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Oral Absorption DDI Assessment Using PBPK, AI & Regulatory Perspective

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SimulationsPlus

Session Description and Objectives

- Oral absorption-mediated drug-drug interactions (DDIs) are important in drug development. PBPK modeling provides a mechanistic approach to predict interactions resulting from changes in gastric pH, altered gastric and intestinal transit, and food effects. This presentation highlights recent PBPK applications, including pH-dependent DDIs, transit changes related to GLP-1 receptor agonists, and food effects. Case studies will demonstrate regulatory applications, and we will discuss emerging AI approaches.

- Upon completion, participants will be able to understand what absorption-related DDIs are and their potential impact on absorption and PK of orally administered drugs.
- Understand how PBPK modeling can help to assess absorption-mediated DDIs, such as pH-dependent interactions, food effects, and gastric emptying prolongation due to GLP-1 agonists.
- Understand the role of PBPK M&S in informing study design and regulatory decisions.

Biography and Contact Information

- Grace Fraczkiewicz is Vice President of PBPK Services at Simulations Plus, Inc., where she mentors and manages a team of scientists who provide mechanistic absorption and PBPK modeling consulting services to the pharmaceutical industry.
- She has 26 years of experience using modeling and simulation approaches to integrate knowledge of absorption, PK, PD, efficacy, safety, patient demographics, and pathophysiological factors to answer product development decision-making questions and solve product development problems.
- She oversees and works on over fifty projects per year across all areas of pharmaceutical product development, and she has been involved in numerous studies that informed regulatory decisions.
- She holds a B.S. degree in Chemistry and an M.Sc. in Chemical Physics from Wroclaw University in Poland.
- Contact information: grace.fraczkiewicz@simulations-plus.com

Key Mechanisms of Oral Absorption DDIs

Oral absorption DDIs are primarily driven by drug-induced changes in the gastrointestinal (GI) microenvironment or physiology:

1. **Gastric pH Alterations:** Co-administered acid-reducing agents (ARAs) such as proton pump inhibitors (PPIs), H_2-receptor antagonists, or antacids elevate gastric pH. This significantly impairs the dissolution and absorption of weakly basic drugs that exhibit pH-dependent solubility.

2. **Food Effects:** Food intake modifies GI physiology by increasing bile acid secretion, altering splanchnic blood flow, and delaying gastric emptying, which dynamically impacts drug solubility and transit.

3. **Altered Gastric Emptying Time (GET):** Drugs like GLP-1 receptor agonists or opioids delay gastric emptying. This slows down the delivery of a co-administered oral drug to its primary absorption site in the small intestine, potentially delaying or reducing its peak concentration.

4. **Gastrointestinal Transit Changes:** Prokinetic agents (e.g., metoclopramide) accelerate GI transit. This reduces the residence time for a drug to dissolve and pass through enterocytes, lowering bioavailability for poorly soluble compounds. Antimotility agents (e.g., loperamide, dextromethorphan, dicyclomine) inhibit intestinal transit and gastric emptying.

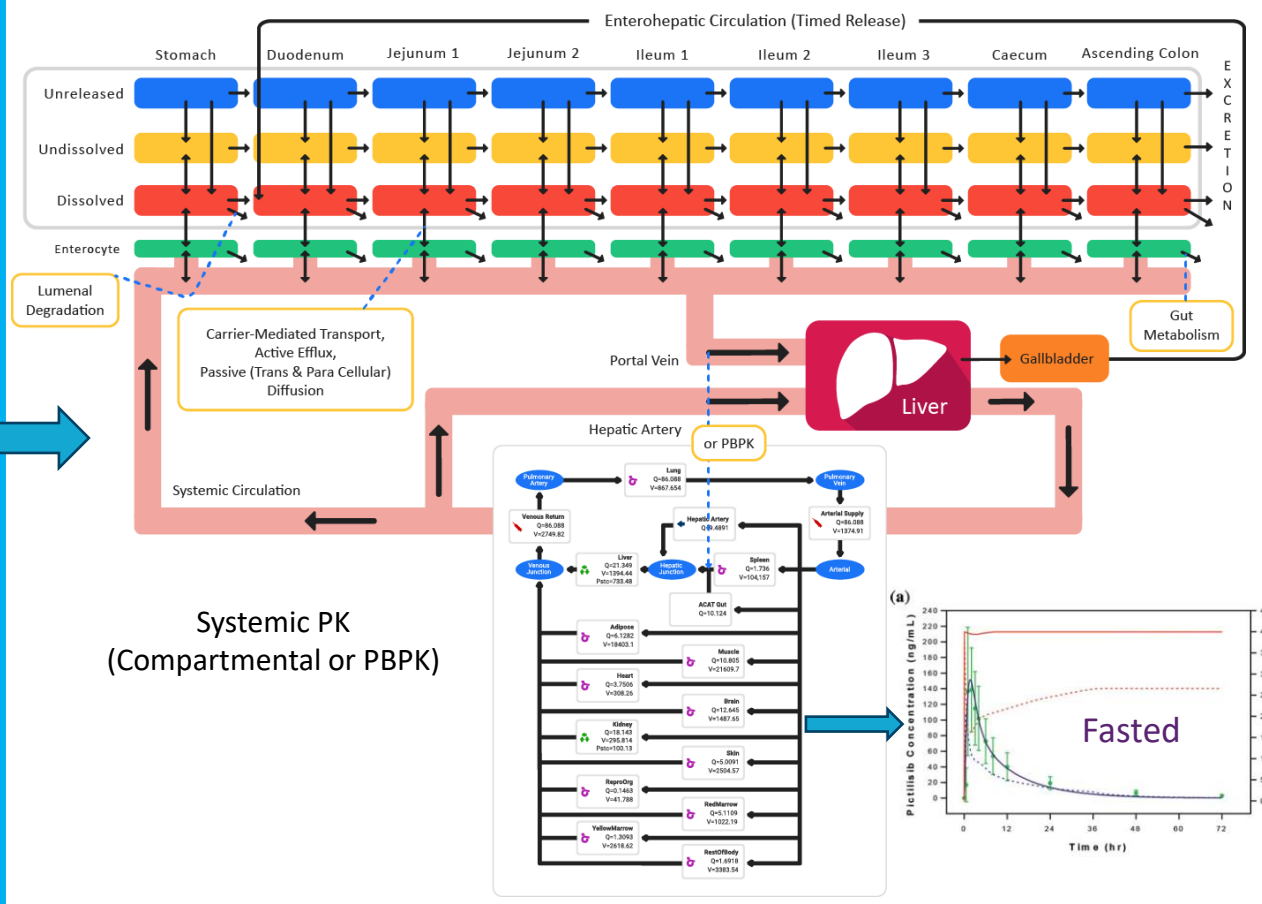
5. **Complexation and Luminal Binding:** Certain drugs or supplements (such as calcium, iron, or antacids containing magnesium/aluminum) chelate with companion medications (e.g., fluoroquinolones, tetracyclines), forming insoluble complexes that completely block absorption.

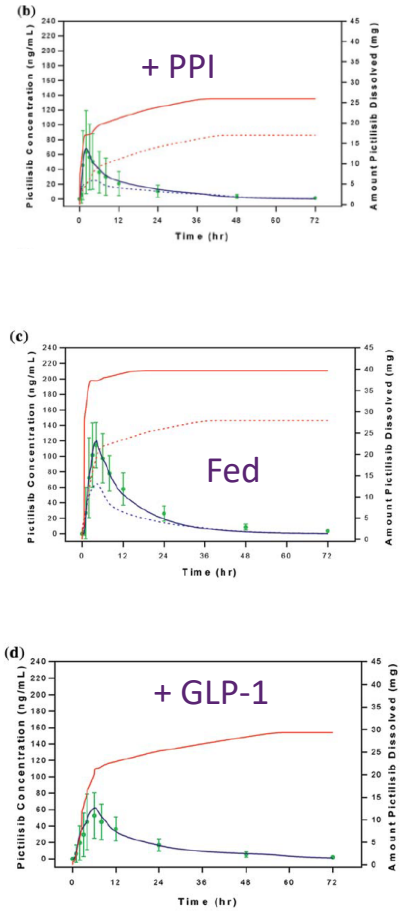
Physiologically Based Absorption and Pharmacokinetics Modeling

Drug substance and product information:

- Dose and dose volume
- Solubility vs. pH profiles
- Permeability
- logP
- pKa
- Dissolution: MR: dissolution profiles; IR: particle size and density
- Diffusion coefficient
- Metabolism/transport
- Protein binding
- Blood-to-plasma ratio

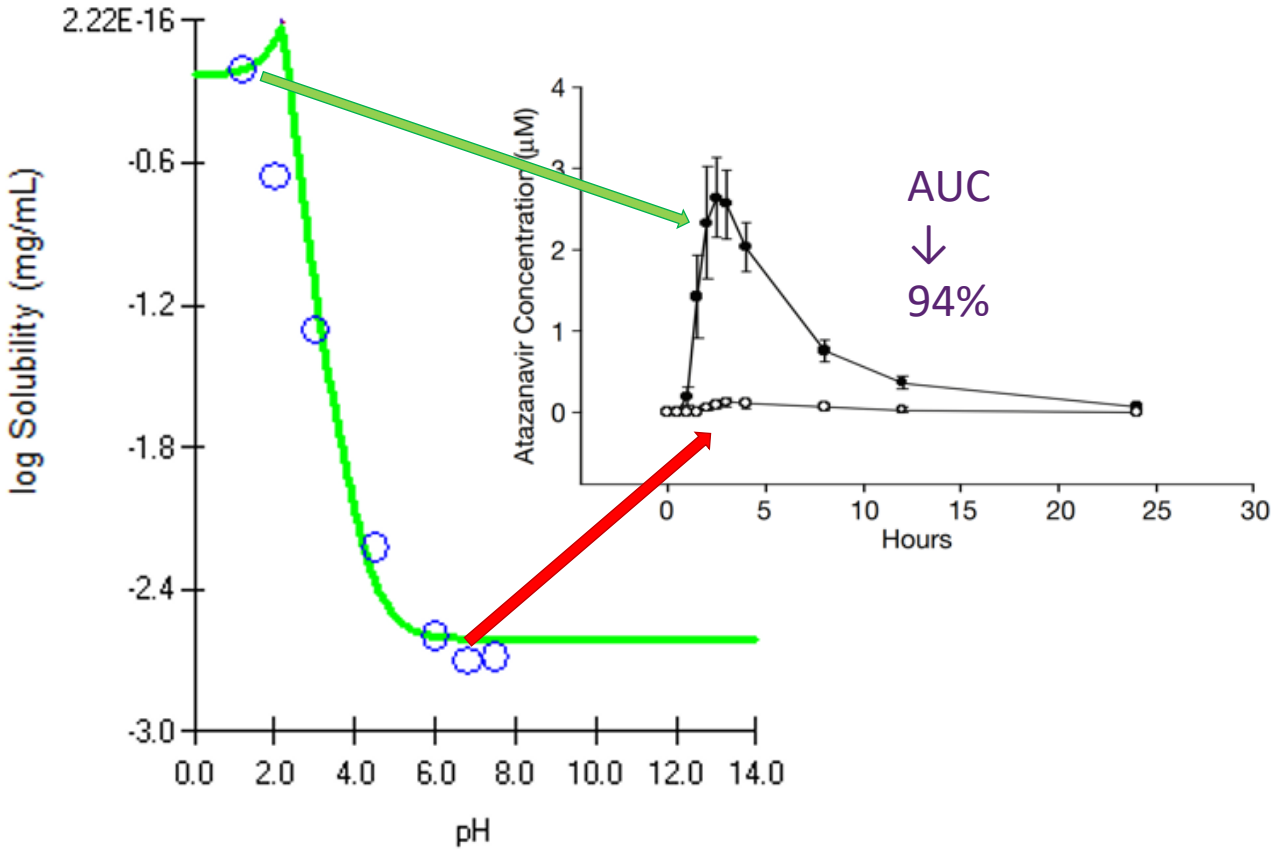
Mechanistic Absorption Model ACAT)

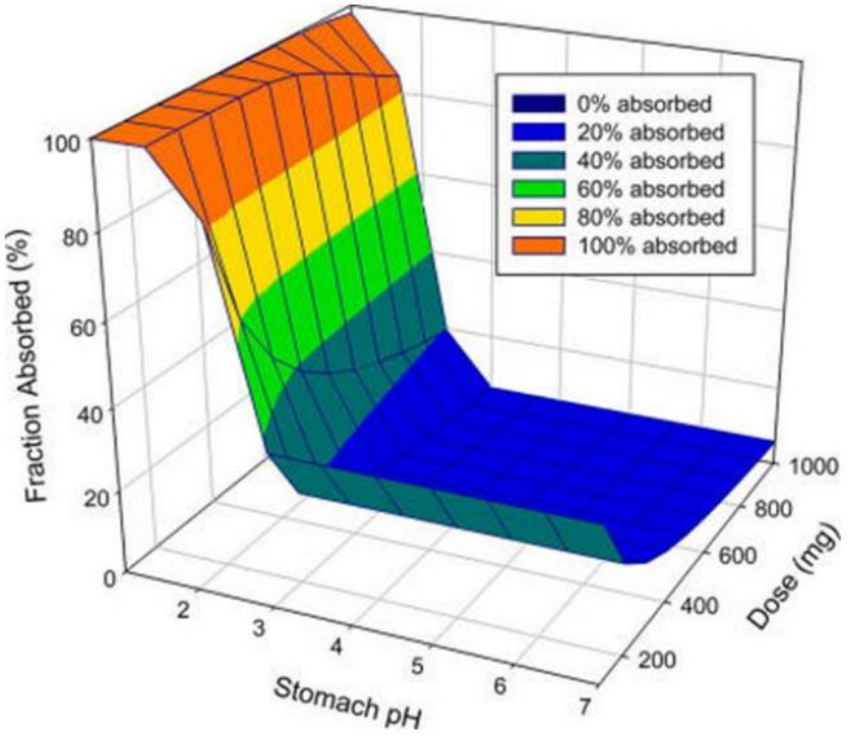




Impact of Gastric pH on PK

The Effect of Acid Reducing Agents on Weak Base Absorption Can be Severe





Examples Submitted to FDA

Drug	Software	Predicted AUCR	Observed AUCR	Predicted Effect	Observed Effect	Predictive performance	Comments	Ref.
Alectinib	GastroPlus	No effect	1.22	No effect	No effect	Same category	Model was submitted to FDA, confirmed by a DDI study with esomeprazole	(1, 2)
Axitinib	GastroPlus	0.82	0.85	No effect	No effect	Same category	Model submitted to FDA	(3, 4)
Panobinostat	**GastroPlus**	**No effect**	**NA**	**No effect**	**NA**	**NA**	**Model was submitted to FDA, DDI study with an ARA was waived**	**(5)**
Ribociclib	GastroPlus SimCyp	No effect	NA	No effect	0.95 (PPI vs none)	NA	Model was submitted to FDA, DDI study with an ARA was waived	(6, 7)
Sebetralstat	**GastroPlus**	**Decrease by up to 30%**	**NA**	**No** to **Weak effect**	**NA**	**NA**	**submitted to FDA, DDI study with an ARA was waived**	**(8, 9)**

The interaction effect magnitude (no, weak, moderate, or strong) is defined based on the definition for the induction effect: no effect if AUCR >= 0.8, weak effect if 0.5<= AUCR < 0.8, moderate effect if 0.2<= AUCR < 0.5, strong effect if AUCR < 0.2, where AUCR is the ratio of AUC in the presence and absence of an acid-reducing agent (ARA).

NA: not available; the default prandial status is fasting condition if not specified.

1. FDA. NDA 208434 Alectinib Clinical Pharmacology Biopharmaceutics Review(s). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208434Orig1s000ClinPharmR.pdf.
2. Parrott NJ, Yu LJ, Takano R, Nakamura M, Morcos PN. Physiologically Based Absorption Modeling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Alectinib. AAPS J. 2016;18(6):1464-1474.
3. FDA. NDA 202324 Aaxitinib Tablets Clinical Pharmacology Biopharmaceutics Review(s) 2025 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202324Orig1s000ClinPharmR.pdf.
4. Dodd S, Kollipara S, Sanchez-Felix M, Kim H, Meng Q, Beato S, Heimbach T. Prediction of ARA/PPI Drug-Drug Interactions at the Drug Discovery and Development Interface. J Pharm Sci. 2019;108(1):87-101.
5. FDA. NDA 205353 Panobinostat Capsules Clinical Pharmacology Biopharmaceutics Review(s) 2025 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205353Orig1s000ClinPharmR.pdf.
6. FDA. NDA 209092 Ribociclib MULTI-DISCIPLINE REVIEW. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209092Orig1s000MultidisciplineR.pdf.
7. Samant TS, Dhuria S, Lu Y, Laisney M, Yang S, Grandeury A, Mueller-Zsigmondy M, Umehara K, Huth F, Miller M, Germa C, Elmeliegy M. Ribociclib Bioavailability Is Not Affected by Gastric pH Changes or Food Intake: In Silico and Clinical Evaluations. Clin Pharmacol Ther. 2018;104(2):374-383.
8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219301s000lbl.pdf
9. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/219301Orig1s000IntegratedR.pdf

Sebetralstat PBPK Model to Evaluate the ARA-mediated DDI

Table 105. Predicted Human PK Parameters Following 600 or 300 mg PO Tablet Administration in the Fasted for Varying Stomach pH

Dose, mg	Stomach pH	F_a (%)	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0\text{-}24h}$ (µg.h/mL)	$AUC_{0\text{-}inf}$ (µg.h/mL)
600 mg	0.5	99	5.33	0.96	15.5	15.8
	1.3	99	5.32	0.96	15.5	15.8
	4.0	89	3.71	1.6	13.7	14.0
	5.0	89	3.70	1.6	13.7	14.0
	6.0	89	3.70	1.6	13.7	14.0
300 mg	0.5	99	2.87	0.88	7.57	7.70
	1.3	99	2.87	0.88	7.56	7.70
	4.0	93	2.15	1.2	7.06	7.24
	5.0	93	2.15	1.2	7.06	7.24
	6.0	93	2.15	1.2	7.06	7.24

Source: the Applicant's response to the FDA IR received on February 13, 2025. The mean ± SD particle radius of drug substance is (b) (4) µm, according to the response to the FDA IR received on February 14, 2025.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; F_a, fraction of drug absorbed; h, hour; PK, pharmacokinetics; PO, by mouth; T_{max}, time to maximum concentration

Impact of particle size distribution on the effect of ARAs

Table 106. Simulated Fraction Absorbed and C_{max} for Drug Substance With the Drug Substance's Mean ± SD Particle Radius of (b) (4) µm

Dose, mg	Gastric pH 1.3 F_a, %	Gastric pH 6 F_a, %	Gastric pH 1.3 C_{max}, µg/mL	Gastric pH 6 C_{max}, µg/mL	C_{max} Ratio [a]
300	96.80	77.68	2.87	1.66	0.58
600	95.75	73.40	5.31	2.96	0.56

Source: Compiled by the reviewer based on the Applicant's response to the FDA IR received on February 14, 2025 and simulation results by the reviewer
[a] C_{max} for gastric pH 6 versus C_{max} for gastric pH 1.3
Abbreviations: C_{max} maximum plasma concentration; F_a, fraction of drug absorbed; SD, standard deviation

Table 107. Predicted Human PK Parameters Following 600-mg PO Tablet Administration in the Fasted and Fed States at Varying Stomach pH for Hypothetical Drug Batch With Median Particle Size of (b) (4)

*PSD Mean Radius (SD) µm	#Prandial state	Stomach pH	Fa (%)	C_{max} (µg/mL)	Tmax (h)	$AUC_{0\text{-}24h}$ (ng•h/mL)	$AUC_{0\text{-}inf}$ (ng•h/mL)
Hypothetical Drug Batch of Dv (b) (4) F (b) (4) (b) (4)	Fasted	0.5	92	5.09	0.96	14,900	15,200
		1.3	92	5.03	0.96	14,800	15,100
		4	60	2.26	1.6	9,608	9,843
		5	60	2.25	1.6	9,599	9,834
		6	60	2.25	1.6	9,599	9,834
	Fed	3	96	3.75	3.0	15,200	15,400
		4.9	95	3.64	3.0	15,100	15,400
		6.4	95	3.64	3.0	15,100	15,400

* Inputted with a log normal distribution and 8 bins
#Selected prandial state is maintained throughout the simulation; meal type for fed state is FDA breakfast
Source: Applicant's response to IR dated March 3, 2025
Abbreviations: C_{max} maximum plasma concentration; F_a, fraction of drug absorbed; h, hour; PK, pharmacokinetics; PO, by month; T_{max}, time to maximum concentration

Inform Product Labeling

Acid-Reducing Agents: Sebetralstat C_{max} is estimated to decrease by up to 56% and $AUC_{0\text{-}inf}$ is estimated to decrease by up to 30% at pH 6 relative to pH 0.5.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219301s000lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/219301Orig1s000IntegratedR.pdf

Fresh from the press: Hovilpri accepted by the FDA on October 9

Software	**GastroPlus**
Predicted AUCR	**0.35**
Observed AUCR	**0.41 (0.35 - 0.47)**
Predicted Effect	**Strong Effect**
Observed Effect	**Strong Effect**
Predictive performance	**AUCR(Sim/Obs) = 0.89**
Comments	**The model was submitted to the FDA and confirmed by a DDI study with esomeprazole. We performed 3D PSA analysis (AUC and Cmax vs. Stomach pH (1-7) and dose) to assess the potential impact of other PPIs, which was used to inform Phase 3 clinical studies. We simulated dose staggering with 300 mg BID ranitidine, which was used for labeling.**

7.2 Potential Effects of Other Drugs on HOVILPRI

Elevation of gastric pH may decrease the systemic bioavailability of HOVILPRI *[see Clinical Pharmacology (12.3)]*, which may reduce its effectiveness or cause drug resistance to HOVILPRI *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

Table 1: Clinically Significant Drug Interactions

Proton Pump Inhibitors/ H2-Receptor Antagonists/Antacids		
Prevention or Management	Proton Pump Inhibitors:	Avoid concomitant use of esomeprazole or rabeprazole with HOVILPRI. Avoid concomitant use of omeprazole or lansoprazole at daily doses above 20 mg with HOVILPRI. Avoid concomitant use of pantoprazole at daily doses above 40 mg with HOVILPRI *[see Dosage and Administration (2.2)]*. Concomitant use of omeprazole, lansoprazole, or pantoprazole below the doses listed above is acceptable, as these lower doses do not reduce pritelivir exposure to a clinically relevant extent.
	H2-Receptor Antagonists:	Take HOVILPRI at least 2 hours before or 12 hours after H2-receptor antagonist intake *[see Dosage and Administration (2.2)]*.
	Antacids:	Take HOVILPRI at least 2 hours before or 2 hours after antacid intake *[see Dosage and Administration (2.2)]*.

HOVILPRI® (pritelivir) tablets

https://www.hovilprihcp.com/pdf/prescribing-information.pdf

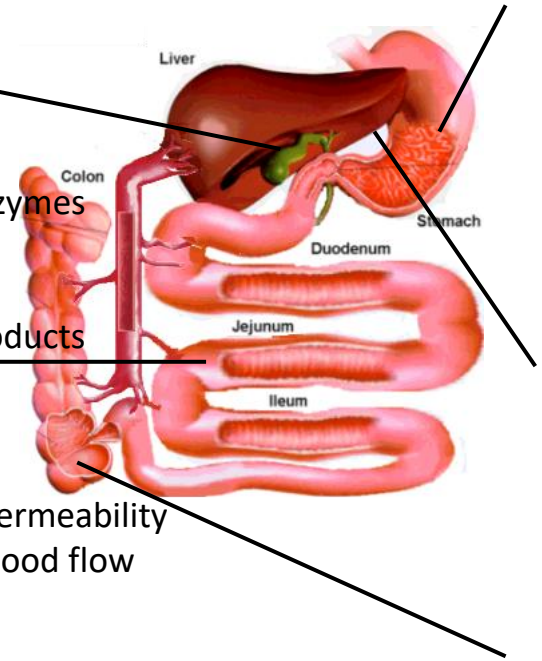
Food Effects

Factors Affecting Oral Absorption Due to the Intake of Food

Physiological Factors

Gall bladder
- Release of bile salts

Small intestine
- Increased intestinal enzymes
- Increased bile salts
- Increased motility
- Increased digestion products
- Increased osmolality
- Potential inhibition of transporters and CYP
- Potential decrease in permeability
- Increased splanchnic blood flow
- Others



Stomach
- Increased pH
- Delayed gastric emptying
- Increased fluid volume
- Increased pepsin
- Increased acid secretion

Pancreas
- Enzyme secretion induced when food is in duodenum
  - Lipases, proteases, nucleases and amyloytic enzymes
- Insulin secretion

Large intestine
- Increased buffer capacity
- Increased fatty acid content
- Increased bile salts
- Decreased surface tension

Partial translation

Drug Product Factors
- Drug solubilization / precipitation
- Drug in vivo dissolution profile
- Saturation of liver enzyme and first pass metabolism

Modified from O'Shea, J.P. et al. PMID: 29956330. https://doi.org/10.1111/jphp.12957

How are we doing on food-effect prediction?

Prospective approach: completely bottom up or model optimized with **fasting** PK data
Middle-out approach: model optimized with **fed** PK data

Reference	Database	Prospective	Middle-out
Li (2018) PMID 29168611	27 compounds, 36 PBPK models, 48 food effect simulations	72% (within 2-fold)	28%
Riedmaier (2020) PMID 32981010	30 compounds, 32 formulations, 50 models	76%	24%
Kesisoglou (2020) PMID: 33205433	27 compounds	56%	44%

Cases may overlap in the three references.
The survey may contain modified-release products.

Regulatory Requirements

- Fasted and fed clinical PK for relevant commercial formulation
- **FDA's May 2026 guidance supports PBPK alongside human food-effect data to investigate mechanisms and guide study design.**
- Regulatory use depends on the specific question, model qualification, and uncertainty.

https://www.fda.gov/media/121313/download

PBPK for Food Effect

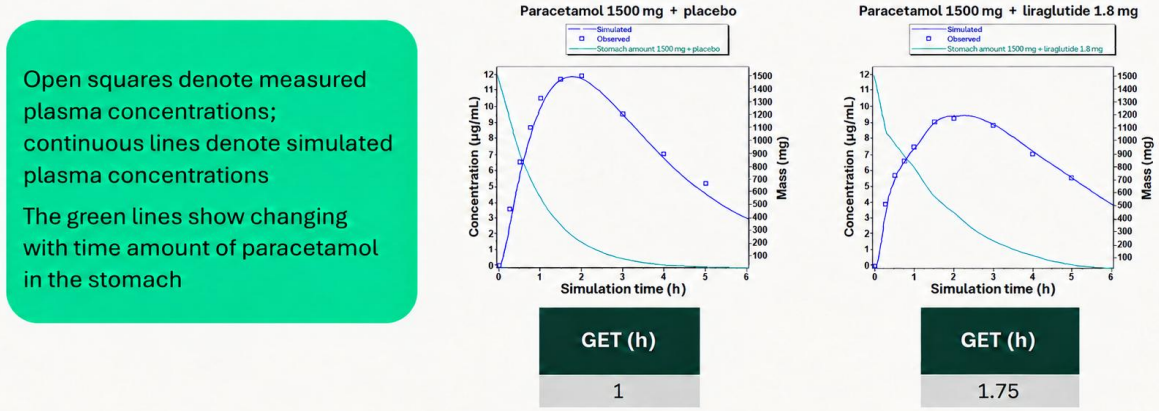
Model	Ceritinib	Sonidegib
Dosage	750 mg QD on an empty stomach (2014), 450 mg QD with food (2017)	200 mg QD on an empty stomach (2015)
Purpose	**Exploratory analysis**	**Exploratory analysis**
Structure	Mechanistic oral absorption	Mechanistic oral absorption
Predictive Performance	Cmax was reasonably predicted, and AUC was under-predicted under fed condition	Under predicted AUC, and Cmax under fed condition
	Observed • High fat meal: ↑AUC 73%, ↑Cmax 41% • Low fat meal: ↑AUC 58%, ↑ Cmax 43%	Observed • High fat meal: ↑AUC 7.4-fold, ↑Cmax 7.8-fold
Considerations	• PMR to evaluate the GI tolerability, efficacy and PK of 450 mg (fed) and 750 mg (fasting)	• Positive exposure-response relationship for safety (Gr 3+ AEs)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205266Orig1s000ClinPharmR.pdf

Altered Gastric Emptying Time (GET)

Deconvolution of Gastric Emptying from Paracetamol Plasma Concentration Obtained with Placebo or Liraglutide 1.8 mg

Figure 1. Observed vs simulated plasma concentration vs time profiles for paracetamol dosed before (left) and after (right) administration of liraglutide 1.8 mg



Deconvolution of gastric emptying based on interaction between paracetamol and liraglutide and its extrapolation to comedications using a PBPK modelling approach

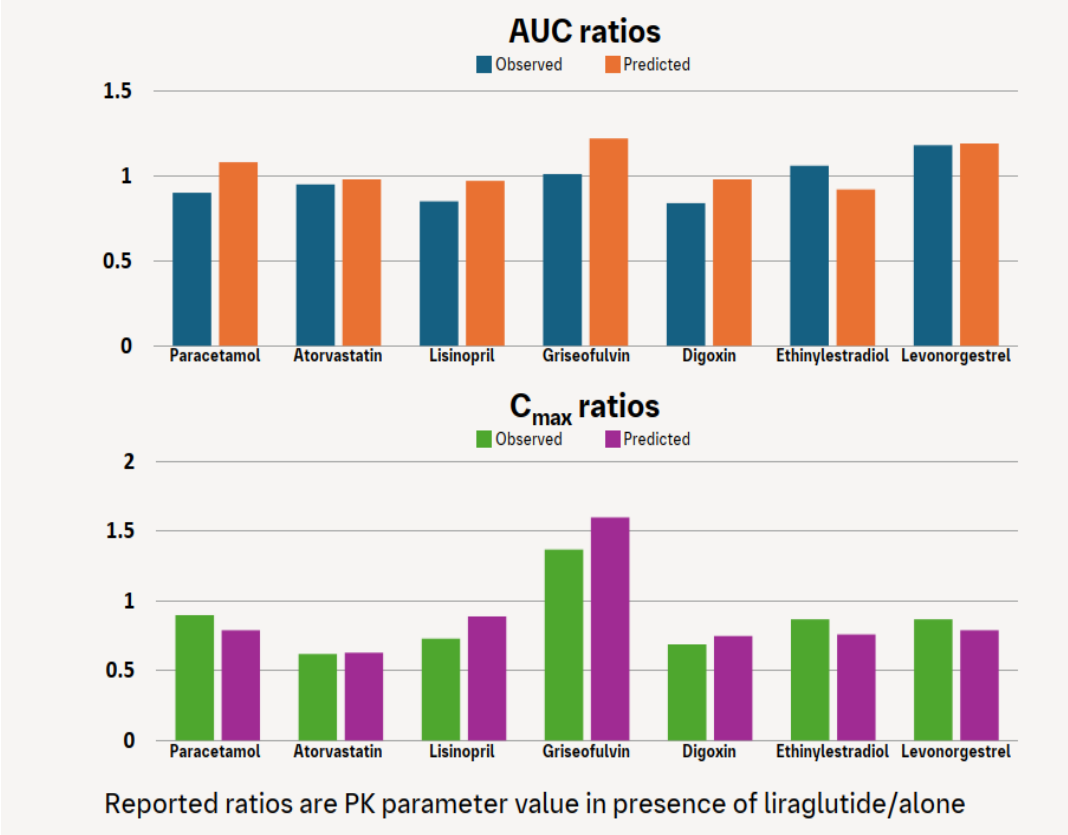
Grace Fraczkiewicz,[1] Revathi Chapa,[1] Angèle Fleury[2]
[1]Simulations Plus, Inc., Research Triangle Park, NC, United States;
[2]Boehringer Ingelheim Pharma GmbH & Co. KG. Biberach, Germany

Presented at: the 33rd Population Approach Group Europe (PAGE) meeting, Thessaloniki , Greece; June 4–6, 2025

- In this study, we deconvolved gastric emptying time from mean paracetamol plasma concentration–time profiles obtained with placebo or liraglutide 1.8 mg.
- We then applied the gastric emptying time to PBPK models of commonly co-administered oral compounds from different BCS classes to determine whether simulations could reproduce the observed impact of liraglutide-induced delayed gastric emptying.

Data extracted from:
1. U.S. Food and Drug Administration. VICTOZA® (liraglutide) prescribing information (August 2017). Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2017/022341s027lbl.pdf. Accessed May 2025.
2. European Medicines Agency. Saxenda® (liraglutide) EPAR. Available at: www.ema.europa.eu/en/medicines/human/EPAR/saxenda (October 2023). Accessed May 2025.

Method qualification based on model prediction of liraglutide interaction studies



- Most PK parameters were predicted within BE limits (not shown) except for ethinylestradiol AUCs, which were marginally below the BE limit of 0.8-fold, and digoxin Cmax and AUC0-inf, which marginally exceeded the upper BE limit of 1.25-fold
- Low-solubility drugs, and drugs that have a high first-pass extraction can be more affected than the other types of drugs by the GE prolongation
- Longer GE can enhance the absorption of the low-solubility and high-permeability drugs either by slowing down the intestinal precipitation process (weak bases) or by increasing intestinal dissolution by reaching solubility limits at later times (lipophilic and not ionizable drugs)
- Griseofulvin belongs to the latter class of drugs and displayed slightly higher absorption and exposure with longer GE; however, this effect was low (~20%)

Deconvolution of gastric emptying based on interaction between paracetamol and liraglutide and its extrapolation to comedications using a PBPK modeling approach

Grace Fraczkiewicz,[1] Revathi Chapa,[1] Angèle Fleury[2]
[1]Simulations Plus, Inc., Research Triangle Park, NC, United States;
[2]Boehringer Ingelheim Pharma GmbH & Co. KG. Biberach, Germany

Raw plasma data for comedications extracted from:
[1] Malm-Erjefalt M et al. Mol Pharm. (2015), 12(11): 4166-73.
[2] https://ClinicalTrials.gov/show/NCT01508858
[3] https://ClinicalTrials.gov/show/NCT00978393
[4] Glerup H et al. Scand J Gastroenterol. (2007), 42(10): 1182-6.

Summary of DDI Evaluations of the Impact of Prolonged GET on the PK of Concomitant Medications for FDA-approved GLP-1 Agonists Programs

Approval date	NDA/BLA	Generic Name	Brand Name	Route of Admin.	Dosing Freq.	DDI Approach	DDI Substrate	Link to Review	Link to Label
9/18/2014	125469	Dulaglutide	Trulicity	SC	QW	Studies	lisinopril, metoprolol, digoxin, oral contraceptives (norelgestromin, ethinylestradiol), atorvastatin, metformin, acetaminophen, warfarin, sitagliptin	Review	Label
4/28/2005	021773	Exenatide	Byetta	SC	BID	Studies	digoxin, lovastatin, lisinopril, acetaminophen, oral contraceptives (ethinylestradiol, levonorgestrel), warfarin	Review	Label
10/20/2017	209210	Exenatide ER	Bydureon	SC	QW	non-NME	Same as Byetta	Review	Label
1/25/2010	022341	Liraglutide	Victoza	SC	QD	Studies	digoxin, lisinopril, atorvastatin, acetaminophen, griseofulvin, oral contraceptives (ethinylestradiol, levonorgestrel), paracetamol	Review	Label
12/23/2014	206321	Liraglutide	Saxenda	SC	QD	Studies	paracetamol (bridging 1.8 mg vs 3 mg on GET)	Review	Label
7/27/2016	208471	Lixisenatide	Adlyxin	SC	QD	Studies	acetaminophen, oral contraceptives (ethinylestradiol and levonorgestrel), atorvastatin, warfarin, digoxin, ramipril	Review	Label
12/5/2017	209637	Semaglutide	Ozempic	SC	QW	Studies	warfarin, atrovastatin, digoxin, oral contraceptives (ethinylestradiol and levonogrestrel), metformin	Review	Label
9/20/2019	213051	Semaglutide	Rybelsus	PO	QD	Studies	lisinopril, warfarin, metformin, digoxin, oral contraceptives (ethinylestradiol, levonorgestrel), furosemide, rosuvastatin, levothyroxine	Review	Label
6/4/2021	215256	Semaglutide	Wegovy	SC	QW	non-NME	Same as Ozempic	Review	Label
5/13/2022	**215866**	**Tirzepatide**	**Mounjaro**	**SC**	**QW**	**Studies, PBPK**	Studies: acetaminophen, oral contraceptives (norelgestromin, ethinyl estradiol) **PBPK: atorvastatin, digoxin, lisinopril, metformin, metoprolol, sitagliptin, and warfarin**	Review	Label
11/8/2023	217806	Tirzepatide	Zepbound	SC	QW	non-NME	Same as Mounjaro	Review	Label

GLP-1 Gastric Emptying: Dulaglutide

Acetaminophen PopPK quantified delayed gastric emptying. Drug-specific PBPK models reproduced lower-dose DDIs, then predicted effects at 4.5 mg.

Single first dose	1.5 mg	4.5 mg
Gastric emptying time ratio	3.1	4.8
Fasted gastric MRT (h)	0.84	1.30

Model estimates, not directly measured gastric transit times [3]

Explicit EU labeling use

The EU SmPC cites PBPK predictions of no major clinically relevant interactions at 4.5 mg.

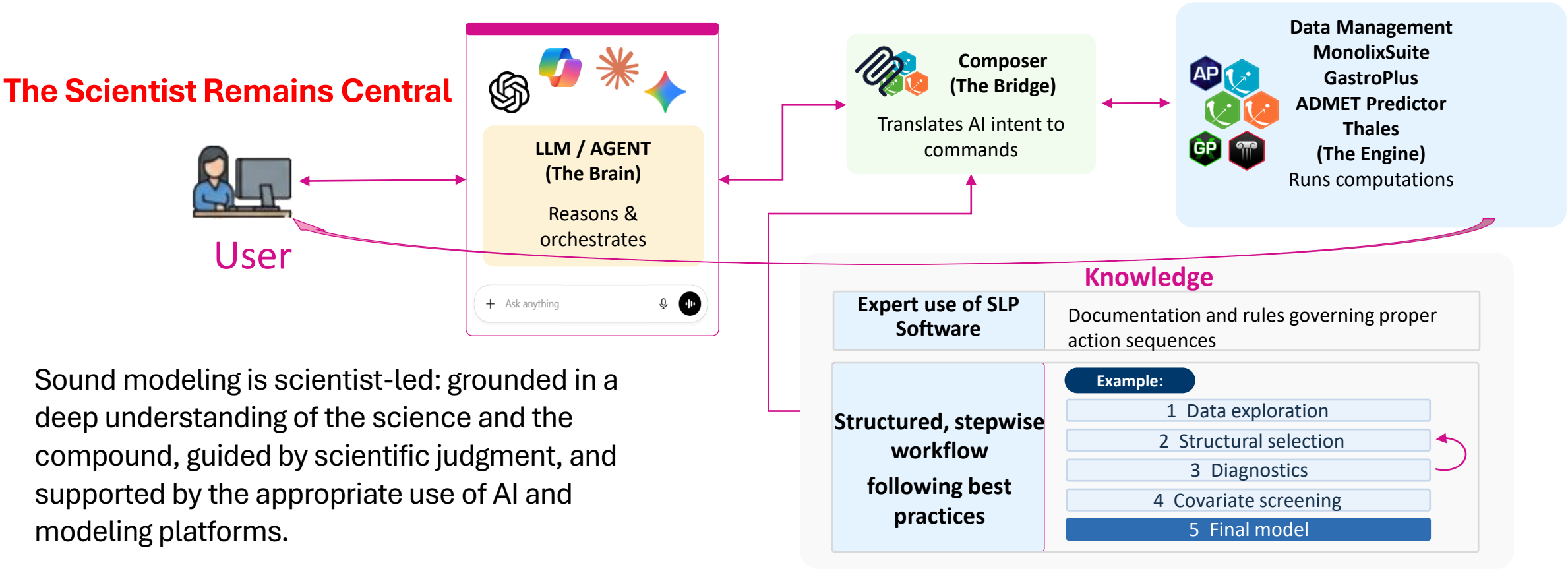
The US label retains limited clinical experience at 3–4.5 mg and monitoring advice for oral drugs with a narrow therapeutic index.

[1] Posada et al. CPT Pharmacometrics Syst Pharmacol. 2025. doi:10.1002/psp4.70101
[2]: https://www.ema.europa.eu/en/documents/product-information/trulicity-epar-product-information_en.pdf
[3]: https://pubmed.ncbi.nlm.nih.gov/40842022/
[4]: https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/125469s065lbl.pdf

How Can AI Help?

Composer is the Operating Layer between Conversation and Science

Our dedicated MIDD operating system connects agentic AI products to our scientific engines.
Everything is anchored by our validated, well-known scientific engines.



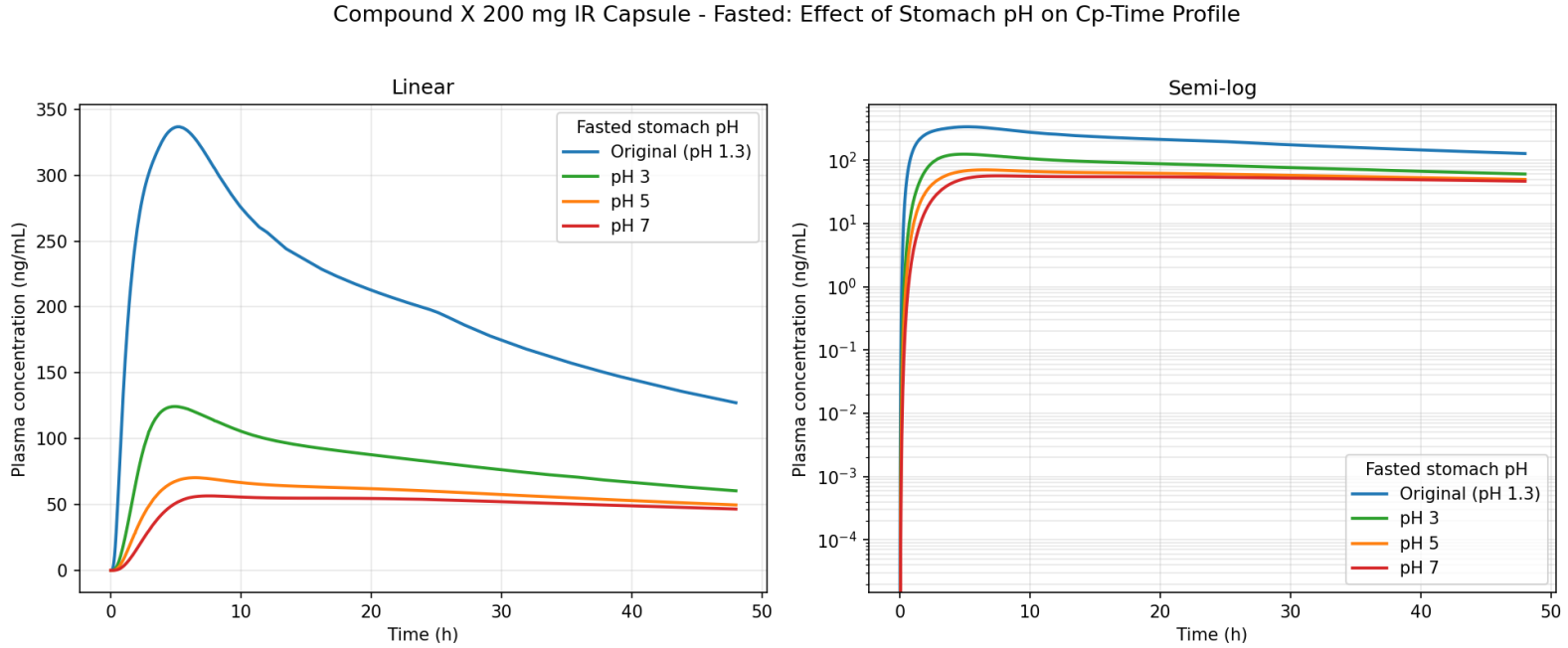
Sound modeling is scientist-led: grounded in a deep understanding of the science and the compound, guided by scientific judgment, and supported by the appropriate use of AI and modeling platforms.

Slide courtesy of P. Kilford

It Starts with the Prompt

Using the GastroPlus project Compound X.gpproject, please copy the simulation and add three new simulations dosing in the fasted state with stomach pH of 3, 5 and 7. Tabulate the impact on Fa, Cmax, AUC and Tmax compared to the original simulation and display all four Cp vs Time profiles on one plot.

Output: Plasma Concentration vs. Time



Output: Interpretation

Interpretation

- **Compound X behaves as a weak base** — absorption and exposure fall steeply as stomach pH rises, consistent with reduced gastric dissolution/solubility at higher pH (a classic PPI/antacid co-administration liability).
- The **largest drop occurs between pH 1.3 and pH 3**; further increases to pH 5 and 7 continue to reduce Fa and Cmax, with diminishing incremental effect.
- **Tmax lengthens** progressively as pH rises (5.1 → 7.7 h), reflecting slower, absorption-rate-limited input.
- Clearance values in the summary scale inversely with bioavailability — these are apparent (CL/F) values driven by the lower F, not a true change in systemic clearance.

Impact of fasted stomach pH on key PK parameters

Scenario	Fa (fraction absorbed)	Cmax (ng/mL)	$AUC_{0-\infty}$ (ng/mL·h)	Tmax (h)
Original (pH 1.3)	0.402	336.8	17,811	5.10
pH 3	0.170	124.4	8,859	4.88
pH 5	0.124	70.4	8,843	6.43
pH 7	0.110	56.5	9,479	7.73

(Fa = fraction absorbed; AUC shown as extrapolated-to-infinity exposure.)

Relative to the original (pH 1.3):

Scenario	Fa	Cmax	$AUC_{0-\infty}$
pH 3	–58%	–63%	–50%
pH 5	–69%	–79%	–50%
pH 7	–73%	–83%	–47%

Output: Table

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Conclusions

- Predicting ARA/PPI effects under fasted conditions does not pose a big challenge if the PBBM model is well validated. This applies to compounds without PPI-related clearance interactions.
- Food effects are more complicated and less reliably predictable just from the physiological changes and drug properties, but still, close to 75% of evaluated cases were predicted correctly. Also, food effects are mostly low in magnitude.
- GLP-1 stomach prolongation is mostly small in magnitude and predictable when a proper stomach emptying study is conducted with and without a GLP-1 agonist and poses low regulatory risk.
- AI used in a controlled setting in conjunction with validated software tools produces reliable and repeatable results.

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- Viera Lukacova, Ph.D.

Our collaborators:

- AiCuris
- Boehringer Ingelheim
- Kalvista

Questions ?

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Extra Slides

Fresh from the press: Hovilpri accepted by the FDA on October 9



Proton pump inhibitors (PPIs): Co-administration of a single oral dose of 100 mg pritelivir (on Day 1) with esomeprazole 40 mg once daily (from Day -3 to Day 1; 4 days total) decreased C_{max} by approximately 76% and AUC by approximately 59% compared to pritelivir administered alone *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Drug Interactions (7.2)]*.

In the Phase 3 trial (PRIOH-1, Parts C-F), pritelivir exposures were evaluated for participants who received concomitant omeprazole or lansoprazole (≤20 mg daily), pantoprazole (≤40 mg daily), or an H2-receptor antagonist (with pritelivir administered at least 2 hours before or 12 hours after the H2-receptor antagonist). Pritelivir exposures in participants receiving these acid-reducing agents were not clinically meaningfully different from those in participants who did not receive any acid-reducing agents *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Drug Interactions (7.2)]*.

Table 3: Changes in Pharmacokinetics of Pritelivir in the Presence of Co-administered Drugs

Co-administered Drug and Regimen	**Pritelivir Regimen**	**N**	**Geometric Mean Ratio (90% CI) of Pritelivir Pharmacokinetics with/without Co-administered Drug (No Effect=1)**		
			$AUC_{0\text{-}inf}$	**$AUC_{0\text{-}last}$**	**C_{max}**
Esomeprazole 40 mg once daily	100 mg single dose	15	0.41 (0.36, 0.48)	0.41 (0.35, 0.47)	0.24 (0.20-0.30)

Abbreviations: N=number of participants included in the pharmacokinetic analysis, CI= confidence interval, AUC= area under the concentration-time curve, C_{max}= maximum concentration

7.2 Potential Effects of Other Drugs on HOVILPRI

Elevation of gastric pH may decrease the systemic bioavailability of HOVILPRI *[see Clinical Pharmacology (12.3)]*, which may reduce its effectiveness or cause drug resistance to HOVILPRI *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

Table 1: Clinically Significant Drug Interactions

Proton Pump Inhibitors/ H2-Receptor Antagonists/Antacids		
Prevention or Management	Proton Pump Inhibitors:	Avoid concomitant use of esomeprazole or rabeprazole with HOVILPRI. Avoid concomitant use of omeprazole or lansoprazole at daily doses above 20 mg with HOVILPRI. Avoid concomitant use of pantoprazole at daily doses above 40 mg with HOVILPRI *[see Dosage and Administration (2.2)]*. Concomitant use of omeprazole, lansoprazole, or pantoprazole below the doses listed above is acceptable, as these lower doses do not reduce pritelivir exposure to a clinically relevant extent.
	H2-Receptor Antagonists:	Take HOVILPRI at least 2 hours before or 12 hours after H2-receptor antagonist intake *[see Dosage and Administration (2.2)]*.
	Antacids:	Take HOVILPRI at least 2 hours before or 2 hours after antacid intake *[see Dosage and Administration (2.2)]*.

Ceritinib and Sonidegib Clinical Pharmacology Highlights

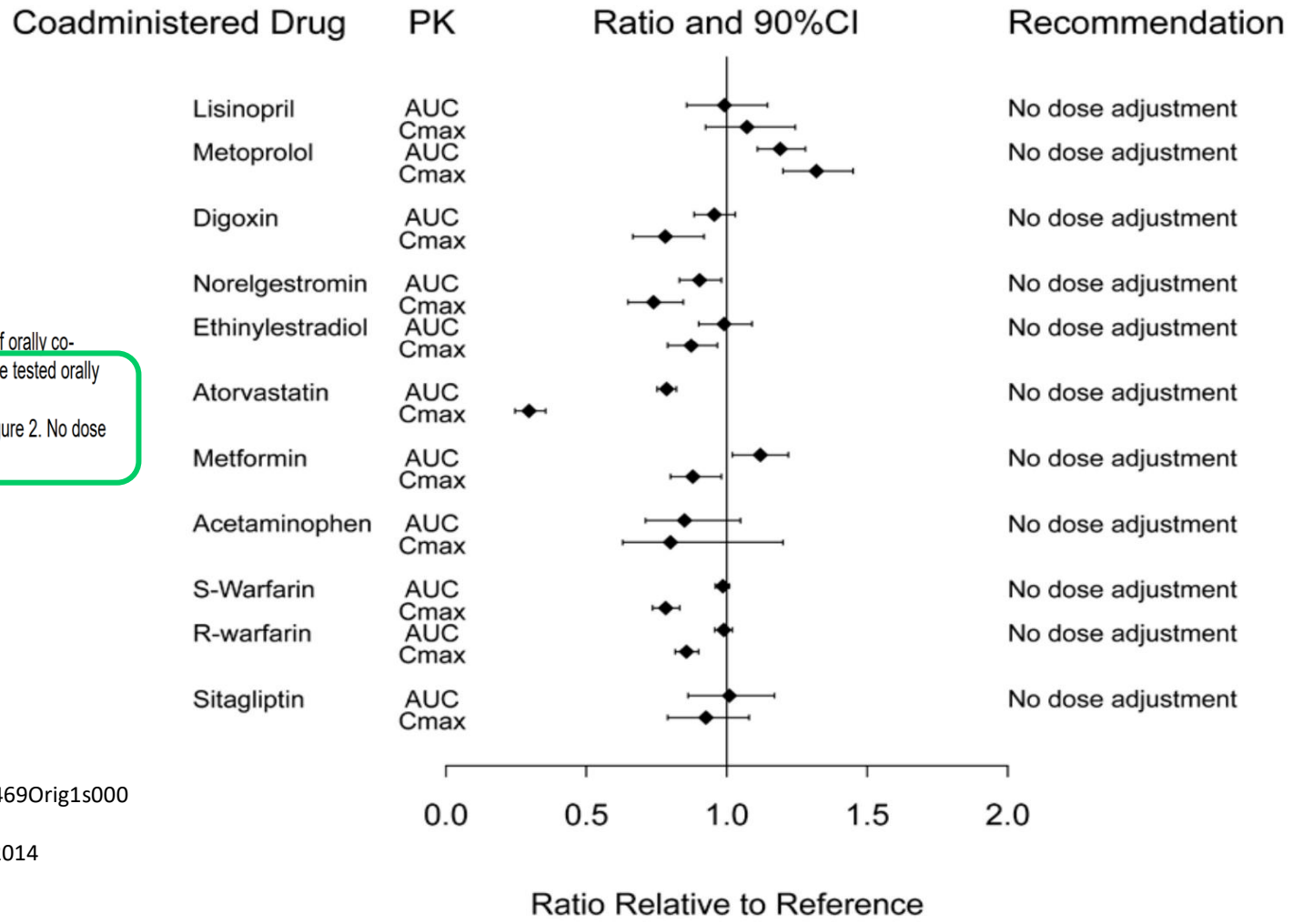
	Ceritinib	Sonidegib
Dosage and indication	ALK positive NSCLC Immediate release capsules / tablets **150 mg** **750 mg QD on an empty stomach (2014), 450 mg QD with food (2017)** PK dose proportionality in the dose range of 50 to 750 mg	hedgehog pathway inhibitor for basal cell carcinoma Immediate release capsules **200 mg** **200 mg QD on an empty stomach (2015)** PK dose proportionality between 100 and 400 mg, and less than dose-proportionality at doses > 400 mg (presumably due to absorption)
Absorption	Tmax: ~1-2 hours High fat meal: ↑AUC 73%, ↑Cmax 41% Low fat meal: ↑AUC 58%, ↑ Cmax 43%	BA < 10%, Tmax ~ 2-4 hours High fat meal: ↑AUC 7.4-fold, ↑Cmax 7.8-fold
Distribution	fup: 3% , Vd/F = 4230 L, B:P = 1.35	Fup < 3%, Vss/F = 9166 L
Metabolism	CYP3A	CYP3A
Excretion	CLss/F = 33.2 L/h, CLsd/F = 88.5 L/h, T1/2 = 41 hours in patients 68% was excreted as unchanged in feces	T1/2 = 28 days
PBPK analysis in the original submission	Applicant's analysis • Assess the effect of CYP3A modulators on ceritinib PK, and propose dosing recommendation for DDI scenarios	Applicant's analysis • Predict the effect of CYP3A modulators on sonidegib PK
	FDA's analysis to explore • Sensitivity of ceritinib exposure to changes in effective permeability • **Food effect** • Sensitivity of ceritinib exposure to changes in gastric pH	FDA's analysis to explore • **Food effect**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205755Orig1s000lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s010lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205266Orig1s000lbl.pdf

Potential for Dulaglutide to Influence the Pharmacokinetics of Other Drugs

Dulaglutide slows gastric emptying and, as a result, may reduce the extent and rate of absorption of orally co-administered medications. In clinical pharmacology studies, dulaglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree.

Pharmacokinetic (PK) measures indicating the magnitude of these interactions are presented in Figure 2. No dose adjustment is recommended for any of the evaluated co-administered medications.

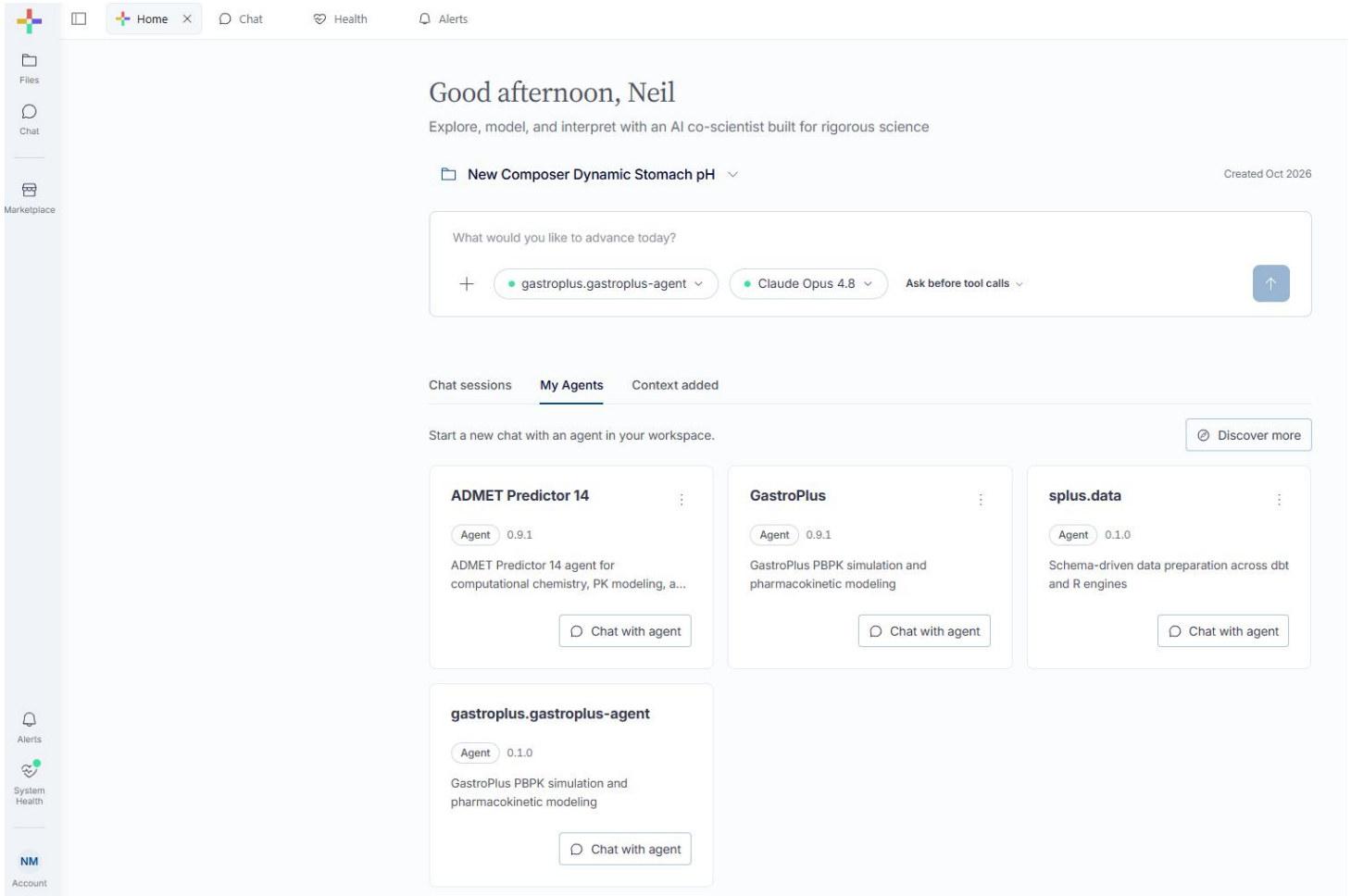


CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 125469Orig1s000
HIGHLIGHTS OF PRESCRIBING INFORMATION
TRULICITY (dulaglutide) injection, for subcutaneous use. Initial U.S. Approval: 2014

Abbreviations: AUC = area under the time-concentration curve; CI = confidence interval; C_{max} = maximum concentration; PK = pharmacokinetics.
Note: Reference group is co-administered medication given alone.

Figure 2: Impact of dulaglutide on the pharmacokinetics of co-administered medications.

S+ Composer: one coordinated hub of scientific workflow



ONE PROGRAM, END TO END

SCIENTIST DIRECTS — **Develop an ACAT/PBPK model for oral midazolam based on the data provided in input.xlsx.**

▼

AI PARSES — **Understands directions, reasons and calls the skills and the tools to automate result with AI reasoning loop**

▼

COMPOSER — **Calls data agent (profile + transform + test), GastroPlus agent**

▼

ENGINES — **ADMET Predictor**
GastroPlus

▼

SCIENTIST REVIEWS

Slide courtesy of P. Kalra, N. Miller