Development and Utilization of a Pharmacokinetic/Pharmacodynamic Model for Vonoprazan to Assess the Relationship Between Dose, Exposure, and pH Holding-Time Ratio

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BACKGROUND

- Vonoprazan, a potassium-competitive acid blocker, suppresses gastric acid secretion rapidly and potently over prolonged periods of time.
- Gastric acid suppression is vital to the healing, and maintenance of healing, of erosive esophagitis (EE) and to the eradication of *Helicobacter pylori* infection.
- Previous Phase 1 clinical trials with vonoprazan demonstrated a dose–response relationship for intragastric pH.[1–3]
- The daily fraction of time that gastric pH is >4 (the pH>4 holding-time ratio [HTR]) is critical for healing of EE, while pH>6 HTR is important for eradication of *H. pylori* infection.
- To understand the vonoprazan dose–exposure–pH HTR relationship, data from a US, Phase 1 pharmacokinetics (PK) and pharmacodynamics (PD) study were combined with data from previous studies conducted in Japan and Europe to generate a PK/PD model for vonoprazan.[1–4]
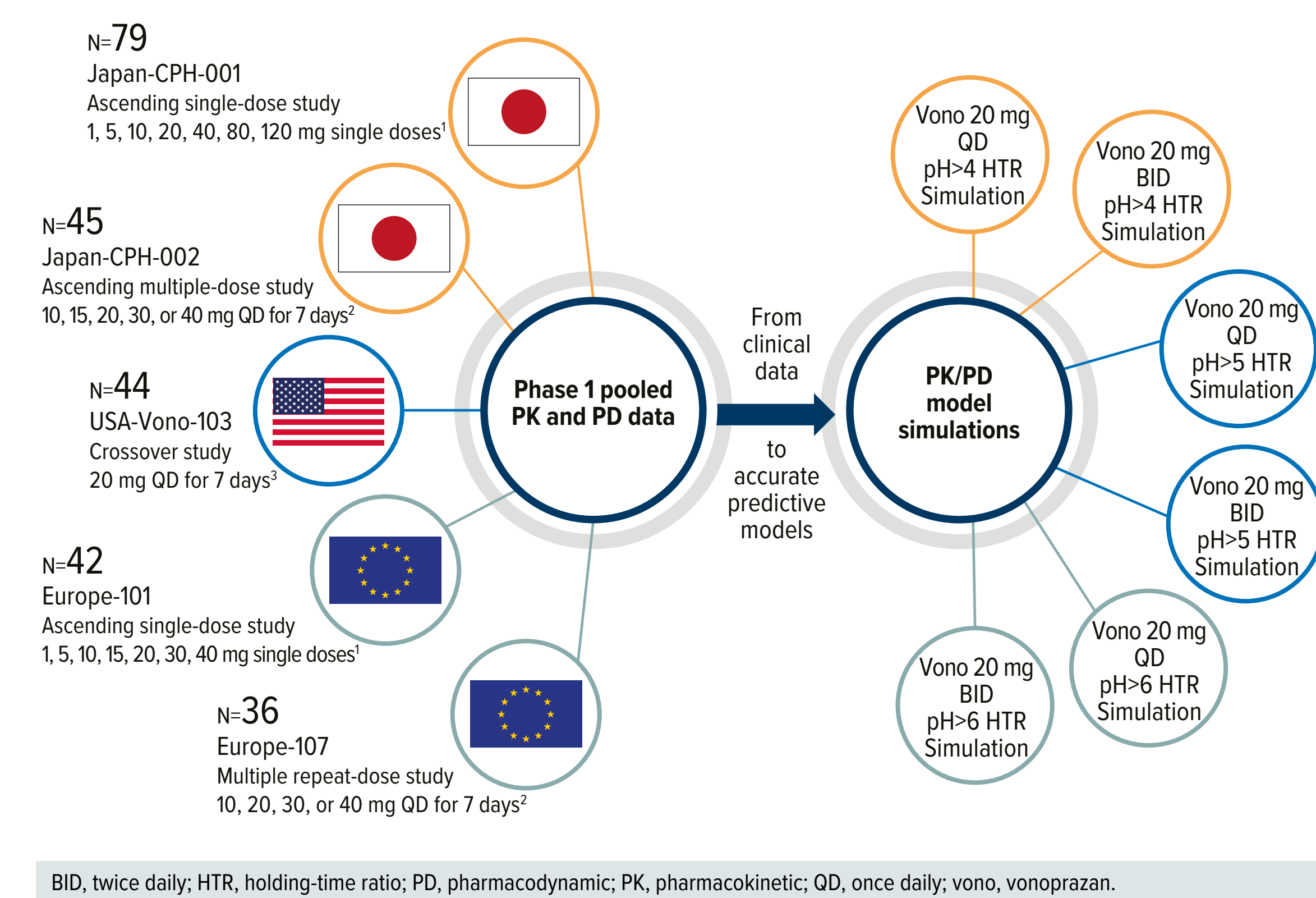
OBJECTIVE

To develop and utilize a PK/PD model to investigate the relationship between vonoprazan dose and exposure and intragastric pH HTR.

METHODS

- Pooled data from five international Phase 1 studies were used to develop three direct-link PK/PD models for pH>4, 5, and 6 HTRs (**Figure 1**).
  - An existing population PK model was used to estimate individual model parameters and to predict PK profiles for study participants on each day with PD measurements.[4]
  - The area under the concentration–time curve between 0 and 24 hours post dose (AUC_{24}) data were merged with pH HTR PD study data.

Figure 1. Study overview: inputs and PK/PD model outputs

BID, twice daily; HTR, holding-time ratio; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily; vono, vonoprazan.

- The PK/PD models were used to characterize the relationship between vonoprazan 20 mg once daily (QD) and 20 mg twice daily (BID) and pH HTR for pH>4, 5, and 6.
- pH HTRs were simulated with between-subject variability; results were summarized as mean and 80% prediction intervals.

RESULTS

Participant demographics and characteristics

- Data from 245 participants were used.
- Demographic details are in **Table 1**.

Table 1. Baseline demographics and characteristics of study participants

	Vono-103	101	107	CPH-001	CPH-002	Total
Sex, n (%)						
Female	12 (28)	–	–	–	–	12 (5)
Male	31 (72)	42 (100)	36 (100)	79 (100)	45 (100)	233 (95)
Age in years, mean (SD)	36.1 (9.1)	26.1 (4.9)	28.0 (7.0)	26.5 (5.3)	27.4 (6.3)	28.1 (7.1)
Weight in kg, mean (SD)	76.7 (12.6)	77.7 (9.6)	75.2 (7.6)	62.7 (5.9)	62.1 (7.0)	69.3 (10.9)
Race, n (%)						
Asian	2 (5)	2 (5)	3 (8)	79 (100)	45 (100)	131 (53)
Black or African American	4 (9)	6 (14)	2 (6)	–	–	12 (5)
Other	5 (12)	1 (2)	–	–	–	6 (2)
White	32 (74)	33 (79)	31 (86)	–	–	96 (39)
Region, n (%)						
Europe	–	42 (100)	36 (100)	–	–	78 (32)
Japan	–	–	–	79 (100)	45 (100)	124 (51)
USA	43 (100)	–	–	–	–	43 (18)
Vonoprazan dose in mg, n (%)						
1	–	6 (14)	–	9 (11)	–	15 (6)
5	–	6 (14)	–	9 (11)	–	15 (6)
10	–	6 (14)	9 (25)	17 (22)	9 (20)	41 (17)
15	–	6 (14)	–	–	9 (20)	15 (6)
20	43 (100)	6 (14)	9 (25)	9 (11)	9 (20)	76 (31)
30	–	6 (14)	9 (25)	–	9 (20)	24 (10)
40	–	6 (14)	9 (25)	17 (22)	9 (20)	41 (17)
80	–	–	–	9 (11)	–	9 (4)
120	–	–	–	9 (11)	–	9 (4)
Baseline pH HTR (%), mean (SD)						
>4	3.8 (3.7)	3.9 (3.3)	6.1 (5.8)	8.6 (6.8)	7.3 (5.9)	6.4 (5.9)
>5	2.4 (2.7)	1.4 (2.0)	3.1 (4.2)	4.8 (4.1)	2.7 (3.1)	3.2 (3.7)
>6	1.3 (1.9)	0.4 (1.2)	0.8 (1.4)	2.1 (2.6)	0.8 (1.6)	1.2 (2.0)

HTR, holding-time ratio; SD, standard deviation.
% values may not total 100 due to rounding.

PK/PD model development

- Model development and the final overall model are described in **Figure 2**.
  - Observed pH HTR data were transformed and characterized using a sigmoid saturation function.
  - Two base models were then developed utilizing AUC_{24} or maximum concentration (C_{max}) as predictor variables.
  - The AUC_{24} model best fit the data.
  - The overall final model estimated baseline pH HTR (E_0), theoretical maximum pH HTR achieved at infinite exposure and time (E_{max}), exposure required to achieve 50% of E_{max} (EC_{50}) as random effects parameters and the time required to achieve 50% of maximum effect (ET_{50}) as a fixed effect parameter.
  - Screening identified Asian race and body weight as relevant covariates.
  - The estimates and 95% confidence intervals (CIs) for all model parameters are shown in **Table 2**.
- The model accurately predicted observed data (**Figure 3**).

Figure 2. PK/PD model development process and overall model
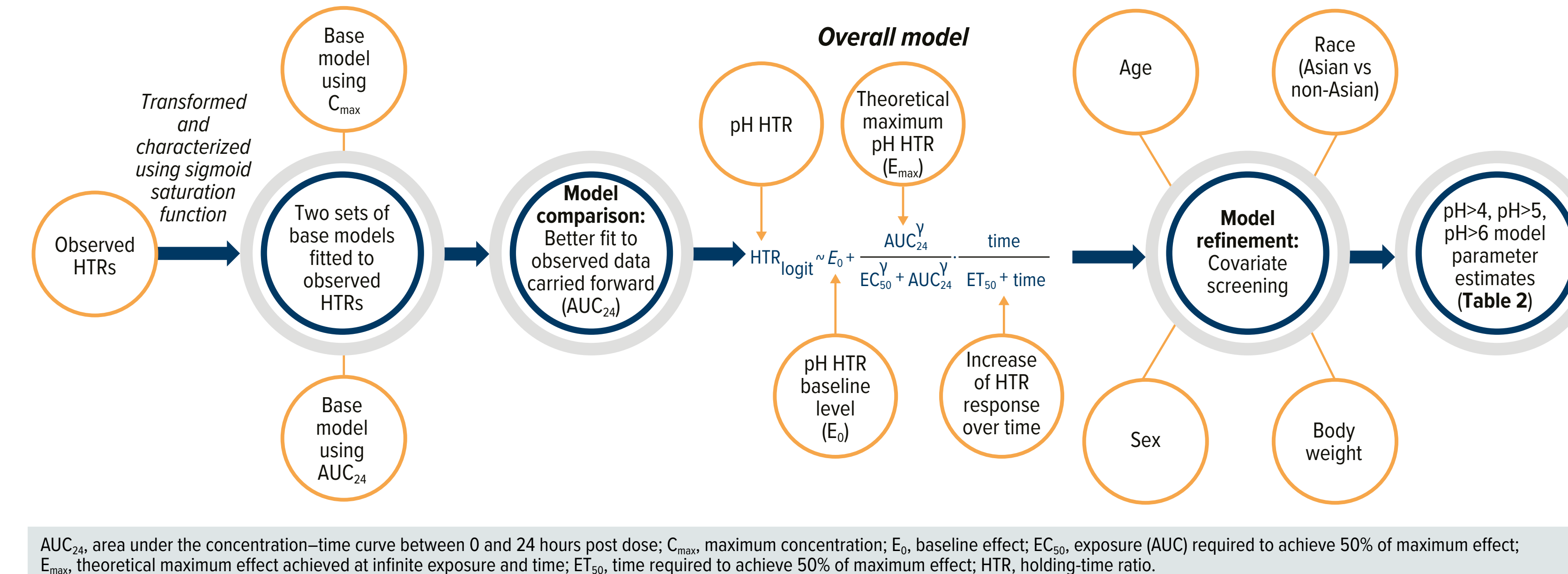
AUC_{24}, area under the concentration–time curve between 0 and 24 hours post dose; C_{max}, maximum concentration; E_0, baseline effect; EC_{50}, exposure (AUC) required to achieve 50% of maximum effect; E_{max}, theoretical maximum effect achieved at infinite exposure and time; ET_{50}, time required to achieve 50% of maximum effect; HTR, holding-time ratio.

Table 2. Estimates and 95% CIs for model parameters

Parameter	Role	pH>4 estimate (95% CI)	pH>5 estimate (95% CI)	pH>6 estimate (95% CI)
E_0	TV (logit)	-2.74 (3.77%) (-2.84 to -2.64)	-3.18 (1.56%) (-3.27 to -3.09)	-3.48 (0.514%) (-3.54 to -3.42)
	Asian-effect (%)	-12.8 (-17.3 to -8.41)	-9.23 (-12.7 to -5.74)	-5.63 (-8.11 to -3.15)
	BSV	0.388 (0.310 to 0.465)	0.276 (0.192 to 0.361)	3.16e-05 (-0.286 to 0.286)
EC_{50}	TV (ng/mL)	48.2 (43.9 to 52.4)	58.8 (53.1 to 64.5)	99.5 (86.2 to 113)
	gamma	1.39 (1.20 to 1.58)	1.34 (1.17 to 1.52)	1.62 (1.30 to 1.94)
	Weight effect (1/kg)	1.50 (0.803 to 2.19)	1.81 (1.19 to 2.44)	–
	BSV	0.319 (0.259 to 0.379)	0.310 (0.252 to 0.368)	0.235 (0.102 to 0.368)
E_{max}	TV (logit)	4.80 (102%) (4.53 to 5.07)	4.83 (102%) (4.44 to 5.23)	2.17 (91.9%) (1.65 to 2.70)
	Weight effect (1/kg)	–	–	-0.0187 (-0.0265 to -0.0108)
	BSV	1e-04 (6.80e-05 to 0.000132)	1e-04 (5.42e-05 to 0.000146)	0.781 (0.505 to 1.06)
ET_{50}	TV (days)	0.432 (0.384 to 0.481)	0.427 (0.369 to 0.485)	0.348 (0.274 to 0.422)
RUV	add.err. (logit)	0.528 (0.475 to 0.580)	0.545 (0.493 to 0.596)	0.498 (0.457 to 0.539)

E_0 and E_{max} were estimated on the logit-scale as the pH HTRs were logit-transformed; back-transformed estimates on the original percent scale are given for these parameters in round brackets.
add.err., additive error; BSV, between-subject variability; CI, confidence interval; E_0, baseline effect; E_{max}, theoretical maximum effect achieved at infinite exposure and time; EC_{50}, exposure required to achieve 50% of maximum effect (E_{max}); ET_{50}, time required to achieve 50% of maximum effect; HTR, holding-time ratio; RUV, residual unexplained variability; TV, typical value.

Figure 3. Prediction-corrected visual predictive checks comparing observed and model-predicted data
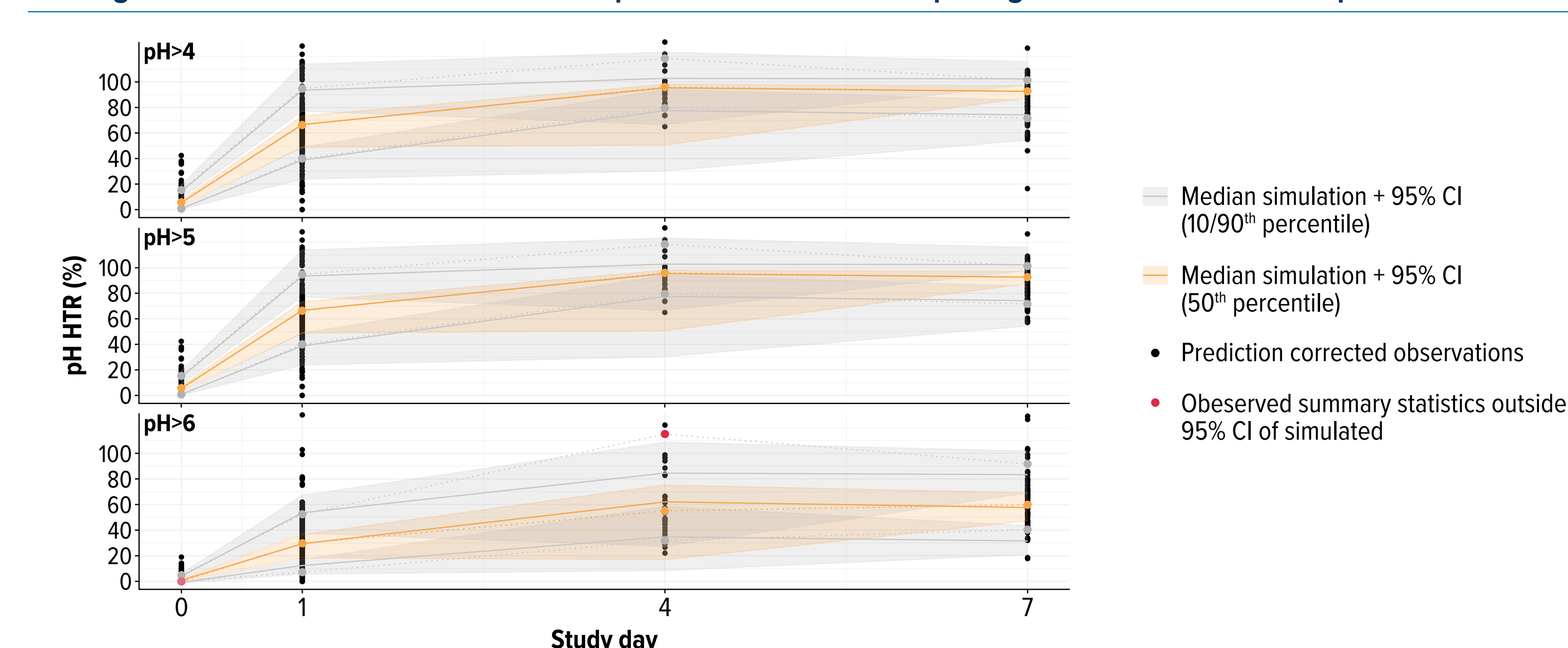

Individual (prediction-corrected) observations are shown as black dots and summarized as median (orange), 10th and 90th percentiles (gray), shown as dots connected by dotted lines. In addition, 1,000 simulations were performed and summarized using the same summary statistics (median, 10th, and 90th percentile). Subsequently, these 3,000 summary statistics were visualized as solid lines (medians) and shaded bands (95% CIs). Red dots indicate cases where the observed summary statistics were outside of the 95% CI of the simulated summary statistics.
CI, confidence interval; HTR, holding-time ratio.

PK/PD model simulations

- Vonoprazan 20 mg QD and BID were predicted to give pH>4 HTRs of 89.7% and 98.1%, respectively, by Day 7 (**Figure 4**).
- Vonoprazan 20 mg BID, which is the dose approved by the FDA as part of *H. pylori* eradication regimens, was predicted to provide a pH>6 HTR of approximately 75% by Day 7.

Figure 4. Predicted back-transformed mean and 80% prediction interval pH HTRs at Days 0 (pre-treatment), 1, 7, and 14
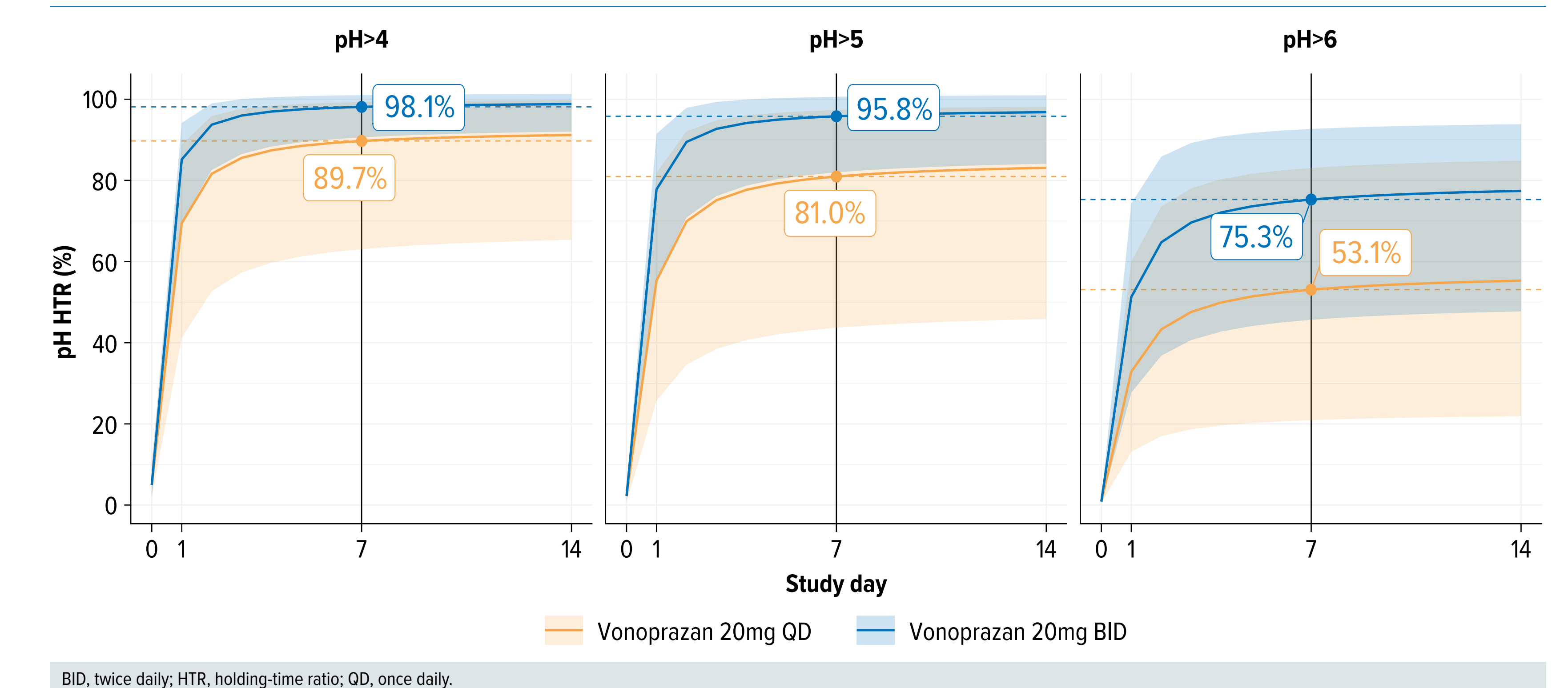
BID, twice daily; HTR, holding-time ratio; QD, once daily.

CONCLUSIONS

- Model simulations indicate that vonoprazan provides high, dose-dependent pH HTRs and therefore consistent, dose-dependent control of 24-hour intragastric acidity.
- Prolonged acid control with vonoprazan includes the overnight period:
  - Low nighttime pH is associated with more severe esophagitis than when pH is controlled.[5,6]
  - Nocturnal heartburn significantly impacts daily life.[7]
  - Successful eradication of *H. pylori* is associated with shorter durations of nocturnal acid breakthrough than unsuccessful eradication.[8]
- Our model precisely predicted observed clinical data, supported the choice of vonoprazan dose, and may help elucidate the mechanisms underpinning observed high EE healing rates and, when combined with antimicrobials, *H. pylori* eradication rates seen with vonoprazan in clinical trials.

Conflicts of interest

CS Consulting: Phathom Pharmaceuticals; **CWH** Consulting: Phathom Pharmaceuticals; **EL** Employee of Phathom Pharmaceuticals; **DJM** Employee of Phathom Pharmaceuticals; **GL** Consulting: Phathom Pharmaceuticals; **AF** Consulting: Phathom Pharmaceuticals; **RH** Consulting: Phathom Pharmaceuticals.

References

1. Jenkins H, et al. *Aliment Pharmacol Ther* 2015;41(7):636–48.
2. Laine L, et al. *Am J Gastroenterol* 2022;117(7):1158–61.
3. Sakurai Y, et al. *Clin Transl Gastroenterol* 2015;6(6):e94.
4. Scarpignato C, et al. *J Clin Pharmacol* 2022;62(6):801–11.
5. Bell NJ, et al. *Digestion* 1992;51 Suppl 1:59–67.
6. Hunt RH. *Archives Int Med* 1999;159:649–57.
7. Shaker R, et al. *Am J Gastroenterol* 2003;98:1487–319.
8. Kim JI, et al. *Helicobacter* 2002;7:331–6.

Meeting details

Presented at the American College of Gastroenterology (ACG) Annual Scientific Meeting 2022, Charlotte, NC. October 21–26.