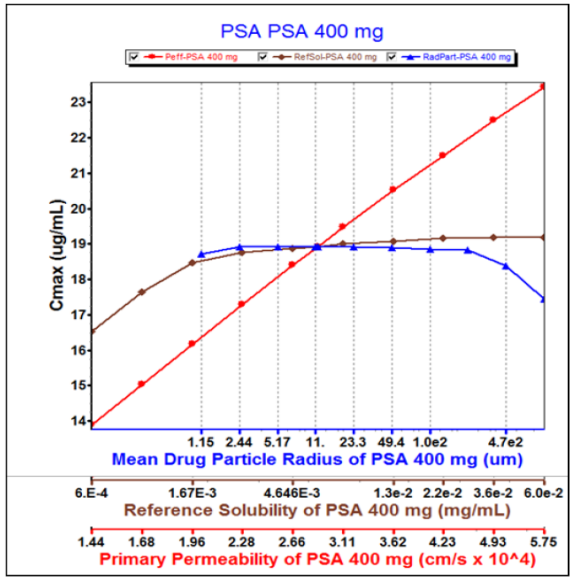
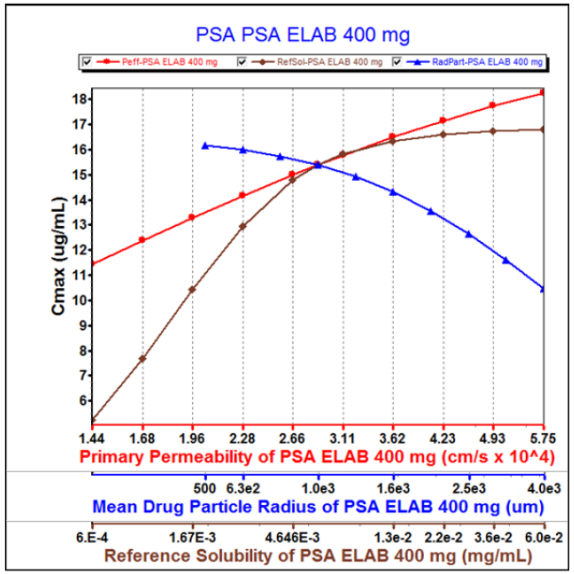


Figure 40 Parameter sensitivity analysis for batch ELAB

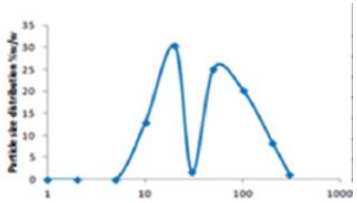


One PSA for each subject and batch (only Cmax)

Peff

Solubility

Particle radius



Gastric residence time, GI volumes and formulation switch are missing. Not presented how single particle radius is related to theoretical particle size distribution pattern for each batch. Preferrable with one PSA for the model.

6. Simulation of the intended scenario

Why use same subjects as in model building? Why stomach pH variability (no gastric release in simulations)? No within subject variability.

- Dissolution profile for batch MPAC (*in vitro* dissolution: 80% 30 min = intended scenario) was used for the simulations.
- Virtual population (n=25) based on subjects included in model building.
- Random stomach pH and gastric recidence time (within observed range) added to each subject to account for between subject variability.
- Within subject variability was not simulated in the virtual trial (pivotal batch 12A015 vs MPAC Q80% 30 min), with the same model used for each treatment within a subject. Predicted confidence intervals from simulated trial are tighter than those observed in clinical studies.
- Conclusion from company: BE expected for batch with Q80% 30 min. Dissolution specification justified.

7. Credibility assessment Matrix

Item	Entry
Investigational product	Lésinurad (ZURAMPIC) is a selective uric acid reabsorption inhibitor, administered orally as an immediate release tablet
Type of model	ACAT PBBM model as implemented in Gastroplus
Scientific Question(s) of Interest	- Is a dissolution specification of Q=80% at 30 min is acceptable for Zurampic (Lesinurad) tablets?
Context of Use	The objective of the model is to predict the dissolution profiles *in vitro* and *in vivo* and related parameters. The modeling package is intended to support the proposed specifications for dissolution and particle size. **Comparative in vitro dissolution data are available to answer the question of interest using the QC method.**

*ACAT = **A**dvanced **C**ompartment **A**bsorption and **T**ransit*

Credibility assessment Matrix

Item	Entry
Model influence	**Low** because the in vitro dissolution data are sufficient to support the proposed threshold to know if an *in vivo* study is necessary.
Decision consequence	Risk based analysis of decision consequence is **low**. No clinical consequence is expected from the modelling results given the availability of the in vitro data with the QC method and given that no different threshold is proposed from the modelling exercise. **If the model had higher impact, (e.g. a lower threshold was proposed in absence of in vitro data), then there would a risk of therapeutic failure. Then noncomparable batches could be commercialized. This could imply therapeutic failures.**
Regulatory impact and Risk assessment	**Low** because the in vitro dissolution data are sufficient to support the proposed threshold to know if an *in vivo* study is necessary.

Credibility assessment Matrix

Item	Entry
Basis for acceptability of MIDD approach	No formal qualification would be requested given the Low regulatory impact. **If the model had higher impact, a qualification of the platform would be requested, as well as demonstration of acceptable model predictive performance and simulation results.**
Output of Model evaluation	Data submitted do not support formal Platform qualification Several issues are identified in the implementation of model building and evaluation.
Model informed decision	**The dissolution specifications are same recommended with the QC method** and are accepted. If the impact was higher, the model could not have been accepted.

8. Conclusions

- **The suggested *in vitro* dissolution specification Q80% 30 min would have been accepted mainly based on the *in vitro* dissolution of the pivotal batches** (Phase 3).
- Low model influence and low regulatory impact.
- Data driven top-down input parameters (Peff, gastric emptying, two fractions of the dose for individual subjects).
- The external model (Excel) to create the virtual particle size distribution is not assessed.
- The verification of the model, with manually adjusting the input dose is not acceptable.
- The virtual trial (model use) using the same subjects as for the model building, and lower variability than observed in clinical studies is questionable.
- **Model would not have been accepted to justify an extended *in vitro* dissolution safe space beyond the Q80% in 30 min**.

Thank you

Any questions?

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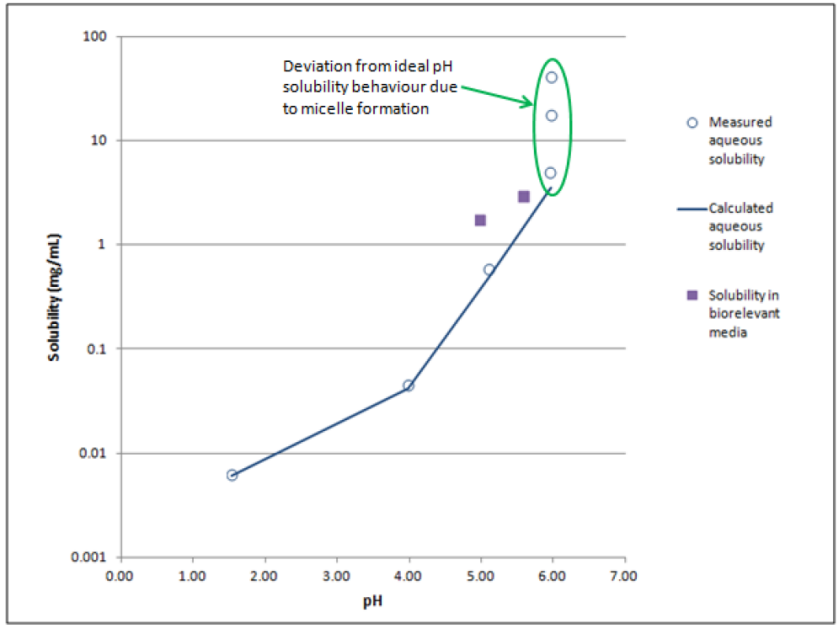
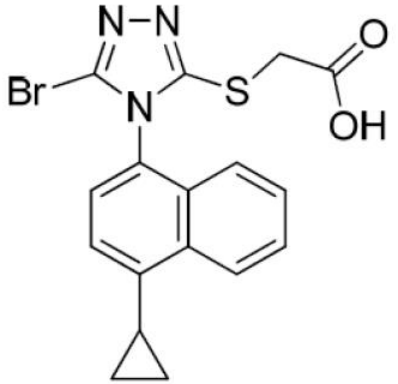
Backup: Biopharmaceutics properties of lesinurad

- BCS 2, with poor solubility at low pH. Good solubility in small intestine.
- Peff ”high”, calculated from Caco-2 Papp (*no data presented*). Supported by high bioavailability; F=”100%”. Log P 2.85, weak acid. API free acid. Dose strength 200 and 400 mg.





Backup: Impact of small intestine lumenal water on systemic exposure of lesinurad.

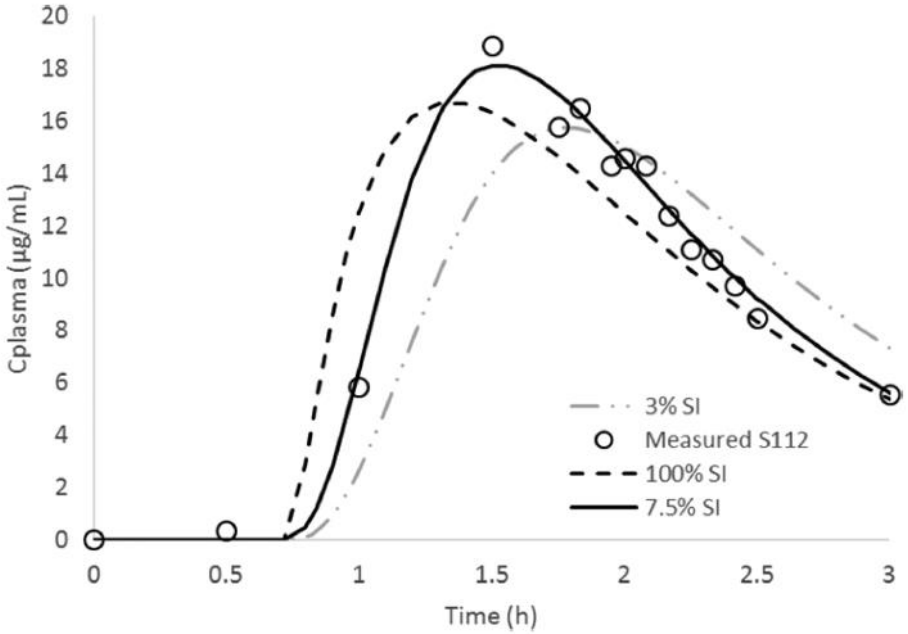


Figure 7. Simulated PK profile vs measured plasma concentrations for S112 following administration of 400 mg 12A015 tablet using Option A.

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