

# Population Pharmacokinetic/ Pharmacodynamic Analysis of Vernakalant Hydrochloride Injection (RSD1235) in Patients With Atrial Fibrillation or Atrial Flutter

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# Vernakalant in Atrial Fibrillation

- Atrial fibrillation (AF)
  - Most common sustained cardiac arrhythmia
  - Frequently leads to hospitalization
  - Major risk factor for stroke
  - Increases the risk of CHF and cardiac events among patients with coronary artery disease (CAD)
- Vernakalant hydrochloride injection
  - Novel, atrial-selective antiarrhythmic agent
  - Blocks both frequency-dependent  $\text{Na}^+$  channels and early-activating  $\text{K}^+$  channels to selectively prolong the atrial refractory period
  - Effectively converts AF to sinus rhythm (SR)

AF=atrial fibrillation; CHF=congestive heart failure; CAD=coronary artery disease; SR=sinus rhythm.

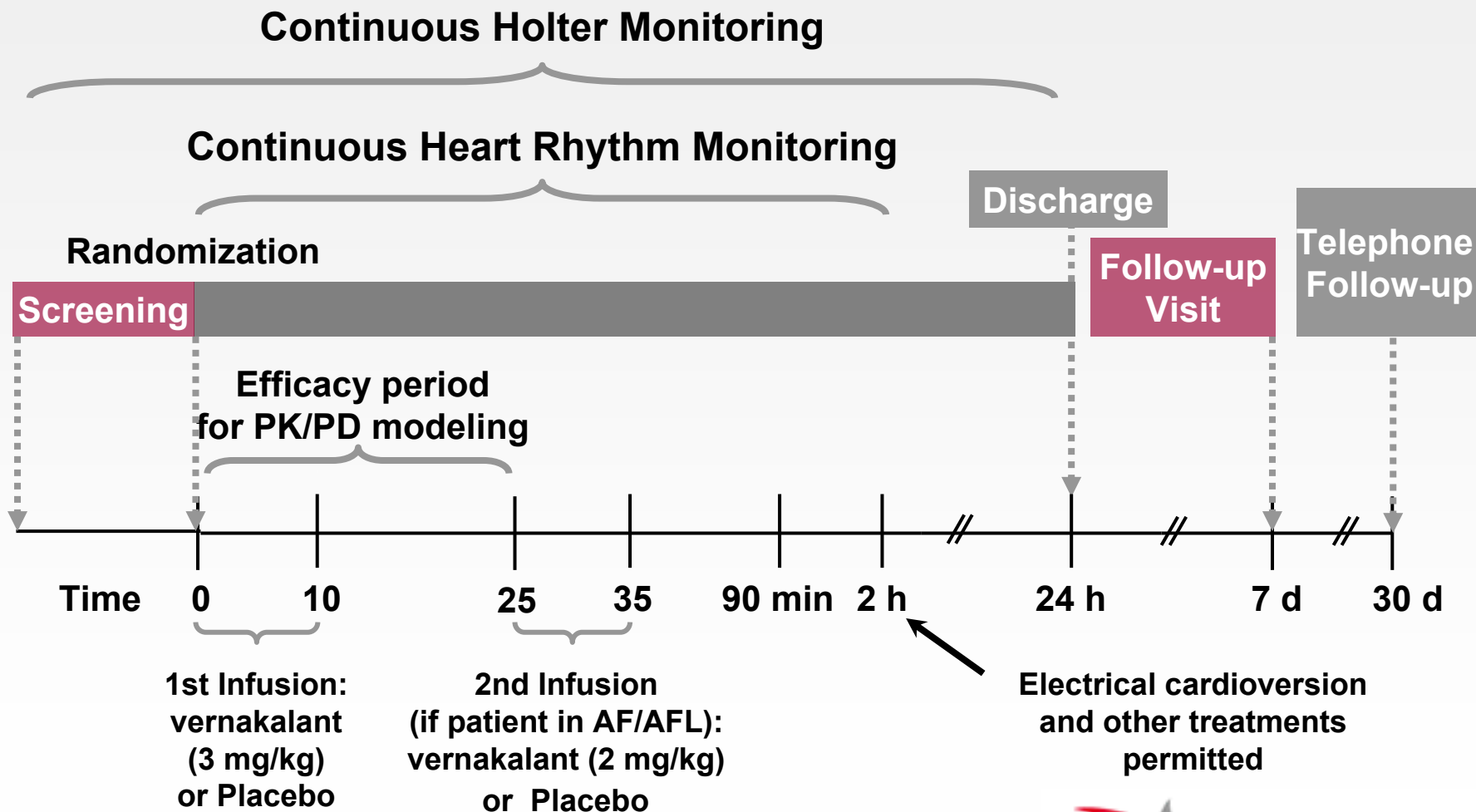


# Objectives

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- Develop a PK/PD model to describe exposure–response relationships for efficacy
  - Incidence of SR conversion
  - Time to SR conversion
- Develop a PK/PD model to describe safety
  - QT-interval prolongation

# Study Design



PK=pharmacokinetic; AFL=atrial flutter.



# Efficacy and Safety Endpoints Used in PK/PD Modeling

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- Efficacy endpoints
  - Proportion of patients with short-duration AF (lasting  $>3$  h but  $\leq 7$  d) who demonstrated conversion to SR within 25 minutes (ie, after the first infusion)
  - Time to conversion
- Safety endpoint
  - Prolongation of QT interval corrected for heart rate with Fridericia's formula (QTcF)

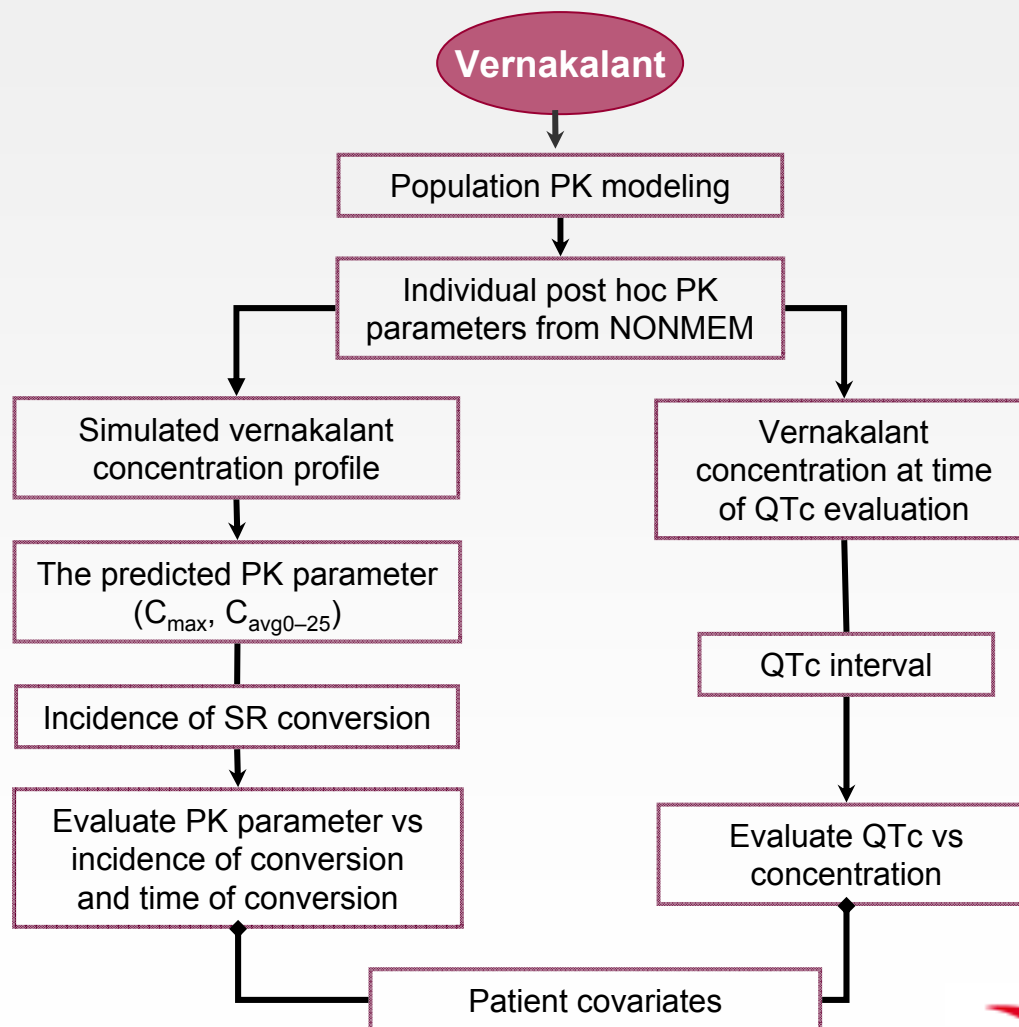


# Covariates Tested

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- Age
- Sex
- Body weight
- History of CHF
- History of CAD
- History of hypertension
- Rhythm status
- Arrhythmia duration
- Arrhythmia type (AF vs AFL)
- Concomitant medications, including
  - Antiarrhythmics if taken within 1 week and concurrent with infusion
  - Antihypertensives if taken within 1 day and concurrent with infusion

# PK/PD Model Development



C<sub>max</sub>=maximum concentration; C<sub>avg0-25</sub>=average concentration from time 0 to 25 min.



# PD Model Selection Process

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- Determine best structural model for concentration effect
- Examine for diurnal variation
- Examine covariates one by one
  - Impact of gender, age, SR status, Cmed etc. in each model parameter was explored
  - Likelihood ratio test to select covariates
  - Acceptance p-value was set to 0.05
- Use backwards selection to determine final model, starting with all single covariate effects
  - Acceptance p-value was set to 0.01



# Incidence of SR Conversion Model

- The best model to describe conversion to SR was a logistic regression model

$$\text{logit} (\text{Pr}(T_{conv} < 25 \text{ min})) = \alpha_{\text{placebo}} \text{ or } \alpha_{\text{vernakalant}}$$

where  $\alpha_{\text{placebo}}$  and  $\alpha_{\text{vernakalant}}$  denote the probability of conversion with placebo and vernakalant, respectively

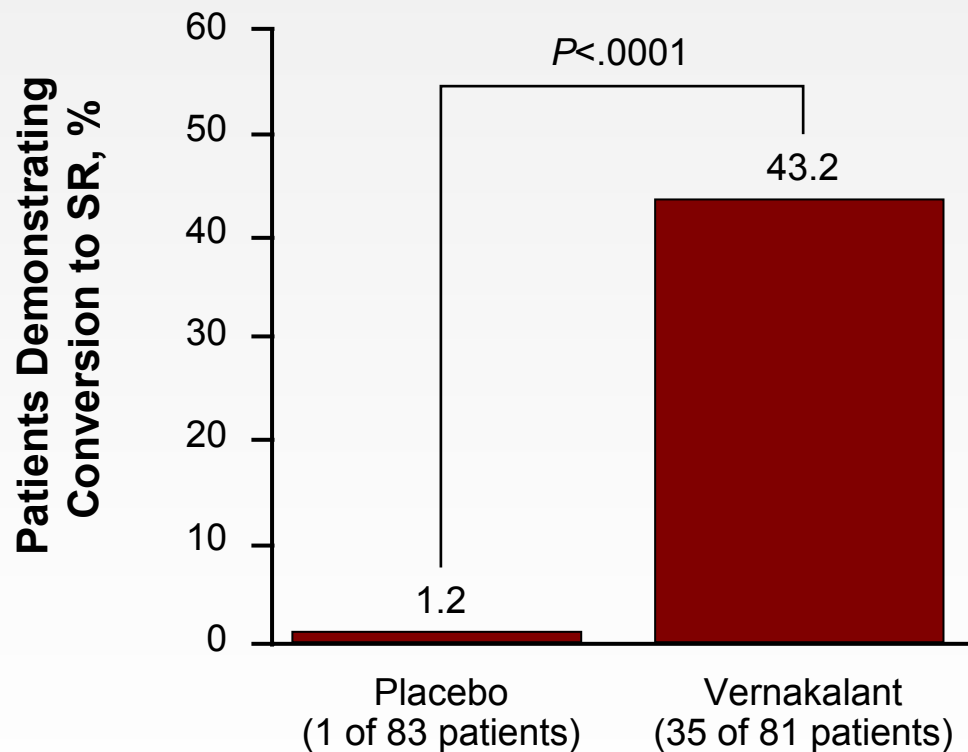
- No covariate significantly improved the model fit (Age, sex, body weight, history of CHF, history of CAD, etc.)

# PD Parameters for the Incidence of SR Conversion Model

Treatment Group	Parameter	Parameter Estimate $\pm$ SE	Probability of SR Conversion Within 25 min, % (95% CI)
Placebo	$\alpha_{\text{placebo}}$	-4.41 $\pm$ 1.01	1.2 (0.2, 8.1)
Vernakalant	$\alpha_{\text{vernakalant}}$	-0.27 $\pm$ 0.22	43.2 (32.9, 54.1)

CI=confidence interval.

# Incidence of SR Conversion After First Infusion





# Time to SR Conversion Model

- Time to SR conversion was best fit by the following relationship

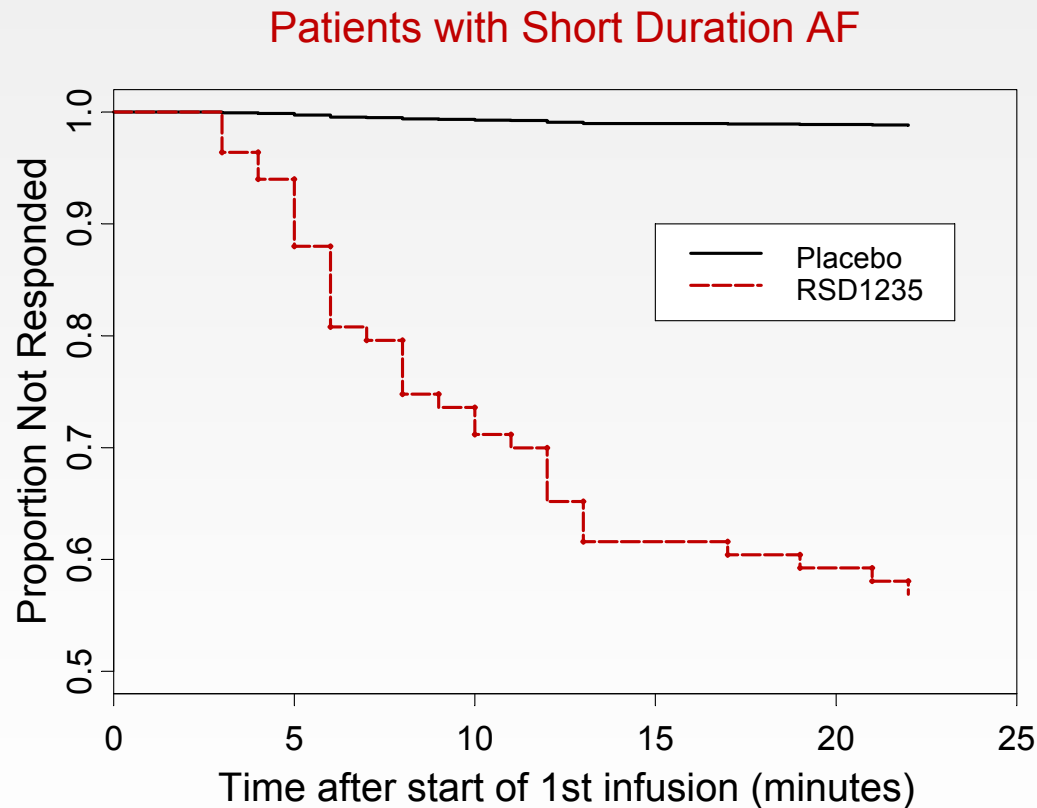
$$h(t) = h_0(t)e^{\beta I(\text{treatment})}$$

where  $h(t)$  is the resultant hazard,  $h_0(t)$  is the baseline hazard, and  $I(\text{treatment})$  is 1 for vernakalant and 0 for placebo

- No covariate significantly improved the model's fit

PK Variable	$\beta$	$e^\beta$	$\beta(\text{SE})$	95% CI	P Value
Treatment	1.92	6.84	0.507	2.53 to 18.5	.00015

# Time to SR Conversion After First Infusion



Kaplan-Meier plot of the proportion of patients that did not covert to sinus rhythm in 25 minutes after start of first infusion.

# Summary of Efficacy Analysis

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- A greater proportion of vernakalant patients converted to SR.
- The model confirmed that vernakalant markedly increases the SR conversion rate. However the data available from Study 04-7-010 alone was insufficient for identifying a concentration-effect relationship.

# QTc Pharmacodynamic Model

Vernakalant plasma concentration–QT interval relationship was best fit by a sigmoidal Emax model

$$QTc(Fridericia)_{ij} = base_{ij} + Eff_{ij} + \varepsilon_{ij}$$

$$base_{ij} = \beta_0 \cdot e^{\eta_i^{base}} + \beta_{tod} \cdot \cos\left(\frac{(time_j + shft) \cdot 2\pi}{24}\right) + \beta_{age} \cdot (Age_i - 61)$$

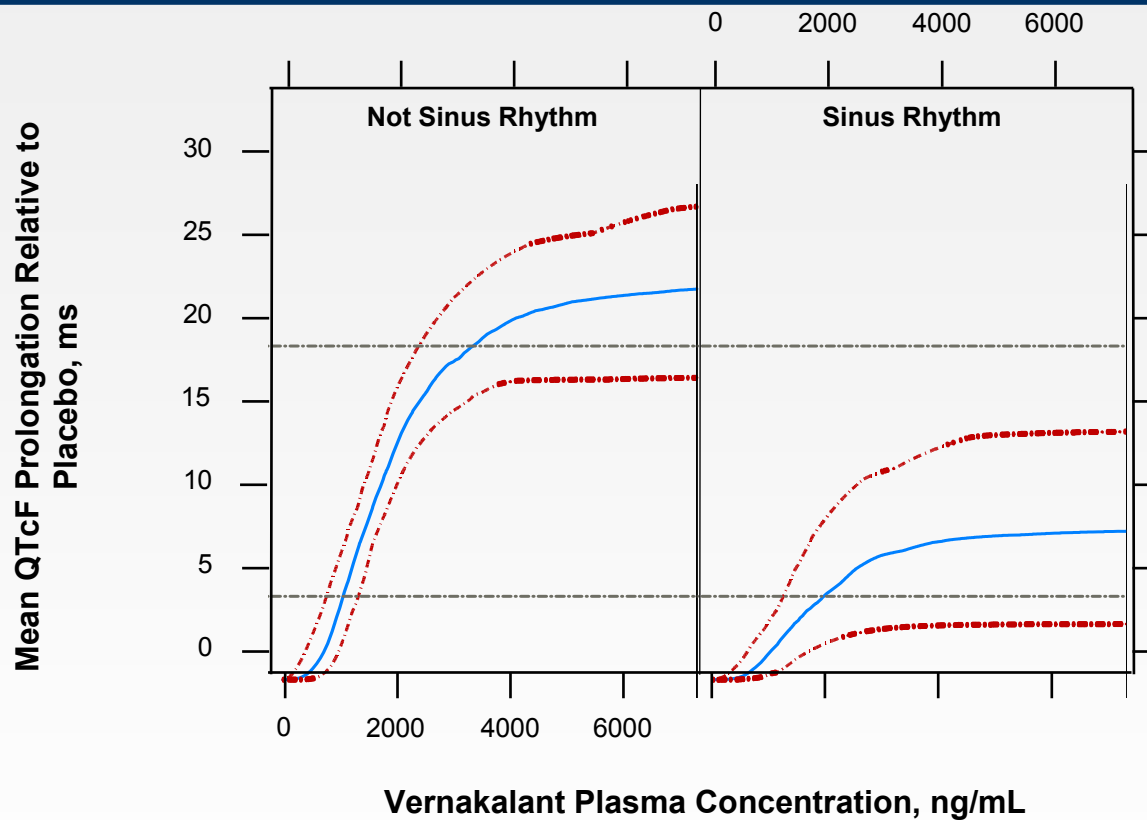
$$Eff_{ij} = \left(Emax \cdot e^{\eta_i^{Emax}} + \beta_{SRS} \cdot SRS\right) \cdot \frac{Cp_{ij}^r}{Cp_{ij}^r + \left(EC_{50} \cdot e^{\eta_i^{EC50}}\right)^r}$$

- $QTc_{ij}$  is the  $j^{\text{th}}$  QTcF measurement for the  $i^{\text{th}}$  patient
- $base_{ij}$  is the expected baseline QTcF for the  $i^{\text{th}}$  patient
- $Eff_{ij}$  is the effect of vernakalant on that patient
- $\varepsilon_{ij}$  is the random error between the estimated and observed QTcF

# QTcF Model Parameters

Parameter	Estimated	95% confidence interval	
$\beta_0$ (ms)	426.0	422.84	429.16
$E_{\max}$ (ms)	20.30	14.22	26.38
$EC_{50}$ (ng/mL)	1730	1326	2133
$\gamma$	3.580	1.01	6.15
$\beta_{\text{tod}}$ (ms)	7.190	4.80	9.58
shft (hr)	-3.140	-3.96	-2.32
$\beta_{\text{age}}$ (ms/yr)	0.351	0.16	0.54
$\beta_{\text{SRS}}$ (ms)	-14.20	-21.9	-6.46

# Effect of Vernakalant Concentration on QTcF



Model predicted population mean QTcF prolongation (relative to placebo) as a function of Vernakalant plasma concentration and sinus rhythm status.

# Summary of QTC Analysis

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- Vernakalant concentration related to prolongation of QTcF, best described by a sigmoidal Emax model
- $EC_{50}$  was 1730 ng/mL. Maximum change in QTcF for patients converting to SR expected to be 6.1 ms while maximum change in QTcF for patients who remained in AF is 20.3 ms
- QTcF varies with time of the day; no differences between men and women
- Age affected baseline QTcF value