APPLICATION OF PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS TO SUPPORT THE DOSE SELECTED FOR AN IMMEDIATE-RELEASE OMEPRAZOLE FORMULATION IN A NEW DRUG PRODUCT

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BACKGROUND

- Proton-pump inhibitors (PPIs) are the preferred agents for therapy and prophylaxis of NSAID- and aspirin-associated gastrointestinal (GI) injury.[1]
- A novel fixed-dose combination drug product is being developed that combines enteric-coated aspirin (EC-ASA) and immediate-release (IR) omeprazole (OME) into a single tablet intended for patients at risk of aspirin-induced gastric ulcers.
- The tablet was designed such that the IR OME is released first into the stomach for early onset of raising gastric pH, followed by the release of EC-ASA when the pH of GI tract exceeds 5.5.
- It is unknown whether an IR OME product would result in a lower plasma exposure than an EC OME product and what dose of IR OME for the PA325 tablet would be optimal for controlling gastric pH at gastroprotective levels.

PURPOSE

A pharmacokinetic (PK) and pharmacodynamic (PD) analysis was conducted to establish the relation between OME plasma exposure and its pharmacological effect of suppressing gastric acid secretion. Results of this analysis were to be used to support the choice of a 20 mg or 40 mg dose of IR OME for the fixed-dose investigational product of EC-ASA (325 mg) and IR OME.

METHODS

Omeprazole PK and PD data from once daily administration of EC formulations of OME were obtained from published literature and from Phase 1 studies conducted by POZEN, Inc.

[1] Bhatt et al. *Circulation* 2008;118:1894-909.

Pharmacokinetic Measure:

Mean daily total plasma exposure to OME, AUC_{0-24} at steady state following repeated once daily dosing of 10 mg, 20 mg, or 40 mg EC OME.

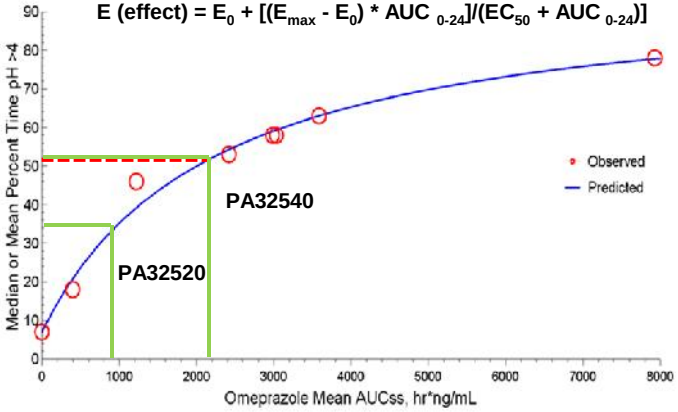
Pharmacodynamic Measure:

Mean or median % time gastric pH > 4.0 during a 24-hour continuous intragastric pH monitoring at steady state following repeated once-daily dosing of 0 mg (baseline), 10 mg, 20 mg, or 40 mg EC OME.

PK/PD Model Description:

The PK-PD relation for OME can be described by a typical pharmacological response model defined by the equation and graph below:

$$E(\text{effect}) = E_0 + [(E_{max} - E_0) * AUC_{0-24}]/(EC_{50} + AUC_{0-24})]$$



E_{max}:	Maximal % time pH > 4.0 over the daily interval at steady state	97.5%
EC_{50}:	Steady-state AUC_{0-24} producing 50% of maximal effect	2212 hr·ng/mL
E_0:	% time pH > 4.0 at baseline (without treatment)	6.9%
r^2:	Coefficient of correlation, between % time gastric pH > 4.0 and steady-state AUC	0.99

Pharmacodynamic Measure Prediction:

For PA32540 (Fixed-Dose Combination of EC-ASA 325 mg and IR-OME 40 mg):

- Plasma OME exposure (mean steady-state AUC_{0-24} of OME) following once daily doses of PA32540 for 7 days was 2187 hr·ng/mL.
- The mean % time gastric pH > 4.0 over 24 hrs is predicted to be **51.9%. (See green line).**
- This is consistent with the actually observed value of **50.5%. (See red dotted line).**

For PA32520 (Fixed-Dose Combination of EC-ASA 325 mg and IR-OME 20 mg):

- Plasma OME exposure (mean steady-state AUC_{0-24} of OME) following once daily doses of PA32520 for 13 days was 939 hr·ng/mL.
- The mean % time gastric pH > 4.0 over 24 hrs is predicted to be **33.9%. (See green line).**

CONCLUSIONS

The PD effect of OME (% time gastric pH > 4.0 over 24 hrs) following repeated once daily dosing of an OME product (either EC or IR), may be predicted using the plasma exposure data (AUC_{0-24}).

The duration that pH exceeded 4.0 for 40 mg IR OME was 52% of time, an optimal duration for gastric mucosal protection, whereas, the duration for 20 mg IR OME was suboptimal at 34% of time.

The PK/PD analysis supports a 40 mg IR OME dose in the fixed-dose tablet combination with 325 mg EC-ASA.

The effectiveness of the 40 mg dose for gastric ulcer reduction is being confirmed in clinical trials with PA32540 in patients requiring aspirin for secondary cardiovascular protection.