A Population Pharmacokinetic Model of Vonoprazan: Evaluating the Effects of Race and Disease Status on Exposure

Carmelo Scarpignato,[1] Eckhard Leifke,[2] Neila Smith,[2] Darcy J. Mulford,[2] Gezim Lahu,[3] Axel Facius,[3] Colin W. Howden[4]

[1]Department of Health Sciences, United Campus of Malta, Msida, Malta; [2]Phathom Pharmaceuticals, Research and Development, Chicago, IL; [3]thinkQ2 AG, Baar, Switzerland; [4]Division of Gastroenterology, University of Tennessee Health Science Center, Memphis, TN

BACKGROUND

- Vonoprazan is a potassium-competitive acid blocker currently under investigation in the US and Europe for non-erosive reflux disease, healing and maintenance of healing of erosive esophagitis (EE), and, in combination with antimicrobials, eradication of *Helicobacter pylori* infection.[1-3]
- Vonoprazan has been approved in Japan and other, mostly Asian and Latin American, countries for a variety of acid-related diseases. The established pharmacokinetic (PK), efficacy and safety profiles for vonoprazan are based primarily on clinical studies in Asian and European healthy volunteers (HVs) and Asian patients.[4]
- Comparison of Japanese and European Phase 1 trials indicates no clinically meaningful differences in PK or pharmacodynamics (PD) between Japanese and non-Japanese HVs.[5,6]
- Population PK allows investigation of the effects of race, disease status and other covariates on drug exposure based on data from a broad sample of clinical studies.

METHODS

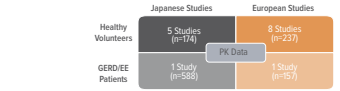
- **Clinical studies and samples:** Analysis set included five studies in Japanese HVs (n=174), eight in European HVs (n=237), one in Japanese EE patients (n=588), and one in European gastroesophageal reflux disease (GERD) patients (n=157; **Figure 1**).
- **Model:** A standard two-compartment model with delayed oral absorption was developed to characterize the systemic exposure to vonoprazan in HVs and patients with EE/GERD (**Figure 2**).
  - The final population PK model includes the following covariates: race (non-Asian [black or white]/Asian), sex, fed/fasted state, baseline body weight, baseline serum creatinine, disease status and age.
- **Characterizing covariate effects on PK:** The model was used to assess the impact of race (Asian vs. non-Asian) and disease status (patients vs. HVs) and other covariate effects on PK parameters (**Figure 2**):
  - Absorption rate (K_a)
  - Clearance (CL)
  - Volume of the second (central) compartment (V_2)
  - Volume of the third (peripheral) compartment (V_3)
- **Characterizing covariate effects on exposure:** The model was used to assess covariate effects on vonoprazan exposure by using it to generate 1,000 simulated PK profiles for a reference participant (48-year-old, male, Asian, HV, with a serum creatinine of 72 µmol/L, and 70 kg body weight, treated with a 20 mg daily dose of vonoprazan under fasted/non-high fat meal conditions), compared with the same participant with one covariate in a different state, eg, GERD/EE patient instead of HV.

OBJECTIVES

To use a population PK approach to characterize differences in vonoprazan exposure between populations and identify clinically relevant covariates, with a focus on race and disease status.

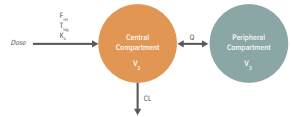
RESULTS

Figure 1. Study Data Included in the Population PK Model



Study doses ranged from 1 to 120 mg.
EE, erosive esophagitis; GERD, gastroesophageal reflux disease; PK, pharmacokinetic.

Figure 2. Model Schematic



The model used was a two-compartment model with delayed oral absorption. F_{rel} and T_{lag} were used in addition to the required PK parameters of K_a, CL, V_2, Q, and V_3.
CL, clearance; F_{rel}, relative bioavailability; K_a, absorption rate; PK, pharmacokinetic; Q, inter-compartmental CL; T_{lag}, absorption delay; V_2, volume of the second (central) compartment; V_3, volume of the third (peripheral) compartment.

Table 1. Summary of Population Characteristics in the Population PK Final Dataset (N=1,156)

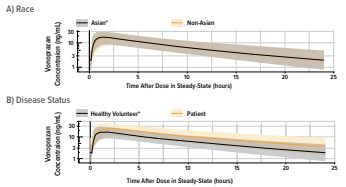
Parameter	Finding
Age, years (mean [SD])	48 (17.7)
Baseline body weight, kg (mean [SD])	69 (12.9)
Baseline creatinine, µmol/L (mean [SD])	73 (21.6)
Race, n (%)	
Asian	768 (66.4)
Black	13 (1.1)
White	371 (32.1)
Other	4 (0.3)
Gender, n (%)	
Male	856 (74.0)
Female	300 (26.0)
Disease status, n (%)	
Healthy volunteers	387 (33.5)
GERD/EE patient	745 (64.4)
Renal impairment	24 (2.1)
CYP2C19 status, n (%)	
EM	650 (56.2)
IM	37 (3.2)
PM	109 (9.4)
Other	84 (7.3)
Not screened	276 (23.9)

EE, erosive esophagitis; EM, extensive metabolizer; GERD, gastroesophageal reflux disease; IM, intermediate metabolizer; PM, poor metabolizer; SD, standard deviation.

POTENTIAL EFFECTS OF RACE AND DISEASE STATUS ON VONOPRAZAN EXPOSURE

- **Figure 3** shows the effect of race and disease status on exposure to vonoprazan.
- Race
  - No clinically meaningful differences in absorption rate (K_a), clearance (CL), volume of the second (central) compartment (V_2) and volume of the third (peripheral) compartment (V_3) were observed between Asian and non-Asian populations.
  - The curves for an Asian and for a non-Asian population are almost completely overlapping, indicating that predicted differences in vonoprazan exposure between Asian and non-Asian populations are minimal and not clinically meaningful.
- Disease status
  - Patients had a reduced absorption rate (K_a), clearance (CL), and volume of the second (central) compartment (V_2) compared with HVs.
  - The curves for an HV and for a patient show extensive overlap, indicating only a small-to-moderate difference in exposure between GERD patients and HVs that is unlikely to be clinically relevant.

Figure 3. Predicted Plasma Concentrations Profiles

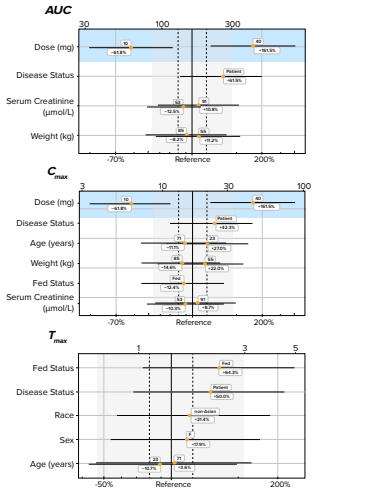


Simulations of typical steady-state 24-hour pharmacokinetic profiles of a reference participant (48-year-old, male, Asian, healthy volunteer, with a serum creatinine at 72 µmol/L, and 70 kg body weight treated with 20-mg daily dose of vonoprazan under fasted/non-high fat meal conditions) with single, modified covariate levels as indicated.
*Reference state. Ribbons indicate 90% prediction intervals (5th to the 95th percentile of the simulations at steady state).

POTENTIAL EFFECTS OF RACE, DISEASE STATUS, AND OTHER COVARIATES ON PK

- **Figure 4** shows identified covariate effects causing at least 10% change from reference.
- Race
  - Non-Asian individuals were predicted to have a slightly later time to maximum concentration (T_{max}) than Asian individuals, but not to a clinically relevant extent.
  - There was no meaningful difference in predicted steady state maximum plasma concentration (C_{max}) or area under the curve (AUC) between Asian and non-Asian individuals.
- Disease status
  - Patients are predicted to have higher steady-state AUC and C_{max}, and a later T_{max} than HVs, but these effects were smaller than the effect of doubling or halving the dose.
- Other covariates
  - Other covariates including age, weight, sex, and serum creatinine had a minimal effect on PK parameters AUC, C_{max}, and T_{max}.
  - Other covariate effects had a smaller impact on vonoprazan exposure than doubling or halving the dose.
- Overall, halving or doubling the dose had a greater effect on vonoprazan exposure parameters than the identified covariates (**Figure 4**).

Figure 4. Covariate Effects on Exposure Parameters



The figure shows identified covariate effects (mean, the 10th and 90th percentile) causing at least 10% mean change from the reference in one or more PK parameters (AUC, C_{max}, T_{max}). Effects of halving and/or doubling the dose on exposure level is shown as a reference and had a far greater effect on the parameters than each of the identified covariates.
AUC, area under the curve (ng x h/mL); C_{max}, maximum plasma concentration (ng/mL); T_{max}, time to maximum concentration (h).

CONCLUSIONS

- The model adequately described vonoprazan PK and the effects of disease state, race, fed/fasting state, sex, age, and baseline body weight on its disposition.
- No investigated covariates had a clinically meaningful impact on vonoprazan exposure that would necessitate dose changes.
- Race (Asian vs. non-Asian) and disease state (HV vs. GERD/EE patient) did not affect vonoprazan exposure in a clinically meaningful way.
- Therefore, the large body of pre-existing clinical data related to vonoprazan in the Asian population can be applied reliably to non-Asian population.

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Conflicts of interest

C. Scarpignato discloses compensation from Phathom Pharmaceuticals as a consultant, advisory board member and speaker and from Takeda as a speaker. E. Leifke, N. Smith, and D. J. Mulford are employees of Phathom Pharmaceuticals; E. Leifke also discloses stockholder interest in Phathom Pharmaceuticals. G. Lahu and A. Facius of thinkQ2 were funded by Phathom Pharmaceuticals to undertake this work. G. Lahu also discloses consultancy fees from Takeda, Arbor Pharmaceuticals, Sanofi, Debiopharm, Vaccibody, Omeros, and Avecia, and A. Facius is a consultant for Phathom Pharmaceuticals. C. W. Howden is a consultant to Phathom Pharmaceuticals, RedHill Biopharma, Ironwood and Allakos, and a speaker for RedHill Biopharma and Almylam. He owns stock in Antibe Therapeutics.

Meeting details

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