DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

Tedisamil is a mixed potassium channel blocker for which approval is sought for conversion of atrial fibrillation and atrial flutter, of duration 3 hours to 45 days, to normal sinus rhythm. Vernakalant is a mixed potassium and sodium channel blocker for which approval is sought for conversion of atrial fibrillation, of duration 3 hours to 7 days, to normal sinus rhythm. Both products have some degree of effectiveness, at least for atrial fibrillation of short duration, but both are clearly less effective than is electrical conversion.

Both products carry with them some proarrhythmic risk, and perhaps other risks. The Committee will be asked to consider the extent to which the risks can be minimized or managed, and then whether the expected risks in practice are commensurate with the benefits achieved. For example, are plans to monitor QT post-infusion adequate?

In considering these products, the Committee will need to consider the spontaneous reversion rate (4% within a 90-minute window in the vernakalant studies), especially for atrial fibrillation of short duration, the safety profile for electrical conversion, the durability of any conversion, and the relative merits of rate control versus conversion.

In short, the Committee is asked to assist in developing a calculus for determining when products for this use are approvable. If it proves to be the case that there are adequate data from these development programs, the Committee is asked to make specific recommendations on approval, and, if not, to identify specific information gaps of consequence.

The reviews raise additional specific issues:

1. The sponsor attempts to compensate for tedisamil's observed differences in rates of Torsade de Pointes in men and women by recommending a lower dose in women. However, women also have somewhat lower rates of conversion at any given dose than men, so lowering the dose in them would appear to reduce any net clinical benefit.

2. Tedisamil also causes bradycardia and hypotension. These are likely to have contributed to the one death in the development program. The Committee will need to consider the extent to which this risk is understood and managed. One aspect of this is the potential interaction with other therapies that produce bradycardia and hypotension, in particular beta-blockers and amiodarone. Bradycardia and hypotension appear to be less of a problem with vernakalant.

3. The tedisamil sponsor is recommending a dosing strategy intended to achieve steady-state plasma levels rapidly and then maintain them for 30 minutes. The Committee will need to consider both the risks associated with the implementation of such a complex dosing scheme, and whether such a scheme was a better idea than a short distribution-limited dosing scheme. Dose selection is simpler for vernakalant (one regimen for all) and the regimen is also simpler (one 10-minute infusion followed, if necessary by a second 10-minute infusion).

4. There were somewhat more thromboembolic events on tedisamil than on placebo, and there was a trend for these events to be dose-related. However, the timing of the events is difficult to reconcile with the kinetics of tedisamil. The Committee will need to consider whether this is a plausible safety issue, too.

CLINICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	22034
Submission Code	1S
Letter Date	12/19/06
Stamp Date	12/19/06
PDUFA Goal Date	10/19/07
Reviewer Name	Salma Lemtouni, M.D, M.P.H.
Review Completion Date	7/05/06
Established Name	Vernakalant hydrochloride
(Proposed) Trade Name	Kynapid
Therapeutic Class	Anti-Arrhythmic
Applicant	Astellas
Priority Designation	S
Formulation	
Dosing Regimen	2 to 5 mg/kg
Indication	Short-term Atrial Fibrillation
Intended Population	Atrial Fibrillation Population

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Abbreviations

ACS	Acute coronary syndrome
ACT I	Atrial Arrhythmia Conversion Trial (number 1)
AFB	atrial fibrillation
AFL	Atrial flutter
ALT	Alanine aminotransferase (also known as SGPT)
ANOVA	Analysis of variance
AST	Aspartate aminotransferase (also known as SGOT)
AV	Atrioventricular
LBBB	Left bundle branch block
RBBB	Right bundle branch block
BMI	Body mass index
CABG	Coronary artery bypass graft
Cmax	Maximum observed concentration of study drug
CEC	Clinical Events Committee
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CPK	Creatine phosphokinase
CPK-MB	MB fraction (isoenzyme) of total creatine phosphokinase
CRF	Case report form
DC	Direct current
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
EF	Ejection fraction
EM	Extensive metabolizer
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
ITT	Intent to treat
LBBB	Left bundle branch block
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
PM	Poor metabolizer
PVCs	Premature ventricular contraction
SR	Sinus rhythm
V-Tach	Ventricular tachycardia

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Vernakalant was shown to be effective in converting AFB (atrial fibrillation) of a recent onset (three hours to seven days) for at least one minute, thus meeting the primary efficacy endpoint of the program. The conversion rate was higher and more significant on the first dose compared to the second dose. Of the subpopulation that went on to receive a second dose, subjects were four times less likely to convert to SR as did subjects who converted on one dose. The non-responding population is different from the responding population in that it was older; had a lower baseline pulse rate, longer ECG intervals including QRS and QTcF and higher baseline systolic blood pressure. Also, a higher proportion of the subjects who did not respond on the first dose had a history of anti-arrhythmic drug intake either prior to enrollment or at baseline.

Maintenance of SR up to 24 hours post-dose was not evaluated as a pre-specified efficacy endpoint. The reviewer tried to indirectly quantify the maintenance in SR. Findings from the provided data show that, except for one subject, who received Vernakalant, none of the subjects who converted to SR went on to be electrically cardioverted. However, the use of concomitant Class I and III anti-arrhythmic drugs tripled at 24 hours post-dose on Vernakalant while it changed slightly on placebo compared to baseline use. It is not know whether the excess use of concomitant anti-arrhythmic drugs on Vernakalant during the 24-hour and seven-day follow-up time-points is associated maintaining SR, or re-establishing SR after Vernakalant failed to maintain it.

The reviewer believes that Vernakalant is effective in converting short-term AFB, but has reservations regarding its safety and benefit-to-risk profile for the following reasons:

- Conversion to and maintenance of SR for only a short period of time (at least one minute per primary analysis), warrants neither the symptomatic improvement of AFB nor the prevention of its complications.
- Vernakalant caused two cases of ventricular fibrillation one of which was fatal (0.14%) in a highly monitored environment. It is very likely that the fatality was precipitated by the subject's aortic stenosis and heart failure, but there are not enough data in this program that would lend support to this hypothesis. The level of exposure to this drug is limited and there is no assurance that other cases of ventricular fibrillation will not occur when exposure to Vernakalant increases and subjects with significant structural heart disease are exposed. In the absence of data, one can only assume that fatal ventricular fibrillation will be observed at a rate of at least 1.4/1000 in subjects with other risk factors of ventricular arrhythmia.
- In its oral repeated dosing formulation in a different program, Vernakalant was associated with another case of fatal ventricular fibrillation.
- Per protocol, subjects with acute myocardial infarction and advanced heart failure (two of the main causes of AFB) were excluded; therefore, the population studied is not representative of the population proposed for Vernakalant indication, and the findings could not be generalizable to the population with short-term AFB at large.

- Other adverse events that further diminish the benefit-to risk-profile of Vernakalant include third degree AV block, life-threatening bradycardia and hypotension; and possibly ventricular tachycardia and dyspnea.

The reviewer would consider supporting approval of Vernakalant for short-term AFB in one of two ways:

1. in a single dose formulation for a population similar to that studied in the program (subjects with no structural or obstructive heart disease and subjects with no advanced CHF). The rational for this proposal rests on the benefit to risk profile that it is influenced by the ventricular arrhythmia fatality along with the observed diminished responsiveness to a second dose compared to the responsiveness on one dose.

2. or in its proposed two-dose formulation for a population similar to that studied in the program with a contraindication in subjects with recent MI, advanced CHF and obstructive heart disease; and commitment to a post-marketing study in a population representative of the general short-term AFB population including recent MI and advanced CHF.

In either case, a post-approval surveillance program should be established to detect serious adverse effects including cardiac and respiratory events.

Also, subjects who are prescribed Vernakalant should receive it in a highly specialized hospital settings, and be closely monitored for a longer duration than proposed by the label.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The subjects studied in this program were relatively healthy patients and they were closely monitored for 24 hours. If approved, Vernakalant should be given in a highly specialized medical setting, and subjects must be closely monitored for a longer duration than proposed in the label.

1.2.2 Required Phase 4 Commitments

If Vernakalant is to be approved as a two-dose regimen, as proposed, the Sponsor must conduct a post-marketing study in subjects with conditions that are known to induce AFB including recent MI and advanced CHF.

A post-approval active surveillance program should be established to detect SAEs especially cardiac events.

1.2.3 Other Phase 4 Requests

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Vernakalant is an anti-arrhythmic that is to be given as an infusion to patients with recent onset of AFB. Two pivotal randomized, double-blind placebo-controlled trials (ACTI and ACTIII) were conducted in patients with AFB or AFL to demonstrate efficacy and safety. Per an

amendment, efficacy evaluation was to focus on AFB alone instead of AFB and AFL, and conversion to normal sinus rhythm was replaced by conversion to sinus rhythm.

A total of 356 with AFB were enrolled and 336 were exposed to either Vernakalant (221) or placebo (115) in ACTI. In ACTIII, a total of 265 with either AFB or AFL were enrolled and 134 were exposed to Vernakalant while 131 received placebo.

The number of subjects considered for efficacy evaluation comes from ACTI (145 on Vernakalant and 115 on placebo) and ACTIII (86 on Vernakalant and 84 on placebo).

Four additional studies: CRAFT, Scene 2, ACT II and ACTIV evaluated safety bringing the total to over a thousand subjects two thirds (728) of whom were exposed to Vernakalant.

-CRAFT, a randomized, double-blind, placebo-controlled trial, enrolled a total of 57 with AFB; and 36 of them received Vernakalant;

-Scene 2, a randomized double-blind placebo-controlled trial, enrolled 60 subjects with AFL; 56 were exposed to study drug and 39 received Vernakalant;

-ACTII, an ongoing randomized double-blind placebo controlled trial; 157 were exposed to study drug and 105 subjects received Vernakalant;

-ACTIV, an ongoing open-label non-controlled trial; enrolled 209 and 193 were exposed Vernakalant;

Other studies considered for safety evaluation include the following:

-1235-SMH1, a Phase 2 open-label dose ascending trial, enrolled 19 subjects undergoing electrophysiological testing with half receiving 2 mg/kg and the other half receiving 4 mg/kg of Vernakalant;

-Study 04-0-195, a Phase 1 open-label single intravenous and single oral doses, crossover, mass-balance study in healthy volunteers enrolled eight subjects who received 240 mg of radio-labeled Vernakalant as an infusion followed by a washout period of 21 days before receiving another 240 mg of radio-labeled Vernakalant as an oral dose;

-Study 1235-1-04-12-01, a randomized, single-blind, placebo-controlled, dose ascending and tolerance study enrolled 23 healthy volunteers who received between 0.10 mg/kg to 5 mg/kg with 12 subjects receiving 2 to 5 mg/kg.

1.3.2 Efficacy

In a population who is not very representative of the overall population with recent-onset AFB, given that subjects with recent MI and subjects with advanced CHF were excluded, it was shown that Vernakalant can effectively convert AFB to SR.

Proposed for efficacy evaluation are ACTI and ACTIII trials. ACTI in patients with AFB and ACTIII in patients with AFB or AFL were multi-center, randomized, double-blind, placebo-controlled trials. Subjects were randomized in strata by duration: > three hours and <= seven days, and > seven days and <= 45 days.

The primary efficacy endpoint was defined as the treatment-induced conversion of AFB, of three hours to seven days duration, to SR for at least one minute within 90 minutes of first infusion. The original primary endpoint was conversion to normal SR, but this was later

amended to SR. Blinding could have been compromised in almost one fourth of the subjects who received Vernakalant because of specific adverse effects such as sneezing and dysgeusia experienced only by subjects who received Vernakalant.

The efficacy program excluded subjects with recent transient ischemic attack or stroke, recent MI, ACS or cardiac surgery; subjects with congestive heart failure NYHA III/IV and subjects with EF < 30%; and subjects with "serious" renal, hepatic, pulmonary and metabolic disease. Therefore, the findings cannot be generalizable to these populations.

Efficacy evaluation for the proposed indication is based on a total of 390 subjects with recent-onset AFB who were exposed to study drug, with 231 on Vernakalant and 159 on placebo, too small a number to identify interactions of Vernakalant with the multiple cardiac conditions that trigger AFB, and the established treatments of AFB especially other anti-arrhytmics and DC cardioversion.

1.3.3 Safety

Vernakalant caused two cases of ventricular fibrillation, one of which was fatal, and they both occurred within minutes of the second dose. The incidence rate of ventricular fibrillation in this population was, probably, low because subjects with recent MI and advanced CHF were excluded. As summarized in 7.1.10 Electrocardiograms (ECGs) page 50, Vernakalant affects myocardial repolarization significantly, and it is not know how it will interact with substantially compromised myocardial tissue and function.

Other adverse events associated with Vernakalant include complete AV block and bundle branch blocks, life threatening hypotension, bradycardia and possibly ventricular tachycardia. Dyseugia, sneezing, pruritus, nausea, paraesthesia and dizziness were significantly associated with Vernakalant (without adjustment for multiplicity), and observed shortly after infusion of the study drug. Other adverse events that showed increasing trends on Vernakalant include cough, dyspnea, diarrhea and sweating.

The Vernakalant program enrolled 1198 subjects; 971 had AFB and 86 had AFL; 778 were exposed to Vernakalant; and 585 subjects were included for short-term AFB. Thirsty six of the subjects who received Vernakalant were healthy volunteers, and another 19 were subjects undergoing electrophysiological evaluation. The range of exposure was 0.1 mg/kg to 5 mg/kg with the majority receiving 2 to 5 mg/kg.

A total of 601 subjects were enrolled in the two pivotal ACTI and ACTIII studies with 390 included for recent-onset AFB, of whom 231 were exposed to Vernakalant.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is an intravenous formulation with the dose ranging between 3 to 5 mg/kg given in two infusions over 10 minutes. A first infusion of 3 mg/kg is given and if conversion to SR does not occur within 15 minutes after the completion of the first infusion, a second infusion of 2 mg/kg is to be administered.

In the Phase II dose ranging CRAFT study, this regimen was reversed, and the first infusion was of 2 mg/kg while the second infusion was of 3 mg/kg. It was not clear why the Sponsor opted to reverse the regimen studied in the CRAFT trial and study the currently proposed regimen in Phase III trials.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies were completed. The interactions explored in this program are with drugs that were given to study subjects out of necessity. Concomitant medication intake was collected and submitted for ACTI, ACTIII, CRAFT and Scene 2. Concomitant medication included Class I and III anti-arrhythmic drugs.

The incidence of adverse events and ventricular arrhythmia were explored by concomitant Class I and Class III anti-arrhythmic drug intake.

1.3.6 Special Populations

Subjects with recent (within 30 days) MI and advanced congestive heart failure, common predisposing factors to AFB, were excluded from the pivotal studies of Vernakalant. .

Subjects with myocardial injury secondary to an acute MI are at high risk of myocardial repolarization disturbances, and it is not known how this will be compounded by the QT prolonging effect of Vernakalant. In conclusion, the findings from this program could not be generalizable to the recent MI population.

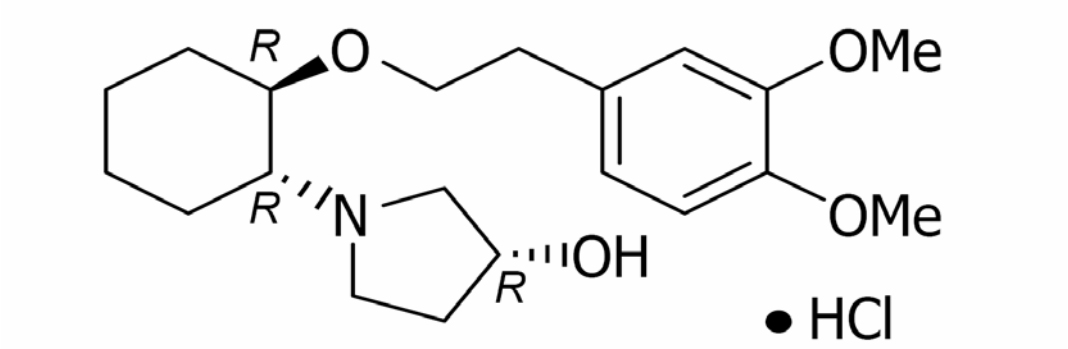
Other populations not studied include subjects with "reversible" causes of AFB defined as secondary to alcohol intoxication, hyperthyroidism, acute pericarditis and pulmonary embolism. Subjects with a history of having failed electrical cardioversion at anytime were also excluded; therefore, there are no data on how these subjects would respond to Vernakalant.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Vernakalant is the active pharmaceutical ingredient in Vernakalant Injection. The molecule is an entirely synthetic enantiomerically pure new chemical entity with three asymmetric centers. Vernakalant is isolated as the monohydrochloride salt.

Figure 1. Molecular Schema of Vernakalant



Vernakalant Chemical Name: 3-Pyrrolidinol, 1-[(1R,2R)-2-[2-(3,4-dimethoxyphenyl)ethoxy] cyclohexyl]-, hydrochloride, (3R)-

Vernakalant structure: $C_{20}H_{31}NO_4 \cdot HCl$

Established name: Vernakalant hydrochloride

Proposed name: Kynapid

Pharmacological class: Vernakalant is not considered to be a Class I or Class III anti-arrhythmic.

Vernakalant was developed for the conversion of AFB or AFL to SR. Vernakalant was studied and is proposed at one or two intravenous dose levels, with the first dose of 3 mg/kg to be followed, in the absence of conversion to SR, by a second dose of 2 mg/kg.

2.2 Currently Available Treatment for Indications

Table 1. Drugs Effective for Cardioversion of AFB (ACC/AHA/ESC guidelines)

Drug	administration	FDA approved
Dofetilide	Oral	Yes
Flecainide	Oral or intravenous	No
Ibutilide	intravenous	Yes
Propafenone	Oral or intravenous	No
Amiodarone	Oral or intravenous	No
Quinidine	Oral	Yes

Pharmacologic therapy is an alternative to DC cardioversion which requires sedation, but is associated with cutaneous burns which is less likely desirable to patients.

2.3 Availability of Proposed Active Ingredient in the United States

Vernakalant has not been marketed in the US or anywhere else in the world.

2.4 Important Issues with Pharmacologically Related Products

Drug products developed and marketed for the termination of AFB have many similarities with Vernakalant because most of them have an effect on potassium and/or sodium channels and, to different extents, affect cardiac repolarization.

2.5 Presubmission Regulatory Activity

At the End of Phase II meeting held in April of 2003, the Division expressed its concern about the extensive list of exclusions, especially exclusion of subjects with current treatment with Class I or Class III antiarrhythmics, and warned the Sponsor about potential limitations of the label in providing real guidance on the clinical use of Vernakalant in the general AF/AFL population.

The Division agreed to conversion of any length of time as a primary endpoint, but expressed interest in the other medications patients would receive, the number that would require cardioversion, and the maintenance of SR.

In a meeting held in November of 2005, the Division expressed its concern regarding the effect of Vernakalant on myocardial repolarization. The Division expressed its concern regarding the small number of subjects in the program, acknowledging their previous agreement on the proposed number of exposed subjects, but warned the Sponsor about the potential problem of the inability to explain any safety signals or mortality observed. The Division warned the Sponsor

about the possibility of language acknowledging the size of the program; or approval denial because of limited exposure.

Upon the Sponsor's request, the Division agreed to granting a deferral of conducting a clinical trial in pediatrics if it were feasible for such trial to be conducted; and to granting a waiver if such trial were not possible.

The Division agreed to the Sponsor's decision not to proceed with an indication for AFL, and that data from Scene 2 and from patients with AFL who were enrolled in ACT III would be used for safety evaluation only.

In a teleconference with the Sponsor held in July of 2004, the Sponsor discussed the addition of three secondary endpoints: 1) time-to-conversion of AFB of duration between 3 hours and 7 days ; 2) time-to-termination of AFB of duration between 3 hours and 45 days ; and 3) time to termination of AFB of duration between 7 days and 45 days with time to termination defined as the absence of AFB for a minimum duration of 1 minute.

The Division related to the Sponsor that if the intent is to use secondary endpoints in labeling, the overall p-value would have to be 0.05.

2.6 Other Relevant Background Information

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.2 Animal Pharmacology/Toxicology

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The data used for this review include trials conducted by the applicant only. Other information used in the review but not contained in the application is information from an annual safety report from the oral formulation program of Vernakalant that is owned by another Sponsor.

4.2 Tables of Clinical Studies

Table 2. Clinical Studies Conducted in the Intravenous Vernakalant Program (Table from Sponsor's Report)

Study Type Status	Study design	Regimen	No. of Subjects E/T/C
Phase I Trials			
1235-1-04-12-01 PK	Ascending SD, SB, PC, R	0.10 to 5.0 mg/kg	29/28/28 Healthy Volunteers
04-0-195 PK	OL, SD, SSC	240 mg 14C-labeled intravenous and PO	8/8/8 Healthy Volunteer
1235-SMH1 PD	OL, ascending dose	2 + 0.5 mg/kg/hr and	19/19/19 EP patients

Study Type Status	Study design	Regimen	No. of Subjects E/T/C
		4 + 1.0 mg/kg/hr	
Phase III Pivotal Trials			
ACT I (0703) E & S	R, DB, PC, MC	3 + 2 mg/kg or placebo	356/336/330 AFB patients
ACT III (010) E & S	R, DB, PC, MC	3 + 2 mg/kg or placebo	276/265/262 AFB or AFL patients
Phase II/III Trials			
CRAFT (1001) PK and E & S	R, DB, PC, PG, MC	0.5 + 1 mg/kg 2 + 3 mg/kg	65/56/56 AFB patients
Scene 2 (0703B) E & S	R, DB, PC, MC	3 + 2 mg/kg or placebo	60/54/53 AFL patients
Phase III Ongoing Trials			
ACT II (0104) E & S	R, DB, PC, MC, PG	3 + 2 mg/kg or placebo	Post valvular or coronary artery bypass graft surgery
ACTIV (012) S	OL, non-comparator, MC	3 + 2 mg/kg	AFB patients

E&S: efficacy and safety; EP: electrophysiology; E/T/C: enrolled, treated, completed; MC: multicenter; PG: parallel group; SB: single blind; SR: SR; SSC: single sequence crossover

4.3 Review Strategy

All trials were reviewed. For safety review, different populations were used with more focus on:

- all subjects included in the program;
- subjects with short-term (> 3 hours and <= 7 days) AFB from ACTI and ACTIII.

For efficacy review, only subjects with short-term AFB from ACTI and ACTIII were used as per the final amended protocols. Even though the Sponsor did not advance the CRAFT study to support the proposed indication, probably because it used a regimen that was the inverse of the dosing sequence in ACTI and ACTIII, the reviewer used the findings from this study to confirm the effect of Vernakalant. The Scene2 trial was omitted from the review of efficacy as done by the Sponsor because the Sponsor is not seeking an indication in AFL.

4.4 Data Quality and Integrity

Sites for DSI inspection were selected based on the number of subjects enrolled in these sites. The two sites that enrolled most subjects were selected and these are located in Denmark.

4.5 Compliance with Good Clinical Practices

DSI data is not in yet at the time of the completion of this review.

4.6 Financial Disclosures

The Sponsor supplied documentation disclosing that they did not engage in any financial arrangement that would affect the study outcome. One of the investigators (Dr. Ip from Lansing, MI) who participated in three trials 0703 (ACTI), 0104 (ACTII) and 703b (Scene 2) held significant equity interest (as defined by 21 CFR 54.2(b)) in Cardiome during the conduct of these studies. Analyses with and without this site did not affect the findings of efficacy.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.2 Pharmacodynamics

Electrophysiological testing of Vernakalant in subjects without significant heart disease showed that Vernakalant prolonged AERP (atrial effective refractory period) and slowed conduction in the atrium and AV node.

No formal QT prolongation study was conducted for this program, but the effect on QT was studied in every trial because Vernakalant was established as a QT prolonging product. For a description of QT assessment in this program, refer to Table 43. Procedure Schedules in ACTI and ACTIII page 74; and for findings on the effect of Vernakalant on QT refer to 7.1.10 Electrocardiograms (ECGs) page 50.

5.3 Exposure-Response Relationships

CRAFT, a dose ranging study conducted in 56 subjects with AFB studied the exposure response of two dose regimen: 0.5 mg/kg to be followed by 1 mg/kg if needed; and 2 mg/kg to be followed by 3 mg/kg if needed.

The studies following CRAFT adopted a regimen that was the inverse of the one studied in this dose ranging study: starting with 3 mg/kg and adding 2 mg/kg if needed.

The safety parameters observed within two hours of starting study drug infusion that showed a dose response, that is they occurred at a higher incidence in subjects who received two doses instead of one dose of Vernakalant, include ventricular fibrillation (the two cases occurred after two doses), complete AV block (2 out of 3), sneezing, paraesthesia, pruritus, hyperhydrosis, injection site paraesthesia, vomiting, dry mouth, atrial tachycardia, injection site reaction and post procedural complications.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication sought by the applicant is as follows: “KADENZA is indicated for the rapid conversion of AFB to SR.” This indication is sought despite the fact that the primary efficacy population was composed of subjects whose AFB was between three hours and seven days duration, and the population whose AFB duration was greater than seven days did not respond to Vernakalant.

6.1.1 Methods

The pivotal studies included subjects with AFB and AFL up to 45 days in duration. The primary analysis targeted subjects with short-term AFB and AFL (> 3 hours and <= 7 days). Subjects with AFL were dropped from the primary efficacy analyses by an amendment.

6.1.2 General Discussion of Endpoints

Vernakalant was developed for and tested in AFB and AFL, but the NDA is seeking an indication in subjects with AFB only. The primary endpoint tested was the conversion to SR for at least one minute. This was discussed with the Division, and even though, it was agreed upon the feasibility of this endpoint, the Division expressed its interest in the other therapies, with conversion activity, subjects might receive, and in the number of subjects maintained in SR longer than the duration specified for the primary endpoint.

Except for the duration part of the primary endpoint, the choice of the primary endpoint is adequate because it is objective, and measurable with a high level of accuracy. The one minute conversion to SR that was chosen by the Sponsor, as a primary endpoint, is problematic in interpreting the benefit of this drug if subjects were not shown to remain in SR after conversion for longer than one minute.

6.1.3 Study Design

Both studies, ACTI and ACTIII, proposed to support efficacy, were adequate and well-controlled for they were randomized, double-blind and placebo-controlled; their study protocols contain clear statements of the objective of demonstrating effectiveness and descriptions of the methods of analyses; they were designed to permit valid comparison with placebo and generate quantitative assessment of the effect of Vernakalant; but even if their sample sizes were predetermined and adequate for efficacy purposes, they were not adequate for safety purposes. Other studies, beside these two, were used for integrated review of safety.

The selection of subjects was based on an objective method of determining AFB/AFL and the subjects were randomized into Vernakalant or placebo treatment groups stratified by the duration of AFB/AFL.

Both subjects and investigators were blinded to the study drug received, and although some of the common adverse events of Vernakalant may have led to un-blinding of investigators and study subject, the conversion to SR was objectively measured using ECG and/or Holter recordings and was determined by the CEC committee in a blinded fashion.

Unblinding as a result of adverse events observed only in subjects who received Vernakalant, even if it was unlikely to have affected efficacy, it could have affected other aspects of the study especially the detection of adverse events. The addition of concomitant medication that would have biased the study outcome was restricted during the first two hours during which the primary endpoint was assessed. Using a placebo control is also a strength to the design of these studies because some subjects convert to SR spontaneously.

6.1.4 Efficacy Findings

Table 3. Conversion to SR within 90 Minutes in ACTI and ACTIII Studies (Statistician Reviewer's Table)

Studies	Placebo	Vernakalant	% difference of success (95% CI)	P-value	Odds Ratio (95% CI)
ACTI	**N=75**	**N=145**	47.7 (38.5, 57.0)	<0.0001	24.0 (6.9, 83.6)
	3 (4.0%)	75 (51.7%)			
ACTIII	**N = 84**	**N = 86**	47.6 (36.3, 58.9)	<0.0001	38.3 (9.2, 159.5)
	3 (3.6%)	44 (51.2%)			

Table 4. Conversion to SR of AFB within 90 Minutes, in ACTI and ACTIII Combined by Dose

Studies	Placebo	Vernakalant
Dose 1	N=159	N=231
	6 (3.77%)	93 (40.26%)
Dose 2	N = 159	N = 132
	6 (3.77%)	26 (19.70%)

As can be seen from this table the odds of converting after failing to do so on one dose are reduced by half.

Subjects who failed to convert on one dose were older, had more exposure to Class I and III anti-arrhythmic therapy at baseline and slower rate AF than subjects who converted on one dose. Subjects who converted on two doses were also younger than the subjects who failed to convert on two doses (57 vs. 63 years of age, respectively).

Table 5. AFB or AFL Reported as Adverse Events 24 Hours Post-Study Drug Infusion in Subjects with Short-Term AFB in ACTI and ACTIII

AE	Placebo N = 159	Vernakalant one dose N = 99	Vernakalant two doses 132
AFB	4 (3%)	3 (3%)	4 (3%)

Table 6. Direct Current Cardioversion in the Short-Term AFB Population in ACTI and ACTIII

Timing of DC cardioversion	Placebo N = 159	Vernakalant one dose N = 99	Vernakalant two doses 132
Within 2H	14 (8.81%)	0 (0%)	3 (2.27%)
Within 24H	101 (63.52%)	1 (1.01%)	75 (56.82%)
24H to 7 D	5 (3.14%)	1 (1.01%)	5 (3.79%)
7D to 30D	1 (0.63%)	0 (0%)	0 (0%)
At anytime	121 (76.1%)	2 (2.02%)	83 (62.88%)

Except for one subject, none of the subjects who converted on one dose of Vernakalant were electrically cardioverted within 24 hours of study drug infusion. Because the conversion rate on the second dose was low, more than half the subjects went on to be electrically cardioverted.

Table 7. Exposure to Other Anti-Arrhythmic Class I And III Medication in Subjects with Short-Term AFB in ACTI And ACTIII in Reference to The Timing of Study Drug Infusion

	Placebo N = 159	Vernakalant one dose N = 99	Vernakalant two doses N=132	Vernakalant All doses N=231
More than 24 hour prior	29 (18.24%)	17 (17.17%)	32 (24.24%)	49 (21.21%)
2 to 24 hour prior	32 (20.13%)	9 (9.09%)	18 (13.64%)	27 (11.69%)
Up to 2 hours prior	0 (0%)	1 (1.01%)	2 (1.52%)	3 (1.3%)
Up to 2 hours post	5 (3.14%)	3 (3.03%)	2 (1.52%)	5 (2.16%)
2 to 24 hour post	42 (26.42%)	18 (18.18%)	42 (31.82%)	60 (25.97%)
More than 24 post	18 (11.32%)	13 (13.13%)	22 (16.67%)	35 (15.15%)
Any use	68	36	65	101

The time categories in the above table were created using time of anti-arrhythmic medication administration. A number of subjects had real time (hour:minutes) missing. The reviewer substituted 00 for the missing hour or minute values.

More subjects on placebo had prior treatment with Class I and III anti-arrhythmic medication within 24 hours of study drug. It is not known why more subjects randomized to placebo received anti-arrhythmic therapy within 24 hours of study drug.

Subjects who did not convert on the first dose of Vernakalant were shown to have received other anti-arrhythmic drugs before and after study drug infusion at a higher rate than those who converted on the first dose or placebo.

The use of anti-arrhythmic medication in the 24 hours following study drug infusion more than doubled on Vernakalant compared to prior use; this could be partly because they were in a hospital setting or because investigators decided to give other anti-arrhythmic therapy to maintain SR. The change from baseline in anti-arrhythmic therapy in the 24 hours following the study drug was smaller on placebo compared to Vernakalant probably because investigators resorted more to DC cardioversion in subjects who received placebo than they did in subjects who received Vernakalant.

Table 8. Anti-arrhythmic Use by Specific Drug in the Short-term AFB Population Considered for Efficacy Analyses

	Placebo N = 159	Vernakalant one dose N = 99	Vernakalant two doses N=132	Vernakalant All doses N=231
SOTALOL	34 (21.38%)	26 (26.26%)	21 (15.91%)	47 (20.35%)
AMIODARONE	21 (13.21%)	9 (9.09%)	24 (18.18%)	33 (14.29%)
PROPAFENONE	14 (8.81%)	3 (3.03%)	18 (13.64%)	21 (9.09%)
PROCAINAMIDE	8 (5.03%)	2 (2.02%)	3 (2.27%)	5 (2.16%)
LIDOCAINE	2 (1.26%)	0 (0%)	3 (2.27%)	3 (1.3%)
DISOPYRAMIDE	0 (0%)	0 (0%)	1 (0.76%)	1 (0.43%)
IBUTILIDE	0 (0%)	0 (0%)	1 (0.76%)	1 (0.43%)
FLECAINIDE	9 (5.66%)	5 (5.05%)	15 (11.36%)	20 (8.66%)
DOFETILIDE	1 (0.63%)	0 (0%)	2 (1.52%)	2 (0.87%)

As can be seen from the table above, anti-arrhythmic use was somewhat similar between the placebo and Vernakalant arms. However, subjects who failed to convert on one dose, except for Sotalol, were exposed to other anti-arrhythmic drugs at a higher rate than those who converted on one dose. This could be explained by investigators being more aggressive in maintaining SR when subjects converted on the second dose after failing to convert on one dose.

Table 9. Conversion to Sinus Rhythm within 90 Minutes in the CRAFT Study (Table from Sponsor's Report)

	Placebo N = 19	Vernakalant N = 18	P-value
Number of subjects with termination	1 (5.3%)	11 (61.1%)	0.0003

This study used the reverse regiment of ACTI and ACTIII starting with 2 mg/kg followed by 3 mg/kg instead of starting with 3 mg/kg followed by 2 mg/kg, but nonetheless, almost two thirds of the subjects converted to SR.

6.1.5 Clinical Microbiology

NA

6.1.6 Efficacy Conclusions

Vernakalant is very effective in converting subjects from short-term AFB to SR for at least one minute duration. The conversion rate on two doses was good, but the strength of association between Vernakalant and conversion to SR was reduced in subjects who failed to convert on the first dose. This led to reviewer to believe that the population who failed to convert on one dose is to some extent resistant to the antiarrhythmic effect of Vernakalant, and somewhat different from the population that responded on one dose. This reasoning led the reviewer to conduct a number of analyses by one vs. dose groups.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The reviewer conducted her own safety analyses. Tables cut and pasted from the Applicant's Report are labeled as "from Sponsor's Report."

The majority of the time, the reviewer utilized data from different of populations to evaluate safety. Following are the characteristics of the populations used for safety analyses and the rational for selecting these populations.

- Pooled populations from all studies including patients with AFB, AFL, post-CABG or post-valvulo-plastic-surgery patients and healthy volunteers; this population was used to increase the power and the precision for the evaluation of rare adverse events such as those secondary to the effect of Vernakalant on cardiac repolarization;
- Population with short-term AF; this population is expected to represent the population in whom the applicant is seeking an indication;
- Other populations depending on studies from which the data summarized were collected;

To assess the likelihood of the relatedness of deaths and other SAEs to the study drug, the reviewer studied selected patient narratives and CRFs.

7.1.1 Deaths

Five deaths were observed in this program, and all of them occurred on Vernakalant (0.6%) in the placebo-controlled trials. One of these deaths occurred on Vernakalant within an hour of study drug infusion.

Table 10. Deaths Occurring in All Studies

Subject #	Cause of death	Vernakalant dose receive/outcome	Additional treatments received	Time to event that caused death	Concomitant morbidities
010 12581038	Ventricular tachycardia/fibrillation	3 + 2mg/kg without conversion		48 minutes	Aortic stenosis

Subject #	Cause of death	Vernakalant dose receive/outcome	Additional treatments received	Time to event that caused death	Concomitant morbidities
703 103807	dissected aortic aneurysm and hemorrhagic cardiac tamponade	3 + 2mg/kg Without conversion	Electrical cardioversion	8 hours	Pneumonia; DM;
703 304804	Pneumonia/respiratory arrest	3mg/kg with conversion	Metoprolol & amiodarone	4 days	Lung cancer
703 103840	Pulmonary edema and cardiac decompensation	3 + 2mg/kg without conversion	Electrical cardioversion Metoprolol & amiodarone	25 days	
01211655246	Internal hemorrhage	3 + 2mg/kg		16 days	

Table 11. Characteristics of the Subjects Who Died and Determination of Reviewer's Opinion on the Relatedness of Death to Vernakalant

Subject #	Cause of death	Age/Sex	AFB Duration	Cardiac Status	Kidney Function	Time to event that caused death	Relatedness
010 12581038	Ventricular tachycardia/fibrillation	64/M	3H-7D	Aortic Stenosis	Mild	48 minutes	Very likely
703 103807	dissected aortic aneurysm and hemorrhagic cardiac tamponade	68/F	3H-7D		Mild	8 hours	Unlikely
703 304804	Pneumonia/respiratory arrest	67/M	3H-7D		Mild	4 days	Very unlikely
703 103840	Pulmonary edema and cardiac decompensation	90/F	8D-45D		Moderate/Severe	25 days	Unlikely
01211655246	Internal hemorrhage	70/F				16 days	Unlikely

7.1.1.1 Reviewers Assessment of the Relatedness of Deaths to the Study Drug

Case 010 12581038:

This case of ventricular fibrillation is very likely related to Vernakalant because the subject became hypotensive within minutes of the first infusion and stabilizing his condition was very difficult despite a number of attempts. As the subject's blood pressure started recovering, a second infusion of the study drug was given. Shortly after the second infusion he developed ventricular arrhythmia and expired. Of interest is that the subject had concomitant aortic stenosis and CHF NYHA class II.

Case703 103807

This case of cardiac tamponade does not seem to be related to study drug. The subject was hospitalized for what was perceived as angina pectoris, but an MI work-up was negative. One day after study drug infusion while she was undergoing gastric endoscopy, her aneurysm dissected and she quickly deteriorated and died.

Case 703 304804

This case of pneumonia and respiratory arrest is very unlikely related to study drug because the subject had had a history of lung cancer and a productive cough when he was randomized into ACTI, he then became febrile and developed pneumonia for which he was treated with antibiotics, but despite treatment he died 4 days after.

Case 703 103840

It is unlikely that the study drug contributed to the chain of events that happened after this subject. The subject suffered from pulmonary edema and respiratory distress before she was enrolled. She was treated throughout the study and after discharge for pulmonary edema and angina.

The subject did not convert to SR and developed complete heart block and severe hypotension after electrical cardioversion that was attempted three hours after the two doses of Vernakalant. Her heart rate recovered immediately after administration of isprenalin. On the same day of the study drug infusion (a little over one hour after the attempt of electrical cardioversion) and on the following two days, she experienced episodes of non-sustained ventricular tachycardia. Also, the day after infusion (about 30 hours post infusion), she experienced episode of Torsade de Pointes (per-narrative, but not CRF). After one of the V-Tach episodes, the subject converted to SR and was initiated on intravenous amiodarone. Her potassium level was normal throughout these events. Electrodes for an external pacemaker were inserted 3 days after study drug and she was reported to have improved with normal heart rhythm and no more occurrences of V-Tach. The pacemaker was removed and the patient was discharged.

Subject was also treated for ACS two days post study drug administration. Twenty four days later, patient was admitted to hospital for severe respiratory distress secondary to lung edema pleural fluid and fast AF. No information available on the patient's condition before discharge and readmission.

Case 01211655246

This death due to internal bleeding is not related to study drug. The subject received two doses of the study drug and converted to SR. Two days post study drug, she developed an ileus and a nasogastric tube was inserted. She was discharged 11 days after being enrolled in ACTIV. She was rehospitalized five days later for internal bleeding that led to her death 9 days later.

7.1.2 Other Serious Adverse Events

Table 12. SAEs Occurring Within the First Two Hours Post Start of Infusion from All Studies

SAEs	Placebo N = 339	Vernakalant N = 778
All events combined	3 (0.9%)	26 (3.3%)
Hypotension	0 (0%)	9 (1.2%)
Bradycardia	0 (0%)	6 (0.8%)
Ventricular fibrillation	0 (0%)	2 (0.3%)
3rd degree AV block	0 (0%)	1 (0.1%)
AFL	0 (0%)	1 (0.1%)
Blood in stool	0 (0%)	1 (0.1%)
GI bleed	0 (0%)	1 (0.1%)
Pulmonary edema	0 (0%)	1 (0.1%)
Sinus arrest	0 (0%)	1 (0.1%)
Suffocation feeling	0 (0%)	1 (0.1%)
Ventricular extrasystoles	0 (0%)	1 (0.1%)
Wide complex tachycardia	0 (0%)	1 (0.1%)
Diarrhea	1 (0.3%)	0 (0%)
Hyperthermia	1 (0.3%)	0 (0%)
Mitral valve incompetence	1 (0.3%)	0 (0%)

SAEs occurred at a frequency that is almost four times as high on Vernakalant within the first two hours of infusion compared to placebo. The number of SAEs was small, and some of them occurred in only one subject each; therefore, it is difficult to interpret the potentiality of relatedness even in the face of mechanistic plausibility which is the case of the one event of third degree AV block and the two ventricular fibrillations. Based on numbers alone, only hypotension and bradycardia could be related to Vernakalant.

Table 13. SAEs Occurring between Two Hours and 24 Hours after Start of Infusion from All Studies

SAES	Placebo N = 339	Vernakalant N = 778
All events combined	12 (3.5%)	13 (1.7%)
Atrial fibrillation	3 (0.9%)	2 (0.3%)
Angina pectoris	1 (0.3%)	1 (0.1%)
AV block complete	0 (0%)	1 (0.1%)
AV block first degree	0 (0%)	1 (0.1%)
Bradycardia	2 (0.6%)	1 (0.1%)
Cardiogenic shock	0 (0%)	1 (0.1%)
Catheter related infection	0 (0%)	1 (0.1%)
Cholecystitis	0 (0%)	1 (0.1%)
Hypoglycemia	0 (0%)	1 (0.1%)
Hypotension	1 (0.3%)	1 (0.1%)
Prolonged QT	0 (0%)	1 (0.1%)
Urinary retention	0 (0%)	1 (0.1%)
Cardiac failure congestive	1 (0.3%)	0 (0%)
Cerebrovascular accident	1 (0.3%)	0 (0%)
Deep vein thrombosis	1 (0.3%)	0 (0%)
Ventricular extrasystoles	1 (0.3%)	0 (0%)
Ventricular tachycardia	1 (0.3%)	0 (0%)

After the initial two hours, the rate of SAEs on placebo became higher than on Vernakalant. The numbers here are also small. Per protocol, subjects could receive other anti-arrhythmic therapies after two hours of study drug infusion which could explain the excess of SAEs on placebo.

SAEs of interest, such as bradycardia and hypotension that were observed within two hours of study drug infusion became very few once blood concentrations of Vernakalant have decreased, more than 2 hours after study drug infusion.

Table 14. SAEs Occurring after 24 Hours post Infusion in All Studies

SAE	Placebo N = 339	Vernakalant N = 778	SAE	Placebo N = 339	Vernakalant N = 778
All events combined	54 (15.9)	80 (10.3)	Sinus arrest	0 (0)	1 (0.1)
AFB	18 (5.3)	30 (3.9)	Tachycardia	0 (0)	1 (0.1)
AFL	5 (1.5)	7 (0.9)	Thrombophlebitis superficial	0 (0)	1 (0.1)
Cardiac failure	0 (0)	5 (0.6)	Transient ischemic attack	0 (0)	1 (0.1)
Pneumonia	1 (0.3)	4 (0.5)	Upper gastrointestinal hemorrhage	0 (0)	1 (0.1)
Bradycardia	0 (0)	2 (0.3)	Valvuloplasty cardiac	0 (0)	1 (0.1)
Coronary artery disease	0 (0)	2 (0.3)	Pulmonary edema	3 (0.9)	0 (0)
Dyspnea	0 (0)	2 (0.3)	Angina pectoris	1 (0.3)	0 (0)
Hemothorax	0 (0)	2 (0.3)	Angina unstable	1 (0.3)	0 (0)
Torsade de pointes	1 (0.3)	2 (0.3)	Anticoagulant therapy	1 (0.3)	0 (0)
Cerebrovascular accident	3 (0.9)	1 (0.1)	Bronchitis acute	1 (0.3)	0 (0)

SAE	Placebo N = 339	Vernakalant N = 778	SAE	Placebo N = 339	Vernakalant N = 778
Hypotension	1 (0.3)	1 (0.1)	Cardiac ablation	1 (0.3)	0 (0)
Postoperative infection	1 (0.3)	1 (0.1)	Cardiac arrest	1 (0.3)	0 (0)
Aortic aneurysm rupture	0 (0)	1 (0.1)	Cardiac pacemaker insertion	1 (0.3)	0 (0)
Atrial tachycardia	0 (0)	1 (0.1)	Cardiomyopathy	1 (0.3)	0 (0)
Back pain	0 (0)	1 (0.1)	Cellulites	1 (0.3)	0 (0)
Chest pain	0 (0)	1 (0.1)	Chest discomfort	1 (0.3)	0 (0)
Colitis ischemic	0 (0)	1 (0.1)	Coagulopathy	1 (0.3)	0 (0)
Embolic stroke	0 (0)	1 (0.1)	Diarrhea hemorrhagic	1 (0.3)	0 (0)
Fatigue	0 (0)	1 (0.1)	Hypercalcemia	1 (0.3)	0 (0)
Hypoglycemia	0 (0)	1 (0.1)	Large intestine perforation	1 (0.3)	0 (0)
INR increased	0 (0)	1 (0.1)	Non-cardiac chest pain	1 (0.3)	0 (0)
Ischemic stroke	0 (0)	1 (0.1)	Peritonitis	1 (0.3)	0 (0)
Mitral valve incompetence	0 (0)	1 (0.1)	Renal failure acute	1 (0.3)	0 (0)
Pericardial effusion	0 (0)	1 (0.1)	Respiratory failure	1 (0.3)	0 (0)
Pleural effusion	0 (0)	1 (0.1)	Syncope	1 (0.3)	0 (0)
Pulmonary congestion	0 (0)	1 (0.1)	Urinary tract infection	1 (0.3)	0 (0)
Respiratory arrest	0 (0)	1 (0.1)	Ventricular tachycardia	1 (0.3)	0 (0)

After 24 hours post study drug, the overall frequency of SAEs is somewhat higher on placebo compared to Vernakalant.

Five cases of cardiac failure were reported in subjects more than 24 hours after having received Vernakalant while none were observed in the subjects who received placebo. The numbers are too small, and it is not known how complete ascertainment of adverse events was at the seven-day follow-up time-point, and whether subjects on both treatment arms were assessed for adverse events comparatively.

Other SAEs considered are those that were reported to have occurred on the repeat-dose oral formulation that belongs to another program currently under development by another Sponsor. The annual report of a study under IND (SR-1005) listed two cases of ventricular fibrillation and another two cases of basilar insufficiency that occurred while the subjects were taking Vernakalant as an oral formulation.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The study drug was permanently discontinued in 28 subjects and temporarily discontinued in two subjects.

Table 15. Study Drug Discontinuations (interruption of infusion) by Dose from All Studies

	Placebo	Vernakalant one dose	Vernakalant two doses	Vernakalant all doses
in All Studies Combined	**N = 339**	**N = 258**	**N = 520**	**N = 778**
All discontinuations	1 (0.3%)	25 (9.7%)	5 (1%)	30 (3. 96%)
Permanently stopped	1 (0.3%)	24 (9.3%)	4 (0.8%)	28 (3.6%)
Temporarily stopped	0 (0%)	1 (0.4%)	1 (0.2%)	2 (0.3%)
Short-term AFB in ACTI & ACTIII	**N = 159**	**N = 99**	**N = 132**	**N = 231**
Discontinuation of study drug	1 (0.6%)	5 (5.1%)	0	5 (2.2%)

Of the subjects who tolerated the first dose and went on to receive the second, fewer subjects discontinued compared to first exposure to Vernakalant. Of the subjects with short-term AFB (3 hours to 7 days) who were enrolled in the two pivotal trials, none was discontinued from the second dose. One of the subjects in ACTI did not tolerate the first dose, but was given a second after which he severely deteriorated and died of ventricular arrhythmia.

7.1.3.2 Adverse events associated with dropouts

Table 16. Adverse Events Leading to Discontinuation of Study Drug in All Studies By Dose

	Placebo N = 339	Vernakalant one dose N = 258	Vernakalant two doses N = 520
Discontinuation for any event	1 (0.3%)	35 (13.6%)	6 (1.2%)
Hypotension	0 (0%)	6 (2.3%)	3 (0.6%)
Bradycardia	0 (0%)	4 (1.6%)	1 (0.2%)
QRS complex prolonged	0 (0%)	2 (0.8%)	0 (0%)
Nausea	0 (0%)	2 (0.8%)	0 (0%)
AFL	0 (0%)	1 (0.4%)	0 (0%)
AV block complete	0 (0%)	1 (0.4%)	0 (0%)
Bundle branch block left	0 (0%)	1 (0.4%)	0 (0%)
Bundle branch block right	0 (0%)	1 (0.4%)	0 (0%)
Burning sensation	0 (0%)	1 (0.4%)	0 (0%)
Cold sweat	0 (0%)	1 (0.4%)	0 (0%)
Dizziness	0 (0%)	1 (0.4%)	0 (0%)
Dysgeusia	0 (0%)	1 (0.4%)	0 (0%)
Dyspnea	0 (0%)	1 (0.4%)	0 (0%)
Electrocardiogram QT prolonged	1 (0.3%)	1 (0.4%)	0 (0%)
Headache	0 (0%)	1 (0.4%)	0 (0%)
Injection site swelling	0 (0%)	1 (0.4%)	0 (0%)
Nasal passage irritation	0 (0%)	1 (0.4%)	0 (0%)
Pallor	0 (0%)	1 (0.4%)	0 (0%)
Pulmonary edema	0 (0%)	1 (0.4%)	0 (0%)
Suffocation feeling	0 (0%)	1 (0.4%)	0 (0%)
Tachycardia	0 (0%)	1 (0.4%)	0 (0%)
Urticaria at pressure points	0 (0%)	1 (0.4%)	0 (0%)
Ventricular bigeminy/extrasystoles	0 (0%)	2 (0.8%)	0 (0%)
Atrial fibrillation	0 (0%)	0 (0%)	1 (0.2%)
Syncope vasovagal	0 (0%)	0 (0%)	1 (0.2%)

It is possible that more discontinuations from the first than the second dose were observed because only people who tolerated the first exposure to study drug received the second dose if needed. Hypotension, bradycardia and conductions disturbances (including AV and bundle branch blocks) were the adverse events that led to discontinuation in more than one subject.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Adverse Events by Severity

Table 17. Adverse Events That Occurred at Any Time by Severity from All Studies

Severity of events	Placebo	Vernakalant	Vernakalant	All Vernakalant

	N = 339	one dose N = 258	two doses N = 520	N = 778
Life-threatening	11 (3.24%)	12 (4.65%)	20 (3.85%)	32 (4.1%)
Severe	27 (7.96%)	23 (8.91%)	44 (8.46%)	67 (8.6%)
Moderate	67 (19.76%)	71 (27.52%)	142 (27.31%)	213 (27.38%)
Cardiac, life-threatening	6 (1.8%)	8 (3.1%)	10 (1.9%)	18 (2.3%)
Cardiac, severe	10 (2.9%)	10 (3.9%)	24 (4.6%)	34 (4.4%)

Severity characterization was completed by investigators and data by severity were categorized as life threatening, severe, moderate and mild. Subjects on Vernakalant experienced more moderate overall adverse events. Cardiac disorders (MedDRA AEBODSYS) that were severe or life-threatening were not different between the treatment arms.

Table 18. Cardiac Adverse Events that Occurred within 2 Hours by Severity from All Studies

Severity of events	Placebo N = 339	Vernakalant one dose N = 258	Vernakalant two doses N = 520	All Vernakalant N = 778
Life-Threatening	1 (0.3%)	4 (1.6%)	2 (0.4%)	5 (0.6%)
Severe	2 (0.6%)	4 (1.6%)	8 (1.5%)	12 (1.5%)
Moderate	1 (0.3%)	10 (3.9%)	4 (0.8%)	14 (1.8%)
Mild	6 (1.8%)	17 (6.6%)	21 (4.%)	38 (4.9%)

Considering adverse events that occurred within two hours of study drug by severity, the numbers are small, but four out of six of the subjects who experienced life-threatening cardiac (MedDRA AEBODSYS) events did when they were first exposed to the study drug.

Except for severe adverse events, fewer subjects who received two doses experienced any other category compared to subjects who did not receive a second dose of Vernakalant. A probable explanation is that subjects who did not tolerate the first exposure did not go on to receive a second dose.

. Table 19. Cardiac Events Occurring within 2 Hours of Study Drug Infusion by Severity from All Studies

Severity of events	Placebo N = 339	Vernakalant one dose N = 258	Vernakalant two doses N = 520	All Vernakalant N = 778
Life Threatening				
Ventricular fibrillation*	0 (0%)	0 (0%)	2 (0.4%)	1 (0.1%)
Bradycardia	1 (0.3%)	2 (0.78%)	0 (0%)	2 (0.26%)
Complete AV block	0 (0%)	1 (0.4%)	0 (0%)	1 (0.1%)
Sinus arrest	0 (0%)	1 (0.4%)	0 (0%)	1 (0.1%)
Severe/Moderate				
Hypotension	2 (0.6%)	10 (3.88%)	10 (1.92%)	20 (2.57%)
Bradycardia	0 (0%)	8 (3.1%)	3 (0.58%)	11 (1.41%)
Bundle branch block left	0 (0%)	1 (0.4%)	2 (0.4%)	3 (0.4%)
Atrial fibrillation	2 (0.6%)	1 (0.4%)	4 (0.77%)	5 (0.64%)
AFL	0 (0%)	2 (0.78%)	3 (0.58%)	5 (0.64%)
Hypertension	0 (0%)	0 (0%)	2 (0.38%)	2 (0.26%)
Atrial tachycardia	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)

Severity of events	Placebo N = 339	Vernakalant one dose N = 258	Vernakalant two doses N = 520	All Vernakalant N = 778
Electromechanical dissociation	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)
Palpitations	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)
Sinus arrest	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)
Supraventricular tachycardia	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)
Ventricular extrasystoles	0 (0%)	1 (0.4%)	1 (0.2%)	2 (0.26%)
Ventricular fibrillation	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)
Angina pectoris	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Bundle branch block right	0 (0%)	1 (0.4%)	0 (0%)	1 (0.1%)
Dilatation atrial	0 (0%)	1 (0.4%)	0 (0%)	1 (0.1%)
Mitral valve incompetence	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Tachycardia	0 (0%)	1 (0.4%)	0 (0%)	1 (0.1%)
Ventricular bigeminy	0 (0%)	1 (0.4%)	0 (0%)	1 (0.1%)
Ventricular tachycardia	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)

One of the ventricular fibrillation was not coded as so. The reviewer included it in this table

It is reasonable to conclude that all the cardiac life threatening adverse events are related to the study drug given that the two ventricular fibrillations occurred within minutes of the completion of the study drug infusion; and bradycardia, AV block and sinus arrest are mechanistically plausible.

In conclusion, even if the number of life-threatening cardiac events occurring immediately (within two hours) after infusion of Vernakalant is small, it is disconcerting that any life-threatening cardiac event occurs at all.

Table 20. Life-Threatening, Severe and Moderate non-Cardiac Events that Occurred within 2 Hours of Study Drug Infusion

	Placebo N = 339	Vernakalant one dose N = 258	Vernakalant two doses N = 520	All Vernakalant N = 778
Nausea	0 (0%)	4 (1.6%)	6 (1.2%)	10 (1.3%)
Dysgeusia	0 (0%)	3 (1.2%)	4 (0.8%)	7 (0.9%)
Hyperhydrosis	0 (0%)	0 (0%)	4 (0.8%)	4 (0.5%)
Dizziness	1 (0.29%)	1 (0.4%)	3 (0.6%)	4 (0.5%)
Cold sweat	0 (0%)	2 (0.8%)	2 (0.4%)	4 (0.5%)
Cough	0 (0%)	2 (0.8%)	2 (0.4%)	4 (0.5%)
Paraesthesia	0 (0%)	1 (0.4%)	3 (0.6%)	4 (0.5%)
Vomiting	0 (0%)	0 (0%)	3 (0.6%)	3 (0.4%)
Sneezing	0 (0%)	0 (0%)	3 (0.6%)	3 (0.4%)
Dysuria	0 (0%)	0 (0%)	2 (0.4%)	2 (0.3%)
Syncope vasovagal	0 (0%)	1 (0.4%)	1 (0.2%)	2 (0.3%)
Dyspnea	0 (0%)	2 (0.8%)	0 (0%)	2 (0.3%)
Fatigue	0 (0%)	2 (0.8%)	0 (0%)	2 (0.3%)
Pulmonary edema	0 (0%)	2 (0.8%)	0 (0%)	2 (0.3%)

Excluding mild adverse events, except for dizziness, all the adverse events that occurred within two hours were on Vernakalant. Even if the numbers are small, it would be hard to dispute the relatedness of these events to Vernakalant because it is hard for chance to be non-random and

play in disfavor of Vernakalant. Except for syncope and pulmonary edema all these adverse events could be tolerable

7.1.4 Other Search Strategies

In animal studies, seizures and respiratory depression were observed at dose levels that were lethal. Two cases of seizure within 24 hours of study drug infusion were observed, one each on placebo and Vernakalant. The effect on respiration and oxygen saturation is discussed under 7.1.9 Vital Signs page 42.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the main studies, adverse events were recorded while study subjects were in the research clinic up to 24 hours or discharge. A seven-day follow-up visit and 30-day phone call were conducted to record adverse events and SR status.

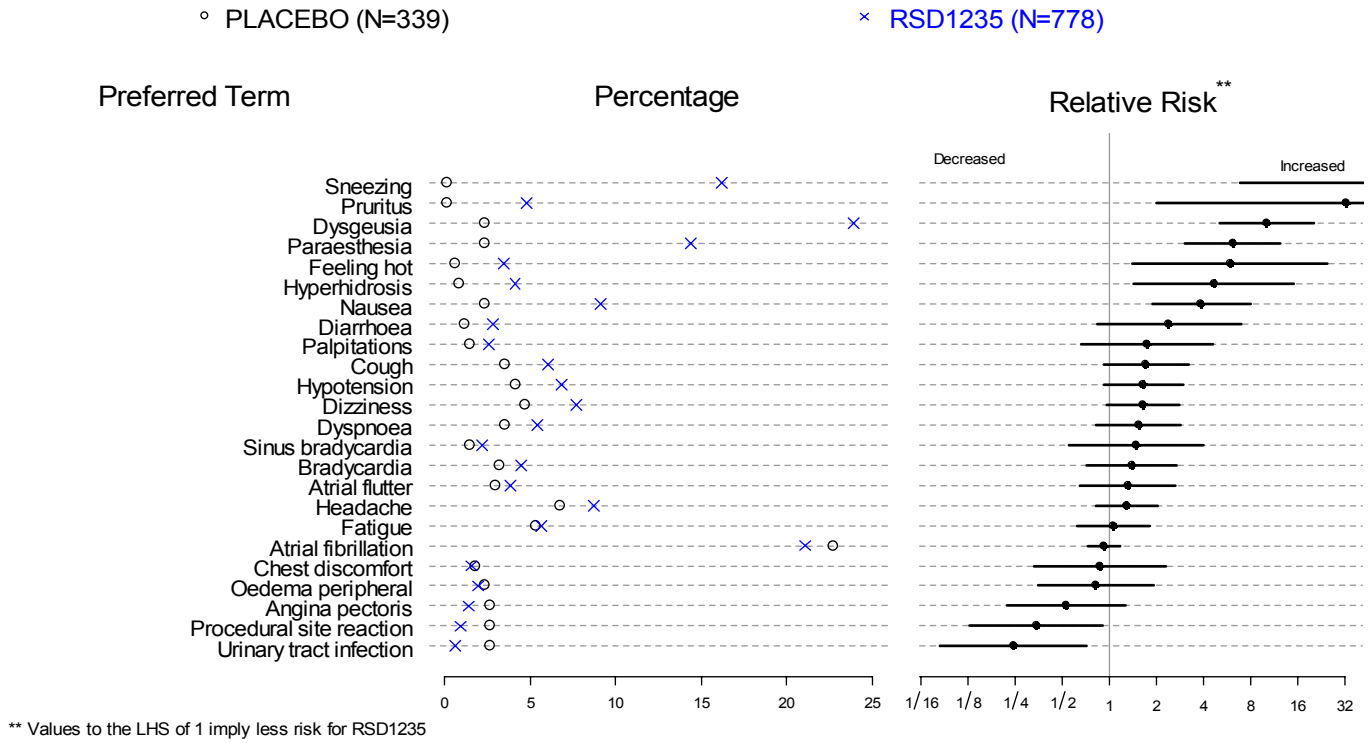
7.1.5.2 Appropriateness of adverse event categorization and preferred terms

MedDRA dictionary was used to categorize adverse events and summary tables used the Preferred Term.

The reviewer conducted her own analyses of adverse events using the reported terms to recode some adverse events for different analyses.

7.1.5.3 Incidence of common adverse events

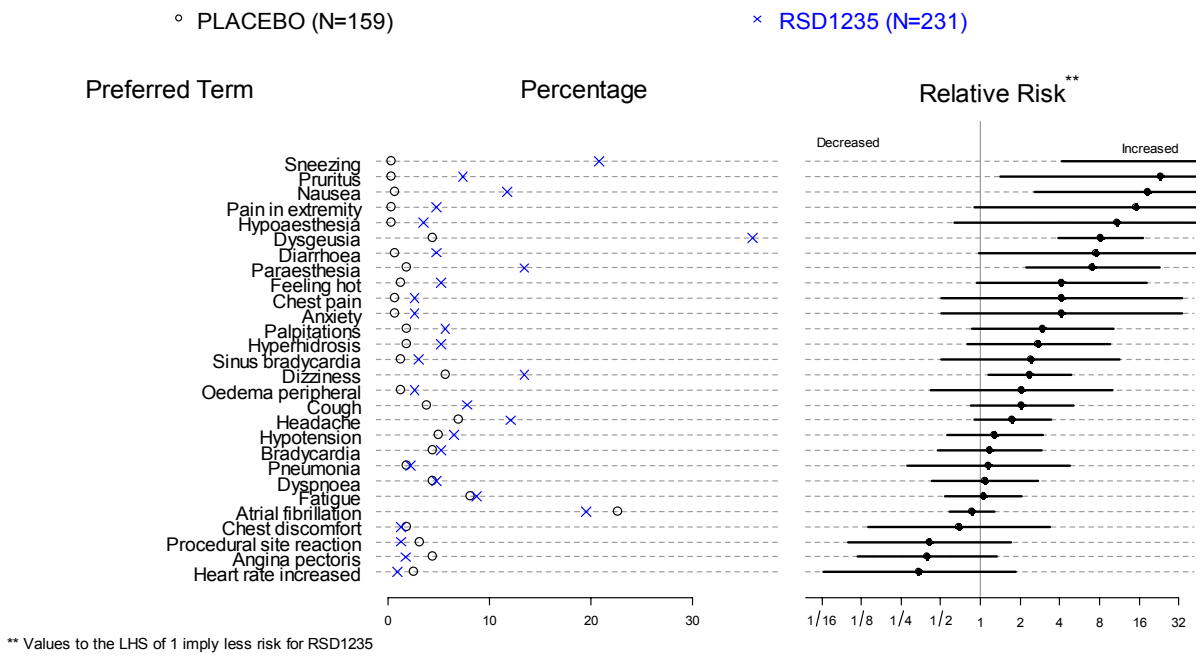
Figure 2. Common Adverse Events Occurring in >= 3% and Higher from All Studies



As can be seen on this figure dysgeusia, sneezing, paraesthesia, nausea, feeling hot, hyperhydrosis are significantly (without adjustment for multiplicity) more frequent in subjects on Vernakalant compared to placebo, while diarrhea, palpitations, cough, hypotension, dizziness, dyspnea, bradycardia and atrial flutter trended toward an increase on Vernakalant compared to placebo.

Because studies were designed to test the efficacy not safety of Vernakalant, some of the significant findings could be the result of multiple testing. Was multiplicity of testing considered and adjusted for in these analyses, not too many of these adverse events would have been found statistically significant.

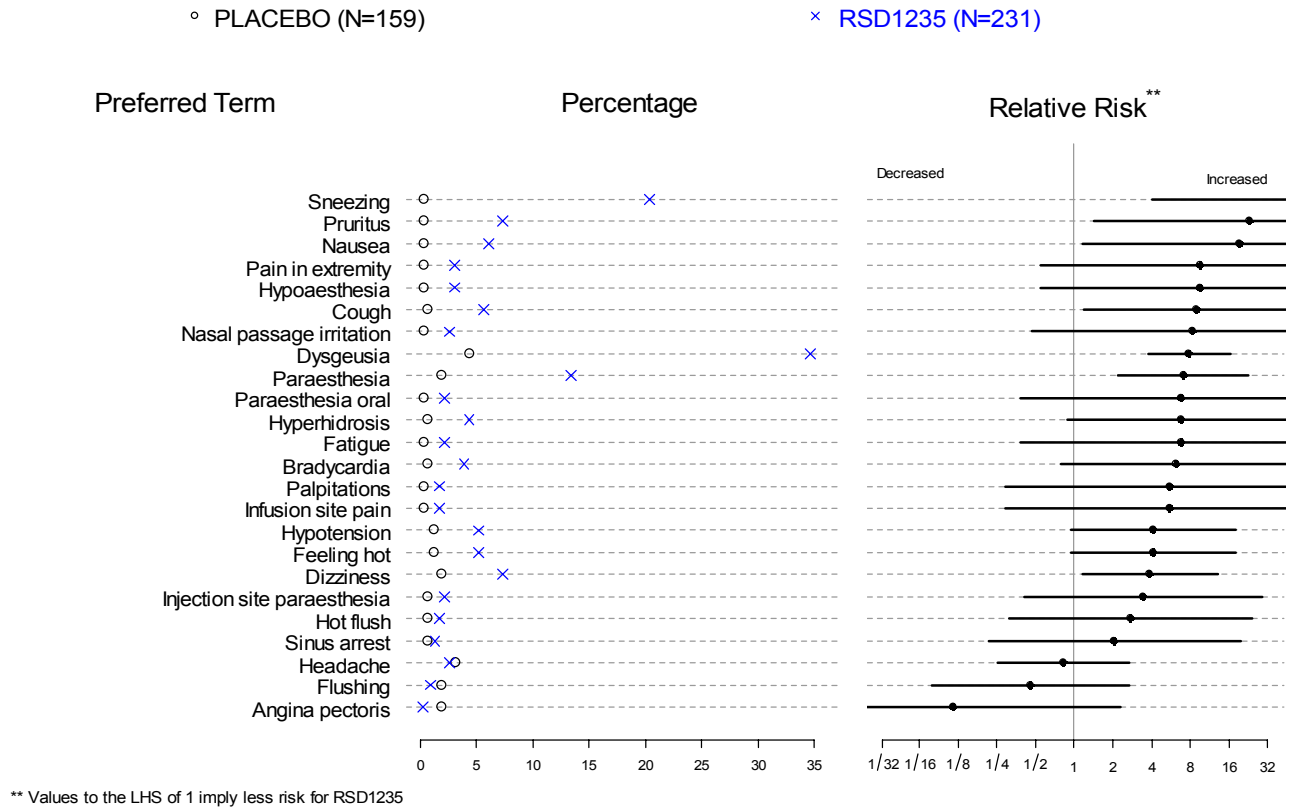
Figure 3. Common Adverse Events Occurring in >= 3% and Higher from Studies in Short-Term AF



** Values to the LHS of 1 imply less risk for RSD1235

In subjects with short-term AFB, sneezing, pruritus, nausea, dysgeusia, paraesthesia, and dizziness were reported more frequently in subjects on Vernakalant compared to those on placebo. Cough, headache, palpitations, diarrhea, hyperhydrosis and feeling hot showed increasing trends on Vernakalant compared to placebo.

Figure 4. Common Adverse Events Occurring within 2 Hours of Study Drug Infusion in >= 1. 5% and Higher from Studies in Short-Term AFB in ACTI and ACTIII Studies

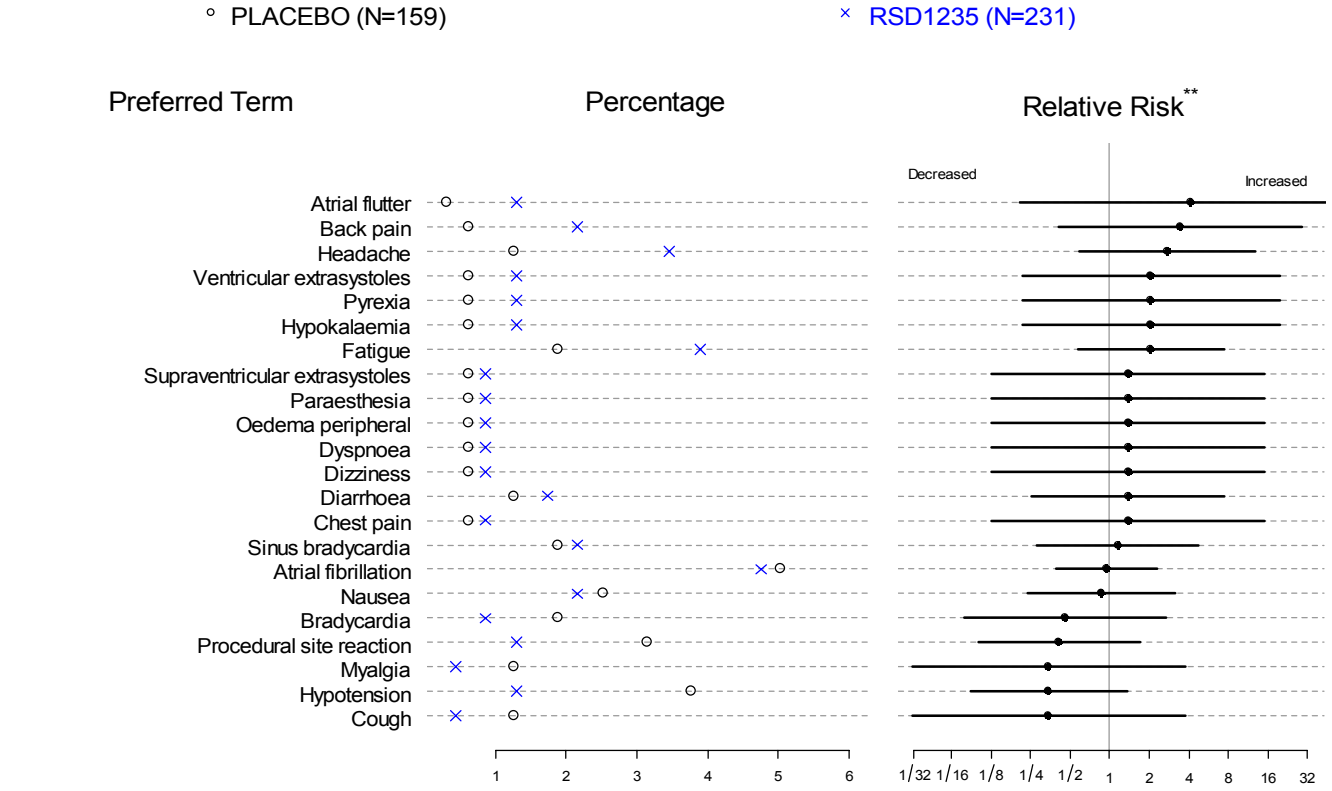


** Values to the LHS of 1 imply less risk for RSD1235

Within two hours of the study drug, sneezing, pruritus, nausea, dysgeusia, paraesthesia, dizziness and cough were again reported more frequently on Vernakalant compared to placebo.

Hypotension, bradycardia, palpitations, sinus arrest, feeling hot, fatigue, pain in extremities, hypoesthesia, nasal passage irritation, oral paraesthesia, hyperhydrosis, infusion site pain, injection site paraesthesia and hot flushes were more common, but not significantly, on Vernakalant compared to placebo.

Figure 5. Common Adverse Events Occurring from Two to 24 Hours Post- Study Drug Infusion in >= 1% and Higher from Studies in Short-Term AFB in ACTI and ACTIII



** Values to the LHS of 1 imply less risk for RSD1235

7.1.5.4 Two to 24 hours post-study drug, the rate of adverse events related to study drug was reduced compared to what was observed within two hours, see Figure 4.Common adverse event tables

Common adverse events are presented above as graphs, as well.

7.1.5.3 Incidence of common adverse events above.

Table 21. Common Adverse Events Occurring up to 24 Hours Post-Infusion in All Studies at a Rate of At Least 2% by Dose

	Placebo N=339	Vernakalant		Vernakalant All
		One dose N=258	Two doses N=520	
Dysgeusia	8 (2.4%)	69 (26.7%)	95 (18.3%)	164 (21.1%)
Sneezing	0 (0%)	26 (10.1%)	80 (15.4%)	106 (13.6%)
Paraesthesia	5 (1.5%)	25 (9.7%)	49 (9.4%)	74 (9.5%)
Nausea	4 (1.2%)	20 (7.8%)	33 (6.3%)	53 (6.8%)
Hypotension	12 (3.5%)	17 (6.6%)	28 (5.4%)	45 (5.8%)
Pruritus	0 (0%)	2 (0.8%)	25 (4.8%)	27 (3.5%)
Atrial fibrillation	18 (5.3%)	8 (3.1%)	24 (4.6%)	32 (4.1%)
Dizziness	9 (2.7%)	13 (5%)	23 (4.4%)	36 (4.6%)
Headache	12 (3.5%)	15 (5.8%)	23 (4.4%)	38 (4.9%)
Hyperhydrosis	2 (0.6%)	6 (2.3%)	22 (4.2%)	28 (3.6%)

	Placebo N=339	Vernakalant		Vernakalant All
		One dose N=258	Two doses N=520	
Cough	4 (1.2%)	16 (6.2%)	16 (3.1%)	32 (4.1%)
Fatigue	6 (1.8%)	9 (3.5%)	16 (3.1%)	25 (3.2%)
Feeling hot	2 (0.6%)	7 (2.7%)	16 (3.1%)	23 (3%)
Bradycardia	7 (2.1%)	13 (5%)	13 (2.5%)	26 (3.3%)
Paraesthesia oral	1 (0.3%)	4 (1.6%)	12 (2.3%)	16 (2.1%)
Atrial flutter	2 (0.6%)	5 (1.9%)	11 (2.1%)	16 (2.1%)
Nasal passage irritation	0 (0%)	4 (1.6%)	11 (2.1%)	15 (1.9%)
Vomiting	1 (0.3%)	2 (0.8%)	11 (2.1%)	13 (1.7%)
Dyspnea	2 (0.6%)	7 (2.7%)	6 (1.2%)	13 (1.7%)
Sinus bradycardia	5 (1.5%)	6 (2.3%)	6 (1.2%)	12 (1.5%)

7.1.5.5 Identifying common and drug-related adverse events

Using causality principles, some adverse events are more likely than others to be related to Vernakalant. The reviewer believes with confidence that the following adverse events are related to Vernakalant:

- sneezing because it is unusual and it occurred within two hours of the infusion of Vernakalant and none of the placebo subjects experienced such event;
- pruritus because, also here, it occurred within two hours of the infusion of Vernakalant, none of the placebo subjects experienced such event, and there seem to be a dose response of event rate by doses one vs. two;
- dysgeusia because it is unusual, it occurred within two hours of the infusion of Vernakalant, and the association between this AE and Vernakalant is strong;
- nausea because of the strong association between this adverse event and Vernakalant;
- hyperhydrosis because of the strength of association and the dose response;
- hypotension, bradycardia, AFL and AV block because they occurred within two hours of the infusion of Vernakalant, and they are mechanistically plausible;

7.1.5.6 Additional analyses and explorations

7.1.6 Less Common Adverse Events

Table 22. Cardiac Events Occurring within 2 Hours of Study Drug Infusion Excluding Cases of AFB/AFL in All

AEs within two hours of infusion	Placebo N = 339	Vernakalant one dose N = 258	Vernakalant two doses N = 520	All Vernakalant N = 778
Atrial tachycardia	0 (0%)	0 (0%)	7 (1.35%)	7 (0.9%)
Palpitations	1 (0.29%)	2 (0.78%)	3 (0.58%)	5 (0.64%)
LBBB	0 (0%)	1 (0.39%)	3 (0.58%)	4 (0.51%)
Ventricular extrasystoles	0 (0%)	2 (0.78%)	2 (0.38%)	4 (0.51%)
AV block, first degree	1 (0.29%)	1 (0.39%)	2 (0.38%)	3 (0.39%)
Angina pectoris	3 (0.88%)	0 (0%)	2 (0.38%)	2 (0.26%)
Ventricular fibrillation	0 (0%)	0 (0%)	2 (0.38%)	2 (0.26%)
Sinus arrest	1 (0.29%)	3 (1.16%)	1 (0.19%)	4 (0.51%)
Sinus tachycardia	0 (0%)	1 (0.39%)	1 (0.19%)	2 (0.26%)
Electromechanical dissociation	0 (0%)	0 (0%)	1 (0.19%)	1 (0.13%)
Supraventricular tachycardia	0 (0%)	0 (0%)	1 (0.19%)	1 (0.13%)
Supraventricular extrasystoles	0 (0%)	2 (0.78%)	0 (0%)	2 (0.26%)
Complete AV block	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)
RBBB	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)
Dilatation atrial	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)
Extrasystoles	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)
Ventricular bigeminy	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)
Ventricular tachycardia	1 (0.29%)	2 (0.78%)	0 (0%)	2 (0.26%)
Mitral valve incompetence	1 (0.29%)	0 (0%)	0 (0%)	0 (0%)
Ventricular arrhythmia	1 (0.29%)	0 (0%)	0 (0%)	0 (0%)

Atrial tachycardia was observed in seven of the subjects who received two doses of Vernakalant but none on placebo or on one dose; and AV block (of different degrees, locations and types), and ventricular events (fibrillation, extrasystoles, etc.) were observed more frequently on Vernakalant.

The numbers are too small and one cannot say with certainty which adverse event is triggered by Vernakalant, especially that the AFB/AFL study population is known to be at high risk of developing similar cardiac events. Given the mechanistic plausibility of some cardiac events, the correlated-ness of these events, and the shown-effect of Vernakalant on ECG parameters, some of these adverse events (including AV/bundle branch blocks and ventricular fibrillation and tachycardia) are likely related to Vernakalant.

Table 23. Less Common Adverse Events Occurring between Two and 24 Hours Post-Infusion in All Studies

AEs occurring two to 24 H post infusion	Placebo N = 339	Vernakalant one dose N = 258	Vernakalant two doses N = 520	All Vernakalant N = 778
Fatigue	4 (1.18%)	6 (2.33%)	9 (1.73%)	15 (1.93%)
AV block, first degree	0 (0%)	1 (0.39%)	4 (0.77%)	5 (0.64%)
Back pain	1 (0.29%)	3 (1.16%)	4 (0.77%)	7 (0.9%)

AEs occurring two to 24 H post infusion	Placebo N = 339	Vernakalant one dose N = 258	Vernakalant two doses N = 520	All Vernakalant N = 778
Dyspnea	2 (0.59%)	1 (0.39%)	4 (0.77%)	5 (0.64%)
Post procedural complication	0 (0%)	0 (0%)	4 (0.77%)	4 (0.51%)
Post procedural pain	0 (0%)	0 (0%)	4 (0.77%)	4 (0.51%)
Asthenia	0 (0%)	1 (0.39%)	3 (0.58%)	4 (0.51%)
AFL	1 (0.29%)	2 (0.78%)	3 (0.58%)	5 (0.64%)
Hyperhidrosis	1 (0.29%)	1 (0.39%)	3 (0.58%)	4 (0.51%)
AV block, complete	0 (0%)	0 (0%)	1 (0.19%)	1 (0.13%)
BBB	0 (0%)	0 (0%)	1 (0.19%)	1 (0.13%)
Dizziness postural	0 (0%)	1 (0.39%)	1 (0.19%)	2 (0.26%)
Dysgeusia	0 (0%)	1 (0.39%)	1 (0.19%)	2 (0.26%)
Hypoesthesia	0 (0%)	2 (0.78%)	1 (0.19%)	3 (0.39%)
Nodal rhythm	0 (0%)	1 (0.39%)	1 (0.19%)	2 (0.26%)
Orthopnea	0 (0%)	1 (0.39%)	1 (0.19%)	2 (0.26%)
Syncope	0 (0%)	1 (0.39%)	1 (0.19%)	2 (0.26%)
Cardiogenic shock	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)
Cyanosis	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)
Pulmonary edema	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)
Respiratory failure	0 (0%)	1 (0.39%)	0 (0%)	1 (0.13%)

Between two and 24 hours post-infusion, AV block of different degrees and types and asthenia were observed solely on Vernakalant, and fatigue was more frequent on Vernakalant especially in the group who converted on one dose. The number of events is very small, but one cannot disregard the excess of AV block (5 first degree and one complete) on Vernakalant. All these blocks occurred after receiving the second dose of Vernakalant. The possible explanations include Vernakalant from the second dose or one of its metabolites lingering around for a longer duration, or exposure to other antiarrhythmic medications that have similar effects that are permitted after two hours post-dose.

7.1.7 Other Adverse Events

The reviewer recoded adverse events for the analysis below.

7.1.7.1 Respiratory (coded under MedDRA Respiratory Disorders) Occurring within 24 Hours of Study Drug Infusion

The reviewer thought it worthwhile summarizing respiratory adverse events because dyspnea was a significant adverse event in pre-clinical research.

Table 24. Respiratory Adverse Events Occurring within Two Hours of Study Drug in Subjects from All Studies

Respiratory Adverse Events	Placebo N=339	Vernakalant N=778
Any respiratory events	6 (1.8%)	62 (8%)
Cough	4 (1.2%)	33 (4.2%)
Dyspnea	2 (0.6%)	14 (1.8%)
Pulmonary edema/congestion	0 (0%)	5 (0.6%)
Suffocation/choking feeling	0 (0%)	3 (0.4%)

Respiratory Adverse Events	Placebo N=339	Vernakalant N=778
Orthopnea	0 (0%)	3 (0.4%)
Pulmonary congestion	0 (0%)	2 (0.3%)
Respiratory failure	0 (0%)	1 (0.1%)
Wheezing	0 (0%)	1 (0.1%)

Within 24 hours of study drug infusion, subjects on Vernakalant experienced more respiratory events than subjects on placebo. This excess is driven by cough, and dyspnea. In light of preclinical findings, the reviewer believes that these clinical findings are unlikely due to chance. Additionally, one of the cases of dyspnea that occurred within two hours of infusion was a healthy volunteer.

7.1.7.2 Central Nervous System

The reviewer though of summarizing CNS in a separate category because, again, preclinical data showed that Vernakalant was associated with seizures.

Table 25. Occurring within 24 Hours of Study Drug Infusion

	Placebo N=339	Vernakalant N=778
Headache	12 (3.5%)	38 (4.9%)
Dizziness	9 (2.7%)	38 (4.9%)
Syncope	0 (0%)	5 (0.6%)
Convulsion	1 (0.3%)	1 (0.1%)

Only selected CNS adverse events are summarized in the table above. As can be seen from the summary above, the only few syncope cases observed in the program occurred on Vernakalant, and dizziness was observed at a higher rate on Vernakalant compared to placebo. Both dizziness and syncope could be due to the hypotensive effect of the drug.

If Vernakalant has a tendency to affect the CNS and cause seizures in humans, as it did in animals (at very high doses) and the risk of this effect is small, this tendency is not apparent in this program because the extent of exposure is limited.

7.1.8 Laboratory Findings

7.1.8.1 Overview of laboratory testing in the development program

7.1.8.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory data were provided for studies ACTI, ACTIII, CRAFT and Scene 2. These studies included subjects with AFB and AFL with 281 subjects on placebo and 430 subjects on Vernakalant. Per protocol, laboratory testing including hematology, clinical chemistry and urinalysis are to be performed at screening, discharge from the study facility and the seven-day follow-up visit. Any abnormality fulfilling prespecified criteria are to be treated as adverse events.

7.1.8.3 Standard analyses and explorations of laboratory data

The laboratory data from all Phase II and III studies in AFB and AFL patients were pooled, and all laboratory parameters were analyzed, but only few (troponin, CPKMB2, potassium, sodium, magnesium) are selected for presentation in this review. The rational for choosing troponin and CPKMB2 is because they are myocardial enzymes; sodium, magnesium and potassium is because Vernakalant blocks sodium and potassium channels, and they can shift quickly given that laboratory parameters were evaluated within hours of the start of the study drug; and CPK levels because these increase with electrical cardioversion. Other laboratory parameters did not change in a way to warrant including a summary here.

7.1.8.3.1 Analyses focused on measures of central tendency

Figure 6. Mean Levels of Selected Laboratory Parameters

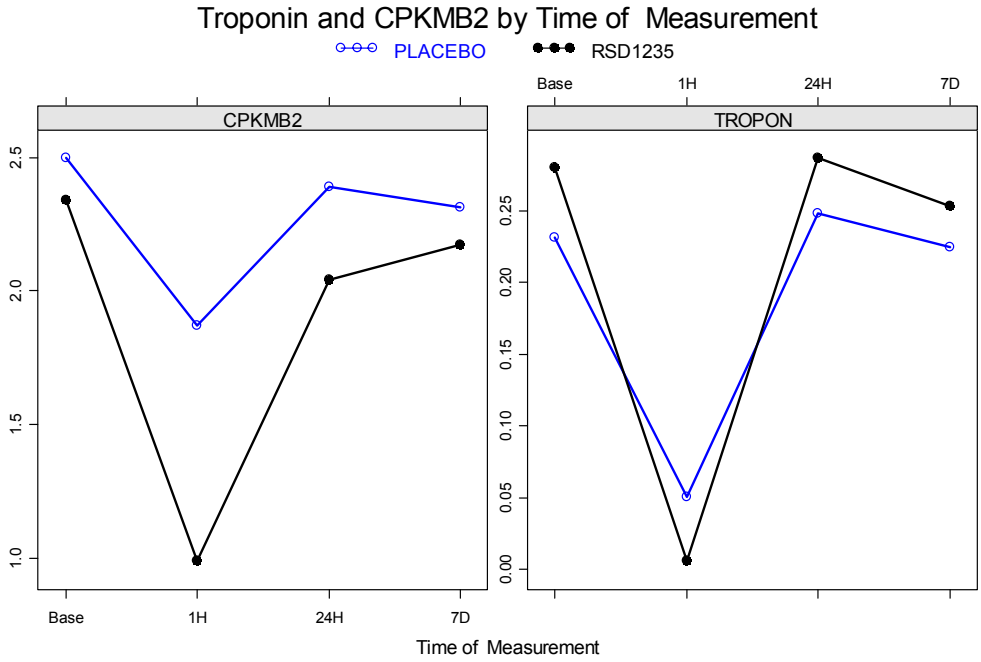
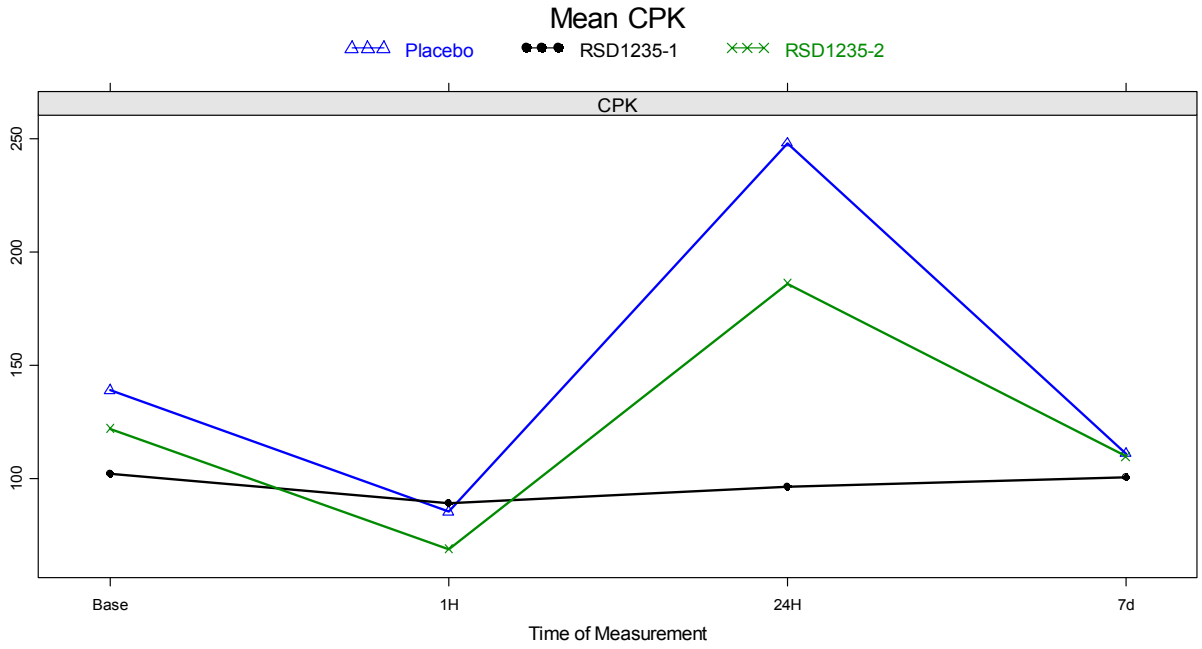
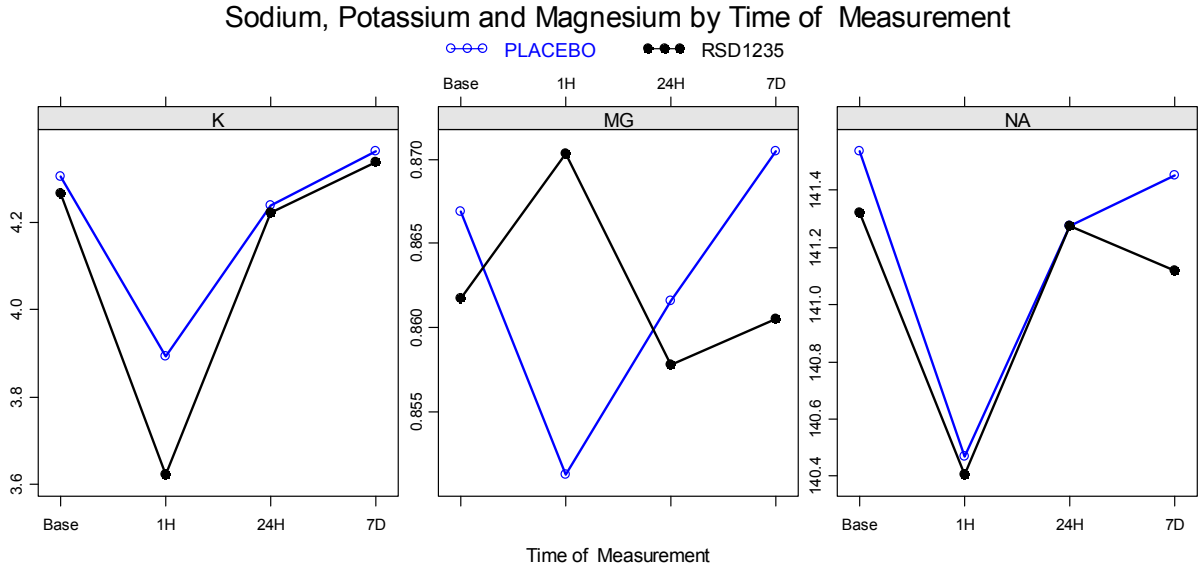


Figure 7. Mean CPK Levels from All Studies Combined



As can be seen from graph above, subjects who did not convert on one dose and subjects on placebo had their CPK levels increased between one and 24 hours post study drug. This could be explained by electrical cardioversion in these subjects.

Figure 8. Mean Levels of Electrolytes



The mean magnesium dipped on Vernakalant one hour after infusion while it peaked on placebo.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for laboratory abnormalities

Very few subjects had a shift of laboratory parameters beyond the pre-specified cutoff limits at any time.

Table 26. Prespecified Marked Outliers of Selected Laboratory Parameters in All Controlled Studies (from Sponsor's Report)

	Placebo N = 174	Vernakalant N = 310
Sodium > 150 mmol/L	1 (0.4%)	7 (1.7%)
BUN > 10.7 mmol/L	1 (0.4%)	6 (1.9%)
Creatinine Phosphokinase > 3xULN	16 (6.2%)	17 (4.3%)

As can be seen from the table above, more subjects on Vernakalant had their sodium and BUN levels above the upper cutoff limit.

Subjects on both Vernakalant and placebo had their CPK increase above three times the upper limit of normal; these proportions went down at the 7-day follow-up visit to 0.8% and 0.5% respectively. The number of subjects shifting to above the pre-specified limit within 24 hours could be explained by electrical cardioversion.

7.1.8.4 Additional analyses and explorations

7.1.8.5 Special assessments

7.1.9 Vital Signs

7.1.9.1 Overview of vital signs testing in the development program

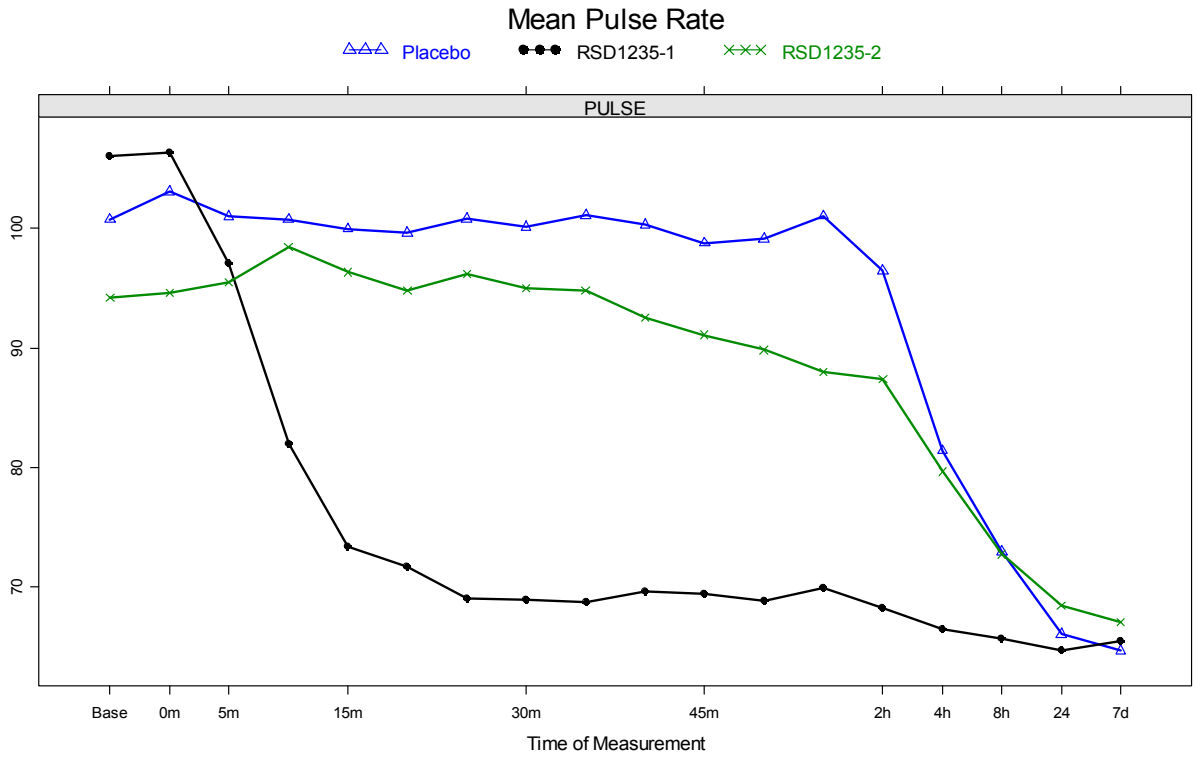
In all trials, vital signs were measured at pre-specified intervals of one and 24 hours post-infusion, and at the seven-day follow-up visit (refer to Table 43. Procedure Schedules in ACTI and ACTIII, page 74).

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of vital signs data

7.1.9.3.1 Analyses focused on measures of central tendencies

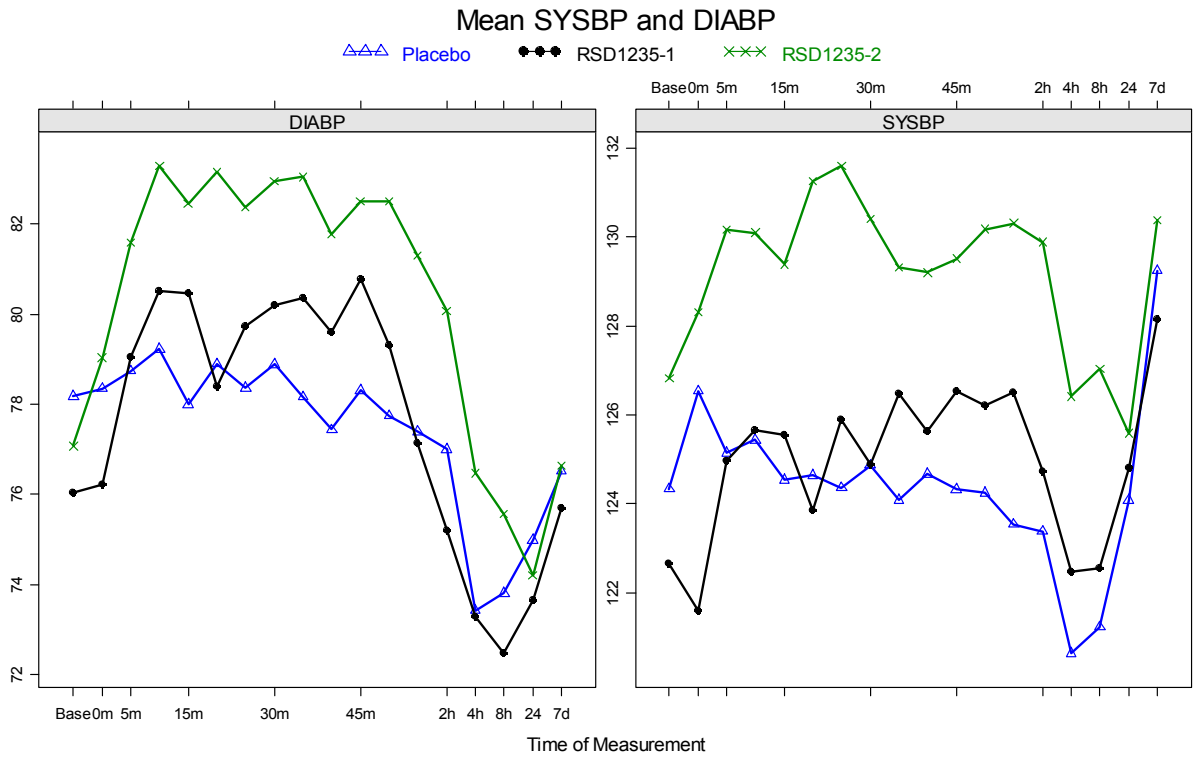
Figure 9. Mean Pulse Rate by Time Point for Subjects with Short-Term AF



The group of subjects with short-term AFB who received one dose of Vernakalant started with a higher mean pulse rate and had a significant decrease in their heart rate because all of them converted to SR.

The group that received two doses had no decrease in pulse rate after the first infusion, if anything, their mean rate increased slightly. But a slight decrease in mean pulse rate was observed around the time of the second infusion and up to 90 minutes which could be explained by conversion to SR of some of the subjects. This group's heart rate decreased significantly starting at 2 hours post study drug which coincides with the time when other anti-arrhythmic therapies and electrical cardioversion were permitted per protocol. The placebo group, also, experienced a decrease in mean pulse rate starting around two hours post study drug.

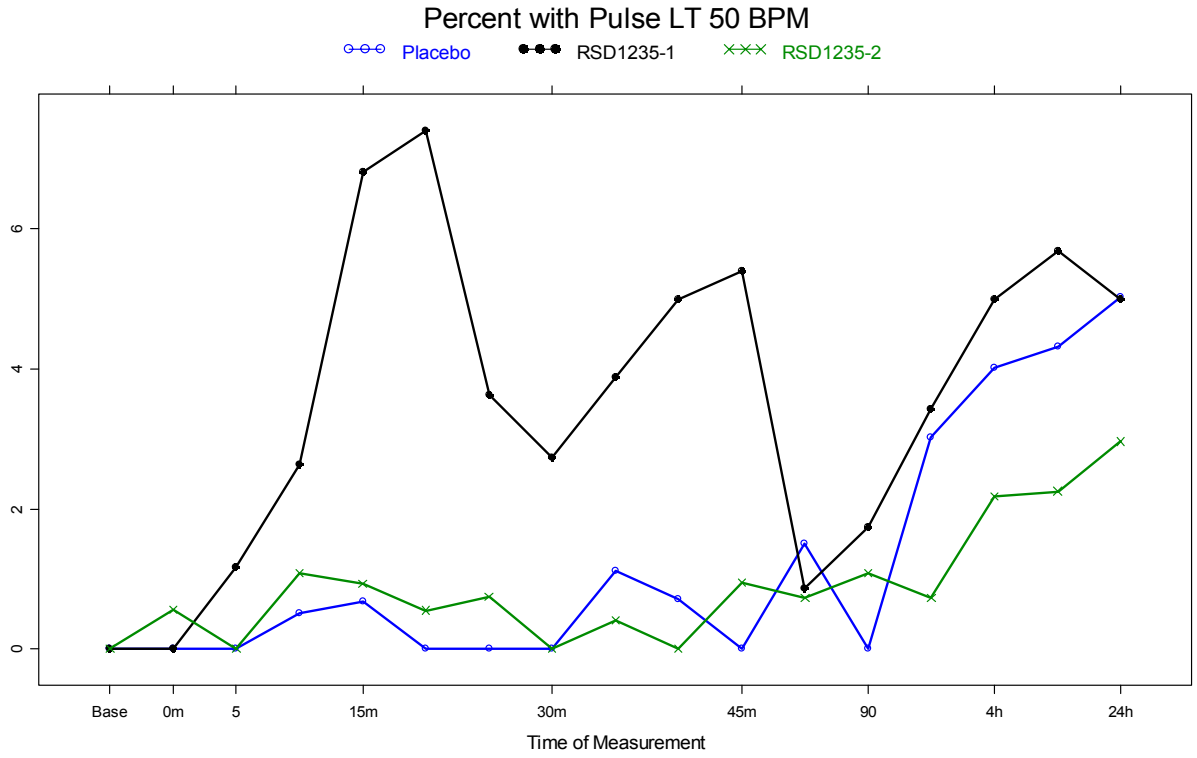
Figure 10. Mean SBP and DBP by Time Point for Subjects in ACTI, ACTIII, CRAFT and Scene 2



The mean systolic and diastolic blood pressure in the subjects who received two doses of Vernakalant was higher at most time-points within two hours of the study drug infusion compared to placebo and subjects who received only one dose of Vernakalant. It is not known why subjects who did not convert on one dose (or at least some of them) reacted with an increased blood pressure while Vernakalant was expected to decrease blood pressure. The reason subjects who received one dose only did not react the same way is probably because they converted to SR, and any blood pressure increasing effect was offset by the effect conversion to SR had on blood pressure.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

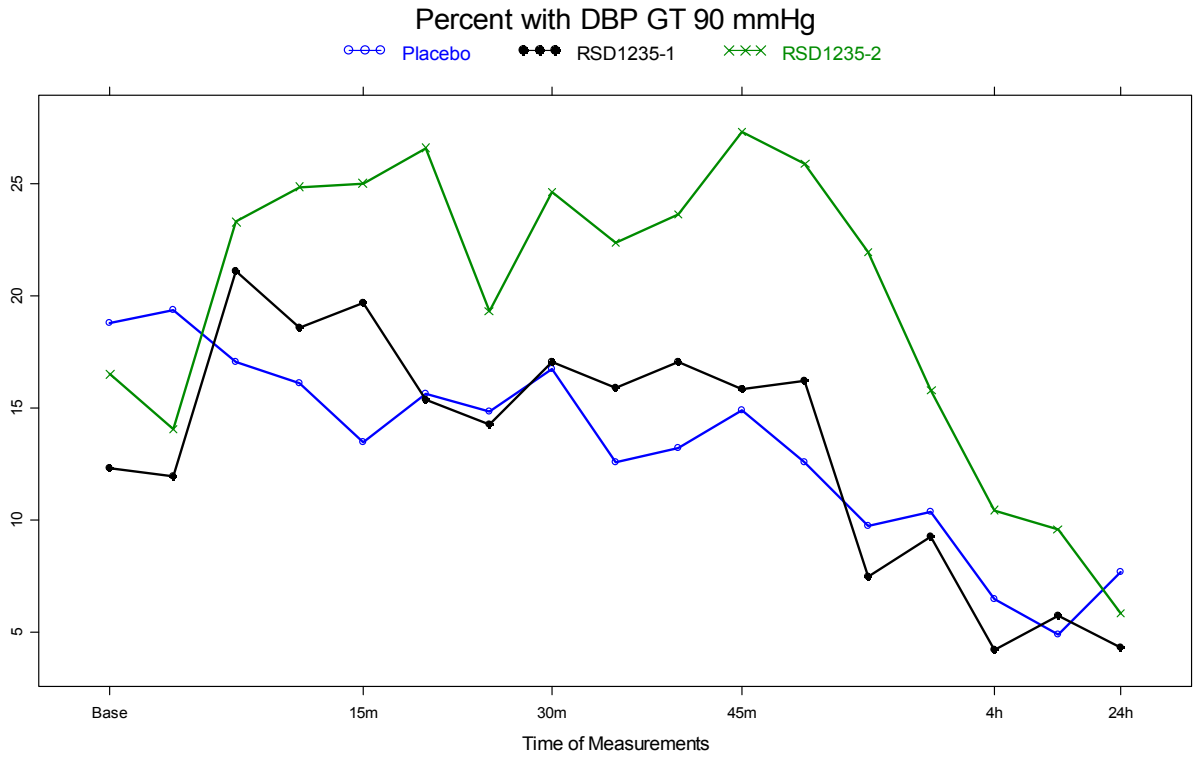
Figure 11. Percent of Subjects with Pulse Less than 50 bpm by Time Point for Subjects in All Studies



The graph above was generated using ECG data. More subjects from the group that converted on one dose of Vernakalant experienced severe bradycardia compared to placebo and subjects who did not convert on one dose and consequently received two. One explanation is that some subjects in this group of responders responded more intensely to Vernakalant and experienced severe bradycardia. Subjects who did not convert on the first dose were at a lower risk of experiencing severe bradycardia, even after the second infusion.

The percentage of subjects with severe bradycardia increased again around 90 minutes post-study drug time-point in all groups. One possible explanation is that after 90 minutes, investigator decided to give other anti-arrhythmic drugs that affect heart rate to either convert subjects who failed to convert to SR or to maintain SR in those who converted on study drug.

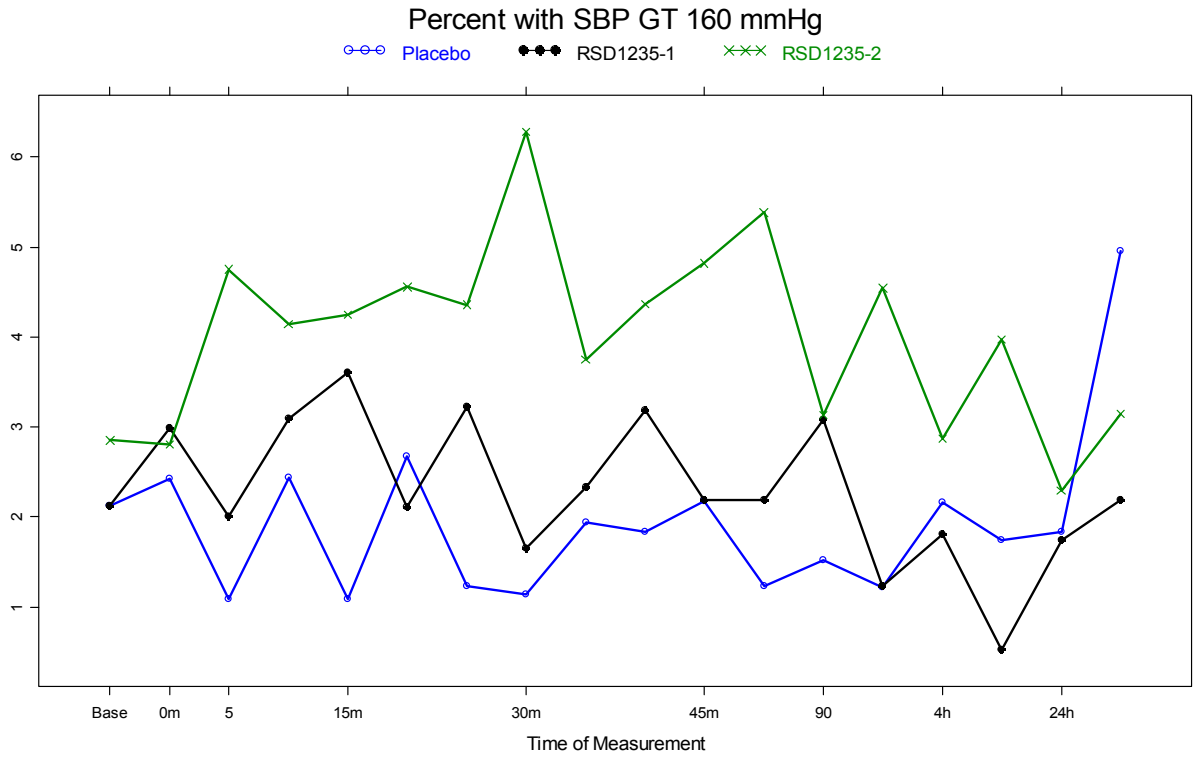
Figure 12. Percent of Subjects with DBP Greater than 90 mmHg by Time Point for Subjects in All Studies



The findings on this graph confirm what was observed in the graph with mean blood pressures. More subjects in the group who did not convert on one dose of Vernakalant experienced an increase in diastolic blood pressure at both infusion times.

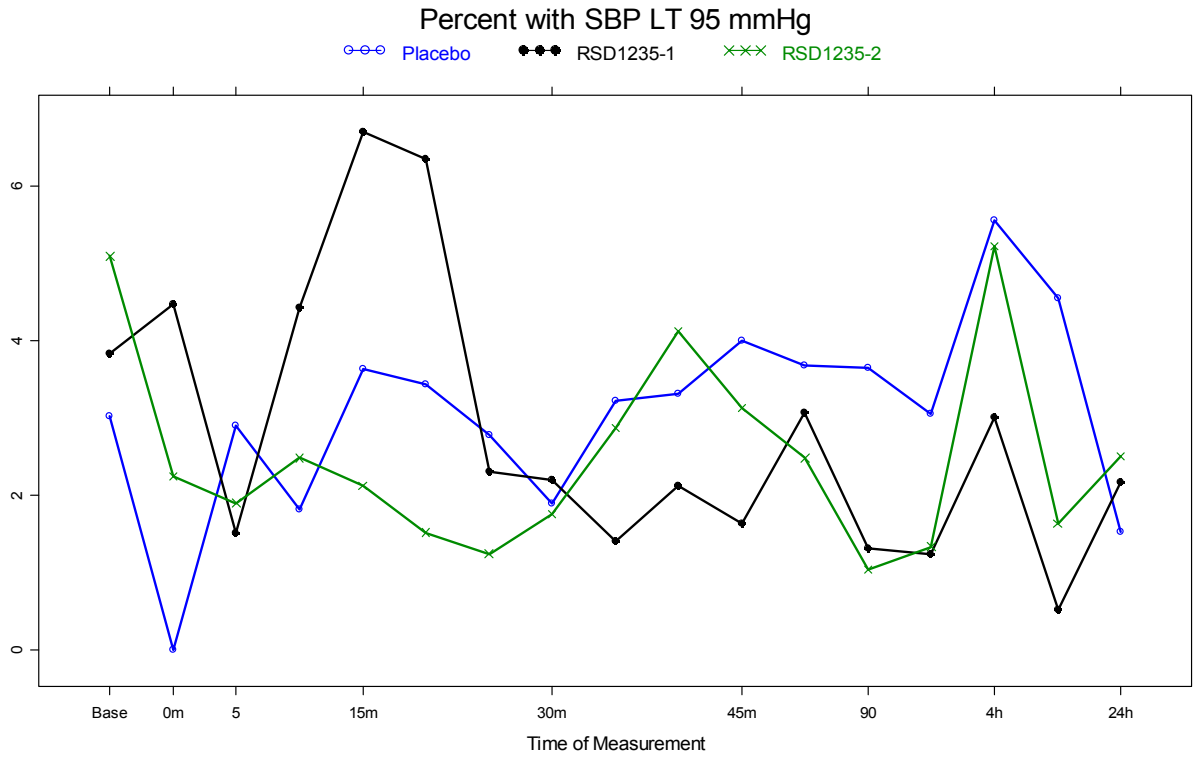
Considering a change from baseline, some of the subjects who received one dose only did also experience an increase in diastolic blood pressure. This increase is likely due to Vernakalant not the status of AFB/AFL because it was observed in subjects who did not convert on the first dose before they received the second dose at the time-point of 35 minutes post first infusion.

Figure 13. Percent of Subjects with SBP Greater than 160 mmHg by Time Point for Subjects in All Studies



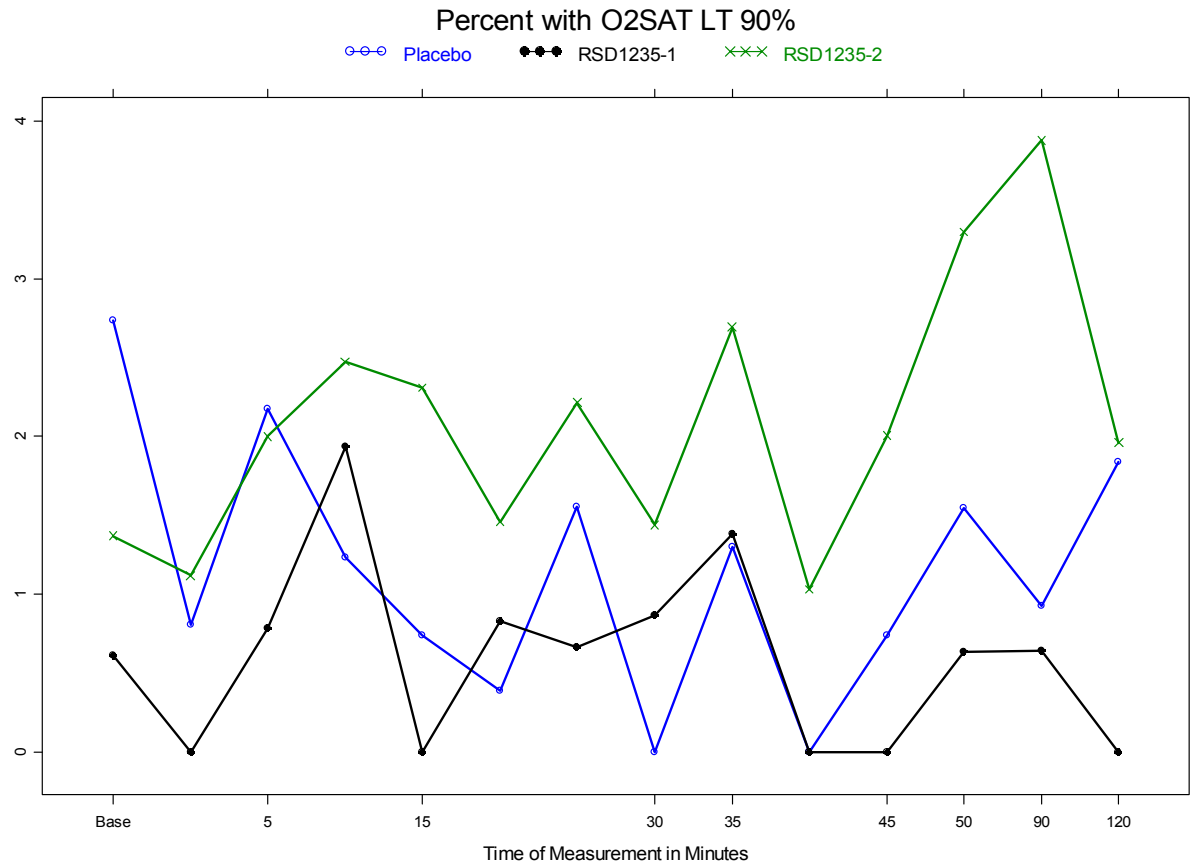
The number of subjects with systolic blood pressure greater than 160 mmHg fluctuates from one time-point to another.

Figure 14. Percent of Subjects with SBP Less than 95 mmHg by Time Point for Subjects in All Studies



More subjects from the group who converted on one dose experienced severe hypotension shortly after their infusion. This effect seems to be related to conversion because in subjects who did not convert on one dose, such effect was not observed after the first dose, but was observed, to a lesser extent, after the second dose (time-point of 35 minutes).

Figure 15. Percent of Subjects with Oxygen Saturation Level Less than 90% by Time Point for Subjects in All Studies



This analysis is completed because preclinical data showed that dyspnea was a SAEs, and because the frequency of respiratory events including cough and dyspnea was higher on Vernakalant compared to placebo.

As can be seen from the graph above, the percentage of subjects with oxygen saturation less than 90 decreased from baseline to Time 0 (time of start of study drug infusion) probably due to oxygen supplementation in the clinic.

Even if the numbers are small, the percentage of subjects with oxygen saturation less than 90% increased within 10 minutes of each infusion of Vernakalant including the second infusion in subjects who failed to convert on the first infusion.

At Minute 90, almost twice as many subjects on two doses of Vernakalant compared to placebo had their oxygen saturation in the lowest quartile of the distribution, 19.1% vs. 10% respectively.

Subjects on Vernakalant had their oxygen saturation compromised (<= 90%) more often than subjects on placebo (8.8% vs. 3.9% respectively) with the subjects who received two doses of Vernakalant being more affected (10.2%).

An association between Vernakalant and a decrease in oxygen saturation is observed. Also, more subjects on Vernakalant experienced cough and dyspnea than subjects on placebo. Therefore, the reviewer concludes that Vernakalant affects the respiratory function adversely

7.1.9.3.3 Marked outliers and dropouts for vital sign abnormalities

Hypotension and bradycardia were listed as factors or contributing factors of the discontinuation of Vernakalant (vs. none on placebo) in 9 (1.2%) and 5 (0.6%) cases, respectively.

7.1.9.4 Additional analyses and explorations

7.1.10 Electrocardiograms (ECGs)

In this section ECG, Holter and telemetry data will be discussed.

7.1.10.1 Overview of ECG testing in the development program, including brief review of preclinical results

There was no formal QT study conducted, but all studies collected ECG data with the purpose of assessing the effect of Vernakalant on QT and other cardiac parameters. ECGs were recorded at screening, baseline; every 5 minutes from time of infusion to 50 minutes post infusion; at 90 minutes post infusion; at Hours 2, 4, 8 and 24 post infusion; and at the seven-day follow-up. Three baseline ECG tracings recorded one minute apart were obtained, but at other time points, only one ECG was recorded. Holter monitoring up to 24 hours post first dose or discharge was also conducted. ECGs and Holter recordings were reviewed, and ECG intervals were calculated by a central reading lab. Panic alerts were reviewed by both the DSMB and the central cardiologist. Cardiac safety was also assessed concurrently using telemetry up to 2 hours post dosing.

7.1.10.2 Selection of studies and analyses for overall drug-control comparisons

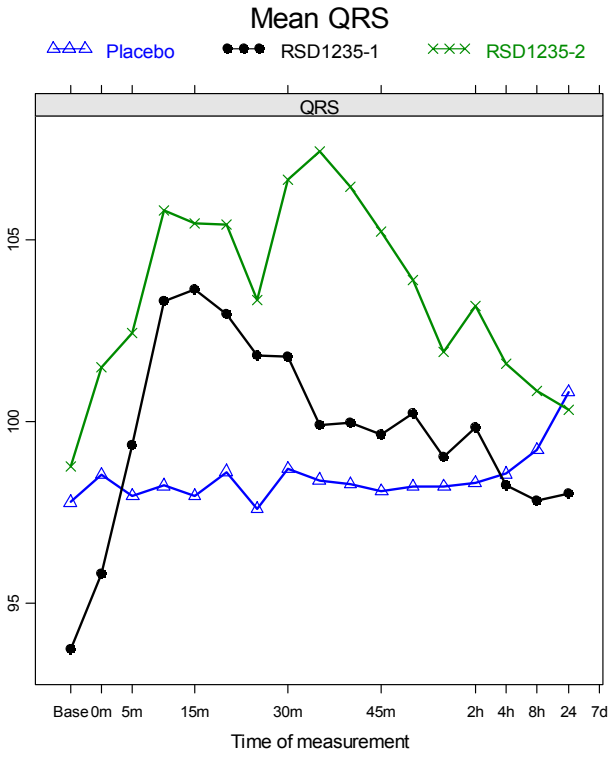
Data on QT was collected in ACTI, ACTIII, ACTIV, ACTII, CRAFT and Scene 2 with a total of 728 subjects on Vernakalant and 333 subjects on placebo. The effect of the study drug on QT interval was summarized using two populations: 1) all subjects exposed in the development program, and 2) subjects in whom Vernakalant was assessed for efficacy (short-term AF).

7.1.10.3 Standard analyses and explorations of ECG data

Unscheduled measurements of ECGs are not included in analyses because data were not submitted per agreement with the Division.

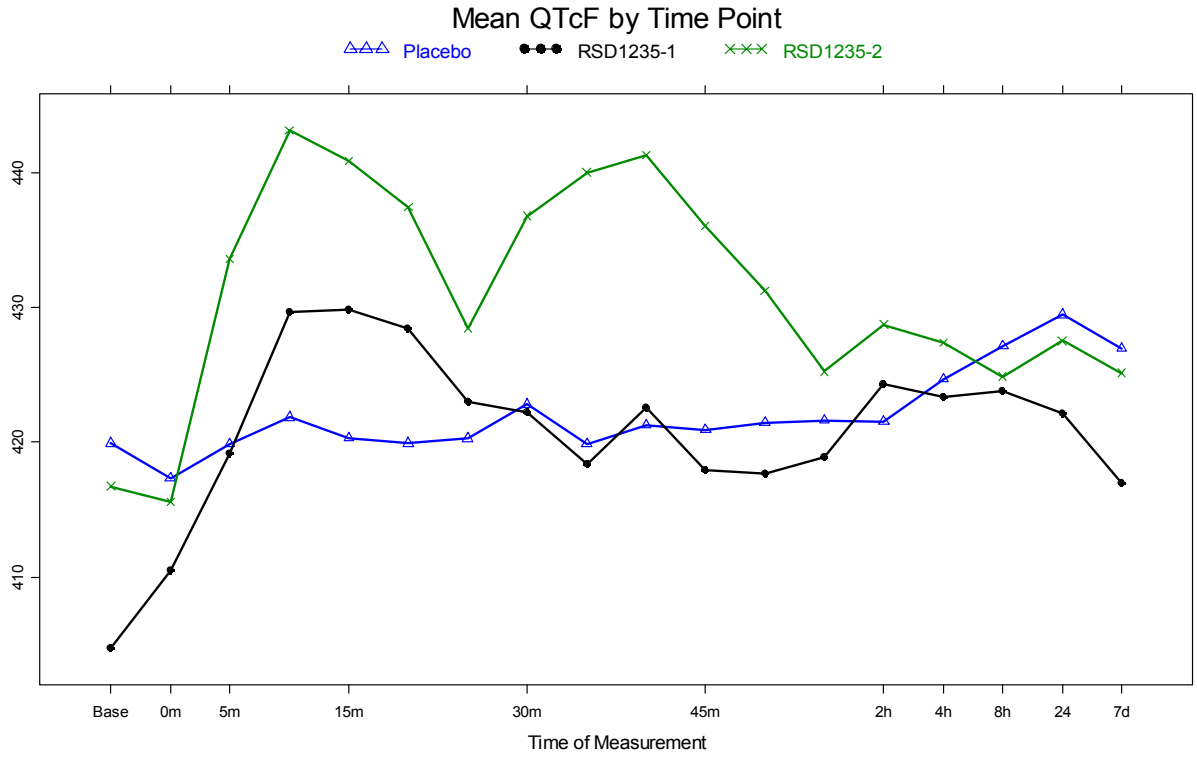
7.1.10.3.1 Analyses focused on measures of central tendency

Figure 16. Mean QRS by Treatment Group at Different Time Points from ACTI, ACTIII, CRAFT and Scene2



Subjects who converted on one dose started with a much shorter QRS interval or higher cardiac beats per minute as was shown by summary of pulse rate. Mean QRS interval increased immediately after infusion and peaked between 10 and 15 minutes post infusion. This occurred in subjects who received one dose, and in subjects who received two doses after each infusion. The fact that QRS was prolonged in subjects who did not convert after the first dose indicates that some of the QRS prolongation effect is due to the effect of Vernakalant. The effect of QRS prolongation in subjects who converted on the first dose and in subjects who received the second dose (some of whom converted) is more pronounced probably because of the additive effect of returning to SR.

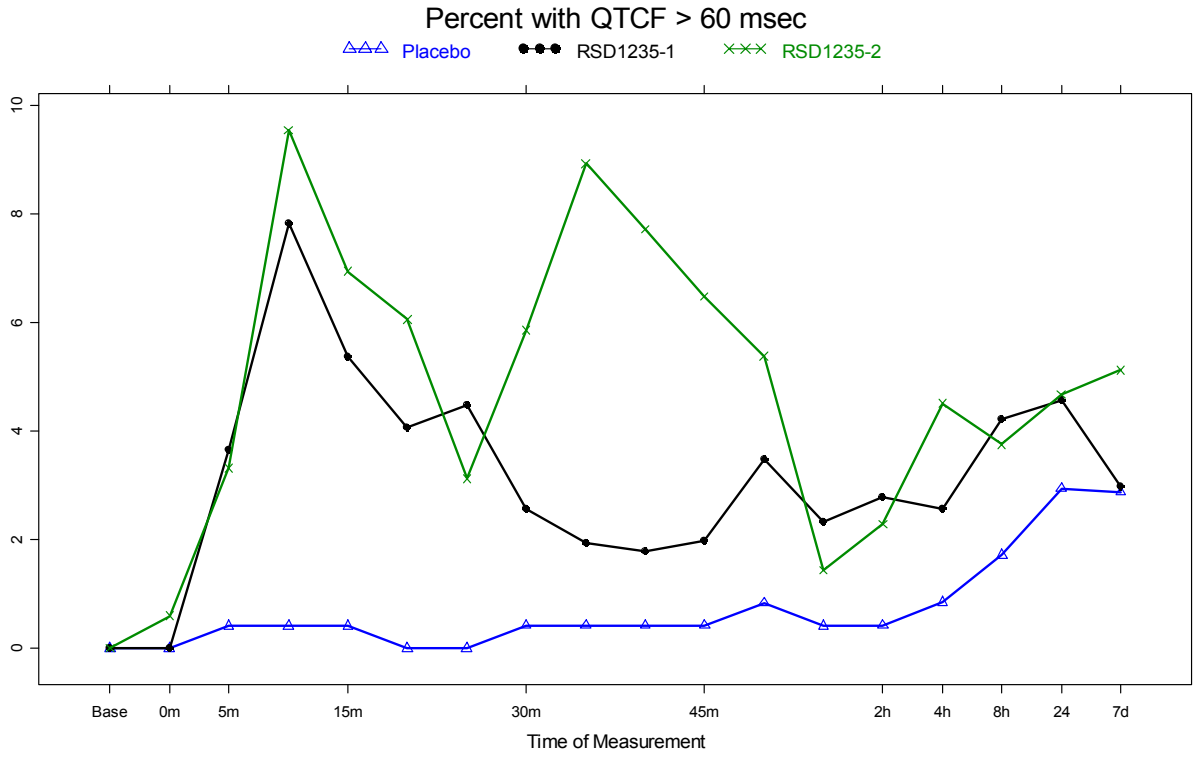
Figure 17. Mean QTcF by Treatment Group at Different Time Points from ACTI, ACTIII, CRAFT and Scene 2



Mean QTcF on Vernakalant increased immediately after the first infusion even in subjects who failed to convert to SR after one dose, and this prolongation was observed after the second infusion as well. QTcF prolongation peaked around 10 minutes post infusion and started declining afterward without ever going down to baseline mean level, especially in subjects who converted on the first dose. This could be explained by the possibility of other antiarrhythmic intake to maintain SR and/or the difficulty of measuring ECG parameters in the presence of atrial arrhythmia at baseline. Vernakalant appears to prolong QT for an average of 15 to 20 minutes.

7.1.10.3.2 Analyses focused on outliers or shifts from normal to abnormal

Figure 18. Percent with a Change from Baseline in QTcF Greater than 60 msec in Subjects from ACTI, ACTIII, CRAFT and Scene 2 by Time Point

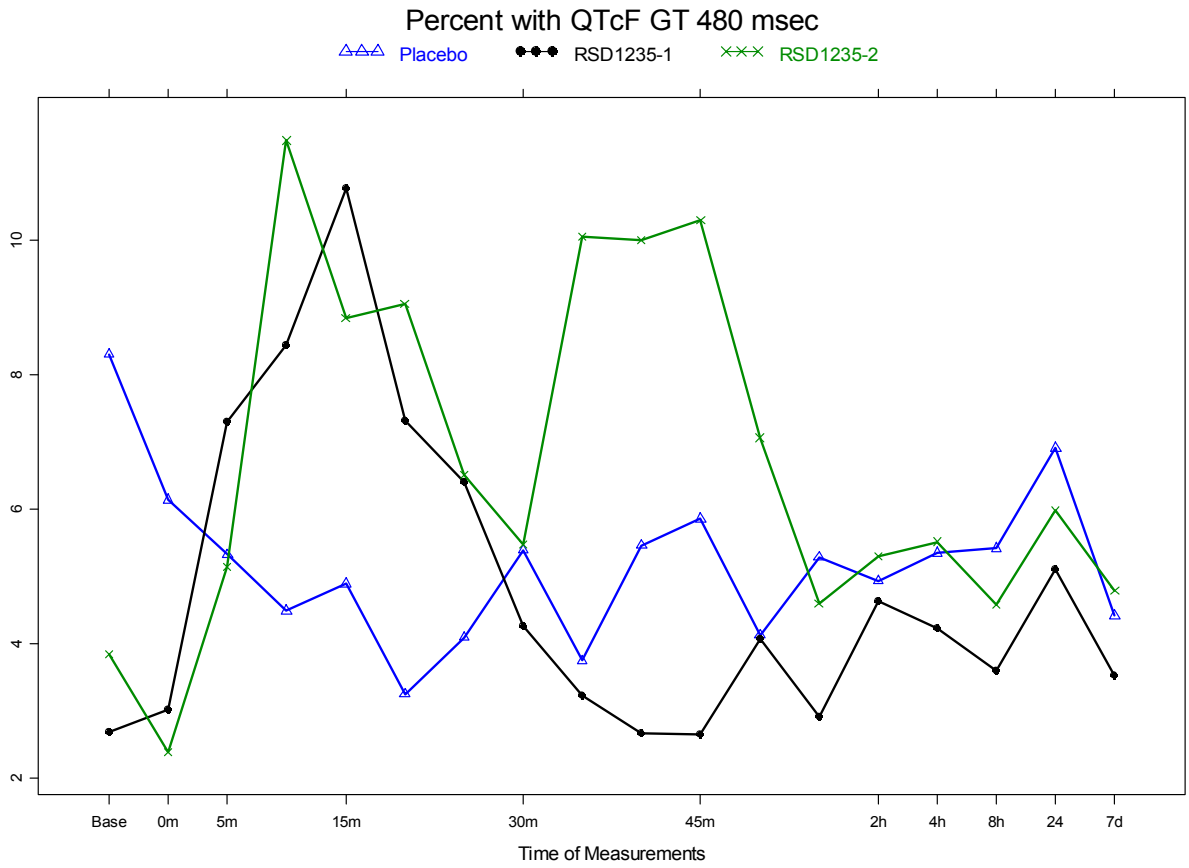


The percentage of subjects with a change from baseline of 60 msec or greater increased immediately after the first dose in both groups of subjects, those who converted and those who did not, and after the second dose in the group who failed to convert on the first dose. This number decreased within 20 minutes of study drug infusion.

The percentage with a change greater than 60 msec started increasing, but to a lesser extent, in all treatment arms after two hours of study drug, and this is probably due to other anti-arrhythmic medications with similar effect on QT that were permitted per protocol two hours after infusion.

Similar distribution of change from baseline in subjects with short-term AFB was observed.

Figure 19. Percent with QTcF Increase Greater than 480 msec in Subjects from ACTI, ACTIII, CRAFT and Scene 2 by Time Point

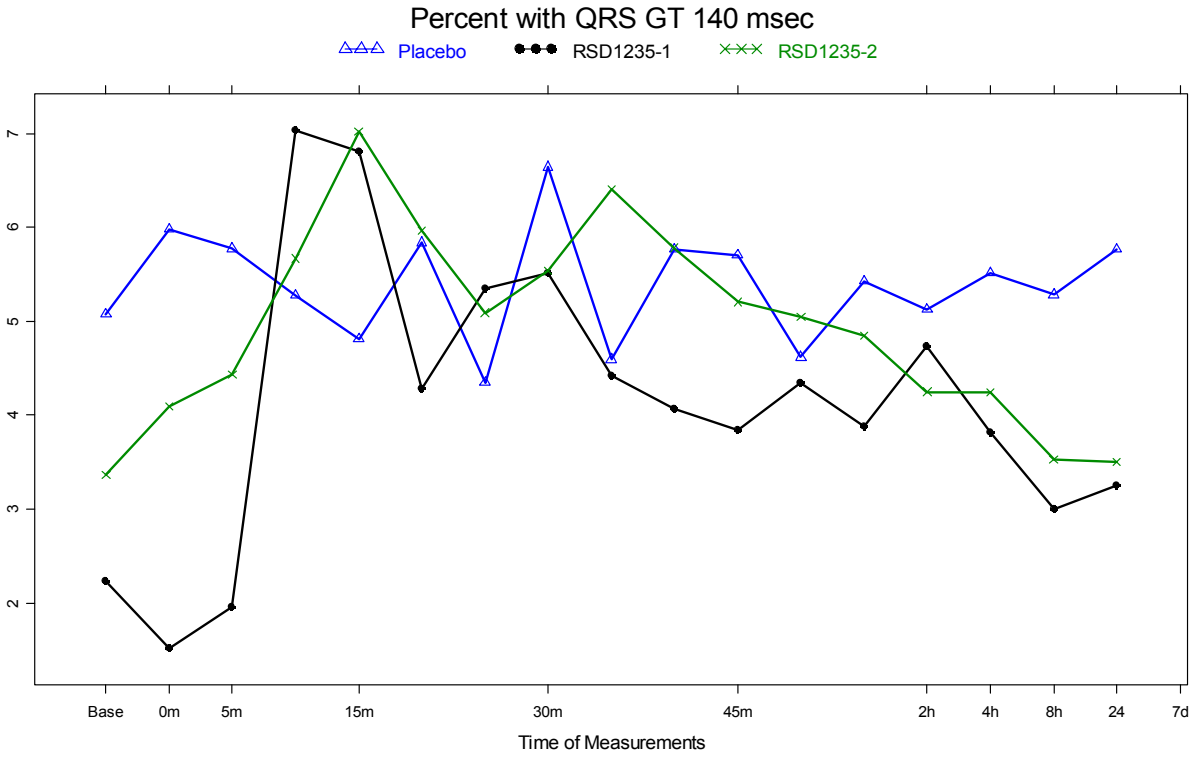


The percentage of subjects with QTcF values greater than 480 msec increased within 10 minutes of the first infusion of Vernakalant in both subjects who converted after the first dose and those who did not, and after the second infusion as well.

In conclusion, the reviewer believes the observed association between QT and Vernakalant is causal because QT prolongation was observed consistently across different analyses, and in both subjects who converted and those who didn't, and because Vernakalant is expected to prolong QT.

In conclusion, the overall effect of Vernakalant on QT is immediate and short-lived with QT values and the percentage of subjects with prolonged QT going back toward baseline values within less than an hour post-infusion. The effect on QT of the second dose does not seem to be additive because all analyses showed that the effect on the second dose is similar in magnitude and duration to that on the first dose.

Figure 20. Percent with QRS Greater than 140 msec in Subjects from ACTI, ACTIII, CRAFT and Scene 2 by Time Point



As can be seen from the figure above, the percentage of subjects with QRS > 140 msec tripled in subjects who converted to SR on one dose, and doubled after each dose in subjects who did not convert on the first dose (compared to baseline) while it did not change on placebo. This prolongation seems to be, at least partly, independent of the conversion status because the same thing was observed in subjects who did not convert on the first dose before they received the second dose.

7.1.10.3.3 Marked outliers and dropouts for ECG abnormalities

ECG abnormalities that led to or contributed to discontinuation from Vernakalant include two cases each bundle branch block, PVCs and prolonged QRS; one case each wide complex tachycardia, third degree AV block and prolonged uncorrected QT . One case of prolonged uncorrected QT led to discontinuation from placebo.

7.1.10.4 Additional analyses and explorations

Datasets for ventricular arrhythmia were provided for ACTI, ACTIII and Scene2. The summary tables below are derived by the reviewer. Because many subjects with AFB or AFL received other anti-Arrhythmic therapies concomitantly, separate analyses were conducted by their use.

Only five cases of ventricular arrhythmia were reported as adverse events and three of these occurred on placebo. The only ventricular arrhythmia event (ventricular tachycardia) that was observed within two hours of study drug infusion occurred on Vernakalant.

The findings portrayed below, concern ventricular arrhythmia from all sources including ECG and Holter monitoring.

Table 27. Ventricular Arrhythmia from All Sources in Subjects from ACTI, ACTIII within Two Hours

	Placebo N=159	One dose N=99	Two Doses N=132	RSD123 Any Dose N=231
Any ventricular arrhythmia	19 (11.9%)	18 (18.2%)	23 (17.4%)	41 (17.7%)
V-Tach	4 (2.5%)	6 (6.1%)	4 (3%)	10 (4.3%)
Non-sustained V-Tach	10 (6.3%)	4 (4%)	10 (7.6%)	14 (6.1%)
Sustained monomorphic V-Tach	0 (0%)	0 (0%)	1 (0.8%)	1 (0.4%)
Tachycardia	0 (0%)	1 (1%)	0 (0%)	1 (0.4%)
Ventricular bigeminy	0 (0%)	1 (1%)	0 (0%)	1 (0.4%)
Ventricular fibrillation	0 (0%)	0 (0%)	1 (0.8%)	1 (0.4%)
Ventricular flutter	0 (0%)	0 (0%)	1 (0.8%)	1 (0.4%)
Ventricular rhythm >= 5 beats	1 (0.6%)	0 (0%)	1 (0.8%)	1 (0.4%)

Non-sustained V-Tach includes unsustained monomorphic V-Tach, unsustained polymorphic V-Tach and unsustained V-Tach as categorized by the Sponsor.

Within two hours of infusion, subjects who received Vernakalant experienced a slight excess in ventricular events compared to placebo. The numbers are small, but the rate of V-Tach almost doubled on Vernakalant compared to placebo.

Table 28. Ventricular Arrhythmia from All Sources in Subjects from ACTI, ACTIII Occurring between Two and 24 Hours

	Placebo N=159	One dose N=99	Two Doses N=132	RSD123 Any Dose N=231
Any ventricular event	25 (15.7%)	12 (12.1%)	21 (15.9%)	33 (14.3%)
Unsustained V-Tach	13 (8.2%)	8 (8.1%)	11 (8.3%)	19 (8.2%)
V-Tach*	7 (4.4%)	2 (2%)	6 (4.5%)	8 (3.5%)
Ventricular rhythm >= 5 beats	2 (1.3%)	1 (1%)	3 (2.3%)	4 (1.7%)
Ventricular extrasystoles	0 (0%)	1 (1%)	1 (0.8%)	2 (0.9%)
Alert - idioventricular rhythm	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Idioventricular rhythm	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Ventricular bigeminy	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)

V-Tach reported as such in the VENTRICULAR ARRHYTHMIA dataset.
Unsustained V-Tach includes unsustained monomorphic and polymorphic V-Tach.

The rates in the above table are similar in both treatment arms because after two hours, other anti-arrhythmic drugs and DC cardioversion were permitted per protocol.

Table 29. Ventricular Arrhythmia from All Sources Occurring Within 24 Hours in ACTI/ACTIII Subjects with Short-Term AFB Who did not receive other Anti-arrhythmic Therapy

	Placebo N=159	One dose N=99	Two Doses N=132	RSD123 Any Dose N=231
Any ventricular event	15 (9.4%)	13 (13.1%)	17 (12.9%)	30 (13%)
All non-sustained V-Tach	7 (4.4%)	6 (6.1%)	6 (4.5%)	12 (5.2%)
V-Tach	5 (3.1%)	5 (5.1%)	6 (4.5%)	11 (4.8%)
Ventricular rhythm >= 5 beats	2 (1.3%)	1 (1%)	2 (1.5%)	3 (1.3%)
Sustained monomorphic V-Tach	0 (0%)	0 (0%)	1 (0.8%)	1 (0.4%)
Ventricular extrasystoles	0 (0%)	1 (1%)	0 (0%)	1 (0.4%)

	Placebo N=159	One dose N=99	Two Doses N=132	RSD123 Any Dose N=231
Ventricular fibrillation	0 (0%)	0 (0%)	1 (0.8%)	1 (0.4%)
Ventricular flutter	0 (0%)	0 (0%)	1 (0.8%)	1 (0.4%)
Ventricular bigeminy	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)

In conclusion, the ventricular events that were of concern to investigators and were reported as adverse events were very few and only one case (ventricular tachycardia) occurred within two hours of infusion of Vernakalant.

In the context of the two ventricular fibrillations that occurred within minutes of the completion of Vernakalant, and the small excess of ventricular events within two hours of infusion of Vernakalant, even if the numbers are very small, the findings of ventricular tachycardia are suggestive of a causal relationship with Vernakalant.

The question to be raised is whether this is worse than been treated by one of the other antiarrhythmic drugs used in practice or DC cardioversion.

The following Alert and Panic Criteria were summarized:

- Any polymorphic VT
- Sustained VT
- Non-sustained V-Tach
- Premature ventricular beats
- 3d degree AV block
- Mobitz type I or mobitz type II 2d degree AV block
- Premature junctional beats
- Premature atrial beats
- Paced rhythm
- Sinus arrhythmia

Table 30. Panic Alerts Occurring up to Two Hours Post Study Drug Infusion in Subjects with Short-Term AFB in ACTI/ACTTIII

	Placebo N = 159	Vernakalant-ALL N = 231
Any panic alert	10 (6.3%)	17 (7.4%)
Heart rate < 40 BPM	6 (3.8%)	5 (2.2%)
Ventricular rhythm >= 5 beats	3 (1.9%)	5 (2.2%)
Third degree AV block	0 (0%)	2 (0.9%)
Myocardial ischemia	0 (0%)	1 (0.4%)
New complete LBBB	0 (0%)	1 (0.4%)
New complete RBBB	0 (0%)	1 (0.4%)
QT interval > 500 msec (uncorrected)	1 (0.6%)	1 (0.4%)
Ventricular flutter	0 (0%)	1 (0.4%)

Table 31. Panic Alerts Occurring from Two to 24 Hours Post Study Drug Infusion in Subjects with Short-Term AFB in ACTI/ACTTIII

	Placebo N = 159	Vernakalant-ALL N = 231
Any Panic alert	26 (16.4%)	29 (12.6%)
Heart rate < 40 bpm	12 (7.5%)	11 (4.8%)
QT interval > 500 msec (uncorrected)	6 (3.8%)	7 (3%)
Ventricular rhythm >= 5 beats	5 (3.1%)	6 (2.6%)
Third degree AV block	2 (1.3%)	4 (1.7%)
Myocardial ischemia	0 (0%)	1 (0.4%)
New complete right bundle branch block	1 (0.6%)	0 (0%)

There seem to be no difference in the rate of panic alerts between the treatment arms at any time.

Table 32. V-Tach on Holter Over-read

V-Tach present	Placebo N = 246	Vernakalant-1 N = 185	Vernakalant-2 N = 363	Vernakalant-All N = 548
Subjects with Holter over-read completed	65 (26.42%)	24 (12.97%)	61 (16.8%)	85 (15.51%)
V-Tach present	33 (50.77%)	15 (62.5%)	36 (59.02%)	51 (60%)

Holter over-read was completed on selected subjects from ACTI, ACTIII and ACTIV

Holter over-read was completed in a higher proportion of subjects on placebo compared to Vernakalant. When analyses using subjects in whom Holter over-read was completed it is shown that 10% more subjects on Vernakalant experienced ventricular tachycardia compared to placebo. These data could not be interpreted with confidence because of the biases introduced by the factors that led to Holters over-read.

7.1.11 Immunogenicity

7.1.12 Human Carcinogenicity

7.1.13 Special Safety Studies

The only study that was conducted to assess safety solely is ACTIV which is still ongoing, a Phase 3, multi-center, open-label safety study in subjects with AF. This has been conducted to increase the number of subjects exposed to the study drug because the Division expressed concern regarding the small number of subjects exposed. This study has the limitation of being uncontrolled.

Data from this study are included in all analyses that summarize safety from all studies.

7.1.14 Withdrawal Phenomena and/or Abuse Potential

NA

7.1.15 Human Reproduction and Pregnancy Data

No studies were conducted in pregnant women.

7.1.16 Assessment of Effect on Growth

No studies were conducted in pediatric subjects.

7.1.17 Overdose Experience

No cases of overdose were reported.

7.1.18 Postmarketing Experience

Vernakalant is not marketed anywhere.

7.2 Adequacy of Patient Exposure and Safety Assessments

The concern with safety assessment in the Vernakalant program is the small number of subjects exposed to the study drug. Less than a 1000 subjects were exposed to Vernakalant. This is of concern because Vernakalant tends to affect cardiac repolarization and there were two cases of ventricular fibrillation on Vernakalant, one of which was fatal.

Most of the subjects studied were adequately tested for the effect of Vernakalant on the heart using telemetry monitoring, ECG recordings and Holter monitoring.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The populations analyzed for safety are in summarized in Table 2. Clinical Studies Conducted in the Intravenous Vernakalant Program, page 17.

7.2.1.1 Study type and design/patient enumeration

7.2.1.2 Demographics

Table 33. Demographics of Subjects from All Trials by Dose

Parameter	PLACEBO N = 339	Vernakalant One dose N = 258	Vernakalant Two doses N = 520	Vernakalant-All N = 778
Gender				
Female	108 (31.86%)	71 (27.52%)	169 (32.5%)	240 (30.85%)
Male	231 (68.14%)	187 (72.48%)	351 (67.5%)	538 (69.15%)
Age (years)				
Mean	62.25	57.67	63.38	61.7
STD	12.76	15.91	13.43	14.03
Min	20.00	19.00	21.00	19
Median	63.00	59.50	65.00	63.0
Max	90.00	90.00	94.00	94
Age group #1				
< 65 yrs	181 (53.39%)	155 (60.08%)	257 (49.42%)	412 (52.96%)
>= 65 yrs	158 (46.61%)	103 (39.92%)	263 (50.58%)	366 (47.04%)
Age group #2				
< 75 yrs	283 (83.48%)	223 (86.43%)	399 (76.73%)	622 (79.95%)
>= 75 yrs	56 (16.52%)	35 (13.57%)	121 (23.27%)	156 (20.05%)
Race				
White	330 (97.35%)	245 (94.96%)	498 (95.77%)	743 (95.5%)

Parameter	PLACEBO N = 339	Vernakalant One dose N = 258	Vernakalant Two doses N = 520	Vernakalant-All N = 778
Non-white	9 (2.65%)	13 (5.04%)	22 (4.23%)	35 (4.5%)
Baseline diagnosis				
AF	304 (89.68%)	228 (88.37%)	439 (84.42%)	667 (85.73%)
AFL	28 (8.26%)	5 (1.94%)	53 (10.19%)	58 (7.46%)
Unknown	1 (0.29%)	2 (0.78%)	1 (0.19%)	3 (0.39%)
AF/AFL duration				
3 hours - 7 days	247 (72.86%)	212 (82.17%)	334 (64.23%)	546 (70.18%)
8 days - 45 days	86 (25.37%)	23 (8.91%)	158 (30.38%)	181 (23.26%)
Missing	6 (1.77%)	23 (8.91%)	28 (5.38%)	51 (7.01%)

The demographic analyses used an updated dataset that was submitted with the 120-day safety update.
Other baseline characteristic analyses used datasets that were originally submitted.

Table 34. Other Baseline Characteristics from All Trials by Dose

Parameter	Placebo	Vernakalant one dose	Vernakalant two doses	Vernakalant All doses
Pulse N	**315**	**226**	**476**	**702**
Mean	105.79	110.89	98.72	102.64
SD	26.29	25.89	26.21	26.7
Median	100.67	106.67	93.17	97.33
Min	54	58	49	49
Max	179	203	191	203
QRS N	**315**	**224**	**476**	**700**
Mean	97.4	94.45	98.7	97.34
SD	18.48	14.32	17.38	16.57
Median	93.67	92.33	96	95
Min	74	67	67	67
Max	218	167	202	202
QTcF N	**296**	**217**	**451**	668
Mean	417.71	404.61	414.72	411.43
SD	30.84	27.02	28.39	28.33
Median	413.5	401.67	412.67	410.33
Min	350.33	352.67	276.67	276.67
Max	536.33	505.33	514.67	514.67
SBP N	**330**	**235**	**491**	726
Mean	123.81	121.93	125.8	124.55
SD	15.48	14.57	16.17	15.76
Median	123.5	120.67	125.67	124
Min	93	91	90	90
Max	166	171	175	175
DPB N	**330**	**235**	**491**	726
Mean	77.25	75.08	76.21	75.84
SD	11	10.14	10.93	10.69
Median	77.83	76.67	77	77
Min	47	39	7	7
Max	105	96	102	102

Analyses of pulse were done using from ECG data
Denominators are different by test depending because data were not collected in all subjects.

Subject who received one dose were younger than subjects who received two doses and those who received placebo; they also had higher pulse rate and shorter QRS interval, shorter QTcF interval, and slightly lower blood pressure than the other two groups, at baseline. These differences were maintained when subjects with short-term AFB only were considered. When both doses were combined, some of the differences either disappeared or were reduced. This can only be explained by the responsiveness characteristics that determine who happen to be included in the one dose group.

7.2.1.3 Extent of exposure (dose/duration)

Table 35. Extent of Exposure to Vernakalant in all Studies (from Sponsor's Report)

Summary of exposure (mg/kg)	Vernakalant
Exposure by number of doses	**N = 778**
One dose	258 (23.10%)
Two doses	520 (46.55%)
Distribution of exposure	
N	778
Mean (mg/kg)	4.2
Std	1.18
Min	0.1
Median	5.0
Max	5.0
Categorized exposure (mg/kg)	
0.1	1(0.2%)
0.25	1(0.2%)
0.5	5(0.8%)
1.0	5(0.8%)
1.5	17(2.7%)
2.0	11(1.7%)
2.3	10(1.6%)
3.0	172(27.1%)
4.0	4(0.6%)
4.6	9(1.4%)
5.0	392(61.7%)

The 8 subjects who received 240 mg in study 04-0-195 are excluded from this table.

Table 36. Extent of Exposure to Vernakalant in All Studies (from Sponsor's Report)

	Placebo	Vernakalant
Randomized	364	833
Exposed to study drug	339	778
Dose #1 completed		
Yes	338 (99.7%)	760 (97.7%)
No	1 (0.3%)	18 (2.3%)
Dose #2 started		
Yes	327 (96.5%)	520 (66.8%)
No	12 (3.5%)	258 (33.2%)
Dose #2 completed		
Yes	326 (99.7%)	512 (98.5%)
No	1 (0.3%)	8 (1.5%)
In Controlled studies		
Dose #1 completed		

	Placebo	Vernakalant
Yes	280(99.6%)	418(97.2%)
No	1(0.4%)	12(2.8%)
Dose #2 started		
Yes	277(98.6%)	304(70.7%)
No	4(1.4%)	126(29.3%)
Dose #2 completed		
Yes	276(99.6%)	299(98.4%)
No	1(0.4%)	5(1.6%)

There were more discontinuations from Vernakalant than from placebo. There were more discontinuations from the first dose than from the second dose.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The only other data available concern an oral formulation of Vernakalant that was given repeatedly.

7.2.2.1 Other studies

Table 37. Clinical Studies Conducted in the Oral Formulation Owned by Another Sponsor

Study #	Subjects	Placebo N	Vernakalant N
MB (IND)	Healthy volunteers	0	8
SR-1005 Phase II (IND)	AF	73	146
Drug interaction with metoprolol (NIND)	Healthy volunteers	0	36
Repeat dosing	Healthy volunteers	10	45
PK (NIND)	Renal impairment		24
Regional absorption (NIND)	Healthy volunteers		12

The findings of SR-1005 per an annual report, provided by the Sponsor, of the oral formulation were summarized to provide comprehensive safety review of Vernakalant.

Only a brief summary of oral Vernakalant safety in study SR-1005 is described in this review because the formulation given is different (oral and repeat dose).

The oral formulation program is owned by a different Sponsor, and Astellas does not have access to the data in that program. . Therefore, the few summary tables provided in this review from the oral formulation are cut and pasted from this annual report.

In the oral program, adverse events that might be relevant to the program under review include one case of fatal ventricular fibrillation that occurred 4 days after initiation of study drug, and two cases of vertebro-basilar insufficiency.

7.2.2.2 Postmarketing experience

NA

7.2.3 Adequacy of Overall Clinical Experience

The overall exposure to Vernakalant is less than a 1000 subjects. For adverse events that are rare, the extent of exposure is not adequate. Additionally, only few subjects with structural heart

disease, especially recent MI and CHF, were included. This class of drugs can cause serious arrhythmic events and an extent of exposure of less than 1000 subjects is not enough. Also, whether Vernakalant would have the same effect on respiration (dyspnea) and CNS (seizures), as it did in animals at very high doses, cannot be concluded from this program.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Per the toxicology reviewer, all pre-clinical testing was completed in an adequate manner.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of study subjects were completed while subjects were in a clinical research facility. Monitoring of vital signs and ECG parameters, and eliciting of adverse events were completed adequately.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

To assess the effect of the study drug on cardiac safety, extensive ECG monitoring during and after the study drug infusion, and Holter monitoring for 24 hours post infusion were conducted.

In the context of the fatality that resulted from ventricular fibrillation in one subject, the other ventricular fibrillation that was successfully defibrillated in another subject, the reviewer recommends post-marketing surveillance of serious cardiac events.

7.2.8 Assessment of Quality and Completeness of Data

The overall data submitted were complete and well organized. The reviewer worked very closely with the Sponsor and requested additional analysis datasets that were provided as an aid for the review. The reviewer did not rely on the Sponsor's reported summaries and tabulations, but generated her own summaries.

7.2.9 Additional Submissions, Including Safety Update

The reviewer conducted her own safety analyses and generated summaries, graphs and tabulations that included the updated safety.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Only selected adverse events are discussed here. The two cases of ventricular fibrillation one of which was fatal are very likely related to the study drug. In the context of the effect of Vernakalant on myocardial repolarization, the risk of similar events, if and when Vernakalant is approved, is probable. The data available do not provide enough power to accurately estimate the risk of ventricular fibrillation, nor do they represent the population at high risk of AFB for all studies excluded subjects with recent myocardial infarction and advanced stage CHF. Ventricular tachycardia, even if the numbers are very small, is also potentially related to the study drug.

Adverse event that are related to the study drug with a level of certainty include bradycardia, hypotension, AV block and pruritus. Adverse events that are likely related to the study drug include cough and dyspnea.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The incidence of adverse events, and the effect of Vernakalant on ECG intervals and on vital signs were explored using mostly two different populations. This pooling and splitting were done with the following reasoning:

-to increase the power for the purpose of improving the precision of rare cardiac adverse events that are suspected to be related to Vernakalant;

-to enrich the population and control for potential covariates such as those that are specific to patients with short-term AF;

-to assess the safety of Vernakalant in the population in whom it primary efficacy was evaluated.

The populations most commonly used are two. Population number one includes the overall number of subjects from all studies including healthy subjects, and subjects with AFB or AFL. This population totals a little over 1000 subjects and about two thirds were exposed to Vernakalant. Population number two includes only subjects with short-term AFB with a total of almost 400 subjects and about 60% were exposed to Vernakalant.

7.4.1.2 Combining data

Pooling was conducted by combining subjects, without weighing, from studies in different populations to increase the power and better estimate the risk of adverse events.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The study drug was given in one or two doses. Only people who failed to convert to SR received the second dose.

Ventricular fibrillation was observed in two subjects who received two doses of Vernakalant and in no subjects who received a single dose or placebo. Pruritus was observed more commonly on two doses than one.

7.4.2.2 Explorations for time dependency for adverse findings

The extent of time dependency explored in this review includes two intervals: the first covers the two hours post-infusion because pharmacokinetic and pharmacodynamic data showed that most of Vernakalant and its effect dissipated by the end of two hours.

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.3.1 Age

Table 38. Adverse Events Occurring within Two Hours of Study Drug Infusion by Age < 65 and >= 65)

Adverse Events	Placebo < 65 N = 181	Placebo >= 65 N = 158	Vernakalant < 65 N = 412	Vernakalant >=65 N = 366
Sneezing	0 (0%)	0 (0%)	43 (10.44%)	63 (17.21%)
Dysgeusia	6 (3.31%)	2 (1.27%)	113 (27.43%)	50 (13.66%)
Paraesthesia	2 (1.1%)	2 (1.27%)	46 (11.17%)	27 (7.38%)
Hypotension	1 (0.55%)	2 (1.27%)	24 (5.83%)	12 (3.28%)
Dizziness	5 (2.76%)	1 (0.63%)	20 (4.85%)	10 (2.73%)
Paraesthesia oral	0 (0%)	1 (0.63%)	11 (2.67%)	5 (1.37%)
Atrial tachycardia	0 (0%)	0 (0%)	5 (1.21%)	2 (0.55%)
LBBB	0 (0%)	0 (0%)	1 (0.24%)	2 (0.55%)
Dyspnea	0 (0%)	0 (0%)	6 (1.46%)	2 (0.55%)
QRS complex prolonged	0 (0%)	0 (0%)	0 (0%)	2 (0.55%)
Injection site paraesthesia	1 (0.55%)	0 (0%)	7 (1.7%)	2 (0.55%)
Pulmonary edema	0 (0%)	0 (0%)	0 (0%)	2 (0.55%)
Rhinitis	0 (0%)	0 (0%)	0 (0%)	2 (0.55%)
Chest pain	0 (0%)	0 (0%)	3 (0.73%)	1 (0.27%)
Hypoesthesia oral	0 (0%)	0 (0%)	5 (1.21%)	1 (0.27%)
Ventricular extrasystoles	0 (0%)	0 (0%)	3 (0.73%)	1 (0.27%)
Blood pressure diastolic increased	0 (0%)	0 (0%)	3 (0.73%)	0 (0%)
Injection site pain	0 (0%)	0 (0%)	3 (0.73%)	0 (0%)
Palpitations	1 (0.55%)	0 (0%)	4 (0.97%)	0 (0%)
Sinus tachycardia	0 (0%)	0 (0%)	2 (0.49%)	0 (0%)
Syncope vasovagal	0 (0%)	0 (0%)	2 (0.49%)	0 (0%)
Ventricular fibrillation	0 (0%)	0 (0%)	2 (0.49%)	0 (0%)

The two cases of pulmonary edema that were observed within two hours were in elderly subjects. If these were related to Vernakalant, it would be concerning because elderly subjects are more likely to have cardiovascular and respiratory diseases that might make pulmonary edema more life threatening.

The two ventricular fibrillation cases that were observed occurred in younger subjects. However, based on these data, there is no evidence that this subgroup is at a higher risk than the older group with regard to ventricular arrhythmia.

7.4.2.3.2 Gender

Table 39. Adverse Events Occurring within 24 Hours by Sex in At Least 2% on Vernakalant

	Placebo		Vernakalant	
	F 108	M 231	F 240	M 538
Dysgeusia	2 (1.85%)	6 (2.6%)	52 (21.67%)	131 (24.35%)
Paraesthesia	3 (2.78%)	3 (1.3%)	27 (11.25%)	82 (15.24%)
Sneezing	0 (0%)	0 (0%)	49 (20.42%)	76 (14.13%)
Hypotension	5 (4.63%)	7 (3.03%)	10 (4.17%)	36 (6.69%)
Nausea	1 (0.93%)	3 (1.3%)	26 (10.83%)	28 (5.2%)
Vomiting	0 (0%)	1 (0.43%)	10 (4.17%)	3 (0.56%)

	Placebo		Vernakalant	
	F 108	M 231	F 240	M 538
Dizziness	2 (1.85%)	7 (3.03%)	11 (4.58%)	25 (4.65%)
Headache	6 (5.56%)	6 (2.6%)	18 (7.5%)	23 (4.28%)
Atrial fibrillation	6 (5.56%)	12 (5.19%)	11 (4.58%)	23 (4.28%)
Hyperhidrosis	0 (0%)	2 (0.87%)	6 (2.5%)	23 (4.28%)
Pruritus	0 (0%)	0 (0%)	15 (6.25%)	21 (3.9%)
Bradycardia	2 (1.85%)	5 (2.16%)	6 (2.5%)	20 (3.72%)
Atrial tachycardia	0	0	6 (2.5%)	1 (0.19%)
Feeling hot	0 (0%)	2 (0.87%)	9 (3.75%)	17 (3.16%)
Fatigue	1 (0.93%)	5 (2.16%)	8 (3.33%)	17 (3.16%)
Nasal passage irritation	0 (0%)	0 (0%)	3 (1.25%)	15 (2.79%)
Paraesthesia oral	0 (0%)	1 (0.43%)	6 (2.5%)	13 (2.42%)
Cough	1 (0.93%)	3 (1.3%)	22 (9.17%)	12 (2.23%)
AFL	0 (0%)	2 (0.87%)	5 (2.08%)	11 (2.04%)
Sinus bradycardia	1 (0.93%)	4 (1.73%)	5 (2.08%)	9 (1.67%)
Dyspnea	3 (2.78%)	0 (0%)	4 (1.67%)	9 (1.67%)
Injection site paraesthesia	0 (0%)	2 (0.87%)	8 (3.33%)	7 (1.3%)
Procedural site reaction	3 (2.78%)	5 (2.16%)	1 (0.42%)	5 (0.93%)
Diarrhea	3 (2.78%)	0 (0%)	6 (2.5%)	4 (0.74%)
AV block ,first degree	0 (0%)	1 (0.43%)	4 (1.67%)	4 (0.74%)
ECG QT prolonged	2 (1.85%)	0 (0%)	1 (0.42%)	4 (0.74%)
Angina pectoris	3 (2.78%)	1 (0.43%)	0 (0%)	4 (0.74%)
Dry mouth	0 (0%)	0 (0%)	6 (2.5%)	3 (0.56%)
Flushing	2 (1.85%)	2 (0.87%)	3 (1.25%)	3 (0.56%)

Nausea and vomiting, pruritus, cough, atrial tachycardia, sneezing were more commonly observed in women compared to men, and hypotension was slightly more commonly observed in men. These unbalances by sex could be a chance finding.

7.4.2.4 Explorations for drug-disease interactions

7.4.2.4.1 Renal Function

Renal function was assessed in a subgroup of subjects only, and it was determined using an estimated creatinine clearance (mL/min):

Normal: > 80
Mild impairment: 50 – 80
Moderate impairment: 30 – 50
Severe impairment: < 30

Table 40. Adverse Events Occurring within 2 Hours of Study Drug by Renal Function

	Placebo			Vernakalant		
	Normal N=112	Mild N=112	Moderate/Severe N=30	Normal N=189	Mild N=138	Moderate/Severe N=50
Sneezing	0 (0%)	0 (0%)	0 (0%)	39 (20.63%)	39 (28.26%)	9 (18%)
Dysgeusia	5 (4.46%)	2 (1.79%)	0 (0%)	74 (39.15%)	37 (26.81%)	6 (12%)
Nausea	0 (0%)	0 (0%)	0 (0%)	10 (5.29%)	11 (7.97%)	6 (12%)
Dizziness	3 (2.68%)	3 (2.68%)	0 (0%)	11 (5.82%)	6 (4.35%)	5 (10%)
Hypotension	1 (0.89%)	1 (0.89%)	1 (3.33%)	14 (7.41%)	7 (5.07%)	4 (8%)

	Placebo			Vernakalant		
	Normal N=112	Mild N=112	Moderate/Severe N=30	Normal N=189	Mild N=138	Moderate/Severe N=50
Vomiting	0 (0%)	0 (0%)	0 (0%)	2 (1.06%)	2 (1.45%)	2 (4%)
Fatigue	1 (0.89%)	0 (0%)	0 (0%)	3 (1.59%)	6 (4.35%)	1 (2%)
Burning sensation	0 (0%)	0 (0%)	0 (0%)	1 (0.53%)	2 (1.45%)	0 (0%)
Cold sweat	0 (0%)	0 (0%)	0 (0%)	1 (0.53%)	3 (2.17%)	0 (0%)
Injection site reaction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2.17%)	0 (0%)
Lacrimation increased	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2.17%)	0 (0%)
Paraesthesia oral	0 (0%)	0 (0%)	0 (0%)	5 (2.65%)	8 (5.8%)	0 (0%)

There were few subjects with severe renal impairment, a reason why moderate and severe were lumped in one category. Within 2 hours of study drug infusion, nausea and dizziness were more common in subjects with moderate to severe renal dysfunction and these could be a chance finding especially that the denominator of the moderate to sever category is very small. Pharmacokinetic parameters were not studied in subjects with renal impairment. The reviewer cannot determine whether the excess observed in the above adverse events is truly due to an interaction of Vernakalant and the renal function.

7.4.2.4.2 Liver Function

Exploration of the interaction of the study drug with liver function (normal vs. abnormal) was not possible because only a little over half the subjects in the program had their liver function assessed and the number of subjects with abnormal liver function was very small, less than 10% of all subjects tested.

The exploration of the interaction of the study drug with recent MI and CHF, known potential causes of recent AFB, was not possible because these subjects were excluded from the studies.

7.4.2.5 Explorations for drug-drug interactions

7.4.2.5.1 Drug-Drug Interaction with Regard to overall Adverse Events

Table 41. Adverse Events Occurring within 24 Hours of Study Drug by Concomitant Class I and III Anti-arrhythmic Medication Use

	Placebo Class I/III antiarrhythmic use		Vernakalant Class I/III antiarrhythmic use	
	No N = 217	Yes N = 122	No N = 579	Yes N = 199
Dysgeusia	5 (2.3%)	3 (2.46%)	105 (18.13%)	59 (29.65%)
Sneezing	0 (0%)	0 (0%)	66 (11.4%)	40 (20.1%)
Paraesthesia	3 (1.38%)	2 (1.64%)	48 (8.29%)	26 (13.07%)
Nausea	3 (1.38%)	1 (0.82%)	35 (6.04%)	18 (9.05%)
Dizziness	3 (1.38%)	6 (4.92%)	20 (3.45%)	16 (8.04%)
Hypotension	6 (2.76%)	6 (4.92%)	31 (5.35%)	14 (7.04%)
Pruritus	0 (0%)	0 (0%)	14 (2.42%)	13 (6.53%)
Headache	10 (4.61%)	2 (1.64%)	26 (4.49%)	12 (6.03%)
Fatigue	5 (2.3%)	1 (0.82%)	15 (2.59%)	10 (5.03%)
Hyperhidrosis	0 (0%)	2 (1.64%)	18 (3.11%)	10 (5.03%)
Feeling hot	1 (0.46%)	1 (0.82%)	14 (2.42%)	9 (4.52%)
Nasal passage irritation	0 (0%)	0 (0%)	7 (1.21%)	8 (4.02%)

	Placebo Class I/III antiarrhythmic use		Vernakalant Class I/III antiarrhythmic use	
	No N = 217	Yes N = 122	No N = 579	Yes N = 199
Paraesthesia oral	1 (0.46%)	0 (0%)	9 (1.55%)	7 (3.52%)
Sinus bradycardia	3 (1.38%)	2 (1.64%)	5 (0.86%)	7 (3.52%)
Hypoesthesia	0 (0%)	0 (0%)	4 (0.69%)	5 (2.51%)
Asthenia	0 (0%)	1 (0.82%)	0 (0%)	4 (2.01%)
Dry mouth	0 (0%)	0 (0%)	4 (0.69%)	4 (2.01%)
ECG QT prolonged	1 (0.46%)	1 (0.82%)	1 (0.17%)	4 (2.01%)
Hot flush	0 (0%)	1 (0.82%)	1 (0.17%)	4 (2.01%)
Injection site paraesthesia	2 (0.92%)	0 (0%)	5 (0.86%)	4 (2.01%)
Eye irritation	0 (0%)	0 (0%)	0 (0%)	3 (1.51%)
Hypoesthesia oral	0 (0%)	0 (0%)	4 (0.69%)	3 (1.51%)
Supraventricular extrasystoles	2 (0.92%)	0 (0%)	2 (0.35%)	3 (1.51%)

All of the adverse events summarized above were observed more frequently in subjects on concomitant Class I and III anti-arrhythmic drug use.

7.4.3 Causality Determination

The adverse events that are likely to be causally related to Vernakalant are believed to be so because of at least one of the following arguments: they are supported by the mechanism of action of Vernakalant, they occurred within minutes of start of infusion, their rate decreased and the imbalance between study groups disappeared once the study drug has, supposedly, cleared from the body.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

8.2 Drug-Drug Interactions

8.3 Special Populations

The rate of adverse events was compared by age categories and except for sneezing, there were no differences between the two age groups with regard to adverse events that occurred within 2 hours of study drug infusion.

Renal function was not assessed in almost half (43%) of the subjects, and the subjects with severely compromised renal function was small. More data are needed to be able to adequately assess the degree of severe renal impairment on the effect of Vernakalant.

It is not known whether Vernakalant is safe in subjects with compromised liver function because only 35 of the subjects who experienced an adverse event in the Vernakalant program were determined to have abnormal liver function and this number is too small to conduct any meaningful comparisons between the treatment arms.

Vernakalant was not investigated in pregnant or lactating women.

8.4 Pediatrics

Per the Minutes, the Division agreed to grant a deferral if it were feasible for a trial to be conducted in a pediatric population, or a waiver if it were not possible for such trial to be conducted.

8.5 Advisory Committee Meeting

8.6 Literature Review

8.7 Postmarketing Risk Management Plan

See 9.3.1Risk Management Activity, page 70.

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

Vernakalant was shown to be very effective in converting short-term (> 3 hours and <= 7 days) AFB to SR for at least one minute. The subjects who converted on the first dose were younger and had a baseline heart rate relatively higher than the subjects who did not convert on the first dose. Conversion on the second dose was less than half that on the first dose, and the two ventricular fibrillation cases occurred on two doses; therefore, challenging the benefit to risk profile of a second dose.

Both pivotal studies were not designed to show whether SR would be maintained beyond the one-minute primary time-point. . . Analyses at follow-up time points showed that the proportions of subjects who were in SR were similar in both the placebo and Vernakalant arms. . However, it is not known whether some subjects reverted to AFB and were treated with another anti-arrhythmic drug that could explain why they were in SR at follow-up time-points. Indirect analyses, such as the rate of DC cardioversion in subjects who received Vernakalant and exposure to anti-arrhythmic drugs were used to assess the maintenance of SR beyond one minute. Per these analyses, it appears that conversion to SR was maintained beyond one minute, especially in subjects who converted to SR on the first dose.

9.2 Recommendation on Regulatory Action

The reviewer considers supporting approval of Vernakalant for short-term AFB in one of two ways:

3. in a single dose formulation for a population similar to that studied in the program (subjects with no structural or obstructive heart disease and subjects with no advanced CHF). The rational for this proposal rests on the benefit to risk profile that it is influenced by the ventricular arrhythmia fatality along with the observed diminished responsiveness to the second dose compared to the responsiveness on one dose. The reviewer understands that there is the possibility that the fatality was precipitated by the subject's aortic stenosis, but there are not enough data in the program that lend support to this hypothesis.

4. or in its proposed two-dose formulation for a population similar to that studied in the program with a contraindication in subjects with recent MI, advanced CHF and obstructive heart disease, with commitment to a post-marketing study in a population representative of the general short-term AFB population including recent MI and CHF.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Because of the serious arrhythmias observed on Vernakalant, this drug should be given in highly specialized hospital settings only, and subjects must closely monitored for at least one hour after one dose or 90 minutes after the first infusion if they receive two doses.

9.3.2 Required Phase 4 Commitments

If Vernakalant is to be approved as a two-dose regimen, as proposed, the Sponsor must conduct a post-marketing study including subjects with conditions that are known to induce AFB including subjects with recent MI and subjects with advanced CHF.

A post-approval surveillance program should be established to detect SAEs, especially cardiac events, and to determine whether the respiratory and CNS preclinical findings are relevant to humans.

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

9.5 Comments to Applicant

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Pivotal Studies ACTI and ACTIII

ACTI

"A Phase 3 Prospective, Randomized, Double-Blind, Placebo-Controlled, Multi-Centered Tolerance and Efficacy Study of Vernakalant in Patients with Atrial Fibrillation"

This study was initiated in August of 2003 and was completed in November of 2004.

ACTIII

"A Phase 3 Prospective, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Tolerance and Efficacy Study of Vernakalant in Subjects with AFB or AFL"

This study was initiated in June of 2004 and completed in August of 2005.

10.1.1.1 Study objectives

ACTI

The primary objective was to demonstrate the effectiveness of Vernakalant in the conversion of short-term AFB (> 3 hours and <= 7 days) to normal SR. Treatment was considered successfu1 if AFB was converted to SR for a minimum of one minute duration by 90 minutes post start of first infusion. Secondary objectives included the assessment of the safety of Vernakalant, monitoring blood levels of Vernakalant and assessing safety up to the 30-day follow-up.

ACTIII

The primary objective was similar to that in ACTI. In addition to the secondary objectives in ACTI, the following were assessed as well: the proportion of subjects with AF/AFL > 3 hours and <= 45 days; the proportion of subjects with AF/AFL > 7 and <= 45 days who convert to SR for a minimum of one minute within 90 minutes of first exposure; and the time from first exposure to first conversion to SR for a minimum duration of one minute.

10.1.1.2 Inclusion/Exclusion Criteria in ACTI and ACTIII

Inclusion and exclusion criteria in both ACTI and ACTIII were similar, in the few instances where they were not, a note is added regarding what is different.

To be included were subjects 18 of age or older; with sustained AFB in ACTI and sustained AF/AFL in ACTIII of duration greater than 3 hours and less than 45 days; with adequate anticoagulant therapy; who are hemodynamically stable (SBP > 90 and < 160 mmHg, and DBP < 95 mmHg); and weigh between 45 and 136 kg (dose to be based on weight of 113 kg if weight > 113 kg).

To be excluded were subjects with known or suspected prolonged QT, familial long QT syndrome, previous Torsade de Pointes, Brugada syndrome; known bradycardia, sick-sinus syndrome or QRS > 0.14 s unless managed with pacemaker; QT (uncorrected) > 0.440 s; ventricu1ar rate less than 50 bpm as documented by a 12-lead ECG; (AFL in ACTI); unstable

CHF NYHA IV or CHF requiring intravenous inotropes; MI, ACS or cardiac surgery within 30 days of study entry; reversible causes of AFB such as alcohol intoxication, hyperthyroidism, acute pericarditis or pulmonary embolism; serious disease (pulmonary, hepatic, metabolic, renal, gastrointestina1, CNS or psychiatric), end stage disease or any other disease that could interfere with the study; failed DC cardioversion; uncorrected electrolyte imbalance (serum potassium < 3.5mEq/L must be corrected prior to enrollment); clinical evidence of digoxin toxicity; intravenous Class I or III antiarrhythmic drugs or IV amiodarone within 24 hours prior to dosing; women who are pregnant, nursing or without an effective form of birth control.

10.1.1.3 Restrictions

Patients may receive rate control drugs such as β-adrenergic blocking agents, calcium antagonists or digoxin, as long as heart rate is > 50 bpm and the loading dose or bolus these agents precedes Vernakalant by at least two hours.

Also not permitted: caffeine; smoking from screening until 24 hours after dosing; herbal remedies or alternative medicines from screening until 24 hours after dosing; over-the-counter medications especially cold medicines from screening until 24 hours after dosing; and DC cardioversion or any additional antiarrhythmic medication within two hours post study drug unless the investigator judges it is necessary to restore normal SR (NSR) more quickly.

10.1.1.4 Dose Stopping Criteria in ACTI and ACTIII

The infusion may be terminated prematurely if any of the following is observed: QT (uncorrected) of 550 msec or a prolongation >25% of baseline, HR < 50 bpm (in ACTI), or SBP < 85 or > 190 mm Hg (all verified by three consecutive measurements); new bundle branch block or QRS prolongation of 50% of control; any polymorphic V-Tach; intolerable side effects as determined by the Investigator or any changes in cardiac rhythm or atrioventricular conduction that, in the investigator's opinion, is a threat to patient safety.

Additionally in ACTIII, heart rate between 40 and 50 bpm lasting 30 seconds or more in conjunction with symptoms of bradycardia or heart rate < 40 bpm with or without symptoms of bradycardia lasting 30 seconds or more (verified by two 12-lead ECGs 30 seconds apart); asymptomatic V-Tach lasting 30 seconds or longer, or symptomatic V-Tach of any duration; one or more sinus pauses of 5 seconds or greater or complete heart block.

10.1.1.5 Study Design of ACTI and ACTIII

These were multi-center, double-blind, placebo-controlled, randomized trials in which patients with atrial arrhythmia (AFB in ACTI and AF/AFL in ACTIII) were stratified by arrhythmia duration (> 3 hours and <= 7 days or > 7 days <= 45 days). Atrial arrhythmia is determined by the CEC using three baseline 12-lead ECG tracings, see 10.2.1Definition of AFB and page 88.

Table 42. Planned Randomization and Stratification in ACTI and ACTIII

	ACTI		ACTIII	
Diagnosis	AF		AFB and AFL	
Treatment arms	Placebo	Vernakalant	Placebo	Vernakalant
> 3 H <= 7 days	80	160	80	80
> 7 and <= 45 days	40	80	40	40
Total	120	240	120	120

10.1.1.6 Study conduct

AFB or AFL is to be determined using three baseline ECG recordings within 10 minutes before the first infusion. Each patient was considered for cytochrome P450 2D6 characterization. ECGs are to be recorded at pre-specified intervals and interpreted on site for patient management. Holter monitoring is to be conducted from admission to discharge; and both ECG and Holter recordings are to be interpreted by Central Reading Laboratories.

Patients are to be monitored for a minimum of 8 hours and up to 24 hours post dose and prior to being released. Two follow-ups were to occur, one visit approximately one-week post dose and a telephone call approximately 30 days post-dose. If discharged prior to 24 hours, subjects were to complete discharge evaluation and return to the research facility to complete the 24-hour post-dose evaluation and return the Holter monitors.

All study staff with the exception of the site pharmacist are to be blinded. Emergency code break reports were forwarded by the pharmacist to investigators prior to dosing to enable break the blind in the case of medical emergency.

10.1.1.7 Study Procedures in ACTI and ACTIII

Table 43. Procedure Schedules in ACTI and ACTIII

	Screen	**T=0M Baseline**	**T=10M Start 1st infusion**	**T=25M End 1st infusion**	**T=35M 2d infusion**	**T=45M End 2d infusion**	**T=45M**	**T=90M**	**T=2h**	**T=4h**	**T=8h**	**T=24h Discharge**	**1 week visit**	**30-day phone**
IC	X													
Incl/Excl criteria	x													
Medical history	X													
Physical exam	x											X		
AFB symptoms	x	X						X				x	x	X
Pregnancy test	X													
Serum potassium	X													
TEE/Atrial size/EF	X													
ECG	X	X	Every 5 minutes from T=0 to T=50					X	X	X	X	X	X	
Telemetry		Continuous telemetry monitoring from baseline to a minimum of 2 hours post-dose (up to 8 hours, if possible)												
Vital signs	X	X	Every 5 minutes from T=0 to T=50					X	X	X	X	X	X	
Holter	Holter monitoring from screening baseline to 24 hours post-baseline													
Clinical chemistry		X										X	X	
Hematology		X										X	X	
PK evaluation		X	X	X	X	X	X	X	Only in ACTIII			X		
Concomitant Meds	X	←----------through dosing and follow-up												
Adverse events		←----------through dosing and follow-up												
Limited physical examination													X	
Questionnaire														ACTI

10.1.1.8 Study drug administration

Vernakalant consisted of a formulation that required dilution in normal saline and administration via an intravenous infusion using a pump over 10 minutes. Patients received up to two doses, 3.0 mg/kg in the first infusion and 2.0 mg/kg in the second infusion depending on whether the primary endpoint of conversion was achieved or not. Placebo (saline) is to be given in the same manner as the active drug.

10.1.1.9 Other therapies

Additional antiarrhythmic medication and electrical cardioversion were permissible as long as they are administered at least two hours post study drug dosing. β-adrenergic blocking agents, calcium antagonists or digoxin were permitted as long as heart rate is > 50 bpm and the loading dose or bolus supplementation of these agents preceded Vernakalant by at least two hours.

10.1.1.10 Study Efficacy Evaluation and Efficacy Variables in ACTI and ACTIII

Primary efficacy is to be determined using the population with short-term AFB duration (> 3 hours and <= 7 days). The outcome of treatment effect is to be adjudicated by a blinded-CEC using Holter recordings.

Primary Efficacy Parameters

The primary efficacy endpoint in both ACTI and ACTIII was the treatment-induced conversion of AFB to normal SR for a duration of at least one minute within 90 minutes of first exposure to study drug in subjects with short-term AFB (> 3 hours and <= 7 days).

Secondary Efficacy Parameters

Secondary efficacy parameters were similar to the primary efficacy parameter but were based on two different populations depending on the duration of atrial arrhythmia: > 3 hours and <= 7 days; and > 7 days and <= 45 days.

10.1.1.11 Study safety evaluation

During the clinic stay, safety is to be evaluated using regular vital sign measurements; 12-lead ECG recordings; telemetry and Holter monitoring; physical examinations; clinical chemistry, hematology and urinalysis; adverse event recording. The study was regularly monitored by an un-blinded DSMB. For schedule of safety evaluation components, see link: Table 43. Procedure Schedules in ACTI and ACTIII page 74.

Safety evaluated from dosing to the 30-day telephone contact included the following:

- unscheduled emergency department or doctor's visit;
- increased/decreased use of medications or use of new medications;
- recurrence of AF;
- any genera1 reported improvement/worsening of health;

10.1.1.12 Statistical methodology

Efficacy analyses

Primary efficacy analyses in both ACTI and ACTIII were to test the superiority of Vernakalant to placebo in converting subjects with AFB of > 3 hours and <= 7 days duration to normal SR for at least one minute at any time within 90 minutes of first exposure to study drug. The incidence of conversion to SR on Vernakalant and placebo are to be compared using the Cochran Mantel-Haenszel (CMH) test.

The statistical test was two-sided with significance 1evel of 0.001 for the interim analyses and 0.049 for the final analyses.

Secondary analyses are to be conducted if the primary endpoint demonstrated a significant positive finding and to be tested in the following sequence:

- time to conversion of AFB to SR in patients with AFB duration between 3 hours and 7 days;
- time to termination of AFB (defined as absence of AFB or AFL) in patients with AFB duration between 3 hours and 45 days;
- the proportion of patients with AFB duration between 3 hours and 45 days who have treatment induced termination of AFB within 90 minutes of first exposure;
- time to termination of AFB in patients with AFB duration between 7 and 45 days;
- proportion of patents with AFB duration between 7 and 45 days who have treatment induced termination of AFB within 90 minutes of first exposure to study drug.

Handling of missing data

A response of failure is to be imputed for the primary and secondary endpoints for patients who received any amount of study medication and who were electrically cardioverted prior to 90 minutes, and for patients who withdraw after infusion of any amount of study drug prior to observing the endpoint and prior to 90 minutes.

Safety analyses

Treatment emergent adverse event summary tables using MedDRA preferred term coding are to be presented. These tables are to be broken by number of infusions of Vernakalant. The latter were not submitted by the Sponsor, but this analysis was completed by the reviewer.

Vital signs and 12-lead ECG intervals are to be summarized by time points and change from baseline values. These are to be analyzed using one way ANOVA. A subset of these data set consisting of ECG variables from the time of conversion to NSR to 24 hours post-infusion is to be summarized by time points and change from baseline values.

Unscheduled measurements of ECGs would neither be included in summary table or analyses.

Holter variables (total number of detected beats, maximum heart rate, total number of tachycardia runs) are to be analyzed for differences between rates and densities pre-infusion, post first infusion and post second infusion if relevant.

Summary statistics of laboratory parameters measured at baseline, the period following study drug administration, before discharge from the study facility and at follow-up are to be tabulated. Summary table of within-/out-of-range and clinically significant abnormal values of the laboratory parameters are to be presented in shift tables.

Analyses populations

The primary and secondary efficacy analysis populations are to be the ITT population which would consist of all randomized patients, whether or not they received study medication. Patients that spontaneously convert in the period between randomization and treatment are to be censored from the ITT analyses.

The safety population was to consist of all patients who were randomized and have at least one post-baseline safety measure.

Interim analysis

An interim analysis is to be conducted when data for 50% of study target enrolment were collected. A 0.001 spending on alpha was pre-specified for this interim analysis.

Sample size

Assuming an estimated conversion rate of 50% on Vernakalant vs. 25% on placebo in patients with AFB > 3 hours and <=7 days and a conversion rate of 30% on Vernakalant vs. 5% on placebo in patients with AFB > 7 days and <=45 days; Sample sizes were estimated to detect a difference at the significance level of 0.05 and with powers of 97% and 93%Table 42. Planned Randomization and Stratification in ACTI and ACTIII page 73).

10.1.1.13 Study Committees

The Clinical Event Committee (CEC)

The CEC is to be made up of members with expertise in arrhythmia. They may or may not be investigators in this trial. Their responsibilities included adjudicating the cause of death (cardiac vs. non-cardiac); type of death (sudden vs. non-sudden); cause of hospitalizations (AFB, other cardiac cause, or non-cardiac causes); verification of conversion to normal SR; and verification of arrhythmia at baseline. The criteria for adjudication were developed by the committee.

The Data Safety & Monitoring Board (DSMB)

The DSMB is to be made up of members who are experienced in the participation in DSMB related activities in clinical trials. None of them are to be participants in these trials or be involved in any other way with processing of data. Their responsibilities included monitoring the overall conduct of the studies; receiving and reviewing reports of SAE; reviewing periodic reports of safety data by blinded treatment group; and making recommendations to Cardiome and the Steering Committee. The DSMB developed the criteria for unblinding of results and for stopping rules.

10.1.1.14 Findings from ACTI and ACTIII

Table 44. ACTI and ACTIII Enrollment by Country (Table from Sponsor's Report)

Study and Country	Placebo	Vernakalant
ACTI		
Canada	23(20.0%)	74(33.5%)
Denmark	59(51.3%)	102(46.2%)
Sweden	18(15.7%)	26(11.8%)
USA	15(13.0%)	19(8.6%)
ACTIII		
Denmark	52 (39.7%)	52 (38.8%)
Canada	20 (15.3%)	27 (20.1%)
USA	23 (17.6%)	24 (17.9%)
Argentina	17 (13.0%)	14 (10.4%)
Sweden	16 (12.2%)	14 (10.4%)
Mexico	1 (0.8%)	3 (2.2%)
Chile	2 (1.5%)	0

Table 45. Summary of Analyses Populations in ACTI (Table from Sponsor's Report)

Parameter	Number (%) of Subjects	
	Placebo	Vernakalant
Overall Population		
N (all randomized subjects	119	237
All Randomized Subjects	119 (100.0%)	237 (100.0%)
Full Analysis Set (Safety Set)	115 (96.6%)	221 (93.2%)
Per Protocol Set	112 (94.1%)	220 (92.8%)
AFB > 3 hours and <= 7 days N	79	158
All Randomized Subjects	79 (100.0%)	158 (100.0%)
Full Analysis Set (Safety Set)	75 (94.9%)	145 (91.8%)
Per Protocol Set	72 (91.1%)	144 (91.1%)
AFB > 7 days and <= 45 days N	40	79
All Randomized Subjects	40 (100.0%)	79 (100.0%)
Full Analysis Set (Safety Set)	40 (100.0%)	76 (96.2%)
Per Protocol Set	40 (100.0%)	76 (96.2%)

Table 46. Summary of Analysis Population in ACTIII (Table from Sponsor's Report)

	Placebo	Vernakalant
All subjects with AF	121	119
Full analysis set (safety set)	121 (100.0%)	118 (99.2%)
Per protocol set	118 (97.5%)	116 (97.5%)
> 3 hours and <= 7days N	84	86
Full analysis set (safety set)	84 (100.0%)	86 (100.0%)
Per protocol set	81 (96.4%)	84 (97.7%)
> 7 days and <= 45 days N	37	33
Full analysis set (safety set)	37 (100.0%)	32 (97.0%)
Per protocol set	37 (100.0%)	32 (97.0%)

Table 47. Disposition of Subjects with Short-Duration AFB in ACTI and ACTIII Studies

ACTI	Placebo N = 75	Vernakalant N = 145
Dose 1 completed	75	139 (95.9%)

ACTI	Placebo N = 75	Vernakalant N = 145
Dose 1 discontinued	0	6 (4.14)
Dose 2 started	74 (98.67%)	84 (57.93%)
Dose 2 completed	73 (98.6%)*	82 (97.6%)**
Dose 2 discontinued	1 (1.4%)	2 (2.4%)**
ACTIII	**Placebo N = 84**	**Vernakalant N = 86**
Dose 1 completed	83 (98.8%)	82 (95.3%)
Dose 1 discontinued	1 (1.2%)	4 (4.65)
Dose 2 started	81 (96.43%)	48 (55.81)
Dose 2 completed	81 (100%)*	48 (100%)**
Dose 2 discontinued	0	0

**Used the number starting dose 2 as a denominator

Table 48. Summary of Baseline AFB Characteristics in ACTI (from Sponsor's Report)

	Placebo	Vernakalant	P-value
AFB Duration Category			
>3 hours - <= 7days	75 (65.2%)	145 (65.6%)	0.943
>7 days - <= 45 days	40 (34.8%)	76 (34.4%)	
Subjects with a pacemaker	6 (5.2%)	9 (4.1%)	0.630
Duration of AFB symptoms (hours)			
Short-Term N	75	145	0.337
Mean ± SD	36.2 ± 36.32	45.0 ± 48.18	
Median	28.4	28.2	
Range	1.2 – 165.0	1.2 – 371.9	
Subjects with a pacemaker	6 (8.0%)	4 (2.8%)	0.094
Long-Term N	39	71	0.975
Mean ± SD	581.2 ± 350.33	605.6 ± 293.48	
Median	465.2	613.0	
Range	18.2 - 1081.6	130.4 - 1040.8	
Subjects with a pacemaker	0	5 (6.6%)	0.163

Table 49. Summary of Comorbidities in Subjects with Short-Term AFB in ACTI and ACTIII (Table from Sponsor's Report)

ACTI	Placebo N=75	Vernakalant N= 145
Hypertension	32 (42.7%)	57 (39.3%)
Pacemaker	1 (1.3%)	1 (0.7%0
Ischemic heart disease	1 (1.3%)	0 (0.0%)
Ventricular tachycardia	1 (1.3%)	0 (0.0%)
Myocardial infarction	3 (4.0%)	8 (5.5%)
CHF	No status given for ACTI	
ACTIIII	**Placebo N=84**	**Vernakalant N=86**
Hypertension	28(33.3%)	41(47.7%)
Hyperlipidemia	21(25.0%)	31(36.0%)
Atrial fibrillation	70(83.3%)	72(83.7%)
AFL	11(13.1%)	11(12.8%)
Pacemaker	3(3.6%)	1(1.2%)
Ischemic heart disease	10(11.9%)	5(5.8%)
Ventricular tachycardia	1(1.2%)	1(1.2%)
Myocardial infarction	4(4.8%)	5(5.8%)

ACTI	Placebo N=75	Vernakalant N= 145
CHF	26 (30.95%)	28 (32.56%)

Table 50. Summary of Vital Signs at Baseline in Subjects with Short-Term AFB in ACTI (Table from Sponsor's Report)

	Placebo N=75	Vernakalant N=145
Systolic PB mmHg N	74	144
Mean	121.4	122.0
STD	15.52	16.78
Min	98	90
Median	120.2	120.7
Max	158	169
Diastolic BP mmHg N	74	144
Mean	76.3	76.6
STD	10.73	9.86
Min	55	39
Median	76.7	77.6
Max	105	98
Heart rate (bpm) N	74	144
Mean	100.8	99.2
Std	22.25	25.86
Min	66	55
Median	97.5	92.5
Max	154	185
Respiration rate N	73	143
Mean	16.2	16.3
STD	2.72	3.38
Min	10	9
Median	16.0	16.0
Max	24	26

P-values are from the one-way ANOVA
Systolic and diastolic blood pressure values were calculated from the mean of 3 baseline measurements.

No differences in vital signs are observed between the treatment arms except for a difference in baseline median heart rate.

Table 51. Vital Signs at Baseline in Subjects with Short-Term AFB in ACTIII (Table from Sponsor's Report)

Parameter	Placebo N=84	Vernakalant N=86	P-value
Systolic PB mmHg N	84	86	0.302
Mean	120.3	122.5	
STD	13.31	13.63	
Min	93	97	
Median	120.8	120.3	
Max	153	166	
Diastolic BP mmHg N	84	86	0.010 **
Mean	78.8	75.1	
STD	9.64	9.17	
Min	55	52	
Median	79.8	75.2	

Parameter	Placebo N=84	Vernakalant N=86	P-value
Max	95	98	
Heart rate (bpm) N	83	86	0.366
Mean	106.8	103.4	
Std	25.06	23.92	
Min	58	60	
Median	102.7	98.8	
Max	162	168	
Respiration rate N	83	86	0.407
Mean	16.5	17.0	
STD	3.81	3.36	
Min	8	10	
Median	16.0	16.0	
Max	29	24	
Oxygen saturation (%)	84	86	0.336
Mean	96.7	97.0	
STD	1.97	1.90	
Min	90	91	
Median	97.0	97.0	
Max	100	100	

P-values from one-way ANOVA
HR is from continuous ECG parameters

The statistically significant difference in diastolic blood pressure could be a chance finding as a result of the many hypotheses that are tested.

Table 52. Demographic and Baseline Characteristics in Short-Term AFB in Subjects in ACTI and ACTIII (Table from Sponsor's Report)

	ACTI		ACTIII	
	Placebo N=75	Vernakalant N=145	Placebo N=84	Vernakalant N=86
Gender				
Male	48(64.0%)	102(70.3%)	57(67.9%)	61(70.9%)
Female	27(36.0%)	43(29.7%)	27(32.1%)	25(29.1%)
Race				
White	73(97.3%)	138(95.2%)	84(100.0%)	86(100.0%)
Black	0(0.0%)	2(1.4%)	0	0
Other	2(2.7%)	5(3.4%)	0	0
Age (years) N	75	145	84	86
Mean	59.9	60.4	59.7	59.3
STD	11.78	13.97	14.77	15.82
Min	39	25	27	22
Median	60.0	61.0	59.0	60.5
Max	85	86	90	89
Categorized age				
<65 yrs	49(65.3%)	88(60.7%)	51(60.7%)	54(62.8%)
>=65 yrs	26(34.7%)	57(39.3%)	33(39.3%)	32(37.2%)
Weight (kg) N	75	145	84	86
Mean	81.9	83.4	83.6	86.5
STD	15.91	16.75	16.21	13.86
Min	55	47	48	61
Median	80.0	81.0	83.5	84.8
Max	120	147	130	118

	ACTI		ACTIII	
	Placebo N=75	Vernakalant N=145	Placebo N=84	Vernakalant N=86
BMI N	74	144	Not reported for this study	
Mean	26.6	27.0		
STD	4.10	4.83		
Min	20	18		
Median	26.5	26.6		
Max	38	50		
Tobacco use				
Current smoker	12(16.0%)	20(13.8%)		
Ex-smoker	28(37.3%)	51(35.2%)		
Non-smoker	35(46.7%)	74(51.0%)		

Table 53. Background Use of Concomitant Medications in Short-Term AFB in ACTI and ACTIII (Table from Sponsor's Report)

ACTI	**Placebo N=75**	**Vernakalant N=145**
Class I antiarrhythmics	8(10.7%)	9(6.2%)
Class III antiarrhythmics	2(2.7%)	10(6.9%)
Oral or IV beta blockers	42(56.0%)	80(55.2%)
Calcium channel blockers	19(25.3%)	27(18.6%)
Sotalol	16(21.3%)	21(14.5%)
Digoxin	15(20.0%)	26(17.9%)
ACTIII	**Placebo N=84**	**Vernakalant N=86**
Class I antiarrhythmics	6(7.1%)	16(18.6%)
Class III antiarrhythmics	8(9.5%)	6(7.0%)
Beta blockers	49(58.3%)	52(60.5%)
Calcium channel blockers	20(23.8%)	16(18.6%)
Sotalol	6(7.1%)	7(8.1%)
Digoxin	13(15.5%)	5(5.8%)

Background use in ACTI is defined as any medication which started prior to the first infusion
Baseline use in ACTIII is defined as medication use during the 7 day period prior to study drug infusion
Class I include antiarrhythmics: procainamide, propafenone, disopyramide, flecainide
Class III include antiarrhythmics: amiodarone, ibutilide

The difference between the treatment arms in Class I antiarrhythmic and digoxin background concomitant medication in ACTIII could have been a chance finding because the sample size is too small for randomization to distribute all background characteristics evenly between the treatment arms. To have an effect on either efficacy or safety of Vernakalant, the effect or interaction between these drugs and Vernakalant would have to be sizable to have a meaningful effect on outcomes.

The excess of Class I antiarrhythmic drugs trended in different directions depending on which study. Efficacy was similar in both ACTI and ACTIII while the proportion of subjects on Class I antiarrhythmic in the latter study trended in the other direction.

The excess of digoxin on placebo trended consistently in the same direction in both studies and to a lesser extent in ACTI. This excess could be to chance or it could be that the placebo group's cardiovascular status was somewhat worse than of the group randomized to Vernakalant. If this

was the case, the adverse event profile of Vernakalant and possibly its efficacy profile could have been biased toward a better outcome.

10.1.2 Other Studies

10.1.2.1 CRAFT Study

"A Phase IIa Prospective, Randomized, Double-blind, Placebo- Controlled Dose-ranging, Multi-Centered, Tolerance and Efficacy Study of Vernakalant in Patients Recent Onset Atrial Fibrillation"

The objectives were to determine the safety, efficacy and tolerability of Vernakalant in a step-dose design for the termination of recent onset atria1 fibrillation (new and recurrent); and to define an efficacious dose for use in a larger Phase IIb study.

A total of 60 subjects are to be randomized to two dose regimens: 0.5 mg/kg followed (if needed) by 1.0 mg/kg; and 2 mg/kg to be followed (if needed) by 3 mg/kg. The follow-up and assessment of endpoints were similar to what was done in ACTI and ACTIII. The population targeted for enrollment was similar to that enrolled in ACTI and ACTIII. Monitoring and follow-up of subjects were similar to those in ACTI and ACTIII.

The primary endpoint is the termination of AFB during the infusion and 30-minutes post-infusion; and the secondary endpoints are the number of patients in normal SR at 0.5, 1 and 24 hours post-dosage, and time to conversion.

10.1.2.2 Scene 2

"A Phase II/III Prospective, Randomized, Double-Blind, Placebo-Controlled, Multi-Centered Tolerance and Efficacy Study of Vernakalant In Patients with AFL"

The primary study objective was to demonstrate the effectiveness of 3.0 mg/kg and an additional 2.0mg/kg, if required, of Vernakalant in the conversion of AFL to SR. Treatment is to be considered successful if there was a treatment-induced conversion of AFL to SR for a minimum of one-minute duration within 90 minutes of first infusion of study drug.

Scene 2 is a multinational, multicenter, randomized, double-blind, placebo-controlled study in which subjects with AFL are to be randomized in short- and long-term strata of AFL (duration >3 hours and <=7 days; and >7 days and <= 5 days).

Three hundred subjects are to be enrolled, with 240 with short-term AFL and 120 with long-tem AFL. In each duration stratum, subjects are to be randomized in a 2:1 ratio to Vernakalant and placebo respectively. Subjects targeted for enrollment were similar to those in the other studies except that they have AFL instead of AF. Monitoring and follow-up of subjects were similar to those in ACTI and ACTIII.

The primary efficacy endpoint was the treatment-induced conversion of short-term AFL to normal SR for duration of a minimum of one minute within 90 minutes of first infusion. Vernakalant was found to be not effective in AFL. Data from this study was useful in safety analyses.

10.1.2.3 ACTII (ongoing)

"A Phase III Study of the Conversion Efficacy and Safety of Repeated Intravenous Doses of Vernakalant in Subjects with Atrial Fibrillation or Flutter Following Valvular and/or Coronary Artery Bypass Graft"

The primary objective of this study is to demonstrate the effectiveness of RSB1235 compared to placebo in the conversion of post-CABG and/or valvular surgery atrial arrhythmia (AFL or AF) to SR.

The secondary objectives are to examine the effect of a second dose of Vernakalant on the rate of conversion of atrial arrhythmia to SR and to assess overall safety of RSB1235 in this population.

10.1.2.3.1 Study design

This is a multi-national, multi-center double-blind, randomized, placebo-controlled trial in subjects with rhythm of sustained AFB or AFL (duration of 3 – 72 hours) occurring between 24 hours and 7 days after CABG and/or valvular surgery.

Subjects are to be randomized and receive up to two 10-minute infusions of either study drug or placebo. The first infusion of Vernakalant (3 mg/kg) or placebo followed by a second infusion of Vernakalant (2 mg/kg) or placebo if arrhythmia is not terminated during or following the observation period after the first infusion.

The treatment is to be considered successful if there were a conversion of the index arrhythmia to SR for a minimum duration of 1 minute within 90 minutes post first infusion without interventions other than the study drug.

A total of 210 subjects with atrial arrhythmia from US, Canada, Europe, India and South America are to be randomized in a 2:1 ratio to Vernakalant or placebo, respectively.

To be included are subjects 18 years or older, with recent (within 7 days) CABG or valvular surgery, documented (12-lead ECG recording) AFB or AFL of duration between 3 and 72 hours occurring 24 hours to 7 days of surgery at time of randomization and documented (12-lead ECG recording) normal SR within 2 weeks before surgery.

Exclusion criteria are similar to those in ACTI and ACTIII except for few differences including the cutoff for QT using QTcB > 460 msec instead of uncorrected QT > 500 msec, and some of the factors predisposing to AF/AFL that are innate to this population (such as MI), but were excluded in other protocols.

10.1.2.3.2 Safety evaluation

Safety evaluation is similar to that in ACTI and ACTIII. All randomized subjects who received any amount of study medication are to be included in the population used for safety analyses.

Except for SAEs which are collected up to 30 days post study drug, tabulations is to cover adverse events up to seven days after the start of study drug.

An independent DSMB monitors the conduct of the study by reviewing reports of SAEs and periodic reports of safety data by treatment group. Interim safety evaluations are performed by an independent statistician when data are collected from 25% and 50% of the planned enrollment. These data are unblinded and provided to the DSMB.

Table 54. Subject Disposition in ACTII (from Sponsor's Report)

	PLACEBO N = 61	Vernakalant N = 123
Randomized	61(100.0%)	123(100.0%)
Received any study medication	52(85.2%)	105(85.4%)
Received dose one of study medication	52(85.2%)	105(85.4%)
Received dose two of study medication	50(82.0%)	67(54.5%)
Successful DC cardioversion after 90 minutes	5(8.2%)	5(4.1%)
Completed study (30 day visit)	52(85.2%)	104(84.6%)
Safety set	52(85.2%)	105(85.4%)

At the time of this report, patients are still been enrolled in the ACTII study.

Table 55. Demographics of Subjects in ACTII (from Sponsor's Report)

Full analysis set	Placebo N = 52	Vernakalant N= 105
Gender		
Male	38 (73.1%)	80 (76.2%)
Female	14 (26.9%)	25 (23.8%)
Race/ethnic origin		
White	48 (92.3%)	99 (94.3%)
Non-white	4 (7.7%)	6 (5.7%)
Age (years)		
Mean	67.9	68.3
Std	6.50	7.72
Min	54.0	45.0
Median	68.0	69.0
Max	80.0	82.0
Categorized age		
< 65 yrs	13 (25.0%)	28 (26.7%)
>= 65 yrs	39 (75.0%)	77 (73.3%)

10.1.2.4 ACTIV (ongoing)

"A Phase III, Multi-Center, Open-Label Safety Study of Vernakalant in Subjects with Atrial Fibrillation"

This is a multi-center multinational Phase 3, open label safety trial in which a total of approximately 240 subjects with AFB duration of greater than 3 hours and less than or equal to 45 days are to be enrolled.

The objective of this study is to evaluate the safety of Vernakalant in subjects with AF

To be included were subjects 18 of age or older, with symptomatic sustained AFB of duration greater than 3 hours and less than 45 days; adequate anticoagulant therapy; hemodynamically stable (SBP > 90 and < 160 mmHg, and DBP < 95 mmHg); weigh between 45 and 136 kg.

In addition to the exclusions of ACTI and ACTIV subjects with cardiogenic or septic shock or other forms of shock requiring vasopressors or mechanical ventilation; significant valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy or constrictive pericarditis; acute pericarditis are to be excluded. Restrictions and stopping criteria are similar to those of ACTI and ACTIII.

Except for ECG monitoring schedules and few other differences, monitoring and safety evaluation procedures are similar to those in ACTI and ACTIII. ECG tracings in ACTIV are to be taken less frequently between the first infusion and 45 minutes post infusion, at 10, 25, 35 and 45 minutes instead of every 5 minutes in this time interval.

The sample size of 240 subjects was not based on statistical methodology, but was intended to supplement safety data.

Table 56. AFB Status in ACTIV and Study Drug Intake (from Sponsor's Report)

Parameter	Vernakalant N=209
Enrolled	209(100.0%)
3 hours -7 days	139(66.5%)
8 days - 45 days	54(25.8%)
Received any portion of first dose	193(92.3%)
Did not receive any study medication	16(7.7%)
First dose discontinued	4 (2.1%)
Received any portion of dose 2	122 (58.4%)
Second dose discontinued	
First DC cardioversion between 1.5 and 24 hours	81 (38.8%)
First DC cardioversion attempted after 24 hours	5 (2.4%)

The 4 discontinuations of the first dose were 2 new BBB or QRS prolongation and 2 intolerable side effects.

Table 57. Demographics of Subjects in ACTIV

Parameter	Vernakalant N=193
Gender	
Male	124(64.2%)
Female	69(35.8%)
Race/ethnic origin	
White	185(95.9%)
Non-white	8(4.1%)
Age (years)	
Mean	62.7
Std	12.80
Min	24
Median	63.0
Max	94
Categorized age	
< 65 yrs	102(52.8%)
>= 65 yrs	91(47.2%)

SAEs reported in this study include elevation of troponin levels in a 75 year-old female after converting on 2 doses of the study drug.

A serious sinus arrest occurred four hours post one infusion of study drug and conversion. The subject experienced serious QRS prolongation during the infusion;

The second dose was not given because of pulmonary edema in a 66 year old female with no known history of CHF.

One subject converted then reverted to AFB 13 minutes after converting to SR on the first dose, was given the second dose and converted again.

10.1.2.5 Study 1235-1-04-12-01

"A Phase I, Prospective, Randomized, Single-Blind, Placebo- Controlled, Ascending-Dose, Tolerance Study of Vernakalant in Healthy Volunteers with Preliminary Pharmacokinetic Assessment"

The objective of this study was to determine the safety of ascending single doses of intravenous Vernakalant and to assess the pharmacokinetic parameters in healthy normal volunteers.

Doses tested included 0.10 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 4.0 mg/kg, 5.0 mg/kg, 6.0 mg/kg and 7.0 mg/kg. A total of 38 healthy subjects were planned to be enrolled with one subject each in the 0.1 and 0.25 mg/kg; 4 subjects each in the remaining doses; and 8 subjects total in placebo. Continuation of dosing after 4 mg/kg was subject to IRB approval.

The study had criteria for stopping dosing or reducing the dose and these included a PR > 240 msec, QTc > 500 msec, HR decrease > 30% or HR fall to <= 40 bpm, BP decrease of > 25% or SBP fall to less than 80 mmHg, evidence of BBB or other serious conduction disturbance.

Safety was evaluated using vital signs an 12-lead ECGs monitored at frequent and close interval, continuous telemetry, Holter monitoring, laboratory parameters, and AE information collection.

ECGs are to be interpreted by a board-certified cardiologist selected by the Sponsor. Holter monitor data are to be read at a central reading center.

Table 58. . Study Drug Exposure in 1235-1-04-12-01

Placebo	RSD 1235 0.1	RSD 1235 0.25	RSD 1235 0.5	RSD 1235 1.0	RSD 1235 2.0	RSD 1235 4.0	RSD 1235 5.0
6	1	1	4	5	4	4	4

Disposition

A total of 29 subjects were enrolled, dosed and completed study. One subject was discontinued because the intravenous catheter was displaced out of the vein leading to tissue infiltration; and was replaced by another subject.

10.1.2.6 Study 04-0-195

A Phase I, Open-Label, Single Intravenous Dose and Single Oral Dose, Mass-Balance Study to Assess the Disposition of 14c-Labeled Rsd1235 in Healthy Human Volunteers

Study conducted between April and August of 2005.

The objectives of this study were to define the pharmacokinetics and disposition of Vernakalant and its metabolites and to obtain a mass balance estimate after a single (oral and intravenous) 240 mg dose of 14C-labeled Vernakalant; and to assess safety and tolerability of Vernakalant.

Study design

This was a phase 1, open-label, crossover, single-center, single intravenous and oral dose, mass-balance study in healthy volunteers. Subjects were administered study drug as inpatients and

remained confined for one week following each dose, with a subsequent 2-week follow-up period as an outpatient. Enrollment was stratified by CYP2D6 genotype to enroll 6 extensive metabolizers and 2 poor metabolizers.

Eight subjects were enrolled and admitted to the clinic, received 240 mg C-labeled Vernakalant as a 10 minute intravenous infusion, remained confined through Day 8, were released for 13 days and returned on Day 21, and were dosed with 240 mg oral C-labeled formulation on Day 22. Subjects were discharged on Day 29 and returned to the clinic on Day 42 for end of study procedures.

Safety is evaluated through vital signs, physical examinations, 12-lead ECGs, telemetry, monitoring and recording all AEs and SAEs and laboratory evaluations see .

Subject disposition

All 8 subjects enrolled in the study completed. There were no discontinuations.

10.2 Definitions

10.2.1 Definition of AFB and AFL

AFB is characterized by atrial activity which is either absent or chaotic both in amplitude and in rate.

AFL is characterized with a regular atrial rate of 220-320 bpm with a typical saw tooth pattern in leads II, III and aVF and predominantly negative flutter waves in V6 and positive or biphasic in Vl.

10.2.2 ECG alert criteria:

The following are alert criteria that were used to identify cardiac ECG events:

- Heart rate < 45 bpm
- 460 msec < QT Interval < 50G msec (uncorrected)
- Second degree AV block (Mobitz Type I)
- Second degree AV block (Mobitz Type II)
- Supraventricular tachycardia other than sinus tachycardia
- Idioventricular rhythm
- Accelerated idioventricular rhythm
- Complete RBBB
- Complete LBBB

10.2.3 ECG Panic Alert Criteria

- The following are panic alert criteria used to identify
- Heart rate < 40 bpm
- QT interval > 500 msec (uncorrected)
- Third degree AV block
- Ventricular tachycardia
- Ventricular fibrillation
- Ventricular flutter
- Torsades de pointes

- Possible MI
- Myocardial ischemia
- Acute MI
- New onset complete RBBB
- New onset Complete Left Bundle Branch Block

10.2.4 Holter Panic Alert Criteria

- Heart rate < 40 bpm
- Third degree AV block
- Ventricular tachycardia
- Ventricular flutter
- Ventricular Fibrillation
- Torsade de Pointes

Additionally, all ventricular runs > 5 beats will be summarized based on the interpretation of the Chair of the DSMB.

The distribution of the following rhythms will be summarized, based on the review of 12 lead ECG data by the CEC at each time point a 12 lead ECG is collected; Sinus rhythm, AFL, Atrial fibrillation, Any polymorphic ventricular tachycardia; Sustained ventricular tachycardia; Non-sustained ventricular tachycardia (>3 consecutive beats if ventricular origin); 3" degree AV block; Mobitz type II 2"' degree AV block; Mobitz type I (Wenckebach) 2"' degree AV block; premature ventricular beats; premature junctional beats; premature atrial beats; Paced rhythm; Sinus arrhythmia; and Other cardiac rhythm.

The manual over read 12-lead ECG data will be used for all ECG data summaries and listings.

10.2.5 AF/AFL symptom assessment

shortness of breath; palpitations; chest tightness/pains; dizziness; edema; fatigue; rapid heart beats; diaphoresis; orthopnea; PND; nausea; syncope; irregular pulse; vomiting; cough; headaches;

10.2.6 30-day follow-up phone call questionnaire

- How are you feeling?
- Have you experienced any of the following: shortness of breath; palpitations; chest tightness/pains; dizziness; edema; fatigue; rapid heart beats; diaphoresis, orthopnea; PND; nausea; syncope; irregular pulse; vomiting; cough; or headaches? Which symptoms are you experiencing? How frequent are these symptoms?
- Have you experienced any pain or discomfort? When and how often?
- Have you had any problems with your heart since the treatment? When and how often? Have you had any incidences of AFB since the treatment? When and how often? Have you had any other medical problems since the treatment? %hen and how often? Have you gone to an emergency department or had an unscheduled doctor's visit since the treatment? When and why?
- Have you started to take any new medicines/treatments since enrollment in the threatening? When, how frequently, which medications, what dosage?

- Have you increased or decreased any of your medications since you received treatment? When, which medications, what are the changes?

10.2.7 Amendments to studies

Protocol Amendment	Amendment Date	Subjects Enrolled	Description of major changes
ACT I, Database Lock 14 Dec 2004			
Original Protocol (serial 023)	23 May 2003	127	-
1 (serial 32)	16 Dec 2003	229	Modified primary objective from “conversion to normal SR” to “conversion to SR” Added secondary efficacy analysis for patients with AFB of 7 to 45 days duration
ACT III, Database Lock 23 Sep 2005			
Original Protocol (serial 41)	31 Mar 2004	253	-
1 (serial 066)	24 Mar 2005	22	Increase sample size from 240 to 280 patients Revised statistical methodology to be consistent with other phase III studies
2 (serial 073)	3 Jun 2005	0	Changed the primary end point to exclude evaluation of patients with AFL Changed secondary study endpoint to match the ACT I study
CRAFT, Database Lock 23 Aug 2002			
Original Protocol (serial 008)	15 Aug 2001	0	-
1 (serial 009)	25 Sep 2001	0	Modified efficacy evaluation Modified analysis of blood and urine samples Modified inclusion criteria for non-pregnant women
2 (serial 010)	12 Oct 2001	0	Modified inclusion and exclusion criteria and dose stopping criteria
3 (serial 010	19 Oct 2001	18	Modified randomization and blind breaking procedures, Modified exclusion criteria relative to blood pressure
4 (serial 011)	20 Dec 2001	15	Clarified post-dose monitoring of patients, Clarified handling of samples for PK analyses
5 (serial 013)	20 Feb 2002	22	Increased expected length of study, Clarified treatment of patients with AFL, Increased the maximum weight of the patients allowed
6 (serial 014)	25 Mar 2002	0	Updated data within the preclinical data section
7 (serial 017)	10 Jun 2002	1	Modified the randomization to allow all arms of the study to fully enroll
Scene 2, Database Lock 15 Jan 2005			
Original Protocol (serial 023)	23 May 2003	31	-
1 (serial 32)	16 Dec 2003	29	Modified primary objective from “conversion to normal SR” to “conversion to SR”
ACT II, Ongoing Study			

Protocol Amendment	Amendment Date	Subjects Enrolled	Description of major changes
Original Protocol (serial 031)	16 Dec 2003	0	-
1 (serial 042)	5 May 2004	20	Clarified inclusion and exclusion criteria and the timing of various clinical monitoring activities
2 (serial 054)	3 Nov 2004	149	Expanded scope to include patients undergoing both valvular and CABG surgery
3 (serial 090)	7 Apr 2006	15	Added Secondary efficacy endpoints related to time of conversion and to the evaluation of conversion based on Holter and 12 lead ECG data Added Exploratory Efficacy Measurements and Analyses Added an unblinded safety evaluation
4 (serial 099)	2 Jan 2007	0	Added a second unblinded safety evaluation Extended expected length of study
ACT IV, Ongoing			
Original Protocol (serial 079)	12 Aug 2005	38	-
1 (serial 088)	20 Feb 2006	80	Added PK sampling, Clarified use of rate controlling medications
Administrative Change 1 (serial 091)	12 Apr 2006	136	Increased Sample size from 120 to 240 patients

10.3 Line-by-Line Labeling Review

Not completed here.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY REVIEW

NDA:	**22-034 N000**
Submission Dates:	**12/19 2006,** 2/06, 3/16, 5/10, 6/05 2007
Brand Name:	**Kadenza**
Generic Name:	**Vernakalant**
Dosage Form & Strength:	IV solution, 200 mg/10 mL single dose vial
Indication:	Rapid conversion of atrial fibrillation to sinus rhythm
Applicant:	Astellas Pharma, Inc.
Submission:	Original NDA
Divisions:	DPEI and Cardio-Renal Drug Products, HFD-110
Primary Reviewer:	Elena V. Mishina, Ph.D.
Team Leaders:	Patrick Marroum, Ph.D.
Pharmacometrics Consult:	**C.** Tornoe, Ph.D.
Pharmacometrics Team Leader:	Y. Wang, Ph.D.

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1 EXECUTIVE SUMMARY

Astellas Pharma, Inc. submitted NDA 22-034 - Kadenza (Vernakalant Hydrochloride IV Solution) on December 19, 2006 pursuant to Section 505 (b) of the Federal Food, Drug and Cosmetic Act and to 21 CFR §314.50. Kadenza is proposed for the rapid conversion of atrial fibrillation to sinus rhythm.

Vernakalant is a novel anti-arrhythmic agent, it is pharmacologically active through potassium and sodium channel blockade (e.g., I_{Kr}, I_{to}, and I_{Na}) resulting in selective prolongation of the atrial effective refractory period and rate-dependent reduction of atrial conduction velocity.

Kadenza will be marketed as an IV solution, 200 mg/10 mL per single dose vial.

The recommended initial infusion of KADENZA is 3 mg/kg infused over 10 minutes. If conversion to sinus rhythm does not occur within 15 minutes after the end of the initial infusion, a second 10-minute infusion of 2 mg/kg may be administered.

The submission included 7 clinical studies where PK of vernakalant was assessed, including two pivotal trials. The sponsor also conducted several in vitro studies to assess the metabolism by CYP450, binding to plasma protein and displacement of vernakalant by several drugs which could be possibly co-administered in the clinic. All studies were reviewed.

1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 22-034. The CPB information provided in NDA 22-034 is acceptable. The following comments should be properly addressed by the sponsor.

***COMMENTS*:**

1. The interactions with P-glycoproteins have not been assessed. PGP transport of vernakalant should be characterized in vitro using at least two PGP inhibitors.
2. The labeling comments should be addressed by the sponsor.

1.2 PHASE IV COMMINMENTS:

None.

_____ Date_____

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

_____

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on September 17, 2007

Attendees: .

cc list: NDA 22-034, MehulM, MarroumP, MishinaE, Bawaja, HFD 110 BIOPHARM

1.3 Summary of OCPB Findings

1.3.1 Background

Astellas Pharma, Inc. is seeking the approval of KADENZA™ (vernakalant hydrochloride injection) for rapid conversion of atrial fibrillation (AF).

1.3.2 Current Submission

NDA 22-034 contains 7 clinical studies where PK of vernakalant was assessed, including two pivotal trials. The sponsor performed two Phase I studies: a dose-ranging study to find a maximum tolerated dose and a mass-balance study. In addition, the sponsor conducted several in vitro studies to assess the hepatic metabolism by CYP450 and the potential for vernakalant to inhibit CYP450 enzymes, the binding to plasma protein and displacement of vernakalant by several drugs which could be possibly co-administered in clinic. All these studies were reviewed.

Pharmacokinetics

A two-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed vernakalant (RSD1235) concentrations following 3+2 mg/kg 10 minute IV infusions separated by 15 minutes.

Body weight was found to be a significant covariate for RSD1235 pharmacokinetics.

In poor CYP2D6 metabolizers (PMs), RSD1235 clearance was found to decrease by 64% compared to extensive metabolizers (EMs). The C_{max} for PMs was not significantly different from EMs. The estimated terminal population half-life ($t_{1/2,\beta}$) is 3.2 and 8 hrs for CYP2D6 EMs and PMs, respectively.

Age, renal function, presence of CHF, concomitant CYP2D6 inhibitors (amiodarone, cimetidine, fluoxetine, paroxetine and ranitidine) and concomitant beta-blockers (diltiazem and verapamil) did not influence the clearance of RSD1235. Race and hepatic function did not influence the clearance of RSD1235 in this study population; however, very few patients (8%) were not Caucasians and/or had markers of impaired hepatic function.

The typical volume of the central compartment in males was estimated to be 51.0 L in males and 26.4 L in females. When accounted for the differences in body weight, the gender differences were not significant.

Absorption, Distribution, Metabolism, Excretion

Vernakalant is administered by a two (3+2 mg/kg) 10 minute infusions. At the end of the infusion, Cmax was about 5 mcg/mL and declined sharply after that being close to LLOQ at 24 hours. The bioavailability following a 240 mg oral dose of 14C-RSD1235 was 41% for extensive metabolizers and 90% for poor metabolizers (N=2).

The steady-state volume of distribution (V_{ss}) estimate of 1.77 L/kg (147 L for 83 kg patient) indicating a high degree of tissue distribution.

The plasma protein binding of RSD1235 in human plasma is approximately 53% to 63% at therapeutic concentrations.

Vernakalant is cleared both by the liver and the kidney, however, the hepatic and renal clearances were not reported.

Cytochrome P4502D6 is the predominant enzyme involved in the O-demethylation metabolism of vernakalant. The inhibitory potential of vernakalant was very weak for CYP450 1A2, 2C9, 2C19, 2E1, and 3A4. The in vitro studies suggested that vernakalant is neither a reversible nor

irreversible inhibitor of the above mentioned cytochromes and it is a moderate (IC_{50}=20.1 mcM) and competitive (K_i =3 mcM) inhibitor of CYP2D6.

Drug-drug interaction information
The in vivo PK interactions of vernakalant with other drugs have not being evaluated in this NDA.
The interactions with P-glycoproteins have not been assessed. The sponsor should determine whether vernakalant is a substrate or inhibitor of PgP or any other transporters.

Pediatric Patients
The pharmacokinetics of vernakalant in children has not being studied in this NDA.

Exposure-Response Relationships
Effectiveness
Logistic regression analyses were performed using efficacy data from evaluable patients in studies 04-7-010 and 1235-703. The analyses indicate that conversion to normal sinus rhythm within 90 minutes after start of the vernakalant infusion is not correlated with RSD1235 exposure (Cmax) within the studied exposure range under 3+2 mg/kg dosing regimen.
Patients with their most recent onset of atrial fibrillation episode less than 7 days from vernakalant dosing had significant higher response rates compared to patients with duration of the most recent episode >7 days.

Safety
Vernakalant was found to prolong the QT interval with a mean predicted QT change from baseline of 20 and 23 msec at the mean peak RSD1235 concentration (Cmax) of 3660 and 4330 ng/mL after vernakalant doses of 3 and 3+2 mg/kg, respectively.
The mean ΔQTcF is predicted to return to normal within 6 hours for CYP2D6 EMs and 12 hours for PMs after single 3 mg/kg and 12 and 24 hours after 3+2 mg/kg.
ECG monitoring should be continued for at least 6 hours postdose until the QTc is within normal limits for CYP2D6 EMs and 12 hours for CYP2D6 PMs receiving 3 mg/kg.

Benefit-Risk Ratio/ Dosage Regimen
The drug has demonstrated a benefit over placebo in patients with AF.

Biopharmaceutics
No information on biopharmaceutics was submitted for the NDA 22-034.

2 QUESTION BASED REVIEW

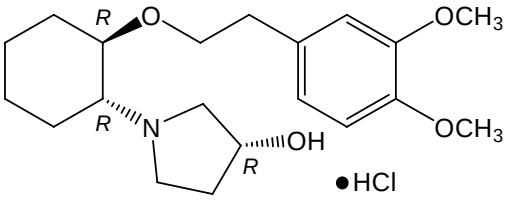
2.1 General Attributes

History of Regulatory Development

NDA 22-034 was originally submitted for review 03/30/2006. This submission was issued a Refusal to File (RTF) Letter on 05/18/2006. The RTF Letter did not have any comments from clinical pharmacology. NDA 22-034 was re-submitted on 12/19/2006.
The information submitted in the NDA 22-034 in support of the safety and efficacy of vernakalant injection has been derived from studies conducted under the following INDs:
IND 61,848 (vernakalant hydrochloride injection) and IND 70,371 (oral formulation of vernakalant hydrochloride held by Cardiome Pharma Corp.)
Kadenza (vernakalant hydrochloride injection) is a novel antiarrhythmic agent that achieves rapid conversion of AF to sinus rhythm through potassium and sodium channel blockade (e.g., I_{Kur}, I_{to} and I_{Na}) resulting in selective prolongation of the atrial effective refractory period and rate-dependent reduction of atrial conduction velocity.
The sponsor is seeking the approval of Kadenza (vernakalant hydrochloride injection) for rapid conversion of atrial fibrillation (AF).

Highlights of chemistry and physical-chemical properties of the drug substance and product

Vernakalant hydrochloride (RSD1235) is chemically 3-Pyrrolidinol, 1-[(1R,2R)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl]-,hydrochloride,(3R)- having a molecular weight of 385.93 and a molecular formula of C20H31NO4·HCl. The structural formula of vernakalant hydrochloride is:



The molecule is a synthetic enantiomer with three asymmetric centers. Vernakalant hydrochloride is a white to beige powder hydrochloride salt that is freely soluble in water. KADENZA is supplied as a sterile, nonpyrogenic, clear, colorless to pale yellow aqueous solution. Each mL of KADENZA contains 20 mg vernakalant hydrochloride, 8.4 mg citric acid monohydrate, 2.5 mg sodium chloride and Water for Injection, q.s. Sodium hydroxide or hydrochloric acid is added for pH adjustment to 5.5.

What are the proposed mechanisms of action and therapeutic indication?

The antiarrhythmic activity of vernakalant hydrochloride is mediated by blockade of early activating potassium channels combined with concentration-, voltage- and frequency-dependent

blockade of sodium channels. Vernakalant hydrochloride selectively prolongs atrial refractoriness and rate-dependently slows atrial conduction.

In vitro, vernakalant hydrochloride blocks I_{to}, I_{Kur}, and I_{KAch} and shows an increased block of I_{Na} at depolarized potentials and high frequencies of stimulation. Vernakalant hydrochloride also blocks I_{Kr}; however, this effect is offset by the blockade of the late sodium current. The net effect of this ion channel activity is the basis for the effectiveness and safety of Kadenza in the conversion of AF to sinus rhythm.

What are the proposed dosages and route of administration?

The sponsor recommends that vernakalant will be given as an IV infusion to patients with recent (3 hours to 7 days) onset of AF. The proposed dosing regimen is two IV infusions over 10 minutes. A first infusion of 3 mg/kg is given and if conversion to sinus rhythm does not occur within 15 minutes after the completion of the first infusion, a second infusion of 2 mg/kg is to be administered.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology program includes 7 clinical studies.
An assessment of vernakalant PK and PD in healthy subjects was performed in Study 1235-1-04-12-01, a dose ascending study (single dose); Study 04-0-195, a mass-balance study; 1235-SMH1, a Phase 2 dose ascending trial (2 doses);
The vernakalant pharmacokinetics in patients was assessed in the following studies: 1235-1001, CRAFT, two pivotal trials (1235-0703, ACTI and 04-7-010, ACTIII); and 1235-0703b, ACTI-Scene 2.
Also, metabolism, protein binding and displacement of protein binding with warfarin, quinidine, propranolol, acebutolol, diltiazem, or verapamil were studied in vitro.
The pharmacometric consult regarding the QT interval prolongation, the influence of CYP2D6 genotype, the exposure-response of vernakalant, and the sponsor's population PK data analysis was performed by C. Tornoe

Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes. The sponsor measured the concentrations of RSD1235 and metabolites RSD1231, RSD1385, and RSD1390 in human plasma and human urine by a high performance liquid chromatographic tandem mass spectrometry method. MDS Pharma (St. Laurent, Quebec, Canada) initially developed and validated the method. This method was used at the University of British Columbia (Vancouver, BC, Canada) for analysis of RSD1235 metabolites. The MDS Pharma method was modified and revalidated by Bioanalytical Systems, Inc. (West Lafayette, IN, USA) and Pharma Bio-Research Group B.V. (Assen, The Netherlands) for the bioanalysis of RSD1235 and metabolites.
All assay methods were properly validated and are acceptable, chromatograms were shown

EXPOSURE-RESPONSE RELATIONSHIP

Were the relationship between efficacy endpoints and safety endpoints and drug plasma concentration described?

Yes. Please see the PM review for details.

Dose/Exposure-Effectiveness Relationship

Within the exposure range under the 3+2 mg/kg dosing regimen, there is no evidence of exposure-response (conversion to normal sinus rhythm within 90 min of dosing) using C_{max} as a measure of exposure.
Vernakalant was found to be most effective in patients with a recent onset of an atrial fibrillation episode (i.e. less than 7 days from initiation of vernakalant dosing) compared to patients with episodes for more than 7 days.

Is there evidence of exposure-response?
Within the observed exposure range for the 3+2 mg/kg dosing regimen, there is no evidence of exposure-response (conversion to normal sinus rhythm within 90 min. of dosing) using Cmax as a measure of exposure.
Vernakalant was found to be most effective in patients with recent onset of atrial fibrillation episode (i.e. less than 7 days from initiation of vernakalant dosing) compared to patients with episodes >7 days and <45 days.

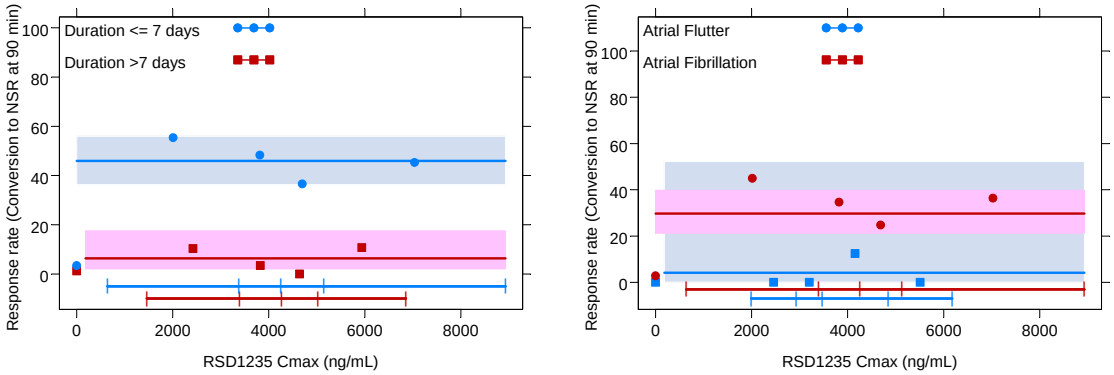


Figure 1. Exposure-response relationship for (left) duration of most recent Afib/Aflut episode less than 7 days (blue) and greater than 7 days (red) and (right) atrial flutter (blue) and atrial fibrillation (red) . The dots represent the mid-quartile RSD1235 peak concentrations and the associated observed response rate with the dots at 0 equal to the placebo response rate. The horizontal bars represent the inter-quartile Cmax ranges for the different subpopulations.

For patients with recent onset of atrial fibrillation (<=7 days), the response rate after 3 mg/kg was 37.5% and 1% for placebo. Patients not responding to the first dose received an additional 2 mg/kg where the response rate was 19% and 2.6% for placebo.

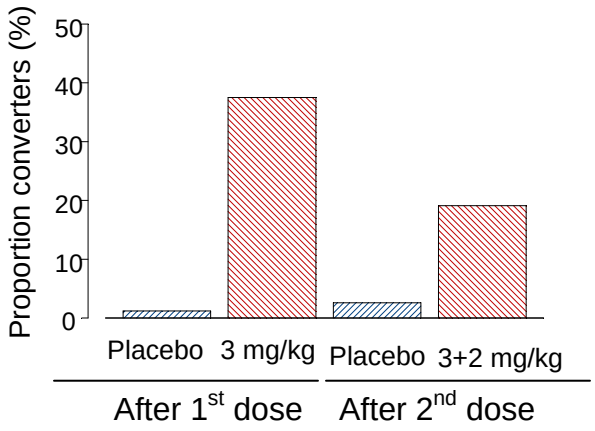


Figure 2. Proportion responders after 1st dose of 3 mg/kg and 2nd dose of 2 mg/kg within the 3 mg/kg non-responders

Duration of the most recent atrial fibrillation episode (<7 or >7 days) was found to be the most important demographic covariate for response. A total of 328 (Active:Placebo N=215:113) out of 632 atrial fibrillation patients had information about how many days since the start of their most recent atrial fibrillation episode.

As seen in **Error! Reference source not found.**, RSD1235 treated patients with <2 days since the start dosing had a response rate of 60-80% (placebo response 4-13%) whereas the response rate in patients with >2 days duration was 10-30% (placebo response 0%).

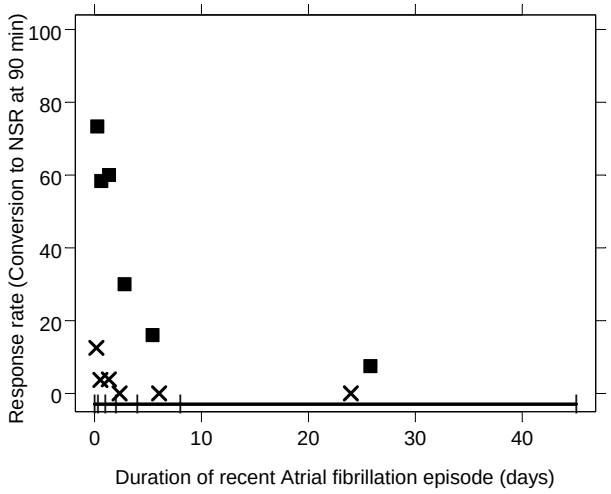


Figure 3. Response rate vs. median duration of recent atrial fibrillation episode in 0-8 hr (Active:Placebo N=15:8), 8-24 hr (Active:Placebo N=48:27), 1-2 days (Active:Placebo N=40:26), 2-4 days (Active:Placebo N=20:8), 4-8 days (Active:Placebo N=25:8), and 8-45 days (Active:Placebo N=67:36) bins. Solid square (RSD1235 treated) and cross (Placebo).

Does vernakalant prolong the QT interval?

Vernakalant was found to prolong the QT interval with a mean predicted QT change from baseline of 21 and 24 msec at the mean RSD1235 C_{max} of 3660 and 4330 ng/mL following 3 and 3+2 mg/kg 10-minute infusions, respectively.

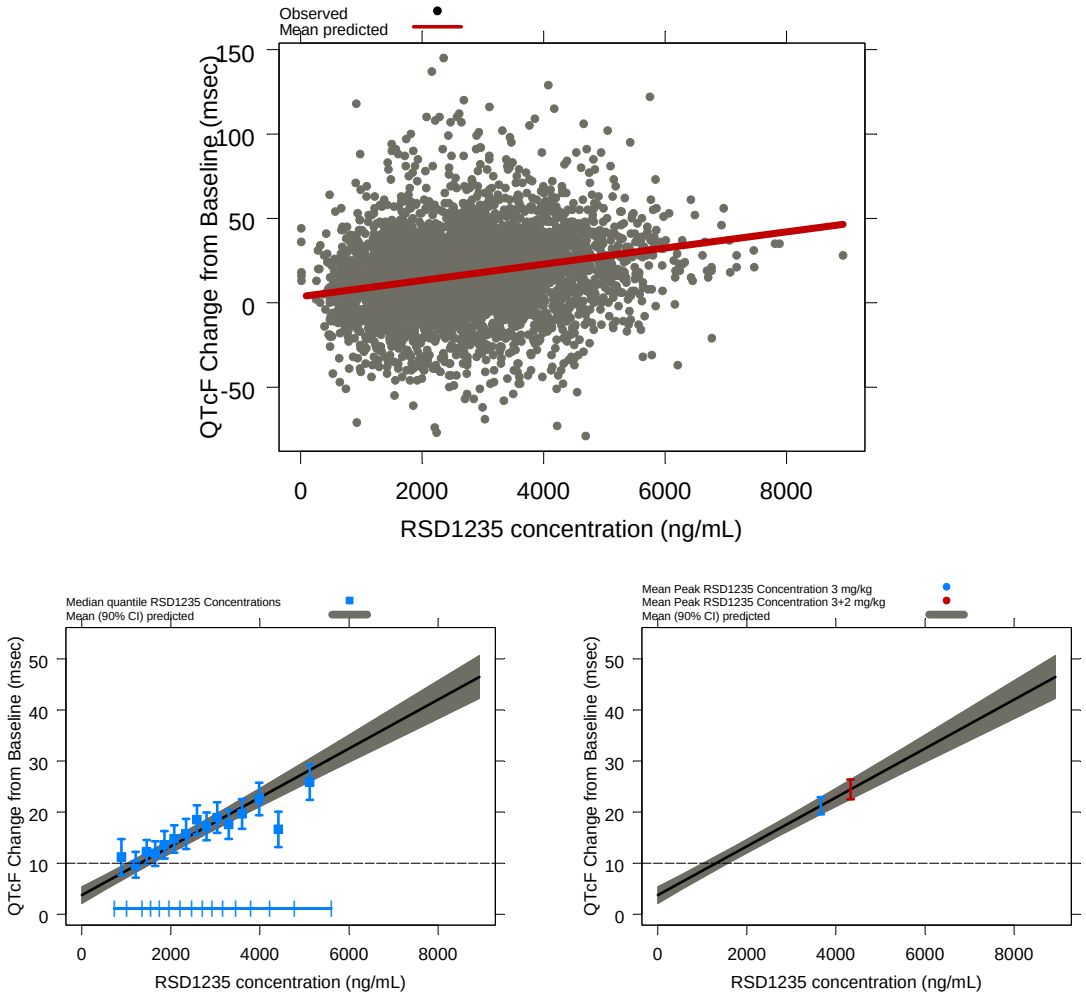


Figure 4. ΔQTcF (Change from Baseline) vs. RSD1235 concentrations. (Top) Observed concentrations vs. □QTcF. (Bottom Left) Median-quantile tedisamil concentrations and associated 90% CI together with the population predictions with 90% confidence interval (solid black line with shaded grey area). The horizontal bars show the observed RSD1235 concentrations divided into 15 bins with equal number of observations. (Bottom Right) Population predictions and associated 90% CI at mean 3 mg/kg (blue) and 3+2 mg/kg (red) peak RSD1235 concentrations

For how long time should patients be monitored after vernakalant dosing?

The population mean QT prolongation is predicted to return below 10 msec within 1 hour after vernakalant dosing for extensive CYP2D6 metabolizers and 2 hours for poor CYP2D6 metabolizers receiving 3 mg/kg and 2 and 8 hours for EMs and PMs receiving 3+2 mg/kg IV infusions. Patients should thus be monitored for at least 1 hours after the end of the IV infusion.

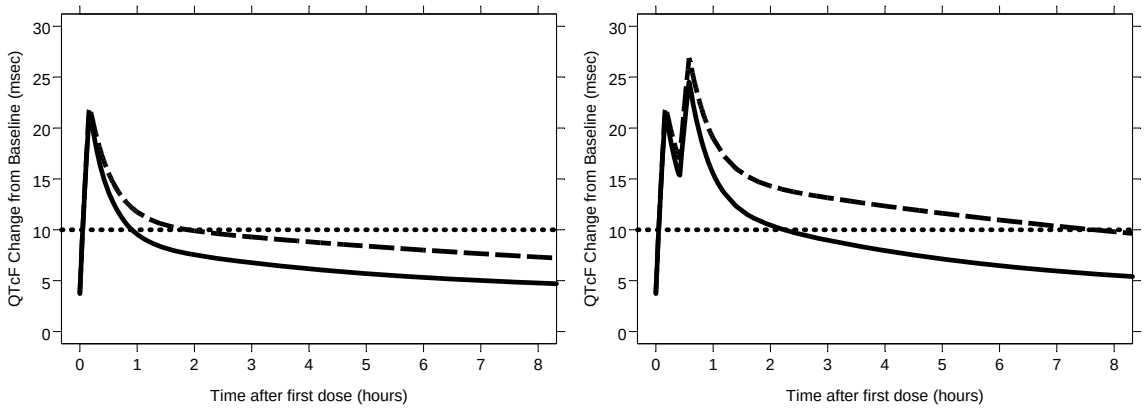


Figure 5. Population predicted RSD1235 concentration-time profiles for poor (PM, dashed) and extensive (EM, solid) metabolizers on after single 3 mg/kg IV infusion over 10 minutes (left) followed by 2 mg/kg IV infusion over 10 minutes (right). The dotted line indicates QTcF of 10 msec.

Do the proposed dosing guidelines maximize benefit-risk ratio?

Yes. Vernakalant is administered in an acute condition and under the close monitoring of conversion of AF to sinus rhythm. The sponsor's proposed dosing regimen is two IV infusions over 10 minutes. A first infusion of 3 mg/kg is given and if conversion to sinus rhythm does not occur within 15 minutes after the completion of the first infusion, a second infusion of 2 mg/kg is to be administered.

PK CHARACTERISTICS OF THE DRUG AND ITS MAJOR METABOLITE(S)

Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The PK parameters of vernakalant are dose proportional over the proposed dose range. In healthy volunteers, RSD1235 Injection demonstrated linear kinetics over the dose range of 0.1 mg/kg to 5 mg/kg following a 10-minute intravenous infusion.
The dose-normalized AUCinf values were similar across the doses (except for the dose of 4 mg/kg. The Cmax values increased in a dose-proportional manner (Figure 7).

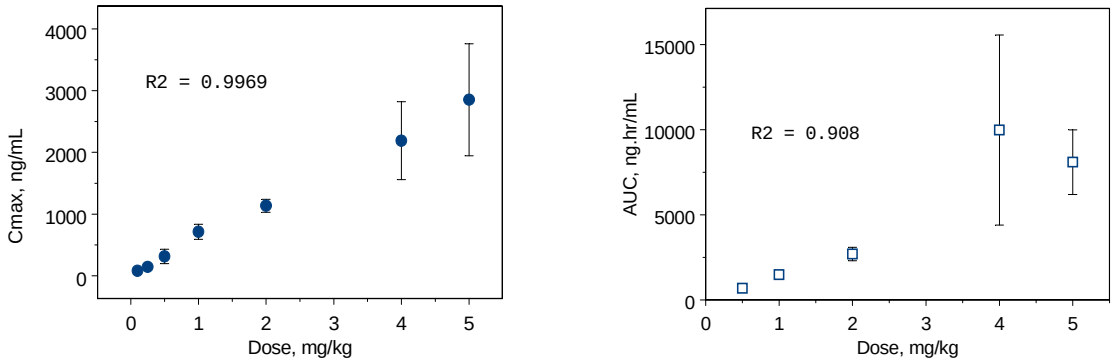


Figure 6. RSD1235 Dose-proportionality, left panel, Cmax, right panel, AUC

How do the PK parameters change with time following chronic dosing?

The proposed dose regimen is not associated with chronic administration.

What are the characteristics of drug absorption (possible transporters and pH impact)?

In atrial fibrillation and/or atrial flutter patients, Cmax was approximately 5 mcg/mL and occurred at the end of the first or second infusion. Median Cmax in the study with the largest atrial fibrillation population was 4245ng/mL for one infusion and 5200 ng/mL for 2 infusions. Plasma concentrations declined sharply at the end of the infusion, and by 24 hours postdose were close to the lower limit of quantification (LLOQ) of the assay (5 ng/mL). Mean elimination t½ was 2.25 hours for extensive metabolizers and it was prolonged in poor metabolizers from 3 to 8 hours (please see PM review).

What are the characteristics of drug distribution (including plasma protein binding?)

Vernakalant is extensively distributed into tissues. In the mass-balance study, its volume of distribution at steady state (Vss) and apparent volume of distribution (Vdz) were estimated as about 130 L and 214 L (respectively). The vernakalant distribution is similar in EMs and PMs and depends only on body weight. The population model (please see PM review) which used the data from the 1235-703 study, estimated Vss as 1.73 L/kg (147 L for a typical 83 kg patient). The plasma protein binding of vernakalant in human plasma has been studied by equilibrium dialysis and ranges from 53% to 63% at RSD1235 plasma concentrations 1.0-5.0 mcg/mL. The exposure (AUC values) to RSD1235 in whole blood was 4-fold higher in EMs and 2-fold higher in PMs in comparison with the same values in plasma. Although this may suggest drug distribution into the red blood cells, the sponsor has not evaluated the vernakalant partitioning to red blood cells.

Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study of vernakalant was performed in 5 EMs and 2 PMs. The data reported for PMs is not statistically solid and should be interpreted with caution.
The major routes of elimination of vernakalant are both hepatic and renal. The drug is extensively metabolized in liver; therefore, only about 9% (EMs) and 24% (PMs) of unchanged drug is excreted in the urine. In clinical studies, the mean urinary recovery was from 7 to 11% (without accounting for the genotype). The mean recovery of total radioactivity in urine was 93% (EMs) and 84% (PMs), and in feces it was 7% (EMs) and 6% (PMs).

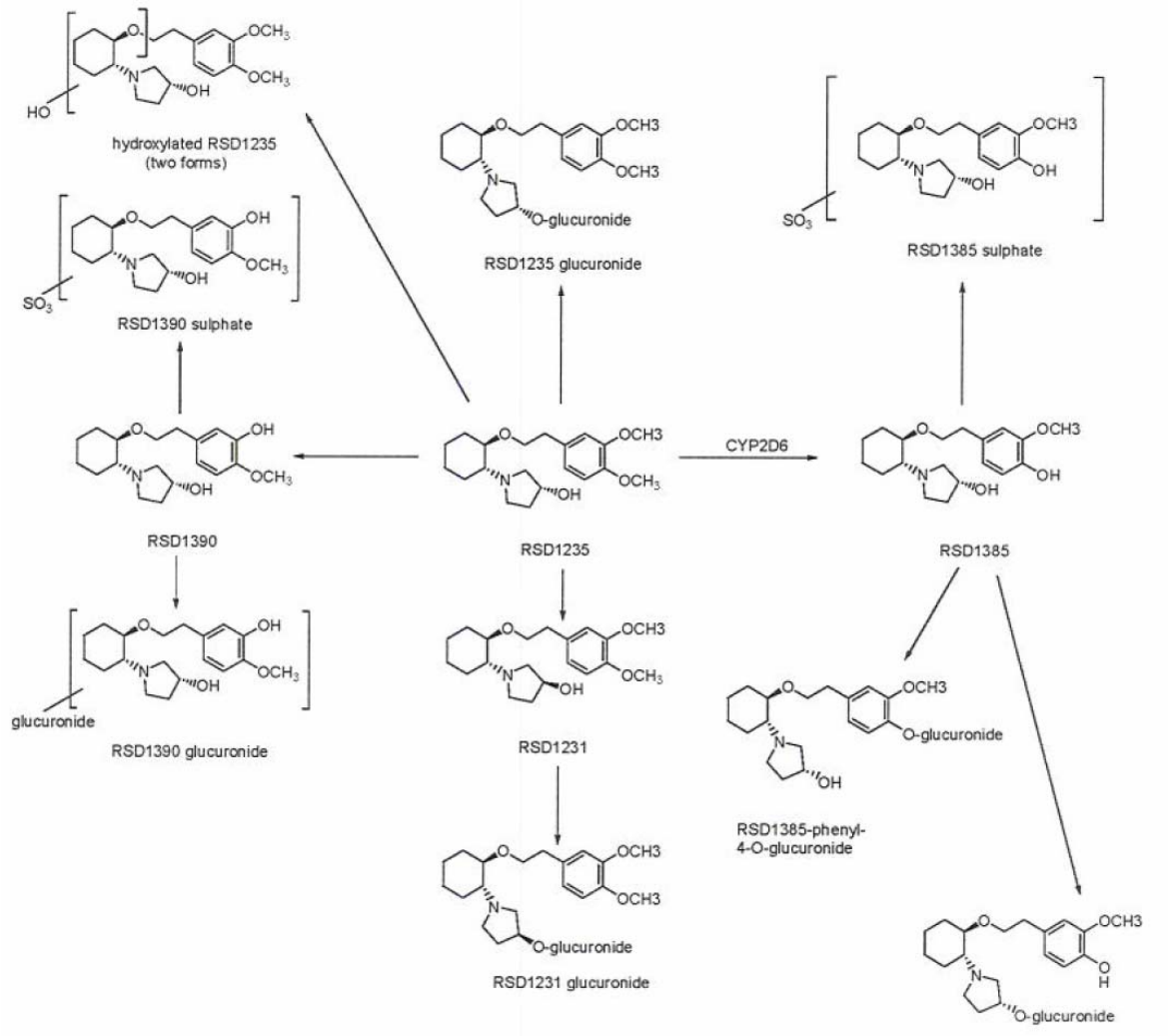
What are the characteristics of drug metabolism?

The main enzyme responsible for the metabolism of vernakalant is CYP2D6.
After incubation of vernakalant with human liver microsomes over one hour, there was a moderate decay (26%) of RSD1235. The rate of formation of the major metabolite, RSD1385 was 13%. CYP3A4 was responsible for the formation of two minor metabolites but the sponsor did not identify them in this in vitro study. The overall extent of metabolism was moderate, less than 30%.

In extensive metabolizers, (EMs) the main metabolic route for RSD1235 is 4-O-demethylation, by CYP2D6, to RSD1385, most of which is rapidly glucuronidated. The parent drug is also glucuronidated. The minor metabolic pathways are sulphatation of the demethylated metabolite, RSD1385, and/or the other demethylated metabolite, RSD1390.

In the general population (EMs) of healthy volunteers and patients with atrial fibrillation or atrial flutter, RSD1385 was the major plasma metabolite, occurring primarily in the glucuronidated form. RSD1385 achieved peak concentrations in plasma at 35-50 minutes. The exposure (AUC value) of EMs to RSD1385 was relatively small, less than 6% of the RSD1235 exposure and its AUC0-90min was dose proportional. Plasma RSD1385 concentrations were generally below the LLOQ (5 ng/mL) at 24 hours after the first infusion.
RSD1390 was undetectable or scarcely detectable; it also quickly converted to the glucuronide and/or sulphate derivative.

In poor metabolizers of CYP2D6 (PMs), the metabolism of RSD1235 is slower and less extensive. Although the RSD1235 Cmax values in both EMs and PMs are similar, the exposure to RSD1235 in PMs was 3 times larger than the same exposure in EMs. In PMs, the proportion of RSD1235 excreted unchanged in the urine was higher (24% vs. 11%). In these subjects, direct glucuronidation of RSD1235 is more important: the glucuronide of RSD1235 accounted for 72% of parent drug. A diastereomer of RSD1235, RSD1231 and its glucuronide, RSD1231G were observed in the poor metabolizers (data from 2 EM subjects) with exposure (AUC) of 14% and 3% of the parent drug. Hydroxylation of RSD1235, which is followed by excretion in the feces, was detected in poor metabolizers, although the data was limited to 2 PM subjects.
Although the comparative activities of the RSD1235 metabolites were not reported, it seems unlikely that they have a considerable impact on the total pharmacologic activity of vernakalant.



What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

Vernakalant is a moderately variable dug. The inter-individual variability for clearance was estimated as 20%, and for volume of distribution as 12 %(V1), and 79% (V2). The variability was explained by body weight as a significant covariate for RSD1235 volume of distribution as well as for clearance. (See PM review for details).

2.3 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

None of these factors was prospectively studied in the NDA.

Age

The population PK model predicts that age would not be expected to be clinically important due to the estimated precision of its effect and lack of effect on interindividual variability.

Race, in particular differences in exposure and/or response in Caucasians, African Americans, and/or Asians

The impact of race on vernakalant PK was not studied, and the data collected (small amount non-white patients) did not allow the proper analyses to be performed. In the final population PK model developed by FDA, race was not found to influence RSD1235 pharmacokinetics.

Gender

Females were found to have lower central volume of distribution in the base PK model as shown by the sponsor. This finding was however due to not having accounted for body weight's influence on RSD1235 PK parameters.
The final population PK model developed by FDA predicts that gender would not be expected to be clinically important due to the estimated precision of its effect and lack of effect on interindividual variability.

Renal Impairment

The impact of renal impairment on the PK of vernakalant was not assessed prospectively.
The sponsor compared the $AUC_{0\text{-}90min}$ and Cmax values of patients in studies 1235-0703 and 1235-0703b and found that there were similar in subjects with a different degree of renal impairment.
The population PK analysis performed by FDA revealed that the RSD1235 clearance was not correlated with CrCL when body weight was used as a covariate. This corresponds well with the fact that RSD1235 primarily is metabolized by CYP2D6.
The label recommendations should indicate that the PK of vernakalant was not assessed in renally impaired patients. Although no dose adjustment recommendation in renal impaired patients can be made, it seems unlikely that renal impairment has a clinically meaningful effect.

Hepatic Impairment

The impact of hepatic impairment on the PK of vernakalant was not assessed. Although no recommendation on dose adjustment can be made, it seems unlikely that the in the clinical setting with only one and possibly two doses of vernakalant administered, hepatic impairment would have a clinically meaningful effect on exposure requiring dosing adjustment.

What pharmacogenetic information is reported and is it important or not?

Vernakalant is metabolized by CYP2D6. Poor metabolizers of CYP2D6 represent 7-14% of general population of Caucasians and more than that in Asians and Africans.

The sponsor performed a mass-balance study evaluating the difference between PK of vernakalant in EMs and PMs. Although the sponsor reported that PMs have slower half-life and larger exposure, the data obtained from 2 PM subjects could not be extrapolated to the whole population. Therefore, the PK data from the pivotal studies were used by the PM reviewer to evaluate the particularity of vernakalant PK in PM subjects.
CYP2D6 genotyping was performed in study 125-0703 but not in study 04-7-010 for which the population PK data analyses were performed by the sponsor. The influence of genotypes on RSD1235 PK could therefore only be investigated in 221 out of 355 patients in the two pivotal studies where 9 and 179 patients were classified as poor (PM) and extensive metabolizers (EM), respectively, and 33 patients CYP2D6 genotype was not identified.
From the base PK model, PMs appear to have lower clearance. After having incorporated body weight as a covariate on CL, Q, V1, and V2, PMs were found to have 86% lower CL compared to EMs. The influence of CYP2D6 genotype on RSD1235 clearance is shown in Figure 7.

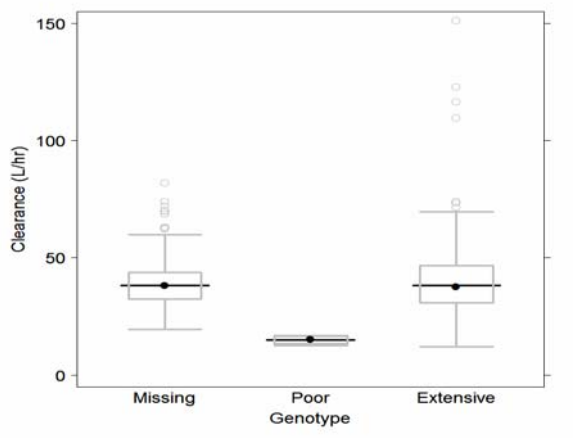


Figure 7. Vernakalant Clearance vs. CYP2D6 Genotype

In the final model, the estimated terminal population half-life ($t_{1/2,\beta}$) is 3.2 and 8 hrs for CYP2D6 EMs and PMs, respectively.
The inclusion of patient 703108804 who was a PM changed the population predicted terminal half life for PMs from 8.9 to 20 hrs (i.e. from 64 to 86% reduction in CL for PMs). He was therefore not included in the final PK analysis but it is likely that the reduction in CL for PMs is greater than 64% compared to EMs at a population mean level.

The population PK predictions following one- or two- 10 minute infusions are shown in Figure 8. The population mean predicted C_{max} after the first 3 mg/kg IV infusion is 3660 and 4330 after the 2 mg/kg IV infusion for EMs.

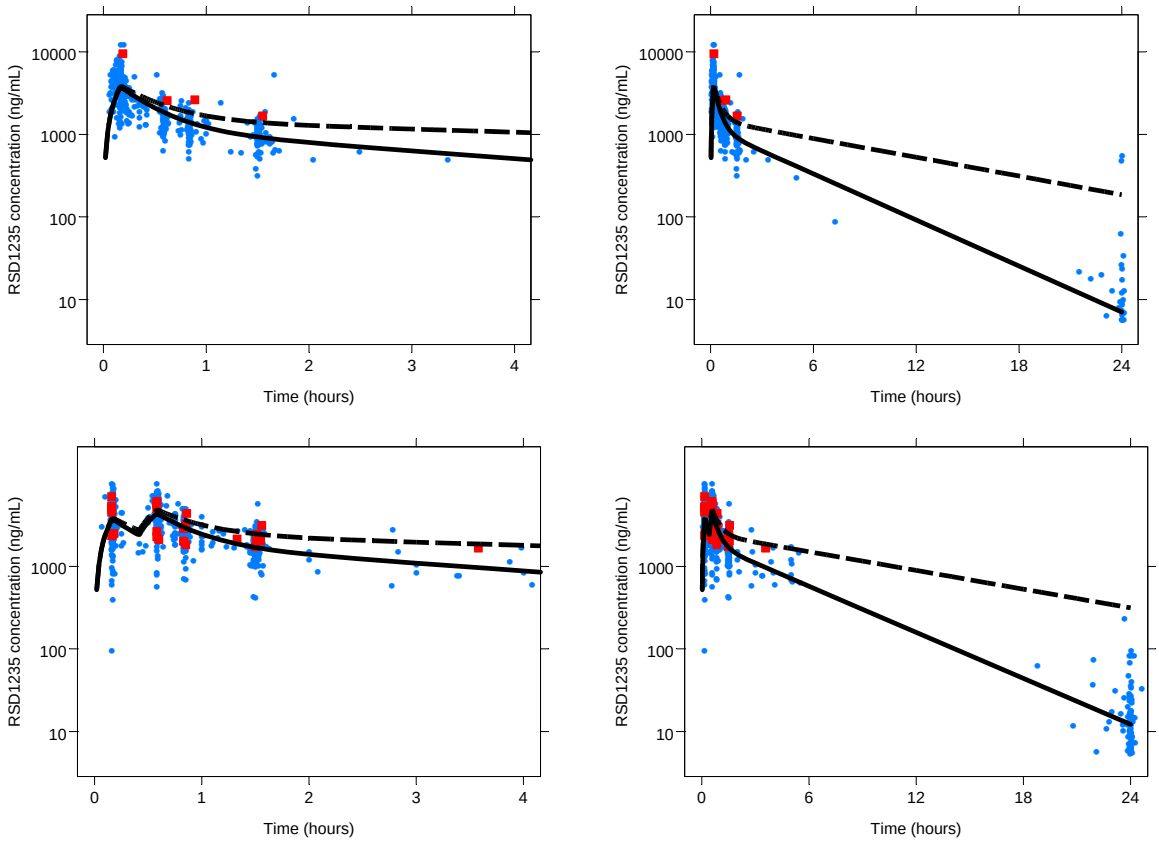


Figure 8. Population predicted RSD1235 concentration-time profiles for poor (PM, dashed) and extensive (EM, solid) metabolizers on the log scale after single 3 mg/kg IV infusion over 10 minutes (top) followed by 2 mg/kg IV infusion over 10 minutes (bottom). (Left) 0-4 and (Right) 0-24 hours profiles. Observed RSD1235 concentrations are shown as blue dots for EMs and missing while PMs are shown as red squares.

2.4 Extrinsic Factors

What extrinsic factors (herbal products, smoking, and alcohol use) influence dose-exposure and/or- response and what is the impact of any differences in exposure on response?

None of the above extrinsic factors were tested in this application.

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. Vernakalant is metabolized by CYP2D6, it is CYP2D6 inhibitor. The inhibition was determined to be moderate (IC50=20.1 mcM) and competitive (Ki=3 mcM). If this enzyme activity will be decreased by coadministration of more potent CYP2D6 inhibitors, the exposure to vernakalant is expected to increase. On the other hand, if the activity of CYP2D6 would

increase by coadministration of CYP2D6 inducers, the exposure to vernakalant is expected to decrease. The sponsor did not perform any formal drug-drug interaction studies.

What other co-medications are likely to be administered to the target population?

A number of drugs (digoxin, calcium channel blockers, beta-blockers, sotalol, and CYP2D6 inhibitors) which have a potential to interact with vernakalant were coadministered in the clinical studies. The sponsor reported that there were no adverse events associated with that coadministration.
Vernakalant is intended for the IV infusion of one or two doses in acute situation with patient monitored in ICU unit. Although the drug-drug interactions were not prospectively studied for this drug, it seems that in the clinic setting the likelihood of clinically important DDI is low.

Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No. The label states: "Use of intravenous Class III antiarrhythmic agents such as ibutilide in patients who received KADENZA has not been studied and should be administered with caution within 4 hours after exposure to KADENZA".

Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No studies were conducted to determine whether vernakalant is a substrate or inhibitor of P-glycoprotein or any other transporter.

Are there other metabolic/transporter pathways that may be important?

The minor metabolic pathway is oxidation by CYP3A4. The plasma concentrations of the RSD1390 metabolite were detected only at early times after the end of infusion, and were below the detection limit of 5 ng/mL at 3-4 hours after the end of infusion.

2.5 General Biopharmaceutics

Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

No biopharmaceutic studies were conducted with RSD1235 injection.

What is the quantitative and qualitative composition of formulation?

RSD1235 Injection is a sterile, isotonic, buffered 20 mg/mL solution of RSD1235 drug substance. Each single-use vial contains 200 mg of RSD1235 drug substance in 10 mL of 40 mM sodium citrate at pH 5.5. RSD1235 Injection is diluted prior to intravenous infusion into the patient.
RSD1235 Injection was manufactured by 2 manufacturers: Patheon and Hospira.
The composition of RSD1235 Injection is shown in Table below.

Table 1. Composition of RSD1235 Injection

Component	Reference to Quality Standard	Function	Quantity per mL (mg)
RSD1235	In-house standard	Drug Substance	20.0
Citric acid, monohydrate	USP	Buffering agent	8.4
Sodium chloride	USP	Tonicity modifier	2.5
Sodium hydroxide	NF	pH adjuster	Adjust to pH 5.5
Hydrochloric acid	NF	pH adjuster	Adjust to pH 5.5
Water for Injection	USP	Drug vehicle	QS

QS: quantity sufficient

Is the proposed dissolution method and specification acceptable?

No in vitro dissolution studies were conducted with RSD1235 injection.

What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None.

2.6 Analytical section

How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The concentrations of RSD1235 and metabolites RSD1231, RSD1385, and RSD1390 were determined in human plasma and human urine by a high performance liquid chromatographic tandem mass spectrometry method. MDS Pharma (St. Laurent, Quebec, Canada) initially developed and validated the method. This method was used at the University of British Columbia (Vancouver, BC, Canada) for analysis of RSD1235 metabolites. The MDS Pharma method was modified and revalidated by Bioanalytical Systems, Inc. (West Lafayette, IN USA) and Pharma Bio-Research Group B.V. (Assen, The Netherlands) for the bioanalysis of RSD1235 and metabolites.

What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The method was validated for RSD1235 and its metabolites at each participating laboratory. The ranges of standard curves, accuracy, precision and other assay characteristics are shown in the Assay Tables for each reviewed study.

Were the validation characteristics of the assay acceptable?

Yes. All assays have their validation reports, see individual study reviews.

What is the overall conclusion regarding NDA 22-034?

Overall the Clinical Pharmacology and Biopharmaceutics section is acceptable.

3 DETAILED LABELING RECOMMENDATIONS

GENERAL

The Agency considered that the overall information regarding Clinical Pharmacology provided in the original NDA 22-034 was appropriate.

CLINICAL PHARMACOLOGY COMMENTS

Labeling Comments:

CLINICAL PHARMACOLOGY Section should state:

Pharmacokinetics
In Healthy Volunteers
Following a 10-minute IV infusion, vernakalant exhibits linear pharmacokinetics for doses ranging from 0.1 mg/kg to 5 mg/kg.

In Patients
Pharmacokinetics were evaluated in two phase 3 studies (n=200 and n=128). The estimated terminal population half-life was 3.2 with a steady-state volume of distribution (Vss) estimate of 1.77 L/kg (147 L for 83 kg patient) indicating a high degree of tissue distribution.
The population mean predicted peak plasma concentration after the first 3 mg/kg IV infusion was 3660ng/mL and 4330ng/mL after the 3+2 mg/kg IV infusion.
A total of 9 patients in study 1235-703 were classified as poor CYP2D6 metabolizers (PMs). The peak plasma concentration and the volume of distribution values of parent (active) drug were similar in both poor and extensive metabolizers (EMs). The exposure of the drug, as well as the rate of elimination increased in PMs compared to EMs. The RSD1235 clearance was found to be 64% lower for PMs (37.4 L/hr vs. 13.6 L/hr) compared to extensive metabolizers increasing the terminal half-life from 3.2 hrs to 8 hrs for CYP2D6 PMs.
Body weight was identified as a significant covariate for RSD1235 volume of distribution as well as clearance.
Age, creatinine clearance, gender, and race were not found to influence RSD1235 pharmacokinetics.

No dose adjustment of KADENZA is needed for special populations (see CLINICAL STUDIES [14]).

Vernakalant hydrochloride is not highly bound to human serum proteins. Free fraction of vernakalant was determined to be approximately 57% in the plasma concentration range of 1.0 to 5.0 mcg/mL.

DRUG INTERACTION:

This Section should state:

No formal drug interaction studies have been conducted with KADENZA. Although in clinical studies KADENZA was coadministered with digoxin, calcium channel blockers (diltiazem and verapamil), and beta-adrenergic blocking agents (metoprolol, atenolol, bisoprolol, carvedilol, nadolol and pindolol), sotalol, or CYP2D6 inhibitors, and warfarin their exact effect on the pharmacokinetics of vernakalant is not known.

4 APPENDICES

4.1 Individual Study Reviews

4.1.1 A PHASE I, PROSPECTIVE, RANDOMIZED, SINGLE-BLIND, PLACEBO-CONTROLLED, ASCENDING-DOSE TOLERANCE STUDY OF RSD1235 IN HEALTHY VOLUNTEERS WITH PRELIMINARY PHARMACOKINETIC ASSESSMENT (1235-1-04-12-01)

Investigator: J C. Kisicki, MD
Study Center: A single-center study.
Studied period: 11 Apr 2001 - 01 Jun 2001
Phase of development: 1

Objectives	• To determine the safety of ascending single doses of intravenous (IV) RSD1235 and to assess the pharmacokinetic parameters in healthy, normal volunteers
Study Design	An ascending dose, single IV dose, single-blind, placebo-controlled, randomized study
Population	29 subjects healthy were enrolled, and 28 subjects completed the study. PK data were reported for 23 subjects who received RSD1235. genotyped for CYP2D6 metabolism. Age: 18 to 55 years, weight: 70 to 100 kg
Treatments	A: either 0.10 mg/kg/150 mL, 0.25 mg/kg/150 mL, 0.50 mg/kg/150 mL of RSD1235 solution, or 150 mL placebo solution B: either 0.5 mg/kg/150 mL or 150 mL placebo solution C: either 1.0 mg/kg/150 mL or 150 mL placebo solution. D: either 2.0 mg/kg/150 mL or 150 mL placebo solution E: either 4.0 mg/kg/150 mL or 150 mL placebo solution F: either 5.0 mg/kg/150 mL or 150 mL placebo solution Placebo: 0.9% sodium chloride solution.
Administration	Single IV dose of 240 mg (10 mL/min by infusion pump)
Lot & Batch Number	RSD1235: Lot No. CTM-F01007 Placebo: Lot No. 74-114-JT
Administration	Approximately 1 hour after a standard meal
Sampling	Plasma: pre-dose, 0 hour, and at 0.167, 0.250, 0.417, 0.667, 1.167, 2.167, 4.167, 6.167, 8.167, and 24.167 hours from the start of the 10-minute infusion of RSD1235. Urine: each time a subject voided and were pooled over the periods: predose (prior to start of infusion), and at 0-1 hour, 1-2 hours, 2-4 hours, 4-8 hours, 8-12 hours and 12 hours-discharge following dose.
PK Assessment	Pharmacokinetic analysis was performed on RSD1235 plasma and urine data. Parameters calculated were Cmax, Tmax, AUC(0-t), AUC(0-inf), T1/2, Kel, CL, and dose-normalized AUC(0-inf) [AUC(0-inf)/Dose], weight-normalized CL (CL/Wt), and weight-normalized Vd (Vd/Wt). For each collection period, urine drug concentration, volume, amount (Ae), dose-normalized Ae (Ae/Dose), excretion rate, cumulative amount (Tot Ae), weight-normalized Tot Ae (Tot Ae/Wt), and dose-normalized Tot Ae (Tot Ae/Dose) were presented. Overall pharmacokinetic parameters were

	presented for each dose level, and included Tot Ae, Tot Ae/Wt, Tot Ae/Dose, renal clearance (CLr), weight-normalized CLr (CLr/Wt), and % dose excreted in urine.
Assay	LC/MS/MS & radioactivity measurement
Safety Assessment	vital signs, physical examinations, 12-lead ECGs, telemetry, adverse event and serious adverse event assessment, and laboratory evaluations (hematology, chemistry and urinalysis).

Results:
The study was stopped at the 5 mg/kg dose level due to Subject 28 meeting the stopping criteria of QTc > 500 msec.

Demographics
Demographic descriptions of the subjects by overall characteristics are summarized below:

Table 2. Demographic characteristics

		Female	Male	All
Race	Black	1	0	1
	Caucasian	6	20	26
	Hispanic	0	1	1
Frame Size	Small	3	2	5
	Medium	4	16	20
	Large	0	3	3
Age	Mean	40	27	30
	S.D.	6	8	9
	Minimum	28	19	19
	Maximum	46	47	47
	N	7	21	28
Weight (kg)	Mean	63.5	77.5	74.0
	S.D.	6.4	6.7	9.0
	Minimum	53.6	68.1	53.6
	Maximum	69.9	93.5	93.5
	N	7.0	21.0	28.0
Height (cm)	Mean	167	181	177
	S.D.	5	5	8
	Minimum	157	173	157
	Maximum	173	191	191

Phenotyping CYP2D6 did not reveal any poor metabolizers.

Assay
The LC/MS/MS method of detection of RSD1235 in human plasma (No. 001614IOOL) and urine (No. 002865/OUO) was developed and validated at MDS PHARMA.

Table 3. Assay Characteristics of RSD1235 in Plasma and Urine

Parameter	Plasma	Urine
Linearity	5 ng/mL to 6037 ng/mL	100 to 9961 ng/mL
Precision (CV %)	≤ 13.7	<12.2
Accuracy, %	- 6.6 to 1.8	-4. 6 to 10.3
LLOQ	5ng/mL	100 ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown	

Pharmacokinetics

Plasma

The mean plasma RSD1235 concentrations versus time curves for the 7 treatment dose levels and for the placebo are presented in.

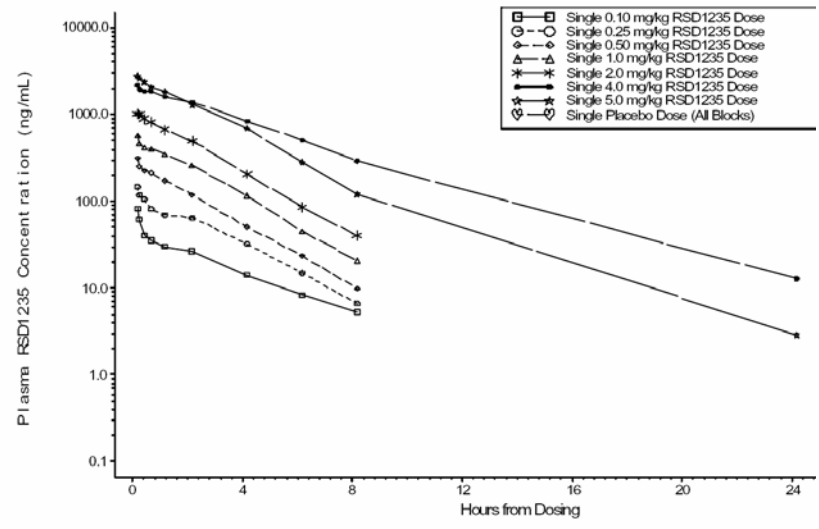


Figure 9. Mean Plasma RSD1235 Concentrations Versus Time

The PK parameters are shown in Table below:

Table 4. Summary of the Pharmacokinetic Parameters of RSD1235

Pharmacokinetic Parameters	0.10 mg/kg Dose Arithmetic Mean	SD	N	0.25 mg/kg Dose Arithmetic Mean	SD	N	0.50 mg/kg Dose Arithmetic Mean	SD	N	1.0 mg/kg Dose Arithmetic Mean	SD	N
Cmax(ng/mL)	82.69	.	1	144.73	.	1	315.71	115.39	4	714.77	121.92	4
Tmax(hr)	0.180	.	1	0.185	.	1	0.192	0.038	4	0.178	0.009	4
AUC(0-t)(ng*hr/mL)	152.04	.	1	333.37	.	1	660.61	131.96	4	1433.51	232.67	4
AUC(0-inf)(ng*hr/mL)	171.48	.	1	350.75	.	1	685.79	142.45	4	1483.23	226.50	4
AUC(0-inf)/Dose((ng*hr/mL)/mg))	22.36	.	1	20.45	.	1	18.47	3.82	4	19.54	4.85	4
T1/2(hr)	2.58	.	1	1.82	.	1	1.66	0.31	4	1.63	0.18	4
Kel(1/hr)	0.269	.	1	0.380	.	1	0.427	0.071	4	0.430	0.049	4
CL(mL/min)	745.491	.	1	814.921	.	1	938.367	233.594	4	894.296	227.213	4
CL/Wt(mL/min/kg)	9.720	.	1	11.879	.	1	12.594	2.885	4	11.424	1.642	4
Vd(L)	166.252	.	1	128.529	.	1	133.049	30.621	4	126.231	33.415	4
Vd/Wt(L/kg)	2.168	.	1	1.874	.	1	1.783	0.367	4	1.615	0.318	4
CLr(mL/min)	170.30	.	1	148.33	.	1	84.29	22.03	4	55.98	19.19	4
CLr/Wt(mL/min/kg)	2.22	.	1	2.16	.	1	1.12	0.26	4	0.71	0.16	4
%Dose Excreted	22.84	.	1	18.20	.	1	9.31	3.17	4	6.17	0.55	4

Pharmacokinetic Parameters	2.0 mg/kg Dose Arithmetic Mean	SD	N	4.0 mg/kg Dose Arithmetic Mean	SD	N	5.0 mg/kg Dose Arithmetic Mean	SD	N
Cmax(ng/mL)	1135.92	104.76	4	2189.70	632.08	4	2851.81	907.35	4
Tmax(hr)	0.217	0.055	4	0.179	0.010	4	0.319	0.245	4
AUC(0-t)(ng*hr/mL)	2598.66	413.36	4	9797.85	5653.01	4	8012.46	1975.01	4
AUC(0-inf)(ng*hr/mL)	2696.94	393.78	4	9982.12	5586.53	4	8097.56	1901.71	4
AUC(0-inf)/Dose((ng*hr/mL)/mg))	19.78	3.25	4	32.91	17.61	4	21.45	4.33	4
T1/2(hr)	1.68	0.22	4	2.56	1.00	4	2.15	0.78	4
Kel(1/hr)	0.418	0.059	4	0.305	0.119	4	0.359	0.132	4
CL(mL/min)	858.664	130.987	4	648.653	361.646	4	806.044	193.274	4
CL/Wt(mL/min/kg)	12.550	1.746	4	8.704	4.872	4	10.755	2.661	4
Vd(L)	125.349	29.352	4	121.351	24.785	4	144.054	38.570	4
Vd/Wt(L/kg)	1.850	0.478	4	1.618	0.330	4	1.881	0.348	4
CLr(mL/min)	90.97	23.64	4	78.75	29.66	4	83.73	12.39	4
CLr/Wt(mL/min/kg)	1.38	0.51	4	1.04	0.35	4	1.11	0.16	4
%Dose Excreted	10.86	3.66	4	15.25	9.02	4	10.58	1.45	4

The dose-normalized AUCinf values were similar across the doses (except for the dose of 4 mg/kg. The Cmax values increased in a dose-proportional manner. Reviewer verified the sponsor's assumptions graphically (below)

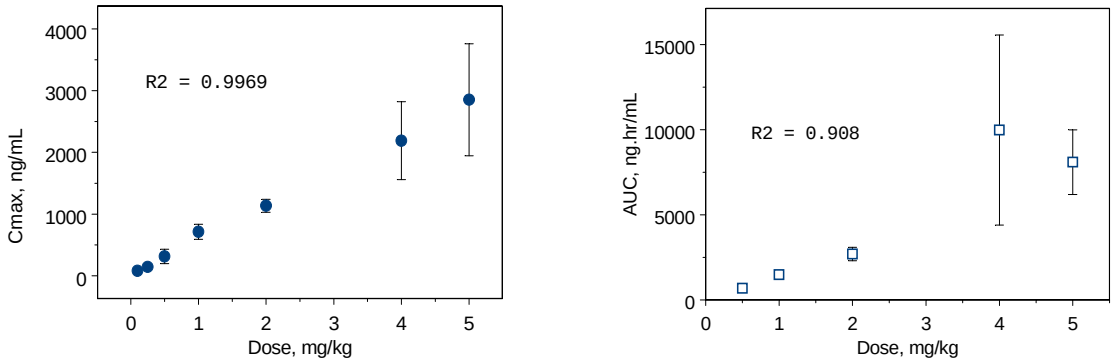


Figure 10. RSD1235 Dose-proportionality, left panel, Cmax, right panel, AUC

RSD1235 has a short elimination half-life ~ 2 hours, a high volume of distribution ~ 2 L/kg indicating extensive deep tissue and/or peripheral tissue binding. The total body clearance of RSD1235 was 794 mL/min and 113 mL/min for renal clearance (CLr).

Urine

The mean weight-normalized cumulative amounts of RSD1235 excreted in urine versus time curves for the 7 dose levels and for placebo are presented in.

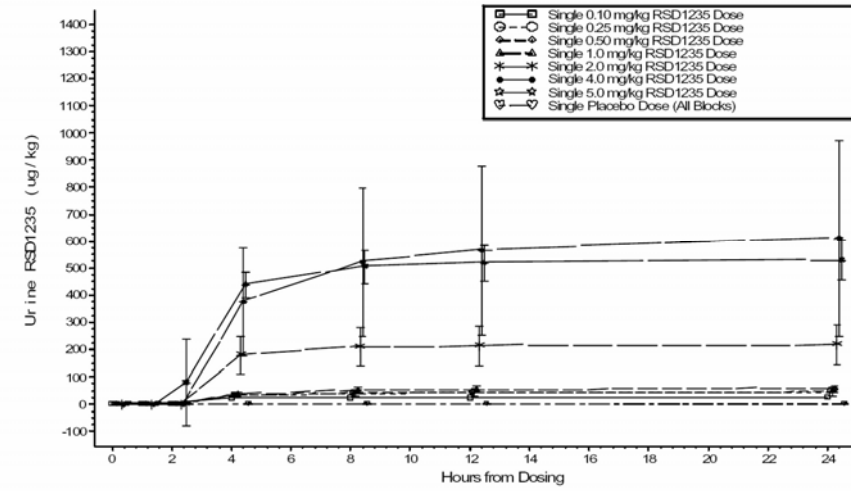


Figure 11. Mean Weight Normalized Cumulative Urine RSD1235 Amount vs Time

For all dose levels, the majority of the dose was excreted in urine by 8 hours postdose; however, detectable RSD1235 concentrations were reported in urine for all subjects in the 12 hours to discharge collection interval.

Total body clearance of RSD1235 ranged from 649 to 938 mL/min, and CLr ranged from 37 mL/min to 170 mL/min. The percent of RSD1235 dose excreted unchanged in urine was approximately 11 $\pm$ 6%, with individual values ranging from 5.4% to 25.8%.

COMMENTS:

1. RSD-1235 showed dose-proportional pharmacokinetics in healthy volunteers. The variability in pharmacokinetics was low.
2. At the dose of 5 mg/kg, the QT interval was prolonged to more than 500 msec. This dose was not further used in humans.

4.1.2 A PHASE I, OPEN-LABEL, SINGLE INTRAVENOUS DOSE AND SINGLE ORAL DOSE, MASS-BALANCE STUDY TO ASSESS THE DISPOSITION OF 14C-LABELED RSD1235 IN HEALTHY HUMAN VOLUNTEERS (04-0-195)

Investigator(s): S.P. van Marle, MD Study Center(s): Pharma Bio-Research Group BV, Stationsweg 163, 9471 GP Zuidlaren, The Netherlands
Study Period: Approximately 4 months
Study Dates: 26 April 2005 - 24 August 2005
Phase 1

Objectives	• To define the pharmacokinetics and disposition of RSD1235 and its metabolites in humans after a single 240 mg intravenous (IV) dose of 14C-labeled RSD1235 and, after a single 240 mg oral dose of 14C-labeled • To obtain a mass balance estimate in humans after a single 240 mg IV dose of 14C-labeled RSD1235, and after a single 240 mg oral dose of 14C-labeled RSD1235, with a 21 day washout period between IV and oral dosing. • To assess safety and tolerability of RSD1235.
Study Design	An open-label, single-center, single IV and oral dose, single sequence crossover, mass-balance study. Subjects were administered study drug as in patients and remained confined for one week following each dose, with a subsequent 2-week follow-up period as outpatients. Enrollment was stratified by CYP2D6 genotype: 6 EM and 2PM Day 1: IV infusion RSD1235. Day 8: Subjects were released on day 21. Day 22: Single oral dose of RSD1235. Day 29: Subjects were released on Day 42 (radioactivity residual measurements)
Population	Eight healthy subjects, genotyped for CYP2D6 metabolism. Age: 18 to 55 years, weight: 70 to 100 kg
Investigational Drug	14C-labeled RSD1235·HCl solution for infusion 14C-labeled RSD1235·HCl gel cap Lot Numbers: 60032NOV04-02 Manufactured by ABC Laboratories, Inc., Columbia, MO, USA.
Dosage	Single IV dose of 240 mg (10 mL/min by infusion pump) Single oral dose of 240 mg with 250 mL of water
Administration	Approximately 1 hour after a standard meal
PK Assessment	Plasma and urine concentration data for RSD1235 and its metabolites are listed and summarized statistically. Plasma, whole blood, urine, feces and saliva total 14C radioactivity data are listed and summarized
Assay	LC/MS/MS & radioactivity measurement
Safety Assessment	vital signs and weight, physical examinations, 12-lead ECGs, telemetry, adverse event and serious adverse event assessment, and laboratory evaluations (hematology, chemistry and urinalysis).

RESULTS
Demographics: All 8 subjects enrolled in the study were male. Six subjects were white, one was

black and one was Asian. The subjects ranged from 21 to 42 years of age, with a median of 32 years.

Five subjects were characterized as "extensive metabolizer" for CYP2D6 genotype, one (Subject 14180005) was an "intermediate metabolizer". Two subjects were CYP2D6 poor metabolizers.

Table 5: Assay Characteristics in Plasma

Parameter	RSD1235		RSD1385		RSD1390	
Linearity	5 ng/mL to 5000 ng/mL		5 ng/mL to 2000 ng/mL		5 ng/mL to 500 ng/mL	
	free	total	free	total	free	total
Precision (CV %)	≤ 10%	<11.7	<8.7	<10.6	<11.5	<13.1
Accuracy, %	0.3 to 4.3	-1.2 to -0.1	-1.0 to 1.6	3.3 to 5.5	-1.1 to 1.4	-4.2 to 3.0
LLOQ	5ng/mL		5ng/mL		5ng/mL	
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown					

Table 6. Assay Characteristics in Urine

Parameter	RSD1235	RSD1385	RSD1390
Linearity	100 ng/mL to 20000 ng/mL	50 ng/mL to 10000 ng/mL	50 ng/mL to 10000 ng/mL
	free	free	free
Precision (CV %)	≤ 3.4	<2.8	< 3.4
Accuracy, %	-9.5 to -3	-8.4 to 1.3	-7.2 to 2
LLOQ	100ng/mL	50ng/mL	50 ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

PK profiles

Plasma

RSD1235 and the 2 phase 1 metabolites, RSD1385 and RSD1390, were known to undergo phase 2 metabolism primarily via glucuronidation. The expected glucuronidated metabolites were measured indirectly after cleavage of the glucuronide. In selected samples a diastereomer of RSD1235, RSD1231 and its glucuronide, RSD1390G were measured using LC/MS/MS-2. The samples selected for analysis using the LC/MS/MS-2 methodology were plasma and urine samples between 0 and 24 hours after the IV infusion for 2 EMs and 2 PMs.

The mean plasma concentration-time profiles for RSD1235 and its metabolites (from both LC/MS/MS and LC/MS/MS-2 methods) are illustrated below. The most apparent differences between extensive and poor CYP2D6 metabolizers were that EMs had higher mean concentrations of RSD1385G, a shorter RSD1235 half-life, and lacked any measurable levels of RSD1231 and RSD1231G in plasma and urine.

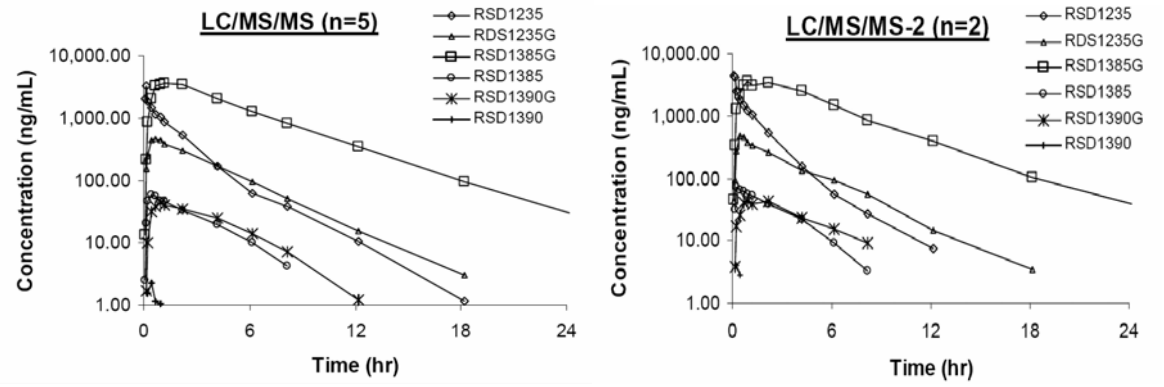


Figure 12. IV Infusion: Mean Plasma RSD1235 and Metabolites Concentrations (ng/mL) for EMs

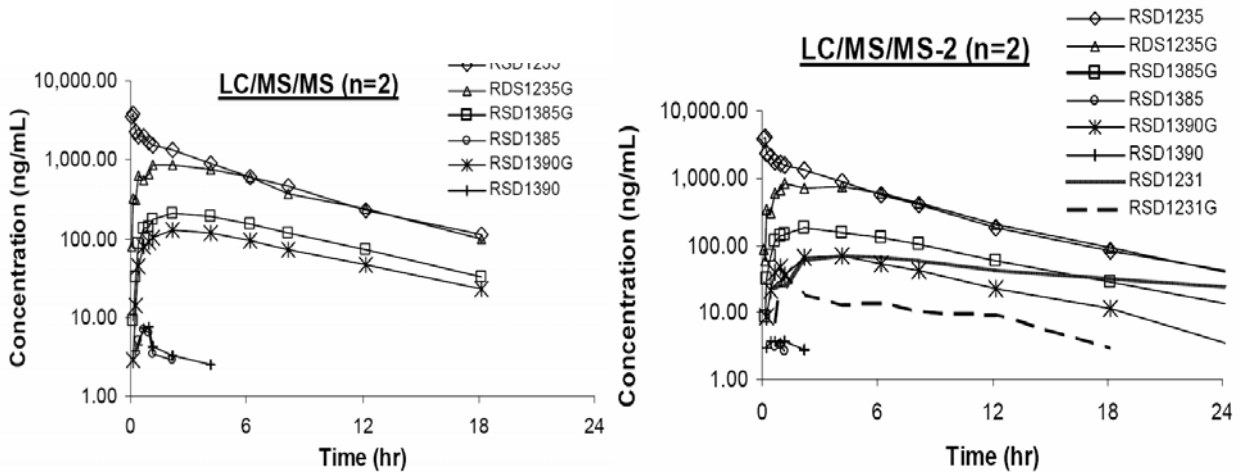


Figure 13. IV Infusion: Mean Plasma RSD1235 and Metabolites Concentrations (ng/mL) for PMs

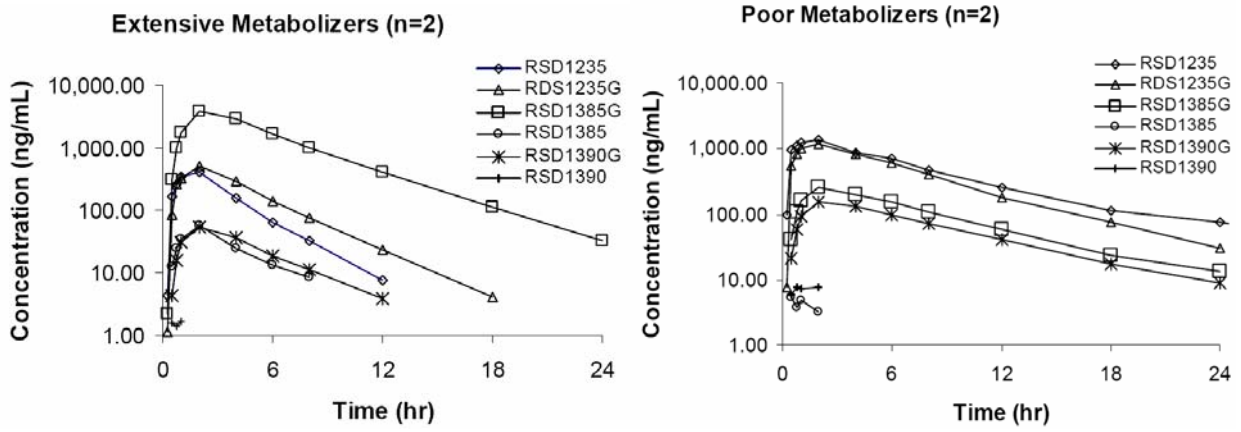


Figure 14. Oral Dose: Mean Plasma RSD1235 and Metabolites Concentrations (ng/mL), LC/MS/MS

The mean terminal half-life of RSD1235 following the IV dose was 2.25 hours for extensive CYP2D6 metabolizers (n=5) and 8.20 hours for the poor CYP2D6 metabolizers (n=2). The mean Vss was 126.38 L for EMs and 132.90 L for PMs. The Vdz was 214.57 L for EMs and 210.64 L

for PMs. The mean plasma clearance of RSD1235 was higher for EMs (65.66 L/hr) compared to PMs (17.66 L/hr). The mean renal clearance was 5.80 L/hr for EMs and 4.17 L/hr for PMs. Following oral dosing, the bioavailability in EMs was lower than in PMs (41.16% vs. 90.04 %) The absorption in all subjects was fast with a mean Tmax of 1.44 hours and a mean Cmax of 898 ng/mL.
The RSD1390 metabolite was not detectable in plasma for most time points throughout the study. The primary metabolite for EMs was RSD1385G. The primary metabolite for PMs was RSD1235G. The EMs convert RSD1235 to RSD1235G at a faster rate (Tmax: 0.52 vs 1.67 hrs) but with a lower Cmax (502 versus 886 ng/mL) compared to PMs. For RSD1385G, the Tmax for EMs occurred slightly faster (1.42 vs. 2.17 hrs) with higher Cmax (3737 versus 203 ng/mL) compared to PMs. For RSD1390G, the Tmax for EMs occurred earlier (0.92 vs. 2.17 hrs) and the Cmax was lower (49.8 vs. 128.8 ng/mL) compared to PMs.

Table 7. Pharmacokinetic Parameters of RSD1235 and Metabolites in CYP2D6 Extensive and Poor Metabolizers Following 240 mg 14C-RSD1235 IV Infusion (method 2)

Analyte	CYP2D6 Metabolism [n]	Arithmetic Mean±SD Parameters [n, if different than rest]			
		C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (hr·ng/mL)
RSD1235	Extensive [2]	4232.50±1798.173	0.17±0.00	2.10±0.251	3965.13±126.817
	Poor [2]	3971.50±1047.225	0.13±0.062	5.66±0.199	11024.43±1239.436
RSD1235G	Extensive [2]	471.00±5.657	0.42±0.000	3.07±0.841	1675.35±121.161
	Poor [2]	942.00±213.546	1.67±0.707	5.22±0.675	7925.05±332.717
RSD1385	Extensive [2]	76.30±12.445	0.46±0.297	1.93±0.035	226.68±104.965
	Poor [2]	6.61 [1]	0.92 [1]	0	0
RSD1385G	Extensive [2]	3613.30±286.378	1.55±0.884	3.58±0.353	22784.69±771.210
	Poor [2]	180.50±48.790	2.17±0.00	5.71±0.680	1935.57±360.299
RSD1390	Extensive [2]	7.86 [1]	0.25 [1]	NA	NA
	Poor [2]	7.44 [1]	0.42 [1]	NA	NA
RSD1390G	Extensive [2]	44.00±4.384	1.55±0.884	3.12±0.787	245.18±23.547
	Poor [2]	70.45±14.345	3.17±1.414	5.88±0.792	770.00±175.403
RSD1231	Extensive [2]	[0]	[0]	[0]	[0]
	Poor [2]	69.55±9.122	4.17±0.000	14.00±0.493	1523.26±190.142
RSD1231G	Extensive [2]	[0]	[0]	[0]	[0]
	Poor [2]	38.45±29.911	2.67±2.121	12.24±4.446	308.83±20.266

Extensive metabolizers: Subject Nos. 1418001 and 1418002
Poor metabolizers: Subjects Nos. 1418007 and 1418008

The LC/MS/MS-2 assay method had different results only for the PMs: it allowed the separation of RSD1231 and RSD1231G from RSD1235 and RSD1235G. The t1/2 of RSD1235 was calculated as 5.66 hours compared to 8.20 hours from the method 1.

Whole Blood
The mean whole blood pharmacokinetic parameters for 14C-RSD1235 are summarized in the Table below.

Table 8. Sponsor's PK Parameters of RSD1235 in Whole Blood

SUBJECT NUMBER	Tmax (hr)	Cmax (ngEq/mL)	AUC(0-t) (hr*ngEq/mL)	AUC(0-inf) (hr*ngEq/mL)	T1/2 (hr)
PM SUBJECTS 7,8					
N	2	2	2	2	2
MEAN	0.17	4817.99	25254.91	26107.09	5.97
STD	0.000	1589.331	4390.186	4594.095	1.611
SE	0.000	1123.827	3104.330	3248.516	1.139
MEDIAN	0.17	4817.99	25254.91	26107.09	5.97
MIN	0.2	3694.2	22150.6	22858.6	4.8
MAX	0.2	5941.8	28359.2	29355.6	7.1
CV	0.0	33.0	17.4	17.6	27.0
GEOMETRIC MEAN	0.17	4685.09	25063.39	25904.19	5.86
EM SUBJECTS 1-4,6					
N	5	5	5	5	5
MEAN	0.72	3891.48	17850.11	18450.10	3.15
STD	0.371	993.979	3237.645	3106.602	0.354
SE	0.166	444.521	1447.919	1389.315	0.158
MEDIAN	0.67	3575.48	19736.86	20033.80	2.99
MIN	0.2	3145.2	12656.8	13291.6	2.9
MAX	1.2	5637.7	20387.7	21026.0	3.8
CV	51.5	25.5	18.1	16.8	11.2
GEOMETRIC MEAN	0.61	3805.77	17584.95	18212.69	3.13

The mean terminal half-life of 14C following the IV dose was 3.15 hours for extensive metabolizers and 5.97 hours for poor metabolizers. The mean terminal t1/2 of 14C following the oral dose was 3.25 hours for extensive metabolizers and 6.73 hours for poor metabolizers.

Urine
The unchanged RSD1235 recovered in urine after the IV dose was 8.78% in EMs, and 24.46% in PMs (over 24 hours post-dose). After the oral dose, recovery of unchanged RSD1235 in the urine was 3.66% for EMs and 23.31% for PMs. The RSD1390 metabolite was not detectable in urine.

Feces
The mean recovery of 14C in feces following the IV dose was 7.28% for EMs and 5.64% for PMs (6.15% and 5.12%).
Following the oral dose, the mean recovery of 14C in feces was 7.68% for EMs and 6.52% for PMs (7.13% and 5.91%).
No radioactivity was detected in the fecal samples collected at the day 42 final assessments visit for any subject.

Saliva
For all subjects, Tmax occurred at 0.4 hours after IV infusion (except Subject 14180006 at 0 hours) and at 2 hours after oral dosing (except Subject 14180007 at 0.5 hours). Compared to the IV infusion, the Cmax was lower after oral dosing in both EMs (256.96 versus 1498.14 ngEq/mL) and PMs (693.21 versus 1435.38 ngEq/mL).

Disposition of ^{14}C-RSD1235-Derived Radioactivity
The mean terminal elimination half-life for 14C-RSD1235-derived radioactivity was 4.59 hours for EMs and 9.46 hours for PMs following the IV dose.

Mean recovery of the radioactivity in urine was 92.9% for EMs and 84.3% for PMs following the IV dose. Following the oral dose, mean recovery of the radioactivity was 91.4% for EMs and 81.7% for PMs.

Table 9. Total Radioactivity, IV dose, PK in plasma

Analyte	CYP2D6 Metabolism [n]	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-infinity}}$ (ng·hr/mL)	$t_{1/2}$ (hr)
^{14}C [ngEq]	Extensive [5]	5943.30± 539.182	1.02± 0.224	32919.65± 5494.678	4.59± 0.603
	Poor [2]	4914.43± 1022.837	0.17± 0.000	37762.55± 921.199	9.46± 0.744
	#14180008 [1]	4191.2	0.2	38413.9	10.0

Table 10. Total Radioactivity, oral dose, PK in plasma

Analyte	CYP2D6 Metabolism [n]	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-infinity}}$ (ng·hr/mL)	$t_{1/2}$ (hr)
^{14}C [ngEq]	Extensive [5]	6348.32± 812.557	2.20± 1.095	32907.65± 5480.122	4.21± 0.522
	Poor [2]	3953.79± 346.191	1.50± 0.707	36955.30± 4555.315	7.78± 2.205

Mean recovery of the radioactivity in feces was 7.28% for EMs and 5.64% for PMs following the IV dose. Following the oral dose, mean recovery of the radioactivity was 7.68% for EMs and 6.52% for PMs.

Mass balance

At 168 hours postdose, mass balance was achieved. The mean total recovery of administered radioactivity for EMs was 99.7% following the IV dose and 98.7% following the oral dose. The mean recovery for PMs was 89.2% (78.4% for subject with acute urine loss hundred percent for the other subject) following the IV dose and 88.2% (82.4% for subject with known discarded urine sample, 94.0% for the other subject) following the oral dose. The results are consistent with the findings that measurable levels of radioactivity in the plasma, urine, and feces not be detected at 160 hours.

Table 11. Mean % of Excreted Dose

Dose	Analyte	CYP2D6 Metabolism [n]	Urine (%)	Feces (%)	Total (%)
IV infusion over 10 min	14C	Extensive [5]	92.938±3.7685 (86.58-96.33)	7.280±3.5007 (4.43-12.77)	99.736±0.3616 (99.33-100.00)
		Poor [2]	84.304±17.1047 (72.21-96.40)	5.639±0.7280 (5.12-6.15)	89.182±15.2995 (78.36-100.00)
	RSD1235	Extensive [5]	8.781±1.5257 (6.60-10.05)		
		Poor [2]	24.446±8.2801 (18.59-30.30)		
Oral	14C	Extensive [5]	91.363±5.8081 (81.72-95.61)	7.677±3.1404 (4.84-11.98)	98.741±2.8143 (93.71-100.00)
		Poor [2]	81.669±7.2821 (76.52-86.82)	6.522±0.8609 (5.91-7.13)	88.192±8.1430 (82.43-93.95)
	RSD1235	Extensive [5]	3.664±1.7352 (1.71-5.72)		
		Poor [2]	23.307±3.5019 (20.83-25.78)		

Metabolite Profile

RSD1235 is extensively and rapidly metabolized predominantly by O-demethylation by CYP2D6 to the 4-O-demethylated metabolite, RSD1385, most of which is rapidly glucuronidated. Direct glucuronidation of RSD1235 is also relatively prominent, while sulphatation of the 4-O-demethylated metabolite, RSD1385, and/or the 3-demethylated metabolite, RSD1390, are minor metabolic pathways. In PMs of CYP2D6, the metabolism of RSD1235 is slower and less extensive. Higher concentrations of unchanged RSD1235 are found in the systemic circulation and a higher proportion is also excreted unchanged in the urine. In these subjects, direct glucuronidation of RSD1235 is an important route of elimination. RSD1231, a diastereomer of RSD1235, and the conjugate RSD1231G were observed in the PMs. Hydroxylation of RSD1235, which is followed by excretion in the feces, was observed in PMs.

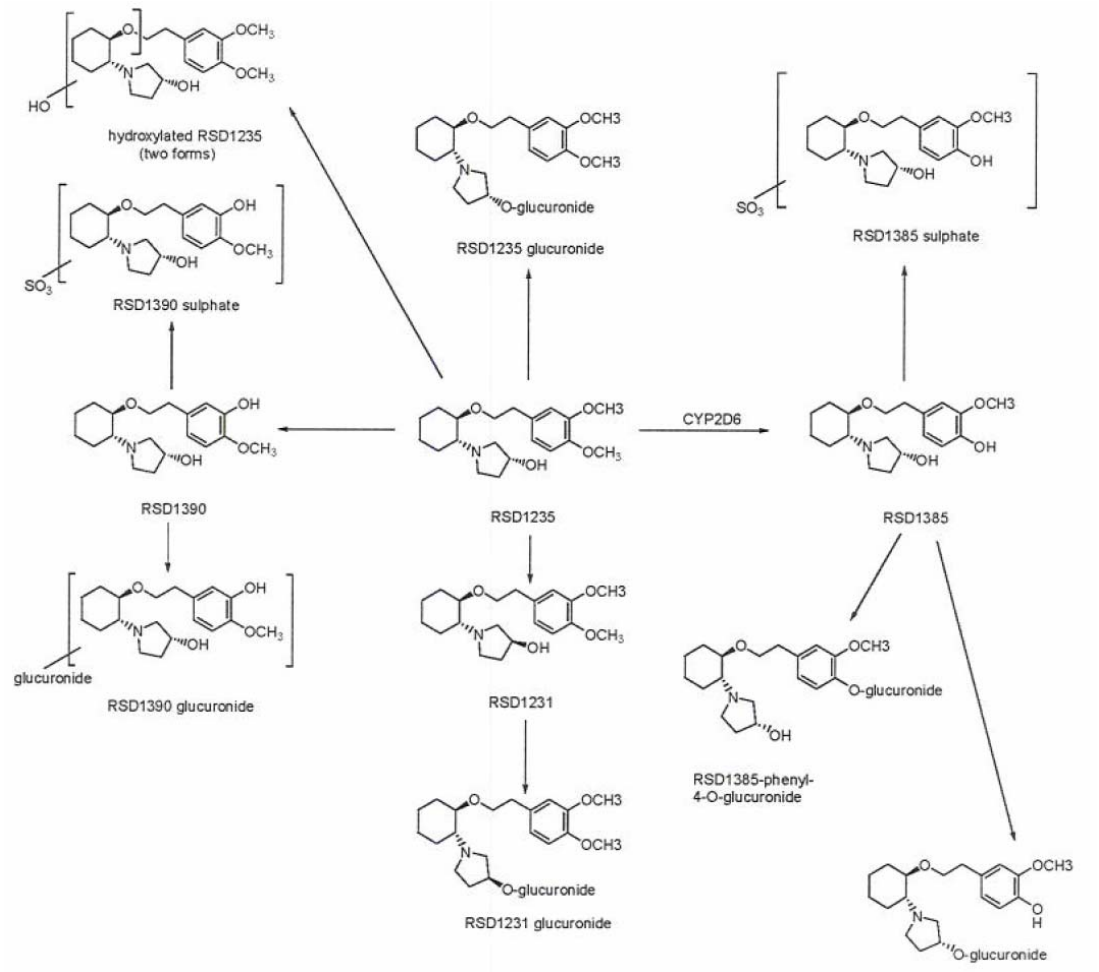


Figure 15. Proposed Metabolic Pathway for R1235 in Humans

Sponsor's Conclusions:

Following a 240 mg IV dose of 14C-RSD1235, the mean terminal elimination half-life for RSD1235 was 2.25 hours for extensive CYP2D6 metabolizers and 8.20 hours for poor CYP2D6 metabolizers.

The bioavailability following a 240 mg oral dose of 14C-RSD1235 was 41.16% for extensive metabolizers and 90.04% for poor metabolizers.

RSD1390 was not detectable in both plasma and urine.

The primary plasma metabolite for extensive metabolizers was RSD1385G, which formed rapidly and was measurable in all extensive metabolizers by the end of the 10-minute infusion. The primary plasma metabolite for poor metabolizers was RSD1235G.

Urinary excretion of unchanged RSD1235 averaged 8.78% for extensive metabolizers and 24.4% for poor metabolizers following the IV dose. For the oral dose, urinary excretion of unchanged RSD1235 was 3.66% for extensive metabolizers and 23.3% for poor metabolizers.

The mean terminal elimination half-life for 14C-RSD1235-derived radioactivity was 4.59 hours for extensive metabolizers and 9.46 hours for poor metabolizers following the IV dose.

Mean recovery of the radioactivity in urine was 92.9% for extensive metabolizers and 84.3% for poor metabolizers following the IV dose. Following the oral dose, mean recovery of the radioactivity was 91.4% for extensive metabolizers and 81.7% for poor metabolizers.

Mean recovery of the radioactivity in feces was 7.28% for extensive metabolizers and 5.64% for poor metabolizers following the IV dose. Following the oral dose, mean recovery of the radioactivity was 7.68% for extensive metabolizers and 6.52% for poor metabolizers.

At 168 hours postdose, mass balance was achieved. The mean total recovery of administered radioactivity for EMs was 99.7% following the IV dose and 98.7% following the oral dose. The mean recovery for poor metabolizers was 89.2% following the IV dose and 88.2% following the oral dose.

Reviewer Comments

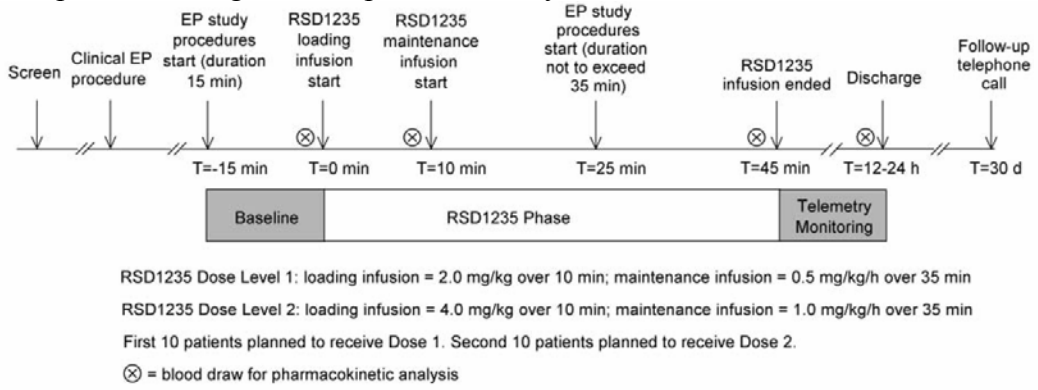
1. This study properly evaluated the mass-balance of RSD-1235 in the 5 extensive metabolizers of CYP2D6.

2. The exposure (AUC values) to RSD1235 in whole blood was 4-fold higher in EMs and 2-fold higher in PMs in comparison with the same values in plasma. The drug distribution into the red blood cells could be speculated; however, the sponsor did not evaluate the plasma: blood partition of the drug.

3. The data reported for PMs should be interpreted with caution. Although the general trend of the increase of excretion RSD1235 as a parent drug in PMs is acceptable, the particular numbers obtained for only 2 PMs cannot be extrapolated to the population of poor metabolizers of CYP2D6. In these 2 subjects, the collection of urine was not appropriate, therefore, the results of urinary excretion of RSD1235 in PMs are not acceptable.

4.1.3 A PHASE IIB, ASCENDING DOSE, OPEN-LABEL STUDY TO DETERMINE THE EFFECT OF AN INTRAVENOUS INFUSION OF RSD1235 ON ATRIAL ELECTROPHYSIOLOGY IN PATIENTS UNDERGOING ELECTROPHYSIOLOGICAL TESTING (1235-SMH1)

Study number: 1235-SMH1
Principal Investigator: G Dickinson, MD
Study center: Cardiome Pharma Corp. 6190 Agronomy Road, 6th Floor Vancouver, British Columbia V6T 1Z3 Canada
Study period: 8 May 2003 to 27 Apr 2005
Phase of development: Phase IIB

Objectives	Primary: To assess the effect of RSD1235 on the atrial effective refractory period (AERP). Secondary: To assess the effect of RSD1235 on: PA interval, AH interval, HV interval, PR interval, QRS duration, QT interval, QTcB, sinus node recovery time (SNRT), atrial monophasic action potential duration (AMAP90), restitution of atrial action potential duration (APD), stimulus artifact to local depolarization (S1-A and S1-V) intervals, Wenckebach cycle length, atrial and ventricular repolarization times (ART and VRT, respectively), ventricular effective refractory period (VERP), ratio of AERP change to VERP change, as well as heart rate, blood pressure, and oxygen saturation.
Study Design	An open-label, single-center phase IIb study 
Study Population	19 subjects who were undergoing electrophysiological testing for ventricular or supraventricular arrhythmias or radiofrequency ablation for supraventricular arrhythmias
Investigational Drug	RSD1235 Lots CTM-F01007 (by Pharmaceutical Development Center, Charleston, SC) and PD03058 (by Patheon, UK). The normal saline (0.9% sodium chloride) used for dilution was obtained by the site from a commercial source.
Dosage and Administration	Treatment N Loading Dose (T=0 to 10 min) Maintenance Dose (T=10 to 45 min) Dose Level 1 10 2.0 mg/kg over 10 min 0.5 mg/kg/h over 35 min Dose Level 2 10 4.0 mg/kg over 10 min 1.0 mg/kg/h over 35 min
Sampling: Blood	Subjects had 4 blood samples drawn: (1) predose (T=0 minutes), (2) end of the loading infusion (T=10 minutes), (3) end of the maintenance infusion (T=45

	minutes), and (4) at discharge. An additional blood sample was to be drawn upon occurrence of a serious adverse event.
Assay	HPLC with LS/MS/MS detection, chromatograms were shown.
PK Assessment	Cmax(ng/mL), Cmax/dose, Tmax (hr), AUC0-24(ng·hr/mL), AUC0-24/dose (ng·hr/mL/mg), CL/F, Vz/F
PD Assessment	ECGs were performed at baseline and 25 min post-dose. The primary PD endpoint was a significant change in AERP values: infusion of RSD1235 vs. baseline
Statistical methods	Pharmacokinetics: Plasma concentrations were summarized at each time point for each dose group. Pharmacodynamics: The effect was measured as the difference between AERP after treatment related to AERP before treatment. Statistical significance was assessed with a Wilcoxon signed rank test. The effect, standard error of the effect and 95% confidence interval of the effect was reported. The 95% confidence interval was estimated using the t-approximation to the normal distribution. This analysis was conducted at each of the three atrial pacing cycle lengths (PCLs): 600 msec, 400 msec and 300 msec. For the planned electrophysiology endpoints PA interval, AH interval, HV interval, PR interval, QRS duration, QT interval, QTcB interval, SNRT, AMAP90, MAP50, DI, S1-A and S1-V intervals, Wenckebach cycle length, ART, VRT, and VERP, similar hypothesis testing was performed

Results

Demographics: A total of 19 subjects completed the study. The demographics are shown in the table below.

Table 12. Subject Demographics

	Treatment Group		Total (N=19)
	Dose Level 1 (N=10)	Dose Level 2 (N=9)	
Gender			
Male	6 (60.0%)	4 (44.4%)	10 (52.6%)
Female	4 (40.0%)	5 (55.6%)	9 (47.4%)
Race			
White	9 (90.0%)	8 (88.9%)	17 (89.5%)
Asian	1 (10.0%)	0 (0%)	1 (5.3%)
Other	0 (0%)	1 (11.1%)	1 (5.3%)
Age (years)			
Mean ± SD	51.5 ± 12.44	44.9 ± 8.22	48.4 ± 10.90
Median	51	43	46
Range	31-71	34-58	31-71
Baseline Weight (kg)			
Mean ± SD	77.7 ± 19.37	74.5 ± 12.77	76.2 ± 16.21
Median	75.1	81.8	77.1
Range	52.0-120.0	60.4-94.0	52.0-120.0
Baseline Height (cm)			
Mean ± SD	172.7 ± 10.67	174.0 ± 6.14	173.3 ± 8.61
Median	172.5	170.0	172.0
Range	157.0-188.0	168.0-183.0	157.0-188.0

Eighteen subjects underwent electrophysiological testing primarily for supraventricular tachycardias as summarized in Table below. One enrolled subject underwent testing primarily for ventricular tachycardia.

Table 13. Primary Arrhythmia for which Subjects Underwent Electrophysiological Testing

Primary Arrhythmia	Treatment Group		Total (N=19)
	Dose Level 1 (N=10)	Dose Level 2 (N=9)	
Supraventricular Tachycardia	10 (100.0%)	8 (88.9%)	18 (94.7%)
Ventricular Tachycardia	0 (0%)	1 (11.1%)	1 (5.3%)

Assay:

Plasma samples and urine samples were assayed according to Bioanalytical Systems, Inc. (BASi) Standard Analytical Procedure. The RSD1235 free base, RSD1385 free base, and RSD1390 free base were extracted from human plasma by solid phase extraction with RSD1221 added as an internal standard.

Table 14. Assay Characteristics in Plasma

Parameter	RSD1235	RSD1385	RSD1390
Linearity	5 ng/mL to 5000 ng/mL	5 ng/mL to 2000 ng/mL	5 ng/mL to 500 ng/mL
	free	free	free
Precision (CV %)	≤ 16.9	<13.4	No data
Accuracy, %	-15.4 to 12.7	-6.0 to 16.4	No data
LLOQ	5ng/mL	5ng/mL	No data
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

Table 15. Assay Characteristics in Urine

Parameter	RSD1235	RSD1385	RSD1390
Linearity	100 ng/mL to 20000 ng/mL	50 ng/mL to 10000 ng/mL	50 ng/mL to 10000 ng/mL
	free	free	free
Precision (CV %)	≤ 3.4	<2.8	< 3.4
Accuracy, %	-9.5 to -3	-8.4 to 1.3	-7.2 to 2
LLOQ	100ng/mL	50ng/mL	50 ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

Pharmacokinetics

Blood was drawn from subjects for analysis of RSD1235 concentration at baseline, T=10 minutes, T=45 minutes, and at discharge. Plasma concentrations are summarized in the table below.

Table 16. Summary of Plasma Concentrations of RSD1235

	Treatment Group	
	Dose Level 1	Dose Level 2
Baseline		
N	10	9
Mean ± SD (ng/mL)	0	0
Median (ng/mL)	0	0
Range (ng/mL)	0	0
10 minutes		
N	10	8
Mean ± SD (ng/mL)	1827.2 ± 834.26	3901.3 ± 2009.8
Median (ng/mL)	1675.0	3110.0
Range (ng/mL)	715.0-3620	2230-8180
45 minutes		
N	10	9
Mean ± SD (ng/mL)	1084.3 ± 279.07	4510.0 ± 7019.9[†]
Median (ng/mL)	1090.0	2190.0
Range (ng/mL)	578.0-1460	1670-23200[†]
Discharge		
N	10	8
Mean ± SD (ng/mL)	24.5 ± 34.58	30.5 ± 32.48
Median (ng/mL)	12.1	18.3
Range (ng/mL)	0.0-106.0	7.5-104.0

Pharmacodynamics

The primary pharmacodynamic endpoint was a significant change in atrial refractoriness, measured as AERP. Results of AERP at atrial PCLs of 600, 400, and 300 msec are summarized in the table below.

Table 17. Effect of RSD1235 on AERP

	Baseline		Drug Treatment		Change from Baseline		
Atrial PCL (msec)	**N**	**Mean ± SEM (msec)**	**N**	**Mean ± SEM (msec)**	**N**	**Mean ± SEM (msec)**	**p-value***
RSD1235 Dose Level 1							
600	10	206.0 ± 10.08	10	219.5 ± 10.18	10	13.5 ± 4.54	0.0078
400	9	188.3 ± 10.21	10	195.0 ± 7.53	9	5.0 ± 3.00	0.1875
300	8	180.0 ± 10.82	10	180.5 ± 4.91	8	-3.1 ± 6.68	0.5313
RSD1235 Dose Level 2							
600	8	202.5 ± 10.86	7	227.9 ± 8.51	7	31.4 ± 5.42	0.0156
400	9	182.2 ± 10.28	9	206.7 ± 8.54	9	24.4 ± 5.92	0.0117
300	9	171.7 ± 8.29	9	192.8 ± 6.72	9	21.1 ± 5.88	0.0156

The mean change in AERP increased significantly ($p<0.05$) from baseline at all atrial PCLs during infusion of RSD1235 Dose Level 2. At Dose Level 1, an increase in the mean change in AERP above baseline was observed during atrial pacing at 600 msec cycle length. The effect on

mean AERP at each atrial PCL tended to be greater for Dose Level 2 than for Dose Level 1, although no statistical test was applied to this difference.
VERP values did not increase significantly at any cycle length in either dose group.
The results of analyses for the secondary endpoints are summarized in the tables below.

Table 18. Change in ECG intervals from baseline during atrial pacing

	Dosing Level 1					Dosing Level 2				
	Baseline		Change			Baseline		Change		
Atrial PCL (msec)	N	Mean ± SEM (ms)	N	Mean ± SEM (ms)	p-value	N	Mean ± SEM (ms)	N	Mean ± SEM (ms)	p-value
PR Interval										
600	9	212.7 ± 14.90	9	15.0 ± 7.89	0.13	8	194.1 ± 6.59	7	27.3 ± 7.26	0.016
400	7	229.9 ± 15.50	5	11.6 ± 15.01	0.63	6	248.8 ± 36.72	4	36.5 ± 22.10	0.25
QRS Duration										
600	9	88.3 ± 2.27	9	0.3 ± 1.68	0.63	8	82.8 ± 1.82	7	6.9 ± 2.52	0.078
400	7	86.3 ± 2.39	5	1.6 ± 3.33	0.88	7	80.1 ± 2.13	6	7.3 ± 3.61	0.063
QT Interval										
600	9	360.7 ± 8.07	9	2.1 ± 6.85	0.78	8	355.5 ± 6.64	7	8.3 ± 6.75	0.30
400	7	328.1 ± 10.96	5	12.6 ± 1.86	0.063	8	306.3 ± 7.00	7	30.3 ± 13.84	0.078
QTcB										
600	9	465.6 ± 10.42	9	2.9 ± 8.93	0.78	8	459.0 ± 8.65	7	10.7 ± 8.79	0.30
400	7	518.9 ± 17.31	5	0.0 ± 20.96	0.63	8	484.6 ± 10.99	7	47.6 ± 21.91	0.078

There were few changes on ECG intervals measured during atrial pacing.
The increases in QT interval or QRS duration were not statistically significant. There was a slight increase in the mean PR interval over baseline that reached significance in the Dosing Level 2 group at 600 msec atrial PCL. The mean increases from baseline in SNRT during atrial pacing at 400 msec and Wenckebach Cycle Length were significant in the Dose Level 2 group. The decrease in S1-A interval change from baseline reached significance only during atrial pacing at 600 msec in the Dose Level 1 group.

Pharmacokinetic/Pharmacodynamic Correlation

The sponsor performed a Spearman Rank Test correlation analyses between plasma levels of RSD1235 and the change in electrophysiology parameters for PK time points. A pooled analysis was also performed including electrophysiology data and plasma concentrations for Dose Level 1 and Dose Level 2 subjects together. Of those electrophysiology parameters that changed significantly from baseline (AERP, SNRT, and PR interval), the correlation coefficients were low, between 0.48 and 0.75.

COMMENTS:

1. Table 18 indicates the mean increase in QTcB by 47.6 ± 21.9 msec at PCL 400 msec at dosing level 2 but change was not statistically significant (p=0.078). The sponsor reported that QTcB in this case are less reliable than QT. However, the mean QT value increase was calculated as 30.3 ± 13.8 msec. Please see the Pharmacometrics review.

2. The pharmacokinetic sampling for this study was not prospectively designed, there were 2 samples obtained per patient but the time points were the same for each patient. Therefore, the correlations between RSD1235 plasma concentrations and electrophysiologic parameters performed by the sponsor are not optimal.

4.1.4 A PHASE IIA PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING, MULTICENTERED, TOLERABILITY AND EFFICACY STUDY OF RSD1235 IN PATIENTS WITH RECENT ONSET ATRIAL FIBRILLATION (CRAFT)

Study number: 1235-1001, CRAFT
Principal Investigators: Denis Roy, MD, Montreal Heart Institute, 5000 Belanger Street Montreal, Quebec H1T 1C8 Canada
Date of first enrolment: 16 January 2002
Date of last completed: 11 July 2002
Phase of Development: 2a

Objectives	To determine the efficacy, safety and tolerability of RSD1235 in a step-dose design for the termination of recent onset atrial fibrillation (AF). To define an efficacious dose for use in a larger phase II trial of RSD 1235. PK: to determine the plasma pharmacokinetic parameters of RSD1235 Injection in a step-dose design for the termination of recent onset atrial fibrillation.
Study Design	A randomized, double-blind, step-dose placebo-controlled, parallel group comparison of two RSD1235 dose groups to matching placebo treatment for termination of recent onset AF in a hospital setting. The 2 dose groups of RSD1235 consisted of doses 0.5 mg/kg and 1.0 mg/kg (efficacy dependent follow-up dose), and 2.0 mg/kg and 3.0 mg/kg (efficacy-dependent follow-up dose).
Study Population	Up to 60 patients were to be enrolled at 20 centers. There were 56 patients who received at least one dose of study drug, and 56 patients who completed the study
Diagnosis and Main Criteria for Inclusion	Male and female patients over 21 years old with recent onset AF (new and recurrent)
Investigational Drug,	RSD1235 Infusion of a single dose over 10 minutes. Batch number: CTM F01007
Reference Product	Placebo: an equivalent volume of commercially available sterile normal saline solution (0.9% sodium chloride) and was administered in the same manner as RSD1235
Dosage and Administration	RSD1235: Two single step-doses of 0.5 mg/kg then 1.0 mg/kg, or 2.0 mg/kg then 3.0 mg/kg. Dose stepping from dose 1 to dose 2 was efficacy response-dependent, i.e., dose 2 was administered if AF had not terminated within 30 minutes of completion of dose 1. Placebo: Two single-doses of placebo. Dose 2 of placebo was administered if AF had not terminated within 30 minutes of completion of dose 1.
Sampling: Blood	Patients in AF or atrial flutter at T1 = 30 min: prior to dose 1, at the end of infusion, at 15, and 30 min post-infusion. After dose 2: at T2= 0, 15, 30, 120, 240, 480 min and 24 hrs (or discharge) post dose. Patients not in AF or atrial flutter at T1 = 30 min: prior to dose 1, at the end of infusion, and at T1 = 15, 30, 120, 240, 480 min and 24 hrs (or discharge) post-dose.

	A sample within 1 min of termination of AF or upon appearance of an SAE
Assay	HPLC with LS/MS/MS detection, chromatograms were shown.
PK Assessment	Plasma drug concentrations for each patient and summary statistics at each time point for each dose were tabulated. Mean plasma concentrations at each time point, and mean plasma concentrations within one minute of termination of AF were presented graphically. Plasma levels upon occurrence of SAEs were listed.
Genotyping	A 7 mL blood sample was collected for CYP2D6 genotyping prior to study drug administration
PD Efficacy	Holter monitor, telemetry, the 12-lead ECG Patients not in AF at 30 minutes post-dose: ECG at T1 = 60, 120, 240, 360, 480, at termination of AF, at the occurrence of an SAE (if applicable), at discharge, at 24 hours post-dose and at Follow-up (1 week ± 3 days). Patients in AF at T1 =30 minutes, and who were administered the second step-up dose of study drug, the ECG was monitored continuously throughout the second dosing (every minute) to 5 minutes post-dose. Thereafter, monitoring was conducted at T2 = 15, 30, 60, 120, 240, 360, 480, at termination of AF, at the occurrence of an SAE (if applicable), at discharge, at 24 hours post-dose and at follow-up (1 week ± 3 days).
PD Safety	Adverse events, clinical laboratory parameters, vital signs

Results

Demographics:

There were 65 patients randomized to this study; 56 patients were treated, and 56 patients completed the study.

Table 19. Demographic Characteristics

		Placebo N=20	0.5 and 1.0 mg/kg RSD1235 N=18	2.0 and 3.0 mg/kg RSD1235 N=18	Total N=56
Gender, n (%)	Male	14 (70.0)	10 (55.6)	10 (55.6)	34 (60.7)
	Female	6 (30.0)	8 (44.4)	8 (44.4)	22 (39.3)
Age (years)	N	20	18	18	56
	Mean (SD)	62.3 (14.52)	63.8 (15.48)	56.6 (17.07)	60.9 (15.70)
	Median	64.0	67.4	60.8	63.6
	Min, Max	35, 83	24, 85	25, 88	24, 88
Height (cm)	N	18	18	18	54
	Mean (SD)	170.4 (10.26)	170.2 (12.05)	170.1 (13.81)	170.2 (11.90)
	Median	172.0	170.6	167.3	170.6
	Min, Max	152, 185	147, 188	152, 198	147, 198
Weight (kg)	N	20	18	18	56
	Mean (SD)	83.1 (19.62)	81.8 (14.73)	80.7 (19.09)	81.9 (17.71)
	Median	79.5	78.8	78.3	78.9
	Min, Max	50, 135	63, 121	47, 130	47, 135
Ethnicity, n (%)	White	19 (95.0)	17 (94.4)	17 (94.4)	53 (94.6)
	Hispanic	0	1 (5.6)	0	1 (1.8)
	Asian	1 (5.0)	0	1 (5.6)	2 (3.6)

The mean and median duration of AF prior to dosing was longer in the 2.0 and 3.0 mg/kg RSD1235 group (mean: 1479.3 minutes, median 1171.0 minutes) than in the 0.5 and 1.0 mg/kg RSD1235 group (mean: 1418.9 minutes, median: 690.0 minutes) or in the placebo group (mean:

1067.1 minutes, median: 800.0 minutes). Since a shorter time in AF is predictive of conversion to NSR, this data indicates that the placebo group was more likely to spontaneously convert to NSR than either of the RSD1235 treatment groups.

Baseline vital signs, oxygen saturation, and ECG patterns were similar between treatment groups.

Table 20. Summary Statistics of Baseline Vital Signs and Oxygen

		Placebo	0.5 and 1.0 mg/kg RSD1235	2.0 and 3.0 mg/kg RSD1235	Total
Systolic blood pressure (mmHg)	N	20	18	18	56
	Mean (SD)	120.5 (15.16)	125.7 (15.21)	126.6 (13.87)	124.1 (14.76)
	Median	119.5	121.5	129.0	122.0
	Min, Max	95, 156	104, 167*	103, 150	95, 167*
Diastolic blood pressure (mmHg)	N	20	18	18	56
	Mean (SD)	75.4 (13.38)	69.6 (14.98)	71.4 (11.38)	72.3 (13.32)
	Median	77.0	72.5	74.5	75.0
	Min, Max	51, 95	42, 90	46, 89	42, 95
Mean blood pressure (mmHg)	N	20	18	18	56
	Mean (SD)	90.4 (12.79)	88.3 (13.03)	89.8 (9.99)	89.6 (11.86)
	Median	90.5	88.8	90.2	90.0
	Min, Max	66, 115	67, 112	70, 109	66, 115
Pulse (beats per minute)	N	20	18	18	56
	Mean (SD)	106.2 (25.21)	106.2 (26.60)	104.7 (26.95)	105.7 (25.75)
	Median	101.5	103.5	101.5	102.5
	Min, Max	71, 161	68, 150	66, 160	66, 161
Respiration rate (breaths per minute)	N	18	17	17	52
	Mean (SD)	17.6 (2.70)	17.5 (3.36)	16.8 (3.63)	17.3 (3.20)
	Median	16.5	18.0	16.0	16.5
	Min, Max	12, 23	8, 24	8, 21	8, 24
Oxygen saturation (%)	N	18	18	18	54
	Mean (SD)	96.7 (2.30)	94.5 (7.01)	97.2 (1.22)	96.1 (4.40)
	Median	97.5	97.0	97.0	97.0
	Min, Max	91, 99	75**, 99	95, 99	75**, 99

Table 21. Summary Statistics of Baseline 12-Lead ECG

		Placebo	0.5 and 1.0 mg/kg RSD1235	2.0 and 3.0 mg/kg RSD1235	Total
QRS interval (msec)	N	20	17	18	55
	Mean (SD)	88.6 (8.90)	81.8 (8.15)	86.6 (11.39)	85.8 (9.83)
	Median	88.0	80.0	87.5	86.0
	Min, Max	74, 106	70, 96	72, 112	70, 112
QT interval (msec)	N	20	17	18	55
	Mean (SD)	319.0 (39.71)	321.1 (33.97)	324.8 (30.90)	321.5 (34.69)
	Median	318.0	322.0	326.0	322.0
	Min, Max	266, 408	252, 382	276, 371	252, 408
QTc interval (msec)	N	20	17	18	55
	Mean (SD)	436.3 (23.35)	415.9 (26.25)	424.4 (17.19)	426.1 (23.69)
	Median	435.5	413.0	428.0	428.0
	Min, Max	397, 486	383, 488	392, 459	383, 488
JT (msec)	N	20	17	18	55
	Mean (SD)	230.4 (37.78)	239.3 (33.82)	238.2 (29.13)	235.7 (33.54)
	Median	228.0	232.0	242.0	238.0
	Min, Max	180, 314	174, 296	196, 284	174, 314
Heart Rate (beats per minute)	N	20	18	18	56
	Mean (SD)	116.4 (24.25)	107.6 (30.32)	105.7 (22.32)	110.1 (25.77)
	Median	121.0	99.5	99.5	105.5
	Min, Max	78, 169	65, 166	74, 138	65, 169

Assay

The LC/MS/MS method of detection of RSD1235 in human plasma (No. 001614IOOL) and urine (No. 002865/OUO) was developed and validated at MDS PHARMA.

Table 22. Assay Characteristics of RSD1235 in Plasma

Parameter	Plasma
Linearity	5 ng/mL to 6037 ng/mL
Precision (CV %)	≤ 13.7
Accuracy, %	-6.6 to 1.8
LLOQ	5ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown

Pharmacokinetics

Low Dose

The patients who did not convert to normal sinus rhythm within 30 min post infusion at 0.5 mg/kg were administered a second infusion at 1.0 mg/kg. One patient converted to normal sinus rhythm after only 1 minute of infusion at RSD1235 plasma concentration of 307 ng/mL.

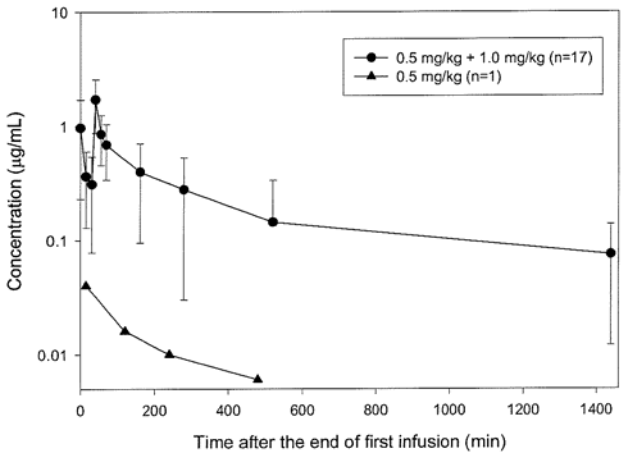


Figure 16. Mean plasma concentrations of RSD1235 after a single dose of 0.5 mg/kg RSD1235 and after a dose of 0.5 mg/kg RSD1235 followed by 1.0 mg/kg RSD1235

High Dose

Patients from the high dose group were initially administered RSD1235 as a 10 minute infusion at 2.0 mg/kg. Those patients who did not convert to normal sinus rhythm within 30 minutes post-infusion were administered a second infusion at 3.0 mg/kg. Seven patients converted to normal sinus rhythm within this time and were not administered the second dose. The median plasma level at conversion to normal sinus rhythm was 1304 ng/mL (range of 1100 to 3489 ng/mL).

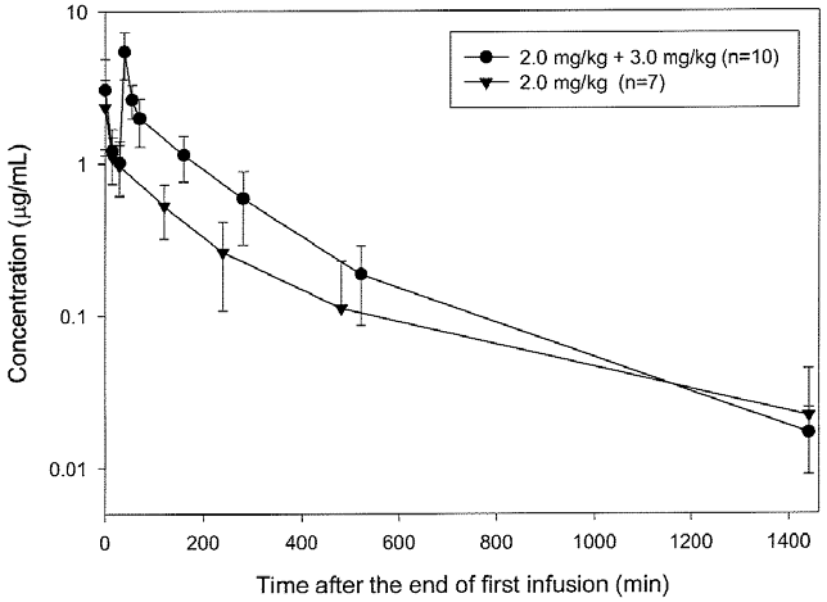


Figure 17. Mean plasma concentrations of RSD1235 after a single dose of 2 mg/kg RSD1235 and after a dose of 2 mg/kg RSD1235 followed by 3 mg/kg RSD1235

Out of 35 patients with PK data, 25 were genotyped for CYP2D6. Two of them were poor metabolizers of 2D6.

Table 23. Summary of PK parameters – Comparison between CYP206 genotypes

Dose		**0.5/1 mg/kg**	**0.5/1mg/kg**	**2.0 mg/kg**	**2.0/3.0 mg/kg**
CYP2D6 Genotype		Extensive	Poor	Extensive	Extensive
C_{max} (ng/mL)	Mean	1808.185	1857.015	2710.190	5843.243
	S.D.	668.2672	343.0811	1349.6772	2194.7483
	Range	596.34-2468.18	1614.42-2099.61	1360.85-4521.16	2816.66-8551.86
	Median	2128.305	1857.015	2727.280	5359.135
	n	10	2	5	8
AUC_{inf} (ng·min/mL)					
	Mean	172995.5	926672.5	212601.6	614367.8
	S.D.	45178.75	30420.98	69441.81	208472.03
	Range	103052-256710	905162-948183	134380-278674	348466-995801
	Median	163830.4	926672.5	246756.3	611954.0
	n	9	2	5	7
$t_{1/2}$ (min)	Mean	164.31	507.55	141.14	171.52
	S.D.	60.465	49.837	49.321	38.998
	Range	96.0-297.8	472.3-542.8	92.2-211.0	116.4-227.8
	Median	147.53	507.55	129.07	178.29
	n	9	2	5	7

Pharmacodynamics

Uncorrected QT interval mean and median values increased from Baseline (mean: 324.8 msec) in the 2.0 and 3.0 mg/kg RSD1235 dose group, beginning soon after the start of the first infusion. There was no change in QT values from the end of the first infusion T1 = 0 (mean: 358.0 msec), until 30 minutes post dose T1 = 30 minutes (mean: 358.9 msec). Following the second infusion, for the remaining 11 patients in AF, QT intervals again appeared to increase slightly from T2 = 0 (mean: 343.5 msec) to T2 = 30 (mean: 363.1 msec).

Table 24. Mean and Median QTc Intervals (msec) (Bazett)

Time period		Placebo	0.5 and 1.0 mg/kg RSD1235	2.0 and 3.0 mg/kg RSD1235	P-value*
Baseline	N	20	17	18	
	Mean (SD)	436.3 (23.35)	415.9 (26.25)	424.4 (17.19)	
	Median	435.5	413.0	428.0	0.1096
T_1 = -8 minutes (during infusion)	N	17	17	18	
	Mean (SD)	427.7 (16.32)	422.9 (23.90)	434.1 (29.07)	
	Median	427.0	418.0	433.0	0.4207
T_1 = -5 minutes (during infusion)	N	19	16	18	
	Mean (SD)	437.6 (22.92)	424.9 (21.63)	443.7 (32.58)	
	Median	434.0	418.5	444.5	0.5148
T_1 = -3 minutes (during infusion)	N	19	15	18	
	Mean (SD)	437.1 (24.95)	418.7 (22.71)	452.9 (36.11)	
	Median	435.0	428.0	451.0	0.1363
T_1 = 0 minutes (completion of infusion)	N	19	17	17	
	Mean (SD)	429.5 (22.17)	418.5 (26.05)	448.8 (35.51)	
	Median	431.0	414.0	453.0	0.0664
T_1 = 5 minutes (post-infusion)	N	20	17	16	
	Mean (SD)	431.9 (23.93)	418.5 (19.69)	439.2 (33.30)	
	Median	430.0	416.0	436.0	0.5008
T_1 = 15 minutes (post-infusion)	N	19	18	17	
	Mean (SD)	421.2 (25.47)	417.3 (21.78)	428.9 (25.26)	
	Median	413.0	415.5	421.0	0.3593
T_1 = 30 minutes (post-infusion)	N	15	13	15	
	Mean (SD)	436.7 (30.39)	414.8 (10.95)	421.7 (16.86)	
	Median	442.0	413.0	414.0	0.0715
T_2 = 0 minutes (completion of infusion)	N	16	17	11	
	Mean (SD)	435.7 (31.93)	413.8 (46.39)	446.8 (55.11)	
	Median	419.5	425.0	423.0	0.6914
T_2 = 30 minutes (post-infusion)	N	18	16	10	
	Mean (SD)	422.1 (22.09)	425.9 (20.05)	425.1 (28.35)	
	Median	423.0	423.5	421.5	0.6942
60 minutes following the last infusion	N	20	16	17	
	Mean (SD)	432.2 (29.74)	422.3 (23.92)	424.6 (28.08)	
	Median	425.0	422.0	418.0	0.3892

The sponsor concluded that the slower heart rates in patients converting to sinus rhythm may influence the increase in QT interval.

REVIEWER COMMENTS:

1. There were only 2 poor metabolizers of CYP2D6 in a low dose group. RSD1235 had a prolonged t1/2 (7.1 and 8.4 hours) in these patients, the exposure (AUC) increased by 4-9 folds in comparison with the extensive metabolizers. Although the size of the group does not allow for solid conclusions, a tendency of the half life to increase in poor metabolizers can be observed.

4.1.5 A PHASE III PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTRED TOLERANCE AND EFFICACY STUDY OF RSD1235 IN PATIENTS WITH ATRIAL FIBRILLATION (1235-0703 ACTI)

Investigator: Garth Dickinson, Cardiome Pharma Corp
Study Center(s): 19 sites in Denmark, 13 sites in Canada, 6 sites in the United States and 6 sites in Sweden.
Study period: August 1, 2003 - November 1, 2004
Phase of development: Phase III

Objectives	Primary: to demonstrate the effectiveness of 3.0 mg/kg and an additional 2.0 mg/kg if required, of RSD1235 in the conversion of atrial fibrillation (AF) to sinus rhythm for a minimum of one-minute duration by hour 1.5 (Time 0 = start of first infusion). Secondary: to assess the safety of RSD1235 in this subject population. To monitor the blood levels of RSD1235 in this subject population
Study Design	A multinational, multicenter, prospective, randomized, double-blind, placebo-controlled study. Subjects were randomized 2:1 (RSD1235:placebo) to receive up to two 10-minute infusions. Subjects remained in the study unit ~ 24 hours after the initiation of treatment with a follow-up visit on day 7
Study Population	Subjects 18 years of age or older with a diagnosis of AF ranging in duration from more than 3 hours to less than or equal to 45 days (a total of 356 subjects were enrolled, 237 with short duration AF and 119 with long duration AF)
Investigational Drug Reference Drug	A single dose of 3.0 mg/kg RSD1235 was diluted in normal saline and administered via infusion pump over 10 minutes. If the subject was in AFL or AF at the end of the 15-minute observation period, a dose of 2.0 mg/kg RSD1235 was administered according to the same method. Lot Numbers: PD030508 (manufactured by Patheon UK, Ltd.). 13791-42 (manufactured by SRI International). The placebo: sterile normal saline solution (0.9% sodium chloride) and was administered in the same manner as RSD1235
Sampling: Blood	Baseline, 10, 35, 50, 90 min and 24 hours post dose and upon the occurrence of a SAE or upon treatment induced conversion of AF to sinus rhythm. Urine was collected each time the subject voided. The percent RSD1235 (free base) excreted as unchanged drug in urine was calculated by correcting the RSD1235 injection (HCL salt) dose for potency.
Assay	HPLC with LC/MS/MS detection, chromatograms were shown.
PK Assessment	A non-compartmental PK analysis was performed on 3 sets of plasma concentration-time data: all data, data excluding IQR outliers, and data excluding SD outliers.
Statistical methods	For each of the 3 analytes (RSD1235, RSD1385, and RSD1390), summary statistics were calculated for plasma concentrations at each time point and each dose level and corresponding mean concentration-

	time profiles were summarized. The Tukey interquartile range (IQR) and SD methods were used to assess concentration outliers. Only subjects with complete urine PK samples collected for 24 hours and subsequently assayed for RSD1235 concentrations were included in the analysis.
Genotyping	CYP2D6 genotype was determined by DNA diagnostics, Capio Diagnostik AB in Eskilstuna, Sweden. Analysis of CYP2D6 *1, *3, *4, *6, *7 and *8 was performed using SNP (single nucleotide polymorphism) analysis on the real-time polymerase chain reaction (PCR) equipment ABI 7000. CYP2D6 *5 and 2XN were analyzed using a polymerase chain reaction (PCR) with two primer pairs.

Assay:
Determination of the plasma concentration of guanfacine in the clinical samples following liquid-liquid extraction was performed by HPLC with detection by tandem mass spectrometry (MS/MS). A validation report of the determination of RSD1235, RSD1385, and RSD1390 in human plasma and urine were performed by Bioanalytical Systems, Inc. 2701 Kent Avenue West Lafayette, IN 47906 in March - April 2005, BASi Report 01000-04739-1 by Mark Gehrke, Ph.D.

Table 25. Assay Characteristics in Plasma

Parameter	RSD1235	RSD1385	RSD1390
Linearity	5 ng/mL to 6 mcg/mL	5 ng/mL to 2 mc/gmL	5 ng/mL to 500 ng/mL
Precision (CV %)	≤ 16.4	<7.1	<5.6
Accuracy, %	-15.4 to 12.7	-6.0 to 16.4	-19.6 to 9.0
LLOQ	5ng/mL	5ng/mL	5ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

Table 26. Assay Characteristics in Urine

Parameter	RSD1235	RSD1385	RSD1390
Linearity	100 ng/mL to 20 mcg/mL	50 ng/mL to 10mcg/mL	50 ng/mL to 10 mcg/mL
Precision (CV %)	≤ 5.8	<9.5	< 6.3
Accuracy, %	-9.5 to -3	-8.4 to 1.3	-7.2 to 2
LLOQ	100ng/mL	50ng/mL	50 ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

Demographics
Subject demographics shown in the table below.

Table 27. Summary of Subject Demographic Characteristics

Parameter	Number (%) of Subjects Placebo (N = 115)	Number (%) of Subjects RSD1235 (N = 221)	P-value†
Gender			
Male	75 (65.2%)	159 (71.9%)	0.203
Female	40 (34.8%)	62 (28.1%)	
Ethnic origin			
White	113 (98.3%)	212 (95.9%)	0.818
Black	0	2 (0.9%)	
Asian	0	2 (0.9%)	
Other‡	2 (1.7%)	5 (2.3%)	
Age (Years)			
N	115	221	
Mean ± SD	61.5 ± 11.29	62.3 ± 13.70	0.583
Min	39	25	
Median	62.0	63.0	
Max	85	90	
Categorized Age			
<65 years	68 (59.1%)	121 (54.8%)	0.443
≥65 years	47 (40.9%)	100 (45.2%)	
Height (cm)			
N	114	220	0.887
Mean ± SD	175.1 ± 9.72	175.0 ± 10.47	
Min	151	140	
Median	176.0	175.0	
Max	196	198	
Weight (kg)			
N	115	221	0.925
Mean ± SD	84.0 ± 15.86	84.2 ± 16.84	
Median	82.0	82.0	
Body Mass Index			
N	114	220	0.926
Mean ± SD	27.4 ± 4.33	27.4 ± 4.80	
Median	27.1	27.1	
Tobacco Use			
Current Smoker	17 (14.8%)	29 (13.1%)	0.554
Ex-smoker	50 (43.5%)	86 (38.9%)	
Non-smoker	48 (41.7%)	106 (48.0%)	

Pharmacokinetics

RSD1235

The sponsor compared the mean plasma RDS1235 profiles after the first and second dose in the figure below (data were cut of at 90 min post start of infusion). This plot does not show the variability of the RSD1235 plasma concentrations which was observed in this study.

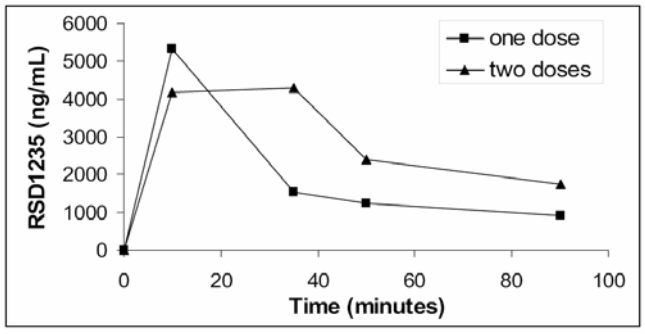


Figure 18. Sponsor's plot of RSD1235 plasma concentrations vs. time

The individual subjects RSD1235 plasma concentration after the first infusion are shown below. Interestingly, in the patients who were genotyped as the extensive metabolizers of CYP2D6, RSD1235 plasma concentrations were still measurable at 24 hours post-dose although the sponsor reported that its half-life is about 3 hours.

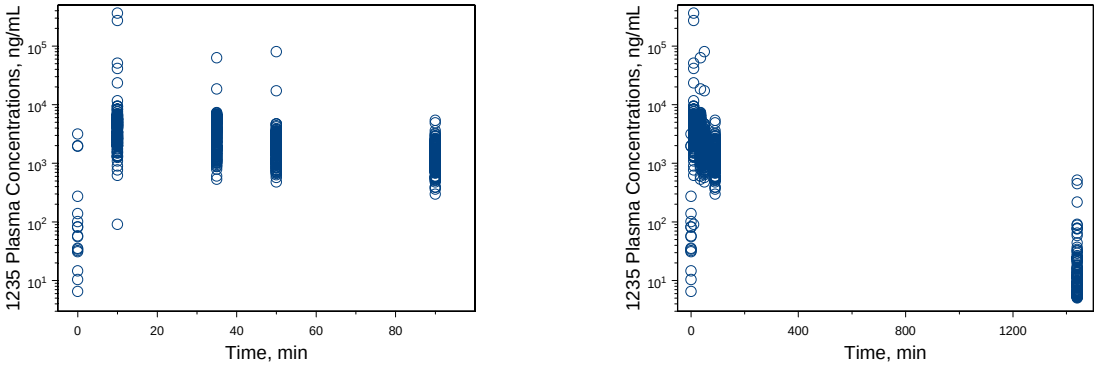


Figure 19. RSD1235 Plasma Concentrations vs. Time after the start of Infusion

When the reviewer plotted the plasma concentration data of the poor metabolizers of CYP2D6 vs. time, only few of them had quantifiable plasma concentrations at 24 hours (reported half life was about 8 hours).

The summary of mean RSD1235 plasma concentration at the specified sampling times is shown below:

TREATMENT GROUP = RECEIVED ONLY THE FIRST INFUSION OF RSD1235

SUBJECT NUMBER	SCHEDULED TIME 0	MIN 10	MIN 35	MIN 50	MIN 90	HR 24
N	68	66	62	66	64	56
MEAN	30.11	14784.39	1810.47	2428.68	985.03	22.43
STD	236.424	54999.387	2209.218	9704.127	594.019	90.125
MEDIAN	0.00	4225.00	1505.00	1170.00	870.50	0.00
MINIMUM	0.00	0.00	607.00	480.00	297.00	0.00
MAXIMUM	1950.00	364000.00	18500.00	80000.00	4910.00	515.00

The sponsor calculated PK parameters of RSD1235 using the whole data set after the first infusion are shown in the table below.

Table 28. PK parameters of RSD1235 after the first dose

Parameter	AUC (0-90) ng.hr/mL	AUClast ng.hr/mL	Cmax
Mean	3985	6283	16090
STD	7734	9641	78363
Median	2523	3012	4300
Min	1067	1067	1780
Max	52403	5572	613000

These data indicate that there is a very high variability in the data. The sponsor did not have any reasonable explanation how to evaluate if this data set had the outliers. The Tukey test is not an adequate test for outliers in this study

RSD1385

The plasma concentrations of RSD1385 are shown below.

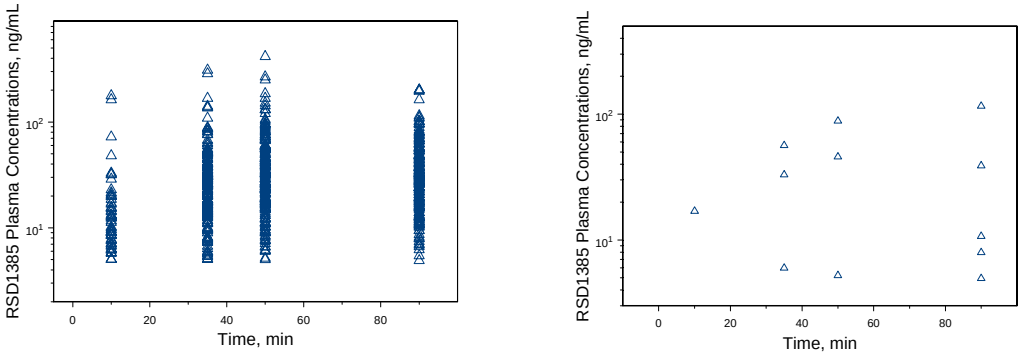


Figure 20. RSD1385 Plasma Concentrations vs. Time after the start of Infusion, EMs, Left, PMs, right

Mean plasma metabolite RSD1385 concentration peaked at minute 35 - 50 in both the 1 and 2 RSD1235 dose subsets. Surprisingly, the plasma concentrations of the major metabolite were similar in EMs and PMs.

Twenty-four hours after the first dose, the plasma concentrations of the metabolite RSD1385 were generally below the LLOQ of 5 ng/mL in both dose group (Table below).

Table 29. RSD1385 Plasma Concentrations

TREATMENT GROUP = RECEIVED ONLY THE FIRST INFUSION OF RSD1235

SUBJECT NUMBER	SCHEDULED TIME 0	MIN 10	MIN 35	MIN 50	MIN 90	HR 24
N	68	66	62	66	64	61
MEAN	0.00	6.59	32.06	30.14	26.87	0.00
STD	0.000	21.380	41.095	36.508	27.746	0.000
MEDIAN	0.00	0.00	21.10	22.30	20.60	0.00
MINIMUM	0.00	0.00	0.00	0.00	0.00	0.00
MAXIMUM	0.00	166.00	292.00	273.00	205.00	0.00

Table 30. PK parameters of RSD1385 after the first dose

Parameter	AUC (0-90) ng.hr/mL	AUClast ng.hr/mL	Cmax
Mean	37	37	37
STD	48	46	41
Median	26	26	26
Min	5	0	0
Max	353	340	292

The variability of Cmax and AUC values for the major metabolite was also very high with CV more than 100%.

RSD1390

The individual plasma concentrations of metabolite RSD1390 are shown in the Figure below. It was below the LLOQ of 5 ng/mL in the majority of patients.

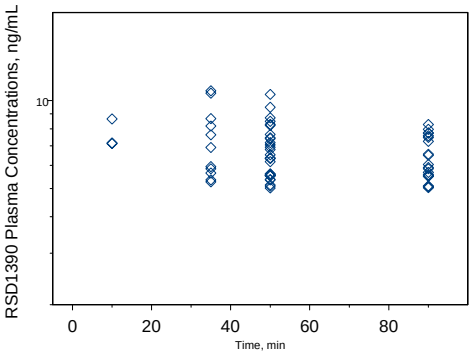


Figure 21. RSD1390 Plasma Concentrations vs. Time after the start of Infusion

Urine RSD1235 Excretion.

The percent dose of RSD1235 excreted as unchanged drug in 24 hours was similar in the 1 and 2 dose subsets.

Table 31. RSD1235 Urine Excretion

Parameter	Treatment Groups	
	1 Dose RSD1235	2 Doses RSD1235
Total dose excreted in 24 hours (mg)		
N	34	63
Mean	19.4	35.5
SD	11.5	30.3
Median	18.4	32.5
Minimum	30.8	0
Maximum	46.4	22.8
Percent dose excreted in 24 hours (%)		
N	34	63
Mean	8.93	9.44
SD	4.430	6.219
Median	8.51	8.99
Minimum	0.12	0
Maximum	17.0	44.6

On average, about 9% of the RSD1235 dose was excreted as unchanged drug in urine over the first 24 hours.

Plasma RSD1235 Exposure and Conversion

The sponsor attempted to evaluate if there is a correlation between the RSD1235 plasma concentrations and conversion of atrial fibrillation to sinus rhythm. The PK parameters of

RSD1235 in the groups of subjects who converted and those who did not convert were similar; however, this conclusion should be interpreted with caution because the sponsor used for the comparison the data sets which were censored without any reasonable explanation.

COMMENTS

1. The sponsor performed an intense plasma sampling in the first 1.5 hours post start of the infusion followed by one sample at 24 hours. This plasma sampling scheme did not allow a proper estimation of the PK parameters.
2. The sponsor censored the data using the Tukey criteria. These criteria cannot be used to censor these data, the outliers rather could be found according to the protocol deviations, genotyping and other factors. None of the reasonable explanations for the censoring data was given. Therefore, the reviewer used the whole data set to evaluate graphically the profiles of the parent drug and metabolites.
3. Surprisingly, the RSD1235 plasma profiles in EMs and PMs were very similar. Although many of the EMs had measurable plasma levels of RSD1235 up to 24 hours post-dose, none of the PMs had detectable plasma concentrations at 24 hours.
4. The variability of RSD1235 PK parameters was very high. The parameters estimated after the first dose had CV of 200-500% (for AUC0-90 and Cmax respectively). The variability of RSD1385 was also very high with CV >100% for both AUC and Cmax.
5. The relationship between the RSD1235 plasma concentrations and conversion of atrial fibrillation to sinus rhythm cannot be established for this study.
6. The most common serious adverse event in the 30-day follow-up period was the recurrence of atrial fibrillation. There were mild and transient effects on QRS and QTc intervals noted in the peri-infusion period associated with expected peak RSD1235 plasma levels. The relationship between RSD1235 plasma concentrations and adverse events was not established.

4.1.6 A PHASE II/III PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTRED TOLERANCE AND EFFICACY STUDY OF RSD1235 IN PATIENTS WITH ATRIAL FLUTTER (1235-0703B, ACTI, scene 2)

Investigator: Garth Dickinson, Cardiome Pharma Corp
Study Center(s): 9 sites in Denmark, 8 sites in Canada, 5 sites in the United States and 2 sites in Sweden.
Study period: 14 August 2003 - 08 September 2004
Phase of development: Phase II/III

Objectives	Primary: to demonstrate the effectiveness of 3.0 mg/kg and an additional 2.0 mg/kg if required, of RSD1235 in the conversion of atrial flutter (AFL) to sinus rhythm for a minimum of one-minute duration by hour 1.5 (Time 0 = start of first infusion). Secondary: to assess the safety and to assess the efficacy of RSD1235 in lowering the ventricular response rate in this subject population.
Study Design	A multinational, multicenter, prospective, randomized, double-blind, placebo-controlled study. Subjects were randomized 2:1 (RSD1235:placebo) to receive up to two 10-minute infusions. Subjects remained in the study unit ~ 24 hours after the initiation of treatment with a follow-up visit on day 7
Study Population	Subjects 18 years of age or older with a diagnosis of AFL ranging in duration from more than 3 hours to less than or equal to 45 days (a total of 60 subjects were planned for enrollment and 54 completed the study)
Investigational Drug Reference Drug	A single dose of 3.0 mg/kg RSD1235 was diluted in normal saline and administered via infusion pump over 10 minutes. If the subject was in AFL or AF at the end of the 15-minute observation period, a dose of 2.0 mg/kg RSD1235 was administered according to the same method. Lot Numbers: PD030508 (manufactured by Patheon UK, Ltd.). 13791-42 (manufactured by SRI International). The placebo: sterile normal saline solution (0.9% sodium chloride) and was administered in the same manner as RSD1235
Sampling: Blood	Baseline, 10, 35, 50, 90 min and 24 hours post dose. Urine was collected each time the subject voided. The percent RSD1235 (free base) excreted as unchanged drug in urine was calculated by correcting the RSD1235 injection (HCl salt) dose for potency.
Assay	HPLC with LC/MS/MS detection (Table), chromatograms were shown.
PK Assessment	A non-compartmental PK analysis was performed on 3 sets of plasma concentration-time data: all data, data excluding IQR outliers, and data excluding SD outliers.
Statistical methods	For each of the 3 analytes (RSD1235, RSD1385, and RSD1390), summary statistics were calculated for plasma concentrations at each time point and each dose level and corresponding mean concentration-time profiles were summarized. The Tukey interquartile range (IQR) and SD methods were used to assess concentration outliers. Only subjects with complete urine PK samples collected for 24 hours and subsequently

	assayed for RSD1235 concentrations were included in the analysis.
Genotyping	CYP2D6 genotype was determined by DNA diagnostics, Capio Diagnostik AB in Eskilstuna, Sweden. Analysis of CYP2D6 *1, *3, *4, *6, *7 and *8 was performed using SNP (single nucleotide polymorphism) analysis on the real-time polymerase chain reaction (PCR) equipment ABI 7000. CYP2D6 *5 and 2XN were analyzed using a polymerase chain reaction (PCR) with two primer pairs.

Results:

Demographics: Twenty (20) subjects enrolled into and completed the study.

Table 32. Summary of Subject Demographic Characteristics

Parameter	Treatment Groups Placebo (N = 15)	Treatment Groups RSD1235 (N = 39)	P-value†
Gender			
Male	12 (80%)	26 (66.7%)	0.508
Female	3 (20%)	13 (33.3%)	
Ethnic origin			
White	15 (100%)	36 (92.3%)	1.000
Black	0	2 (5.1%)	
Asian	0	1 (2.6%)	
Age (Years)			
N	15	39	
Mean ± SD	68.5 ± 10.78	66.9 ± 10.52	0.608
Minimum	51	41	
Median	67.0	68.0	
Maximum	86	83	
Categorized Age			
<65 years	6 (40%)	18 (46.2%)	0.684
≥65 years	9 (60%)	21 (53.8%)	
Height (cm)			
N	15	39	
Mean ± SD	171.9 ± 10.18	172.4 ±10.96	0.878
Minimum	149	141	
Median	173	173	
Maximum	188	190	
Weight (kg)			
N	15	39	0.882
Mean ± SD	88.3 ± 23.71	87.4 ± 18.10	
Minimum	59	48	
Median	78	82	
Maximum	137	124	
Body Mass Index			
N	15	39	0.819
Mean ± SD	29.7± 6.99	29.3± 5.32	
Minimum	22	21	
Median	26.9	27.6	
Maximum	48	43	
Tobacco Use			
Current Smoker	2 (13.3%)	6 (15.4%)	0.603
Ex-smoker	8 (53.3%)	15 (38.5%)	
Non-smoker	5 (33.3%)	18 (46.2%)	

Assay

Determination of the plasma concentration of RSD-1235 and its metabolites in the clinical samples following liquid-liquid extraction was performed by HPLC with detection by tandem mass spectrometry (MS/MS).

A validation report of the determination of RSD1235, RSD1385, and RSD1390 in human plasma and urine were performed by Bioanalytical Systems, Inc. 2701 Kent Avenue West Lafayette, IN 47906 in April, 2005, BASi Report 01000-04739-1 by Mark Gehrke, Ph.D.

Table 33. Assay Characteristics in Plasma

Parameter	RSD1235	RSD1385	RSD1390
Linearity	5 ng/mL to 6000 ng/mL	5 ng/mL to 2000 ng/mL	5 ng/mL to 500 ng/mL
	free	free	free
Precision (CV %)	≤ 16.4	<7.1	<5.6
Accuracy, %	-15.4 to 12.7	-6.0 to 16.4	-19.6 to 9.0
LLOQ	5ng/mL	5ng/mL	5ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

Table 34. Assay Characteristics in Urine

Parameter	RSD1235	RSD1385	RSD1390
Linearity	100 ng/mL to 20000 ng/mL	50 ng/mL to 10000 ng/mL	50 ng/mL to 10000 ng/mL
Precision (CV %)	≤ 5.8	<9.5	< 6.3
Accuracy, %	-9.5 to -3	-8.4 to 1.3	-7.2 to 2
LLOQ	100ng/mL	50ng/mL	50 ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

Pharmacokinetics.

The sponsor censored the PK data using Tukey method. This method of excluding outliers is not plausible for these data. The whole data set was used by the reviewer for graphic exploration.

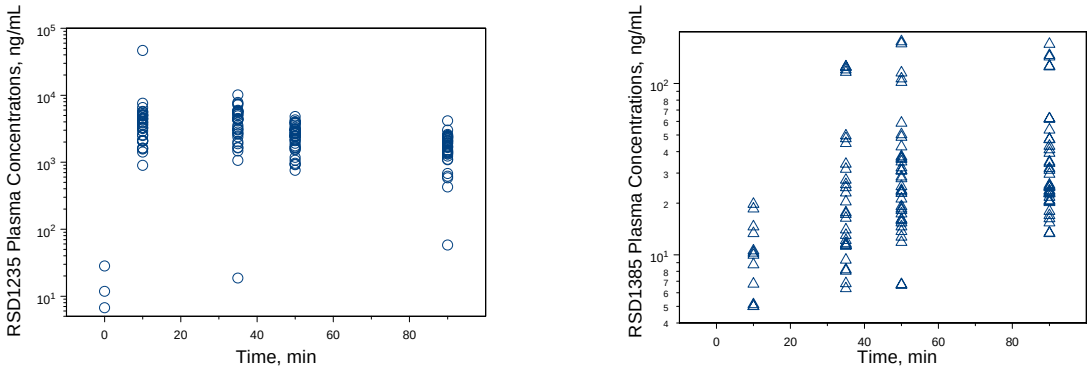


Figure 22. Plasma profiles of RSD1235 (left) and RSD1385 (right)

Mean plasma RSD1235 concentration peaked at the end of the 10-minute infusion (T=10, 3112 ±1210 ng/mL) for subjects who received a single infusion of RSD1235 and at the end of the second 10-minute infusion (T=35 min, 4847 ±1936 ng/mL) for subjects who received both RSD1235 infusions. RSD1235 plasma concentrations decreased rapidly following the end of infusion. At 24 hours following the start of the first RSD1235 infusion, the individual plasma

concentrations were between 6 and 1910 ng/mL. The Cmax to the major metabolite, RSD1385 was 49 ± 67 ng/mL after the first infusion and 48 ± 44 ng/mL after the second infusion and at 24 hours post-dose it was between 5.2 and 11.8 ng/mL.

Metabolite RSD1390 was not quantifiable in plasma.

Urinary Excretion
RSD1235 urinary excretion was similar to the values calculated in the study 703.

Table 35. Urinary Excretion of RSD1235

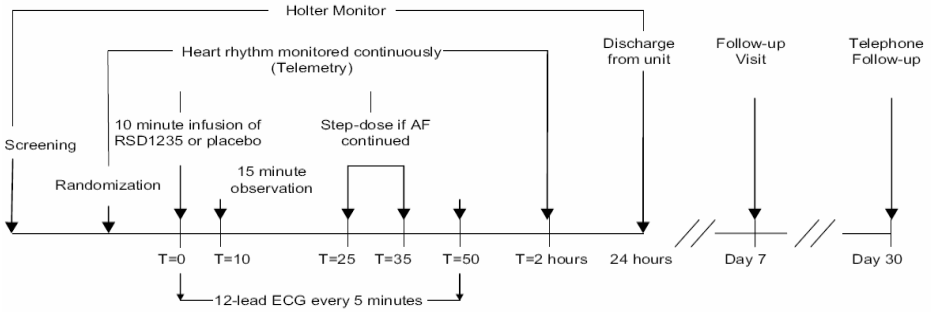
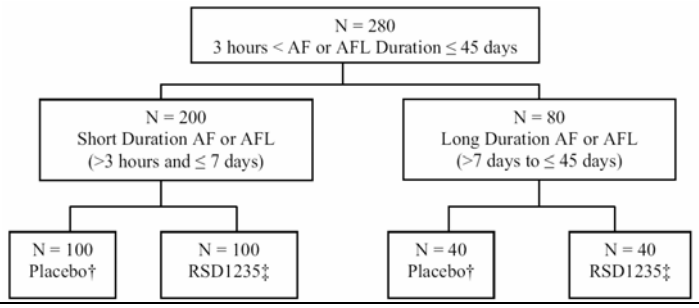
Parameter	Treatment Groups	
	1 Dose RSD1235	2 Doses RSD1235
Total dose excreted in 24 hours (mg)		
N	2	15
Mean	22.1	29.5
SD	4.26	22.1
Median	22.1	30.8
Minimum	19.1	0.94
Maximum	25.1	86.0
Percent dose excreted in 24 hours (%)		
N	2	15
Mean	9.54	7.33
SD	4.69	5.22
Median	9.54	6.38
Minimum	6.22	0.19
Maximum	12.85	18.43

REVIEWER COMMENTS:

1. The comments for study 703 are applicable for this study. The plotting of the data without censoring indicates that the inter-patient variability in plasma concentrations for RSD1235 and its metabolite, RSD1385 were very high.
2. The urinary excretion data were very similar to the data obtained in study 703.

4.1.7 A PHASE III PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTRED TOLERANCE AND EFFICACY STUDY OF RSD1235 IN PATIENTS WITH ATRIAL FIBRILLATION OR ATRIAL FLUTTER (04-7-010 ACT III)

Responsible Investigator: Therese Kitt, M.D. Astellas Pharma US,
Study Center(s): 49 sites in the United States, Canada, Scandinavia and Latin America.
Study period: 27 June 2004 - 01 August 2005
Phase of development: Phase III

Objectives	Primary: to demonstrate the efficacy of RSD1235 compared to placebo, in the conversion of AF or AFL to sinus rhythm. Treatment was considered successful if there was a treatment-induced conversion of AF or AFL to sinus rhythm for a minimum of one minute within 90 minutes of the start of the first infusion. Secondary: to assess the safety of RSD1235 in subjects with AF or AFL; to demonstrate the efficacy of RSD1235 in the termination of AF or AFL Others: to monitor blood levels of RSD1235 in this subject population; to monitor safety over the period of the study until 30 days after dosing
Study Design	A phase 3, multi-center, randomized, double-blind, placebo-controlled study of RSD1235 in subjects with AF or AFL with a duration that was greater than 3 hours but did not exceed 45 days. Each center was expected to randomize 4 to 6 subjects. Subjects within each stratum were centrally randomized in a 1:1 ratio to receive up to two 10-minute infusions of either RSD1235 or placebo treatment. Subjects randomized to RSD1235 received 3.0 mg/kg during the first infusion and 2.0 mg/kg during the second infusion, if required. 
Population	A total of 280 subjects were planned for enrollment, stratified by duration of baseline AF or AFL 

Investigational Drug	A single dose of 3.0 mg/kg RSD1235 was diluted in normal saline and administered via infusion pump over 10 minutes. **RSD1235 Lot Number(s)** — **Manufacturer** PD04008, PD04116 — Patheon UK, Ltd. Kingfisher Drive, Covingham, Swindon Wiltshire SN3 5BZ, England
Reference	Placebo was normal saline
Sampling: Blood	Subjects who received only one infusion had 3 blood samples: predose, end of the first infusion (T=10 minutes) and at any one of the following time-points: T=15, 25, 35, 45 minutes, or T=1, 1.5, 3, 5, 8, 12, 18, or 24 hours. Subjects who received both infusions had 4 blood samples: predose, end of the first infusion (T=10 minutes) and end of the second infusion (T=35min) and at any one of the following time-points: T=15, 25, 45 minutes, or T=1, 1.5, 3, 5, 8, 12, 18, or 24 hours. An additional blood sample was drawn within one minute of conversion to sinus rhythm (except when a subject was electrically cardioverted) and upon occurrence of a serious adverse event
Assay	HPLC with LC/MS/MS detection, chromatograms were shown.
PK Assessment	Pharmacokinetics will be assessed using population methods
Genotyping	CYP2D6 genotype was determined by DNA diagnostics, Capio Diagnostik AB in Eskilstuna, Sweden. Analysis of CYP2D6 *1, *3, *4, *6, *7 and *8 was performed using SNP (single nucleotide polymorphism) analysis on the real-time polymerase chain reaction (PCR) equipment ABI 7000. CYP2D6 *5 and 2XN were analyzed using a polymerase chain reaction (PCR) with two primer pairs.

Assay:
Determination of the plasma concentration of RSD-1235 and its metabolites in the clinical samples following liquid-liquid extraction was performed by HPLC with detection by tandem mass spectrometry (MS/MS). A validation report of the determination of RSD1235, RSD1385, and RSD1390 in human plasma and urine were performed by Bioanalytical Systems, Inc. 2701 Kent Avenue West Lafayette, IN 47906 in March - April 2005, BASi Report 01000-04739-1 by Mark Gehrke, Ph.D.

Table 36. Assay Characteristics in Plasma

Parameter	RSD1235	RSD1385	RSD1390
Linearity	5 ng/mL to 6 mcg/mL	5 ng/mL to 2 mc/gmL	5 ng/mL to 500 ng/mL
Precision (CV %)	≤ 16.4	<7.1	<5.6
Accuracy, %	-15.4 to 12.7	-6.0 to 16.4	-19.6 to 9.0
LLOQ	5ng/mL	5ng/mL	5ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

Table 37. Assay Characteristics in Urine

Parameter	RSD1235	RSD1385	RSD1390

Linearity	100 ng/mL to 20 mcg/mL	50 ng/mL to 10mcg/mL	50 ng/mL to 10 mcg/mL
Precision (CV %)	≤ 5.8	<9.5	< 6.3
Accuracy, %	-9.5 to -3	-8.4 to 1.3	-7.2 to 2
LLOQ	100ng/mL	50ng/mL	50 ng/mL
Reviewer Comment	The assay characteristics and specificity are satisfactory, chromatograms are shown		

Demographics
Subject demographics shown in the table below.

Table 38. Demographic Characteristics

		Treatment Group		
		Placebo N = 131	**RSD1235 N = 134**	**P-value†**
Gender	Male	87 (66.4%)	94 (70.1%)	0.513
	Female	44 (33.6%)	40 (29.9%)	
Race	White	129 (98.5%)	133 (99.3%)	0.619
	Black	2 (1.5%)	1 (0.7%)	
Country	Denmark	52 (39.7%)	52 (38.8%)	0.696
	Canada	20 (15.3%)	27 (20.1%)	
	USA	23 (17.6%)	24 (17.9%)	
	Argentina	17 (13.0%)	14 (10.4%)	
	Sweden	16 (12.2%)	14 (10.4%)	
	Mexico	1 (0.8%)	3 (2.2%)	
	Chile	2 (1.5%)	0	
Age, y	N	131	134	
	Mean ± SD	61.5 ± 13.41	60.9 ± 14.61	0.724
	Median	61.0	62.0	
	Min - Max	27 – 90	22 – 89	
Categorized age	< 65 y	76 (58.0%)	76 (56.7%)	0.831
	≥ 65 y	55 (42.0%)	58 (43.3%)	
Weight, kg	N	131	134	
	Mean ± SD	84.1 ± 16.18	87.1 ± 16.64	0.139
	Median	84.4	84.0	
	Min - Max	48 - 130	53 - 143	

Pharmacokinetics/Pharmacodynamics
The study included sparse pharmacokinetic (PK) and dense pharmacodynamic (PD) data obtained after one or two 10- minute infusions of RSD1235 injection.
The data obtained in this study were analyzed using a population approach. The separate report "Population Pharmacokinetic-Pharmacodynamic Analysis for RSD1235 Injection in Atrial Fibrillation or Atrial Flutter" was submitted and was reviewed by the pharmacometric (PM) reviewer (please see PM review).

4.1.8 IN VITRO METABOLIC STABILITY OF RSD1235 IN HUMAN, DOG, RAT AND MONKEY LIVER MICROSOMES (Report No. BA010628-01)

Investigator: L. Clohs, Ph.D.
Bio-Analytical Chemistry Department, 3650 Wesbrook Mall, VANCOUVER, BC, CANADA VGS 2L228
Date: June 2001

Objectives	To determine the metabolic stability of RSD1235 in human, dog, rat, and monkey liver microsomal incubates
Microsomal Incubations	RSD1235 (50 pM) was incubated with human, dog, rat, cynomolgus and rhesus monkey liver microsomes (1 mg/mL) in a mixture (200 mcL) consisting of' phosphate buffer (67 mM, pH 7.4) and beta-NADPH (2 mM) for either 0 or 60 minutes at 37 ºC.

Results
RSD1235 showed moderate decay in human and dog liver microsomes (73% and 75% recovery, respectively) but was extensively metabolized in rat, cynomolgus and rhesus monkeys with only 16%, 31% and 36% recovery after 60 minutes incubation at 37 ºC, respectively.

Table 39. Recovery (%) of RSD1235 and formation of metabolites after drug incubation at 37 ºC for 60 minutes with liver microsomes (1 mg/mL)

	migration time ratio	human[a]	dog[a] beagle	rat[a] Sprague-Dawley	monkey[b] cynomolgus	monkey[b] rhesus
RSD1235	0.73	73%	75%	16%	31%	36%
metabolite 1	0.76	14%	7%	10%	41%	27%
metabolite 2	0.93	nd	nd	8%	nd	nd
metabolite 3	0.98	nd	nd	9%	nd	nd

Only one metabolite (metabolite 1) of RSD1235 was detected in human, dog and monkey (cynomolgus and rhesus) liver microsomal incubates. RSD1235 was stable under the assay conditions with >97% recovery after 60 minutes incubation in buffer (67 mM phosphate, pH 7.4) and beta-NADPH (2 mM) at 37 ºC.

REVIEWER COMMENTS

1. This was a preliminary study of the metabolism of RSD1235 in liver microsomes.

4.1.9 EVALUATION OF DRUG-DRUG INTERACTION (Report # TTP-NFV-M0001)

Investigator: L. Clohs, Ph.D. Noitran Pharmaceuticals
Bio-Analytical Chemistry Department, 3650 Wesbrook Mall, VANCOUVER, BC, CANADA VGS 2L228
Date: June 2001

Objectives	To determine the possible inhibition of human liver CYP 450 isozymes, IC50 and Ki of RSD1235 and identify the specific isozymes responsible for its metabolism
Investigated Compound	RSD1235 Batch 7 Lot 4 BP-67-21. The compound was an off-white powder stored in a clear glass scintillation vial stored at 4 ºC
Isozyme Metabolism	Human liver microsomes (P450 isozymes 1A2, 2D6, 3A4, 2C9, 2C19, and 2E1) incubation for 60 min at 37 ºC. The metabolism for RSD1235 was performed by incubating the drug at a final concentration of 50 pM in the presence of 50 mM phosphate buffer (pH 7.4), 2 mM NADPH, 2.5 pmol expressed isozyme or 1.0 mg/ml human liver microsomes. The reactions were terminated with 0.5% TFA. The samples were then centrifuged at 14,000 rpm for approximately 10 minutes. The supernatant was analyzed by HPLC.
Data Analyses	IC50 and Ki were determined

Results

Table 40. Positive control substrates and metabolites

Enzyme	Positive Control Substrates	Positive Control Metabolite
Human liver microsomes	7-ethoxycoumarin	7-hydroxycoumarin
CYP1A2	Phenacetine	acetaminophen
CYP2D6	Bufuralol	1-hydroxybufuralol
CYP2C9	Diclofenac	4-hydroxydiclofenac
CYP2C19	S-Mephenytoin	4-hydroxymephenotoin
CYP3A4	Testosterone	6-hydroxytestosterone
CYP3A4	Midazolam	1`-hydroxymidazolam
CYP2E1	Chlorozoxazone	4-hydroxydiclofenac

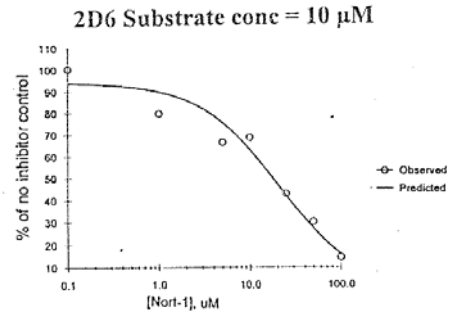
RSD1235 Metabolism
The metabolism of RSD1235 by pooled human liver microsomes produced one major metabolite that eluted at 7.35 minutes. Two minor metabolites were also observed with retention times at 4.09 and 4.98 minutes. The isozyme responsible for the production of the major metabolite was CYP2D6. The two minor metabolites were produced by CYP3A4, and no metabolism associated by any of the other isozymes.

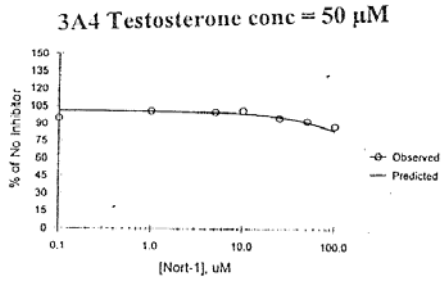
IC50 Determination

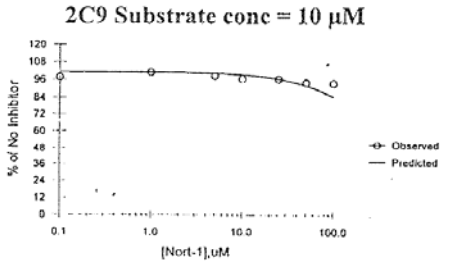
Table 41. IC50 Measurement in human liver microsomes pool with probe substrates

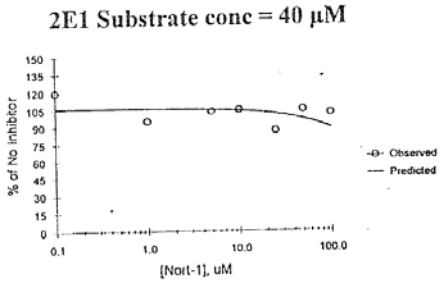
Isozyme	Probe Substrates	Km, uM	Positive Control (prototypical inhibitors)	Concentrations of positive controls (inhibitors)	Positive Control (IC_{50}, µM)
CYP1A2	Phenacetine	25.0	Furafylline	0, 0.1, 1.0, 5.0, 10.0,25.0 and 50.0 uM	3.0
CYP2D6	Bufuralol	10.0	Quinidine	0,0.01,0.05,0.10,1.00,5.00 and 10.00 uM	0.04
CYP2C9	Diclofenac	10.0	Sulphenazole	0, 0.1, 1.0, 5.0, 10.0,25.0 and 50.0 uM	0.6
CYP2C19	S-Mephenytoin	25.0	Tranylcypromine	0, 0.1, 1.0, 5.0, 10.0,25.0 and 50.0 uM	2.6
CYP3A4	Testosterone	50.0	Ketoconazole	0,0.01,0.05,0.10,1.00,5.00 and 10.00 uM	1.1
CYP3A4	Midazolam	5.0	Ketoconazole	0,0.01,0.05,0.10,1.00,5.00 and 10.00 uM	2.9
CYP2E1	Chlorozoxazone	40.0	Diethyldithiocarbamic acid	0, 0.1, 1.0, 5.0, 10.0,25.0 and 50.0 uM	33.7

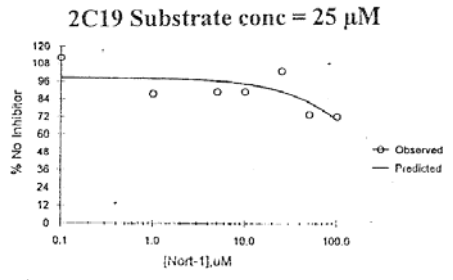
The only isozyme which was inhibited by RSD1235 was CYP2D6 with IC50 20.1 mcM. The results indicated that RSD1235 has no inhibition capability towards other P450 isozymes.

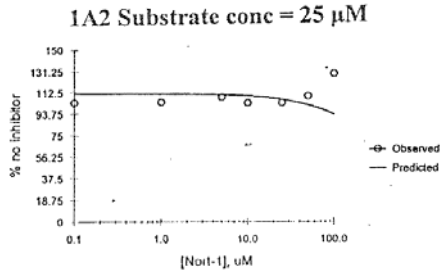












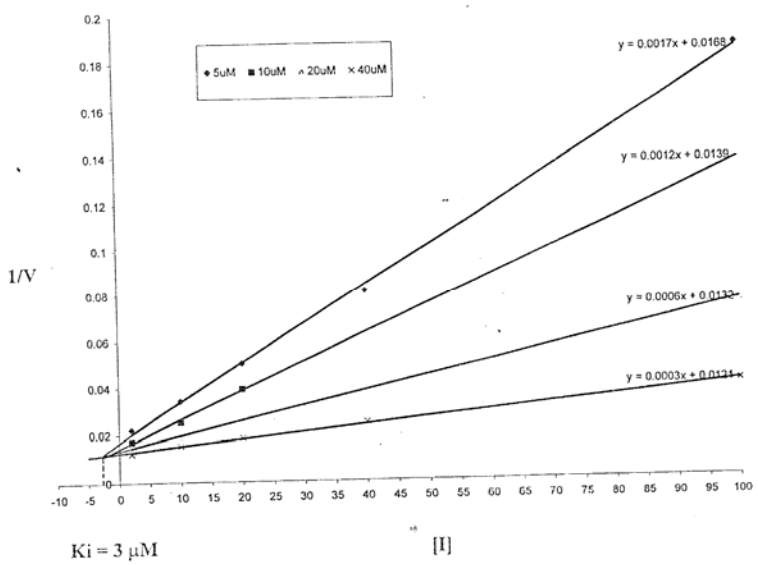


Figure 23. Ki Determination, Dixon Plot

Conclusion:

1. RSD1235 is primarily metabolized by CYP2D6 in human liver microsomes. The two minor metabolites are produced by CYP3A4. The overall extent of metabolism in human liver microsomes by P-450 isozymes after 60 minutes of incubation is moderate (< 30%).
2. RSD1235 only inhibits CYP2D6, and no other major CYP isoenzymes (1A2, 2C9, 2C19, 2E 1, 3A4-testosterone, 3A4-midazolam). The inhibition was determined to be moderate (IC50=20.1 mcM) and competitive (Ki=3 mcM).

4.1.10 PROTEIN BINDING STUDY OF RSD1235

PART I – FREE FRACTION DETERMINATION OF RSD1235

Investigator: L. Clohs, Ph.D. Noitran Pharmaceuticals
Analytical Chemistry Department, 3650 Wesbrook Mall, VANCOUVER, BC, CANADA VGS 2L228
Date: June 2000

Objectives	To determine the binding of RSD1235 In rat plasma by ultrafiltration and In human serum by equilibrium dialysis
Design I	The rat plasma with RSD1235 was incubated in a water-bath at 37 ºC for 30 min to allow the binding process to reach equilibrium. After incubation, the total drug concentration was determined. The remaining plasma solution was ultrafiltrated to determine the free drug concentration.
Design II	Binding was tested in human serum using equilibrium dialysis. The RSD1235 final concentrations in serum were 5, 2,5 and 1 mcg/ml.

Results
The table below shows the results for the free fraction determination of RSD1235 in rat plasma by ultrafiltration. At a plasma concentration of 2.5 mcg/ml, the free fraction of RSD1235 was determined to be 54%. The loss of drug to the filter membrane was minimal (2%).

Table 42. Free Fraction of RSD1235 Determined in Rat Plasma by Ultrafiltration.

Compound	Total Levels (μg/ml) average ± s.d.	Free Levels (μg/ml) average ± s.d.	Recovery of Drug After Incubation	Non-Specific Binding of Drug to Filter Membrane	Free Fraction (%)
RSD1235	2.5 ± 0.1	1.4 ± 0.1	102%	2%	54

The table below shows the results for the free fraction determination of RSD1235 in human serum by equilibrium dialysis. RSD1235 is moderately bound to human serum proteins. Low protein binding for this compound was also obtained in rat plasma. At concentrations of 5.0, 2.5 and 1.0 pg/ml, the free fractions of RSD1235 were determined to be 63, 55 and 53% respectively. No concentration-dependent binding was observed for RSD1235 at the serum concentration range studied (1-5 mcg/ml). RSD1235 was stable in serum at the three concentrations tested after the 30 min incubation period and the 4 h dialysis period.

Table 43 Free Fractions of RSD1235 in Human Serum Determined by Equilibrium Dialysis

Compound	Plasma Concentration (µg/ml)	Free Fraction (%) average ± s.d.
RSD1235	5.0	63 ± 4
RSD1235	2.5	55 ± 6
RSD1235	1.0	53 ± 6

PART II – BINDING COMPETITION STUDY OF RSD1235 AND WARFARIN IN HUMAN SERUM

The free levels of warfarin in the presence and absence of an equimolar concentration of RSD1235 were compared. Comparison of the free levels obtained for RSD1235 in the presence and absence of an equimolar concentration of warfarin was also made. Competition studies were determined by equilibrium dialysis.
Peak area ratios (PAR) of drug/internal standard were calculated for each sample. An increase in the free drug levels in the dialysate would result in an increase in the ratio dialysate/reference. No increase in free levels of warfarin was observed when RSD1235 was present in plasma at an equimolar concentration (Table below).

Table 44. Competitive binding of warfarin vs. RSD1235

	RSD1235 and Warfarin	Warfarin only
PAR dialysate/reference (average ± s.d.)	1.54 ± 0.04	1.50 ± 0.05
ratio warfarin and RSD1235/warfarin only	1.02	
% increase in free levels	no increase	

The table below compares the protein binding of RSD1235 alone and in the presence of warfarin.

Table 45. Competitive binding of RSD1235 vs. warfarin

	RSD1235 and Warfarin	RSD1235 only
PAR dialysate/reference (average ± s.d.)	6.74 ± 0.48	6.89 ± 0.22
ratio warfarin and RSD1235/RSD1235 only	0.98	
% increase in free levels	no increase	

Displacement of drug from the protein binding sites was not detected for RSD1235 in the presence of an equimolar concentration of warfarin or for warfarin in the presence of an equimolar concentration of RSD1235. Results suggest that no change in free fractions will occur during concomitant therapy of RSD1235 and warfarin.

4.1.11 STUDY OF RSD1235 AND QUINIDINE IN BINDING COMPETITION FOR HUMAN SERUM PROTEIN (Report No. BA010919-01)

Investigator: L. Clohs, Ph.D. Noitran Pharmaceuticals
Analytical Chemistry Department, 3650 Wesbrook Mall, Vancouver, BC, Canada VGS 2L228
Date: September, 2001

Objectives	To determine the free fraction of RSD1235 at 130 mcM in human serum after ultrafiltration in the presence and in the absence of an equimolar concentration of quinidine. To determine the free fraction of quinidine at 130 mcM in human serum in the presence and in the absence of an equimolar concentration of RSD1235.
Design	The free fractions of RSD1235 and quinidine in human serum were determined by ultrafiltration and compared to free levels in serum when both drugs were present at equimolar concentrations (130 mcM).

Results

The free fractions for RSD1235 alone in serum and in the presence of quinidine were similar, 58% and 65%, respectively. The free fractions for quinidine alone in serum and in the presence of RSD123S were similar, 12% and 15%, respectively. The displacement of drug from protein binding sites was not observed for RSD1235 in the presence of an equimolar concentration of quinidine, nor for quinidine in the presence of an equimolar concentration of RSD1235.

Comment:

1. This study was conducted at supra-therapeutic concentration (129 mcM) for quinidine and for RSD1235, and there was no competition observed between RSD1235 and quinidine for the displacement from the serum protein binding sites.

4.1.12 STUDY OF RSD1235 AND PROPRANOLOL IN BINDING COMPETITION FOR HUMAN SERUM PROTEIN (Report No. BA010920-01)

Investigator: L. Clohs, Ph.D. Noitran Pharmaceuticals
Analytical Chemistry Department, 3650 Wesbrook Mall, Vancouver, BC, Canada VGS 2L228
Date: September, 2001

Objectives	To determine the free fraction of RSD1235 at 130 mcM and 13 mcM in human serum after ultrafiltration in the presence and in the absence of an equimolar concentration of propranolol. To determine the free fraction of propranolol at 130 pM and 13 mcM in human serum in the presence and in the absence of an equimolar concentration of RSD1235.
Design	The binding competition between RSD1235 and propranolol for human serum proteins was investigated at two drug concentrations (130 and 13 mcM). The free fractions of RSD1235 and propranolol in human serum were determined by ultrafiltration and compared to free levels in serum when both drugs were present at equimolar concentrations.

Results

No competition by displacement from the serum protein binding sites was observed between RSD1235 and propranolol at the two concentrations tested, as reflected by the similarity in free fractions obtained when the drugs were incubated alone or in the presence of the other. At 130 mcM, the free fractions for RSD1235 alone in serum and in the presence of propranolol were 65% and 71%, respectively.

Table 46. Free fractions of RSD1235 and propranolol in human serum

drug	serum concentration	free fraction alone	free fraction in the presence of competing drug	conclusion
RSD1235	130 μM	65%	71%	no displacement
propranolol	130 μM	27%	28%	no displacement

The free fraction of propranolol determined in this study (27-28%) is approximately two-fold higher than the values reported in the literature. However, this study used higher propranolol plasma concentration than in the literature (0.3-0.8 mcM). Therefore, the study using drug concentrations at 13 mcM was conducted.

Table 47. Free fractions of RSD1235 and propranolol in human serum

drug	serum concentration	free fraction alone	free fraction in the presence of competing drug	conclusion
RSD1235	13 μM	52%	54%	no displacement
propranolol	13 μM	12%	15%	no displacement

At 13 mcM, the free fractions for RSD1235 were 52% and 54%, respectively. At 130 mcM, the free fractions for propranolol alone in serum and in the presence of RSD1235 were 27% and 28%, respectlvely. At 13 mcM, the free fractions for propranolol were 12% and 15% respectively.

Comments:

1. The free fractions for both RSD1235 and propranolol in human serum decreased with a decrease in the drug concentration from 130 to 13 mcM; the free fraction for RSD1235 was reduced from 65 to 52%, while that for propranolol was lowered from 27 to 12%. The sponsor reported that the difference in binding for RSD1235 was not significant; however, a statistical test was not performed.
2. The two-fold decrease in free fraction propranolol at the studied concentration is significant. The sponsor explained it as a concentration-dependent binding to $alfa_1$-acid glycoprotein (AAG). AAC is present in plasma at low concentrations (~22 mcM) and the saturation of the AAC binding sites may occur at the high plasma drug concentrations.
3. AAC is also the major binding protein for the diastereomeric mixture comprised of RSD1235. Since its binding to AAG is lower compared to propranolol, it may be the reason of comparatively small increase of free fraction of RSD1235 at high drug concentrations.

Comment to MO:

4. The interaction between propranolol and RSD1235 was not assessed in vivo. Propranolol as well as RSD1235, are metabolized mainly by CYP2D6. This study cannot substitute for the in vivo DDI study between these drugs. The clinical implications of the possible coadministration of these drugs should be assessed by MO.

4.1.13 STUDY OF RSD1235 AND ACEBUTOLOL IN BINDING COMPETITION FOR HUMAN SERUM PROTEIN (Report No. BA011011-01)

Investigator: L. Clohs, Ph.D. Noitran Pharmaceuticals
Analytical Chemistry Department, 3650 Wesbrook Mall, Vancouver, BC, Canada VGS 2L228
Date: October, 2001

Objectives	To determine the free fraction of RSD1235 at 130 mcM in human serum after ultrafiltration in the presence and in the absence of an equimolar concentration of acebutolol. To determine the free fraction of acebutolol at 130 mcM in human serum in the presence and in the absence of an equimolar concentration of RSD1235.
Design	The free fractions of RSD1235 and acebutolol in human serum were determined by ultrafiltration and compared to free levels in serum when both drugs were present at equimolar concentrations (130 mcM).

Results
No competition by displacement from the serum protein binding sites was observed between RSD1235 and acebutolol, as reflected by the similarity in free fractions obtained when the drugs were incubated alone or in the presence of the competing drug. The free fractions for RSD1235 alone in serum and in the presence of acebutolol were 68% and 72%, respectively. The free fractions for acebutolol alone in serum and in the presence of RSD1235 were 71% and 74%, respectively.

Table 48. - Free fractions of RSD1235 and acebutolol in human serum

drug	serum concentration	free fraction alone	free fraction in the presence of competing drug	conclusion
RSD1235	130 μM	68%	72%	no displacement
acebutolol	130 μM	71%	74%	no displacement

Comment:
1. This study was conducted at supra-therapeutic concentration (130 mcM) for acebutolol and for RSD1235. There was no competition observed between RSD1235 and acebutolol for the displacement from the serum protein binding sites.

4.1.14 STUDY OF RSD1235 AND VERAPAMIL IN BINDING COMPETITION FOR HUMAN SERUM PROTEIN (Report No. BA010914)

Investigator: L. Clohs, Ph.D. Noitran Pharmaceuticals
Analytical Chemistry Department, 3650 Wesbrook Mall, Vancouver, BC, Canada VGS 2L228
Date: September, 2001

Objectives	To determine the free fraction of RSD1235 at 130 mcM in human serum after ultrafiltration in the presence and in the absence of an equimolar concentration of verapamil. To determine the free fraction of verapamil at 130 pM in human serum in the presence and in the absence of an equimolar concentration of RSD1235.
Design	The free fractions of RSD1235 and verapamil in human serum were determined by ultrafiltration and compared to free levels in serum when both drugs were present at equimolar concentrations (130 mcM).

Results
No competition by displacement from the serum protein binding sites was observed between RSD1235 and verapamil, as reflected by the similarity in free fractions obtained when the drugs were incubated alone or in the presence of the competing drug. The free fractions for RSD1235 alone in serum and in the presence of verapamil were 68% and 71%, respectively. The free fractions for verapamil alone in serum and in the presence of RSD1235 were 21% and 17%, respectively.

Table 49. Free fractions of RSD1235 and verapamil in human serum

drug	serum concentration	free fraction alone	free fraction in the presence of competing drug	conclusion
RSD1235	130 μM	68%	71%	no displacement
verapamil	130 μM	21%	17%	no displacement

Comment:
This study was conducted at supra-therapeutic concentration (130 mcM) for acebutolol and for RSD1235. There was no competition observed between RSD1235 and verapamil for the displacement from the serum protein binding sites.

4.2 Biopharmaceutics

No biopharmaceutics study was performed with RSD1235 injection.

4.2.1 Dissolution Method and Specifications

No in vitro dissolution studies were conducted with RSD1235 injection.

4.3 Pharmacometrics Review

NDA:	22-034
Drug name:	Kadenza (Vernakalant Hydrochloride)
Indication:	Atrial Fibrillation
Proposed Regimen (Sponsor):	3+2 mg/kg 10 min IV infusions 15 min apart
Applicant:	Astellas
OCP Reviewer	Elena V. Mishina, Ph.D.
PM Reviewer:	Christoffer W. Tornoe, Ph.D.
PM Team Leader:	Yaning Wang, Ph.D.
Type of Submission:	Standard
Submission Date:	December 19, 2006
PDUFA Date:	October 19, 2007

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

The pharmacokinetics of RSD1235 was evaluated in 354 patients with atrial fibrillation or flutter from two pivotal vernakalant studies (04-7-010 and 1235-0703). A two-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed RSD1235 concentrations following 3+2 mg/kg 10 minute IV infusions separated by 15 minutes.

Body weight was found to be significant covariate for RSD1235 pharmacokinetics.

Poor CYP2D6 metabolizers (PMs) were found to have 64% lower RSD1235 clearance compared to extensive metabolizers (EMs). PMs and EMs have similar Cmax while PMs have higher AUC compared to Ems. The lower clearance in PMs led to prolonged half-life from 3 to 8 hours.

Vernakalant was found to prolong the QT interval with a mean predicted QT change from baseline of 21 and 24 msec at the mean peak RSD1235 concentration (C_{max}) of 3660 and 4330 ng/mL after vernakalant doses of 3 and 3+2 mg/kg, respectively.

Logistic regression analyses were performed using efficacy data from evaluable patients in studies 04-7-010 and 1235-703. The analyses indicate that conversion to normal sinus rhythm within 90 minutes after start of the vernakalant infusion is not correlated with RSD1235 exposure (C_{max}) within the studied exposure range under 3+2 mg/kg dosing regimen.

For patients with recent onset of atrial fibrillation (<=7 days defined by sponsor), the response rate after 3 mg/kg was 37.5% and 1% for placebo. Patients not responding to the first dose received an additional 2 mg/kg where the response rate was 19% and 2.6% for placebo.

Duration of most recent atrial fibrillation was the most significant demographic covariate for response. Patients with onset of Atrial fibrillation less than 2 days before RSD1235 dosing had a significant higher response rate of 60-80% compared to the response rate of atrial fibrillation patients with >2 days duration with a response rate in the range of 10-30%.

2 QUESTION BASED REVIEW

Does CYP2D6 genotype influence RSD1235 pharmacokinetics?

RSD1235 clearance was found to decrease by 64% for poor CYP2D6 metabolizers with a terminal half-life of 8 hours for poor metabolizers compared to 3 hours for extensive metabolizers. The C_{max} for PMs is not significantly different from EMs.

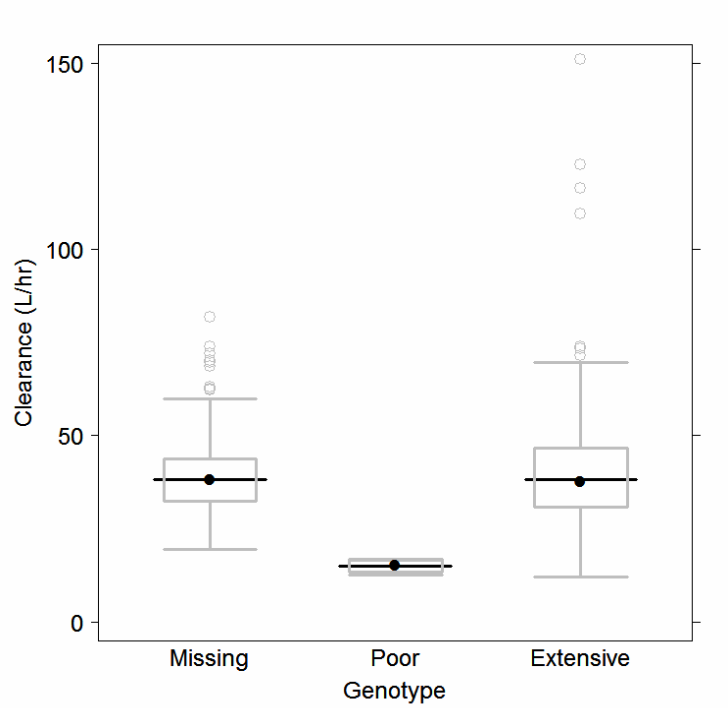


Figure 1 Population PK clearance estimates for missing, poor, and extensive CYP2D6 metabolizers.

Is there evidence of exposure-response?

Within the observed exposure range for the 3+2 mg/kg dosing regimen, there is no evidence of exposure-response (conversion to normal sinus rhythm within 90 min. of dosing) using C_{max} as a measure of exposure.

Vernakalant was found to be most effective in patients with recent onset of atrial fibrillation episode (i.e. less than 7 days from initiation of vernakalant dosing) compared to patients with episodes >7 days and <45 days.

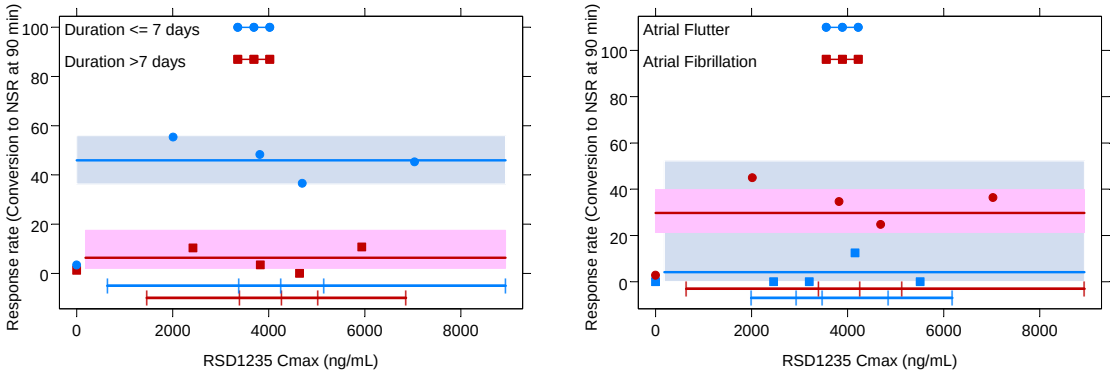


Figure 2. Exposure-response relationship for (**left**) duration of most recent Afib/Aflut episode less than 7 days **(blue)** and greater than 7 days **(red)** and **(right)** atrial flutter **(blue)** and atrial fibrillation **(red)** . The dots represent the mid-quartile RSD1235 peak concentrations and the associated observed response rate with the dots at 0 equal to the placebo response rate. The horizontal bars represent the inter-quartile C_{max} ranges for the different subpopulations.

For patients with recent onset of atrial fibrillation (<=7 days), the response rate after 3 mg/kg was 37.5% and 1% for placebo. Patients not responding to the first dose received an additional 2 mg/kg where the response rate was 19% and 2.6% for placebo.

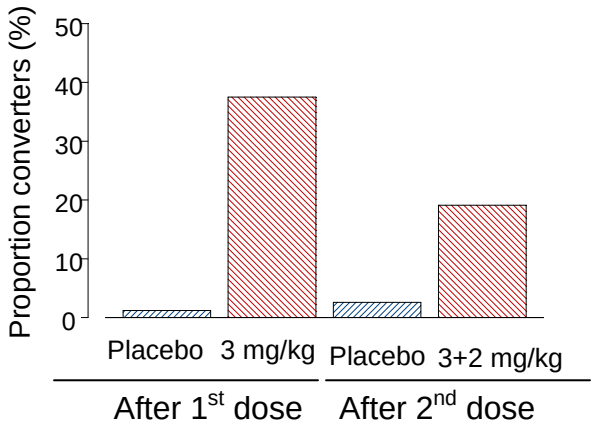


Figure 3. Proportion responders after 1st dose of 3 mg/kg and 2nd dose of 2 mg/kg within the 3 mg/kg non-responders.

Duration of the most recent atrial fibrillation episode (<7 or >7 days) was found to be the most important demographic covariate for response. A total of 328 (Active:Placebo N=215:113) out of 632 atrial fibrillation patients had information about how many days since the start of their most recent atrial fibrillation episode.

As seen in Figure 4, RSD1235 treated patients with <2 days since the start dosing had a response rate of 60-80% (placebo response 4-13%) whereas the response rate in patients with >2 days duration was 10-30% (placebo response 0%).

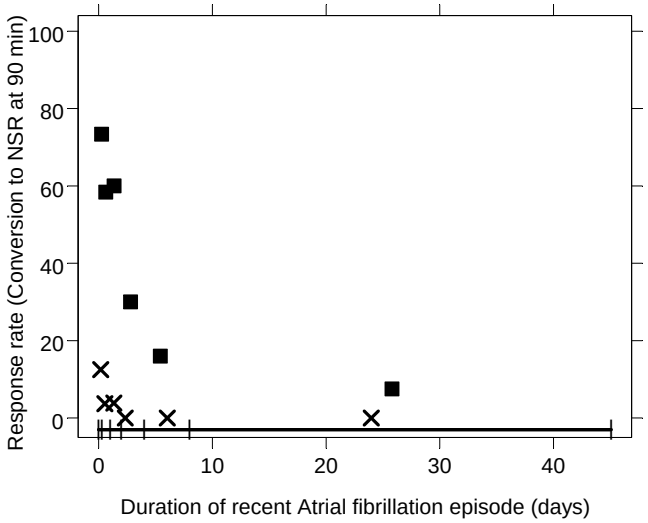


Figure 4. Response rate vs. median duration of recent atrial fibrillation episode in 0-8 hr (Active:Placebo N=15:8), 8-24 hr (Active:Placebo N=48:27), 1-2 days (Active:Placebo N=40:26), 2-4 days (Active:Placebo N=20:8), 4-8 days (Active:Placebo N=25:8), and 8-45 days (Active:Placebo N=67:36) bins. Solid square (RSD1235 treated) and cross (Placebo).

Does vernakalant prolong the QT interval?

Vernakalant was found to prolong the QT interval with a mean predicted QT change from baseline of 21 and 24 msec at the mean RSD1235 C_{max} of 3660 and 4330 ng/mL following 3 and 3+2 mg/kg 10-minute infusions, respectively.

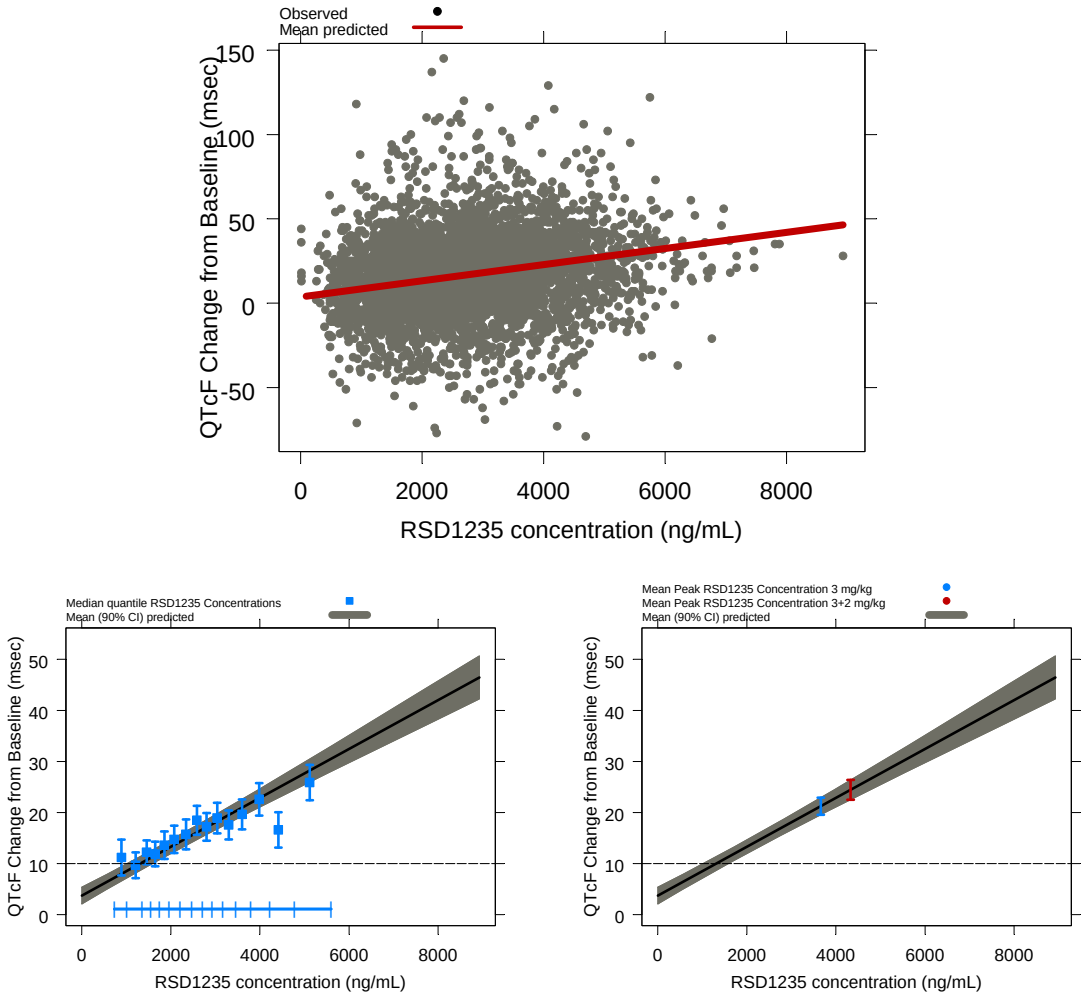


Figure 5. ΔQTcF (Change from Baseline) vs. RSD1235 concentrations. **(Top)** Observed concentrations vs. ΔQTcF. **(Bottom Left)** Median-quantile tedisamil concentrations and associated 90% CI together with the population predictions with 90% confidence interval (solid black line with shaded grey area). The horizontal bars show the observed RSD1235 concentrations divided into 15 bins with equal number of observations. **(Bottom Right)** Population predictions and associated 90% CI at mean 3 mg/kg (blue) and 3+2 mg/kg (red) peak RSD1235 concentrations.

For how long time should patients be monitored after vernakalant dosing?

The population mean QT prolongation is predicted to return below 10 msec within 1 hour after vernakalant dosing for extensive CYP2D6 metabolizers and 2 hours for poor CYP2D6 metabolizers receiving 3 mg/kg and 2 and 8 hours for EMs and PMs receiving 3+2 mg/kg IV infusions. Patients should thus be monitored for at least 1 hours after the end of the IV infusion.

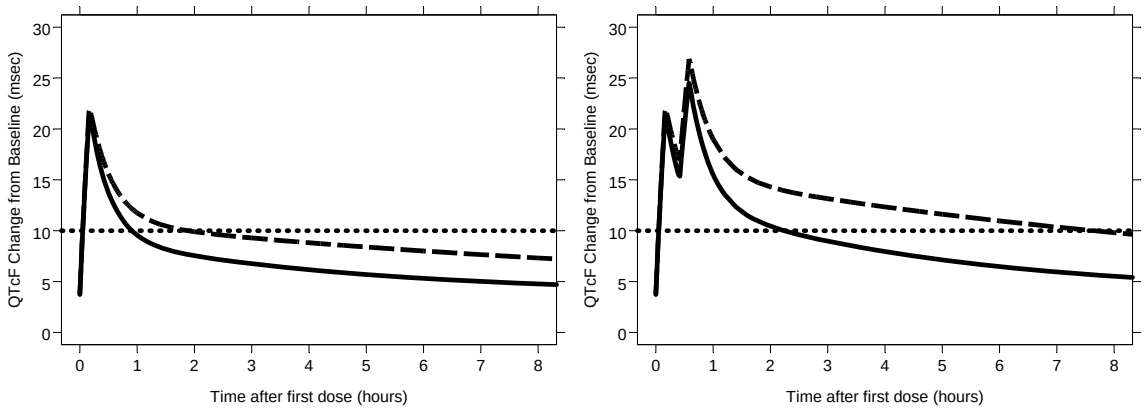


Figure 6. Population predicted RSD1235 concentration-time profiles for poor (PM, dashed) and extensive (EM, solid) metabolizers on after single 3 mg/kg IV infusion over 10 minutes (left) followed by 2 mg/kg IV infusion over 10 minutes (right). The dotted line indicates ΔQTcF of 10 msec.

3 RECOMMENDATIONS

The Pharmacometrics Staff in Office of Clinical Pharmacology finds that the NDA is acceptable.

4 INTRODUCTION

Atrial fibrillation and atrial flutter are the most commonly encountered cardiac arrhythmias in clinical practice, affecting approximately 2.3 million people per year in the United States.

RSD1235 Injection is an intravenous antiarrhythmic agent for the rapid conversion of atrial fibrillation. RSD1235 achieves conversion to sinus rhythm through potassium and sodium channel blockade (e.g., I_{Kur} , I_{to} and I_{Na}). RSD1235 Injection shows enhanced ion channel blockade under the conditions of atrial fibrillation with associated slowing of atrial conduction velocity and prolongation of the atrial effective refractory period.

4.1 AIMS OF ANALYSIS

The goals of the population pharmacokinetic/pharmacodynamic analysis are:

- To develop a population pharmacokinetic (PK) model for the HCl salt form of RSD1235 using data collected in the phase III study 04-7-010.
- Quantify variability in RSD1235 PK and to determine factors that influence RSD1235 PK, e.g. the influence of age, gender, race, body weight, hepatic and renal function, presence of cardiovascular disease, concomitant CYP2D6 inhibitors and beta-blockers.
- Calculate individual metrics of exposure to RSD1235 for subsequent exposure-response analyses.
- To determine the relationship between pharmacokinetic and pharmacodynamic variables (QT interval, sinus rhythm (SR) conversion, and systolic blood pressure (S4BP)). This analysis will identify and quantify the effects of covariates and estimate the magnitude of inter- and intra-individual variability.

5 SPONSOR'S POPULATION PK/PD ANALYSIS

5.1 BACKGROUND

In a phase 1 study, RSD1235 was shown to have linear pharmacokinetics in the dose range 0.1 to 5 mg/kg. The volume of distribution was calculated to be 1.6 to 2.2 L/kg, indicative of extensive tissue distribution. Systemic clearance was reported to be 39 to 56 L/h. RSD1235 is known to be eliminated primarily by O-demethylation by cytochrome P450 (CYP) 2D6 and to a lesser extent by CYP 3A4. Renal excretion was shown to account for approximately 11% of the administered dose. RSD1235 is approximately 60% bound to plasma proteins, and has an intermediate hepatic extraction ratio meaning that hepatic clearance of RSD1235 is not sensitive to changes in hepatic blood flow, plasma protein binding or intrinsic metabolic activity.

5.2 STUDY DESIGN

Study 04-7-010 was a phase 3 prospective, randomized, double-blind, placebo-controlled, multi-center, safety and efficacy study in which subjects were eligible for enrollment based on baseline arrhythmia (AF or AFL) and stratified based on arrhythmia duration, as follows:

- 200 subjects with AF or AFL greater than 3 hours and less than or equal to 7 days (short duration)
- 80 subjects with AF or AFL greater than 7 days and less than or equal to 45 days (long duration)

Subjects were randomized to receive a 10-minute infusion of 3 mg/kg RSD1235 or placebo followed by a 15-minute observation period, then followed by an efficacy-dependent 10-minute infusion of 2 mg/kg RSD1235 or placebo if required and deemed safe. The second dose was administered to subjects who were in AF or AFL at the end of the 15-minute observation period. Dosing was discontinued if changes in vital signs, cardiac function or adverse events (AE) posed a safety threat.

The primary endpoint was the proportion of subjects with short duration AF (>3 and ≤ 7 days) who had treatment-induced conversion of AF to sinus rhythm (SR) within 1.5 hours of first exposure to RSD1235 and for a minimum duration of 1 minute. Time taken from first infusion to first conversion to SR for a minimum duration of 1 minute within this particular patient group (AF > 3 hr and ≤ 7 days) was derived as a secondary efficacy endpoint.

Safety evaluations (vital sign and electrocardiogram assessments) were performed every 5 min from 0 to 50 min, at 1.5, 2, 4 and 8 h, and at conversion to SR, occurrence of a serious AE, at discharge, and at the follow-up visit (1 week ± 3 days). Systolic blood pressure (SBP) and QT interval (the time elapsing from the beginning of the QRS complex to the end of the T wave in an electrocardiogram, representing the total duration of electrical activity of the ventricles) data were used to build safety model.

Blood samples for PK evaluation were collected at the following times: baseline (prior to the first infusion), end of the first infusion (10 min), end of the second infusion, if administered (35 min) and at one of the following time points: 15, 25, 35, 45 min, 1, 1.5, 3, 5, 8, 12, 18, 24 h. An additional sample was scheduled to be collected within one minute of conversion to SR and upon occurrence of a serious adverse event during the primary hospital admission.

5.3 DATA

There were 276 subjects and 1053 plasma concentration records in the database. An analysis data set, including all subjects that received study drug, was derived from this database. Subsequently, placebo subjects were excluded and two data sets were constructed for development and evaluation of the population pharmacokinetic model: a model development data set and a model evaluation data set.

5.3.1 Data Exclusions

Pharmacokinetic data

A total of 11 out of 276 subjects (7 placebo, 4 RSD1235) did not receive study drug and were excluded. The resulting analysis data set included 265 subjects and 1053 plasma concentration records.

Eight plasma concentration records were excluded from the analysis data set:

- 3 samples had interference and no assay result was recorded (subject ID 1154, 1178 and 2017),
- one sample did not have a time of sampling recorded (subject ID 1126),
- one sample was drawn from a subject who did not receive study drug (subject ID 1102), and
- 3 subjects had measurable pre-dose concentrations (subject ID 1111, 2029 and 2048). Pre-dose (zero) concentrations were also excluded (137 samples).
- Subjects assigned to receive placebo and their associated samples (522 samples from 131 subjects) were excluded.

The model evaluation data set comprised the remaining 386 RSD1235 plasma concentration measurements from 134 subjects.

The following data was subsequently excluded to form the model development data set:

1. Twenty-one plasma concentration records from six subjects (ID 1019, 1033, 1080, 1086, 1109 and 1188) were excluded from the model development data set because the dose or duration of infusion differed by more than 10% from the nominal values. The six subjects were retained in the model evaluation data set. For the model evaluation data set, the administered dose was calculated as the volume of infusate multiplied by the infusate concentration.

2. Nine outliers, defined as individual plasma concentration measurements greater than 3 standard deviations from the mean concentration within a specified time interval were identified, as follows:

Subject Number	Plasma Concentration (ng/mL)	Time Interval
1066	19600	Up to 10 min post-dose
2019	32400	Up to 10 min post-dose
2028	21300	Up to 10 min post-dose
1089	6480	12 to 36 min post-dose
1097	6180	12 to 36 min post-dose
2024	7390	12 to 36 min post-dose
2060	7370	12 to 36 min post-dose
1003	4210	≥ 36 min post-dose
1010	3420	≥ 36 min post-dose

The PK model development data set included 362 RSD1235 plasma concentration measurements from 128 subjects. Seven plasma concentrations that were recorded as below the assay limit of quantitation were considered to be missing (coded as missing dependent variable in NONMEM).

Thirty-nine subjects received 1 infusion of RSD1235 while the majority (89 subjects, 70%) received 2 infusions of RSD1235. Eighty-four percent of plasma concentration measurements were drawn within 1 hour of the start of either infusion; 16 samples (4%) were collected after 6 h from the start of either infusion.

Pharmacodynamic data

Three patients (1032, 1135, 2028) were deleted from the PD analysis data set due to missing diagnosis of AF or AFL.

Safety measurements at screening, follow-up, and unscheduled time were removed from the analysis data set. Four patients (1088, 2002, 2034, 2042) were excluded because of missing baseline QT values, leaving a total of 250 patients with 4147 QT measurements. Two patients (1008, 1149) had missing values of baseline SBP, a plot of baseline SBP vs. screening SBP along with a linear fit suggested that the screening values could be used as baseline values. The final PD analysis data set included 254 patients with data on SR conversion events and 4152 SBP measurements.

5.3.2 Covariate Data

Age, gender, race, body weight, serum creatinine, creatinine clearance, renal function category, total bilirubin, serum albumin, presence of CHF, concomitant CYP 2D6 inhibitors and beta-blockers were considered as possible covariates. New York Heart Association (NYHA) functional status classification was not available in 81% of subjects in the RSD1235 treatment group and therefore was not included as a covariate as initially intended.

Concomitant CYP 2D6 inhibitors included amiodarone, buproprion, cimetidine, citalopram, diphenhydramine, doxepin, escitalopram, fluoxetine, hydroxyzine, metoclopramide, paroxetine, ranitidine and sertraline. Clinically-relevant concomitant CYP 2D6 inhibitors included amiodarone, cimetidine, fluoxetine, paroxetine and ranitidine. With the exception of amiodarone and beta-blockers, which were considered to be concomitant if taken within one week and one day, respectively, of RSD1235 administration, medications were considered to be concomitant if they were being taken concurrently with RSD1235 administration.

Renal function was classified as normal, mild, moderate or severe impairment, as suggested in the FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function. Severe renal impairment was defined as a subject with creatinine clearance (CL_{CR}) < 30 mL/min, moderate renal impairment was defined as $CL_{CR} \geq 30$ mL/min and $CL_{CR} < 50$ mL/min, mild renal impairment was defined as $CL_{CR} \geq 50$ mL/min and $CL_{CR} < 80$ mL/min and normal renal function was defined as $CL_{CR} \geq 80$ mL/min.

For all continuous covariates, baseline values were included in the NONMEM dataset. Missing values for serum creatinine, creatinine clearance, serum albumin (subject ID 1194 and 2027) and total bilirubin (subject ID 1131, 1132, 1166, 1194 and 2027) were assigned the median value for the population.

5.4 METHODS

5.4.1 Population PK Analysis

The data were analyzed using the following approach.

- First, an exploratory graphical analysis of the data was performed using S-plus. Raw concentration *vs.* time plots were examined in order to provide a preliminary model structure.
- Second, structural models were fit to the data and assessed using the first order (FO) method in NONMEM program. Inter-individual variability terms were added to the pharmacokinetic parameters and the form of the residual error model was evaluated during the model development process. The process was guided by examination of diagnostic plots to assess the goodness of fit of the model to the data.
- Third, distributions of individual parameter estimates were obtained in NONMEM. Symmetry of the individual parameters about the estimated median parameter was assessed graphically.

- Fourth, sources of variability in RSD1235 pharmacokinetics were identified. Initially, parameter-covariate relationships were explored graphically and using generalized additive models (GAM) in S-plus. In addition, covariates were screened one at a time in NONMEM. Significant parameter-covariate relationships thus selected were included in a full tentative pharmacokinetic model. Covariates were excluded from the model using a stepwise deletion method in which the statistical significance of each parameter-covariate relationship was tested using a likelihood ratio test. The model thus obtained was the final tentative model. Final covariate selection was based on the likelihood ratio test in NONMEM.

Parameter estimates were examined to ensure that they were well-estimated and plausible. Confidence intervals were estimated for each population parameter as $\theta \pm Z$ *(SE)*, where θ is a population parameter estimate, SE is its associated standard error and Z is the interval coefficient for a standardized normal distribution (Z = 1.96 for a 95% confidence interval).

Parameter estimation was performed using the first order conditional estimation (FOCE) method in NONMEM. This method linearizes the random-effects variables around each subject's estimated random effect. At each stage of the analysis, the model was evaluated graphically and refined as necessary. Once this process was complete, the resultant model was considered the final population pharmacokinetic model for RSD1235. Finally, parameter estimates for the final model were obtained.

Structural Models
Based on graphical evaluation of RSD1235 plasma concentration *vs*. time profiles, one and two-compartment structural models were evaluated.

Covariate Models
Continuous covariates (centered about standard values) were included in the model as follows:

$$\theta_i = \theta_T \cdot \left(\frac{Cov_i}{Cov_{med}} \right)^{K_{\theta-cov}}$$

where Cov_i is the value of the covariate for the i^{th} participant, Cov_{med} is the median value of the covariate and $K_{\theta-cov}$ represents the influence of the covariate, Cov, on the parameter, θ_T.

Categorical covariates were introduced in the model as follows:
$\theta_i = \theta_T \cdot \exp(Cov_i \cdot K_{cov})$

where Cov_i is a binary variable. For gender, Cov_i was coded as 1 for female and 0 for male. Similarly, indicator variables were used to evaluate the effects of race, CHF, renal function category and concomitant medications on clearance.

Inter-Individual Variability
Inter-individual variability was modeled for all pharmacokinetic parameters as follows:

$\theta_i = \theta_T \cdot \exp(\eta_i)$

where θ_{ij} is the parameter for the i^{th} participant, θ_T is the typical value of the parameter in the population, and η_i is a random inter-individual effect with mean 0 and variance ω^2. η is referred to as ETA in subsequent sections of this report.

Intra-Individual Variability

Two residual (intra-individual) error models were tested. Initially, residual variability was assumed to be proportional to the prediction and was modeled as follows:

$$y_{ij} = \hat{y}_{ij} \cdot \left(1 + \varepsilon_{ij}\right)$$

where y_{ij} and $\hat{y}_{ij}$ represent the j^{th} observed and predicted concentration, respectively, for the i^{th} participant, and ε is the random residual effect, which is normally distributed (equation 2) or log normally distributed (equation 3) with mean 0 and variance σ^2.

In the final population PK model, residual variability was assumed to be log normally distributed, as follows:

$$\ln\left(y_{ij}\right) = \ln\left(\hat{y}_{ij}\right) + \varepsilon_{ij}$$

5.4.2 Population PD Analysis

Exposure-Efficacy

The primary efficacy endpoint used for modeling was the proportion of subjects with atrial fibrillation (AF) of greater than 3 hours and less than or equal to 7 days in duration (short duration), who had the first treatment-induced conversion of AF to sinus rhythm (SR) within 25 minutes. The time of SR conversion within this particular patient group was derived as the secondary efficacy endpoint.

To describe and model the efficacy data, the individual post-hoc PK parameter values were employed along with the individual dosing histories to calculate the plasma drug concentrations and determine the maximum concentration (Cmax) and the average exposure ($Cavg_{0\text{-}25}$) for correlation to covariates and pharmacodynamic variables.

For a patient with short duration AF, the probability of having SR conversion was modeled using a logistic regression model and the time of SR conversion was modeled using a Cox regression hazard model. The influence of patient covariates, including gender, history of congestive heart failure (CHF), history of coronary artery disease (CAD), history of hypertension, sinus rhythm status (SRS), and presence of concomitant medications (CMED) were examined for their effects on the efficacy response. These models were examined using the glm (general linear model) function in S-PLUS.

Exposure-Safety

Systolic blood pressure (SBP) and QT interval (the time elapsing from the beginning of the QRS complex to the end of the T wave in an electrocardiogram, representing the total duration of electrical activity of the ventricles) data with AF or atrial flutter (AFL) were used to build PK/PD models related to safety. These safety evaluations were performed every 5 minutes from 0 to 50 minutes, at 1.5, 2, 4 and 8 hours, at conversion to SR, at occurrence of a serious adverse event (SAE) and at discharge and at a follow-up visit (1 week ± 3 days). Data on QT interval vs. drug concentration were obtained from 12-lead ECG measurements. Correction of QT interval for heart rate (QTc) was evaluated using the Bazett and Fridericia formulae. Examination of Bazett's corrected QT (QTcB)

interval showed that this adjustment over-compensated for heart rate, particularly at high heart rates. Therefore, Fridericia's corrected QT (QTcF) interval was used for critical assessments of the exposure-response.

The effect of drug plasma concentration was evaluated according to Emax or sigmoidal Emax models. The influence of patient covariates, including age, gender, body weight, history of CHF, history of CAD, history of hypertension, SRS, AF duration, arrhythmia type (AF vs. AFL), and CMED were examined for their effects on pharmacodynamics. The influence of diurnal variation on the population PK/PD model was also investigated and incorporated into the model. These models were examined using the NONMEM program.

Data Analysis

Data was analyzed in a four-step process, i.e.

- First, possible exposure-response relationship was examined graphically. This exploratory analysis was performed using S-PLUS. The response vs. natural logarithm RSD1235 plasma concentration was plotted to visualize the data and to identify potential outliers. This graphical analysis also provided us an impression of the structural model and the nature of the residual error (constant variance or constant coefficient of variation).

- Second, the base pharmacodynamic model (excluding covariates) was fit to the data and assessed using NONMEM or S-PLUS. The goodness of fit of the model was evaluated. In the case of poor model diagnostics, the model would be modified and/or further refined to ensure a good fit of the base model to the data. This process of model evaluation and refinement occurred at this step, as well as at each subsequent step of the data analysis process.

- Third, for QT and SBP model development distributions of individual parameter estimates (using the NONMEM posthoc estimates) and covariates were explored in S-PLUS. Symmetry of the individual parameters about the estimated median parameter was assessed. Parameter-covariate relationships were evaluated by multiple linear regression modeling.

- Finally, all covariates selected in the linear regression analysis and any additional covariates present in the base model were introduced into the pharmacodynamic model for subsequent evaluation in NONMEM. Covariates were excluded from the model using a stepwise backward deletions method. The statistical significance of each parameter-covariate relationship was tested using a likelihood ratio test. At each stage of the analysis, the least significant parameter-covariate relationship was excluded from the model until no further deletions were possible. Diagnostic plots were examined and when no further model refinements were possible, the resultant model was considered to be the final population pharmacodynamic model for RSD1235.

5.5 RESULTS

5.5.1 Exploratory PK Analysis

Table 1 describes the baseline characteristics for subjects in the analysis data set (all subjects who received study medication).

Table 1: Baseline population characteristics for the analysis data set.

Characteristic	Number of Subjects or Median (Range)		
	All	Placebo	RSD1235*
Number of Subjects	265	131	134
Gender (M/F)	181/84	87/44	94/40
Race (White/Black/Hispanic)	243/3/19	120/2/9	123/1/10
CHF (N/Y)	211/54	105/26	106/28
NYHA (1/2/3/Missing)	17/26/3/219	6/12/3/110	11/14/0/109
Concomitant CYP 2D6 Inhibitor (N/Y)[#]	192/73	94/37	98/36
Concomitant Clinically Relevant CYP 2D6 Inhibitor (N/Y)[##]	210/55	99/32	111/23
Concomitant Beta-Blocker (N/Y)	94/171	44/87	50/84
Renal Function (Normal/ Mild/ Moderate/ Severe)[#]	126/110/27/2	57/61/11/2	69/49/16/0
Age (yr)	62 (22, 90)	61 (27, 90)	62 (22, 89)
Weight (kg)	84 (48.3, 142.7)	84.4 (48.3, 129.7)	84.0 (52.5, 142.7)
Serum Creatinine (mg/dL)	1 (0.6, 2.3)	1 (0.6, 2.1)	1 (0.6, 2.3)
Creatinine Clearance (mL/min)**	78 (29, 711)	76 (29, 711)	81.5 (31, 179)
Serum Albumin (g/dL)	4.2 (2.5, 5.2)	4.2 (2.5, 5.0)	4.1 (2.9, 5.2)
Total Bilirubin (mg/dL)	0.6 (0.1, 2.2)	0.7 (0.2, 2.2)	0.6 (0.1, 2.1)

*Model Evaluation Data Set; **Calculated by Cockroft-Gault equation.

[#]Concomitant CYP 2D6 inhibitors included amiodarone, buproprion, cimetidine, citalopram, diphenhydramine, doxepin, escitalopram, fluoxetine, hydroxyzine, metoclopramide, paroxetine, ranitidine and sertraline

[##]Clinically-relevant concomitant CYP 2D6 inhibitors included amiodarone, cimetidine, fluoxetine, paroxetine and ranitidine

Figure 7 shows relationships among covariates for the model development set. In general, females were older, had lower body weights and lower creatinine clearances than males and creatinine clearance was correlated with body weight and inversely correlated with age.

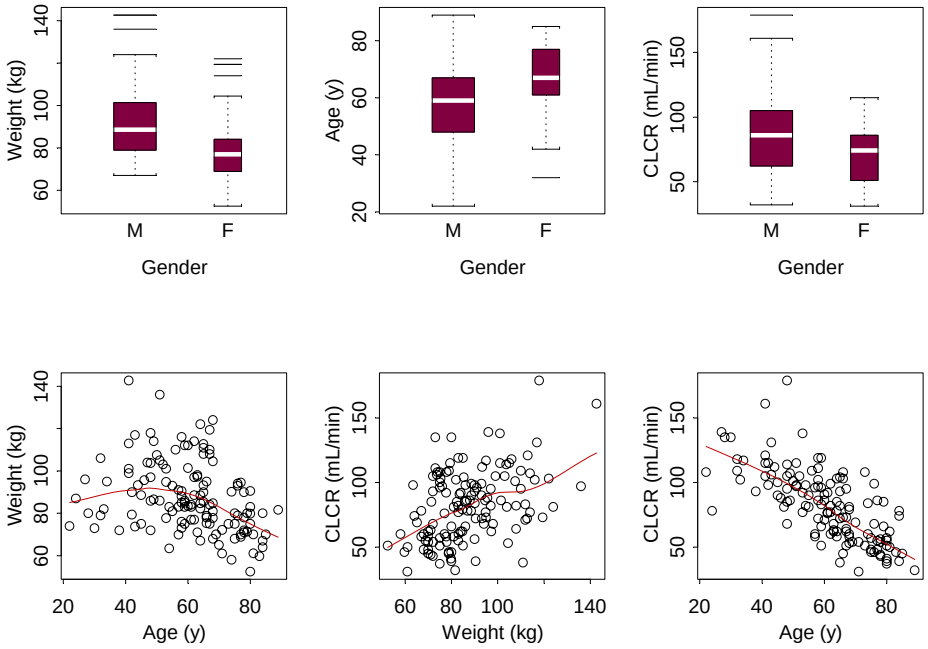


Figure 7: Relationships among covariates (excludes one creatinine clearance estimate > 300 mL/min). In the upper panel, box widths are proportional to square root of number of observations (i.e., fewer observations for females than males). In the lower panel, circles are individual data points and red line is a smooth local regression curve (loess).

Figure 8 shows RSD1235 plasma concentrations *vs*. time from the start of infusion for subjects in the model development set.

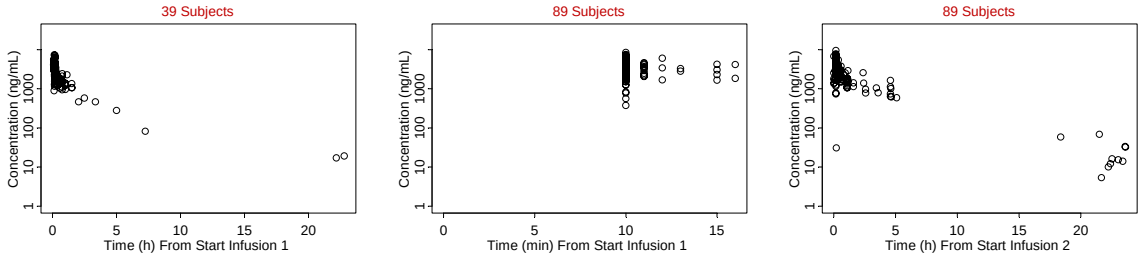


Figure 8: Plasma concentration vs. time plot of RSD1235 in 39 subjects who received only one infusion (left panel) and in 89 subjects who received two infusions (middle and right panel).

Figure 9 shows median dose-normalized plasma concentration vs. time profiles following the first and second infusions by gender.

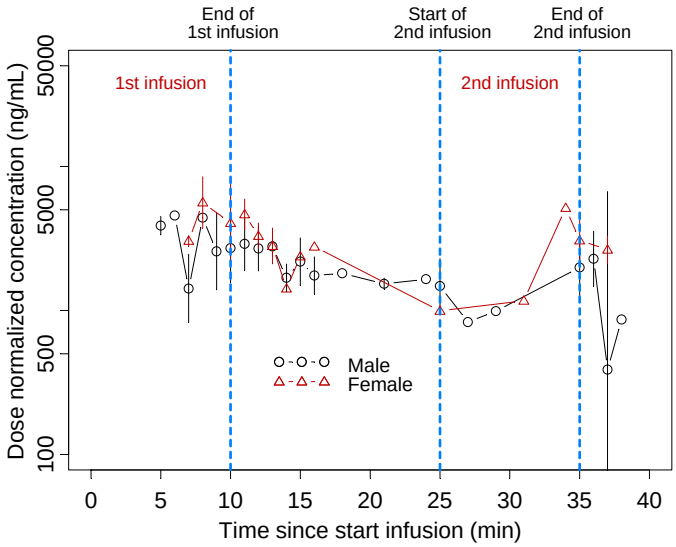


Figure 9: Geometric mean dose-normalized concentrations of RSD1235 vs. time by gender. The points are the geometric mean of concentrations. The vertical lines represent ± 1SD in the ln (concentration) domain, after back-transformation to the absolute scale. The concentrations are normalized to a dose of 240 mg. There were 16 non-scheduled samples prior to the termination of the first infusion in the full data set whose collection was triggered by a conversion event or AE. The PK analysis was performed with and without these samples. The results indicate that these samples don't affect the PK analysis results.

5.5.2 Population PK Analysis

Base Model

A one-compartment model was initially tested based on previous exploratory analysis of phase I data. However, the one-compartment model failed to capture the biphasic disposition of RSD1235 apparent at late times (> 6 h after start of infusion). A two-compartment model improved the fit. Diagnostic plots showed that the two-compartment model captured the shape of the plasma concentration vs. time curve both during infusion and post-infusion. A log-normal residual error model was selected based on graphical evaluation of diagnostic plots.

The base model was parameterized in terms of systemic clearance (CL), inter-compartmental clearance (Q) and volumes of the central (V_c) and peripheral (V_p) compartments.

The variance for the inter-individual variability term on Q was very small, likely due to the paucity of samples characterizing the peripheral compartment (at late times, 6 – 25 h after the dose). Therefore, the inter-individual variability term on Q was fixed to zero in the final parameter estimation. A variance-covariance matrix was estimated; the correlation between V_c and CL was calculated to be 0.6.

Covariate Model

Graphical and GAM analyses revealed that body weight was correlated with CL while V_c was correlated with gender.

Parameter estimation was performed using the FOCE method in NONMEM. Stepwise addition of covariates to the base model in NONMEM identified only an effect of gender on V_c. The equation for V_c was as follows:

$$V_c\ (\mathrm{L}) = V_{c_{Typ}} \cdot \exp(K_{Vc-Sex} \cdot Sex)$$

In the above equation, Sex is an indicator variable with the value 0 for male subjects and 1 for female subjects. The subscript Typ refers to the typical (or median) value for that parameter.

The model was evaluated after excluding samples collected within 1 minute of conversion to SR. Samples were excluded for subjects 1072, 1076, 1094, 1140, 1167, 1172, 1181, 2035 and 2038. The base model and the final model were fit to this data set and the results obtained were consistent with previous results.

Final PK Model

Final pharmacokinetic parameter estimates for the HCl salt form of RSD1235, estimated using the FOCE method with interaction in NONMEM, are presented in Table 2.

Table 2: Typical pharmacokinetic parameters, standard error of estimates and variability estimates for HCl salt form of RSD1235.

Parameter (unit)	Estimated	SE*	95% Confidence Interval	Estimated Variability (%)**
Vc (L) – male	51.0	5.1	40.9, 61.1	
Vc (L) – female	26.4			
Vp(L)	103	5.6	92.0, 114	
Q (L/h)	230	18.5	194, 266	
CL (L/h)	34.4	1.5	31.5, 37.3	
$K_{Vc\text{-}SEX}$	-0.657	0.161	-0.973, -0.341	
ω^2_{Vc}	0.609	0.131	0.352, 0.866	78.0
ω^2_{Vp}	0.070	0.029	0.015, 0.126	26.5
ω^2_{CL}	0.107	0.031	0.047, 0.167	32.7
$\omega^2_{CL\text{-}Vc}$	0.155	0.051	0.055, 0.255	
$\omega^2_{CL\text{-}Vp}$	0.066	0.020	0.028, 0.105	
$\omega^2_{Vc\text{-}Vp}$	0.010	0.035	-0.058, 0.078	
σ^2	0.066	0.011	0.044, 0.087	25.6

*SE=standard error of parameter estimate; **Variability: inter-individual variability=$\sqrt{\omega^2}$; residual variability=$\sqrt{\sigma^2}$.

Calculated pharmacokinetic parameters (based on the nominal protocol) are tabulated in Table 3.

Table 3: Calculated pharmacokinetic parameters (based on the nominal protocol) for HCl salt form of RSD1235.

Parameter (unit)	Calculated Value
Male	
Cmax (ng/mL) – first dose	3284
Cmax (ng/mL) – second dose	3512
$AUC_{0\text{-}1.5}$ (ng*h/mL)	3260
$AUC_{0\text{-}\infty}$ (ng*h/mL)	11656
$T_{1/2\beta}$ (h)	3.3
Female	
Cmax (ng/mL) – first dose	4769
Cmax (ng/mL) – second dose	4564
$AUC_{0\text{-}1.5}$ (ng*h/mL)	3801
$AUC_{0\text{-}\infty}$ (ng*h/mL)	11662
$T_{1/2\beta}$ (h)	2.9

Calculations based on the nominal protocol and body weight of 80 kg.

Figure 10 shows the central volume of distribution-gender relationship that was retained in the final population pharmacokinetic model.

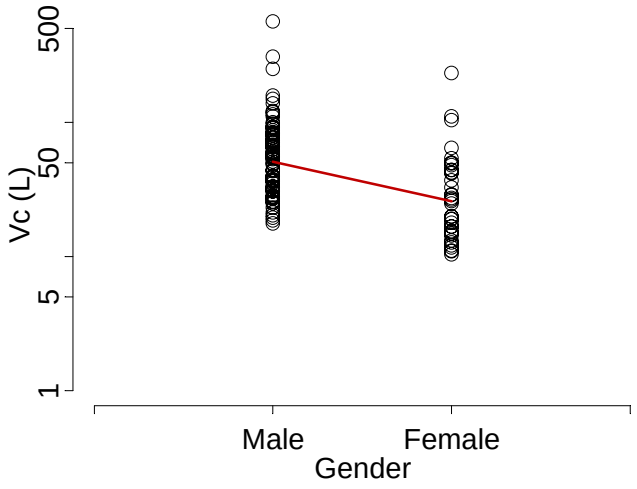


Figure 10: Significant parameter-covariate relationship is shown for V_c and gender. Circles are the individual parameter estimates from NONMEM and the red line represents the typical (population) predicted parameter estimates.

Figure 11 shows the relationship between predicted concentrations and measured concentrations. While the predicted concentrations match the measured concentrations satisfactorily, there is some misfit at low concentrations (left panel). These samples were collected at late times (6 – 25 h) after the start of dose administration and represent 4% of measurable plasma concentrations. The misfit may have been corrected using a more complex (e.g. 3-compartment) model, however, on the basis of the paucity of data to characterize the model, a more complex model was deemed to be not supported by the data.

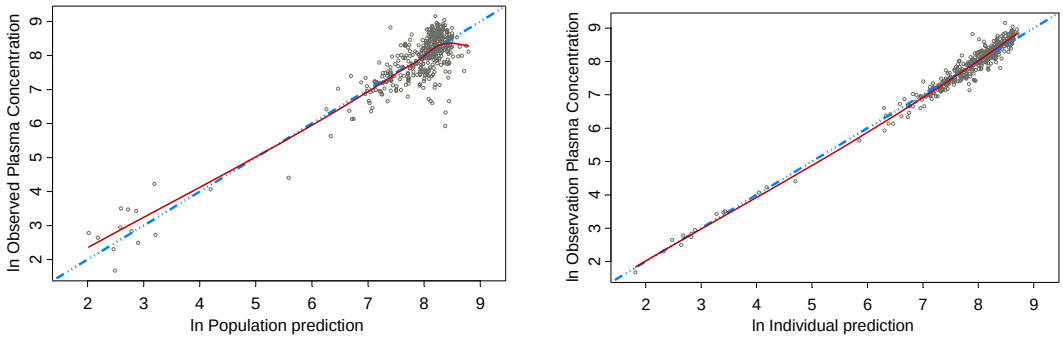


Figure 11: Measured vs. population predicted plasma concentrations of RSD1235 (left panel) and individual predicted plasma concentrations of RSD1235 (right panel) for the model development data set. Predicted concentrations are obtained from the covariate corrected model in NONMEM. The blue dashed line is the line of unity; the red line is a smooth local regression curve (loess).

Figure 12 and Figure 13 show that the residual errors are approximately normally distributed over time and predicted concentration. Although there is underestimation of high plasma concentrations at the end of the infusion due to large variability in plasma concentration measurements at those times (46% variability at the end of the first infusion and 37% at the end of the second infusion), the data is described reasonably. The mean and standard deviation of the weighted residuals were computed to determine whether the mean was significantly different from zero and the standard deviation approximated 1. The mean and standard deviation of weighted residuals are –0.05 and 1.035, respectively, indicating that the model parameters describe the data.

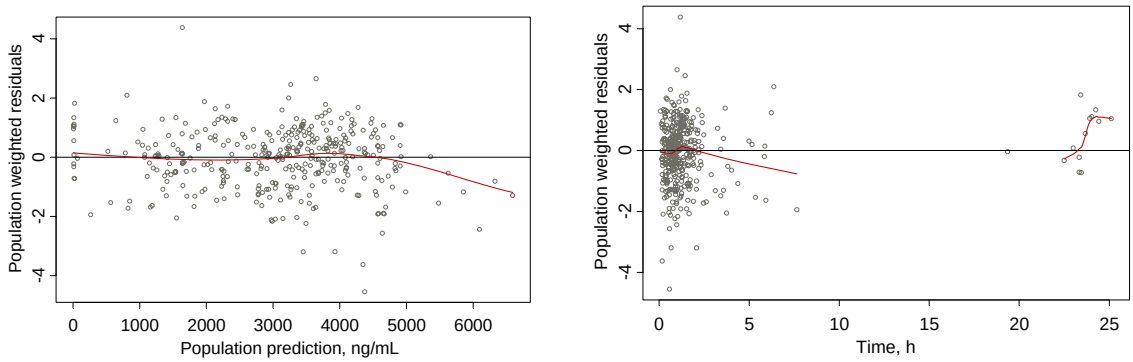


Figure 12: Population weighted residuals vs. population predicted plasma concentrations of RSD1235 (left panel) and population weighted residuals vs. time since the first dose (right panel) for the model development data set. The red line is a smooth local regression curve (loess) showing the relationship between two variables.

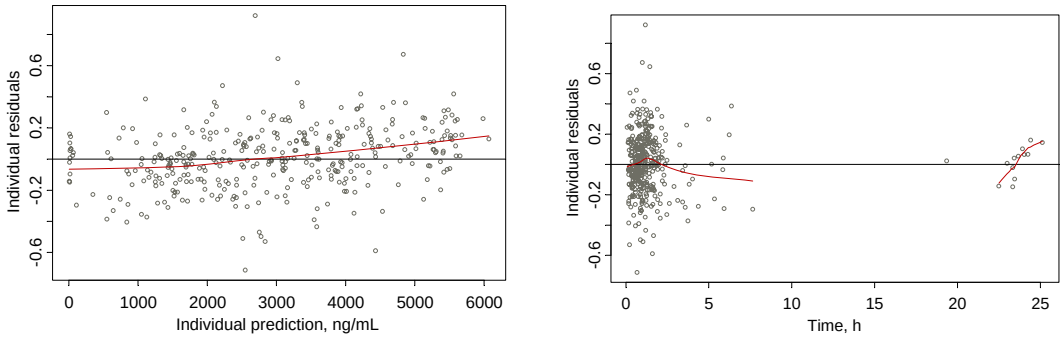


Figure 13: Individual residuals vs. individual predicted plasma concentrations of RSD1235 (left panel) and individual residuals vs. time since the first dose (right panel) for the model development data set. The red line is a smooth local regression curve (loess) showing the relationship between two variables.

5.5.3 Exposure-Response Analysis

Sinus Rhythm Conversion

Treatment with RSD1235 Injection resulted in a significant improvement in the incidence of conversion. A greater proportion of RSD1235 subjects with short duration AF (42/81, 51.9%) converted to SR within 90 minutes compared to placebo subjects (3/83, 3.6%). This 48.3% difference in treatment-induced AF conversion to SR was statistically significant ($p < 0.0001$). For the PK/PD analysis described in this report SR conversion was restricted to conversion with the first infusion up to 25 min, when the second infusion was administered to patients who did not respond to the first infusion. This restriction was necessary to avoid confounding PK/PD assessment with the difference in proportion of responders between the two groups of patients who received one of two doses of the titration design used for this study. The proportion of short duration AF patients that converted to SR within 25 minutes was significantly greater for RSD1235-treated patients (35/81, 43.2%) than for placebo treated patients (1/83, 1.2%) ($p < 0.0001$). In the overall AF study population (AF duration greater than 3 hours and less than 45 days), the rates of conversion to SR within 90 minutes were 3.4% (4/119) for placebo and 39.8% (45/113) for the RSD1235 treated patients.

Development of a model to describe the first treatment-induced SR conversion data led to a model of the form:

$$\text{logit}\left(\Pr\left(Tconv < 25 \ \ \min\right)\right) = \begin{cases} \alpha_{placebo}, & \text{treatment = placebo} \\ \alpha_{RSD1235}, & \text{treatment = RSD1235} \end{cases}$$

where *Tconv* denotes the time of conversion, $\alpha_{placebo}$ and $\alpha_{RSD1235}$ denote the logit-probability of the SR conversion for the placebo patients and RSD1235-treated patients, respectively.

The pharmacodynamic model parameters for the incidence of SR conversion are presented in Table 4.

Table 4. PD parameters for the incidence of SR conversion model

Treatment group	Parameter	Estimated	SE	The probability of having SR conversion within 25-min, with 95% confidence interval (%)
Placebo	$\alpha_{placebo}$	-4.41	1.01	1.2 [0.2, 8.1]
RSD1235	$\alpha_{RSD1235}$	-0.27	0.22	43.2 [32.9, 54.1]

Similarly, the time of SR conversion was best described by a Cox proportional hazard model of the form:

$$h\left(t\right) = h_0\left(t\right)e^{\beta I_{RSD1235}}$$

where $I_{RSD1235} = 1$ for treatment with RSD1235 and 0 for placebo, *h(t)* denotes the resultant hazard for the respective SR conversion event and the respective conversion time (*t*). The term $h_0(t)$ is called the *baseline hazard*; it is the hazard for the respective individual when all independent variable values are equal to zero.

The pharmacodynamic model parameters for the time of SR conversion are presented in Table 5.

Table 5. PD parameters for the time of conversion model

PK variable	exp(β)	95% confidence interval		p value
		Lower	Upper	
Treatment	6.84	2.53	18.5	0.00015

Figure 14 shows a Kaplan-Meier plot of the time to SR conversion data for placebo and RSD1235-treated patients. Both models indicate that the proportion of non-converters over 25 minutes interval is significant lower in the RSD1235-treated group than that in the placebo group. However neither modeling approach permitted characterization of a relationship between plasma drug concentration and the occurrence or timing of SR conversion.

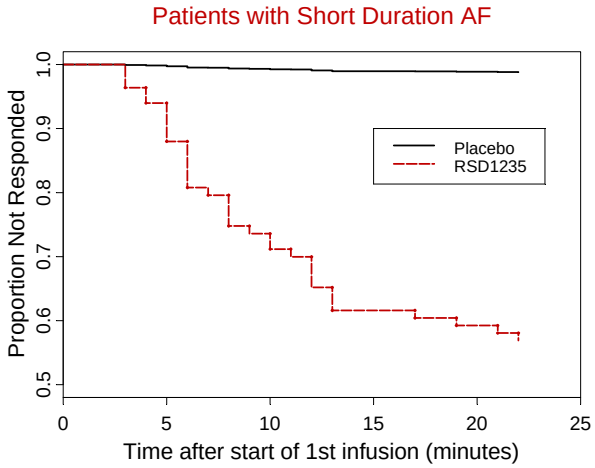
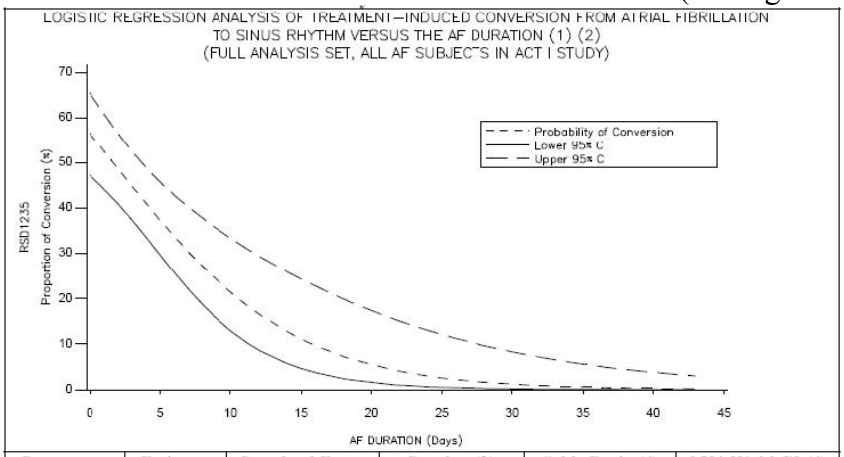


Figure 14. Kaplan-Meier plot of the proportion of patients that did not covert to sinus rhythm over time up to 25 minutes after start of first infusion.

Based on logistic regression analysis, increased likelihood of conversion was significantly associated with briefer duration of atrial fibrillation (see Figure 15).



Parameter	Estimate	Standard Error	P-value (3)	Odds Ratio (4)	95% Wald CI (4)
AF duration	-0.15635	0.03758	<0.0001***	0.855	(0.795, 0.921)

Figure 15 Logistic regression analysis of treatment-induced conversion from atrial fibrillation to sinus rhythm versus the duration of atrial fibrillation.

5.5.4 Exposure-Safety Analysis

SBP and QT interval data were used to build PK/PD models related to safety. The focus of the safety modeling was to describe the relationship between RSD1235 plasma concentration and potential SBP variation and QT prolongation. To find the estimated concentration at the time of SBP and QTc measurement, post-hoc estimates of individual PK parameters were obtained from the population PK analysis and the expected concentration corresponding to each SBP and QTc measurement was calculated, given each patient's dosing history.

QTc Analysis

The QT interval varies with heart rate, as shown in Figure 16. , and there are a number of methods for calculating the corrected QT interval (QTc). The Fridericia correction method was found to be less dependent on heart rate and therefore used for the analysis.

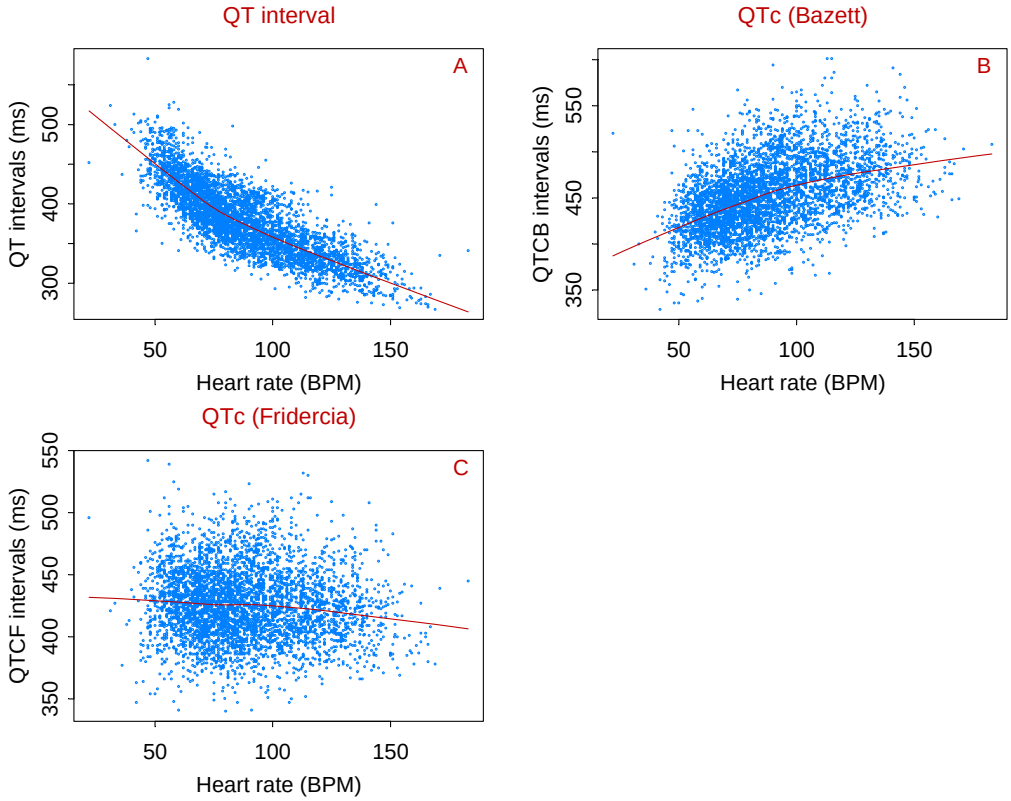


Figure 16: Comparison of QT correction methods.

The relationship between QTcF and RSD1235 concentration on the log-scale is shown in

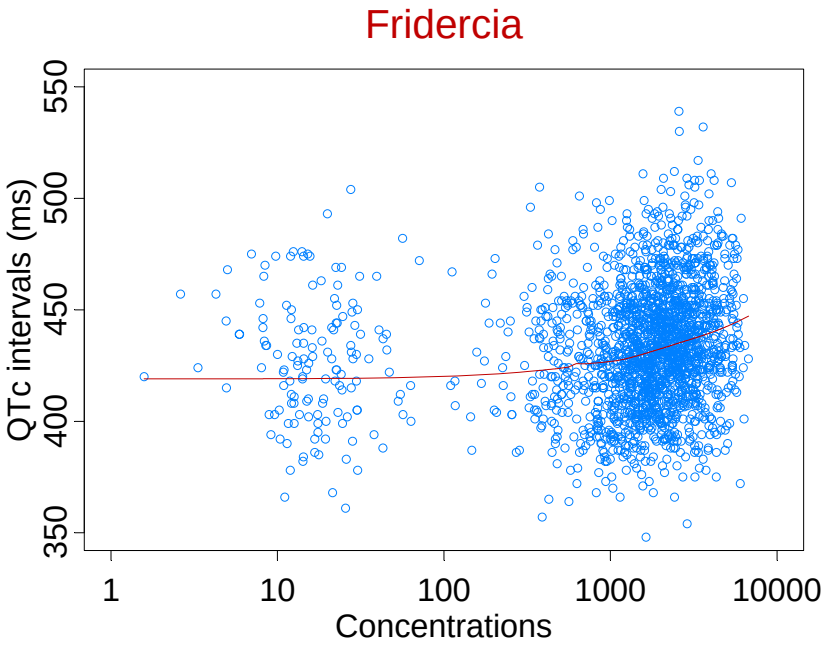


Figure 17. along with local smoothing curves in red.

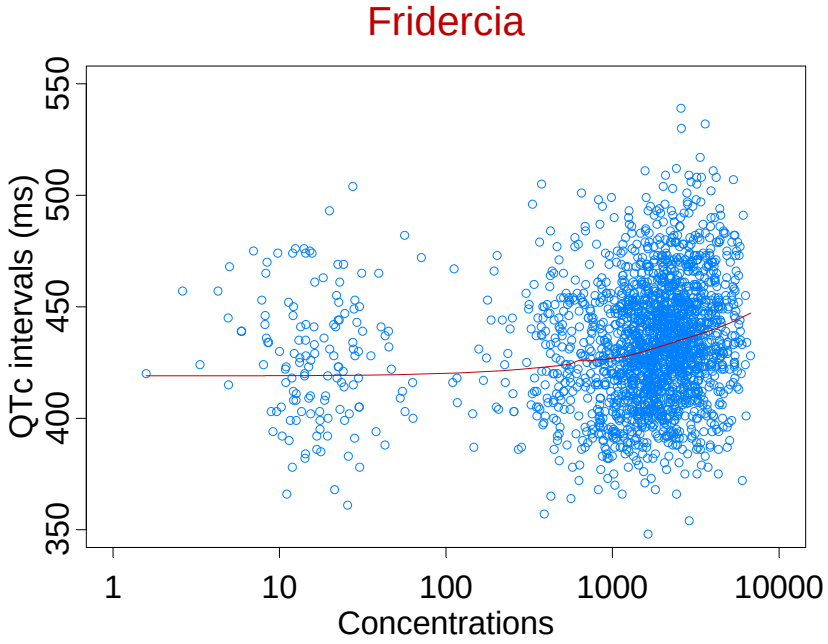


Figure 17: Plot of QTc vs. RSD1235 concentration (log domain) with loess smooth.

The sigmoidal E_{max} model was found to be the best base model to describe the data, i.e.

$$Eff^{1235} = E_{\max} \cdot \frac{Cp^{r}}{Cp^{r} + EC_{50}{}^{r}}$$

Plots of base model residuals (model-fitted values – observed values) vs. time of day for the ECG measurement and examination of the literature suggested that inclusion of diurnal variation could be important. A correction to the *base* model of the form

$$f\left(TimeOfDay\right)=\cos\left(\frac{2\pi\cdot\left(TimeOfDay_i+shft\right)}{24}\right).$$

resulted in a significant improvement in model fit.

Plots of QTcF versus RSD1235 concentration (time ordered) did not reveal any consistent pattern, e.g., hysteresis, which would suggest a time lag between drug exposure and effect, so no attempt was made to model such a time lag.

To identify predictive covariates, covariates were initially added to baseline QTcF, E_{max} and EC_{50} one at a time in a forward inclusion process. Covariates yielding an improvement in the fit (a likelihood ratio > 3.84 for 1 parameter, $p<0.05$) were retained for further analysis. The parameters showing a significant improvement in the fit were the effects of age, CHF, CMED, and arrhythmia type on baseline QTcF, the effects of arrhythmia type on EC_{50}, and the effects of SRS, CAD, and CHF on E_{max}. A model containing these covariate effects served as the base model for the backward elimination step described in the next section.

The final model for QTcF was as follows:

$$QTc(Fridericia)_{ij}=base_{ij}+Eff_{ij}^{1235}+\varepsilon_{ij}$$

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

$$Eff_{ij}^{1235}=\left(Emax\cdot e^{\eta_i^{E\max}}+\beta_{SRS}\cdot SRS\right)\cdot\frac{Cp_{ij}^{r}}{Cp_{ij}^{r}+\left(EC_{50}\cdot e^{\eta_i^{EC50}}\right)^{r}}$$

where QTc_{ij} is the j^{th} QTcF measurement for the i^{th} patient, $base_{ij}$ is the expected baseline QTcF for the i^{th} patient occurring at the time of day for measurement j, Eff_{ij}^{1235} is the effect of RSD1235 on that patient, and ε_{ij} is the random error between the estimated and observed QTcF measurement. In the model of baseline QTcF, β_0 is the expected population baseline (426 ms), β_{age} is a linear coefficient for the covariate of age, age is centered about the population mean value of 61 years, and η_i^{base} is the random variability in baseline QTcF among patients. The cosine term accounts for diurnal variation, shft is start of the cycle and βtod is the amplitude. In the model of effect of RSD1235, Emax is maximum response on treatment, EC_{50} is the concentration to achieve 50% of maximal effect, β_{SRS} is a linear coefficient for the covariate of SRS, SRS is 0 if AF, 1 otherwise, and η_i^{max} is the random variability in E_{max} among patients, and η_i^{EC50} is the random variability in EC_{50} among patients.

The pharmacodynamic model parameters are presented in Table 6. The maximum change in QTcF for patients converting to SR is expected to be 6.1 ms (i.e. 20.3-14.2 ms) while maximum change in QTcF for patients who remained in AF is 20.3 ms. EC50 is 1730 ng/mL. It is noted that most patients had RSD1235 concentrations well above this EC50 at the end of the first infusion. The residual variability between measurements within a subject was 15.9 ms.

Table 6. Final parameter values for sponsor's QTcF model.

Parameter	Estimated	SE	95% confidence interval		CV (%)
β_0 (ms)	426	1.61	422.84	429.16	0.38
E_{max} (ms)	20.3	3.1	14.22	26.38	15.27
EC_{50} (ng/mL)	1730	206	1326	2133.76	11.91
γ	3.58	1.31	1.01	6.15	36.59
β_{tod} (ms)	7.19	1.22	4.80	9.58	16.97
shft (hr)	-3.14	0.417	-3.96	-2.32	-13.28
β_{age} (ms/yr)	0.351	0.097	0.16	0.54	27.52
β_{SRS} (ms)	-14.2	3.95	-21.9	-6.46	-27.82
$\omega^2_{\beta 0}$	0.0025	0.00027	0.00	0.00	10.98
ω^2_{Emax}	0.269	0.096	0.08	0.46	35.58
ω^2_{EC50}	0.097	0.063	-0.03	0.22	65.08
σ^2	253	10.6	232.2	273.8	4.19

* CV=SE/Estimate*100%

Figure 18 shows that the predicted QTcF intervals match the measured QTcF intervals satisfactorily and the residual errors are symmetrically distributed about zero and have an approximately constant variance over time and predicted QTcF intervals. It suggests that the data is reasonably well described by this model.

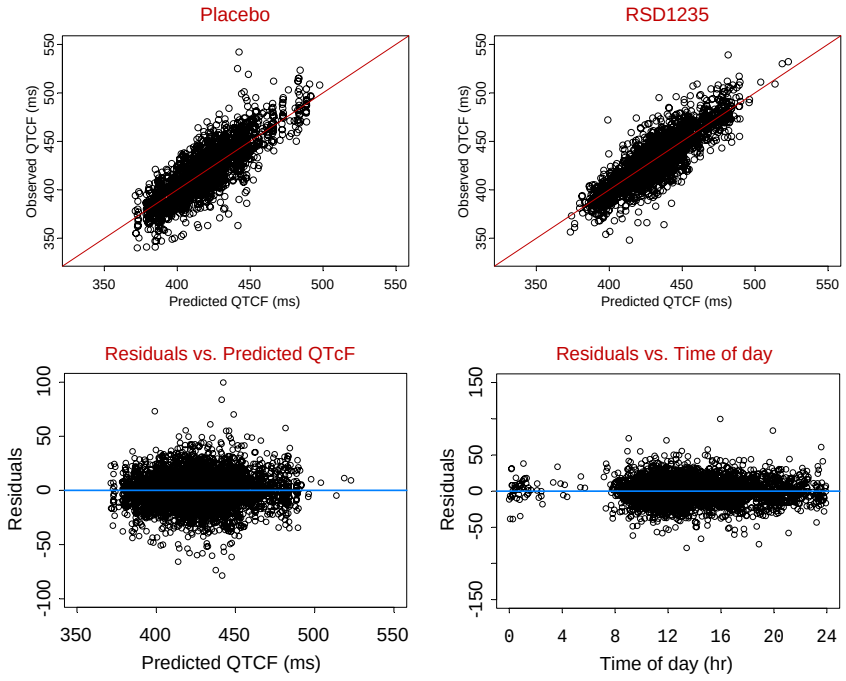


Figure 18. Diagnostic plots showing agreement of fitted QTcF results to observed data. Top: Measured vs. predicted QTcF. Predicted QTcF are obtained from post-hoc individual predictions. Bottom: Residuals vs. predicted QTcF and time of day. Data from 250 subjects are plotted.

Figure 19 shows that the covariate model accurately describes the relationship between individual parameter estimates and important covariates.

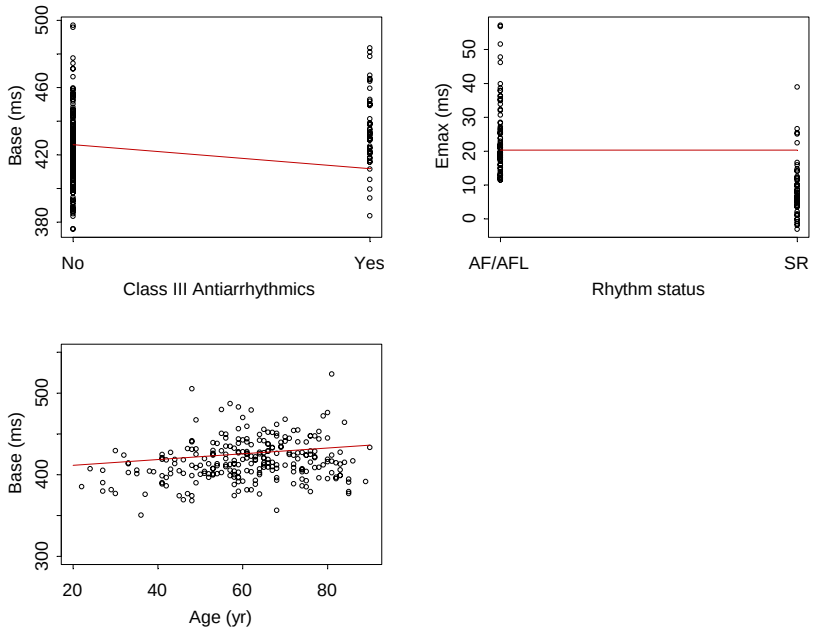


Figure 19. The estimated model parameters, base or Emax vs. antiarrhythmics classes, rhythm status, and age. The parameter estimates are the post-hoc predictions of NONMEM. The line represents a model fit.

Figure 20 shows the model captures both the expected behavior and the variability in the relationship of QTcF to drug concentration. Figure 20 shows the response on a linear concentration scale, illustrating the trend to a maximal response and log-scale to display effects at high (>5000 ng/mL) and at low (<1000 ng/mL) concentrations. Reference line is the upper 95% percentile concentration resulting from treatment with RSD1235.

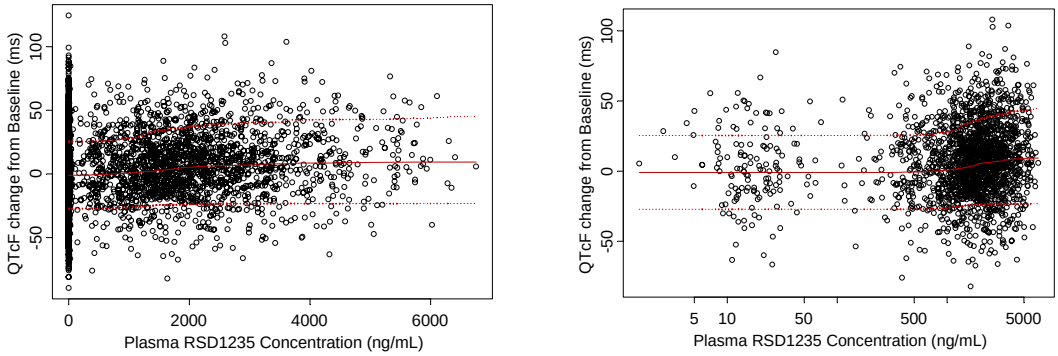


Figure 20. The comparison of observed and simulated QTcF change from baseline vs. plasma RSD1235 concentration for 10,000 simulated subjects. Left is linear concentration scale and right is Log concentration scale. Points represent the observed data. The dashed lines represent the simulated 5 and 95 percentiles, while the solid line gives the expected median response.

Figure 21 depicts model-predicted population mean QTcF prolongation as a function of RSD1235 plasma concentration. Putting this into context, the peak RSD1235 plasma concentrations observed in Study 04-7-010 had a median of 4380 ng/mL; the 5th and 95th percentiles were 1150 and 7200 ng/mL, respectively.

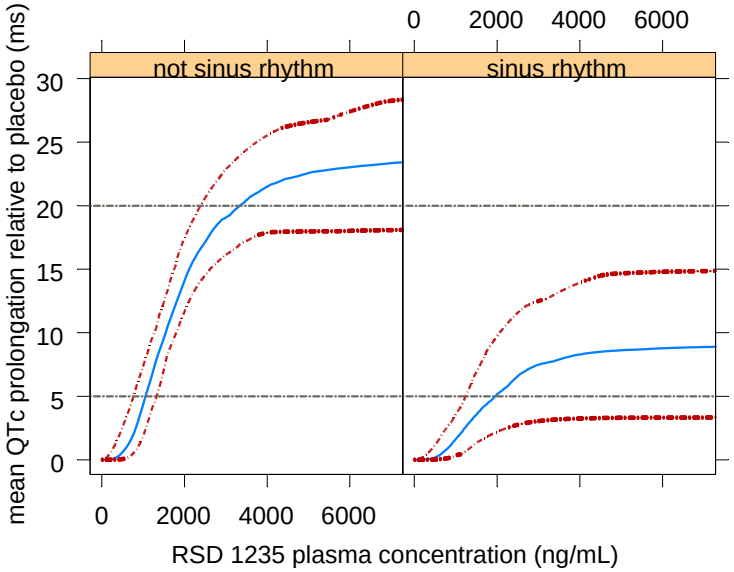


Figure 21. Model-predicted population mean QTcF prolongation (relative to placebo) as a function of RSD1235 plasma concentration and sinus rhythm status (median and 90% prediction interval reflecting uncertainty in the predicted population mean).

Systolic Blood Pressure

The relationship between SBP and RSD1235 concentration on the normal- and log-scale is shown in Figure 22 along with local smoothing curves in red.

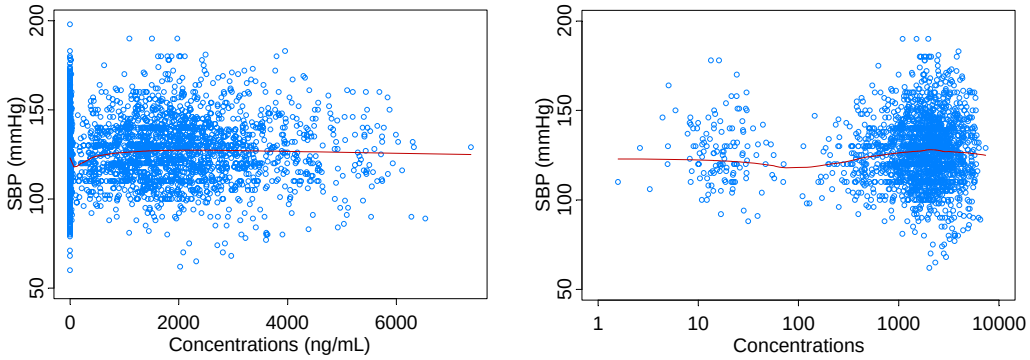


Figure 22: Plot of SBP vs. RSD1235 concentration with loess smooth.

A sigmoidal model similar to the one used for QTcF was chosen as the base model for SBP.

To identify predictive covariates, covariates were initially added to baseline SBP, E_{max} and EC_{50} one at a time in a forward inclusion process. Covariates yielding an improvement in the fit (a change in a likelihood ratio > 3.84 for 1 parameter, $p<0.05$) were retained for further analysis. The parameters showing a significant improvement in the fit were the effects of age and history of hypertension on baseline SBP, the effects of SRS, age, weight, CMED (antihypertensives), CHF, and rhythm type on E_{max}, and the effects of CHF and CAD on EC_{50}. A model containing these covariate effects served as the base model for the backward elimination step described in the next section.

The final model for SBP was as follows:

$$SBP_{ij} = base_{ij} + Eff_{ij}^{1235} + \varepsilon_{ij}$$

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

$$Eff_{ij}^{1235} = \left(Emax \cdot e^{\eta_i^{E\max}}\right) \cdot \frac{Cp_{ij}^r}{Cp_{ij}^r + \left(EC_{50} \cdot e^{\eta_i^{EC50}}\right)^r}$$

where SBP_{ij} is the j^{th} SBP measurement for the i^{th} patient, $base_{ij}$ is the expected baseline SBP for the i^{th} patient occurring at the time of day for measurement j, Eff_{ij}^{1235} is the effect of RSD1235 on that patient, and ε_{ij} is the random error between the estimated and observed SBP measurement. In the model of baseline SBP, β_0 is the expected population baseline (122 mmHg), age is centered about the population mean value of 61 years, and η_i^{base} is the random variability in baseline SBP among patients. The cosine term accounts for diurnal variation.

The final SBP model parameters are presented in Table 7. The maximal drug effect on SBP was estimated to be 3.25 mmHg with an estimated EC_{50} of 1140 ng/mL. It was noted that most patients had RSD1235 concentrations well above this EC50 at the end of the first infusion. The lows Emax value indicates that the maximal amount of blood pressure change induced by the drug is relatively small.

Table 7. Final model parameter values for SBP model.

Parameter	Estimated	SE	95% confidence interval		CV (%)
β_0 (mmHg)	122	0.933	120.2	124	0.8
E_{max} (mmHg)	3.25	0.76	1.76	4.74	23
EC_{50} (ng/mL)	1140	107	930.28	1350	9
γ	4.98	2.39	0.29	9.66	48
β_{tod} (mmHg)	1.37	0.665	0.07	2.67	49
shft (hr)	-35.9	2.03	-39.87	-31.9	-6
β_{age} (mmHg/yr)	0.233	0.068	0.09	0.37	29
$\omega^2_{\beta 0}$	0.013	0.001	0.01	0.015	8
ω^2_{Emax}	1.56	0.372	0.83	2.29	24
σ^2	84.3	4.29	75.89	92.7	5

* CV = SE / Estimate × 100%

Figure 23 shows that the predicted SBP match the measured SBP satisfactorily and the residual errors are normally distributed over time and predicted SBP. It suggests that the data is described reasonably.

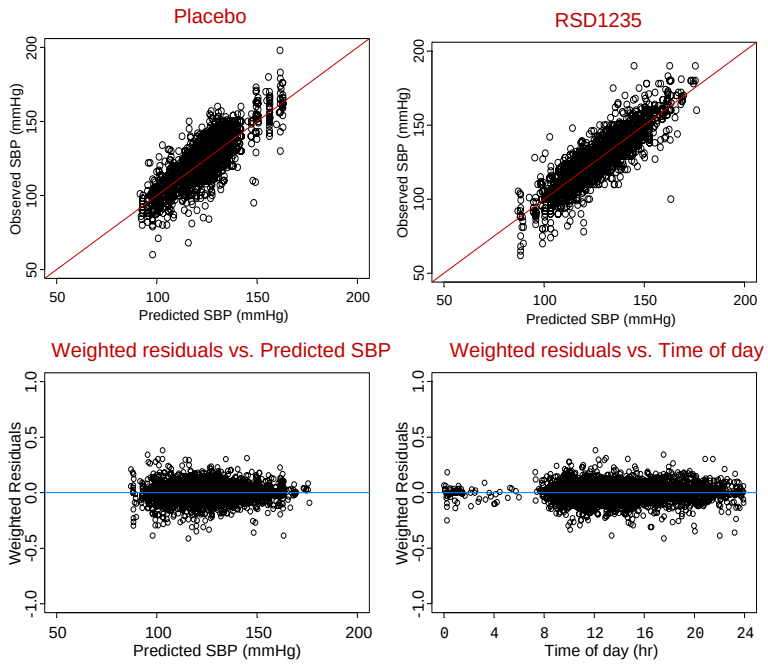


Figure 23. Diagnostic plots showing agreement of fitted SBP results to observed data. Top: Measured vs. predicted SBP. Predicted SBP are obtained from post-hoc individual predictions. Bottom: Residuals vs. predicted SBP and time of day. Data from 254 subjects are plotted.

Figure 24 shows that the covariate model accurately describes the relationship between individual parameter estimates and important covariates.

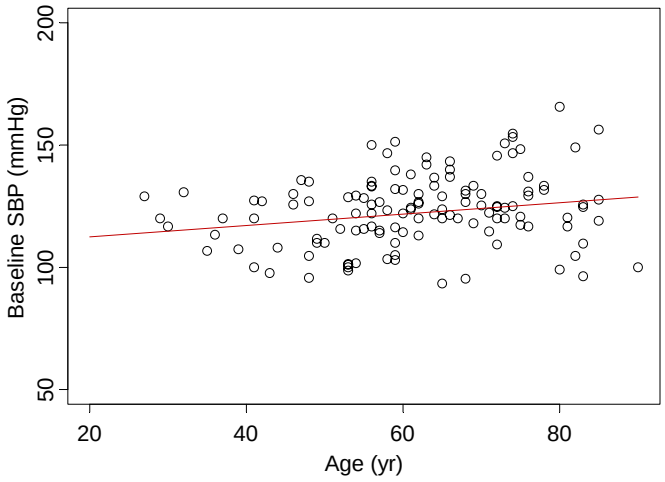


Figure 24. The estimated model parameter, base vs. age. The parameter estimates are the post-hoc predictions of NONMEM. The line represents a model fit.

Figure 25 shows the effects of age, time of day, and RSD1235 treatment on the SBP. Each bar represents the influence of a single variable on SBP. The most influential variables are at the top. The vertical line is the SBP in the typical subject (60 yrs, dose at 8:00 AM, and plasma RSD1235 concentration is 1140 ng/mL=EC_{50}). For example, SBP would be expected to increase to near 130 mmHg in an 80 year-old subject. In contrast, the effects of RSD1235 are minimal.

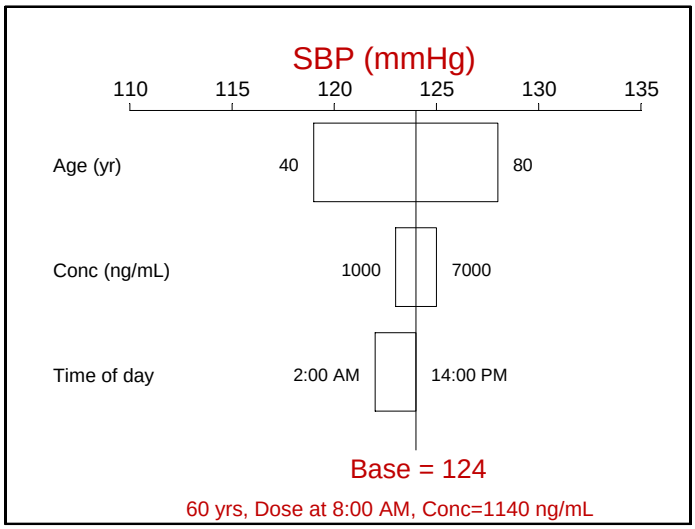


Figure 25. Sensitivity plot comparing the effect of the potential factors on SBP. The solid vertical reference line is the SBP in the typical subject. The label at each end of the bar represents the influential factor that produces that SBP. The length of each bar describes the potential impact of that particular factor on SBP.

Figure 26 shows the model captures both the expected behavior and the variability in the relationship of SBP to drug concentration. Figure 26A shows the response on a linear concentration scale, illustrating the trend to a maximal response and log-scale (B) to display effects at high (>5000 ng/mL) and at low (<1000 ng/mL) concentrations. Reference line is the upper 95% ile concentration resulting from treatment with RSD1235.

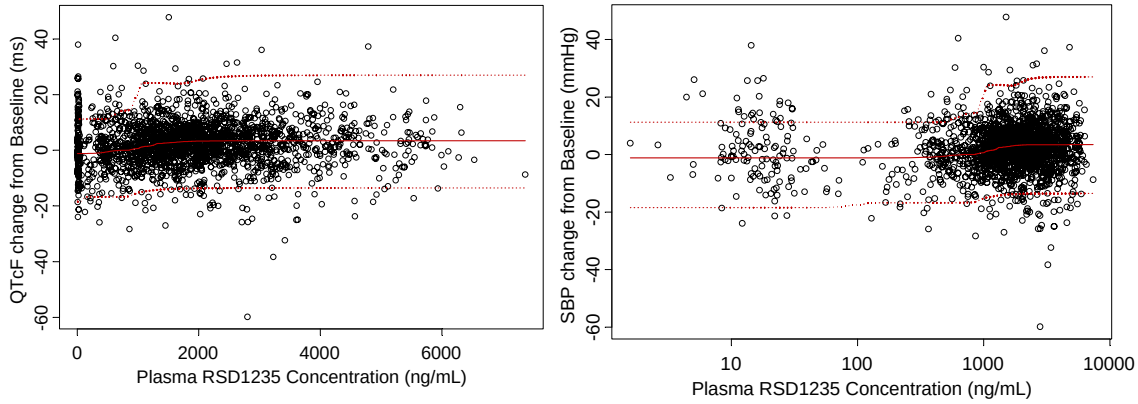


Figure 26. The comparison of observed and simulated SBP change from baseline vs. plasma RSD1235 concentration for 10,000 simulated subjects. Left is linear concentration scale and right is Log concentration scale. Points represent the observed data. The dashed lines represent the simulated 5 and 95 percentiles, while the solid line gives the expected median response.

Hypotension is defined as SBP less than or equal to 85 mmHg. 10% (13/128) of patients had hypotension in placebo group and 8% (10/126) of patients had hypotension after being given RSD1235 (within 24 hours). The relationship between hypotension and plasma RSD1235 concentration is shown in Figure 27.

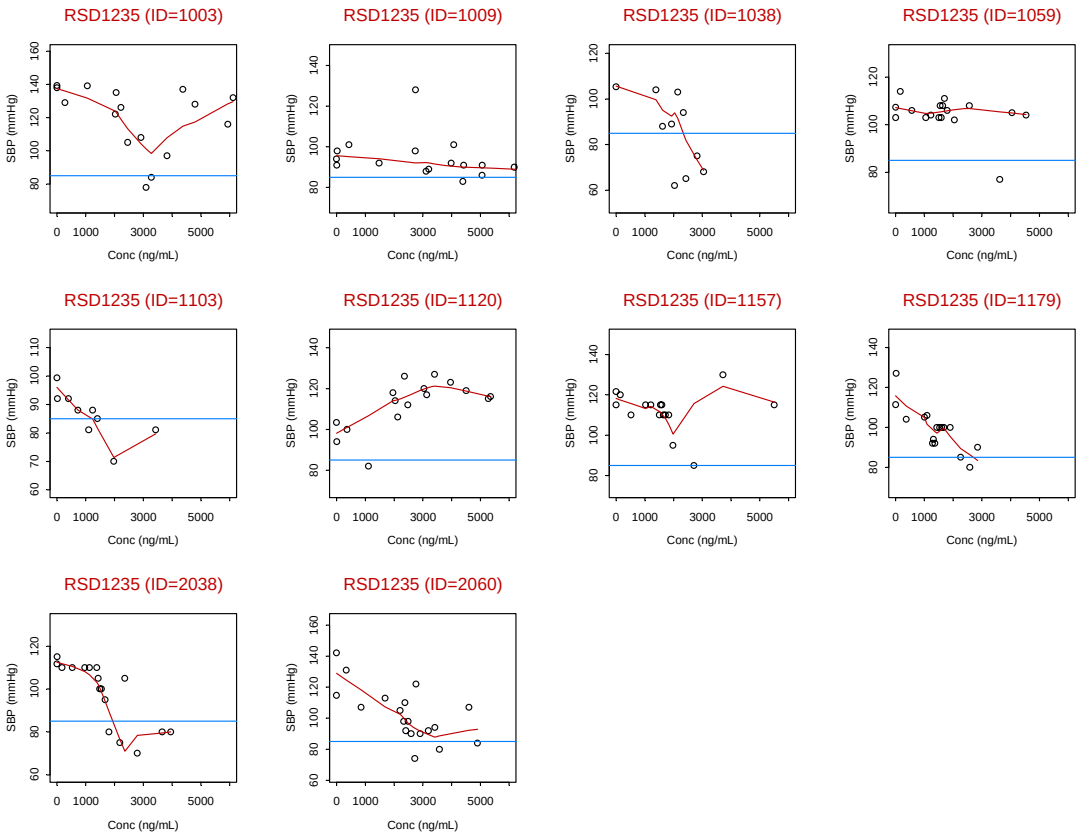


Figure 27. The relationship between hypotension and plasma RSD1235 concentration.

4.2% (5/120) of patients had hypotension in placebo group and 7.2% (9/125) of patients had hypotension after being given RSD1235 within 60 minutes.

5.6 SPONSOR'S CONCLUSIONS

Population PK

A two-compartment pharmacokinetic model described the disposition of the HCl salt form of RSD1235. The population median (or typical) estimated clearance was 34.4 L/h (or 8.2 mL/min/kg for a 70 kg adult) and was similar to that reported previously in healthy volunteers. Inter-individual variability in CL was estimated to be 33%.

Age, presence of CHF, concomitant CYP 2D6 inhibitors and concomitant beta-blockers did not influence the clearance of RSD1235. Race did not influence the clearance of RSD1235 in this study population, although it should be noted that 92% of study participants were Caucasian. Hepatic function (as measured by laboratory markers) was also assessed; however, very few patients had markers of impaired hepatic function. Creatinine clearance in the study population ranged from 31 to 179 mL/min. The majority of subjects (51.5%) in the model development set had normal renal function, while 36.7% and 11.7% had mild and moderate renal impairment, respectively. No subjects had severe impairment. Renal function did not influence the clearance of RSD1235 in the study population.

The typical volume of the central compartment in males was estimated to be 51.0 L. It was approximately half that value, or 26.4 L in females. The lower volume of the central compartment in females may reflect lower body weights of females (median 75 kg) compared with males (median 89 kg) in the study population.

As a result of reduced volume of the central compartment, females would be expected to have higher maximum RSD1235 plasma concentrations than males following the same dose, and this result was confirmed by the data. However, a gender difference in volume of distribution was not observed previously in healthy volunteers, and this finding remains to be validated with the addition of data from other studies and for other dosing regimens. The clinical implications of the finding of a reduced volume of the central compartment in females in this study population will be assessed in the exposure-response analysis.

The typical volume of the peripheral compartment was estimated to be 103 L. Estimates of inter-individual variability for central and peripheral volumes were 78% and 27%, respectively. The typical steady-state volume of distribution (V_{ss}) calculated as the sum of the central and peripheral volumes of distribution, was 154 L in males and 129 L in females, while the volume of distribution during the terminal phase of the plasma concentration vs. time curve ($V_{d\beta}$) calculated by dividing RSD1235 clearance by the slope of the terminal phase, β, was 165 L. However, it should be noted that there was a low number of data points (4% of measurable plasma concentrations) defining the terminal phase. In comparison, $V_{d\beta}$ in healthy volunteers was reported to be approximately 125 L.

Exposure-Response (Conversion to Normal Sinus Rhythm)

- Treatment with RSD1235 results in a significant improvement in the incidence of conversion. A greater proportion of RSD1235 subjects with short duration AF converted to SR within 25 minutes (35/81, 43.2%) and within 90 minutes (42/81, 51.9%) compared to placebo subjects.
- The model that best describes the relationship between RSD1235 plasma concentration and the incidence and timing of SR conversion confirmed that RSD1235 markedly increases the SR conversion rate. However the data available from Study 04-7-010 alone was insufficient for identifying a concentration-effect relationship. This was not surprising since the model evaluated only the first dose level of RSD1235. It is possible that a concentration-effect relationship might be identified by combining the results of multiple studies some of which involve the use of other dose levels of RSD1235.

QT Analysis

- The relationship between the plasma concentration of RSD1235 was best described by a sigmoidal E_{max} model. Maximum change in QTcF for patients converting to SR is expected to be 6.1 ms while maximum change in QTcF for patients who remained in AF is 20.3 ms. EC50 is 1730 ng/mL. Age affected baseline QTcF value. Note that most patients had RSD1235 concentrations well above this EC50 at the end of the first infusion.

Systolic Blood Pressure

- The relationship between RSD1235 concentration and SBP can be described using a sigmoidal Emax model, with typical E_{max} of 3.25 mmHg, and EC_{50} of 1140 ng/mL. Age affected baseline SBP.
- This Emax value indicates that the maximal amount of blood pressure change induced by the drug is relatively small.

6 REVIEWER'S COMMENTS ON SPONSOR'S ANALYSIS

- The volume of distribution in females was found to be half that in males (51.0 L in males and 26.4 L) by the sponsor. Females are therefore expected to have higher C_{max} compared to males following the same dose which was not observed previously in healthy volunteers. Body weight also appears to be a significant covariate and should have been incorporated in the model before evaluating gender differences.
- Sponsor did not include study 1235-010 which has CYP 2D6 genotype information in the population PK analysis which would help to explain some of the variability in clearance.
- The concentration-QT analysis should only have been performed on the available data up to 2 hours after the first infusion since other therapies were permitted after this time point.

The identified deficiencies in sponsor's analysis are addressed in the reviewer's analysis.

7 REVIEWER'S ANALYSIS

The methods described in Sponsor's analysis in Sections 5.4 are identical to those used for the reviewer's analysis.

Data from pivotal study 1235-010 was included in reviewer's analysis to further quantify the PK of RSD1235 plus investigate whether CYP2D6 genotype information (only obtained in study 1235-010) can explain some of the variability in the PK of RSD1235.

Pharmacokinetic measurements above 15,000 ng/mL from extensive metabolizers and above 100,000 ng/mL for poor metabolizers in study 1235-010 were removed from the population PK analysis since they were considered to be outliers. A total of 11 measurements (5 samples above 100,000 ng/mL and 6 above 15,000 ng/mL for EMs) were thus removed. Furthermore, patient 703108804 (who was classified as a PM) was removed since all concentration measurements were above 15,000 ng/mL except one.

7.1 POPULATION PK ANALYSIS

7.1.1 Base Model

Sponsor's base model was identical to reviewer's base model using data from study 010 and 703. The observed and predicted concentration-time profiles for reviewer's base PK model are shown in Figure 41 together with the goodness-of-fit graphs in Figure 42.

7.1.2 Covariate model

RSD1235 clearance and volume were found to be correlated with body weight (see Figure 43-Figure 45) and was included as covariate for CL, Q, V1, and V2 in the final model.

Females were also found to have lower central volume of distribution in the base PK model as shown by the sponsor. This finding was however due to not having accounted for body weight's influence on RSD1235 PK parameters.

The same argument can be made for the apparent relationship between RSD1235 clearance and CrCL which was calculated using Cockcroft-Gault formula using age, body weight, and serum creatinine. When using body weight as a covariate, RSD1235 clearance was no longer correlated with CrCL. This corresponds well with the fact that RSD1235 primarily is metabolized by CYP2D6.

CYP2D6 genotyping was performed in study 125-0703 but not in study 04-7-010. The influence of genotypes on RSD1235 PK could therefore only be investigated in 221 out of 355 patients in the two pivotal studies where 9 and 179 patients were classified as poor (PM) and extensive metabolizers (EM), respectively, and 33 patients CYP2D6 genotype was not identified. From the base PK model, PMs appear to have lower clearance. After having incorporated body weight as a covariate on CL, Q, V1, and V2, PMs were found to have 86% lower CL compared to EMs. The identified relationship between body weight and CL, Q, V1, and V2 are shown in Figure 28 together with poor metabolizers influence on RSD1235 clearance.

No other demographic covariates (age, race, renal function) were found to influence RSD1235 pharmacokinetics.

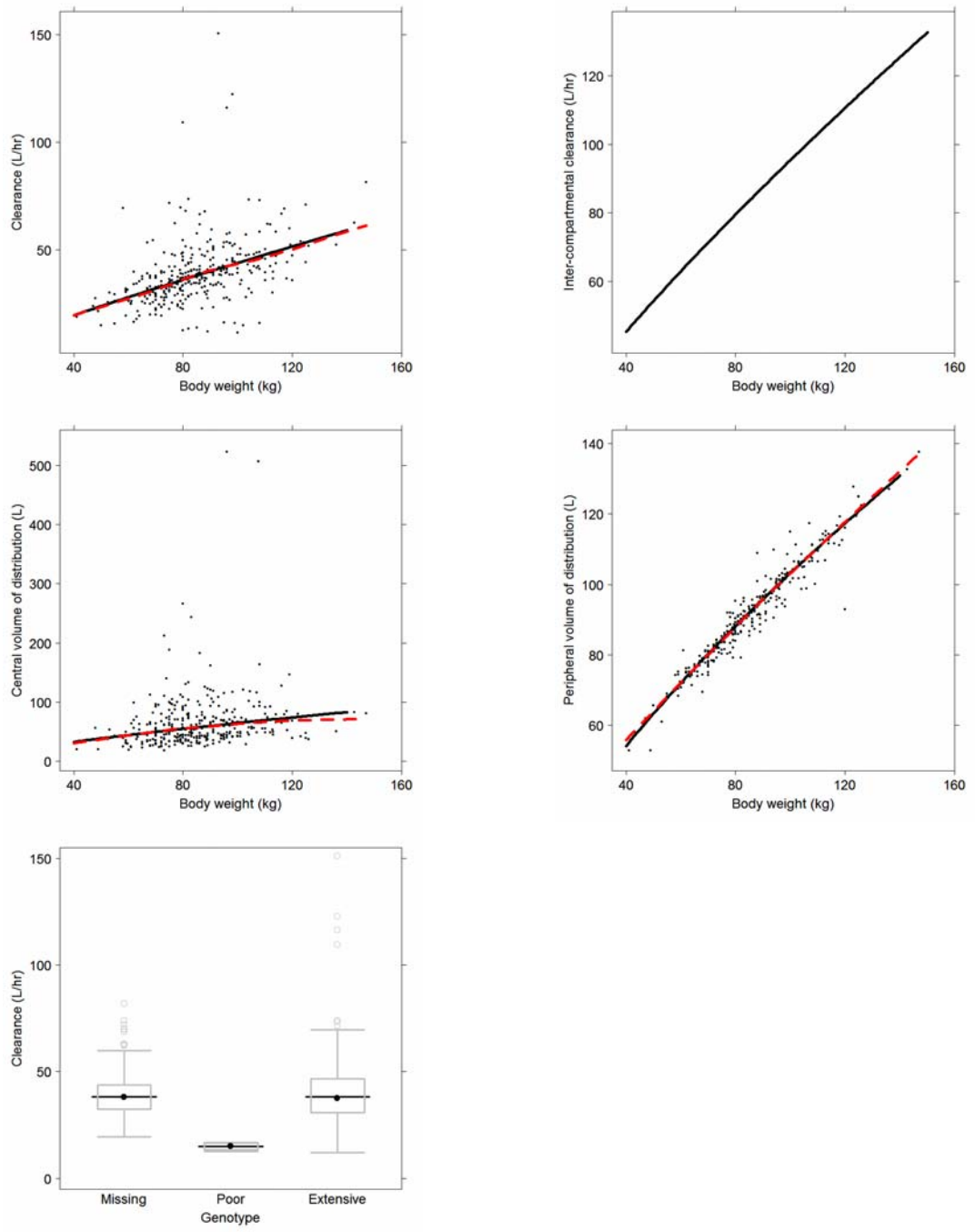


Figure 28 Identified covariate-PK parameter relationships. (Top Left) Body weight influence on RSD1235 clearance, (Top Right) Body weight influence on inter-compartmental clearance, (Middle Left) Body weight influence on central volume of distribution, (Middle Right) Body weight influence on peripheral volume of distribution, and (Bottom Left) Genotype influence on RSD1235 clearance. The solid black lines are the population model predictions and the dotted red lines are the smoothing local regression.

7.1.3 Final PK Model

The PK parameter estimates for the reviewer's final PK model are shown in Table 8 and the goodness-of-fit graphs are shown in Figure 47.

Table 8 Reviewer's Final PK Model Parameter Estimates.

		Population parameters		Inter-individual variability	
Parameter	**Unit**	**Estimate**	**%RSE**	**Estimate (CV%)**	**%RSE**
Fixed-Effects Parameters					
CL	[L/hr]	37.4	2.89	36.6	19.9
Q	[L/hr]	82.0	5.27	*	-
V_1	[L]	56.2	3.35	53.1	12.1
V_2	[L]	90.5	2.49	13.0	78.7
Covariate-relationships					
CL-WT exponent	[-]	0.878	17.2	-	-
Q-WT exponent	[-]	0.813	27.3	-	-
V_1-WT exponent	[-]	0.747	20.5	-	-
V_2-WT exponent	[-]	0.705	20.4	-	-
Reduction in CL for CYP2D6 PM vs. EM	[%]	63.6	11.5	-	-
Intra-Individual Variability					
Proportional error	[CV%]	28.9	5.19	-	-

*Not estimated

The estimated distribution population half-life is 0.3 hrs and the terminal population half-life ($t_{1/2,\beta}$) is 3.2 and 8 hrs for CYP2D6 EMs and PMs, respectively, with a steady-state volume of distribution (V_{ss}) estimate of 1.77 L/kg (147 L for 83 kg patient) indicating a high degree of tissue distribution.

Including patient 703108804 who was a PM changed the population predicted terminal half life for PMs from 8.9 to 20 hrs (i.e. from 64 to 86% reduction in CL for PMs). He was therefore not included in the final PK analysis but it is likely that the reduction in CL for PMs is greater than 64% compared to EMs at a population mean level.

The population PK predictions following one- or two- 10 minute infusions are shown in Figure 29. The population mean predicted C_{max} after the first 3 mg/kg IV infusion is 3660 and 4330 after the 2 mg/kg IV infusion for EMs.

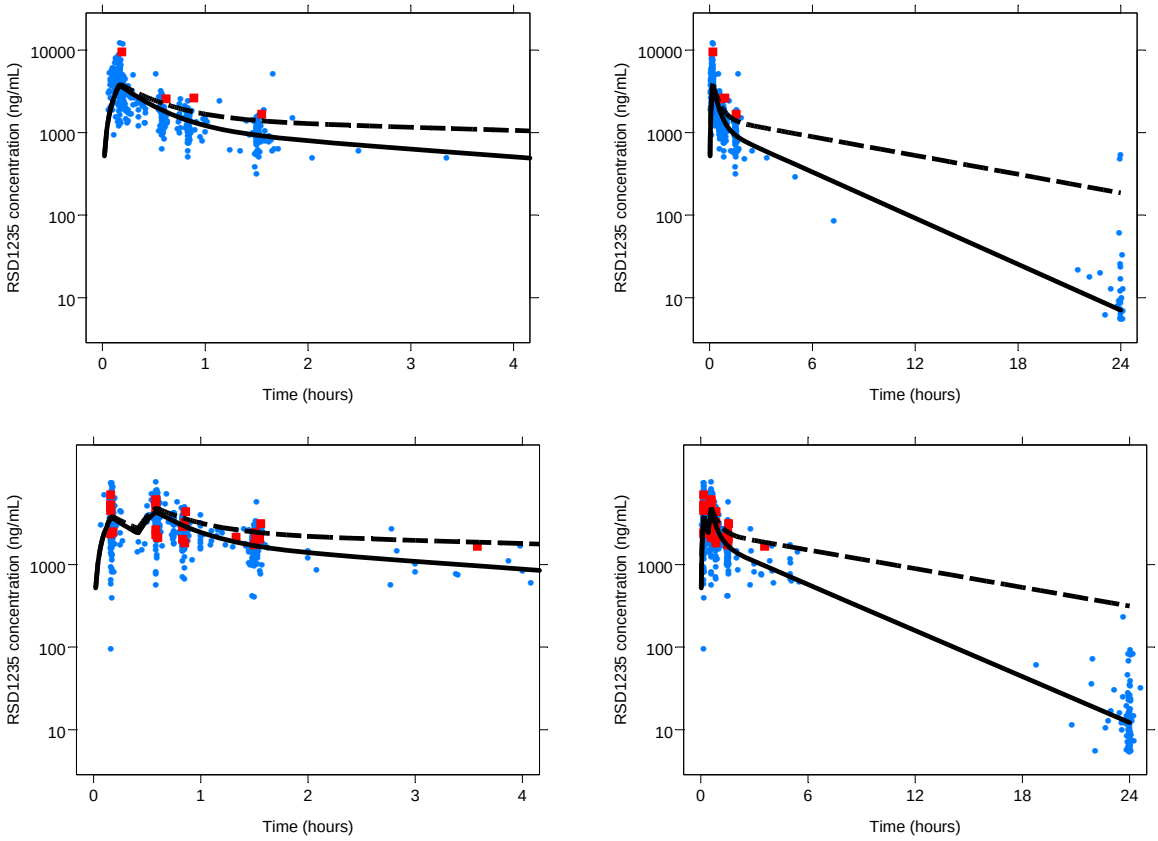


Figure 29. Population predicted RSD1235 concentration-time profiles for poor (PM, dashed) and extensive (EM, solid) metabolizers on the log scale after single 3 mg/kg IV infusion over 10 minutes (top) followed by 2 mg/kg IV infusion over 10 minutes (bottom). (Left) 0-4 and (Right) 0-24 hours profiles. Observed RSD1235 concentrations are shown as blue dots for EMs and missing while PMs are shown as red squares.

7.2 QT ANALYSIS

The mean QTcF time profile for placebo and RSD1235 treated patients are visualized in Figure 30 with a mean change from placebo of around 25 msec at the end of the first and second infusion.

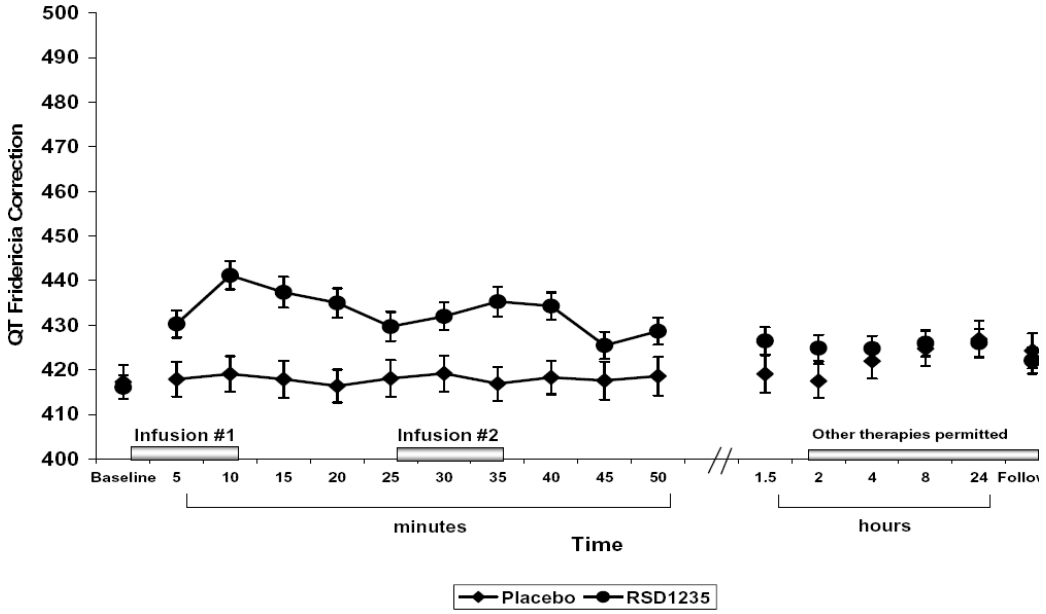


Figure 30 Mean QTcF time profile for placebo and RSD1235 treated patients.

The categorical analysis of QTcF and QTcF change from baseline (ΔQTcF) are summarized in Table 9.

Table 9 Categorical analysis of QTcF and QTcF Change from baseline

	QTcF		ΔQTcF (change from baseline)	
	>450 msec	>500 msec	>30 msec	>60 msec
RSD1235	62.0%	10.2%	62.0%	10.2%
Placebo	33.8%	5.5%	33.8%	5.5%

7.2.1 Base Concentration-QTc Model

The concentration-QTc analysis was performed using the ΔQTcF (change from baseline) for the vernakalant treated patients only to avoid modeling the placebo time course with diurnal variations. Data up to 2 hours post infusion was used since other therapies were permitted beyond this time point.

The PK model was used to predict each individual's concentration at the time of QT recording.

Linear, log-linear, and E_{max} models were explored with the linear model fitting the data best. The parameter estimates from the base concentration-QTcF analysis can be found in Table 10.

Table 10 Reviewer's Base Concentration-QTcF Linear Model Parameter Estimates.

		Population parameters		Inter-individual variability
Parameter	**Unit**	**Estimate**	**RSE (%)**	**SD**
Intercept	[msec]	3.74	28.1	14.3
Slope	[msec/(mcg/mL)]	4.76	7.35	4.04
Residual error (SD)	[msec]	17.4	2.58	-

7.2.2 Covariate Concentration-QTc Model

Only baseline QTcF was identified as a covariate on the intercept (see Figure 31 Left). No covariates were found to influence the slope of the concentration-QTcF relationship (see Figure 53 and Figure 54).

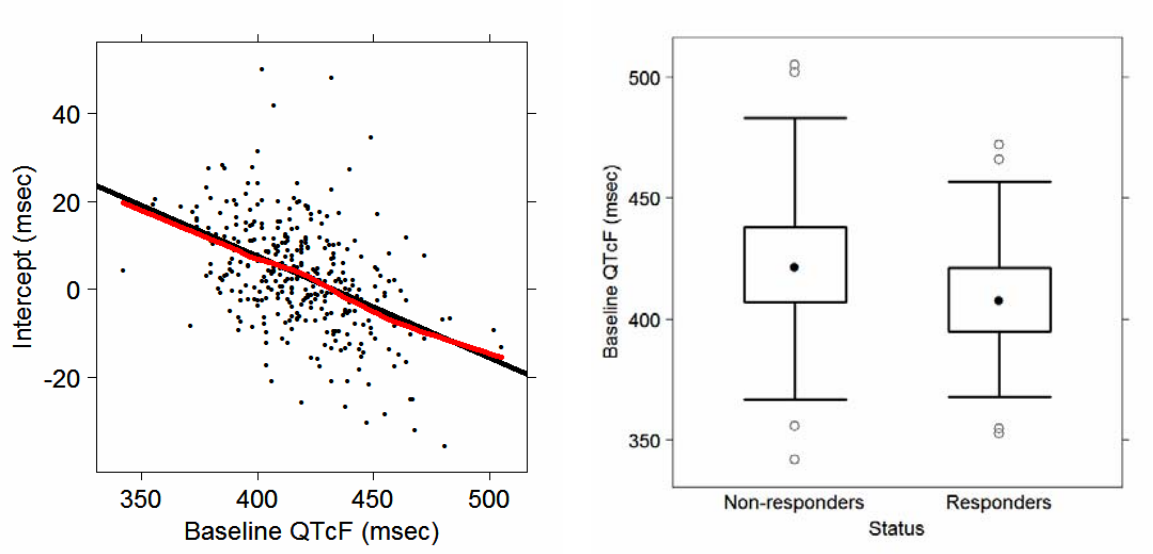


Figure 31 (Left) Relationship between intercept and baseline QTcF. Black line represents the model prediction and the red line is a smoothing local regression line. (Right) Baseline QTcF for non-responders and responders.

Unlike the sponsor's analysis, conversion status was not found to influence the slope of the concentration-QT relationship. Since patients who responded to vernakalant had lower baseline QTcF compared to non-responders (see Figure 31 Right) and sponsor did not use baseline QTcF as a covariate for the intercept, they falsely concluded that responders have lower maximum QT prolongation compared to non-responders.

7.2.3 Final Concentration-QTcF Model

The parameter estimates from the final concentration-QTcF analysis are shown in Table 11 and the goodness-of-fit graphs are shown in Figure 51-Figure 52.

Table 11 Reviewer's Final Concentration-QTcF Linear Model Parameter Estimates.

		Population parameters		Inter-individual variability
Parameter	**Unit**	**Estimate**	**RSE (%)**	**SD**
Intercept	[msec]	3.72	27.2	13.4
Percentage reduction in intercept pr. msec change in baseline QTcF from mean baseline QTcF of 417 msec	[%]	-6.21	32.7	-
Concentration-Slope	[msec/(mcg/mL)]	4.80	7.27	4.00
Residual error (SD)	[msec]	17.4	2.57	-

The mean predicted ΔQTcF after 3 mg/kg IV infusion over 10 minutes was 21 msec (90% CI 20-23 msec) at the mean predicted Cmax of 3660 ng/mL.

For patients receiving 3+2 mg/kg 10 minute infusions 15 minutes apart, the mean predicted ΔQTcF was 24 msec (90% CI 23-26) at the mean predicted Cmax of 4330 ng/mL.

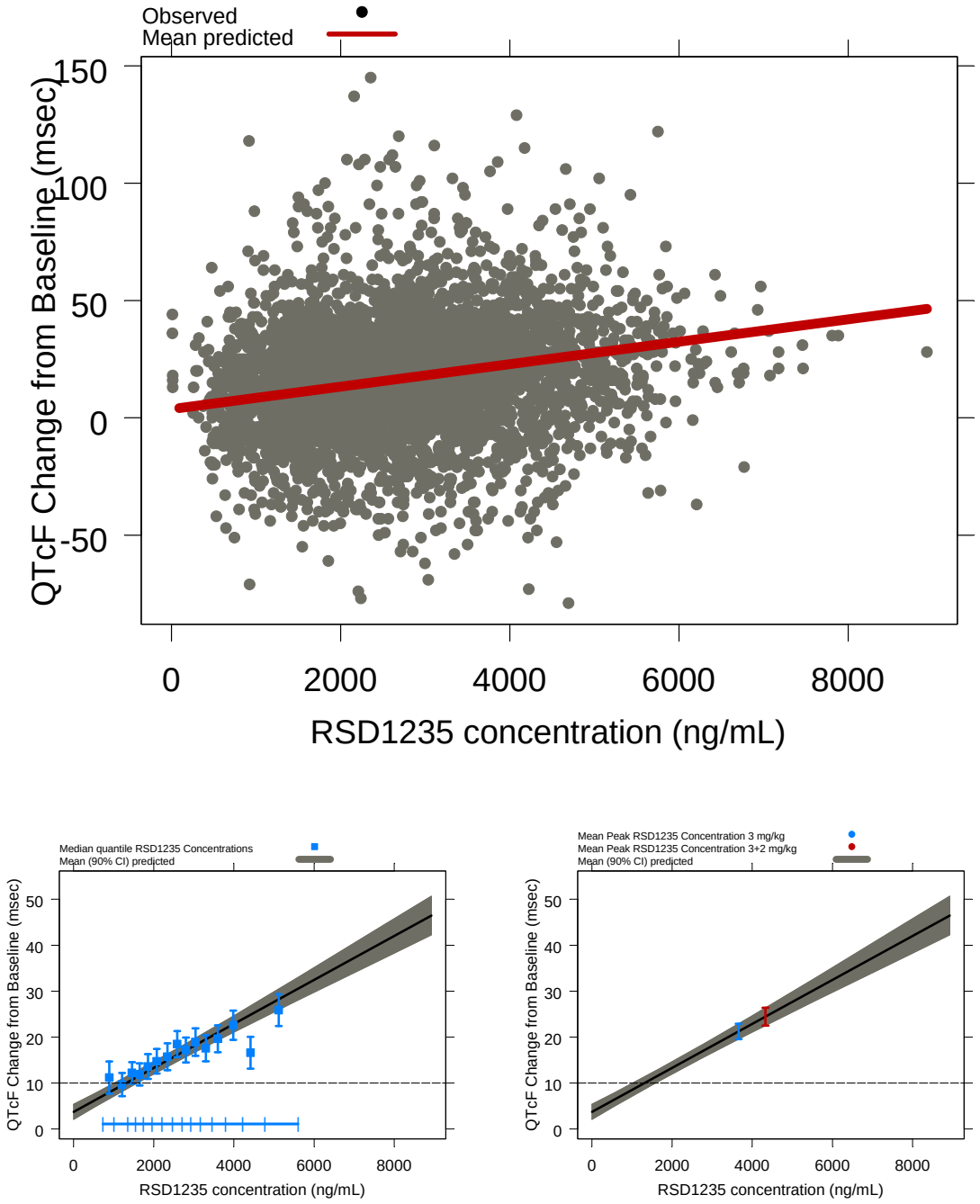


Figure 32. ΔQTcF (Change from Baseline) vs. RSD1235 concentrations. **(Top)** Observed concentrations vs. ΔQTcF. **(Bottom Left)** Median-quantile tedisamil concentrations and associated 90% CI together with the population predictions with 90% confidence interval (solid black line with shaded grey area). The horizontal bars show the observed RSD1235 concentrations divided into 15 bins with equal number of observations. **(Bottom Right)** Population predictions and associated 90% CI at mean 3 mg/kg (blue) and 3+2 mg/kg (red) peak RSD1235 concentrations.

The population mean predicted QT prolongation-time profiles for a typical 83 kg subject receiving one or two vernakalant doses are illustrated in Figure 33.

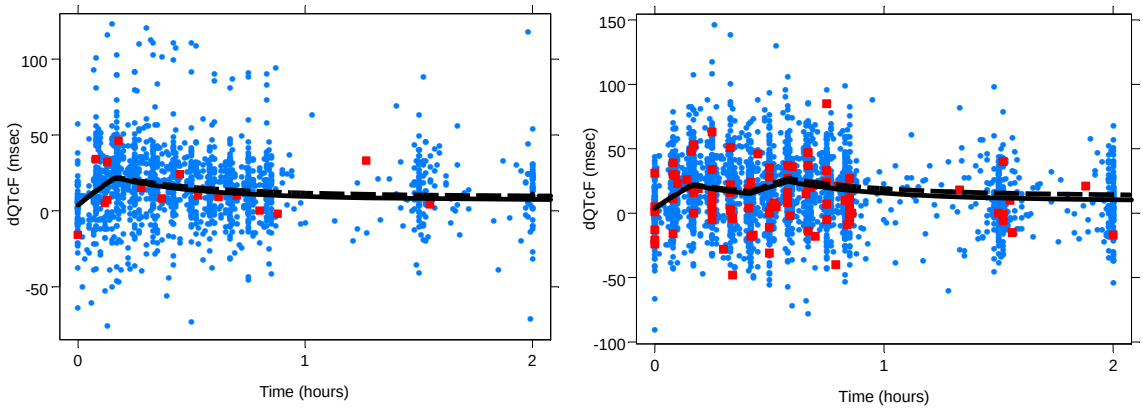


Figure 33. Population predicted RSD1235 ΔQTcF-time profiles for poor (PM, dashed) and extensive (EM, solid) metabolizers on after single 3 mg/kg IV infusion over 10 minutes (top) followed by 2 mg/kg IV infusion over 10 minutes (bottom). Observed ΔQTcF are shown as blue dots for EMs and red squares for PMs.

It takes approx. 1 and 2 hours for the typical patients' ΔQTcF to return below 10 msec, corresponding to RSD1235 concentrations below 1300 ng/mL, after 3 and 3+2 mg/kg vernakalant dosing while CYP2D6 PMs patients return below 10 msec after approx. 2 and 8 hours after 3 and 3+2 mg/kg doing (see Figure 34).

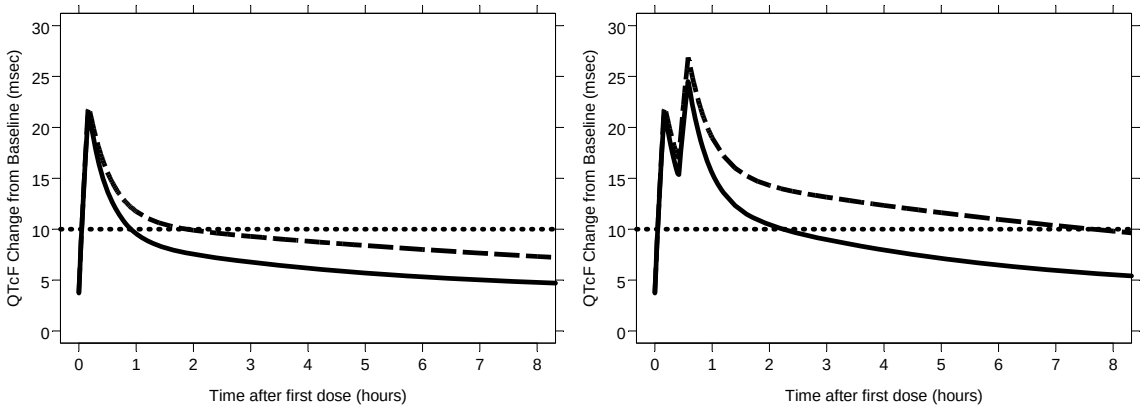


Figure 34. Population predicted RSD1235 concentration-time profiles for poor (PM, dashed) and extensive (EM, solid) metabolizers on after single 3 mg/kg IV infusion over 10 minutes (left) followed by 2 mg/kg IV infusion over 10 minutes (right). The dotted line indicates ΔQTcF of 10 msec.

7.3 SYSTOLIC BLOOD PRESSURE ANALYSIS

No direct relationship between RSD1235 concentration and change from baseline in systolic blood pressure was identified in study 010 and 703 (see Figure 36).

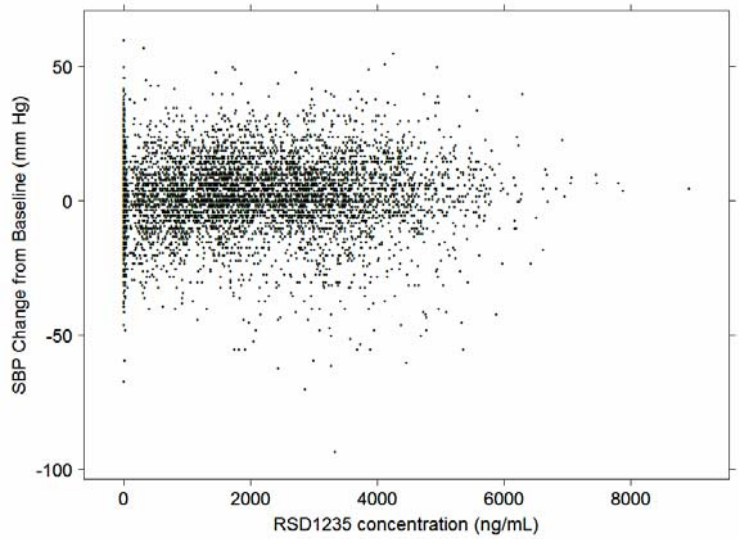


Figure 35. Observed change from baseline in systolic blood pressure vs. RSD1235 concentration

The change in systolic blood pressure (SBP) does however appear to be correlated with the exposure to RSD1235 illustrated by the mean (±SE) time course in ΔSBP for placebo, 3 mg/kg and 3 mg/kg extensive and poor metabolizers (see Figure 36).

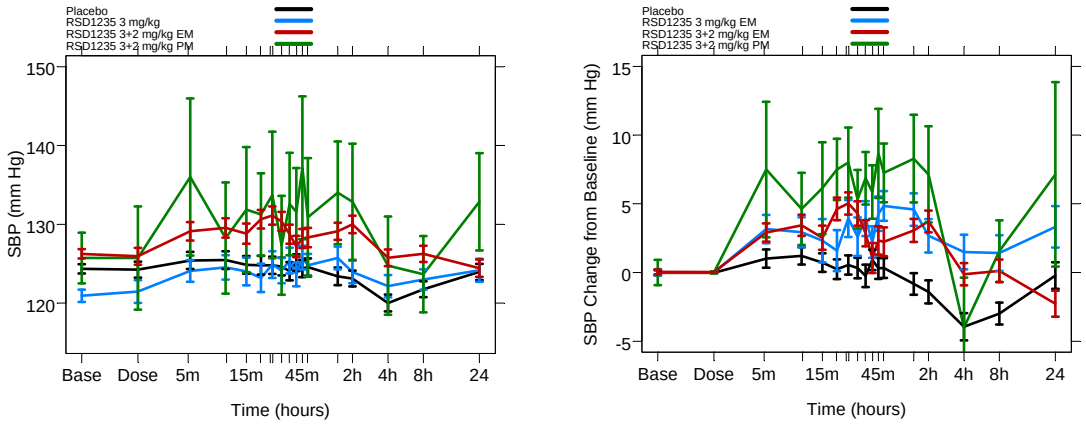


Figure 36. Mean (±SE) systolic blood pressure **(left)** and change from baseline in systolic blood pressure **(right)** for placebo **(black)**, 3 mg/kg **(blue)**, 3+2 mg/kg extensive metabolizers **(red)**, and poor metabolizers **(green, N=8)**. *Patients were allowed to receive other medications two hours postdose

7.4 EXPOSURE-RESPONSE ANALYSIS

The exposure-response analysis was performed using the individual predicted C_{max} concentration as the exposure parameter and the response was conversion to normal sinus rhythm at 90 min after start of the vernakalant infusion.

The probability of having conversion to normal sinus rhythm was modeled using a logistic regression model of the general form

$$logit(\Pr(Conv \le 90\,\min)) = \alpha_{Intercept} + \beta_0 \cdot Cov + \beta_1 \cdot Exposure$$

where Exposure is C_{max} centered around the median value and Cov is any potential covariate.

The exposure-response analysis parameter estimates are shown in Table 12.

Within the predicted exposure range under 3+2 mg/kg dosing regimen, there was no evidence of exposure-response using C_{max} as a measure for exposure (see Figure 37). Vernakalant appears to work better for patients with the duration of their most recent episode less than 7 days from vernakalant dosing.

Table 12 Reviewer's Exposure-Response (Conversion to normal sinus rhythm at 90 min) Logistic Response Parameter Estimates.

Parameter	Covariate	Estimate	RSE (%)	P-value	Odds Ratio (95% CI)
$\alpha_{Intercept}$	Placebo, Duration> 7 days, Atrial flutter	-7.96	14.8	<0.0001	-
β_{TRT}	Active	3.07	13.1	<0.0001	21.6 (9.8-47.7)
$\beta_{Duration}$	Duration ≤7 days	2.53	15.3	<0.0001	12.5 (5.9-26.7)
$\beta_{Diagnosis}$	Atrial fibrillation	2.29	45.9	0.02296	9.8 (1.3-77)

The odds of converting to normal sinus for patients treated with vernakalant are 22-fold (95% CI 9.8-47.7) of that for placebo-treated patients. The odds of converting to normal sinus rhythm increases by a factor 13 (95% CI 5.9-26.7) for patients with their most recent episode of Afib/Aflut less than 7 days before vernakalant dosing compared to > 7 days. Atrial fibrillation patients were also found to be more likely to respond to treatment compared to atrial flutter patients with an odds ratio of 9.8 (95% CI 1.3-77).

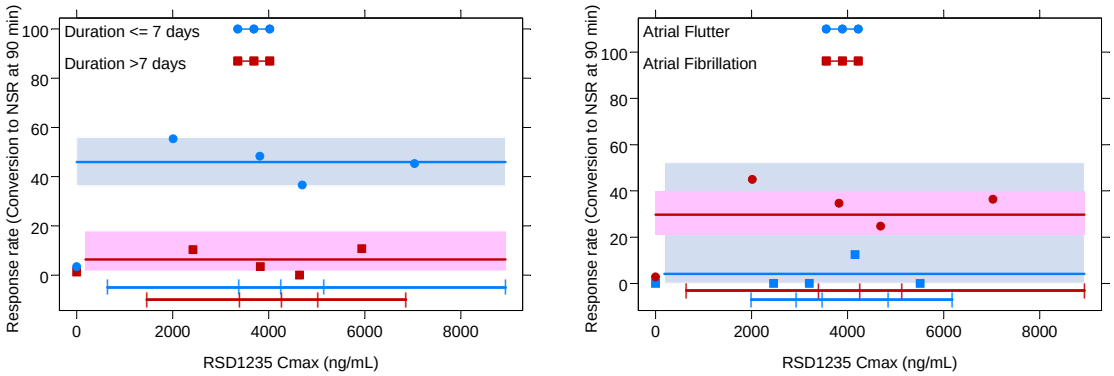


Figure 37. Exposure-response relationship for (**left**) duration of most recent Afib/Aflut episode less than 7 days **(blue)** and greater than 7 days **(red)** and **(right)** atrial flutter **(blue)** and atrial fibrillation **(red)** . The dots represent the mid-quartile RSD1235 peak concentrations and the associated observed response rate with the dots at 0 equal to the placebo response rate. The horizontal bars represent the inter-quartile C_{max} ranges for the different subpopulations.

For patients with recent onset of atrial fibrillation (<=7 days), the response rate after 3 mg/kg was 37.5% and 1% for placebo. Patients not responding to the first dose received an additional 2 mg/kg where the response rate was 19% and 2.6% for placebo (see Figure 38).

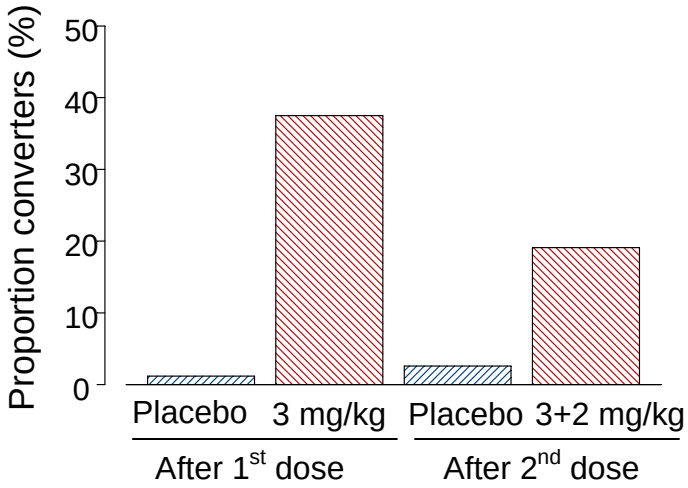
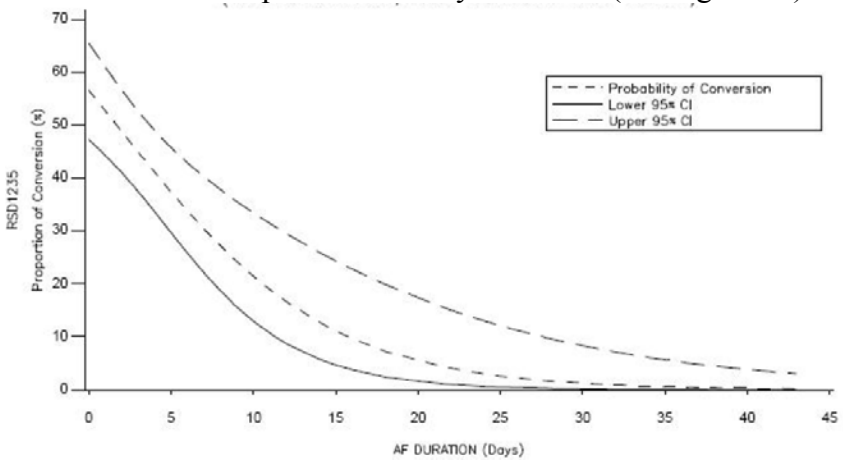


Figure 38. Proportion responders after 1st dose of 3 mg/kg and 2nd dose of 2 mg/kg within the 3 mg/kg non-responders.

The sponsor performed a logistic regression of conversion to normal sinus rhythm vs. duration of atrial fibrillation for patients in study 1235-703 (see Figure 39).



Source: Sponsor's Figure 7 in summary of clinical efficacy

Figure 39. Logistic regression analysis of conversion to normal sinus rhythm vs. duration of atrial fibrillation.

Duration of the most recent atrial fibrillation episode (<7 or >7 days) was found to be the most important demographic covariate for response. A total of 328 (Active:Placebo N=215:113) out of 632 atrial fibrillation patients had information about how many days since the start of their most recent atrial fibrillation episode.

As seen in Figure 4, RSD1235 treated patients with <2 days since the start dosing had a response rate of 60-80% (placebo response 4-13%) whereas the response rate in patients with >2 days duration was 10-30% (placebo response 0%).

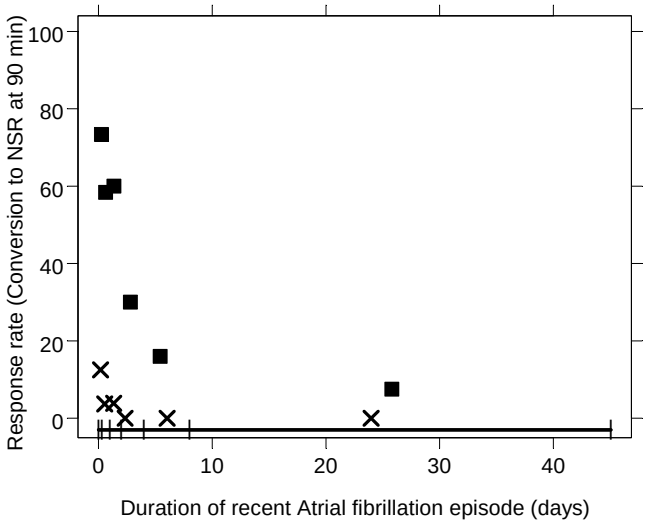


Figure 40. Response rate vs. median duration of recent atrial fibrillation episode in 0-8 hr (Active:Placebo N=15:8), 8-24 hr (Active:Placebo N=48:27), 1-2 days (Active:Placebo N=40:26), 2-4 days (Active:Placebo N=20:8), 4-8 days (Active:Placebo N=25:8), and 8-45 days (Active:Placebo N=67:36) bins. Solid square (RSD1235 treated) and cross (Placebo).

8 PHARMACOMETRIC REVIEW CONCLUSIONS

The overall conclusions for the Pharmacometric review are:

Population Pharmacokinetic Analysis Conclusions

- A two-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed RSD1235 concentrations following 3 and 3+2 mg/kg 10 minute IV infusions separated by 15 minutes in 354 atrial fibrillation/flutter patients from the two pivotal studies 04-7-010 and 1235-0703.
- The estimated terminal population half-life ($t_{1/2,\beta}$) was 3.2 with a steady-state volume of distribution (V_{ss}) estimate of 1.77 L/kg (147 L for 83 kg patient) indicating a high degree of tissue distribution.
- The population mean predicted C_{max} after the first 3 mg/kg IV infusion was 3660 and 4330 after the 2 mg/kg IV infusion.
- A total of 9 patients in study 1235-703 were classified as poor CYP2D6 metabolizers (PMs). The RSD1235 clearance was found to be 64% lower for PMs compared to extensive metabolizers increasing the terminal half-life from 3.2 hrs to 8 hrs for CYP2D6 PMs.
- Body weight was identified as a significant covariate for RSD1235 volume of distribution as well as clearance.
- Age, creatinine clearance, gender, and race were not found to influence RSD1235 pharmacokinetics.

QT Analysis Conclusions

- The population PK/PD relationship between QTcF and RSD1235 concentrations was adequately described by a linear model.
- The mean predicted change from baseline QTcF was 21 msec (90% CI 20-23) at the mean RSD1235 C_{max} of 3660 ng/mL following 3 mg/kg IV infusion over 10 minutes.
- For patients receiving 3+2 mg/kg 10 minute infusions 15 minutes apart, the mean predicted ΔQTcF was 24 msec (90% CI 23-26) at the mean predicted Cmax of 4330 ng/mL.
- The mean ΔQTcF is predicted to return below 10 msec within 1 hours for CYP2D6 EMs and 2 hours for PMs after single 3 mg/kg and 2 and 8 hours after 3+2 mg/kg.

Exposure-Response Analysis Conclusions

- Within the predicted exposure range under 3+2 mg/kg dosing regimen, there was no exposure-response relationship using Cmax as a measure of exposure.
- For patients with recent onset of atrial fibrillation (<=7 days defined by sponsor), the response rate after 3 mg/kg was 37.5% and 1% for placebo. Patients not responding to the first dose received an additional 2 mg/kg where the response rate was 19% and 2.6% for placebo.
- Patients with their most recent onset of atrial fibrillation episode less than 2 days from vernakalant dosing had significant higher response rates around 60-80% compared to patients with duration of the most recent episode >2 days with 10-30% response rate.

9 APPENDICES

9.1 GOODNESS-OF-FIT GRAPHS FOR REVIEWER'S BASE PK MODEL

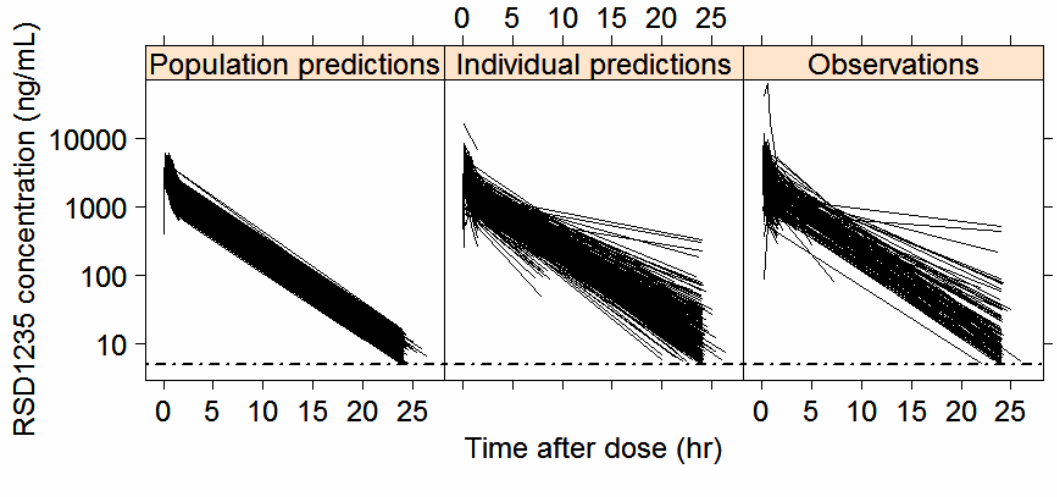


Figure 41 RSD1235 concentration-time profiles for population predicted (left), individual predicted (middle), and observed (right) concentrations for reviewer's base PK model.

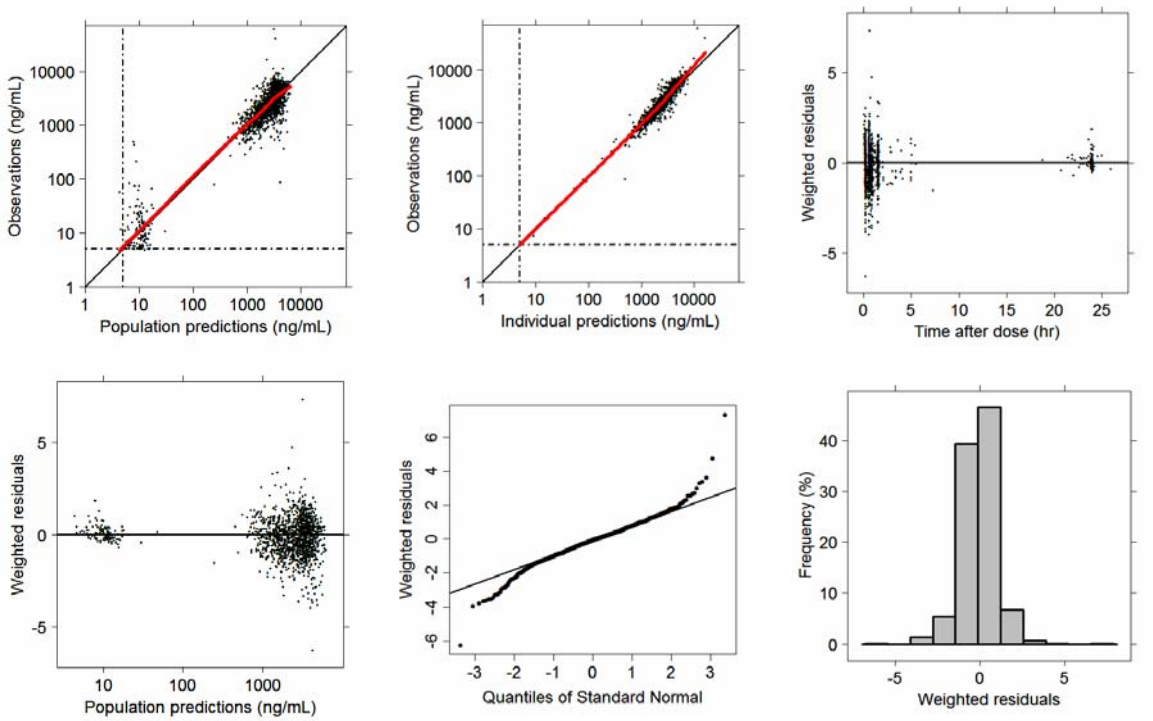


Figure 42 Goodness-of-fit graphs for reviewer's base PK model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the solid red line is a smoothing regression line.

9.2 COVARIATE-PK PARAMETER RELATIONSHIPS FOR BASE PK MODEL

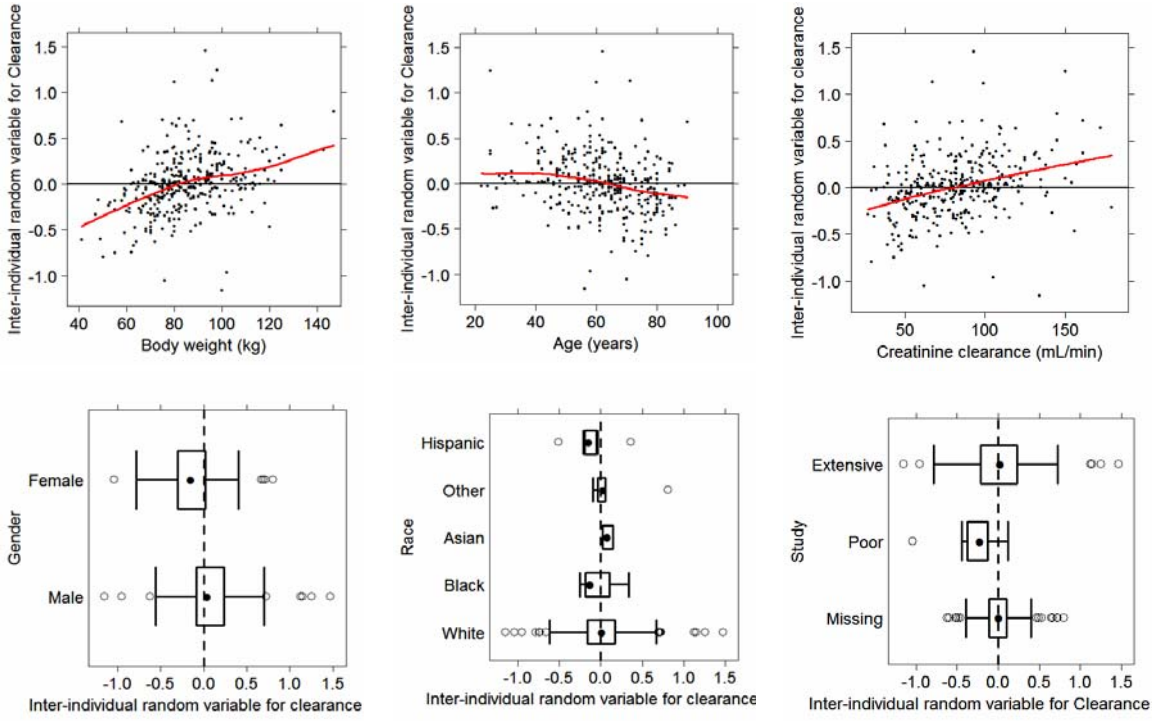


Figure 43 Graphical analyses of inter-individual random variability in clearance-covariate relationships from base PK model.

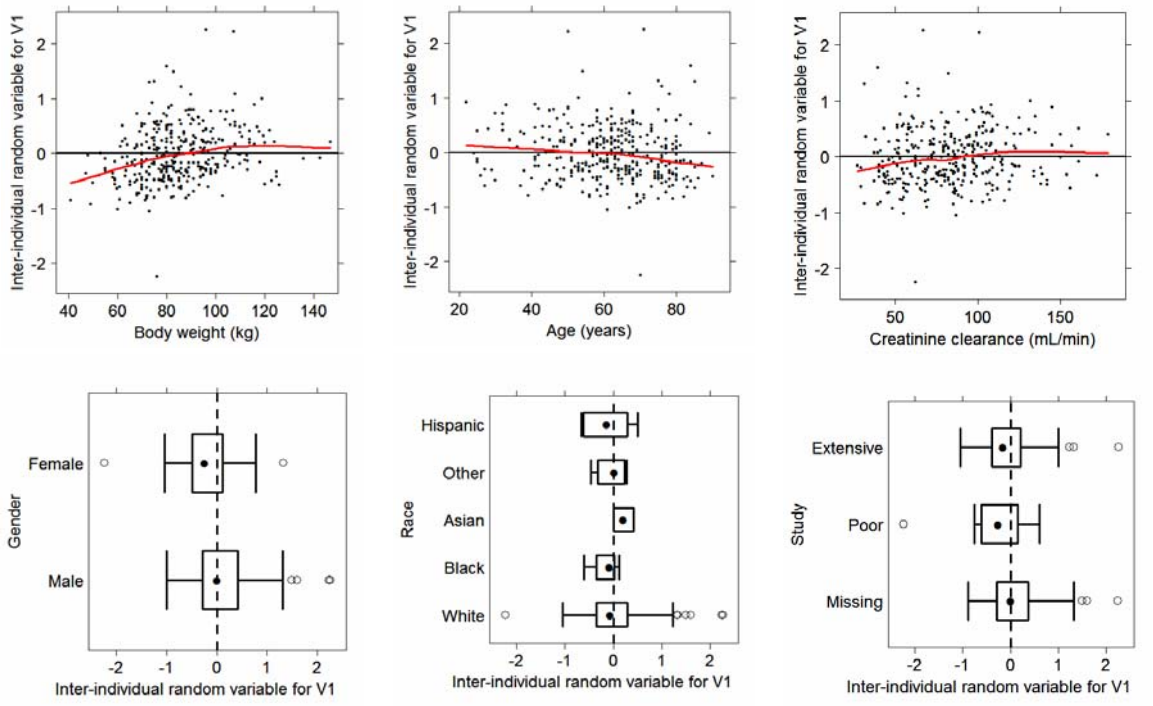


Figure 44 Graphical analyses of inter-individual random variability in central volume of distribution-covariate relationships from base PK model.

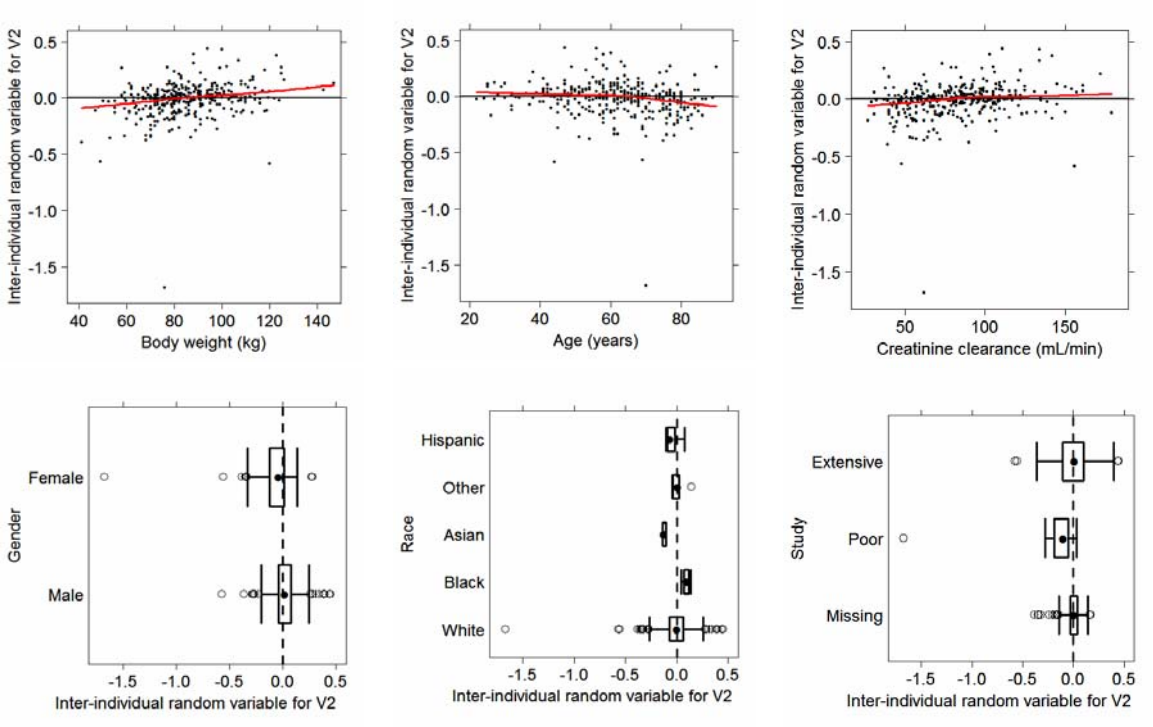


Figure 45 Graphical analyses of inter-individual random variability in peripheral volume of distribution-covariate relationships from base PK model.

9.3 GOODNESS-OF-FIT GRAPHS FOR REVIEWER'S FINAL PK MODEL

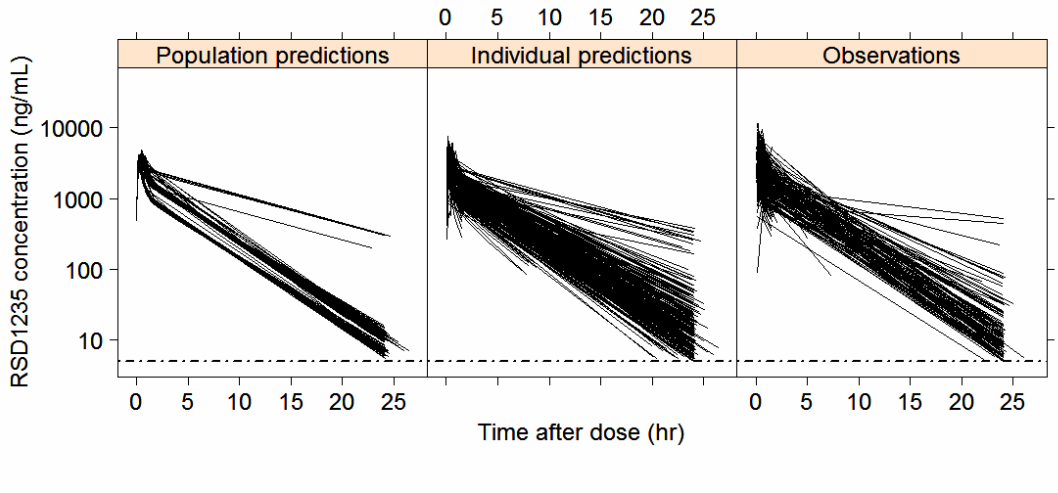


Figure 46 RSD1235 concentration-time profiles for population predicted (left), individual predicted (middle), and observed (right) concentrations for reviewer's final PK model.

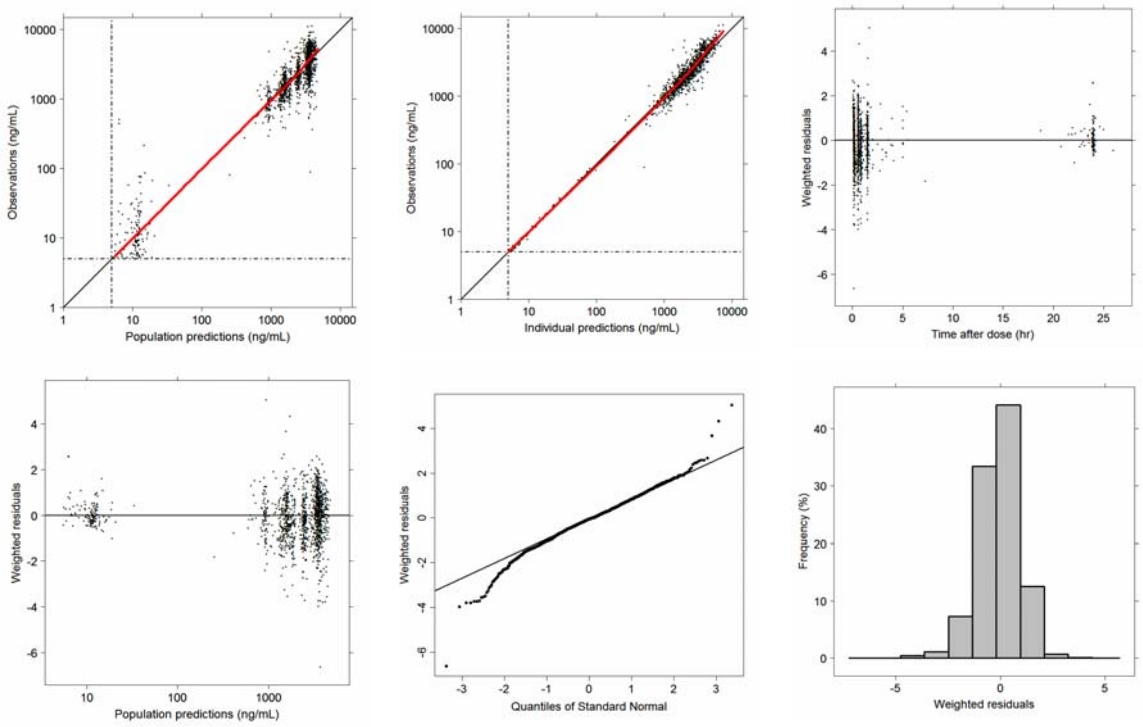


Figure 47 Goodness-of-fit graphs for reviewer's final PK model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the solid red line is a smoothing regression line.

9.4 COVARIATE-PK PARAMETER RELATIONSHIPS FOR FINAL PK MODEL

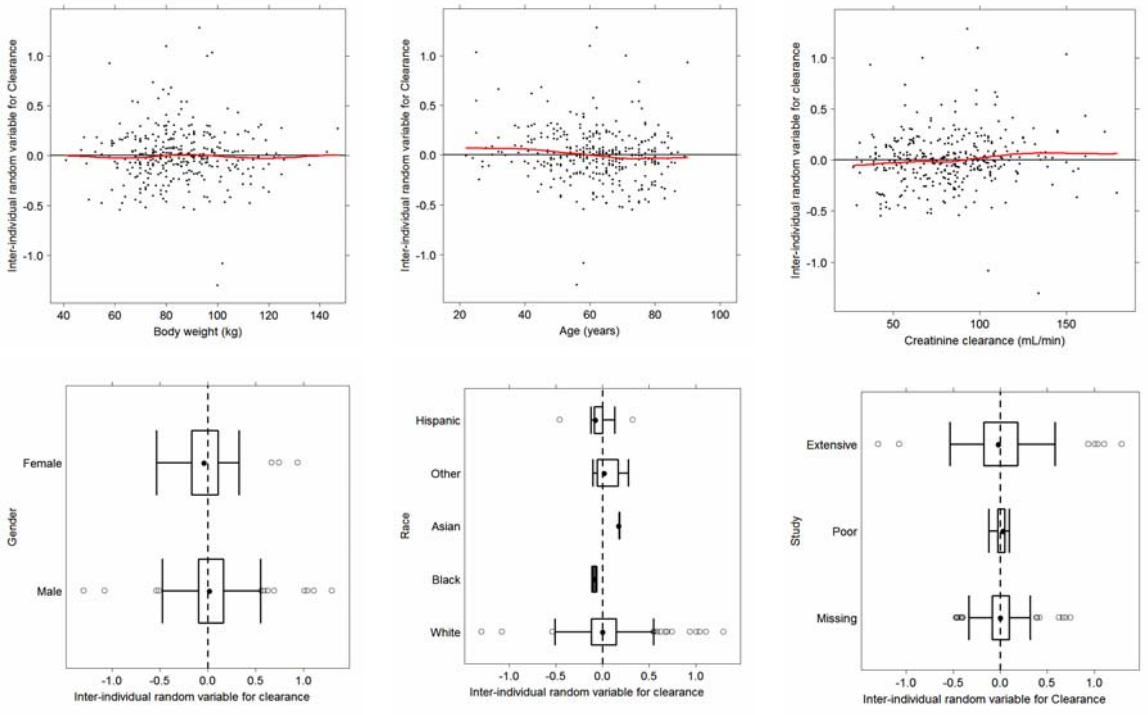


Figure 48 Graphical analyses of inter-individual random variability in clearance-covariate relationships from final PK model.

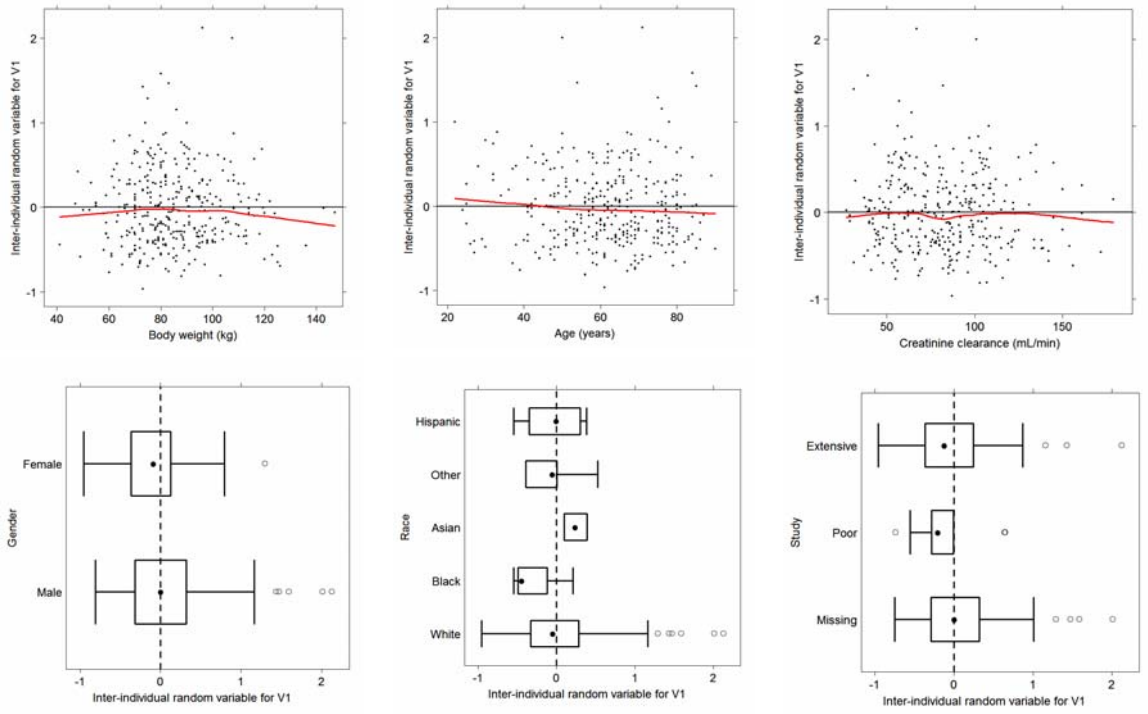


Figure 49 Graphical analyses of inter-individual random variability in central volume of

distribution-covariate relationships from final PK model.

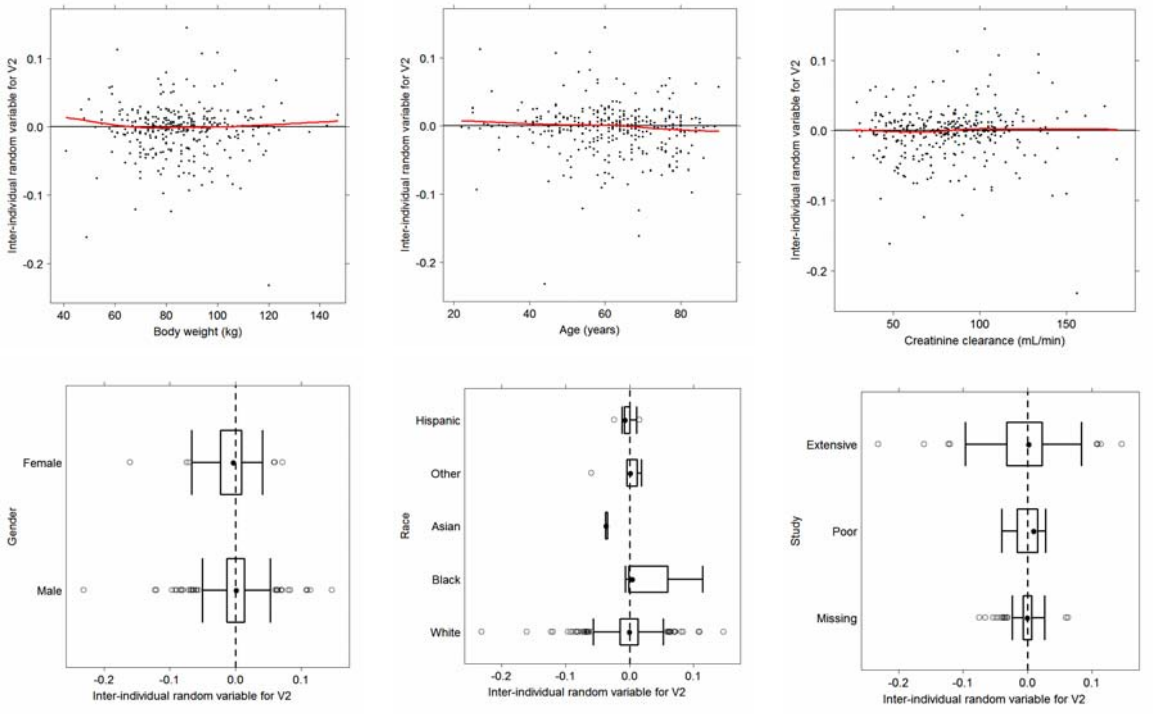


Figure 50 Graphical analyses of inter-individual random variability in peripheral volume of distribution-covariate relationships from final PK model.

9.5 GOODNESS-OF-FIT GRAPHS FOR REVIEWER'S FINAL QT MODEL

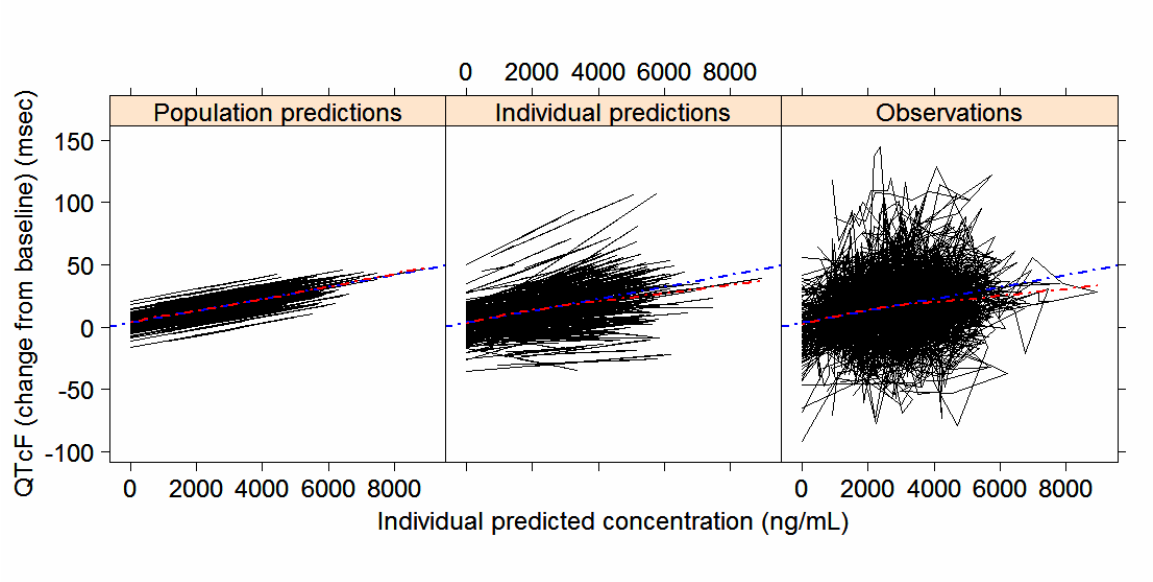


Figure 51 QTcF concentration profiles for population predicted (left), individual predicted (middle), and observed QTcF (right) for reviewer's final QT model. The dotted blue line is the population mean prediction and the dotted red line is a smoothing regression line.

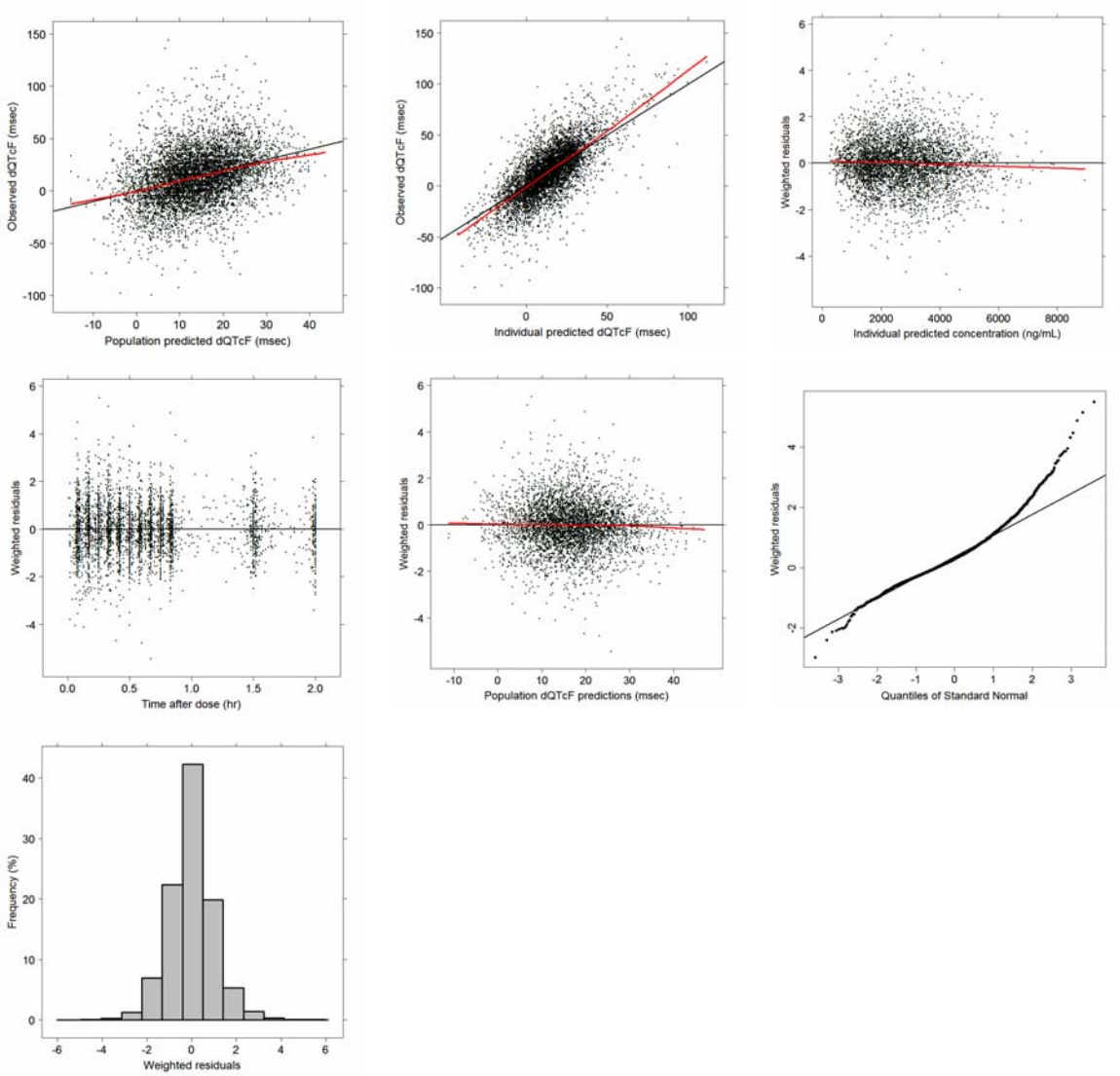


Figure 52 Goodness-of-fit graphs for reviewer's final QT model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. individual predicted RSD1235 concentration (top right), time after dose (middle left), and population ΔQTcF predictions (middle center), quantiles of standard normal (middle right), and a histogram of weighted residuals (bottom left). The solid black line is the line of unity/identity and the solid red line is a smoothing regression line.

9.6 COVARIATE-QT PARAMETER RELATIONSHIPS FOR FINAL QT MODEL

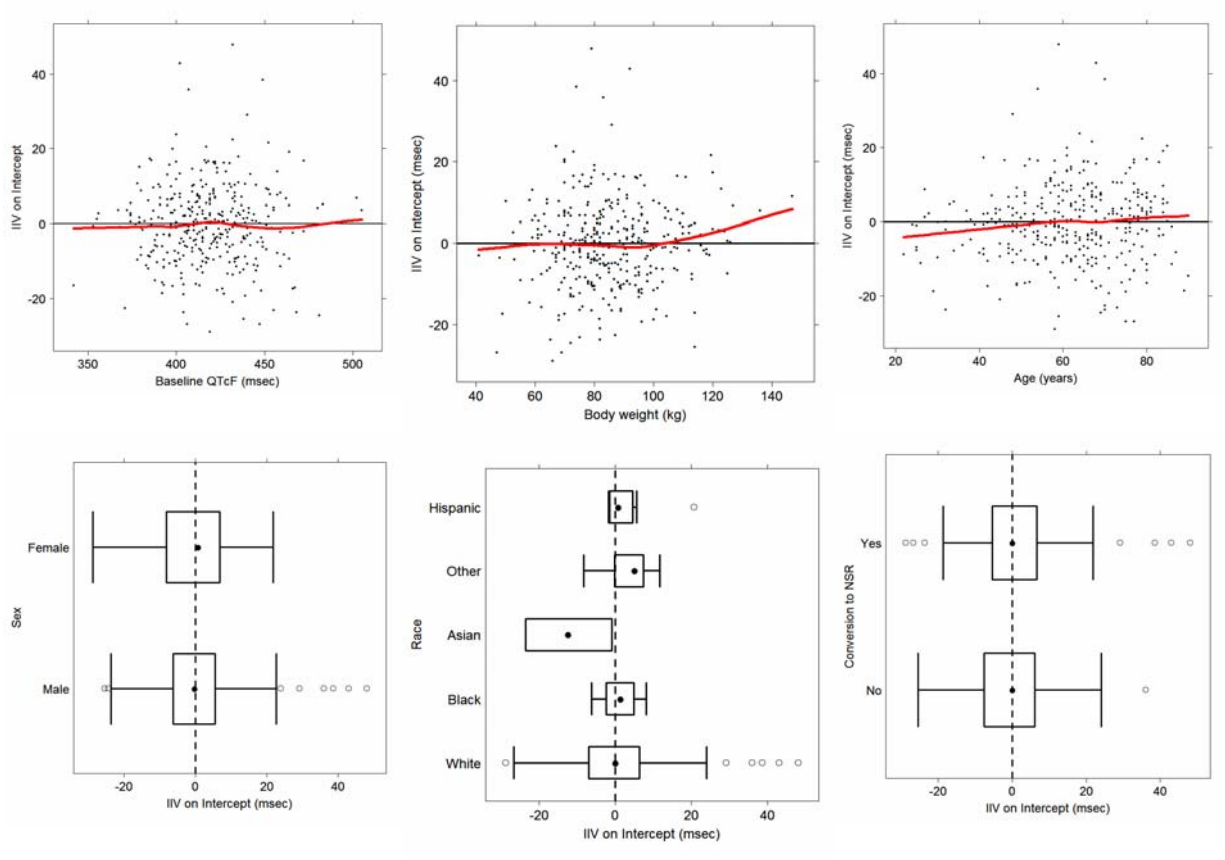


Figure 53 Graphical analyses of concentration-QTcF intercept-covariate relationships from final QT model.

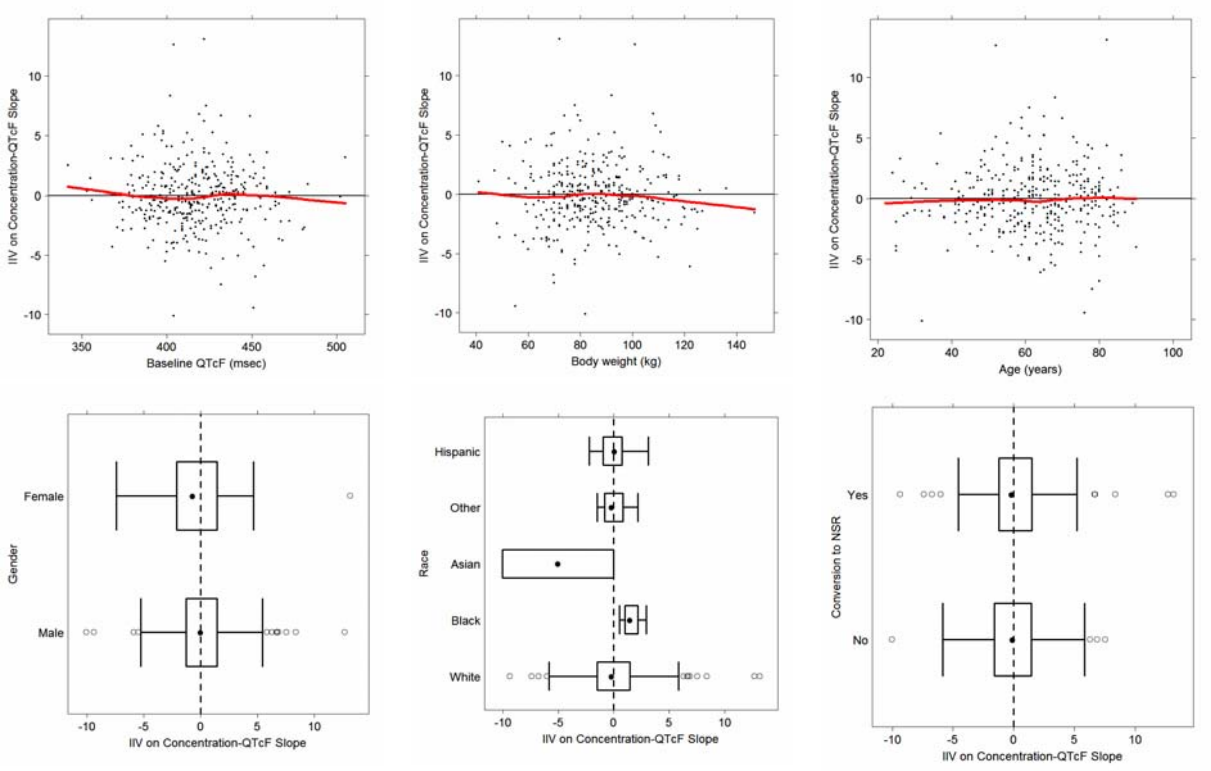


Figure 54 Graphical analyses of concentration-QTcF slope-covariate relationships from final QT model.

4.4 Appendix: Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	22-034	Brand Name	Kadenza
OCPB Division (I, II, III)	DIV-1	Generic Name	vernakalant
Medical Division	Cardio-Renal	Drug Class	Anti-arrhythmic agent for the rapid conversion of atrial fibrillation through potassium and sodium channel blockade (e.g., IKur, Ito and INa).
OCPB Reviewer	ELENA MISHINA	Indication(s)	ADHD
OCPB Team Leader	P. Marroum	Dosage Form	200 mg/10 mL single use vial
INDs		Dosing Regimen	3 mg/kg infused over 10 minutes
Date of Submission	1/13, 2006	Route of Administration	IV injection
Estimated Due Date of OCPB Review	9/30/ 2007	Sponsor	Astellas Inc
PDUFA Due Date	10/31/ 2007	Priority Classification	S

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	1		
Blood/plasma ratio:				
Plasma protein binding:	x	1		
Pharmacokinetics (e.g., Phase I) -	x	1		
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:	X	1		
multiple dose:	X	1		
Dose proportionality -				
fasting /non-fasting single dose:	X	1		
fasting /non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		
In-vivo effects of primary drug:				
In-vitro:	X	5		
Subpopulation studies -				
ethnicity:		1		
gender:		1		
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	3		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	3		
Population Analyses -				

Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				Reference IR tablets
Bioequivalence studies -				
traditional design; single /multi dose:				
replicate design; single /multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	X			
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Electrophysiololgy Study				
Pharmacodynamic studies	X			
Total Number of Studies	14+references			
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?		none		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 22-034, HFD-850(Lee), HFD-860 (Marroum, Mehta, Mishina), Biopharm (CDER)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elena Mishina
11/9/2007 01:37:55 PM
BIOPHARMACEUTICS

Christoffer Tornoe
11/9/2007 01:41:38 PM
BIOPHARMACEUTICS

Yaning Wang
11/9/2007 01:44:19 PM
BIOPHARMACEUTICS

Patrick Marroum
11/9/2007 03:03:24 PM
BIOPHARMACEUTICS

STATISTICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #:	22034
DRUG NAME:	RSD1235
INDICATION:	Rapid conversion of AF to NSR
APPLICANT:	Astellas Pharma US Inc.
DATE OF RECEIPT:	01/04/2007
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics I
STATISTICAL REVIEWER:	Steve Bai, Ph.D. (HFD-710)
CONCURRENT REVIEWER:	H.M. James Hung, Ph.D. (HFD-710)
MEDICAL DIVISION:	Division of Cardio-Renal Drug Product (HFD-110)
CLINICAL TEAM:	Salma Lemtouni, M.D. (HFD-110)
PROJECT MANAGER:	Russell Fortney (HFD-110)

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The current submission is to determine the effectiveness of RSD1235 Injection in the conversion of atrial fibrillation or atrial flutter to sinus rhythm. Treatment was considered successful if there was a treatment-induced conversion of atrial fibrillation to sinus rhythm for a minimum of one minute duration within 90 minutes following the start of the first infusion. The data from this submission provided the significance evidence for the RSD1235 Injection effectively and rapidly converted atrial fibrillation to sinus rhythm in subjects with atrial fibrillation of >3 hours and ≤ 7 days.

1.2 Brief Overview of Clinical Studies

Two adequate, well-controlled, phase 3 studies provide independent substantiation of the efficacy of RSD1235 Injection for the rapid conversion of atrial fibrillation to normal sinus rhythm:

- **ACT I (Study 1235-0703) -** A phase 3, prospective, randomized double-blind, placebo-controlled, multicenter, tolerance and efficacy study of RSD1235 Injection in patients with atrial fibrillation.
- **ACT III (Study 1235-0504/04-7-010) -** A phase 3 prospective, randomized, double-blind, placebo-controlled, multicenter, tolerance and efficacy study of RSD1235 Injection in patients with atrial fibrillation or atrial flutter.

The development program was multinational; ACT I and ACT III were conducted at 93 sites in Argentina, Canada, Chile, Denmark, Mexico, Sweden, and the United States. Subjects enrolled in the RSD1235 Injection phase 3 studies were at least 18 years of age, hemodynamically stable with arrhythmia duration greater than 3 hours but not more than 45 days. Subjects were stratified for enrollment according to the duration of AF: 240 with AF duration > 3 hours and ≤ 7 days (short duration AF cohort) and a planned 120 with AF duration > 7 days and ≤ 45 days (long duration AF cohort). Subjects within the two strata were then randomized 2:1 (RSD1235: placebo) to receive up to two 10-minute infusions.

The primary efficacy endpoint for both ACT I and ACT III was the proportion of subjects with short duration atrial fibrillation who converted to sinus rhythm for a minimum duration of one minute within 90 minutes of first exposure to RSD1235 Injection.

1.3 Statistical Issues and Findings

The primary analysis of efficacy was based on the Full Analysis Set (FAS) which was defined *a priori* in the individual studies as all randomized subjects with atrial fibrillation who received any amount of study drug (active drug or placebo). Baseline and demographic characteristics were compared between treatment groups using a one-way analysis of variance (ANOVA) with a fixed effect for treatment for continuous variables and a chi-square test for categorical variables.

The primary efficacy analysis utilized the Cochran-Mantel-Haenszel test stratified by country. The frequency and percentage of successes and failures for each treatment group, the difference in the percentage of successes between treatment groups, the asymptotic 95% confidence interval (CI) of the difference in success between treatment groups, and the P-value for the difference between treatment groups were calculated. In addition, the Mantel-Haenszel Odds Ratio (OR) of the RSD1235 Injection group versus the placebo group along with 95% CI was also estimated.

In the short-duration atrial fibrillation cohort, both studies showed statistically significantly greater percentage of subjects in the RSD1235 Injection group converted to sinus rhythm for a minimum duration of one minute within 90 minutes as compared with the placebo group.

Table 1 Conversion of Atrial Fibrillation to Sinus Rhythm

Study	Placebo	RSD1235	% Difference of Success (95% CI)	P-value	Odds Ratio (95% CI)
ACT I	3/75 (4.0%)	75/145 (51.7%)	47.7 (38.5, 57.0)	<0.0001	24.0 (6.9, 83.6)
ACT III	3/84 (3.6%)	44/86 (51.2%)	47.6 (36.3, 58.9)	<0.0001	38.3 (9.2, 159.5)

[Source: Sponsor's Study Reports]

2 INTRODUCTION

2.1 Overview

The primary study objective of ACT I and ACT III were to demonstrate the effectiveness of 3.0 mg/kg followed by 2.0 mg/kg if required, of RSD1235 Injection in the conversion of atrial fibrillation to sinus rhythm. Treatment was considered successful if there was a treatment-induced conversion of atrial fibrillation to sinus rhythm for a minimum of one minute duration within 90 minutes following the start of the first infusion.

ACT I was a phase 3, multinational, multicenter, prospective, randomized, double-blind, placebo-controlled study in subjects with baseline atrial fibrillation greater than 3 hours in duration but not exceeding 45 days. A total of 360 subjects at least 18 years of age were to be stratified for enrollment according to their duration of atrial fibrillation in a 2:1 ratio: 240 with short-duration atrial fibrillation cohort and 120 with long-duration atrial fibrillation cohort. Subjects within each stratum were centrally randomized 2:1 (RSD1235: placebo) to receive a 10-minute infusion of placebo or RSD1235 Injection 3.0 mg/kg followed by a 15-minute observation period and a second 10-minute infusion of placebo or RSD1235 Injection 2.0 mg/kg if the subject was in atrial fibrillation or atrial flutter at the end of the observation period.

ACT III had the exact same study design as ACT I. A total of 280 subjects at least 18 years of age were to be stratified for enrollment according to their duration of atrial fibrillation or atrial flutter: 200 subjects with short-duration cohort and 80 subjects with long duration cohort. Subjects within each stratum were centrally randomized 1:1 (RSD1235: placebo) to receive a 10-minute infusion of placebo or RSD1235 Injection 3.0 mg/kg followed by a 15-minute observation period and a second 10-minute infusion of placebo or RSD1235 Injection 2.0 mg/kg if the subject was in atrial fibrillation or atrial flutter at the end of the observation period.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\Cdsesub1\EVSPROD\NDA022034\0000\m5\datasets of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The study description in this section is based on the sponsor's study report, any discrepancy between the study report and the study protocol will be discussed in the section of statistical reviewer's findings and comments.

3.1.1 PROTOCOL 1235-0703 (ACT I)

3.1.1.1 Study Objective of ACT I

The primary study objective was to demonstrate the effectiveness of 3.0 mg/kg, and 2.0 mg/kg if required, of RSD1235 in the conversion of AF to sinus rhythm. Treatment was to be considered successful if there was a treatment-induced conversion of AF to sinus rhythm for a minimum of one-minute duration within 90 minutes (time 0 = start of first infusion).

3.1.1.2 Study Design

This was a multinational, multicenter, prospective, randomized, double-blind, placebo-controlled study with a plan to enroll 360 subjects 18 years of age or older with a diagnosis of AF ranging in duration from more than 3 hours to less than or equal to 45 days. Subjects were stratified for enrollment according to the duration of AF: 240 subjects with AF duration > three hours and ≤ seven days (short-duration AF cohort) and a planned 120 subjects with AF duration > seven days and ≤ 45 days (long-duration AF cohort). Subjects within the two strata were then randomized 2:1 (RSD1235: placebo) to receive up to two 10-minute infusions as follows:

- RSD1235: a 10-minute infusion at a dose of 3 mg/kg followed by a 15-minute observation and a second 10-minute infusion at a dose of 2 mg/kg if the subject was in atrial fibrillation or atrial flutter at the 25-minute time point.
- Placebo: a 10-minute, vehicle/saline infusion of a volume equivalent to a RSD1235 dose followed by a 15-minute observation and a second 10-minute, vehicle/saline infusion of a volume equivalent to a RSD1235 dose if the subject was in atrial fibrillation or atrial flutter at the 25-minute time point.

3.1.1.3 Efficacy Measures

The primary efficacy endpoint was the proportion of subjects with short-duration AF who had a treatment-induced conversion of AF to sinus rhythm within 90 minutes of first exposure to study medication and for a minimum duration of one minute.

The secondary efficacy endpoints were:

- Time to conversion of AF to sinus rhythm in subjects with short-duration AF.

- Time to termination of AF in the overall population.
- The proportion of subjects in the overall population who had a treatment-induced termination of AF within 90 minutes after first exposure to study medication.
- Time to termination of AF in subjects with long-duration AF.
- The proportion of subjects with long-duration AF who had a treatment-induced termination of AF within 90 minutes after first exposure to study medication.

3.1.1.4 Statistical Analysis Plan

The primary endpoint was tested utilizing a 5% alpha level. If the primary endpoint demonstrated a statistically significant positive finding, then each of the secondary endpoints was to be tested at a 5% alpha level according to the fixed sequence listed in Section 3.1.1.3.

The Cochran Mantel-Haenszel (CMH) test stratified by center was used to compare the proportion of subjects with short-duration AF who had treatment-induced conversion of AF to sinus rhythm for a minimum duration of one minute within 90 minutes of first exposure to study medication.

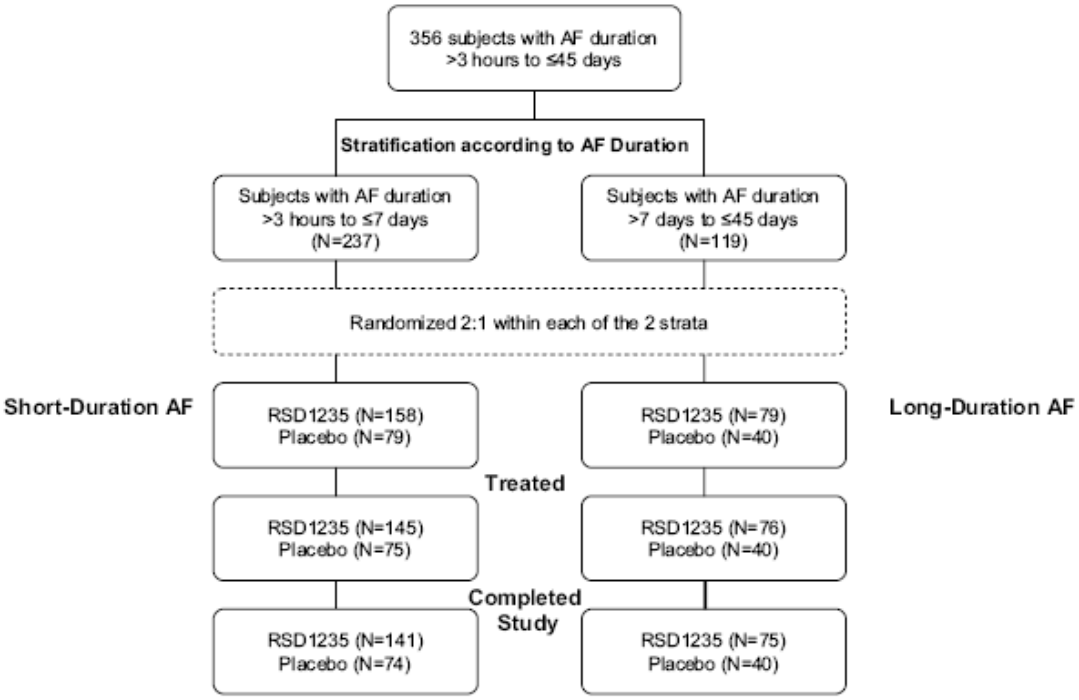
In the secondary efficacy analysis, all the time to event endpoint were analyzed by Product-Limit method and the two treatment groups were compared using the Log Rank Test. The proportional endpoints were analyzed by the analogous analysis method to those used for the primary efficacy endpoint.

3.1.1.5 Patient Disposition, Demographic and Baseline Characteristics

This study was conducted at 44 sites: Denmark (19), Sweden (6), Canada (13) and the United States (6). Total study enrollment achieved 356 of the protocol planned 360 subjects in the overall population (98.9%): 237/240 (98.7%) planned subjects with short-duration AF and 119/120 (99.2%) planned subjects with long-duration AF. See the Figure 3.1 for detailed disposition of the subjects.

In the overall subject population, the two treatment groups were similar in terms of demographics (age, gender, racial distribution) and other baseline characteristics (height, body weight, body mass index [BMI] and tobacco use). A similar distribution of demographic and baseline characteristics was seen in the cohort of subjects with short duration AF and in the cohort of the subjects with long-duration AF.

Figure 3.1 Disposition of Subjects



[Source: See Sponsor's Study report Figure 1]

3.1.1.6 Primary Efficacy Results

The primary efficacy endpoint was the proportion of subjects with short-duration AF who had a treatment-induced conversion of AF to sinus rhythm within 90 minutes after first exposure to study drug that lasted for a minimum duration of one minute. In subjects with short-duration AF, a greater proportion of RSD1235 recipients (75/145, 51.7%) compared with placebo recipients (3/75, 4.0%) converted to sinus rhythm within 90 minutes. This 47.7% difference in treatment-induced AF conversion to sinus rhythm was statistically significant (P<0.0001), see Table 2 for details.

Table 2 Conversion of AF to NSR within 90 Minutes (Short Duration AF)

Site/Country	Treatment Group		% difference of success	P-value	Odds Ratio (95% CI)
	Placebo (N=75)	RSD1235 (N=145)			
All Sites	3 (4.0%)	75 (51.7%)	47.7	<0.0001	24.0 (6.89, 83.65)

[Source: Reviewer's results and it verified the sponsor's results]

3.1.1.7 Secondary Efficacy Results

There five secondary efficacy endpoints in the current study. Since the Section 3.1.1.6 resulted in a statistically significantly positive finding, then each of the secondary endpoints was tested at a

5% alpha level according to the specified sequence. The findings for each of the secondary analysis are listed below:

1. In subjects with short-duration AF, RSD1235 recipients experienced a shorter time from first study drug exposure to first conversion of AF to sinus rhythm (minimum duration of 1 minute) within 24 hours of first exposure to study drug compared with placebo recipients ($P < 0.0001$).
2. In the overall population, A statistically significantly shorter time to first treatment-induced termination of AF was observed in the RSD-1235 treated subjects compared with placebo-treated subjects ($P<0.0001$).
3. In the overall population in the full analysis set, a statistically significant ($P<0.0001$) greater proportion of RSD1235 recipients (80/221, 36.2%) compared with placebo recipients (3/115, 2.6%) had treatment-induced termination of AF within 90 minutes after receiving study drug.
4. No statistically significant differences in the time to termination of AF were observed between treatment groups in the FAS or PPS for subjects with long-duration AF. According to the statistical analysis plan, no further secondary endpoints will be tested from this point on.

3.1.1.8 Efficacy Conclusions

The reviewer validated the applicant's results according to the protocol, except for the proportion of RSD1235 subjects who had conversion in the overall population. However, the difference is very minimal, 37.6% vs. 36.2%, which made no impact to the significance result. In conclusion, this study demonstrated that RSD1235 rapidly converted AF to sinus rhythm in subjects with short-duration AF.

3.1.2 PROTOCOL 04-7-010 (ACT III)

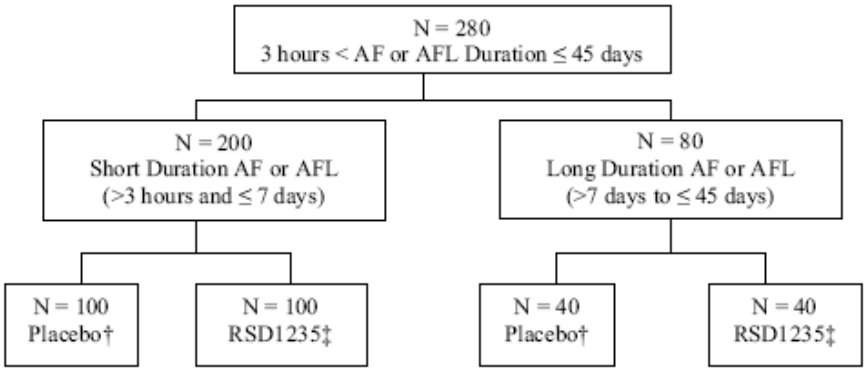
3.1.2.1 Study Objectives of ACT III

The primary objective was to demonstrate the efficacy of RSD1235 compared to placebo, in the conversion of AF or AFL to sinus rhythm. Treatment was considered successful if there was a treatment-induced conversion of AF or AFL to sinus rhythm for a minimum of one minute within 90 minutes of the start of the first infusion.

3.1.2.2 Study Design

This study was a phase 3, multi-center, randomized, double-blind, placebo-controlled study of RSD1235 in subjects with AF or AFL with a duration that was greater than 3 hours but did not exceed 45 days. A total of 280 subjects were planned for enrollment, stratified by duration of baseline AF or AFL: 200 subjects with short-duration AF or AFL and 80 subjects with long duration AF or AFL. Subjects within each stratum were centrally randomized in a 1:1 ratio to receive up to two 10-minute infusions of either RSD1235 or placebo treatment. The stratification and randomization plan is outlined in Figure 3.2.

Figure 3.2 Stratification and Randomization Plan



[Source: Sponsor's Study Report Figure 1]

3.1.2.3 Efficacy Measures

The primary efficacy endpoint was the proportion of subjects with short-duration AF who had a treatment-induced conversion of AF to sinus rhythm for a minimum duration of one minute within 90 minutes of first exposure to study drug.

The secondary efficacy endpoints were:

- Time from first study drug exposure to first conversion of AF to sinus rhythm within 24 hours of first study drug exposure for subjects with short-duration AF.
- The proportion of subjects with AF who had treatment induced AF termination within 90 minutes of first exposure to study drug.
- The proportion of subjects with short-duration AF or AFL who had treatment-induced AF or AFL termination within 90 minutes of first exposure to study drug.
- The proportion of subjects with AF or AFL who had treatment-induced AF or AFL termination within 90 minutes of first exposure to study drug.
- The proportion of subjects with long-duration AF who had treatment-induced AF termination within 90 minutes of first exposure to study drug.
- The proportion of subjects with long-duration AF or AFL who had treatment-induced AF or AFL termination within 90 minutes of first exposure to study drug.
- The proportion of subjects with AFL who had treatment induced AFL termination within 90 minutes of first exposure to study drug.

3.1.2.4 Statistical Analysis Plan

The Act III's analysis plan is exactly the same as described in Section Statistical Analysis Plan3.1.1.4.

3.1.2.5 Patient Disposition, Demographic and Baseline Characteristics

This study was conducted at 49 sites in Argentina (6), Chile (1), Canada (9), Sweden (5), Denmark (13), Mexico (1), and the United States (14). Total study enrollment achieved 276 of the protocol planned 280 subjects in the overall subject population (98.6%). A total of 265 subjects (131 placebos, 134 RSD1235) received study drug and are included in the full analysis

set/safety set. Overall, 94.9% (262/276) of subjects who were randomized completed the study. A total of 14 subjects were withdrawn from the study prior to completion, see Table 3.

Table 3 Summary of Subject Completion

	Number (%) of Subjects		
Subject Status	**Placebo (N = 138)**	**RSD1235 (N = 138)**	**Total (N = 276)**
Completed study	129 (93.5%)	133 (96.4%)	262 (94.9%)
Reason for withdrawal			
Randomized but never received study drug	7 (5.1%)	4 (2.9%)	11 (4.0%)
Adverse event (primary reason)	0	1 (0.7%)†	1 (0.4%)
Lost to Follow-up	1 (0.7%)	0	1 (0.4%)
Other	1 (0.7%)	0	1 (0.4%)

[Source: Sponsor's Study Report Table 3]

In the overall subject population, the placebo treatment group and the RSD1235 treatment groups had similar demographic characteristics. Furthermore, demographic results for the subgroups of subjects with AF, short-duration AF, long-duration AF, and AFL were similar.

3.1.2.6 Primary Efficacy Results

In subjects with short-duration AF, a greater proportion of subjects treated with RSD1235 converted to sinus rhythm (for a minimum duration of one minute) within 90 minutes of first exposure to study drug compared to subjects treated with placebo (44/86 [51.2%] versus 3/84 [3.6%]). The 47.6% difference was statistically significant ($P < 0.0001$), see Table 4.

Table 4 Conversion of AF to Sinus Rhythm within 90 Minutes – Subjects with Short-Duration AF

Site/Country	Treatment Group		% difference of success	P-value	Odds Ratio (95% CI)
	Placebo (N=84)	RSD1235 (N=86)			
All Sites	3 (3.6%)	44 (51.2%)	47.6	<0.0001	38.3 (9.2, 159.5)

3.1.2.7 Secondary Efficacy Results

Since the analysis of the primary efficacy endpoint resulted in a statistically significant positive finding, each of the secondary endpoints was tested at a 5% alpha level according to the sequence specified a priori.

1. Subjects with short-duration AF who were treated with RSD1235 experienced a shorter time from first study drug exposure to first conversion of AF to sinus rhythm (minimum duration of 1 minute) within 24 hours of first exposure to study drug compared to subjects treated with placebo ($P < 0.0001$)
2. A greater proportion of subjects with AF who were treated with RSD1235 experienced treatment-induced AF termination within 90 minutes of first exposure to study drug compared to subjects treated with placebo (47/119 [39.5%] versus 45/121 [3.3%]). The difference was statistically significant ($P < 0.0001$).

3. A greater proportion of subjects with short-duration AF or AFL who were treated with RSD1235 experienced treatment-induced conversion from AF or AFL to sinus rhythm (minimum duration of one minute) within 90 minutes of first exposure to study drug compared to placebo recipients (45/101 [44.6%] versus 3/98 [3.1%]). The difference was statistically significant ($P < 0.0001$).
4. A greater proportion of subjects with AF or AFL (>3 hours and □ 45 days) who were treated with RSD1235 experienced treatment-induced AF or AFL termination (minimum duration of one minute) within 90 minutes of first exposure to study drug exposure compared to subjects treated with placebo (48/138 [34.8%] versus 4/138 [2.9%]). The difference was statistically significant ($P < 0.0001$).
5. There was no statistically significant difference between the two treatment groups in the proportion of subjects with long-duration AF who had treatment induced AF termination (minimum duration of one minute) within 90 minutes o first exposure to study drug. According to the statistical analysis plan, no further secondary endpoints will be tested from this point on.

3.1.2.8 Efficacy Conclusions

The reviewer validated most of the applicant's conclusions according to the protocol. In conclusion, this study demonstrated that RSD1235 was effective at rapidly converting short-duration AF to sinus rhythm within 90 minutes compared to placebo treatment.

3.2 Evaluation of Safety

Please read Dr. Lemtouni's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

4.1.1 ACT I

Summary statistics for the proportion of subjects had treatment induced conversion of AF to sinus rhythm within 1.5 hours by age and sex is listed in Table 5. Based on the table results, we see that RSD1235 performed numerically better than the placebo in all subgroups. There are no summary statistics for the race subgroups because 96.7% of subjects are Whites.

Table 5 Proportion of conversion to NSR based on Age and Sex of ACT I

Parameter	RSD1235	Placebo
< 65		
No. Subjects	88	49
No. Converted	49	2
Response Rate	55.7%	4.1%
>=65		
No. Subjects	57	26
No. Converted	26	1
Response Rate	45.6%	3.9%

Male		
No. Subjects	102	48
No. Converted	53	2
Response Rate	51.9%	4.2%
Female		
No. Subjects	43	27
No. Converted	22	1
Response Rate	51.2%	3.7%

4.1.2 ACT III

Summary statistics for the proportion of subjects had treatment induced conversion of AF to sinus rhythm within 1.5 hours by age and sex is listed in Table 6Table 5. Based on the table results, we see that RSD1235 performed numerically better than the placebo in all subgroups. There are no summary statistics for the race subgroups because 98.9% of subjects are Whites.

Table 6 Proportion of conversion to NSR based on Age and Sex of ACT III

Parameter	RSD1235	Placebo
< 65		
No. Subjects	54	51
No. Converted	30	1
Response Rate	55.6%	2.0%
>=65		
No. Subjects	32	33
No. Converted	14	2
Response Rate	43.8%	6.1%
Male		
No. Subjects	61	57
No. Converted	31	1
Response Rate	50.8%	1.8%
Female		
No. Subjects	25	27
No. Converted	13	2
Response Rate	55.0%	7.4%

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Two adequate, well-controlled, phase 3 studies, ACT I and ACT III, provide independent substantiation of the efficacy of RSD1235 Injection for the rapid conversion of atrial fibrillation to normal sinus rhythm.

In both Act I and ACT III, the short-duration atrial fibrillation cohort, a statistically significantly greater percentage of subjects in the RSD1235 Injection group converted to sinus rhythm for a minimum duration of one minute within 90 minutes as compared with the placebo group, recall Table 1.

ACT I also provided following significance findings: The time to first treatment-induced conversion of atrial fibrillation to sinus rhythm was statistically and clinically significantly shorter in the short-duration atrial fibrillation and overall population in the RSD1235 Injection group compared with the placebo control group. Furthermore, in the overall population, a statistically significant greater percentage of subjects in the RSD1235 Injection group converted to sinus rhythm for a minimum duration of one minute within 90 minutes compared with the placebo group. ACT III also had similar significance findings from its secondary analyses, see Section 3.1.2.7 for details.

5.2 Conclusions and Recommendations

The data from this submission provided the significance evidence for the RSD1235 Injection effectively and rapidly converted atrial fibrillation to sinus rhythm in subjects with atrial fibrillation of >3 hours and ≤ 7 days.

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/s/

Steven Bai
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James Hung
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ELLIS F. UNGER, M.D.
Deputy Director, DCRDP

DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS

Secondary Review

Date: 13 November 2007

NDA: 22-034 (Vernakalant injection for rapid conversion of atrial fibrillation to sinus rhythm)

Reviewer: Ellis F. Unger, M.D., Deputy Director, DCaRP

Through: Norman Stockbridge, M.D., Ph.D., Director, DCaRP

To: The File

Subject: This is the secondary review of vernakalant injection for rapid conversion of atrial fibrillation; NDA 22-034, Astellas Pharma US, Inc.

This secondary review is based, in part, on the primary reviews from the following disciplines: Chemistry (Ramsharan D. Mittal), Preclinical Pharmacology and Toxicology (John E. Koerner), Clinical Pharmacology and Biopharmaceutics, (Elena Mishina), Clinical (Salma Lemtouni), and Statistics (Steve Bai).

1. Background and Introduction

Vernakalant Injection (vernakalant) is a novel, intravenous antiarrhythmic agent for conversion of atrial fibrillation (AF). The antiarrhythmic activity of vernakalant is mediated by blockade of early activating potassium channels combined with concentration-, voltage- and frequency-dependent blockade of sodium channels (i.e., I_{Kur}, I_{to}, and I_{Na}). Vernakalant hydrochloride selectively prolongs atrial refractoriness and rate-dependently slows atrial conduction. The applicant is seeking the indication "for rapid conversion of AF to sinus rhythm." The drug substance is referred to as RSD1235 in this document. Vernakalant is not marketed anywhere.

Pharmacologic agents are commonly used for conversion of AF to sinus rhythm, either alone or in combination with DC cardioversion. Drugs are less effective than DC cardioversion and are associated with the risk of serious ventricular dysrhythmias; however, they have advantages over DC cardioversion in that they do not require conscious sedation or anesthesia, and tend to be better accepted by patients. Systemic thromboembolism, and embolic stroke in particular, are feared complications of conversion of AF to sinus rhythm, but there is no evidence that the risk of embolic events differs between treatment modalities. For pharmacologic conversion of AF up to 7 days in duration, the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines for the Management of Patients With Atrial Fibrillation recommend ibutilide (I.V.), dofetilide (oral), flecainide (oral or I.V.), or propafenone (oral or I.V.) with a class IA recommendation/ level of evidence.[1] Ibutilide and dofetilide have indications for conversion of AF to sinus rhythm in the U.S.; flecainide and propafenone do not.

[1]Fuster V., et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation) *J Am Coll Cardiol*. 2006;48:854-906

A substantial fraction of patients with AF convert spontaneously to sinus rhythm within 24 to 48 hours. In one small study, 10 of 21 subjects who received placebo converted to sinus rhythm by 8 hours![2] Spontaneous conversion is less frequent in patients with AF of longer duration. Similarly, the efficacy of pharmacologic agents is greatest with AF of recent onset, and diminishes with time, particularly after 7 days.[1] (Only oral dofetilide has an ACC/AHA/ESC class IA recommendation for pharmacological cardioversion of atrial fibrillation present for > 7 days.)

For all AF therapies designed to restore sinus rhythm, reversion to AF after conversion to sinus rhythm is an important issue that represents loss of benefit (i.e., "conversion-reversion"), but it can be argued that this relates to the general strategy of attempting to restore sinus rhythm in patients with AF (in contrast with rate control alone), rather than to the specific treatment modality utilized (drugs or DC cardioversion).

2. Regulatory History and Status

The data submitted in support of the safety and efficacy of vernakalant have been derived from studies conducted under IND 61,848 (vernakalant hydrochloride injection) and IND 70,371 (oral formulation of vernakalant hydrochloride, held by Cardiome Pharma Corp.).

The original application was filed March 30, 2006. In response to the original NDA submission, the Division issued the applicant a "Refuse to File" letter under 21 CFR 314.101(d) on May 30, 2007, because of various deficiencies and inconsistencies in the data. A meeting was held July 6, 2006, to discuss the deficiencies, and corrective actions were planned. The applicant submitted another application on December 19, 2006. Important concerns and agreements are summarized below:

2.1 From meeting minutes of the End of Phase 2 Meeting, April 30, 2003:

a. The Division and Office raised concerns regarding "…the trial's unusually extensive exclusion criteria, which may lead to the study of an unrealistic population." Specific concerns were raised by the Office Director regarding exclusion of patients currently treated with Class I or Class III antiarrhythmic agents. The sponsor agreed to reevaluate their exclusion criteria.

b. The Sponsor proposed a total exposure of 648 subjects to intravenous Vernakalant, prior to NDA filing. The Office agreed "…that the number of patients will be adequate to demonstrate the safety and efficacy of RSD1235 IV."

c. "Dr. Temple said that it would be useful to determine if the use of RSD1235 affects electrical cardioversion. The Sponsor explained that all patients in whom treatment with RSD1235 is not successful will probably be cardioverted. Therefore, they should be able to gather enough useful information to characterize any effects that RSD1235 has on subsequent cardioversion."

2.2 A teleconference was held July 9, 2004 to discuss the statistical analytical plan.

[2]Capucci A, Lenzi T, Boriani G, et al. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. *Am J Cardiol* 1992;70:69.

a. The Agency agreed that “conversion to sinus rhythm” would be an acceptable 1° efficacy endpoint for ACT I.

b. With regard to the 2° endpoints, the Agency noted that the overall p-value would need to be 0.05 for 2° endpoints to be used in labeling or promotion.

c. The FDA statistician confirmed that the “Full Analysis Set” conforms to the “Intent-to-treat” philosophy and that it would be acceptable for efficacy analyses.

Reviewer's Comment: In fact, the “full analysis set” was planned to be the “as-treated” population. If there was a basis for the division to accept the “as-treated” population as the appropriate population for the 1° efficacy analysis, it was not captured in the minutes.

2.3 From meeting minutes of the Pre-NDA Meeting, November 1, 2005:

a. The Division raised concerns regarding the effect of vernakalant on ventricular repolarization, noting concerns regarding episodes of Torsades de Pointes that occurred in the development program, and the lack of a formal Thorough QT study. The sponsor explained how QT interval was assessed in the clinical program, and the Division agreed that it appeared that they would have enough data to address the Division’s concerns. The Division asked the sponsor to perform an analysis of QT as a function of drug plasma levels.

b. The Division expressed concern regarding the total number of subjects exposed to vernakalant in the development program. Acknowledging that the Division had agreed to the number in an earlier meeting, Dr. Stockbridge cautioned that “…the potential problem with a small development program is the inability to explain any safety signals or mortality observed. The wide confidence limits associated with any small development program, are not reassuring to the Division in terms of safety. It is possible that language acknowledging the size of the program and the corresponding confidence of mortality would be included in the labeling, or it may be deemed to be not enough exposure for approval. Dr. Stockbridge stated that it would be helpful if the sponsor were able to show that the deaths and TdP occurrences seen in the development program were not related to drug exposure. Dr. Stockbridge stated that will be a review issue that would not likely affect filing. “

c. Pediatric Waiver - The sponsor noted that the prevalence of AF is estimated to be 0.1% among adults younger than 55 years, and that no patients under < 18 years were enrolled in vernakalant clinical studies. The Sponsor questioned whether the Division would grant a full pediatric waiver. Dr. Stockbridge stated that the Division is unsure if a program evaluating AF is possible in the pediatric population, but would grant a deferral or waiver, depending on whether it is feasible to conduct a trial in a pediatric AF population.

d. The sponsor explained that for the 1° endpoint in the phase 3 pivotal sties is the proportion of patients with AF of >3 hours to ≤ 7 days duration who had treatment-induced conversion to sinus rhythm (≥ 1 minute) within 90 minutes of first exposure, and that the primary analysis set for efficacy is the “full analysis set:” all randomized patients who received any portion of a dose of study drug. The sponsor questioned whether this would support an indication of “rapid conversion of atrial fibrillation to sinus rhythm.”

Dr. Stockbridge requested a data analysis that would illustrate the distribution in time to conversion from AF to normal sinus rhythm and reversion to AF, if applicable. A life table analysis was suggested. The sponsor confirmed that the 1° endpoint evaluated patients in AF

from 3 hours to 7 days. The sponsor stated that there was a profound difference in efficacy based on the time in AF. In response, Dr. Stockbridge suggested the sponsor also conduct an analysis of likelihood of conversion based on the amount of time in AF.

3. Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls reviewer concluded that the submission is adequate, with no pending issues. The application was considered APPROVABLE, with a final recommendation to be made after the current Good Manufacturing Practices status of one of the drug substance facilities is updated by the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

4.1. General Nonclinical Pharmacology/Toxicology Considerations

Vernakalant is a nonselective potassium and sodium channel blocker that is proposed for intravenous (IV) use for patients with atrial fibrillation (AF), for the conversion of AF to sinus rhythm. Vernakalant non-selectively blocks potassium (I_{Kr}, I_{Ks}, I_{Kur} and I_{to}) and sodium (I_{Na}) currents in atrial and ventricular myocytes, as well as cloned human potassium and sodium channels, with inhibitory concentrations for potassium and sodium channels in the same range. Vernakalant affected cardiac action potential parameters *in vitro*, depressing maximal upstroke velocity in guinea pig papillary muscle. *In vivo*, vernakalant prolonged atrial and ventricular refractoriness, consistent with sodium and potassium channel blockade.

Paraphrased from the "Review and Evaluation of Pharmacology and Toxicology Data" by Dr. Koerner:

Pharmacokinetics and Metabolism

Vernakalant is to be administered by the I.V. route; therefore, absorption is not an issue. Following I.V. administration to rats and dogs, vernakalant exhibits large volumes of distribution. Plasma half-life was substantially shorter in rats than humans, but similar in dogs and humans. In a rat mass balance study with I.V. administration of ^{14}C-labeled vernakalant, distribution of drug-related radioactivity was rapid and extensive, with high radioactivity observed in the gastrointestinal contents, bile and urine. Plasma radioactivity was cleared within 8 hours of administration, whereas radioactivity persisted in the intestine, kidney and urinary bladder for up to 72 hours after dosing.

The major human metabolites are RSD 1385, RSD 1390 and, in poor metabolizers, RSD 1231 (a vernakalant isomer). These metabolites block the same ion channels as the parent with similar or lower potencies. Glucuronide conjugates of these metabolites are also observed, but block these channels only weakly.

Vernakalant plasma protein binding was not extensive in any species evaluated. Free vernakalant hydrochloride in plasma was 56% in humans, and similar in dogs, rats and rabbits.

The primary human route of excretion is through the kidney.

Safety Pharmacology

Vernakalant administration was associated severe central nervous systems (CNS) toxicity, inducing convulsions in rats and dogs within minutes of administration, and resolving rapidly

following completion of drug infusion. (Seizures were also observed in pregnant rabbits in reproductive toxicology studies). Prodromal observations included head shaking, excessive salivation, licking, tremors and uncoordinated gait. Compared on the basis of body surface area, convulsions occurred at exposures only marginally higher than that of the human therapeutic dose, with no observed adverse effect levels (NOAELs) in rats only 2-3 fold higher than the human therapeutic dose and NOAELs in dogs similar to the human therapeutic dose.

Vernakalant also produced adverse effects on the cardiovascular and respiratory systems. Vernakalant lowered blood pressure and heart rate at doses that exceeded (4-fold) those necessary for antiarrhythmic activity in anesthetized dogs. Respiratory depression and arrest were observed in rats within minutes of vernakalant administration in the dose range of 20-75 mg/kg/2 min (10-38/mg/kg/min).

The effect of vernakalant on ventricular defibrillation threshold (DFT), i.e., energy needed to defibrillate the ventricle, was not evaluated in animals or humans. Vaughan Williams classification IA, IB and IC antiarrhythmic agents, which block sodium channels, increase the ventricular DFT, whereas Class III antiarrhythmic agents, which block potassium channels, decrease the ventricular DFT. Because vernakalant blocks both channels, it has the potential to increase or decrease the DFT, depending on which effect predominates.

4.2. Carcinogenicity

Vernakalant tested negative for mutagenicity in the bacterial mutation assay at the limit dose of 5 mg/plate, and for genotoxicity in the *in vitro* mouse lymphoma assay. Vernakalant tested positive for clastogenicity *in vitro* in the absence and presence of metabolic activation in Chinese hamster ovary cells, but tested negative for chromosomal aberrations in the *in vivo* mouse micronucleus assay at the maximally tolerated dose.

4.3. Reproductive Toxicology

Vernakalant was evaluated for reproductive toxicity in rats given I.V. doses up to 40 mg/kg/day and in rabbits given I.V. doses up to 30 mg/kg/day, which were greater than maximally tolerated doses in both species.

Vernakalant hydrochloride tested negative for adverse effects on fertility and early embryonic development in rats, as well as perinatal/postnatal function in rats.

Vernakalant hydrochloride also tested negative for teratogenicity in rabbits, but was associated with the presence of a relatively rare malformation (omphalocele) when given to pregnant rats at intravenous doses of 20 and 40 mg/kg/day. On a body surface area basis, this exposure is only marginally higher than the human therapeutic dose.

4.4. Summary of Major Pharmacology-Toxicology Issues

The major safety-related pharmacology-toxicology findings associated with I.V. vernakalant are:

- CNS toxicity in rats, dogs and pregnant rabbits at exposures only marginally higher than that of the human therapeutic dose.
- Teratogenicity in rats at an exposure only marginally higher than that at the human therapeutic dose.

- Positive genotoxicity *in vitro* in Chinese hamster ovary cells, although negative results *in vivo* in the mouse micronucleus test at the maximum tolerated dose.
- The effect of vernakalant on ventricular defibrillation threshold (DFT) was not evaluated. "

4.5 Pharmacology Toxicology Reviewer's Recommendations

Recommendation for Approvability: "Approvable," with two reservations: 1) vernakalant produced convulsions in animals with relatively small safety margins; and 2) a recommendation that the sponsor determine the effects of vernakalant on ventricular defibrillation threshold in a study using a concurrent positive control, e.g., lidocaine.

5. Clinical Pharmacology/Biopharmaceutics

The vernakalant NDA includes contains 7 clinical pharmacokinetic studies, including two pivotal trials. The sponsor performed two Phase 1 studies: a dose-ranging study to determine the maximum tolerated dose, and a mass-balance study. In addition, the sponsor conducted *in vitro* studies to assess the hepatic metabolism by CYP450 and the potential for vernakalant to inhibit CYP450 enzymes, the binding to plasma protein and displacement of vernakalant by several drugs which could be possibly co-administered in the clinic. All studies were reviewed by the clinical pharmacology reviewer.

5.1 General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

Pharmacokinetics: Following two intravenous infusions of 3.0 mg/kg and 2.0 mg/kg, each over 10 minutes and separated by 15 minutes, vernakalant's pharmacokinetics could be described by a two-compartment pharmacokinetic model with first-order elimination. In poor CYP2D6 metabolizers, vernakalant clearance was 64% of that in extensive metabolizers, but Cmax did not differ. The estimated terminal population half-life (t1/2,β) was 3.2 and 8 hrs for CYP2D6 extensive and poor metabolizers, respectively. Age, renal function, presence of CHF, concomitant CYP2D6 inhibitors (amiodarone, cimetidine, fluoxetine, paroxetine and ranitidine) and concomitant beta-blockers (diltiazem and verapamil) did not influence the clearance. Race and hepatic function did not influence the clearance in this study population; however, very few patients (8%) were non-Caucasians and/or had markers of impaired hepatic function. The typical volume of the central compartment was estimated to be 51.0 L and 26.4 L in males and females, respectively. However, when differences in body weight were factored in, the gender difference was not significant.

Absorption and Distribution: Vernakalant is administered by a two (3+2 mg/kg) 10 minute infusions. At the end of the first and second infusions, Cmax was 4.2 and 5.2 mcg/mL, respectively, and declined sharply after that, decreasing to the lower limit of quantification at 24 hours. The steady-state volume of distribution estimate was 1.77 L/kg (147 L for 83 kg patient), indicating a high degree of tissue distribution. The plasma protein binding of RSD1235 in human plasma is approximately 53% to 63% at therapeutic concentrations.

5.2 Drug-drug interactions: *In vivo* pharmacokinetic interactions of vernakalant with other drugs were not evaluated in this NDA. The interactions with P-glycoproteins have not been assessed. In the opinion of the clinical pharmacology reviewer, the sponsor should determine whether vernakalant is a substrate or inhibitor of P-glycoproteins or any other transporters. P-glycoprotein transport of vernakalant should be characterized *in vitro* using at least two P-glycoprotein inhibitors.

5.3 Metabolism and Elimination: Vernakalant is cleared both by the liver and the kidney, however, the hepatic and renal clearances were not reported. CYP4502D6 is the predominant enzyme involved in the O-demethylation metabolism of vernakalant. The inhibitory potential of vernakalant was very weak for cytochrome P450 1A2, 2C9, 2C19, 2E1, and 3A4. The *in vitro* studies suggested that vernakalant is neither a reversible nor irreversible inhibitor of the above cytochromes, and is a moderate and competitive inhibitor of CYP2D6.

5.4 Demographic interactions/special populations:

Intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) were not prospectively studied in the NDA. The clinical pharmacology reviewer stated that data from the population PK model predicts that neither age nor gender would not be expected to importantly affect vernakalant pharmacokinetics. Moreover, the reviewer considered it unlikely that renal or hepatic impairment would have a clinically meaningful effect or require dosage adjustment.

The pharmacokinetics of vernakalant have not been studied in pediatric patients in this NDA.

5.5 Thorough QT study or other QT assessment: A formal Thorough QT study was not performed for this antiarrhythmic agent. In the conventional clinical trials, vernakalant was found to prolong the QT interval with mean predicted QT changes from baseline of 20 and 23 msec at the mean peak concentrations of 3660 and 4330 ng/mL after vernakalant doses of 3 mg/kg and 3 + 2 mg/kg, respectively. After a single 3 mg/kg dose, the mean ΔQTcF is predicted to return to normal within 6 hours for CYP2D6 extensive metabolizers and within 12 hours for poor metabolizers. After the 3 + 2 mg/kg regimen, ΔQTcF is predicted to return to normal after 12 and 24 hours for extensive and poor metabolizers, respectively. The clinical pharmacology reviewer suggests that ECG monitoring should be continued for at least 6 hours post-dose until the QTc is within normal limits for CYP2D6 extensive metabolizers, and 12 hours for CYP2D6 poor metabolizers receiving 3 mg/kg. (Additional information is presented with further discussion in section 7.2.4. of this review.)

5.6 Exposure-Response Relationships: Logistic regression analyses were performed using efficacy data from evaluable patients in studies ACT I and ACT III. The analyses indicate that conversion to sinus rhythm within 90 minutes after start of the vernakalant infusion is not correlated with RSD1235 exposure (Cmax) within the studied exposure range under 3+2 mg/kg dosing regimen.

6. Clinical/Statistical

6.1.1. Dose identification/selection and limitations

CRAFT was the phase 2a dose-ranging study in patients with recent onset AF. Dose selection was based upon *in vitro* electrophysiological activity and plasma concentrations observed in a canine study. Subjects in CRAFT were randomized to receive 0.5 + 1 mg/kg vernakalant, 2 + 3 mg/kg vernakalant, or placebo, and rates of AF conversion were 61%, 11%, and 5%, respectively, establishing a dose-response. For the pivotal studies, the 5 mg/kg total dose was selected; however, the dosing sequence was reversed based on PK considerations.

Reviewer's Comment: CRAFT demonstrated, fairly convincingly, that vernakalant at doses only marginally lower than 5 mg/kg used in the pivotal studies (1.5 mg/kg) had minimal activity for the restoration of sinus rhythm. The principal toxicity of concern on the basis of the non-clinical studies (i.e., seizures) did not appear to be an issue in the clinical program, and it would be feasible, but not necessary, to study doses higher than those used in the pivotal studies in order to try to enhance efficacy. Subjects would require judicious monitoring if such studies were undertaken.

6.1.2. Phase 3 Clinical Studies Essential to Regulatory Decision

Proof of effectiveness of vernakalant for the conversion of atrial fibrillation (AF) to sinus rhythm is based on two similar multinational, randomized, double-blind, placebo-controlled, phase 3 studies: Study 1235-0703 (ACT I) and Study 1235-0504/04-7-010 (ACT III), considered together in this section. Details of the ACT I and ACT III study designs, procedures, and results are summarized in the Clinical and Statistical Reviews by Dr. S. Lemtouni and Dr. S. Bai, respectively, with key points and additional analyses summarized below.

Design

Both studies enrolled subjects with AF, 3 hours to 45 days in duration. Subjects were stratified at enrollment by duration of AF symptoms: "short-duration AF," defined as AF duration > 3 hours and ≤ 7 days, and "long-duration AF," defined as AF duration > 7 to ≤ 45 days.

- ACT I was planned to enroll 360 subjects with 2/3 of the population to have "short-duration" AF, and 1/3 of the population to have "long-duration" AF. Subjects within each stratum were randomized 2:1 (vernakalant:placebo).

- ACT III was planned to enroll 280 subjects with 5/7 and 2/7 of the population (n=200; n=80) to have "short-" and "long-duration" AF, respectively. Subjects within each stratum were randomized 1:1 (vernakalant:placebo). Initially, the sponsor posited a role for vernakalant in the conversion of atrial flutter (AFL) to sinus rhythm, and ACT III initially enrolled subjects with either AF or AFL. However, during the conduct of the study, the results of study 1235-0703B (Scene 2) became available, showing failure of vernakalant to convert subjects with AFL. The Sponsor made the decision not to pursue the AFL indication at that juncture, and ACT III was amended to discontinue enrollment of AFL subjects; previously enrolled AFL subjects were excluded from the 1° endpoint.

Both studies enrolled adults with AF (or AFL for ACT III) and typical symptoms present for > 3 hours and ≤ 45 days, who were hemodynamically stable and receiving adequate anticoagulant therapy. Subjects with uncorrected QT interval > 440 msec, a history of torsade de pointes or Brugada syndrome, subjects with ventricular response < 50/min or sick-sinus syndrome (in absence of a pacemaker), QRS interval >0.14 seconds (in absence of a pacemaker), ventricular rate < 50 /min, and unstable Class IV congestive heart failure (CHF) were excluded. Subjects requiring inotropic support, and subjects with myocardial infarction (MI), acute coronary syndrome or cardiac surgery within 30 days were excluded. Subjects with reversible causes of AF such as alcohol intoxication, hyperthyroidism, acute pericarditis or pulmonary embolism were excluded, as were subjects with uncorrected electrolyte imbalances. Subjects who had failed DC cardioversion, subjects with digoxin toxicity, and subjects who had received I.V. Class I or Class III antiarrhythmic drugs or I.V. amiodarone within 24 hours prior to dosing were also excluded from entry. ACT III added significant valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, and constrictive pericarditis as exclusion criteria.

Using central randomization and an Interactive Voice Recording System (IVRS), subjects were assigned to receive one or two 10-minute infusions as follows:

- 10-minute infusion of the test article (vernakalant 3 mg/kg or normal saline placebo);
- a 5-minute observation period; and
- a second 10-minute infusion of test article (vernakalant 2 mg/kg or placebo).

The second infusion was omitted for subjects who had converted to sinus rhythm at time = 25 minutes, or in whom dose-stopping criteria had been met. The dose was capped for subjects weighing > 113 kg (250 lbs). Neither DC cardioversion nor other antiarrhythmic drugs were permitted for > 2 hours after the end of infusion. Identity of the test article was restricted to on-site pharmacists, who prepared a 150 mL saline solution (± vernakalant) for infusion.

Subjects were queried for AF (or AFL) symptoms at baseline, 90 minutes, 24 hours (or discharge, as applicable), at Week 1 follow-up, and by telephone at Day 30. The following symptoms were sought: shortness of breath, palpitations, chest tightness/pains, dizziness, edema, fatigue, rapid heart beats, diaphoresis, orthopnea, paroxysmal nocturnal dyspnea, nausea, syncope, irregular pulse, vomiting, cough, and headache. A transesophageal echo was to be performed at screening, if deemed clinically necessary.

ECGs, blood pressure, and respiratory rate were obtained every 5 minutes from 0 to 50 minutes; at 90 minutes, 2, 4, 8, and 24 hours (or discharge), Day 7, and with conversion to sinus rhythm or a serious adverse event. Subjects were on telemetry from baseline until ≥ 2 hours, and up to 8 hours post-dose, if possible. Holter recording was started at screening and continued until 24 (±4) hours post-dose. Serum chemistry and hematologic assessments were obtained at baseline, 24 hours, and Day 7.

Analytic Features

Conversion of AF to sinus rhythm was confirmed by CEC members blinded to treatment arm, using Holter results. If Holter data were not available or deemed unusable, ECG data were reviewed. The observation of sinus rhythm on two consecutive 12-lead ECG recordings or ECG monitor leads recorded ≥ 1 minute apart was taken as evidence of conversion to sinus rhythm.

The 1° efficacy endpoint in both studies was the proportion of subjects with “short-duration” AF who converted to sinus rhythm for ≥ 1 minute, within 90 minutes of initial exposure to the test agent.

Numerous, largely overlapping 2° efficacy endpoints included:

- time to conversion to sinus rhythm (≥ 1 minute, within 24 hours), “short-duration” AF
- time to conversion to sinus rhythm (≥ 1 minute, within 24 hours) in overall population
- proportion of subjects with conversion (≥ 1 minute, within 90 minutes) in overall population
- time to conversion in subjects with “long-duration” AF (ACT I, only)
- proportion of subjects with “short-duration” AF or AFL who had conversion (≥ 1 minute, within 90 minutes), ACT III, only
- proportion of subjects with AF or AFL (overall population) who had conversion (≥ 1 minute, within 90 minutes), ACT III, only
- proportion of subjects with “long-duration” AF (>7 and ≤ 45 days) who had conversion (≥ 1 minute, within 90 minutes)

- proportion of subjects with "long-duration" AF or AFL who had conversion (≥ 1 minute, within 90 minutes), ACT III, only
- proportion of subjects with AFL ("short-" or "long-duration") who had conversion (≥ 1 minute, within 90 minutes), ACT III, only

The statistical analytic plans were the same for ACT I and ACT III. The 1° endpoint was tested utilizing a 5% alpha level. The analysis for the 1° endpoint utilized a Cochran-Mantel-Haenszel (CMH) test, stratified by country, to compare the proportions of subjects who converted to sinus rhythm in the two treatment groups. If the 1° endpoint was statistically significant, the 2° endpoints were to be tested sequentially at the 5% significance level. The 2° time-to-event endpoints were analyzed using the Product-Limit method, with treatment groups compared using Log Rank. Proportional 2° endpoints were analyzed as per the 1° endpoint, using the CMH test.

The full analysis data set, defined as all randomized subjects who received any amount of study agent, was designated the primary analysis set for the 1° efficacy endpoint. Of note, the sponsor considered this population as synonymous with the intent-to-treat population (ACT I Protocol, version dated November 20, 2006, page 56; ACT III Protocol, version dated June 3, 2005, page 51), and also synonymous with the safety analysis set. The sponsor's rationale was provided in the ACT I Protocol (pp. 55-56):

> "The following changes from the protocol were made to the analysis plan and subsequently approved by FDA. The definition of the intent-to-treat population (designated as the full analysis set in this study report) was modified to exclude subjects that did not receive any study drug. The intention-to-treat principle was preserved despite the exclusion of these subjects because the decision whether or not to begin treatment was not influenced by knowledge of the assigned treatment."

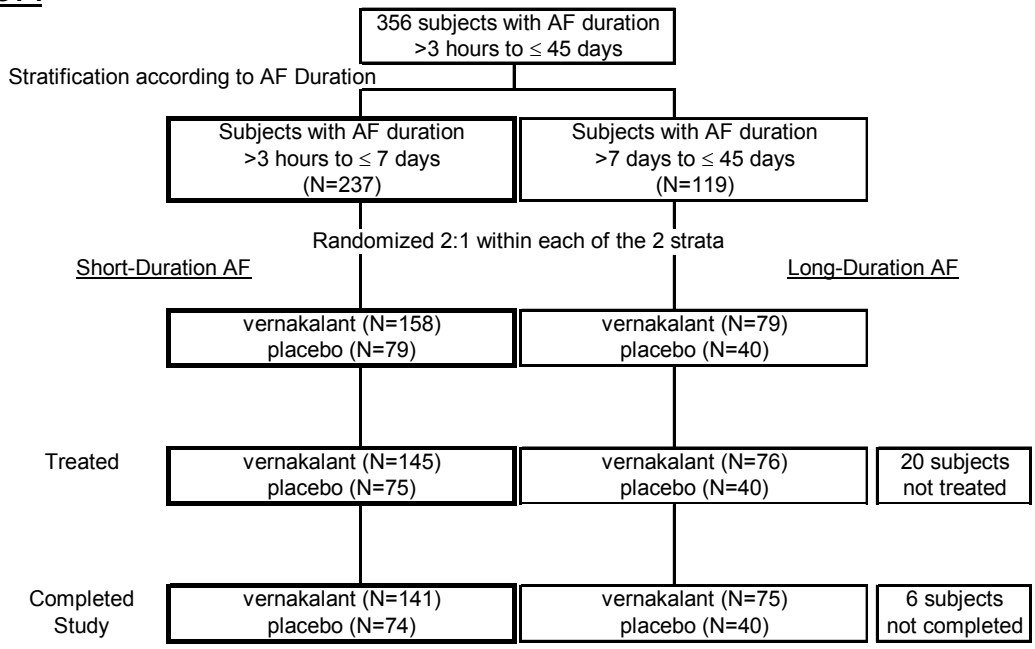
Reviewer's Comments: In fact, the modified "intent-to-treat" population defined by the sponsor is the "as-treated" population. This approach is generally anticonservative, and can inflate the apparent effect size, the degree of inflation related to the fractions of subjects in each treatment group who fail to receive the study agent. In ACT I and III, however, some subjects did not receive the study agent because they converted spontaneously to sinus rhythm in the period between randomization and planned test drug administration. For these studies, therefore, the overall effect of using the "as-treated" versus the "intent-to-treat" population is unpredictable, and dependent on a number of factors. It is worthwhile to compare results of analyses using both methods ("as treated" and "intent-to-treat" populations).

Subjects had a response of "failure" imputed for the primary endpoint if they withdrew after initiation of study drug infusion but prior to observing the endpoint (and prior to 90 minutes), or if they underwent DC cardioversion prior to 90 minutes. As noted above, patients who withdrew prior to receiving study agent were not included in the primary endpoint analysis.

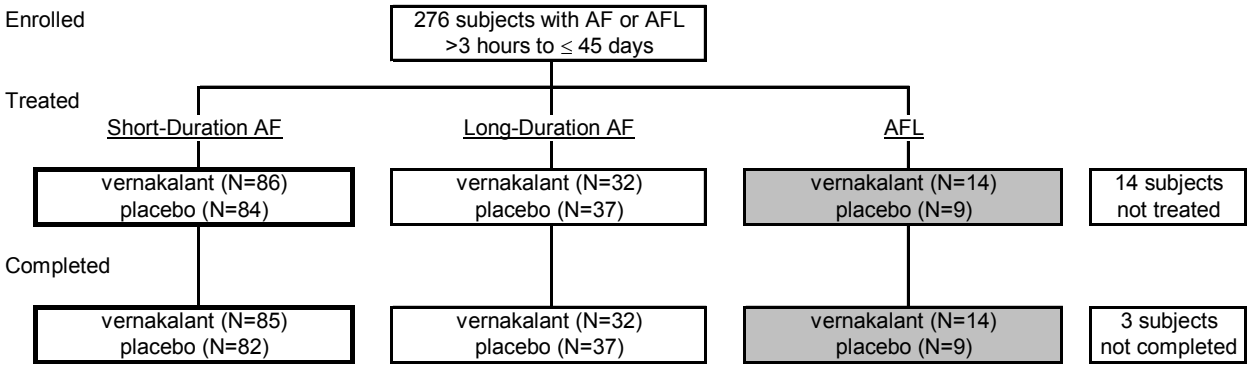
Results

The disposition of subjects in ACT I and ACT III is summarized below:

ACT I



ACT III



ACT I enrolled 356 of the 360 planned subjects. Of the 20 subjects who did not receive study agent, 14 had spontaneously reverted to sinus rhythm, and 6 were not dosed for a number of other reasons (failure to meet entrance criteria, acute myocardial infraction, etc.). Of the 6 subjects who did not complete ACT I, 3 died while on-study (all in the vernakalant group). Overall, 93% of randomized subjects completed ACT I.

ACT III enrolled 276 of the 280 planned subjects. Approximately half of the subjects who were not dosed had converted spontaneously to sinus rhythm before dosing. The others were not dosed largely because of failure to meet inclusion criteria.

Reviewer's Comment: For both studies, reasons for not dosing subjects seem appropriate. Overall, approximately 5% of subjects did not receive study agent; approximately 2/3 of these subjects (~3% overall) did not receive study agent because of spontaneous reversion to sinus rhythm. Subject retention was excellent within both studies, but this is expected given the brief duration of the studies and the nature of the patient population (i.e., the patients are a "captive audience" in that they generally remain in the hospital until stable).

Demographics and Baseline Characteristics

Subjects' demographic and baseline characteristics were fairly well balanced between the vernakalant and placebo groups (Table 1). Of note, only a trivial number of subjects of African ancestry (0.8%) were included in the development program. In ACT I, subjects with preexisting heart failure (CHF) were not excluded from entry provided they weren't functional Class IV; however, a history of CHF was not carefully solicited. In ACT III, 45 subjects (17%) provided a history of preexisting CHF, and 23 received vernakalant. Thus, the clinical performance in CHF patients, an important segment of the AF population, was not well studied in the development program.

Table 1: Demographics and Baseline Disease Characteristics; Baseline Medication Use

	ACT I		ACT III		overall
	placebo	vernakalant	placebo	vernakalant	
N	115	221	131	134	601
Age (years)					
Mean	61.5	62.3	61.5	60.9	61.7
Categorized Age (N, %)					
< 65	68 (59.1%)	121 (54.8%)	76 (58.0%)	76 (56.7%)	341 (56.7%)
≥ 65	47 (40.9%)	100 (45.2%)	55 (42.0%)	58 (43.4%)	260 (43.3%)
Gender (N, %)					
Female	40 (34.8%)	62 (28.1%)	44 (33.6%)	40 (29.9%)	186 (30.9%)
Male	75 (65.2%)	159 (71.9%)	87 (66.4%)	94 (70.1%)	415 (69.1%)
Race (N, %)					
Black	0 (0%)	2 (0.9%)	2 (1.5%)	1 (0.7%)	5 (0.8%)
Caucasian	113 (98.3%)	212 (95.9%)	129 (98.5%)	133 (99.3%)	587 (97.7%)
Other	2 (1.7%)	7 (3.2%)	0 (0%)	0 (0%)	9 (1.5%)
Country (N, %)					
Denmark	59 (51.3%)	102 (46.2%)	52 (39.7%)	52 (38.8%)	265 (44.1%)
Canada	23 (20%)	74 (33.5%)	20 (15.3%)	27 (20.1%)	144 (24%)
USA	15 (13%)	19 (8.6%)	23 (17.6%)	24 (17.9%)	81 (13.5%)
Sweden	18 (15.7%)	26 (11.8%)	16 (12.2%)	14 (10.4%)	74 (12.3%)
Argentina	(0%)	(0%)	17 (13%)	14 (10.4%)	31 (5.2%)
Mexico	(0%)	(0%)	1 (0.8%)	3 (2.2%)	4 (0.7%)
Chile	(0%)	(0%)	2 (1.5%)	0 (0%)	2 (0.3%)
Weight (kg)					
Mean	84	84.2	84.1	87.1	84.8
Median	82	82	84.4	84	83
Left Atrial Size (mm)					
N			29	39	68
Mean (SD)			42.1	42	42.1
Congestive Heart Failure (N, %)			22 (16.8%)	23 (17.2%)	45 (17%)
NYHA Class I			6 (4.6%)	8 (6%)	14 (5.3%)
NYHA Class II			9 (6.9%)	13 (9.7%)	22 (8.3%)
NYHA Class III			3 (2.3%)	0 (0%)	3 (1.1%)
Class missing/unknown			4 (3.1%)	2 (1.5%)	6 (2.3%)
Concomitant Medication Use (N, %)					
Class I antiarrhythmics	8 (7%)	14 (6.3%)	6 (4.6%)	17 (12.7%)	45 (7.5%)
Class III antiarrhythmics	5 (4.3%)	12 (5.4%)	14 (10.7%)	9 (6.7%)	40 (6.7%)
beta-blockers	71 (61.7%)	128 (57.9%)	77 (58.8%)	74 (55.2%)	350 (58.2%)
Calcium channel blockers	27 (23.5%)	40 (18.1%)	26 (19.8%)	21 (15.7%)	114 (19%)
Sotalol	17 (14.8%)	31 (14%)	8 (6.1%)	7 (5.2%)	63 (10.5%)
Digoxin	36 (31.3%)	55 (24.9%)	24 (18.3%)	19 (14.2%)	134 (22.3%)

The leading countries of enrollment were Denmark, Canada, U.S., and Sweden, followed by Argentina, Mexico, and Chile. Overall, 81 subjects (13.5%) were enrolled at U.S. sites, of whom 43 received vernakalant.

Presenting symptoms were typical of the AF patient population, with irregular pulse, palpitations, fatigue, rapid heart rate, dyspnea, and chest pain most common. Concomitant medication use was fairly well-balanced, although there tended to be slightly less use of digoxin and calcium channel blockers in vernakalant groups in both studies. Since both types of drugs are used as a strategy for rate control in AF, this suggests that subjects in the vernakalant group had less severe heart disease, which would favor the placebo group.

Primary Efficacy Endpoint

The results for both studies are summarized in Table 2. Rates of conversion of "short-duration" AF, with symptom duration 3 hours to 7 days, were roughly 50% in both studies, and differences from placebo were highly statistically significant (conversion rates with placebo were ~4% in both studies). For "long-duration" AF, conversion rates in vernakalant treated subjects were <10% and not statistically distinguishable from placebo. The sponsor's results were corroborated independently by the Statistical Reviewer and this 2° reviewer.

Table 2: Conversion of AF to Sinus Rhythm in ACT I and ACT III

Duration of AF	**ACT I**			**ACT III**		
	Vernakalant	**Placebo**	**P-value†**	**Vernakalant**	**Placebo**	**P-value†**
>3 hrs to ≤ 7 days	74/145 (51.0%)	3/75 (4.0%)	<0.0001	44/86 (51.2%)	3/84 (3.6%)	<0.0001
>7 days to ≤ 45 days	4/76 (5.3%)	0/40 (0%)	0.30	3/32 (9.4%)	1/37 (2.7%)	0.33

†Cochran-Mantel-Haenszel test

Examinations on the Primary Endpoint

Intent-to-treat Analysis

This 2° reviewer analyzed the 1° endpoint using the "intent-to-treat" (as randomized) population, rather than the "as treated" population. For "short term" AF, > 3 and ≤ 7 days in duration, when subjects who spontaneously converted to sinus rhythm prior to receiving the test drug are categorized as "successes" (10 subjects randomized to Vernakalant; 3 subjects randomized to placebo), the respective rates of conversion are 53.2% and 7.6%, respectively. These rates, and the absolute delta between rates, are not materially different from the "as-treated" population. Because the difference between the "as-treated" and "intent-to-treat" populations was even less in ACT III, this analysis was not repeated for ACT III. In summary, although the sponsor's use of the "as-treated" population is anti-conservative, the differences between the results of the "as-treated" analyses and the conventional "intent-to-treat" analyses are unimportant, given the effect size. Because the sponsor prospectively planned to use the "as-treated" population, and because the Division did not object, the "as-treated" analysis could be placed in labeling. The results differ little from the "intent-to-treat" analysis.

Subgroup Analyses

Table 3 provides a summary of this reviewer's exploratory subgroup analyses for ACT I (left) and ACT III (right). In general, rates of successful conversion to sinus rhythm are consistent across subgroups, but several points are notable:

Symptom-to-needle time: In both ACT I and ACT III, the sponsor dichotomized subjects by symptom-to-needle time at 7 days, with "short-duration" AF defined at 3 hours $\leq$ 7 days, and "long-term" AF defined as > 7 to 45 days. This dichotomization is consistent with the ACC/AHA/ESC Guidelines. The results of both studies are statistically persuasive for the "short-term" group, but negative for the "long-duration" group. It is not reasonable to assume, however, that 7 days represents a specific break point between efficacy and lack of efficacy.

Table 3: Analyses of the 1° Efficacy Endpoint by Subgroup, AF of 3 Hours to 7 Days Duration

	ACT I				ACT III			
	placebo		vernakalant		placebo		vernakalant	
	N	% who converted	N	% who converted	N	% who converted	N	% who converted
Overall	75	4.0%	145	51.7%	84	3.6%	86	52.3%
Age category								
<65	49	4.1%	88	55.7%	51	2.0%	54	57.4%
65-74	15	6.7%	32	59.4%	18	0%	13	46.2%
>=75	11	0%	25	28.0%	15	13.3%	19	42.1%
Sex								
Male	48	4.2%	102	52.0%	57	1.8%	61	52.5%
Female	27	3.7%	43	51.2%	27	7.4%	25	50.0%
Race								
White	73	4.1%	138	50%	84	3.6%	86	52.3%
Black	0		2	100%	0		0	
Other	2	0%	5	80%	0		0	
Weight quintile								
lowest	20	0.0%	27	59.3%	18	11.1%	14	57.1%
lower	15	0.0%	35	42.9%	15	6.7%	16	68.8%
mid	15	13.3%	25	48.0%	21	0.0%	17	41.2%
higher	8	0.0%	31	51.6%	17	0.0%	22	50.0%
highest	17	5.9%	27	59.3%	13	0.0%	17	47.1%
Site location								
US	10	4.6%	8	50.5%	8	0%	14	35.7%
non-US	65	0.0%	137	51.8%	76	3.9	72	55.6%
Left atrial size								
<40.5 mm					7	0%	13	46.2%
>40.5 mm					6	0%	8	37.5%
Comorbidities								
ischemic heart disease	13	0%	21	47.6%	10	0%	5	60.0%
CHF	4	0%	11	18.2%	11	0%	12	33.3%
hypertension	32	3.1%	57	43.9%	28	0%	41	43.9%
mitral valvular disease	4	0%	7	57.1%	6	0%	4	25.0%
Symptom to needle time (days)								
1	33	6.1%	63	63.5%				
2	27	3.7%	40	60.0%				
3	7	0%	13	38.5%				
4	1	0%	7	14.3%				
5	2	0%	10	20.0%				
6	2	0%	8	12.5%				
7	2	0%	4	50.0%				
Concomitant Medication Use (N, %)								
Sotalol	16	0%	21	52.4%	6	0%	7	100%
Class I antiarrhythmics	8	0%	9	22.2%	6	0%	16	18.8%
Class III antiarrhythmics	2	0%	10	40.0%	7	0%	6	33.3%
Calcium channel blockers	19	5.3%	25	60.0%	20	10.0%	16	50.0%
beta-blockers	34	8.8%	71	56.3%	49	0%	52	51.9%
digoxin	15	6.7%	26	19.2%	71	4.2%	5	20.0%
Tobacco Use (N, %)								
Yes	12	8.3%	20	50.0%				
No	63	3.2%	125	52.0%				

The sponsor collected data on time of symptom onset for subjects in ACT I, permitting an assessment of conversion rate as a function of time. Using logistic regression analysis, the sponsor plotted likelihood of conversion as a function of duration of AF symptoms (Figure 1). The percentage conversion rates from this reviewer's independent analyses (shown in Table 3) are superimposed on the sponsor's plot for days 1 through 7. Note that the success rate falls off sharply after Day 2, and particularly after Day 3. The rate of conversion through days 4, 5, and 6 is 16% (4 of 25). Although the rate was 50% on Day 7, this assessment is based on a sample of only 4 subjects, and may be spurious.

Labeling should be written in such a way as to convey this information to practitioners. The sponsor's logistic regression analysis (Figure 1) seems deceptive, as it suggests that the decrease in success rate is linear with time, through approximately day 13, when there appears to be a slight inflection (See bold arrow in Figure 1). My analysis suggests that the inflection point in this relation occurs much earlier, perhaps after day 3. *The sponsor will need to be clear in labeling and promotional materials that the drug is not indicated for conversion of AF when symptom duration is > 7 days; perhaps the cut-point should be even less than 7 days.*

Race: Given the limited size of the non-white subgroups, it is clear that efficacy in non-whites has not been characterized.

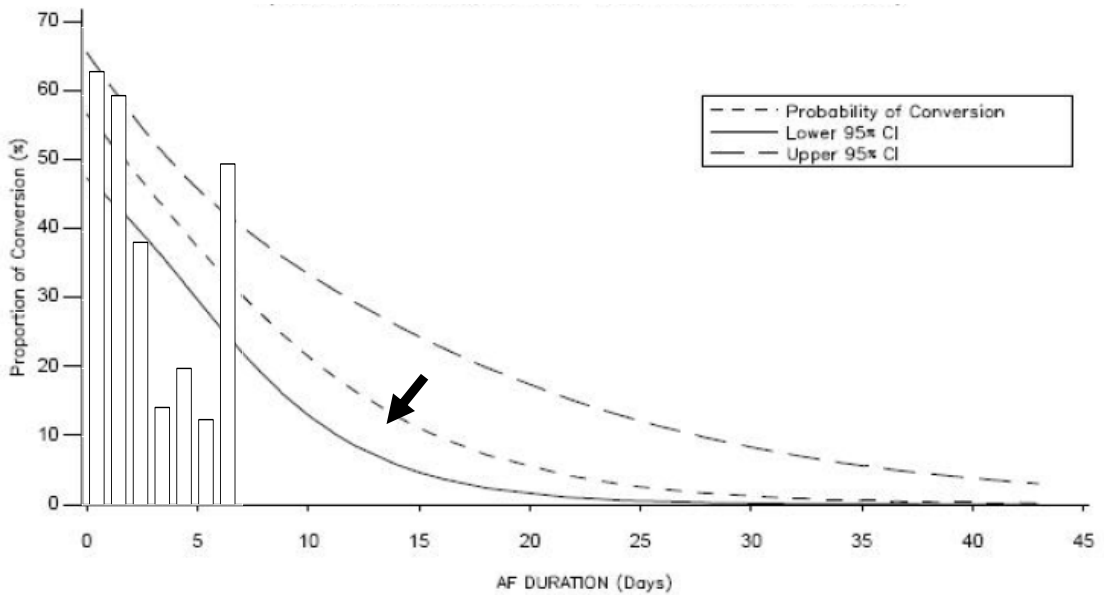
Subgroups by Subject Weight: Based on early pharmacokinetic studies, the sponsor adopted weight-adjusted dosing (mg/kg basis) for vernakalant. In retrospect, it is important to attempt to determine whether that approach was correct. In particular, it is possible that low-weight subjects, having received lower absolute doses of vernakalant, did not receive the same benefit as higher-weight subjects. My analysis shows that rates of AF conversion were consistent across weight quintiles, and this was true in both ACT I and ACT III (Table 3). The similarity in conversion rates across weight quintiles provides a measure of assurance regarding the appropriateness of the weight-adjusted dosing paradigm.

A closely related analysis that merits consideration is a breakdown of conversion rates by absolute dose received, again divided in quantiles. Although such an analysis seems intuitively reasonable, it must be borne in mind that this was essentially a titrated therapy, in that subjects who failed to respond to 3 mg/kg received an additional 2 mg/kg. Given that subjects who received a total dose of 5 mg/kg were less likely to experience pharmacological cardioversion, an analysis of conversion based on absolute dose received is confounded and not of value.

Left Atrial Size: Left atrial size bears relation to the severity and chronicity of structural heart disease, and is a determinant of success in cardioversion of AF. Left atrial size, as determined echocardiographically, was recorded for 34 subjects in ACT III, of whom 21 were randomized to vernakalant. This reviewer calculated a median left atrial size of 40.5 mm. Although subjects with a recorded left atrial size comprised a small subgroup, the conversion rates were similar in subjects with larger and smaller left atrial sizes.

Concomitant Medications: Conversion rates were relatively consistent for different categories of concomitant medications, with Class I antiarrhythmics and digoxin the possible exceptions. Of note, the use of these drugs may be associated with greater chronicity of AF, which may explain the apparent lower rates of AF conversion in these subsets.

Figure 1: Sponsor's Logistic Regression Analysis of Vernakalant-Induced Conversion of AF Versus Duration of AF Symptoms; 2° Reviewer's Analysis Superimposed



Background Cardiovascular Disease: More than half of the subjects reported preexisiting hypertension; congestive heart failure and mitral value disease were less common. Across both studies, rates of conversion in subjects with CHF were somewhat lower than for the population as a whole. Such patients generally have more significant abnormalities of cardiac structure and function, and lower rates of conversion are not surprising. Nevertheless, it would have been desirable to have better characterized efficacy and safety in the CHF patient population.

Sensitivity Analyses on the Primary Endpoint

Persistence of Conversion: The 1° endpoint was defined as conversion to sinus rhythm for 60 seconds, within the first 90 minutes after initiation of infusion of the test agent. Certainly, the 60-second criterion is arbitrary, and could be debated. Persistence of sinus rhythm was a major concern of the 1° Medical Officer in her Clinical Review. In particular, she was concerned about subjects who might convert to sinus rhythm, revert to AF, and receive other modalities (shocks or drugs) for a second termination of AF.

This reviewer examined all of the records in the holter and ECG databases (*ho.xpt* and *eg.xpt*, respectively) in ACT I and ACT III for evidence of AF or sinus rhythm. For example, records such as "sinus rhythm," "atrial fibrillation," and "atrial flutter" had clear meaning. In addition, a considerable fraction of records provided clues to the underlying rhythm: records indicating premature atrial contractions, wandering atrial pacemaker, sinus tachycardia, sinus bradycardia, sinus arrhythmia, and first degree AV block were all interpreted as having a sinus mechanism. All records were individually coded by this reviewer as sinus rhythm, AF, or uninformative. The timing of each record was aligned with data indicating time of initiation of drug and time of conversion to sinus rhythm. In ACT I, only 5 subjects were found to have reverted to AF: 1 subject at 24 hours, and 4 subjects at the 1 week follow-up. Reversion to AF was similarly

infrequent in ACT III. *Thus irrespective of the required time of persistence of sinus rhythm after conversion from AF, the results would have been essentially the same.*

Time Allowed for Conversion: Conversion to sinus rhythm had to occur within 90 minutes to be considered a treatment success. In ACT I, 51.7% of vernakalant-treated subjects in the "short-duration" group converted to sinus rhythm within 90 minutes. The percentages of subjects converting within 30 and 60 minutes were 39.3% and 46.9%, respectively. In ACT III, the percentages of vernakalant-treated subjects in the "short-duration" group converting at 30, 60, and 90 minutes were 43.0%, 47.7%, and 52.3%, respectively. Thus, in the early time period after vernakalant administration, progressively more subjects convert with time, but the selection of a 90-minute endpoint was not critical to the success of the study.

Secondary Endpoints: (as reported by the statistical reviewer):

ACT I
- Time to conversion in "short-duration" AF: $p < 0.0001$
- Time to conversion in overall population ("long-" and "short-duration" AF): $p < 0.0001$.
- For the overall ACT I population, rates of conversion were 3/115 for placebo, 80/221 for vernakalant, 2.6% versus 36.2%, respectively; $p < 0.0001$
- Time to conversion in subjects with "long-duration" AF was not statistically significant, thus the final 2° endpoint was not examined.

ACT III
- Time to conversion in "short-duration" AF: $p < 0.0001$
- For the overall ACT III population, rates of conversion of AF were 5/121 for placebo, 47/119 for vernakalant, 3.3% versus 39.5%, respectively; $p < 0.0001$
- *Proportion of subjects with "short-duration" AF or AFL who had conversion; $p < 0.0001$*
- *Proportion of subjects with AF or AFL (overall population) who had conversion ($\geq$ 1 minute, within 90 minutes); $p < 0.0001$*
- There was no statistically significant difference in the proportion of subjects with "long-duration" AF (>7 and $\leq$ 45 days) who had conversion; therefore, no additional secondary analyses were conducted.

Reviewer's Comment: The highly statistically significant results in the secondary endpoints of ACT III relating to AFL (bullets 3 and 4) have no meaning, as they were driven entirely by subjects with AF. Overall, less than 10% of ACT III subjects had AFL, and results in the AFL subgroup were entirely negative. It is important that results for AF and AFL not be combined for use in promotional materials. The labeling should provide clear information on vernakalant's lack of efficacy in patients with AFL (see also the description of the results of Scene 2, below).

6.1.3. Other Efficacy Studies

- CRAFT was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study of vernakalant in subjects with recent onset AF (3 - 72 hours). Subjects were randomized in a 1:1:1 ratio to receive placebo or one of two doses of vernakalant: 0.5 mg/kg followed by 1.0 mg/kg (0.5+1 mg/kg group) or 2.0 mg/kg followed by 3.0 mg/kg (2+3 mg/kg group). Each dose was administered by 10-minute infusion followed by a 30-minute observation period. The second dose was administered only if AF persisted. The primary endpoint was termination of atrial fibrillation within 30 minutes of the end of infusion. Sixty-five (65)

subjects were randomized from sites in the U.S. and Canada. Nine subjects were randomized but not treated for a variety of reasons, (spontaneous conversion to sinus rhythm, protocol deviations, etc.) One subject was treated but found, in retrospect, to be in sinus rhythm at baseline. Overall, 55 subjects were included in the analysis of efficacy. Rates of conversion were 61.1%, 11.1%, and 5.3% for the 2+3 mg/kg group, 0.5+1 mg/kg group, and placebo groups, respectively.

  - The utility of CRAFT was in demonstrating, fairly convincingly, that a vernakalant dose lower than the 3 + 2 mg/kg used in the Phase 3 studies (i.e., 0.5 + 1 mg/kg) had minimal activity for the termination of AF.

- Scene 2 was the study of vernakalant for conversion of AFL. Only 1 of 39 subjects randomized to vernakalant converted to sinus rhythm. The study has important utility in demonstrating a lack of efficacy of vernakalant in AFL. This has importance because there is overlap between the AF and AFL patient populations, and because medications approved for one indication may be used off-label for the other.

Reviewer's Comment: In the opinion of the 2° reviewer, these strongly negative data support the message that vernakalant should not be used for the treatment of AFL. This should be clearly communicated in labeling.

- ACT II (Atrial Fibrillation Post Cardiac Surgery) was conducted in subjects who developed sustained AF (3 to 72 hours duration) between 24 hours and 7 days following coronary artery bypass surgery and/or cardiac valve surgery. Subjects had to be hemodynamically stable, with pre-operative QTcB $\leq$ 0.46 seconds, post-operative QRS duration $\leq$ 0.14 seconds, and post-operative uncorrected QT interval $\leq$ 0.50 seconds. Use of antiarrhythmic medications was not permitted. Most of the subjects underwent coronary artery bypass surgery. Forty-seven (47) of 100 subjects in the vernakalant group (47%) converted to sinus rhythm, compared to 7/50 (14%) in the placebo group.

- ACT IV was an uncontrolled safety study designed to provide additional safety information on the 3 mg/kg + 2 mg/kg dose regimen of vernakalant injection in patients with AF. Subjects had AF >3 hours to ≤ 45 days duration. The rate of conversion was assessed in this safety study. The 1° efficacy endpoint was the proportion of patients with "short-duration" atrial fibrillation (>3 hours to ≤ 7 days) who experienced conversion to sinus rhythm within 90 minutes of initial exposure to study agent. A total of 167 of 236 enrolled patients had "short-duration" AF, of whom 85 (51%) had treatment-induced conversion to sinus rhythm.

6.2 Safety

6.2.1. General Safety Considerations

Strategy

This analysis is based on examination and integration of data from the SAS transport files for adverse events, vital signs, holter data, and ECGs, as well as the SAS transport files containing information on subject demographics, background diseases, concomitant medications, dosing, and time of conversion. Data submitted in the 120-day safety update were included in the

analyses. Each adverse event record was considered and classified based on its reported term and coded dictionary-derived term in the *ae.xpt* datasets.

Exposure

In total, 778 subjects were exposed to vernakalant in this development program (Table 4). The treated population is reasonably representative of the disease: approximately 2/3 of the subjects were male, and approximately half were over 65 years old with 20% ≥ 75 years of age. (Recent ACC/AHA/ESC Guidelines state that the median age of patients with AF is 75, with men and women equally affected.[3]) The vast majority of subjects who received vernakalant received weight-adjusted doses in a range that is relevant to the proposed use: 94% of subjects received ≥ 3 mg/kg, and 62% received 5 mg/kg. Two-thirds of subjects received 2 doses. In absolute terms, 722 subjects received vernakalant doses of ≥ 3 mg/kg; 480 subjects received doses of 5 mg/kg. To put these numbers into perspective, for drugs used for *chronic treatment* of non-life-threatening conditions, the International Conference on Harmonization E1 guideline recommends exposure of 1500 subjects to support marketing authorization. According to the package insert for ibutilide, an intravenous antiarrhythmic agent approved for conversion of AF or AFL to sinus rhythm, the pre-approval safety database included 586 ibutilide-exposed subjects. When considered in these terms, the overall number of subjects exposed to clinically relevant doses of vernakalant seems marginal but sufficient. Also of note, the Office agreed in the End of Phase 2 Meeting (4/30/2003) that exposure of 648 subjects to the IV formulation of vernakalant would be sufficient.

The weaknesses of the safety database are: very few of the subjects were non-Caucasian, and there was limited exposure in subjects with congestive heart failure. This is unfortunate, because heart failure is common in patients with AF, and places patients at higher risk of adverse events.

[3]Fuster V., et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation) *J Am Coll Cardiol*. 2006;48:854-906

Table 4: Exposure to Vernakalant

	vernakalant		placebo	
	N	%	N	%
Total	**778**	100.0%	**339**	100.0%
Sex				
Male	538	69.2%	231	68.1%
Female	240	30.8%	108	31.9%
Age category				
< 65	412	53.0%	181	53.4%
65 - 74	210	27.0%	102	30.1%
>= 75	156	20.1%	56	16.5%
Race				
White	743	95.5%	330	97.3%
Non-white	35	4.5%	9	2.7%
Dose (mg/kg)				
<3	50	6.5%		0.0%
3 to <5	242	31.3%		0.0%
5	480	62.2%		0.0%
Doses				
1	258	33.2%	12	3.5%
2	520	66.8%	327	96.5%
Site location				
US	126	16.2%	60	17.7%
non-US	652	83.8%	279	82.3%
Comorbidities				
ischemic heart disease	16	2.1%	17	5.0%
CHF	28	3.6%	26	7.7%
hypertension	64	8.2%	53	15.6%
CYP2D6	58	7.5%	32	9.4%
Concomitant Medication Use				
Sotalol	42	5.4%	27	8.0%
Class I antiarrhythmics	38	4.9%	15	4.4%
Class III antiarrhythmics	29	3.7%	24	7.1%
calcium channel blockers	87	11.2%	65	19.2%
beta-blockers	248	31.9%	173	51.0%
digoxin	93	12.0%	67	19.8%

6.2.2. Safety findings from submitted clinical trials

Deaths

There were 4 deaths in the development program, and all occurred in subjects exposed to vernakalant. Three of the 4 deaths occurred in the period 4 to 25 days after vernakalant exposure. They were considered unlikely or very unlikely to have been related to vernakalant by the 1° clinical reviewer, and this 2° reviewer agrees with that assessment.

The single early death was recorded at 48 minutes, and considered by the 1° clinical reviewer as “very likely” related to vernakalant. Again, this 2° reviewer agrees with that assessment. Based on my review of the available records, the subject was a 64 year-old male with baseline congestive heart failure and hypertension. An echocardiogram performed 10 days prior to

enrollment (results entered on case report form, report provided) showed aortic stenosis, and a dilated left ventricle with reduced ejection fraction (40%). By Doppler, the estimated left ventricular outflow tract velocity was ≥ 6 m/sec, corresponding to an aortic valve gradient of 120 mmHg. These findings are consistent with *critical* aortic stenosis. The subject presented to the hospital in AF or AFL. Palpitations and "chest tightness/chest pain" were checked on the case report form as symptoms. (The investigator acknowledged a history of aortic stenosis on the case report form.) The left atrial and left ventricular dimensions were also entered, strongly suggesting that the investigator had access or knowledge of the actual echo report indicating the presence of critical aortic stenosis. On examination, the subject was somewhat hypotensive, with blood pressures as low as 97/59 mmHg recorded at screening, and had a murmur of aortic stenosis. Following vernakalant infusion, the subject did not convert to sinus rhythm but became severely hypotensive, with a nadir blood pressure of 62/42 mmHg recorded at 15 minutes. He required resuscitation with both crystalloids and colloids. After his blood pressure recovered, the second dose of vernakalant was administered. He redeveloped severe hypotension, and ventricular tachycardia soon ensued. DC cardioversion was performed. The subject responded with an organized rhythm, but was pulseless (electromechanical dissociation) and expired. Autopsy revealed marked left ventricular hypertrophy (heart mass 560 g), and severe aortic stenosis.

Reviewer's Comments: Patients with AF and a rapid ventricular response, who are hemodynamically unstable, with hypotension and/or myocardial ischemia, should undergo urgent DC cardioversion. Patients with critical aortic stenosis are particularly vulnerable to hypotension, because coronary autoregulatory mechanisms may be exhausted, and decreases in systemic arterial pressure may directly diminish myocardial perfusion. This subject had an echocardiogram 10 days prior to study entry that was consistent with critical aortic stenosis. Of course in retrospect, this patient should have received DC cardioversion, and should have been excluded from study entry, on the basis of a "…medical condition that, in the judgment of the clinical investigator, might have warranted exclusion or have been contraindicated for safety reasons." Moreover, in light of the hypotension that ensued after the first dose, hypotension so severe that it required fluid and colloid resuscitation, the second dose of the investigational drug should have been withheld in favor of DC cardioversion.

The events in this subject merit consideration for a warning in labeling, although the importance of immediate termination of AF in hemodynamically compromised high risk patients seems more a matter of sound clinical judgment than an issue for labeling. However, because vernakalant may lower systemic blood pressure, it represents a particular risk for patients with hemodynamically significant aortic stenosis.

Dropouts

Dropouts are not an issue for what is essentially a one-time therapy in a development program where the critical monitoring is carried out through only 24 hours. More relevant to the drug's safety and tolerability are discontinuations, considered below.

Discontinuations

Overall, there were 21 discontinuations in vernakalant-treated subjects (3.3%), versus 1 discontinuation in placebo subjects (0.3%). Important adverse events recorded in association with discontinuation included hypotension (6, 0.9%), bradycardia (3, 0.5%), tachycardia (1, 0.2%), and complete AV block (1, 0.2%). These events are discussed in more detail, below.

Serious Adverse Events

The serious adverse events most strongly associated with vernakalant were bradycardia, hypotension, AV block, and sinus arrest (Table 5). All represent derangements in hemodynamics, cardiac rhythm, or conduction, and are discussed separately, below. Of note, the 1° clinical reviewer provided tabulations of serious adverse events between 0 and 2 hours post-test agent, and 2-24 hours post-test agent. The tabulation between 0 and 2 hours captures adverse events related to Vernakalant, but underestimates events related to DC cardioversion, because the protocol directed that cardioversion not be attempted before 2 hours. Since the vast majority of subjects who failed to convert after infusion of the test drug underwent DC cardioversion within 24 hours, the table of serious adverse events capturing 0-24 hours provides a more realistic comparison of serious adverse event rates between vernakalant and placebo.

Table 5: Serious Adverse Events

	Vernakalant	Placebo
	N	N
N, %	**770**	**339**
arrhythmia	44 (5.7)	27 (8.0)
supraventricular	36 (4.7)	23 (6.8)
atrial fibrillation	29 (3.8)	20 (5.9)
bradycardia	9 (1.2)	2 (0.6)
atrial flutter	8 (1)	3 (0.9)
arrhythmia ventricular	5 (0.6)	4 (1.2)
ventricular tachycardia	2 (0.3)	3 (0.9)
torsade de pointes	2 (0.3)	1 (0.3)
ventricular fibrillation	2 (0.3)	0 (0)
tachycardia	4 (0.5)	3 (0.9)
conduction disturbance	3 (0.4)	0 (0)
AV block	3 (0.4)	0 (0)
sinus arrest, pause	2 (0.3)	0 (0)
hypotension	10 (1.3)	2 (0.6)
congestive heart failure	5 (0.6)	1 (0.3)
infection	7 (0.9)	6 (1.8)
bleeding, bruising	5 (0.7)	1 (0.3)
pneumonia	4 (0.5)	1 (0.3)
dyspnea	3 (0.4)	0 (0)
cerebrovascular accident	3 (0.4)	4 (1.2)
gastrointestinal bleed	3 (0.4)	0 (0)
pleural effusion, pleuritis	2 (0.2)	0 (0)

Severe Adverse Events

Severe adverse events were analyzed through 48 hours after administration of the test agent. The severe adverse events most strongly associated with vernakalant were arrhythmia, hypotension, AF, bradycardia, and headache (Table 6). These are largely consistent with the serious adverse events in , and will be discussed below.

Table 6: Severe Adverse Events

	Vernakalant	Placebo
N, (%)	**770**	**339**
arrhythmia	14 (1.8)	2 (0.6)
hypotension	11 (1.4)	2 (0.6)
arrhythmia, supraventricular	10 (1.3)	1 (0.3)
atrial fibrillation	7 (0.9)	1 (0.3)
bradycardia	7 (0.9)	0 (0)
headache	3 (0.4)	0 (0)
arrhythmia ventricular	2 (0.3)	1 (0.3)
weakness, fatigue	2 (0.3)	0 (0)
pain in extremities	2 (0.3)	0 (0)

Common Adverse Events

Common adverse events (i.e., *all* adverse events, including serious and severe adverse events) were analyzed through 48 hours after administration of the test agent; frequencies (% of subjects with an event) are shown in Table 7. Events are tabulated by treatment group, in order of decreasing frequency in the vernakalant group. The difference in frequencies between vernakalant- and placebo-treated subjects is shown at right in the “delta”

Table 7: Common Adverse Events

	Placebo	Vernakalant	Vernakalant, Total Dose Quintile						
			lowest	lower	mid	higher	highest		
N	339	770	159	149	163	144	154		dose
	%	%	%	%	%	%	%	delta	response
dysgeusia	2.4	21.0	27	38	31	29	37	**18.6**	**1.1**
sneezing	0	13.8	10	17	33	18	28	**13.8**	**3.7**
arrhythmia	9.4	13.8	23	27	27	17	12	**4.4**	-3.2
paresthesia, hypoaesthesia	1.5	12.2	15	18	22	16	23	**10.7**	**1.4**
arrhythmia, supraventricular	8	11.7	18	22	22	17	11	**3.7**	-1.9
nausea, vomiting	1.8	7.7	11	13	19	10	6	**5.9**	-1.3
hypotension	3.8	6.8	7	13	13	8	11	**3**	0.3
atrial fibrillation	5	6.2	6	10	12	12	8	1.2	**0.6**
headache	3.2	5.5	6	9	7	10	10	**2.3**	**0.9**
infusion site pain, burning, paresthesia	0.6	5.3	10	10	7	6	8	**4.7**	-0.8
bradycardia	4.1	5.1	6	16	7	6	4	1	-1.4
dizziness	2.1	4.7	6	10	7	6	7	**2.6**	-0.2
weakness, fatigue, somnolence	2.9	4.3	3	12	6	4	8	1.4	0.2
pruritus	0	4.2	2	1	8	7	14	**4.2**	**3**
sweating	0.9	4.2	3	9	8	5	7	**3.3**	0.4
cough	1.5	4.2	7	10	9	3	3	**2.7**	-1.5
feeling hot, burning sensation	0.6	3.6	3	6	6	6	7	**3**	**0.8**
dyspnea	0.6	3	3	7	5	2	6	**2.4**	0.1
atrial flutter	0.3	2.2	4	2	7	3	1	1.9	-0.5
arrhythmia, ventricular	2.9	2.2	5	4	5	1	2	-0.7	-0.9
nasal itching	0	1.9	1	2	4	4	4	1.9	**0.8**
infection	1.2	1.9	4	2	2	5	2	0.7	-0.1
URI, nasal congestion, rhinitis, sore throa	0.3	1.9	4	4	2	2	3	1.6	-0.4
chest pain, unknown cause or non-cardia	1.5	1.8	2	2	3	3	4	0.3	0.5
diarrhea, gastroenteritis	0.9	1.7	4	3	4	2	0	0.8	-0.9
burn, thoracic pain related to cardioversio	2.7	1.4	2	0	2	3	4	**-1.3**	**0.7**
hypertension	0.3	1.4	0	3	2	3	3	1.1	**0.6**
flushing	1.5	1.4	1	2	3	1	4	-0.1	0.5
conduction disturbance	0.3	1.4	2	2	4	3	0	1.1	-0.3
atrioventricular block	0.3	1.4	2	2	4	3	0	1.1	-0.3
bleeding, bruising	0.3	1.4	5	3	1	1	1	1.1	-1
ocular, visual	0.6	1.3	1	1	1	2	5	0.7	**0.9**
tachycardia	3.5	1.3	0	5	2	1	2	**-2.2**	0
premature ventricular contractions	0.9	1.3	4	1	3	1	1	0.4	-0.6
back pain	0.3	1.2	3	1	1	1	3	0.9	0
dry mouth	0	1	1	2	1	1	3	1	0.3
pain in extremities	0.3	1	1	3	1	0	3	0.7	0.1
hypokalemia	1.8	1	2	2	0	3	1	-0.8	-0.1

column (i.e., placebo-subtracted differences). Deltas greater than +2% or <-1% are shown in bold font.

Subjects who received vernakalant were subgrouped by total (non-weight-adjusted) vernakalant dose quintile, to examine the relations between each adverse event and dose, i.e., dose-response. The strength of the dose-response is calculated for each event in arbitrary units (rightmost column,), and events with stronger dose-responses are shown in bold font.

Events where the difference in frequencies between vernakalant- and placebo-treated subjects exceeded 4% include dysgeusia, sneezing, arrhythmia, paresthesia/ hypoesthesia, nausea and vomiting, and pruritus. Adverse events that appear to show a dose-response for vernakalant are sneezing, pruritus, and, to a lesser extent, paresthesia/ hypoesthesia.

Adverse events reported more commonly in subjects who received placebo are tachycardia, chest-wall complications related to cardioversion (burns and thoracic pain), and ventricular arrhythmias. Interestingly, ventricular arrhythmias show a negative dose-response in vernakalant–treated subjects (fewer ventricular arrhythmias with higher vernakalant doses). Also of note, the frequency of chest-wall complications of DC cardioversion was 2.7% for subjects in the placebo group. For the subjects who received vernakalant, approximately half of whom were successfully converted to sinus rhythm, the frequency of chest-wall complications was 1.4%: approximately half of the frequency in subjects who received placebo.

6.2.3 Safety Update

All data from the 120-Day Safety Update were included in these analyses.

6.2.4. Special Safety Concerns

6.2.4.1. Bradycardia

Bradycardia was reported as an adverse event in 5.1% of subjects who received vernakalant and 4.1% of subjects who received placebo. The bradycardia was considered severe in 0.9% of subjects who received vernakalant and none of the control subjects. Bradycardia was reported as a serious adverse event in 1.2% and 0.6% of subjects who received vernakalant and placebo, respectively.

6.2.4.2. QRS Prolongation

In the sponsor's analysis of all phase 2 and 3 controlled studies studies, 4.8% of vernakalant-treated subjects with normal baseline QRS duration developed new-onset QRS prolongation (>140 msec) at any point post-dosing. New-onset QRS prolongation was not observed in any of the placebo subjects at any time point post-dosing. The peak time of QRS prolongation was 15 minutes post-initiation of vernakalant infusion, with 3.8% of subjects affected. By minute 40, approximately half of these subjects had normalization of the QRS interval.

Baseline mean QRS duration was 96.3±15.67 in subjects in the placebo groups and 96.6±15.55 msec subjects who received vernakalant. The QRS duration was essentially unchanged in the placebo group from baseline through hour 8. In vernakalant-treated subjects, the QRS duration increased to a peak mean of 104 msec with each infusion. The maximum placebo-subtracted changes were 7.6 msec and 6.9 msec.

6.2.4.3. QT Prolongation

Evaluation of the QT interval is quite complex in patients with AF.[4] Patients have variable R-R intervals, and many have rapid heart rates. In these studies, analyses of QT are further complicated by the cardioversion itself. Although analysis of QT intervals in these studies is not straightforward, the "noise" is counterbalanced somewhat by the relatively large numbers of subjects, and valid comparisons can be made between subjects who received vernakalant and those who received saline. For all the controlled studies (CRAFT, ACT I, SCENE II, and ACT III), a 12-lead ECG was recorded every 5 minutes from the start of test drug infusion through minute 50, then at Minute 90 and at Hours 2, 4, 8, and 24.

[4] Larroude CE, et. al. Beat-to-beat QT dynamics in paroxysmal atrial fibrillation. Heart Rhythm 3:660-4, 2006.

According to the sponsor's analyses, the mean baseline QT interval using Fridericia's correction (QTcF) was 416.4 ± 28.8 msec in subjects who received placebo and 411.0 ± 27.4 msec in subjects who received vernakalant. Following administration of vernakalant, the QTcF interval increased, with the peak effect observed near the end of the first infusion. Placebo-subtracted QTcF increases were 22.6 msec and 20.1 msec at 10 and 15 minutes, respectively, and 19.1 msec at 35 minutes. At 90 minutes, the mean QTcF was 417.4 ± 31.9 msec in the placebo group and 421.1 ± 30.0 msec in the vernakalant injection group. Following injection of 3.0 plus 2.0 mg/kg vernakalant, QTcF is predicted to return to normal within 12 hours in CYP2D6 extensive metabolizers, and within 24 hours in CYP2D6 poor metabolizers. After administration of the 3.0 + 2.0 mg/kg vernakalant infusions, the population mean QT prolongation is predicted to return below 10 msec within 2 hours after vernakalant dosing for extensive CYP2D6 metabolizers and within 8 hours for poor CYP2D6 metabolizers. After a single dose (3.0 mg/kg), the respective times for extensive and poor metabolizers are 1 and 2 hours. The clinical pharmacology reviewer opined that ECG monitoring should be continued for at least 6 hours post-dose until the QTc is within normal limits for CYP2D6 extensive metabolizers, and 12 hours for CYP2D6 poor metabolizers receiving 3 mg/kg.

Table 8: % of Subjects with ↑QT Interval by Method of Correction, Time, and Treatment

% of Subjects Developing Prolonged QT at Any Time

correction method		threshold (msec)	>450	>480	>500
uncorrected		placebo	32.9	11.1	5.5
		vernakalant	36.3	13.2	5.7
Bazett		placebo	87.4	53.7	34.4
		vernakalant	87.7	64.7	46.9
Fridericia		placebo	42.2	12.1	4.6
		vernakalant	64.3	27.7	11.3

% of Subjects Developing Prolonged QT at T=15 Minutes

		threshold (msec)	>450	>480	>500
uncorrected		placebo	1.6	0.4	0.4
		vernakalant	6.3	2.0	0.7
Bazett		placebo	19.3	8.4	8.0
		vernakalant	43.8	27.3	15.6
Fridericia		placebo	6.2	1.7	1.3
		vernakalant	26.7	7.6	3.2

Table 8 shows results of categorical analyses as percentages of subjects in vernakalant (N=413) and placebo (N=266) groups who developed QT prolongation. The table shows analyses using 3 different cut-offs (450 msec, 480 msec, and 500 msec), with assessments using 3 different methods to correct for heart rate (uncorrected, Bazett's correction, and Fridericia's correction). The left panel shows the percentages of subjects who developed an abnormal QT at any time during the study; the right panel shows the percentages of subjects who developed an abnormal QT at the time of peak drug effect (15 minutes). In this categorical analysis, it is apparent that vernakalant prolongs QT, but the percentages of subjects who develop prolonged QT are sensitive to the cutoff and correction method. Using Fridericia's correction, 7.6% of vernakalant-treated subjects developed QT > 480 msec at the time of peak effect, with 27.7% of subjects developing QT > 480 msec at any time.

6.2.4.4. Atrial Defibrillation Threshold

When a pharmacologic agent fails to restore SR in a patient with AF, it is not unusual to attempt DC cardioversion within a fairly short time-frame. Thus, for pharmacologic agents to be used for conversion of AF to sinus rhythm, it is important to characterize the atrial defibrillation threshold (ADT), if possible, because a given drug may impact the success of subsequent DC cardioversion. A related parameter of importance is the ventricular defibrillation threshold (VDT). A small fraction of patients will develop ventricular tachyarrhythmias and require urgent

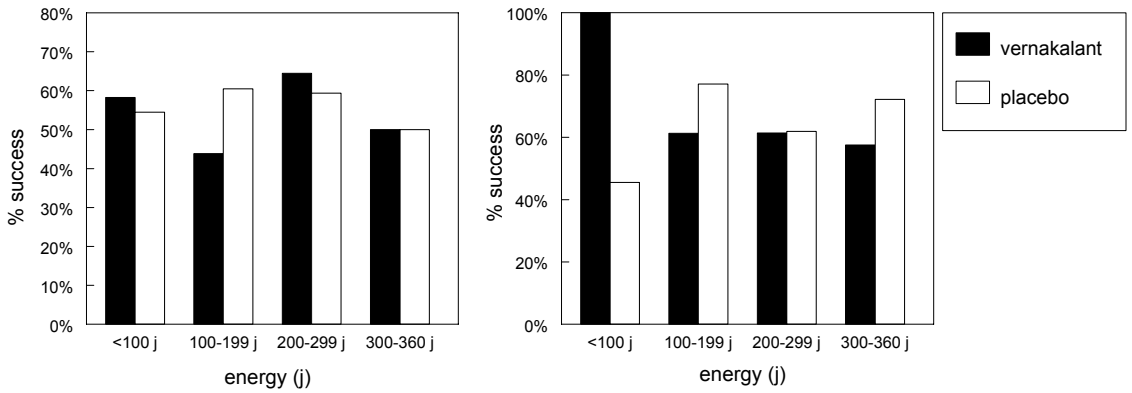
DC cardioversion after receiving a drug for conversion of AF, and the effect of the agent on VDF may be important as well.

Using the *ec.xpt* datasets for ACT I and ACT III, I assessed the success of DC cardioversion by treatment assignment, time, and energy. Briefly, for each shock recorded, the time relative to the start time of test agent infusion was calculated in hours. Recorded shocks were dichotomized by time: shocks recorded within the first 4 hours of the start of test agent infusion (approximately 2 half-lives) were considered separately from those recorded later. The probability of success was calculated for individual energy "bands": 1-99 j, 100-199 j, 200-299 j, and 300-360 j, in essence providing a "dose-response" to shock energy. The probability of success was calculated as:

successful shocks ÷ total shocks X 100%

Note that many subjects were not considered at all in this analysis, (i.e., subjects who did not receive attempts at DC cardioversion); other subjects were counted more than once, based on the number of times DC cardioversion was attempted. Data from ACT I and ACT III were considered together.

Figure 2: Success of DC Cardioversion by Treatment, Time, and Energy, ACT I and ACT III



Of note, the overall "dose-response" appears "flat" for both time periods (i.e., higher energies do not appear to be associated with higher success rates of cardioversion). In terms of the effect of vernakalant on ADT, there is no apparent difference between success rates in subjects who received vernakalant (filled bars) versus placebo (open bars), and no apparent differences in success rates when shocks were delivered before, versus after, 4 hours. This analysis does not suggest that vernakalant has an important effect on ADT.

6.2.4.5. Ventricular Fibrillation; Torsades de pointes

In light of the electrophysiological properties of vernakalant, ventricular fibrillation and torsade de pointes are important safety concerns. There were two subjects with reported ventricular fibrillation, both within 2 hours of initiation of vernakalant infusion. One episode was reported in the subject with aortic stenosis who died (see Deaths, page 21), and the other was reported in a

24 year-old female who developed ventricular fibrillation immediately after DC cardioversion. The investigator implicated defibrillator lead failure, leading to delivery of a non-synchronized shock as the inciting factor in the latter subject.

Torsades de pointes was reported in 4 subjects: with 3 reports in subjects who had received vernakalant, and 1 in a placebo subject. Torsades was unlikely vernakalant-related in two of the subjects: one episode occurred 32 hours post-dosing, and the other on day 17. The third subject developed torsades 2 hours and 20 minutes after initiation of vernakalant infusion, but soon after an infusion of ibutilide. This event was confounded, because ibutilide may have been contributory.

In summary, ventricular fibrillation and torsades de pointes remain concerns with this drug. The sponsor's proposed labeling describes these event in the adverse reactions section of the label, but a warning could be considered, in part because the QT effects of the drug provide plausibility.

6.2.4.6. Ventricular Defibrillation Threshold

The pharmacology-toxicology reviewer raised the lack of evaluation of the ventricular defibrillation threshold (VDT) as an important issue. This parameter cannot be assessed in clinical trials, because ventricular fibrillation is a dire medical emergency, requiring immediate DC cardioversion for survival. The parameter can be assessed in non-clinical studies, and such a study(s) might be considered as a postmarketing commitment.

6.2.4.7. Seizures

Seizures were identified as a particular risk on the basis of the non-clinical studies. Two seizures occurred in this development program, one each in the vernakalant and placebo groups. The seizure in the vernakalant-treated subject occurred 4 hours and 20 minutes after completion of the second vernakalant infusion. Considering the temporal relation between the occurrence of seizures and infusion of the drug substance in animals (i.e., occurring within minutes of administration; resolving rapidly following completion of infusion), the evidence of causality here is not strong.

6.2.5. Discussion of primary reviewer's comments and conclusions

The 1° Clinical Reviewer has a number of important concerns that merit discussion:

a. Maintenance of sinus rhythm following pharmacologic conversion: The 1° clinical reviewer expressed important concerns that the pivotal studies "…were not designed to show whether sinus rhythm would be maintained beyond the one-minute primary time-point." She was concerned that some subjects may have reverted to AF, requiring other antiarrhythmic drugs.

In my analyses of ACT I and ACT III, I analyzed all records in the ECG and Holter datasets, as well as the records in the DC shock datasets. I found that only a tiny fraction of subjects reverted to AF within 24 hours of successful cardioversion. The introduction of antiarrhythmic therapies to these subjects is expected, as part of a strategy to maintain sinus rhythm. The goal of a pharmacologic therapy for conversion of AF is simply to restore sinus rhythm without the need for DC cardioversion. The maintenance of sinus rhythm requires other therapies. Thus, the data seem reassuring in terms of this concern.

b. Limited effectiveness of the second dose: The 1° clinical reviewer "recommends approving Vernakalant as one dose therapy….," a recommendation based on considerations of both efficacy and safety. In terms of efficacy, she notes: "The conversion rate was higher and more significant on the first dose compared to the second dose. Of the subpopulation that went on to receive a second dose, subjects were four times less likely to convert to SR as did subjects who converted on one dose." She also has legitimate concerns about safety, which appears to be less favorable after 2 doses (versus 1). In terms of safety, she notes: "…two cases of ventricular fibrillation one of which was fatal were observed on two doses of Vernakalant, and there are not enough data to conclude whether these events were a random occurrence, or the fatal case was the result of compromised cardiac hemodynamic status….". The 1° Clinical Reviewer highlighted the differences between subjects receiving 1 and 2 doses by presenting many of her analyses by number of doses received (1 versus 2).

It is important to recognize, however, that the vernakalant dosing strategy is, in essence, a titrated therapy, albeit with only two possible steps: patients who fail to convert to sinus rhythm after a first dose are given a second. Thus, the 2-dose subjects represent a selected population, and comparisons of efficacy and safety between subjects who received 1 and 2 doses of vernakalant are confounded. The characteristics cited by the 1° clinical reviewer that appear to be associated with the subpopulation requiring administration of a second dose appear to be markers of more advanced cardiovascular disease. As such, these subjects are less likely to convert to sinus rhythm and more likely to experience adverse events.[5] Based on this logic, this 2° reviewer does not agree with the reasoning of the 1° reviewer in terms of approval of only a single dose regimen. Moreover, it is reassuring that for important adverse events (hypotension, bradycardia, etc.), my analyses do not suggest a dose-response. On the other hand, the conversion rates after one and two doses are well-characterized, and such information could assist practitioners in making risk-benefit decisions for individual patients; therefore, incorporation in labeling of the disparate conversion rates following one and two doses merits consideration.

One issue that was of particular concern in the development program was the subject who died within an hour of vernakalant administration; this subject received 2 vernakalant doses. My conclusion is that this subject, with critical aortic stenosis, AF, a rapid ventricular response, borderline hypotension, and chest pain, should not have been enrolled in the study. For this reason, this subject carries limited weight in my formulation of risk and benefit. For all patients, the pause between the first and second doses provides an opportunity to monitor patients for safety issues (notably hypotension, bradycardia, QT prolongation, and dysrhythmias), such that a second dose can be appropriately withheld if necessary.

c. Approval of a 2-dose regimen for a restricted population: The 1° clinical reviewer would consider approval of the two-dose regimen "for a population similar to that studied in the program with a contraindication in subjects with recent MI, advanced CHF and obstructive heart disease, with commitment to a post-marketing study in a population representative of the general short-term AFB population including recent MI and CHF. "

[5]As an analogy, consider the use of a loop diuretic in patients with acutely decompensated congestive heart failure. Consider a study wherein one diuretic dose would be administered to all patients, with a second dose administered to patients who respond inadequately to the first. On all likelihood, the need for 2 doses would be associated with worse clinical status, lower efficacy, and more adverse events.

In general, I agree with these recommendations. The drug was not studied in patients with recent myocardial infarction, and it was not well-studied in patients with heart failure. Moreover, subjects with heart failure stand out as a subgroup of subjects that received diminished efficacy. The label should reflect the data and the limitations thereof. The issue of a contraindication merits additional discussion as well.

d. Monitoring: The 1° clinical reviewer recommends that "…subjects who are prescribed Vernakalant should receive it in a highly specialized hospital settings, and be closely monitored for at least one hour after one dose or 90 minutes after the first infusion if they receive two doses."

I agree with these recommendations, but it could be argued that monitoring should be *longer*. The clinical pharmacology reviewer suggested that ECG monitoring should be continued for at least 6 hours post-dose until the QTc is within normal limits for CYP2D6 extensive metabolizers, and 12 hours for CYP2D6 poor metabolizers receiving 3 mg/kg.

In terms of the length of time for monitoring post-vernakalant administration, the crux of the issue is whether QT should fully *normalize* before discontinuation of monitoring, whether monitoring through only the period of peak QT prolongation is sufficient (i.e., if the patient survives this period, they are not likely to develop ventricular arrhythmias), or whether some compromise between the two positions is most reasonable. Importantly, vernakalant concentrations are affected by metabolizer status, and for the near and foreseeable future, physicians will not know if their patient is a poor CYP2D6 metabolizer. Given this, it seems reasonable to base recommendations on monitoring on the QT interval. However, physicians are not particularly adept at monitoring QT interval, and a general time-based recommendation, though somewhat illogical, is probably most practical and appropriate. The recommendation could be written to take QT into consideration when discontinuing monitoring.

7 Advisory Committee Meeting

The Cardiovascular and Renal Products Advisory Committee will be convened on December 11-12, 2007, to consider the usefulness of vernakalant as a pharmacological agent for the termination of AF, and to consider safety issues.

8 Conclusions and Recommendations

8.1 Recommended regulatory action

I recommend approval for vernakalant for the conversion of AF to sinus rhythm. The development program provides persuasive demonstration of efficacy, with results substantiated in two independent trials. For both, the results are consistent across subgroups (patients with congestive heart failure not withstanding), and robust to exploration. In particular, the critical definition of successful conversion of AF to sinus rhythm, requiring demonstration of a sustained sinus rhythm for a mere 60 seconds, was unimportant in the demonstration of efficacy. Had the definition of success required demonstration of sustained sinus rhythm for even as long as 24 hours, the studies would have succeeded overwhelmingly on their primary endpoints. Although there were well-founded concerns regarding subjects who might have experienced loss of benefit, i.e., reverted from sinus rhythm to AF, in whom additional modalities were required for "re-conversion," my analyses show that this did not occur to an important degree.

The sponsor is seeking approval for what is in essence a two-step regimen: patients who fail to respond to an initial infusion of 3 mg/kg should receive a second infusion of 2 mg/kg, after an appropriate delay. The primary clinical reviewer considered the efficacy of a single infusion separately from that of two. Because the added benefit of a second infusion was considerably less than that derived from the first, the reviewer considered the possibility of approving only a single-infusion regimen. I tend to view the two-step regimen as a titrated therapy. As such, we expect that patients who require two infusions rather than one have a greater burden of disease. Their likelihood of achieving sinus rhythm tends to be less, and their probability of experiencing adverse events tends to be greater. Thus, the strategy of providing distinct risk-benefit analyses for one versus two infusions seems inherently confounded. On the other hand, there is the opportunity to observe carefully patients between the first and second infusion, and those who respond adversely to the initial infusion should not receive a second.

Ventricular tachyarrhythmias are the principal safety concern for many antiarrhythmic agents. Vernakalant importantly prolongs the QRS and QT intervals, and there was considerable focus and concern regarding ventricular arrhythmias in the vernakalant dossier. Indeed, ventricular fibrillation and Torsades de pointes were reported in subjects relatively soon after vernakalant infusion. Although both events were confounded, the concern remains, and the risk should be included in labeling. One particularly serious event in the vernakalant development program merits discussion. In my opinion, there is little question that the drug led directly to the death of a patient 48 minutes after treatment; however, in retrospect, I believe that this patient should never have been entered into the study. This was an unstable patient, who, for several reasons, should have undergone immediate DC cardioversion. Moreover, in terms of the risk of dysrhythmias and conduction disturbances, it should be borne in mind that pharmacologic agents used for the conversion of AF are administered by highly trained personnel in a monitored setting. Thus, the ramifications of serious dysrhythmias and conduction abnormalities are somewhat less than for typical drugs used in unmonitored settings.

The weakness of the development program is the paucity of subjects studied with verified congestive heart failure and ischemic heart disease. This may be an artifact, to some extent, in that the case report forms for ACT I did not specifically solicit a history of heart failure, hypertension, etc. In any case, many patients with AF have ischemic heart disease, with or without concomitant left ventricular dysfunction or overt heart failure. To gain a more complete assessment of vernakalant's performance characteristics, additional experience in these critical populations should be gained through a post-marketing study(s).

Only a trivial number of subjects of African ancestry (0.8%) were included in the development program. A statement noting the lack of experience in this patient population would be appropriate for labeling.

The sponsor generated definitive data on vernakalant's lack of efficacy in patients with atrial flutter. The label should provide this definitive assessment, to discourage inappropriate use in this patient population.

The primary endpoint in the pivotal trials was based on patients who had AF symptom onset within 7 days, and the division asked the sponsor to conduct an analysis of likelihood of conversion based on the amount of time in AF. The sponsor provided such an analysis (Figure 1); however, it is somewhat deceptive, as it suggests a linear decrease in success rate with time, through 12 or 13 days. In ACT I, where these data were collected, the efficacy of vernakalant drops off strikingly after only two days. This is an important topic for labeling.

8.2 Safety concerns to be followed postmarketing

There should be particular emphasis on hypotension, severe tachyarrhythmias including ventricular fibrillation and torsades de pointes, and conduction abnormalities. That being said, it will be difficult to gain a better characterization of risk on the basis of spontaneous reporting, in part because many events will be confounded. Nevertheless, it will be possible to compare event rates through datamining, using other relevant antiarrhythmic agents as comparators.

8.3 Risk Minimization Action Plan, if any

None recommended, beyond normal pharmacovigilance.

8.4 Postmarketing studies, voluntary or required

Major issues that should be addressed include the following:

1. In a non-clinical study, the sponsor should determine the effects of vernakalant on ventricular defibrillation threshold. The study should include a concurrent positive control, e.g., lidocaine.

2. The sponsor should determine whether vernakalant is a substrate or inhibitor of P-glycoproteins or any other transporters. P-glycoprotein transport of vernakalant should be characterized *in vitro* using at least two P-glycoprotein inhibitors.

3. Additional experience should be in patients with congestive heart failure and ischemic heart disease.

4. Additional experience in non-whites should be considered.

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Ellis Unger
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MEDICAL OFFICER