

Prediction of PPI-mediated gastric pH effects and drug interactions using physiologically based pharmacokinetic modelling

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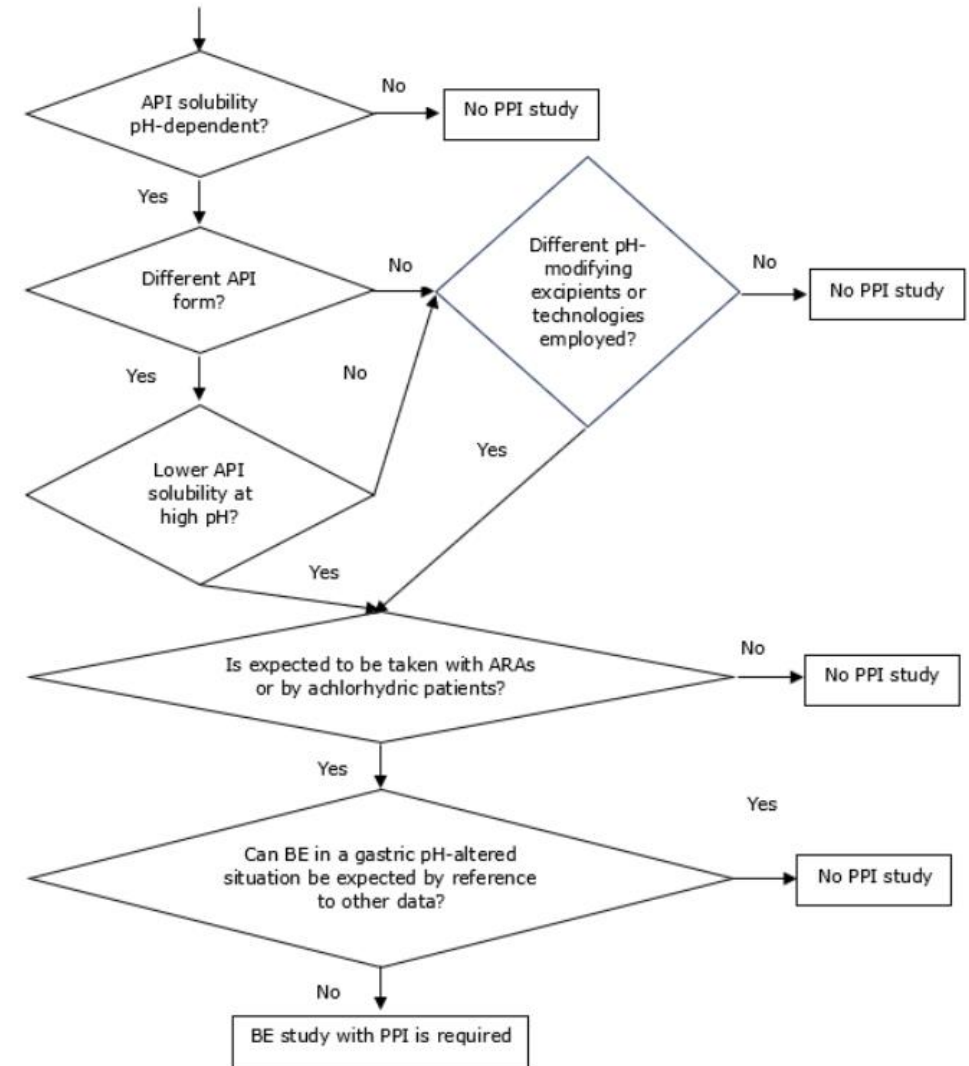


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Current Regulatory Approach to Assessing PPI Effects

- Guideline on the Investigation of Bioequivalence
 - Immediate release medicinal products: fasted bioequivalence study
- Q&A on the Need for Bioequivalence Studies with Acid Reducing Agents (ARA)
- Draft Guideline on the Investigation of Interactions in the Gastrointestinal Tract
- Product Specific Bioequivalence Guidances
 - Dabigatran Etexilate (2025): fasted multiple day pre-treatment with a proton pump inhibitor (PPI)
 - > Waive if both products use the same manufacturing technology and have comparable pH-modifying excipients
 - Palbociclib (2021): fasted multiple day pre-treatment with a PPI, such as pantoprazole (40 mg b.i.d. for 4 days)

Current Regulatory Approach to Assessing PPI Effects



Current Regulatory Approach to Assessing PPI Effects

4.2. Gastric pH: drug-drug interaction with acid reducing agent

Drugs with in vitro solubility that is markedly pH dependent within the physiological pH range (between 1.2 and 6.8), may have their absorption affected by concomitant administration of drugs which change the gastrointestinal pH. If in vitro data indicate that pH-dependent solubility may impact the absorption

Guideline on the investigation of interactions in the gastrointestinal tract
EMA/136069/2026

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of the investigational drug, an in vivo DDI study should generally be performed with an appropriate acid reducing agent (ARA). The potential for a pH-dependent DDI should preferably be evaluated early in clinical development to ensure subsequent efficacy and safety for patients.

Drugs at the highest risk for a clinically relevant interaction with ARAs are weak-bases with low aqueous intrinsic solubility, where increased gastric pH (i.e. $\text{pH} > 4$) can decrease solubility and absorption, potentially leading to loss of efficacy.

Absorption of weak-acidic drugs with low solubility at low pH (~ 1.2) and increased solubility at higher pH may also theoretically be affected by co-administration with an ARA. However, there are currently limited data and the observed effects are generally minor and not considered clinically significant under most circumstances. Therefore, for weak acids the need for a clinical DDI study should be evaluated based on the drug safety profile.

In general, if the drug has pH dependent solubility but exhibits high solubility across the physiological pH range, a DDI study with an ARA is not required. If the tested drug is a modified release formulation with a pH-sensitive release mechanism, gastrointestinal pH modification may affect the drug release and consequently the drug absorption. Further recommendations on in vitro and in vivo investigations to conduct are provided in EMA Guideline on quality of oral modified release products (EMA/CHMP/QWP/428693/2013) and EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), respectively.

- Proton pump inhibitors

Proton pump inhibitors (PPIs) are the most commonly prescribed ARAs. PPIs irreversibly bind to $\text{H}^+ - \text{K}^+ - \text{ATPase}$ thereby reducing gastric acid production. PPI's effect on gastric pH is dose-dependent and is more pronounced and lasts longer than the effect of H_2 antagonists. The baseline gastric acid secretory capacity may not be restored for up to 24–48 h after discontinuing PPI therapy.

In the DDI study, the PPI should be administered for at least 4 days to reach pharmacodynamic steady state. The magnitude of increase of gastric pH and its duration over 24 hours is dependent on the selected PPI and the dose applied. Choice of PPI, dose and timing of dosing between PPI and the medicinal product should be justified.

Additionally, if the investigational drug is a CYP2C19 substrate, it should be considered that many proton pump inhibitors (e.g. omeprazole) are CYP2C19 inhibitors.

Current Regulatory Approach to Assessing PPI Effects

Bioequivalence study design

in case a BCS biowaiver is not feasible or applied

single dose

cross-over

healthy volunteers

☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**

An additional study under conditions of multiple day pre-treatment with a proton pump inhibitor (PPI), such as pantoprazole (40 mg b.i.d. for 4 days), should be conducted in addition to the regular study under fasting conditions.

Background: Solubility of dabigatran etexilate is pH dependent. PPIs may affect the bioavailability of dabigatran differently depending on the formulation.

☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**

An additional study under conditions of multiple day pre-treatment with a proton pump inhibitor (PPI) should be conducted in addition to the regular study under fasting conditions.



Physiologically Based Absorption Modelling to Explore the Formulation and Gastric pH Changes on the Pharmacokinetics of Acalabrutinib

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Pharmacokinetics and Absorption of Posaconazole Oral Suspension under Various Gastric Conditions in Healthy Volunteers[▽]

Gopal Krishna,^{1*} Allen Moton,¹ Lei Ma,¹ Matthew M. Medlock,² and James McLeod¹

Early Clinical Research and Experimental Medicine, Schering-Plough Research Institute, Kenilworth, New Jersey,¹ and PPD Development LP, Austin, Texas²

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Prediction of gastric pH-mediated drug exposure using physiologically-based pharmacokinetic modeling: A case study of itraconazole

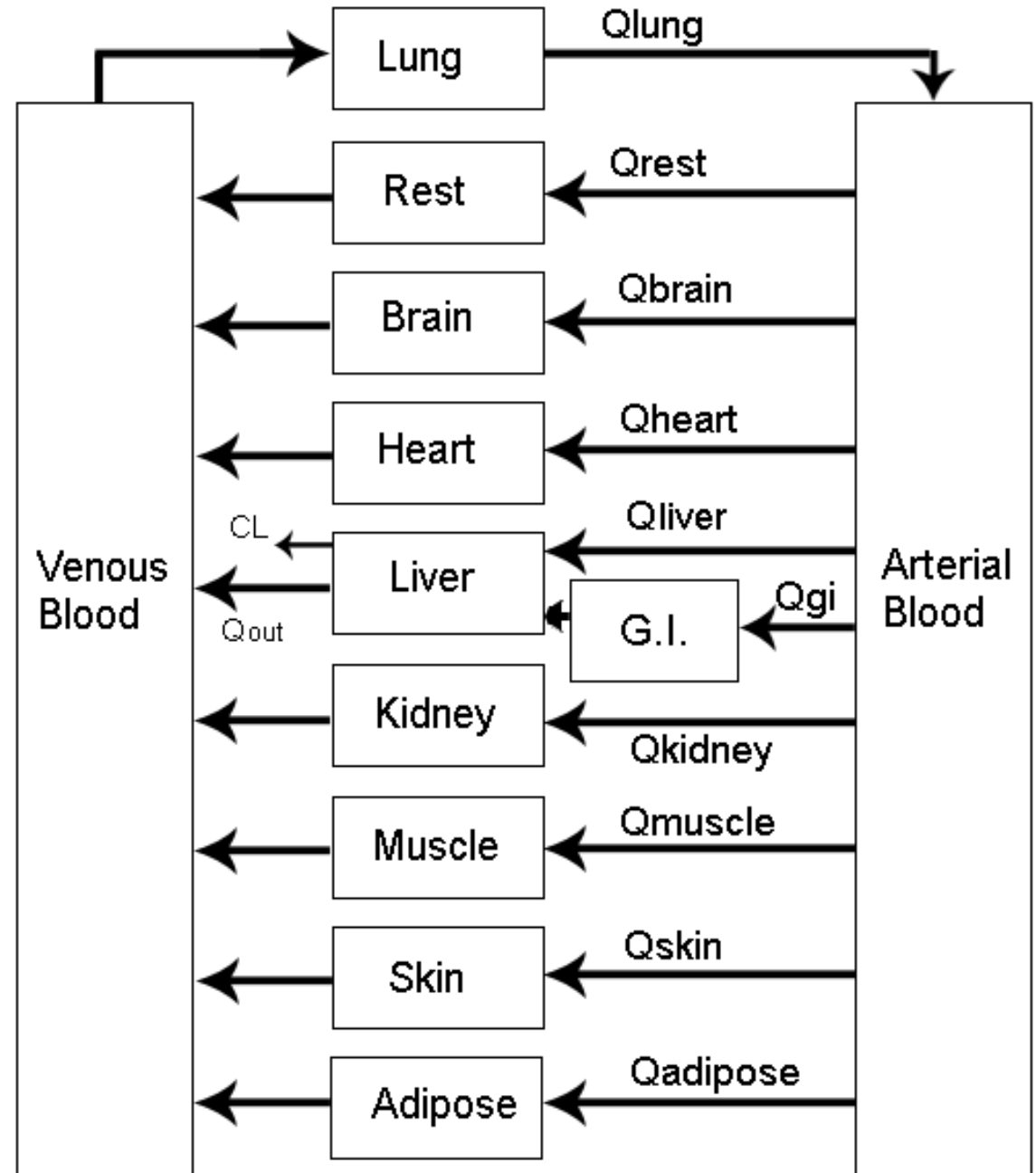
Eunsol Yang^{1,2}  | Kyung-Sang Yu¹ | SeungHwan Lee¹

Physiologically Based Absorption Modelling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Entrectinib

Neil Parrott,^{1,5} Cordula Stillhart,² Marc Lindenberg,³ Bjoern Wagner,¹ Karey Kowalski,⁴ Elena Guerini,¹ Nassim Djebli,¹ and Georgina Meneses-Lorente¹

PBPK Modelling

- Physiological processes and drug-related characteristics
- Body represented as compartments linked by blood flow
- Modeled by equations for drug absorption, distribution, metabolism, elimination
- Separate physiological from drug-specific parameters
- Physiological data available from literature and drug data from lab experiments



Can PBPK modelling reliably simulate the impact of proton pump inhibitors on the pharmacokinetics of immediate-release generic medicines, reducing the need for clinical interaction studies?

Two-step approach



PANTOPRAZOLE MODEL WITH
GASTRIC PH INTERACTION



DABIGATRAN ETEXILATE AND
DABIGATRAN COMBINED MODEL

PBPK modeling to predict the pharmacokinetics of pantoprazole in different *CYP2C19* genotypes

Chang-Keun Cho¹ · Eunvin Ko¹ · Ju Yeon Mo¹ · Pureum Kang¹ · Choon-Gon Jang¹ · Seok-Yong Lee¹  · Yun Jeong Lee² · Jung-Woo Bae³ · Chang-Ik Choi⁴

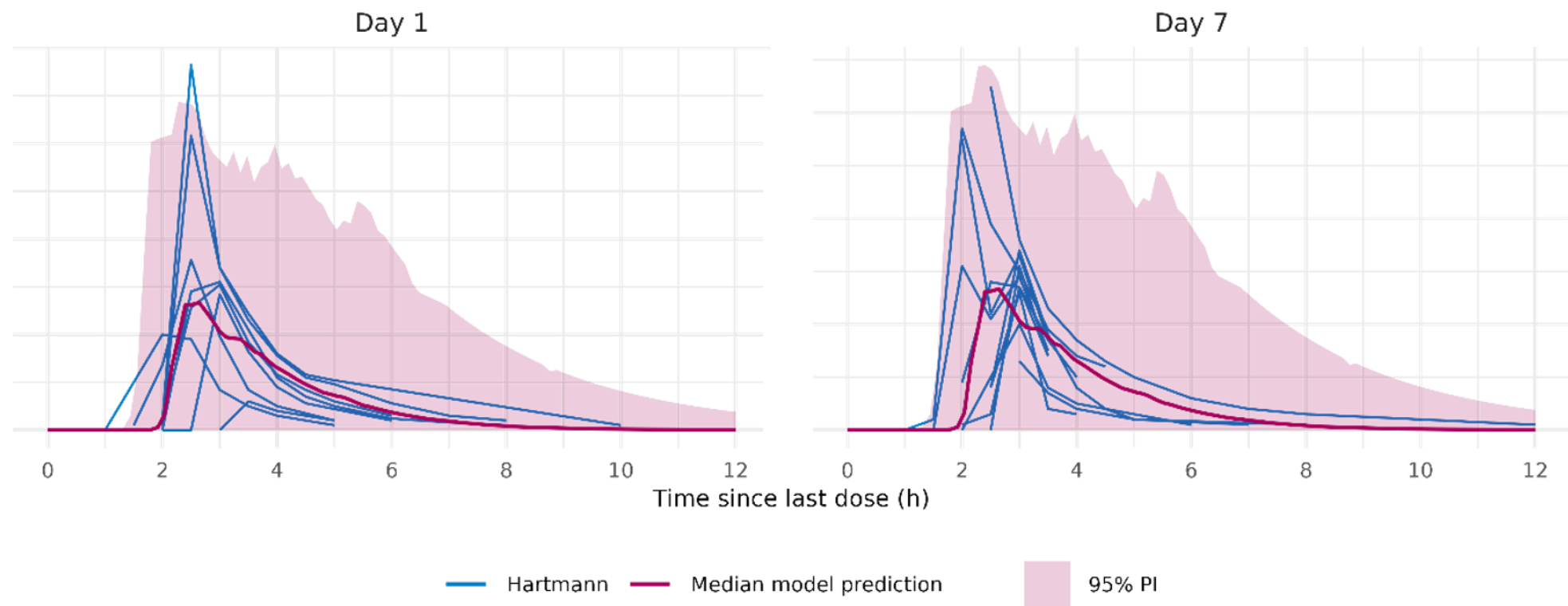
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Twenty-four-hour intragastric pH profiles and pharmacokinetics following single and repeated oral administration of the proton pump inhibitor pantoprazole in comparison to omeprazole

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Implementation of the gastric pH interaction model (1)

Relative proton-pump activity

- r_E = proton pump relative activity
- k_{deg} = degradation rate of proton pump (1/h)
- k_r = rate of proton pump inactivation by PPI (1/h/ μ M)
- C_{eff} = effect concentration (μ M)

$$\frac{dr_E}{dt} = k_{deg} - r_E \times (k_{deg} + k_r \times C_{eff})$$

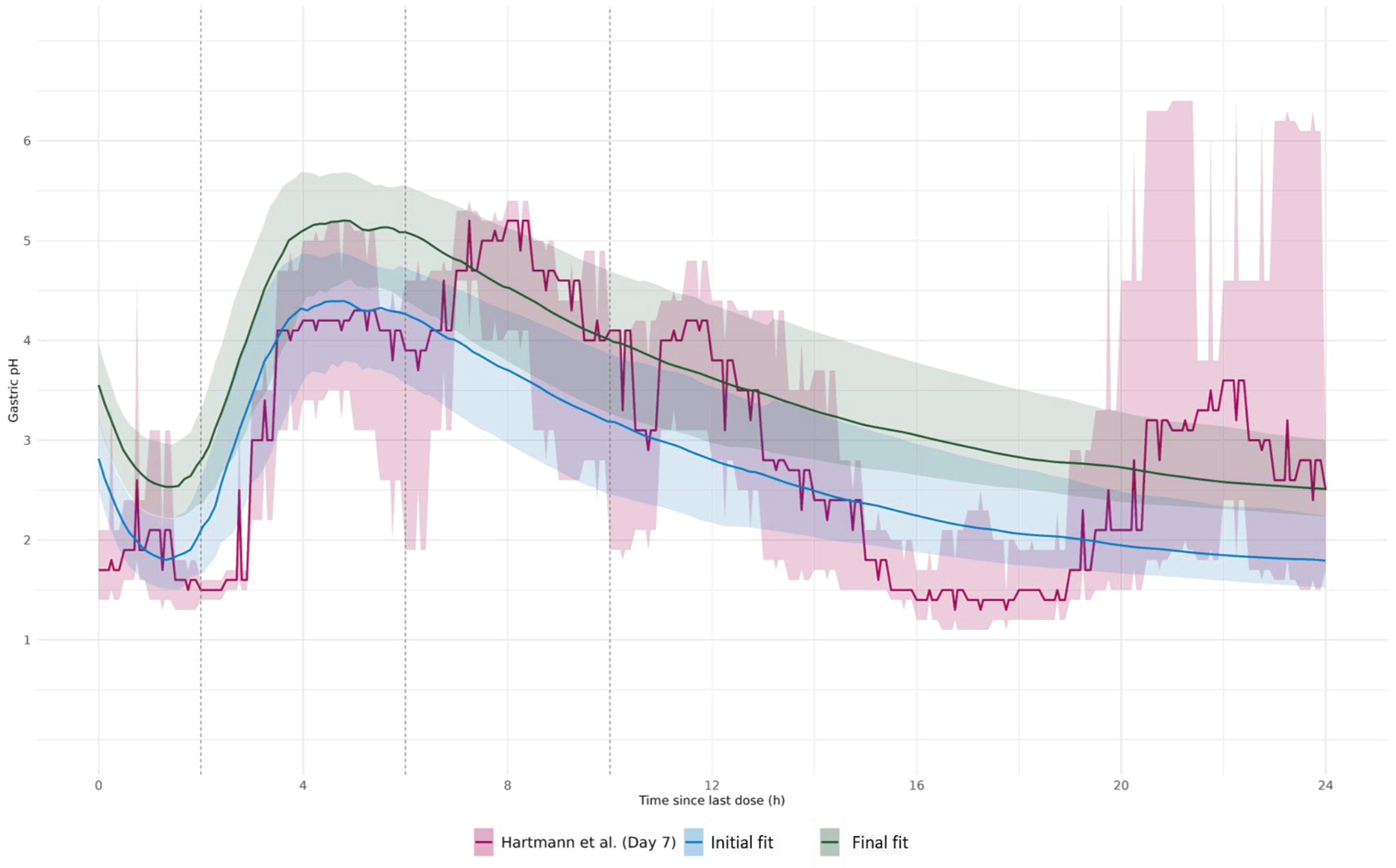
Gastric hydrogen-ion amount

- H^+ = amount of hydrogen ions in the stomach (mmol)
- r_{sec} = gastric secretion rate of hydrogen ions (mmol/h)
- r_E = proton pump relative activity
- K_t = transit rate of H^+ (1/h)

$$\frac{dH^+}{dt} = R_{sec} \times r_E - K_t \times H^+$$

Implementation of the gastric pH interaction model (2)

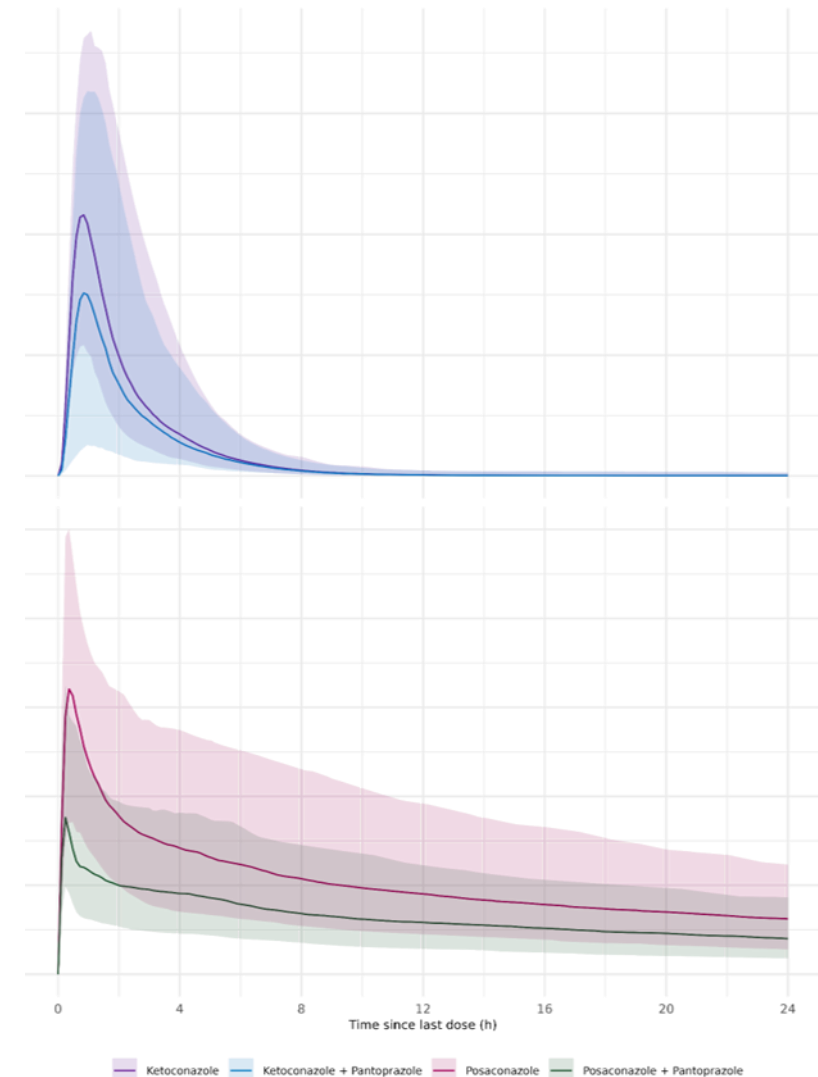
- **Hartmann fitted values (blue line)**
 - Mean intragastric pH over 24 hrs: 2.8
 - Mean percent duration of time with intragastric pH>4: 18
- **Review Kirchheiner et al. (2008)**
 - Mean intragastric pH over 24 hrs: 3.5-3.6
 - Mean percent duration of time with intragastric pH>4: 43.3-53.6
- **Improved fitted values (green line)**
 - Mean intragastric pH over 24 hrs: 3.6
 - Mean duration of time over 24 hrs with intragastric pH>4: 34%



Validation of the gastric pH interaction model

Separate simulations of concomitant administration following 4 days of twice-daily pretreatment with pantoprazole 40 mg

- Ketoconazole (model from: Pathak *et al.*)
 - Precipitation is rapid above pH 5.5, with only ~10% remaining dissolved after 60 min at pH 6
- Posaconazole (model from: Hens *et al.*)
 - Prescribing information reports 46% and 32% reductions in mean C_{max} and AUC_{0-t} when combined with once-daily 40 mg esomeprazole



Validation of the gastric pH interaction model

Simulations showed that following concomitant administration following 4 days of twice-daily pretreatment with pantoprazole 40 mg

- AUC values were reduced to 30-40%
- Cmax values were reduced to approximately 40%
- Tmax showed an increase for ketoconazole and a decrease for posaconazole

Summarizing



Pantoprazole PBPK model: complements existing models and strengthens model-informed study design.



Model-informed approaches: require substantial time and investment; challenging to justify when evidence remains supportive rather than pivotal.



Next steps: continue with the dabigatran etexilate and dabigatran combined model and explore additional drugs.

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Thank you *Questions, perspectives & discussion*

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