PHASE III POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF AZIMILIDE

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ABSTRACT

Purpose
Azimilide (AZ) is a class III antiarrhythmic drug being developed for the treatment of symptomatic atrial fibrillation/flutter (AF/FL) and/or symptomatic paroxysmal supraventricular tachycardia (PSVT). The objectives of this analysis were to develop and validate a population pharmacokinetic (PK) and pharmacodynamic (PD) model.

Methods
AZ concentrations (C) and QTc intervals were pooled from patients enrolled in three Phase III trials. Patients received 35, 50, 75, 100 or 125 mg/day of AZ for a 6-9 month period. A blood sample and QTc interval were obtained for each patient 8 times during the trial. Data were split (80%/ 20%) for model development/validation. NONMEM was used to fit the C-time data to a one compartment model and the QTc-C data to an Emax model. The influence of the following patient covariates on AZ PK and PD parameters was evaluated: age, weight (WTKG), race, gender, alcohol use, tobacco use (TOB), caffeine use, NY Heart Class, cardiac findings, and obesity. The influence of clinical chemistries (ALP, SGPT, SGOT, GGT, LDH, BIL, BUN and CrCl) and concomitant medications (digoxin, warfarin, CYP2D, CYP2E, and CYP3A inhibitors, and CYP3A and general inducers) on AZ PK parameters was also evaluated. The influence of potassium level and concomitant medications (digoxin, warfarin, and tricylics) was also evaluated for AZ PD parameters. The prediction error percent (PEP) and the absolute prediction error percent (APEP) were used to evaluate the validity of the models.

Results
Clearance (L/hr) was [3.92*(WTKG-43)^0.208] with a proportional increase for males and TOB. Volume (L) was [9.88*(WTKG- 43) + 717*(total BIL)^0.348]. The PK/PD analysis showed that EC50 (ng/mL) was [107*potassium level]. The mean Emax (msec) was 61.7 (increase from baseline). All other patient covariates were not statistically significant predictors of CL, V, or EC50. The mean PEP/ APEP for the PK and the PK/PD model validation was 1.11%/ 26% and -0.2%/6.3%, respectively.

Conclusions
Males were found to have 17% higher CL and TOB use increased CL approximately 16%. The change in EC50 was not clinically significant within the normal range of potassium. At 125 mg/day the maximum % increase in the QTc interval was 9 and 10% for males and females, respectively. Both models were essentially unbiased and acceptably accurate.

INTRODUCTION

- Azimilide (AZ) is a class III antiarrhythmic drug being developed for the treatment of symptomatic AF/FL and/or symptomatic PSVT.
- Previous studies have shown orally administered AZ to have the following pharmacokinetic characteristics:
  - > 85% absorbed
  - steady-state volume of distribution (~10 L/kg) consistent with wide tissue distribution
  - Tmax approximately 7 hours
  - terminal exponential half-life about 4 days
  - metabolic clearance predominant, renal clearance represents only 10% of total
- AZ produces dose dependent prolongation of QT and QTc intervals without clinically significant effects on heart rate, PR and QRS intervals.

OBJECTIVE

- Develop and validate a population PK and PD model for AZ

METHODS

Study Design
- Three double-blind Phase III trials; 3 day loading dose phase (twice daily); 6-9 month maintenance phase (once daily)
- Doses: placebo, 35, 50, 75, 100, or 125 mg/day

Data
- Steady-state assumed after 28 days of dosing
- Patient covariates: gender, race, age, weight, obesity, alcohol use, tobacco use, caffeine use, New York Heart Classification, pace-artificial pacemaker spike, and myocardial infarction–intermediate/old
- Measures of liver and renal function: standard clinical chemistries - ALP, ALT, AST, GGT, BIL, BUN, creatinine clearance, and LDH
- PK concomitant medication classes
  - Inhibitors of CYP2D, CYP2E, and CYP3A enzymes
  - Inducers of CYP3A, and general enzymes
  - Digoxin and warfarin
- PD concomitant medications: tricyclic antidepressants, digoxin, and warfarin
- PK and PD datasets randomly divided by dose group; : model development (MD) - 80% and model validation (MV) - 20%

Pharmacostatistical Model
- NONMEM V, using First Order estimation
- PK: One-compartment model; first-order absorption and elimination
  PD: Linear model, Emax model, and sigmoid-Emax model fit to QTc-AZ
- Exponential error model for interindividual variability
- PK: Additive plus constant coefficient of variation error model for residual variability
  PD: Additive error model for residual variability

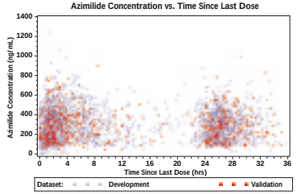
Patient Covariate Analysis
- Bayesian PK parameter estimates that systematically changed more than 20% over the range of the covariate were further evaluated.
- Bayesian PD parameter estimates modeled as function of all covariates using the SAS® linear regression procedure with the forward selection option ($\alpha = 0.05$). Significant covariates were further evaluated.
- Continuous patient covariates modeled using a centered linear model or a centered power model.
- Dichotomous patient covariates and the concomitant medication drug classes modeled as a proportional increase or decrease in the parameter.
- Univariate analyses were performed followed by backward elimination to determine significant patient covariates.

Statistical Analysis
- Statistical significance, univariate analyses $\alpha = 0.05$; backward $\alpha = 0.01$
- Goodness-of-fit of each NONMEM analysis assessed by examination of
  - scatterplots of predicted versus measured observations and versus weighted residuals;
  - %SEM of the parameter estimates; and
  - changes in the estimates of interindividual and residual variability

Validation of Pharmacokinetic and Pharmacodynamic Model
- Final PK and PD models were applied to their respective MV datasets.
- Mean PE% [(Observed-Predicted/Predicted)*100] was used as a measure of bias; mean |PE|% was used as a measure of precision
- Distributions of PE% and |PE|% were also evaluated.

RESULTS OF PHARMACOKINETIC ANALYSIS

Data
- 739 patients (2739 concentrations) with complete dosing histories and available covariate information for MD
- AZ concentration and sample times similar for MD and MV datasets (see figure below).
- Age: 20-89 years; average 63 (MD) and 62 (MV)
  Weight: 43-146 kg; average 84 (MD) and 85 (MV)
  38% of MD patients and 43% of MV patients were female
- Patient categories represented by less than 30 MD patients (5%): Non-Caucasian races, New York Heart Class II and III, paced-artificial pacemaker spike, and myocardial infarction-intermediate/old.
- CYP3A inhibitors and inducers represented approximately 12% of MD and MV data. Digoxin and warfarin represented approximately 50% and 40% of MD and MV, respectively. Other concomitant medication classes represented by less than 5% of patients.



Basic Pharmacokinetic Model
- One compartment model with first order absorption and elimination

Patient Covariate Analyses
- CL: Gender, tobacco use, and weight statistically significant
- V: Weight and total bilirubin statistically significant

Concomitant Medication Analyses
- No medication classes were statistically significant

Final Pharmacokinetic Model

$$\tilde{CL}_j(L/hr) = 3.92 \bullet (WTKG_j - 43)^{0.208} \bullet (1+0.171 \bullet MALE_j) \bullet (1+0.155 \bullet TOB_j)$$

$$\tilde{V}_j(L) = 717 \bullet (BIL_j)^{0.348} + 9.88 \bullet (WTKG_j - 43)$$

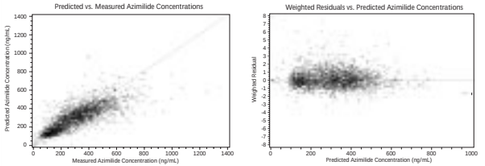
Where:

$\tilde{CL}_j$ = the typical value of clearance for the j^{th} patient;
$\tilde{V}_j$ = the typical value of volume for the j^{th} patient;
$WTKG_j$ = the weight (kg) value of the j^{th} patient;
$MALE_j$ = 1 if the j^{th} patient is male and 0 if the j^{th} patient is female;
TOB_j = 1 if the j^{th} patient currently uses tobacco use and 0 otherwise; and
BIL_j = total bilirubin for the j^{th} patient.

Parameter Estimates and Standard Errors for the Final Pharmacokinetic Model

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
Ka (hr^{-1})	0.497	22.3	55.14	167.8
Cl	3.92	12.3	21.79	10.9
Cl - Male	0.171	21.3		
Cl - Current TOB	0.155	39.7		
Cl – WTKG power	0.208	17.5		
V	717	13.0	34.21	17.8
V – WTKG slope	9.88	18.3		
V – BIL power	0.348	25.9		
[2]Covariance of Cl and V	0.0432	14.4		
[1]Residual Variability				
σ_1^2	0.0248	18.3		
$\left(\frac{\sigma_2}{\sigma_1}\right)$	216	27.5		

[1]Residual variability $(\%CV) = \frac{\sqrt{0.0248\ C^2 + 216^2}}{C} \bullet 100$
69.8% at 50 ng/mL, 20.8% at 250 ng/mL, and 17.2% at 500 ng/mL
[2]Correlation of Cl and V: $r^2 = 0.36$



Model Predictions

Estimated Steady-State Pharmacokinetic Parameters for Weight Ranges by Gender and for the Range of Total Bilirubin Values

Gender	Bilirubin (mg/dL)	Weight (kg)	Cl (L/hr)	V (L)	T 1/2 (hr)	Tmax, ss (hr)	Dose = 100 mg/day			Dose = 125 mg/day		
							AUC	Cmin,ss (ng/mL)	Cmax,ss (ng/mL)	AUC	Cmin,ss (ng/mL)	Cmax,ss (ng/mL)
[1]Male	0.6	78.5	9.6	951	68.6	4.8	10.4	391	465	13.0	489	581
		88.5	10.2	1050	71.5	4.9	9.8	371	437	12.3	463	547
		100	10.6	1163	76.2	4.9	9.4	359	419	11.8	449	524
[1]Female	0.6	61.9	7.2	787	76.2	4.9	13.9	530	620	17.4	663	775
		71.7	7.9	884	77.9	4.9	12.7	484	563	15.8	605	704
		83.2	8.5	997	81.5	4.9	11.8	451	521	14.7	564	652
[2]Male	0.1	88.5	10.2	771	52.5	4.8	9.8	357	448	12.3	447	560
	0.4		10.2	971	66.0	4.8	9.8	367	439	12.3	459	549
	0.6		10.2	1050	71.5	4.9	9.8	371	437	12.3	463	547
	0.7		10.2	1083	73.7	4.9	9.8	372	437	12.3	465	546
	1.5		10.2	1275	86.6	4.9	9.8	377	432	12.3	471	540

[1] Weights represent the 25th, 50th, and 75th percentiles of the model development database, respectively.
[2] Bilirubin values represent the minimum, 25th, 50th, and 75th percentiles, and the maximum of the model development database, respectively.

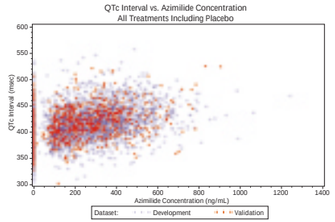
Validation Of The Pharmacokinetic Model

Summary Statistics of the Predicted Error Percents (PE%) and Absolute Predicted Error Percents (|PE|%/PE%) for the Pharmacokinetic Model Validation and Development Datasets

Dataset	Variable	N	Mean (SD)	Median	Minimum	Maximum
Validation	PE%	561	1.11 (34.20)	-2.93	-73.77	200.35
	|PE|%	561	25.98 (22.24)	21.09	0.03	200.35
Development	PE%	2739	1.35 (32.45)	-1.46	-93.59	192.93
	|PE|%	2739	24.17 (21.68)	19.22	0.00	192.93

RESULTS OF PHARMACODYNAMIC ANALYSIS

Data
- 843 patients with 3,828 QTc measurements, including placebo patients for MD.
- AZ concentrations and QTc intervals similar for MD and MV datasets (see figure below)
- Age: 20-89 years; average 63 (MD) and 62 (MV)
  Weight 37-159 kg; average 84 (MD) and 85 (MV)
  Potassium 2.9-7.7 (mEq/L); average 4.3 for MD and MV
  38% of MD patients and 43% of MV patients were female
- Patient categories represented by less than 42 MD patients (5): Non-Caucasian races, New York Heart Class II and III, paced-artificial pacemaker spike, and myocardial infarction-intermediate/old
- Digoxin was represented 37% (MD) and 39% (MV)
  Warfarin was represented by approximately 30% of MD and MV.
  Tricyclic antidepressants were represented by 2% of MD and MV.



Basic PD Model
- Emax model represented the best fit to the AZ concentration – QTc Interval

Patient Covariate Analyses
- Baseline (BL): Gender, New York Heart Class, and Paced- Artificial Pacemaker Spike statistically significant
- EC50: Potassium statistically significant

Concomitant Medication Analyses
- None of the concomitant medication classes were significant for BL or EC50

Final Pharmacodynamic Model

$$\tilde{BL}_j = 392 \bullet (1\text{-}0.0214 \bullet Female_j) \bullet (1+0.0129 \bullet NYHC1_j + 0.0563 \bullet NYHC2_j) \bullet (1+0.0622 \bullet CF_j) \bullet (1\text{-}0.011 \bullet DIG_j)$$

$$\tilde{EC}_{50ij}\ (ng/mL) = 107 \bullet K_{ij}$$

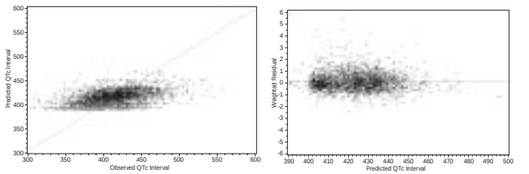
Where:

$\tilde{BL}_j$ = the typical value of baseline QTc interval for the j^{th} patient;
$\tilde{EC}_{50ij}$ = the typical value of EC_{50} at the i^{th} observation for the j^{th} patient;
$Female_j$ = 1 if the j^{th} patient is female and 0 if the j^{th} patient is male;
$NYHC1_j$ = 1 if the j^{th} patient has NYHC I and 0 otherwise;
$NYHC2_j$ = 1 if the j^{th} patient has NYHC II or NYHC III and 0 if otherwise;
CF_j = 1 if the j^{th} patient has a cardiac finding of paced-artificial pacemaker spike and 0 otherwise;
DIG_j = 1 if the j^{th} patient is taking digoxin at baseline and value 0 otherwise; and
K_{ij} = the potassium value at the i^{th} observation in the j^{th} patient

Parameter Estimates and Standard Errors of the Final Pharmacodynamic Model

Parameter	Population Mean		Interindividual Variability	
	Estimate	% SEM	Estimate (%CV)	% SEM
BL (msec)	392	0.29	4.8	7.6
BL - pacemaker spike	0.0622	29.3		
BL - Female	0.0214	19.5		
BL - NYHC I (NYHC 1)	0.0129	57.0		
BL - NYHC II and III (NYHC 2)	0.0563	21.0		
BL - Digoxin (DIG)	-0.011	34.2		
[1]EC_{50} - K (ng/mL azimilide per mEq/L)	107	31.6	62.8	48.6
Emax (msec)	61.7	17.3		
Residual Variability (SD in msec)	20.1	4.1		

[1]The estimate of Emax and K- EC_{50} variable were highly correlated ($r^2 = 0.95$).



Model Predictions

Estimated Pharmacodynamic Parameters and Predicted QTc Intervals at Steady-State

Gender	Weight (kg)	BL[2] (msec)	EC_{50}[3] (ng/mL)	Emax (msec)	Dose = 100 mg/day			Dose = 125 mg/day		
					Cmin,ss[4] (ng/mL)	Predicted QTc (change from baseline)	Cmax,ss[4] (ng/ml)	Predicted QTc (change from baseline)	Cmin,ss[4] (ng/mL)	Predicted QTc (change from baseline)	Cmax,ss[4] (ng/ml)	Predicted QTc (change from baseline)
[1]Male	78.5	392	460	61.7	391	420 (28)	465	423 (31)	489	424 (32)	581	426 (34)
	88.5	392	460	61.7	371	419 (27)	437	422 (30)	463	423 (31)	547	426 (34)
	100	392	460	61.7	359	419 (27)	419	421 (29)	449	422 (30)	524	425 (33)
[1]Female	61.9	400	460	61.7	530	433 (33)	620	436 (36)	663	437 (37)	775	439 (39)
	71.7	400	460	61.7	484	432 (32)	563	434 (34)	605	435 (35)	704	438 (38)
	83.2	400	460	61.7	451	431 (31)	521	433 (33)	564	434 (34)	652	437 (37)

[1] Weights represent the 25th, 50th, and 75th percentiles of the model development database, respectively.
[2] Patients were assumed to have no cardiac findings, a normal NYHC and were not receiving concomitant digoxin.
[3] Patients were assumed to have no potassium value of 4.3 (meq/L), the mean value for the development database.
[4] Patients were assumed to have a total bilirubin value of 0.6 (mg/dL), the mean value of the development database.

Validation Of The Pharmacodynamic Model

Summary Statistics of the Predicted Error Percent (PE%) and Absolute Predicted Error Percents (|PE|%) for the Model Validation and Development Datasets

Dataset	Variable	N	Mean (SD)	Median	Minimum	Maximum
Validation	PE%	952	-0.2 (6.8)	-0.4	-25.1	27.2
	|PE|%	952	5.3 (4.2)	4.3	0.01	27.2
Development	PE%	3828	-0.2 (7.0)	-0.4	-24.9	31.9
	|PE|%	3828	5.4 (4.4)	4.4	0.002	31.9

CONCLUSIONS

- Clearance and volume were significantly related to weight. However, the clearance and volume estimates are fairly similar for the majority of patients within a gender. This finding may be clinically important only for those patients weighing substantially less or more than other patients of their gender.
- Males were found to have an approximately 30% higher clearance but only an approximately 17% higher clearance when adjusted for body weight.
- Smokers were found to have an approximately 16% higher clearance than non-smokers.
- Volume was significantly related to total bilirubin. For bilirubin values ranging from 0.1 to 1.5, the change in volume resulted in only minor changes to the minimum and maximum concentration values. Therefore, this finding is not expected to be clinically important.
- EC_{50} was found to be directly proportional to potassium level. The change in EC_{50} was not clinically important within the normal range of potassium (3.5 - 5.0 meq/L).
- The maximum increase in QTc interval was approximately 62 msec (approximately a 16% increase from baseline) with a 38 msec (approximately a 10% increase from baseline) increase at 600 ng/mL of azimilide for a patient with a potassium level of 4.3 meq/L.
- Validation showed that both models were essentially unbiased and acceptably accurate.