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PKPD Modeling of Vilazodone (VLZ) in Adult Patients with Generalized Anxiety Disorder (GAD)

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Objectives: To characterize the relationship between VLZ exposure, efficacy (Hamilton Anxiety Rating Scale total score [HAM-A]), and safety (changes in sexual functioning questionnaire total score [CSFQ]).

Methods: The analysis was based on the data from three double-blind placebo-controlled Phase 3 studies in adult GAD patients. The data included patients from placebo and VLZ treatment arms (20 and 40 mg/day). A previously developed population PK model was used to predict individual exposure (AUC) for each patient. Non-linear mixed-effects models were developed to characterize the relationship between individually predicted exposure and the longitudinal placebo and vilazodone treatment response for HAM-A and CSFQ scores. Linear and Emax exposure-response relationships were investigated for both; covariate-parameter relationships were also explored. The dropout model was developed to improve the model selection and simulation based diagnostics.

Results: The final PKPD model for HAM-A was a linear model; it predicted higher reduction in HAM-A scores with higher VLZ-exposures (AUCss). The 20 and 40 mg/day treatment arms were predicted to result in a 0.91 and 1.48 point reduction in HAM-A score from placebo at day 56, respectively. The probability of dropout was developed iteratively and was found to be best modeled as a function of HAM-A score and treatment group; it was incorporated into simulation-based diagnostics for HAM-A and CSFQ scores. The CSFQ score was best explained by a step model, i.e. the VLZ-effect was higher compared to placebo (1.96-points for males and 0.97-points for females), independent of VLZ dose.

Conclusions: These data suggest a correlation between VLZ-exposures and changes in CSFQ and HAM-A scores; however, while the reductions in HAM-A scores (i.e., improvement in GAD symptoms) with higher VLZ-exposures were deemed to be clinically meaningful, the increase in CSFQ scores (i.e., worsening of the sexual function) for patients on VLZ treatment was not clinically meaningful and did not increase any further with higher exposure.