



# PBBM of colon absorption & ER drug product performance

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FDA/M-CERSI workshop on Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality, Rockville, Md, US, August 29-31, 2023



# Outline

- Background & Introduction
- PBBM of regional & colon absorption in humans
  - *a priori* approach
- Case Study: Verinurad ER PBBM
- PBBM of ER drug products – Approaches to account for colon absorption
  - *a priori* modeling approach
  - Colon absorption approach
  - Slowest ER variant approach
- Concluding remarks



# Introduction

PBBM currently mainly used for IR drug product applications

ER predictions more complex

- Need to account for regional/colon absorption differences
- Identified gap in the Biopharmaceutics M&S capability

Colon absorption is key for a successful ER product

- Limited colon absorption a main reason why ER development may fail

The colon environment – a formidable absorption barrier

- Dissolution - small water volume, poor agitation, "No" bile acids
- Permeability – low surface area, narrower tighter junctions, transporter expression levels
- Degradation – bacteria-mediated

Development stage appropriate predictive ER PBBMs - Benefits

- Early assessment of probability of success for ER product development
- Reduce development cost & time – smart product design & fewer BA studies
- Regulatory applications - justify specs, IVIVC, biowaivers etc



# Colon absorption & ER drug product assessment overview

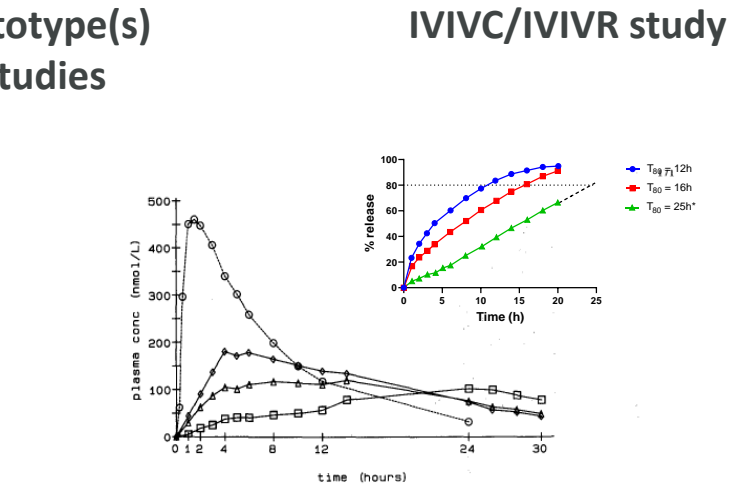
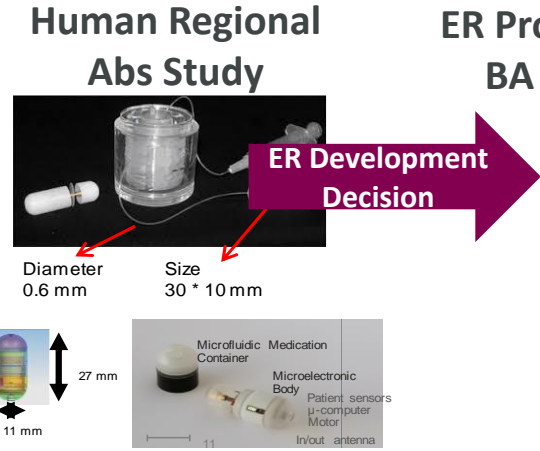
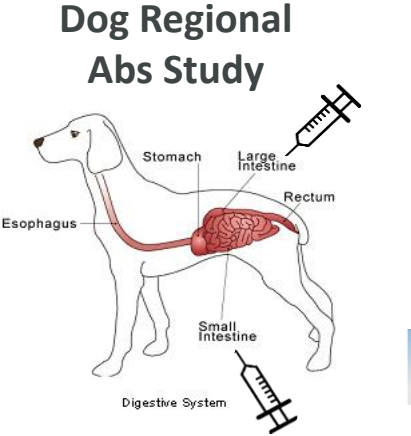
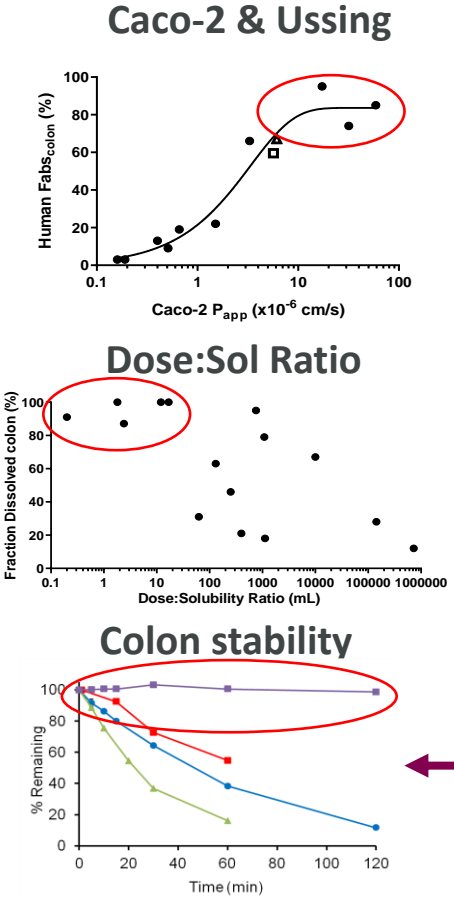


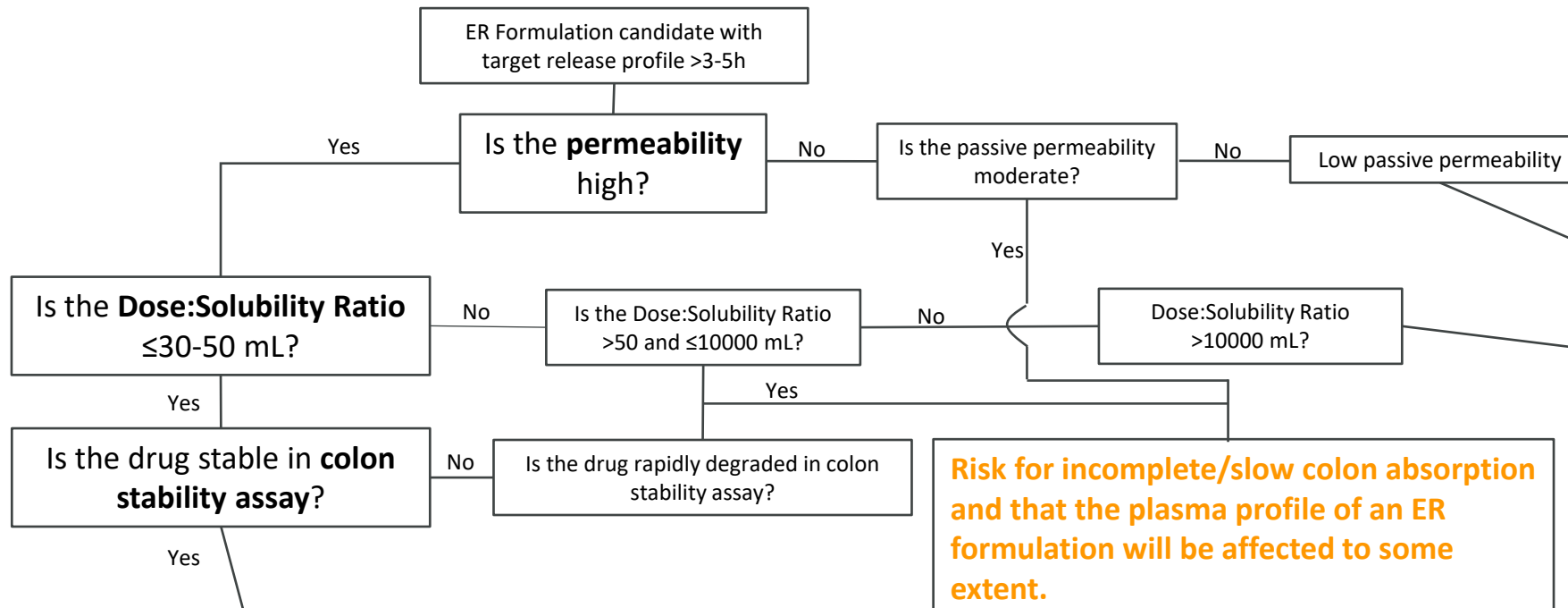
Fig. 1. Mean (n = 10) plasma concentrations of metoprolol after single dose administration of metoprolol succinate 95 mg as an oral solution (○) and three extended-release formulations A (△) and C (□).

Relative bioavailability in colon ( $F_{rel_{colon}} = RBA$ )

**PBBM Applications?**



# In vivo predictive in vitro based colon absorption limitation risk assessment



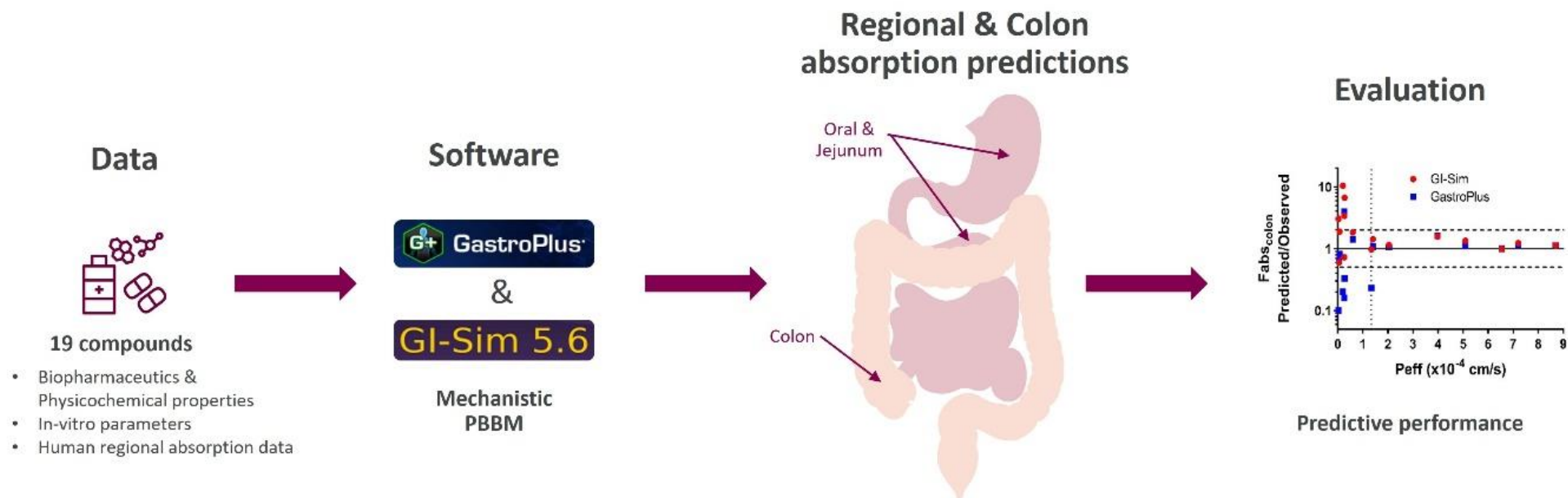
**Low Risk for ER formulation failure due to poor colon absorption**  
Candidate suitable for ER development.

**Risk for incomplete/slow colon absorption and that the plasma profile of an ER formulation will be affected to some extent.**  
Candidate may be suitable for ER. The overall risk level is likely increased if several risk factor are identified.

**High Risk for ER formulation failure due to poor colon absorption**  
Not recommended to initiate ER formulation development unless short release profiles (<3-5h) are feasible.



# Evaluation of PBBM colon absorption prediction performance



## Novel dataset established

- 19 compounds & 24 colon administrations
  - 17 solutions
  - 7 non-solutions - suspension, powder or granules
- Peff range: 0.03-8 x10<sup>-4</sup> cm/s
- Solubility range: 0.0002-43 mg/ml
- Frel<sub>colon</sub> range: 5-100%
- Fabs<sub>colon</sub> range: 3-100%

## Modeling strategy

- a priori modeling approach
  - Dataset allowed absorption focused evaluation
  - Biopredictive & AZ standard in vitro input parameters
- Prediction parameters: AUC<sub>colon</sub>, Frel<sub>colon</sub>, Fabs<sub>colon</sub>

## Prediction performance criteria

Highly Accurate

- **AAFE < 1.25** & AFE between 0.8-1.25
- sufficient for commercial drug product applications

Accurate

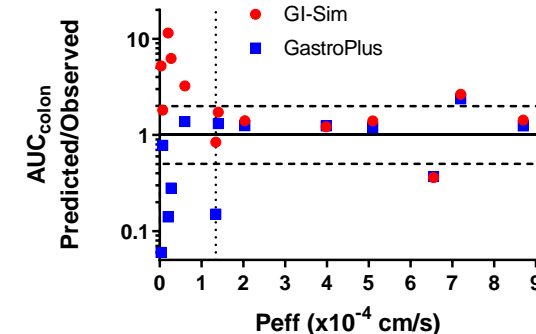
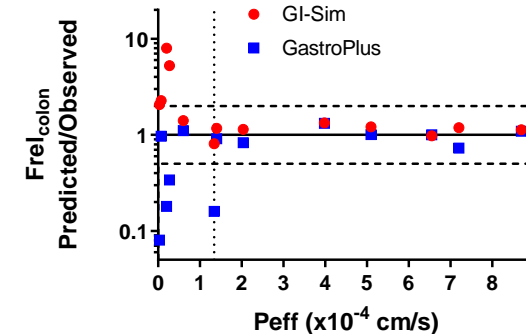
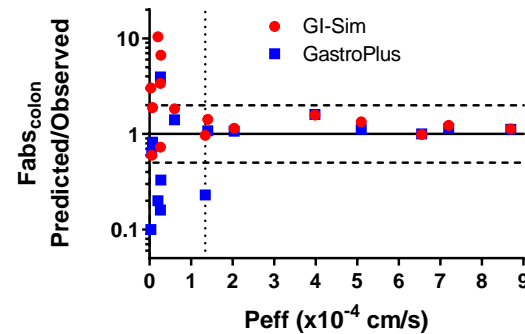
- **AAFE 1.25-2** & AFE within [0.5-0.8]/[1.25-2]
- sufficient for candidate drug selection and early drug product design and development applications



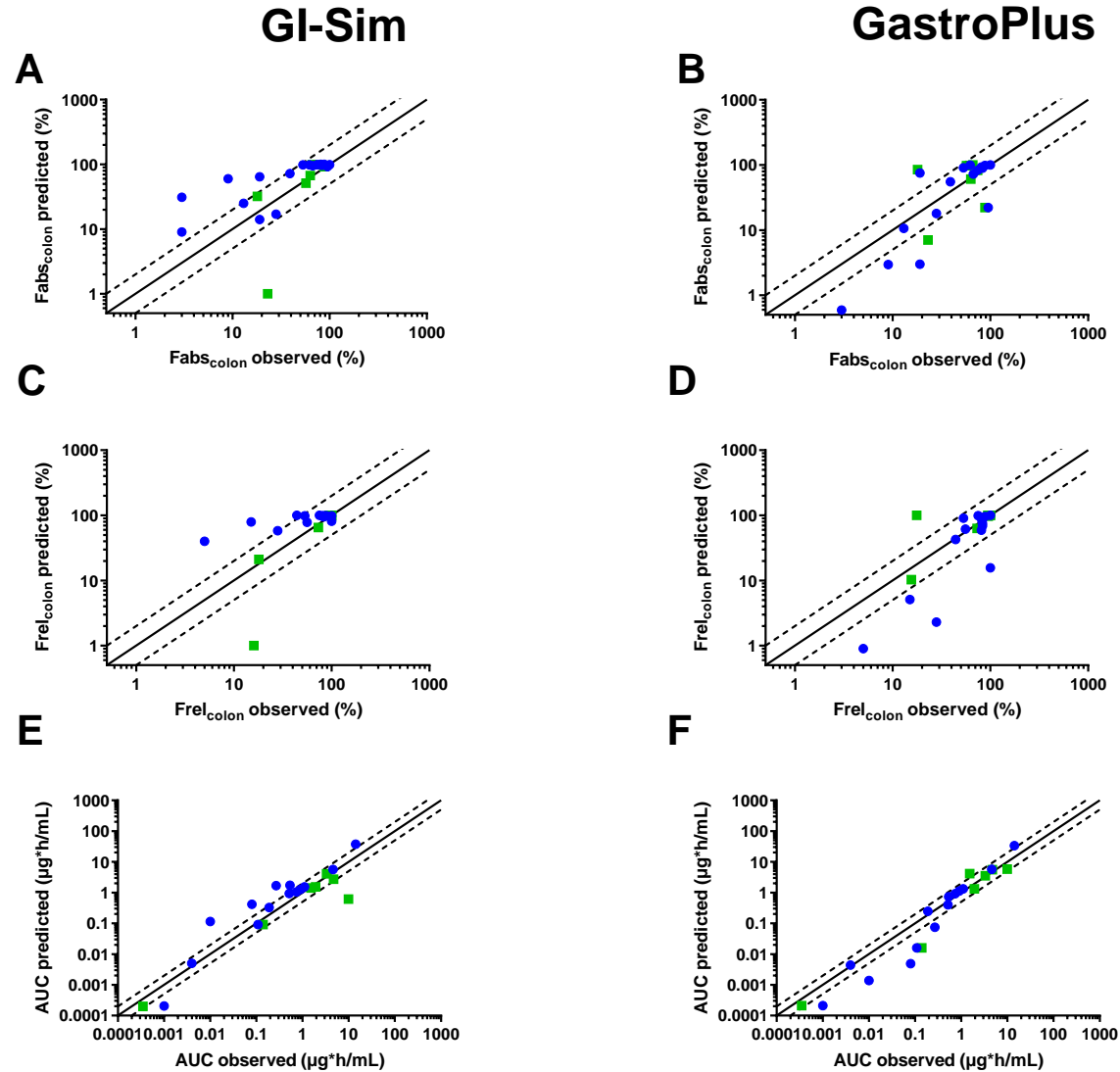
# PBBM of colon absorption - Prediction performance (solutions)

## Colon model evaluation

- Highly Accurate prediction performance not achieved
- High permeability drugs - Accurate predictions (**AAFE: 1.25-2**)
- Low permeability drugs - Poor predictions (**AAFE: >2**)
  - GI-Sim: overprediction
  - GastroPlus: underprediction



# PBBM of colon absorption - Prediction performance



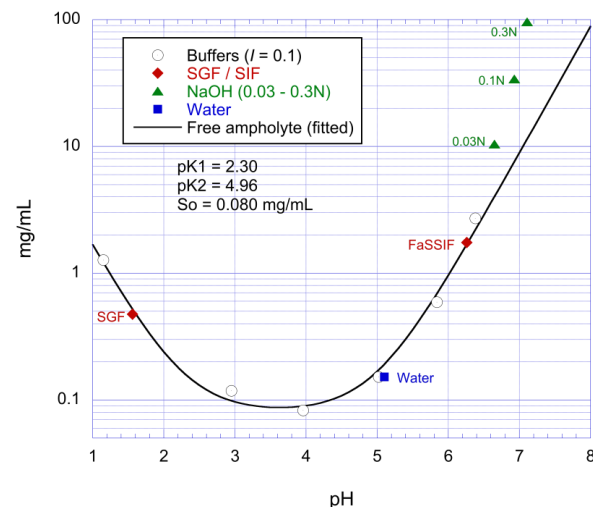
Non-solutions  
Solutions





# Verinurad PBBM ER Case Study

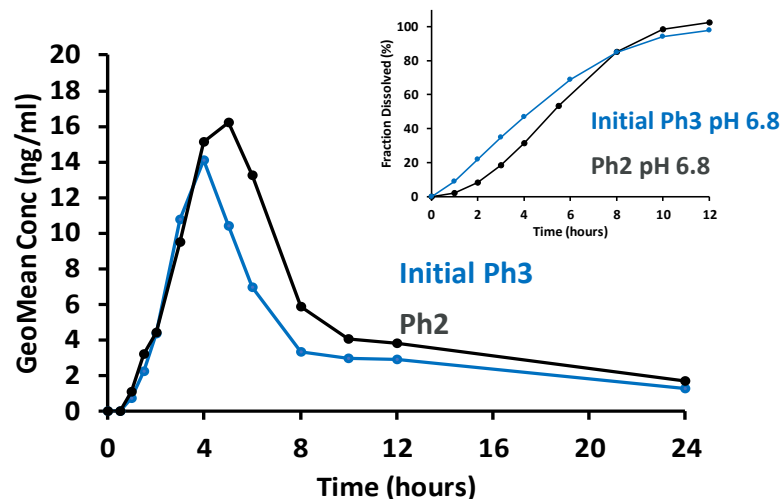
## Biopharmaceutics properties



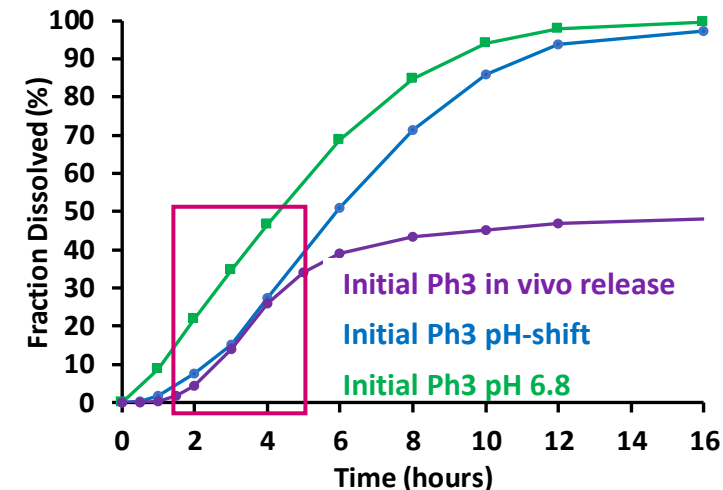
- BCS Class I
- pH-dependent release expected
- Low colon absorption limitation risk

BUT...

## Clinical performance vs in vitro learnings – initial Ph3 ER prototype



- Lower exposure than expected for Ph3 ER prototype based on pH 6.8 release

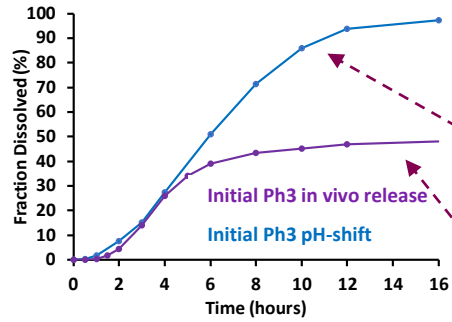


- Extent of absorption: 40-50%
- 3-4 h Absorption window
  - Colon absorption limitation
  - Initial lag-time
- in vivo release better captured with pH-shift release method

Proposal to improve absorption with a faster profile  
– maximize SI release/absorption



# in vitro dissolution/PBBM approach to increase verinurad absorption

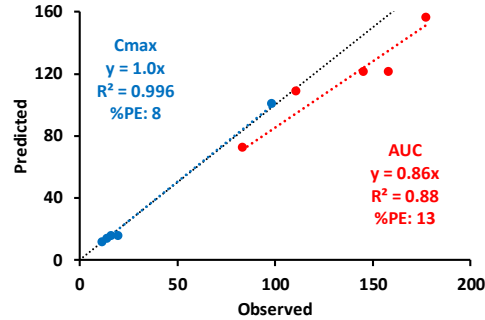


in vivo data on IR and ER Formulations

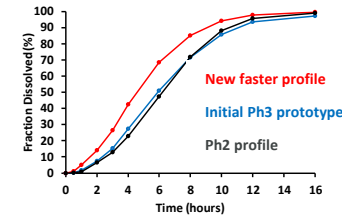
pH- shift dissolution (Weibull)

Colon ASFs fitted to match Initial Ph3 in vivo release

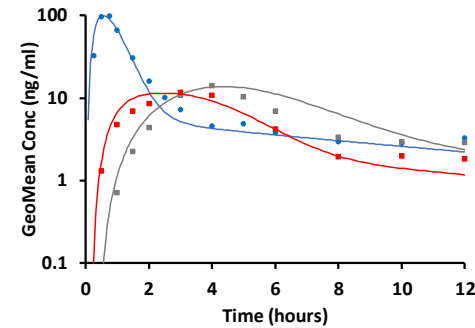
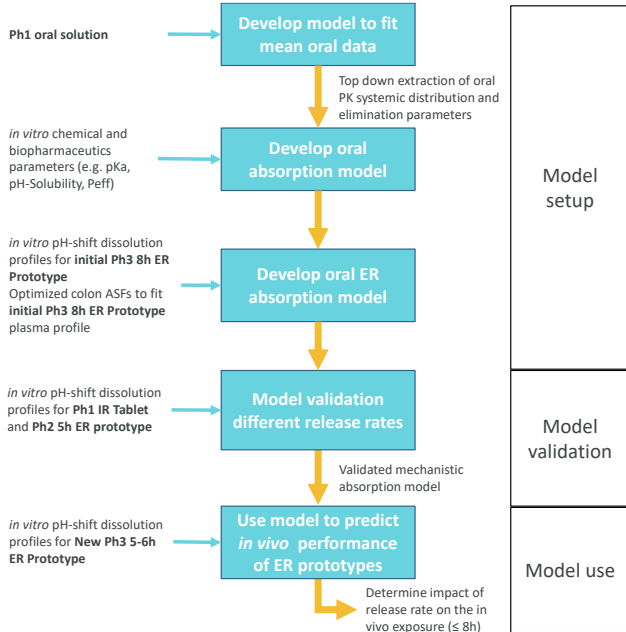
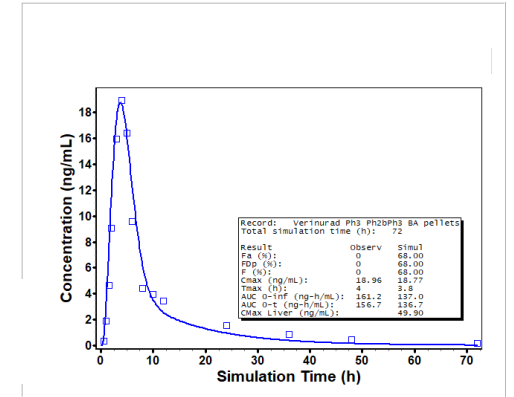
Validated PBBM: Highly Accurate predictions



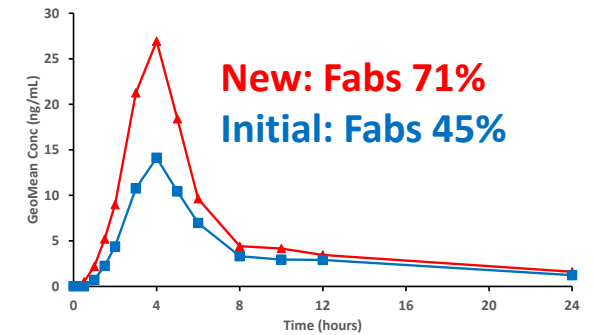
New profile selected BA manufacture BA Prediction



New Ph3: Prediction vs Obs



Initial prototype vs New Ph3

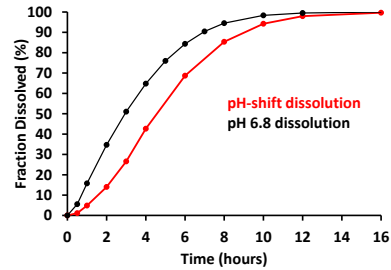
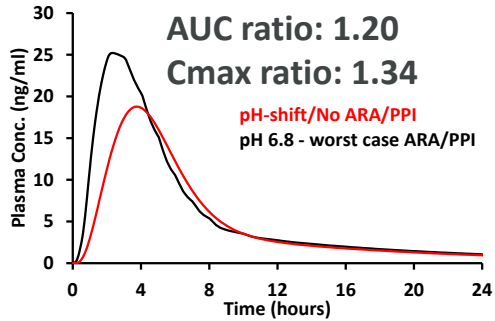


Is this approach generally applicable?

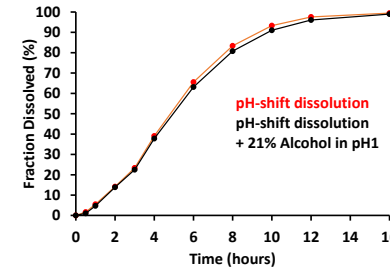
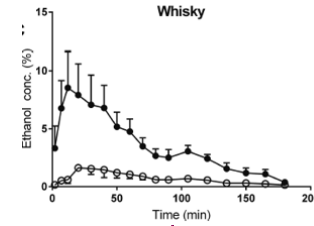
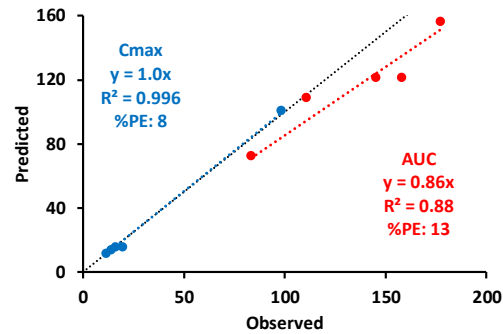


# Verinurad ER PBBM – Additional applications

ARA/PPI DDI  
Predictions  
(worst case)

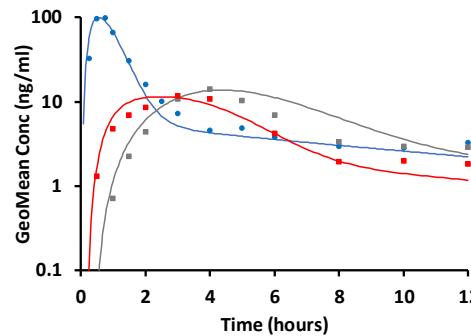


Validated PBBM:  
Highly Accurate predictions



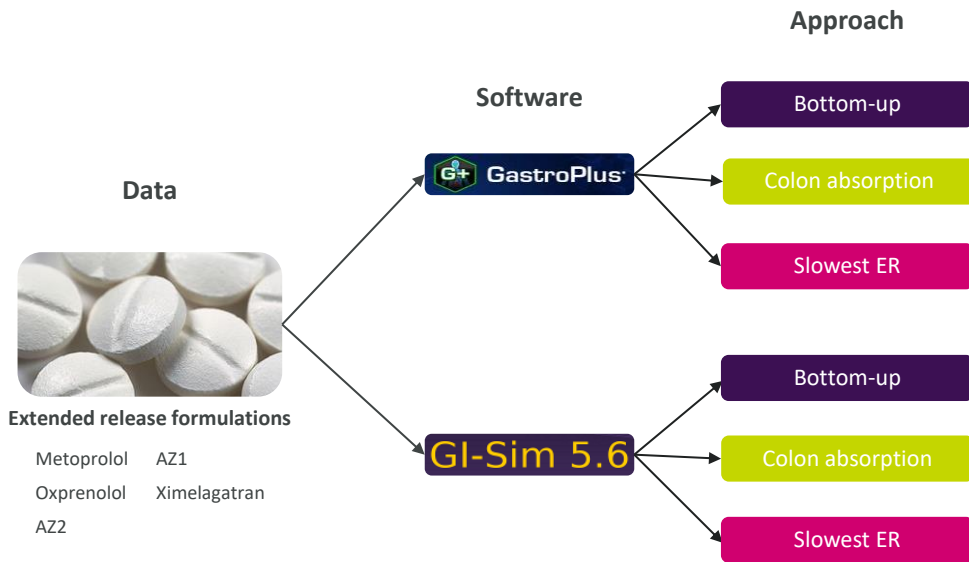
Alcohol Dose  
Dumping Prediction

No effect of Alcohol  
on exposure

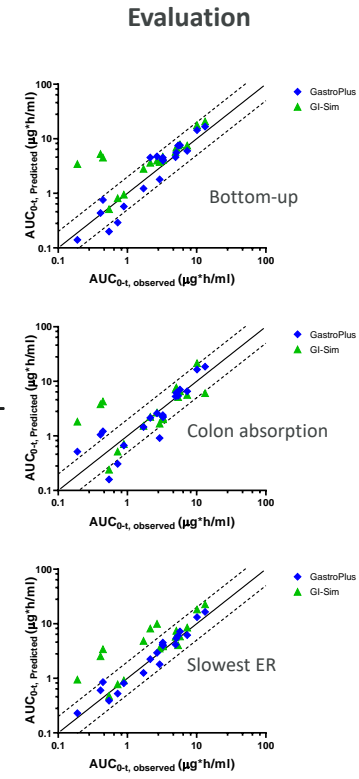
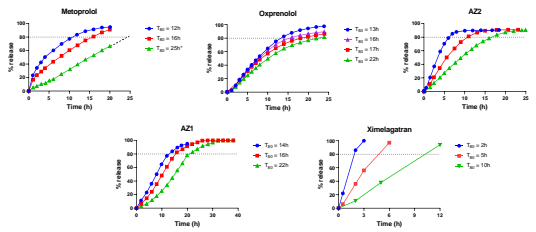


# PBBM of ER - Evaluation of different approaches to account for colon absorption

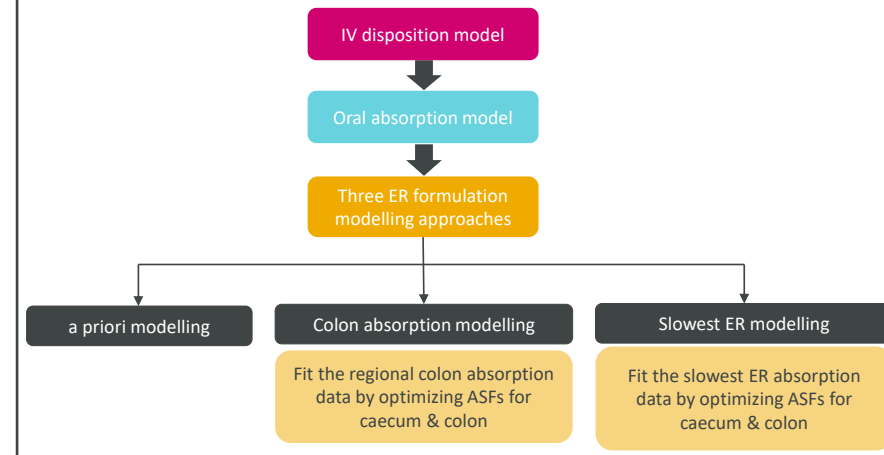
## Modeling Strategy



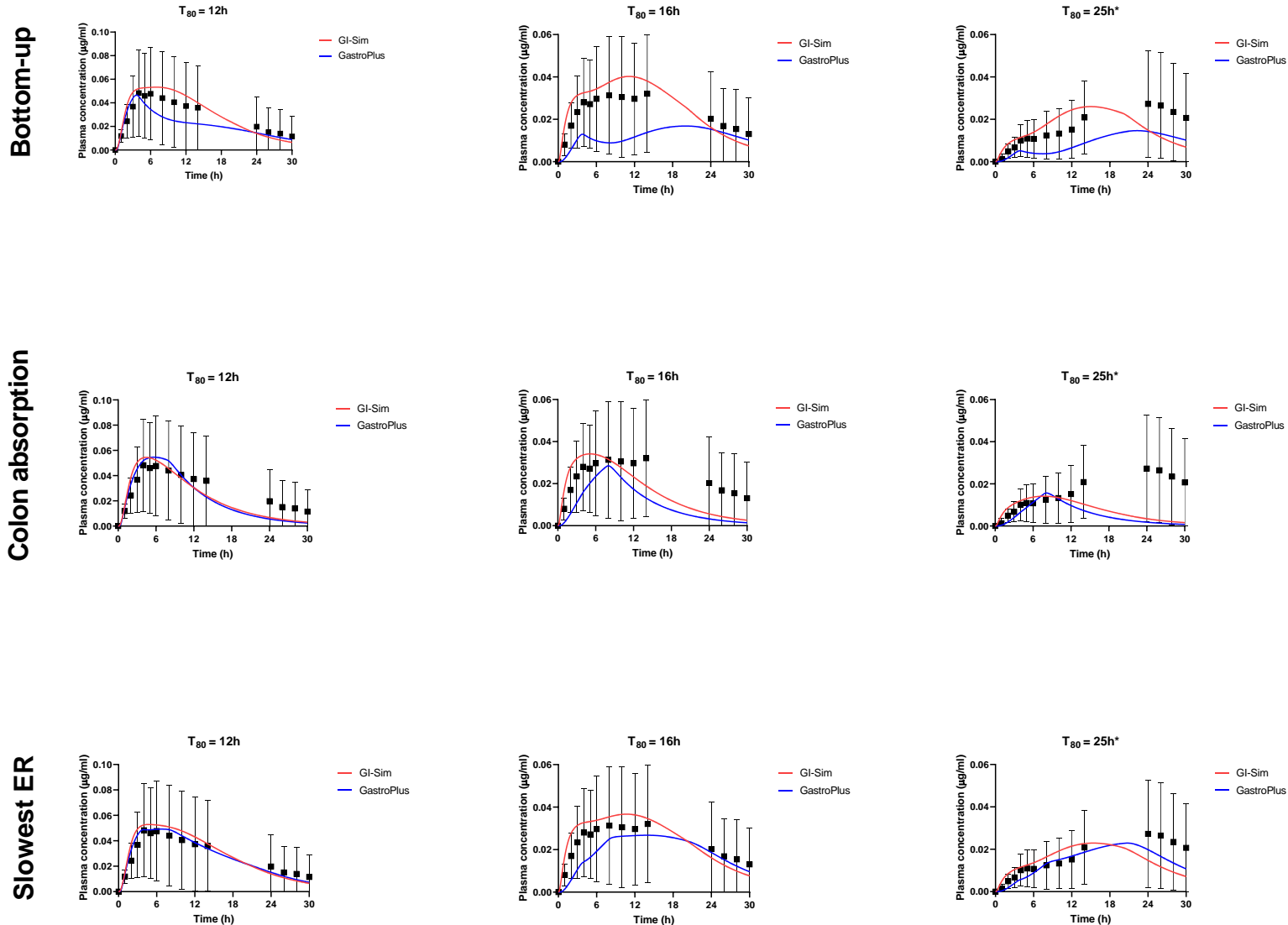
In-vitro release profiles: Slow, Medium and Fast



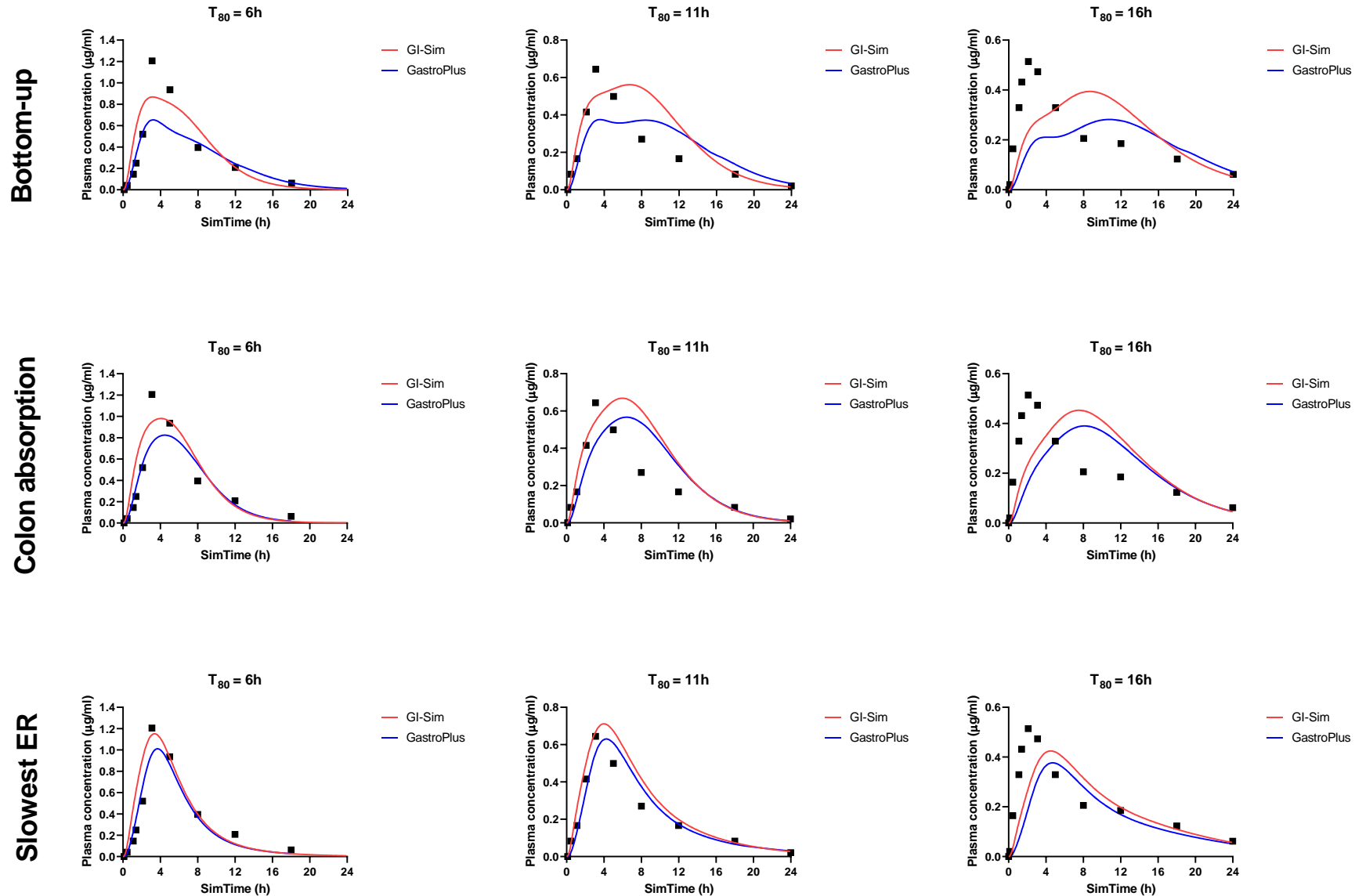
## PBBM Development



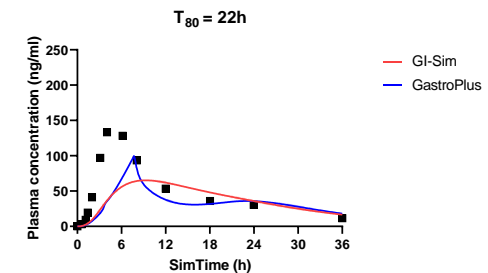
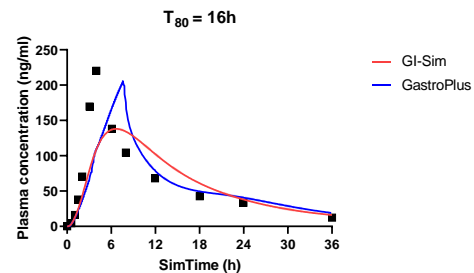
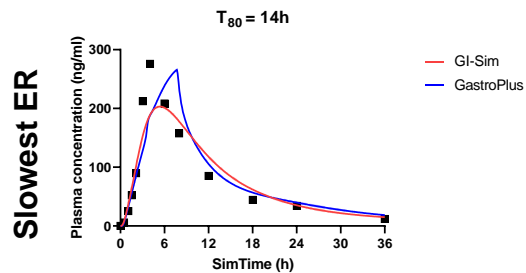
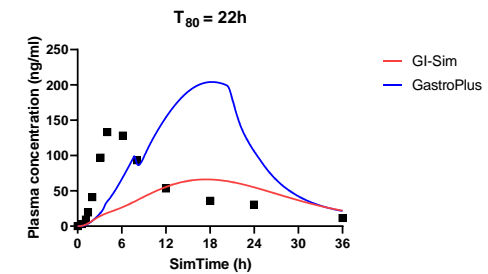
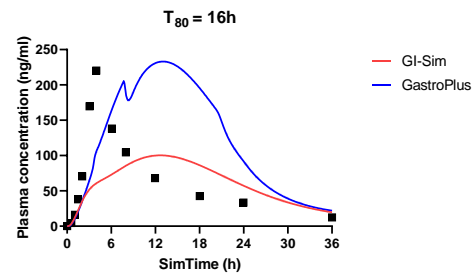
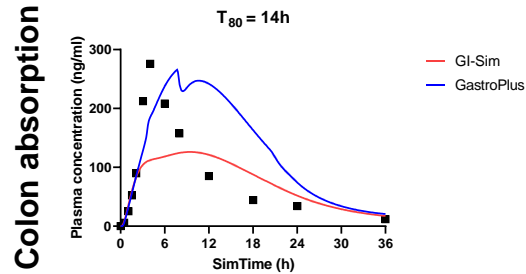
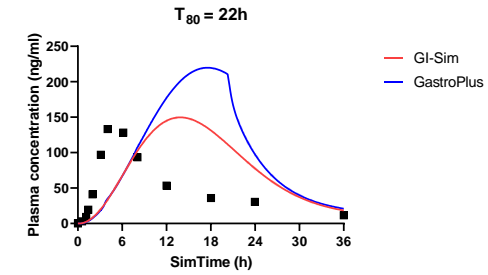
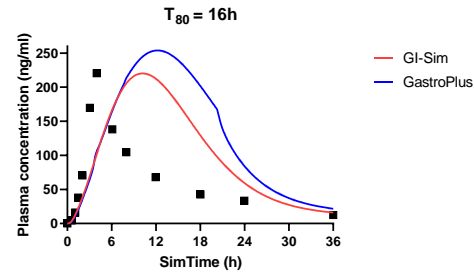
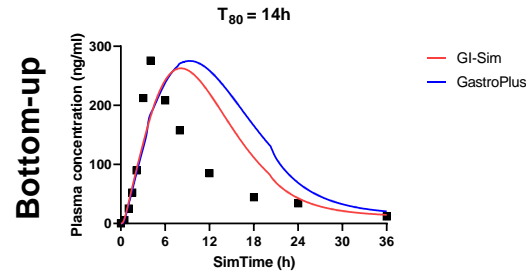
# Metoprolol – Low colon absorption limitation risk



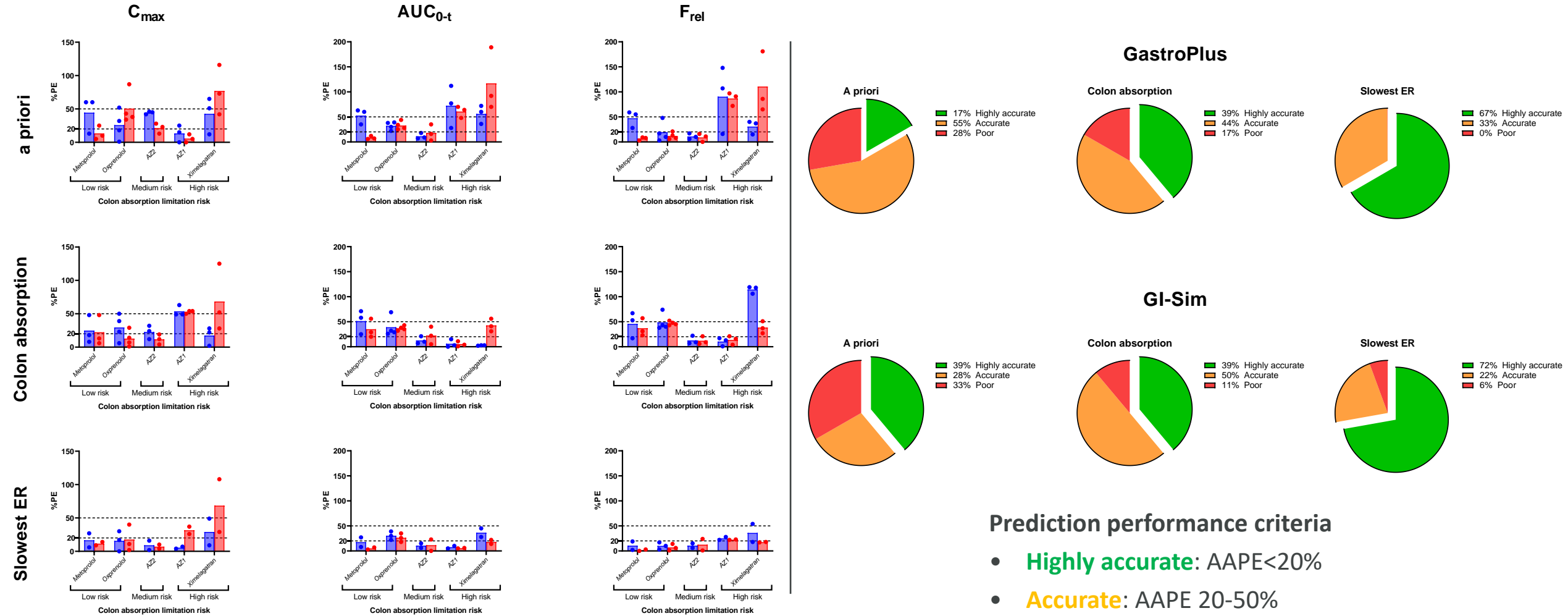
# AZ2 – Medium colon absorption limitation risk (Dissolution/Solubility)



# AZ1 – High colon absorption limitation risk (Solubility)



# PBBM of ER drug products - Prediction performance



## Prediction performance criteria

- **Highly accurate:** AAPE < 20%
- **Accurate:** AAPE 20-50%
- **Poor:** AAPE > 50%





# Concluding remarks

## Prediction of colon absorption

- PBBM can be used to predict regional and colon absorption in humans for high permeability drugs
  - For candidate risk assessment & early product design and development applications
- Low permeability drugs poorly predicted

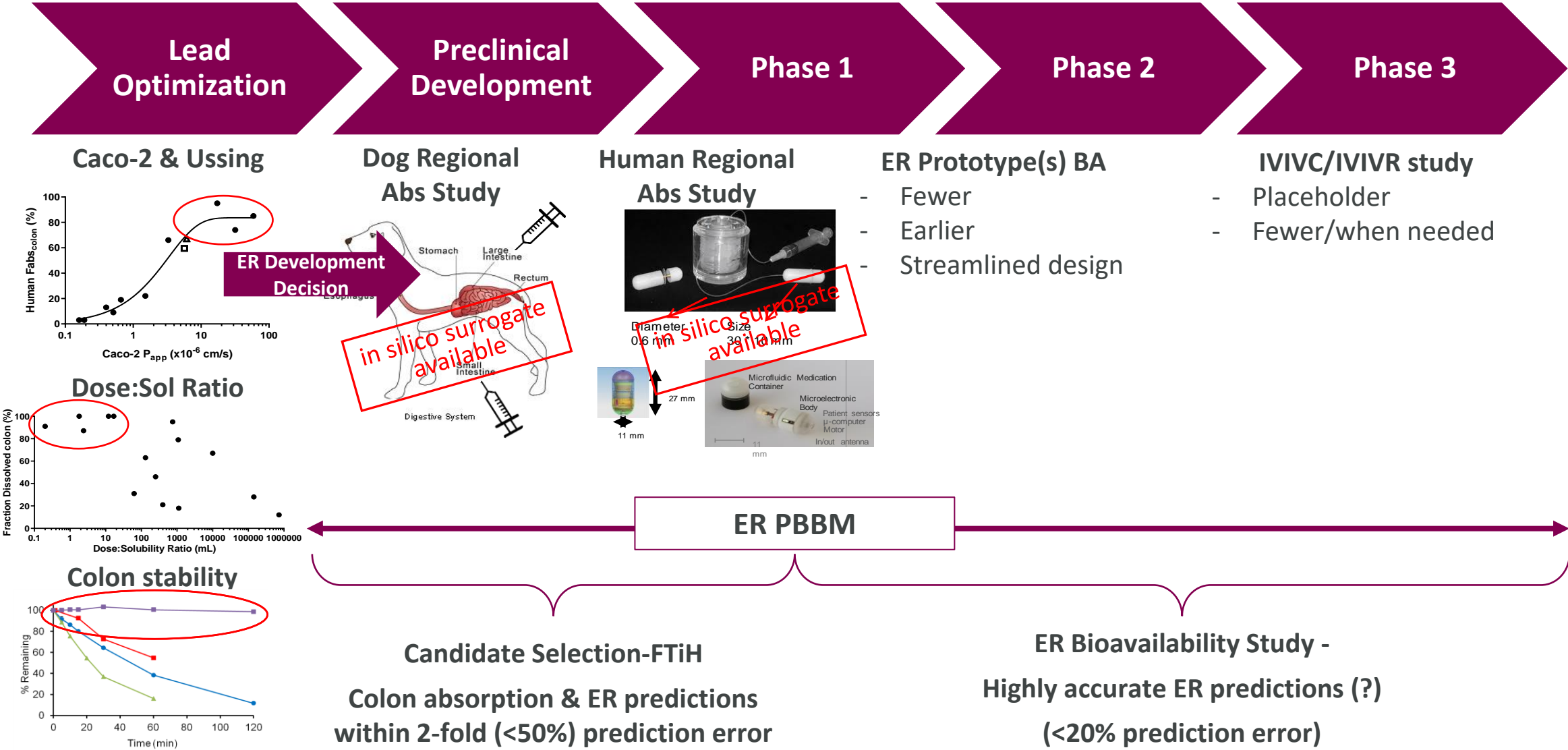
## Prediction of in vivo performance ER drug products

- *a priori* approach sufficient for use during candidate selection and early product design for Low-Medium colon absorption limitation risk drugs
- Slowest ER approach significantly improved prediction performance regardless of colon absorption limitation
  - Opportunity to achieve highly accurate PBBM suitable for ER predictions for commercial/regulatory applications
    - Exception: Permeability limited drugs
  - Opportunity to streamline BA study design for ER drug products
- Limited value in performing human regional absorption studies where the drug is administered to the colon as a bolus to support PBBM development for ER drug products.

## Improved colon models still needed!



# Colon absorption & ER drug product assessment overview - updated



## Christer Tannergren is an employee of AstraZeneca

# Declaration of Interest & Acknowledgement

- **Harshad Jadhav, AZ, KUL**
- **Patrick Augustijns, KUL**
- Bertil Abrahamsson
- Hans Lennernäs, Uppsala University
- Anna Bergendal
- Anders Borde
- Eva Karlsson
- Fredrik Winge
- Lee Ashworth
- James Mann
- Caroline Wingolf
- Christian von Corswant
- Anna-Lena Ungell
- Åsa Sjöberg
- Charlotta Vedin
- **Emma Eckernäs, Gothenburg University**
- **Erik Sjögren, Pharmetheus, Uppsala University**
- **Jonas Fagerberg, Disruptive Pharma**
- David Dahlgren, Uppsala University



This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 956851





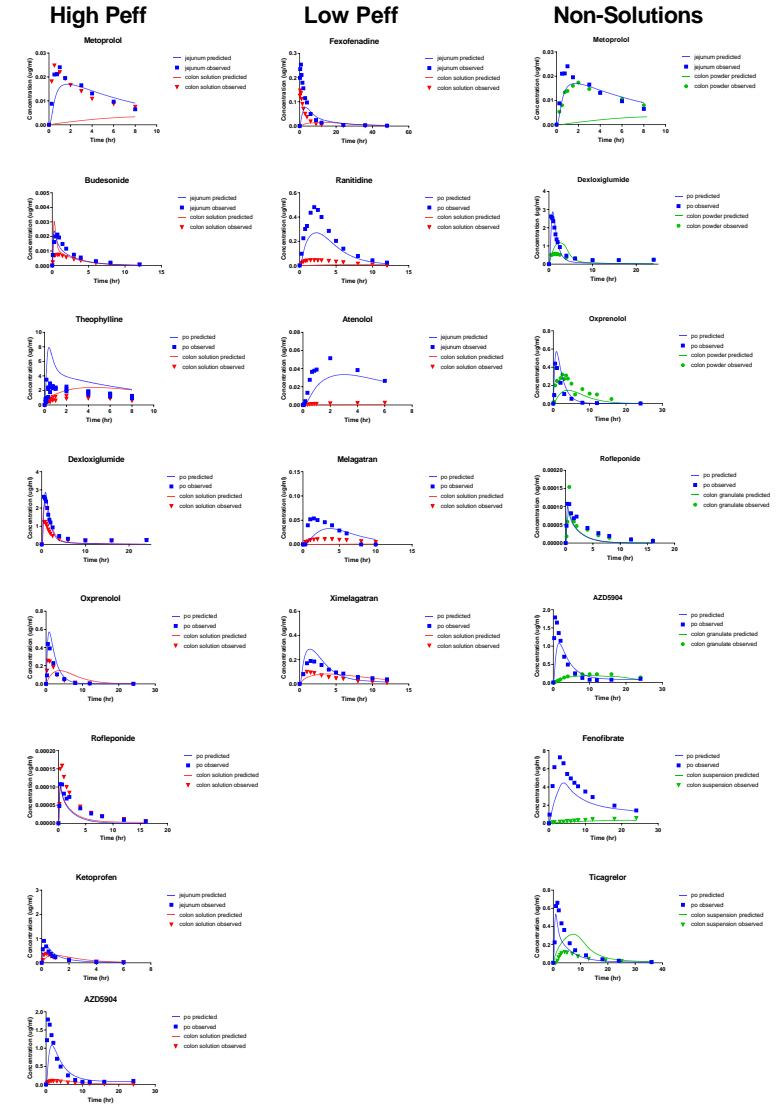
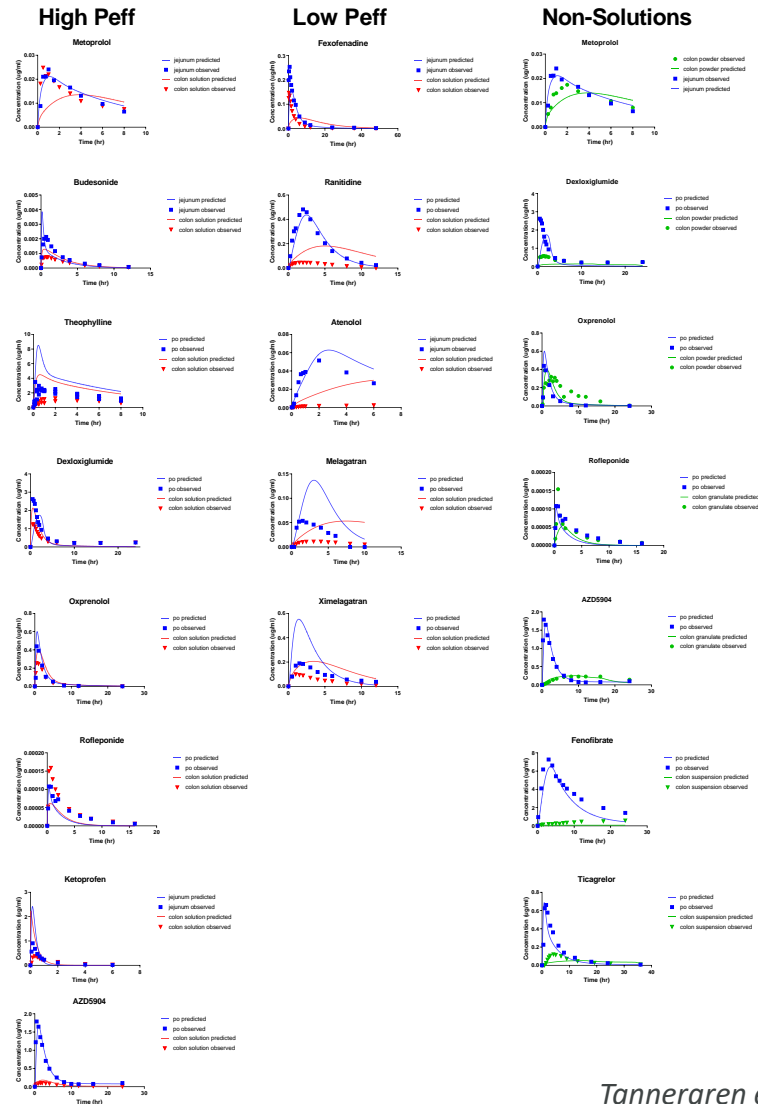
Thank you.



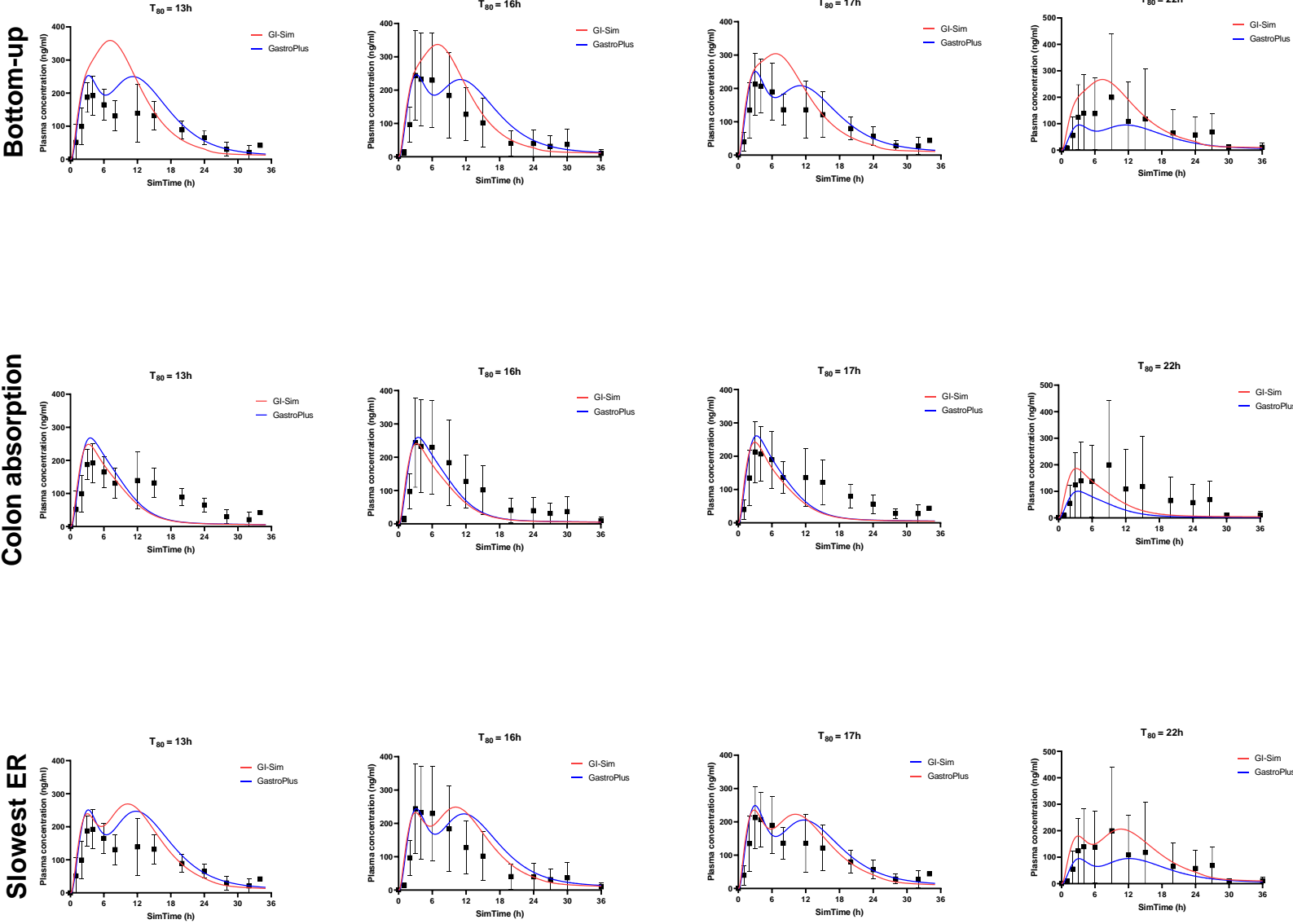
# PBBM of colon absorption – Predicted plasma profiles

## GI-Sim

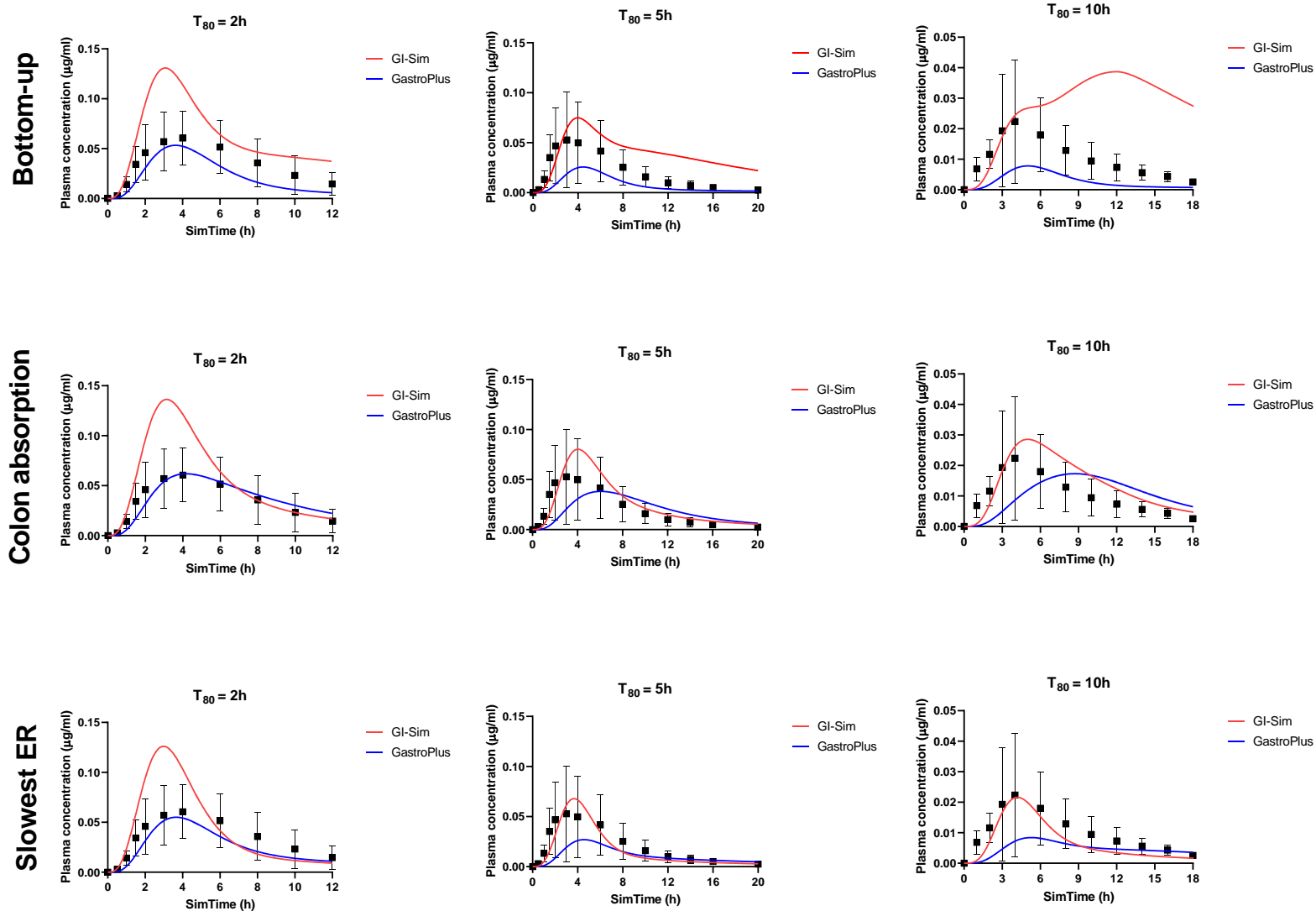
## GastroPlus



# Oxprenolol – Low colon absorption limitation risk



# Ximelagatran – High colon absorption limitation risk (Permeability)



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