**ABSTRACT**

Azimilide (AZ) is a class Ia antiarrhythmic drug being developed for the treatment of symptomatic atrial fibrillation. The objective of this study was to develop and validate a population pharmacokinetic (PK) and pharmacodynamic (PD) model.

**METHODS**

AZ concentrations were obtained for each patient for 50, 75, 100 or 125 mg/day of AZ for a 6-9 month period. A total of 739 patients (2739 concentrations) with complete dosing information were included. The effect of covariates on PK/PD parameters was assessed using the SAS® linear regression procedure with the GLM procedure. The model was further evaluated by goodness-of-fit analysis and Phase III population pharmacokinetics and pharmacodynamics of azimilide (WTKG), race, gender, alcohol use, tobacco use (TOB), PR, Cmax, GGT, LDH, creatinine clearance, and use of concomitant medications (ALP, SGPT, SGOT, drug use, and tobacco use, caffeine use, New York Heart Classification, digoxin, and warfarin) on the elimination rate constant of AZ was performed. The model was further evaluated for residual variability and diagnostic plots. The population mean and median values were 37.5% and 20.1%, respectively.

**RESULTS**

The model was further evaluated by goodness-of-fit analysis and Phase III population pharmacokinetics and pharmacodynamics of azimilide (WTKG), race, gender, alcohol use, tobacco use (TOB), PR, Cmax, GGT, LDH, creatinine clearance, and use of concomitant medications (ALP, SGPT, SGOT, drug use, and tobacco use, caffeine use, New York Heart Classification, digoxin, and warfarin) on the elimination rate constant of AZ was performed. The model was further evaluated for residual variability and diagnostic plots. The population mean and median values were 37.5% and 20.1%, respectively.

**CONCLUSIONS**

- The population mean and median values were 37.5% and 20.1%, respectively.
- The model was further evaluated by goodness-of-fit analysis and Phase III population pharmacokinetics and pharmacodynamics of azimilide (WTKG), race, gender, alcohol use, tobacco use (TOB), PR, Cmax, GGT, LDH, creatinine clearance, and use of concomitant medications (ALP, SGPT, SGOT, drug use, and tobacco use, caffeine use, New York Heart Classification, digoxin, and warfarin) on the elimination rate constant of AZ was performed. The model was further evaluated for residual variability and diagnostic plots. The population mean and median values were 37.5% and 20.1%, respectively.

**INTRODUCTION**

Azimilide (AZ) is a class Ia antiarrhythmic drug being developed for the treatment of symptomatic atrial fibrillation or atrial flutter. AZ was chosen for this study because it has the following pharmacokinetic characteristics: 85% absorbed, terminal exponential half-life about 4 days, represents only 10% of total body clearance, and has a QTc prolongation effect.

**OBJECTIVE**

- Develop and evaluate a population PK/PD model for AZ.

**DATA**

- Patients treated with AZ for a 6-9 month period.
- AZ concentrations were obtained for each patient for 50, 75, 100 or 125 mg/day of AZ.
- A total of 739 patients (2739 concentrations) with complete dosing information were included.

**PARAMETERS**

- V: Volume of distribution
- CL: Clearance
- K: Elimination rate constant
- β: The typical value of baseline QTc interval for the jth patient
- β: The typical value of non-linear saturation parameter for the jth patient
- β: The typical value of clearance for the jth patient
- β: The typical value of Michaelis-Menten parameter for the jth patient
- β: The typical value of first-order rate constant for the jth patient
- β: The typical value of second-order rate constant for the jth patient
- β: The typical value of Michaelis-Menten parameter for the jth patient
- β: The typical value of elimination rate constant for the jth patient

**RESULTS OF PHARMACOKINETIC ANALYSIS**

- Parameter Population Mean
  - Interindividual Variability
  - %CV

**RESULTS OF PHARMACODYNAMIC ANALYSIS**

- Concomitant Medication Analyses
  - The model was further evaluated by goodness-of-fit analysis and Phase III population pharmacokinetics and pharmacodynamics of azimilide (WTKG), race, gender, alcohol use, tobacco use (TOB), PR, Cmax, GGT, LDH, creatinine clearance, and use of concomitant medications (ALP, SGPT, SGOT, drug use, and tobacco use, caffeine use, New York Heart Classification, digoxin, and warfarin) on the elimination rate constant of AZ was performed. The model was further evaluated for residual variability and diagnostic plots.

**MODEL PREDICTIONS**

- QTc 300 Predicted Cmax,ss 300 Predicted Cmin,ss 300 Predicted Cmax,ss 300 Predicted Cmin,ss 300

**VALIDATION OF THE PHARMACOKINETIC MODEL**

- Final Pharmacokinetic Model
  - The final model was validated using the datasets.

**REFERENCES**

- L. Phillips, G.A. Thompson, T. Grasela, and J.R. Agnew
- Pharmacological Outcomes Research, Inc., Williamsburg, VA, USA; Proctor & Gamble Pharmaceuticals, Cincinnati, OH, USA

**CONCLUSIONS**

- Clearance and volume were significantly related to weight. However, the clearance and pharmacokinetic parameters for patients of similar weight and height may vary due to differences in body composition and body fat.
- Azimilide is a class Ia antiarrhythmic drug being developed for the treatment of symptomatic atrial fibrillation or atrial flutter. Azimilide was chosen for this study because it has the following pharmacokinetic characteristics: 85% absorbed, terminal exponential half-life about 4 days, represents only 10% of total body clearance, and has a QTc prolongation effect.

**ACKNOWLEDGEMENTS**

- This study was supported by Proctor & Gamble Pharmaceuticals, Cincinnati, OH, USA.

**APPENDIX**

- The population mean and median values were 37.5% and 20.1%, respectively.

**SURVEY**

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