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	N22,123
Submission Number	N000
Submission Code	505(b)(1)
Letter Date	18-December-2006
Stamp Date	
PDUFA Goal Date	18-October-2007
Reviewer Name	Mehul Desai, M.D.
Review Completion Date	19-June-2007
Established Name	Tedisamil Sesquifumurate
(Proposed) Trade Name	Pulzium® IV Solution 2 mg/mL
Therapeutic Class	Antiarrhythmic
Applicant	Solvay Pharmaceuticals, Inc.
Priority Designation	Standard
Formulation	IV
Dosing Regimen	0.32 mg/kg females, 0.48 mg/kg males administered as an infusion over 30 minutes
Indication	Conversion of Afib/Aflut to NSR
Intended Population	Recent onset Afib/Aflut

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Abbreviations:

AE = adverse event
Afib = Atrial fibrillation
Afl or Aflut = Atrial flutter
AUC = area under the curve
BBB = Bundle branch block
BP = blood pressure
CA = Carcinoma
CNS = Central Nervous System
CVA = Cerebrovascular accident
DBP = diastolic blood pressure
DHCL = dihydrochloride
ECG = Electrocardiogram
EMD = Electromechanical dissociation
HR = heart rate
ICH = International Conference on Harmonization
MI = Myocardial infarction
N/A = not applicable
NSR = Normal sinus rhythm
PE = Pulmonary embolism
QTcB = Bazett's corrected QT
QTcF = Fridericia's corrected QT
SAE = Serious adverse event
SBP = systolic blood pressure
TEAE = treatment emergent adverse event
TESAE = treatment emergent serious adverse event
V fib = Ventricular fibrillation
WBC = White blood cell

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Executive Summary

1.1 Recommendation on Regulatory Action

Pulzium® (tedisamil sesquifumarate) can be approved for use in patients with recent onset (≤48 hours duration) atrial fibrillation that is either newly diagnosed or paroxysmal. Tedisamil has been shown effective on the basis that it is superior to placebo **and** demonstrates evidence of dose response.

The primary endpoint in the development program was the percentage of subjects that converted to normal sinus rhythm (for at least 60 seconds) at any time within 2.5 hours after the initiation of study drug. While this endpoint is a surrogate (in my opinion), it has been accepted by the Division in the past and has served as the basis of approval of a related drug. Secondary endpoint analyses suggest that the effects of tedisamil seen within the first 2.5 hours post study drug administration are retained at 24 hours (refer to Table 45).

Similar to other approved, Class III antiarrhythmic agents (e.g. ibutilide, dofetilide), tedisamil is proarrhythmic as would be expected based on its pharmacologic activity. While tedisamil does not fill an unmet medical need, it may provide an alternative therapeutic option to patients with a recent onset of atrial fibrillation. Based on the currently available data, it can not be determined whether tedisamil possesses a unique safety or efficacy profile because there are no active control comparisons versus currently available therapy.

The data from the tedisamil development program do not convincingly support the efficacy of this drug in converting subjects with atrial flutter to normal sinus rhythm. The number of subjects with atrial flutter in the development program was quite small. The indication for tedisamil use should be limited to those with recent onset (≤ 48 hours) atrial fibrillation.

The approval of tedisamil should be conditional upon on the use of this compound by health care professionals trained in the identification and treatment of acute ventricular arrhythmias and also in the setting of continuous ECG monitoring. The duration of monitoring should be until the QTcF is within normal limits (e.g. 6 to 8 hours or longer). This proposed duration is longer than the 90-minute monitoring proposed by the sponsor. The sponsor should also consider simplifying the dose and dosing regimen as described in more detail in section 1.3.4 in order to decrease the likelihood of medication administration errors. Alternatively, they should focus on a risk management program that will minimize the likelihood of drug administration errors.

1.2 Recommendation on Postmarketing Actions

Current regulations do not require a sponsor to conduct an active control trial versus currently available therapy particularly if a sponsor has demonstrated superiority relative to placebo. While an active control trial of tedisamil versus ibutilide would certainly be of interest it is not required by current regulations.

As discussed in section 10.1.11, it is also interesting to note that 1031 of the 1297 subjects in the integrated ITT population were "non-converters" within or at 2.5 hours post study drug initiation. Of these 1031 "non-converters", 634 (61.5%) did not subsequently receive treatment with DC cardioversion and/or some other antiarrhythmic therapy within 24 hours of study drug initiation. The vast majority of these subjects remained "non-converters" at 24 hours. This suggests that the study investigators felt no urgency to treat these subjects for their arrhythmia. To me, this suggests that the sponsor should attempt to clarify the consequences of treating versus not treating a recent episode of atrial fibrillation. The sponsor should also try to identify a population of sufficiently high risk where the benefits outweigh the risks of treatment with tedisamil.

1.2.1 Risk Management Activity

The sponsor has proposed a risk management plan for tedisamil. Elements of the risk management plan include tools such as a physician checklist (to ensure that the patient is suitable for treatment with tedisamil), an infusion bag sticker, an arrhythmia diagnostic guide, a dose guide and calculator, a QTc guide/calculator, a health care professional administration and monitoring guide, and a healthcare professional website.

It is important to note that ibutilide, an agent pharmacologically related to tedisamil and also indicated for the conversion of atrial fibrillation/flutter to normal sinus rhythm, is currently available in the U.S. without a risk management plan. Many elements or tools in the sponsor's proposed risk management plan are probably not needed as ibutilide is currently marketed without such a plan. However, if the sponsor and the Office of Surveillance and Epidemiology feel that a risk minimization plan is necessary, such a plan should focus on actions to minimize the likelihood of errors in drug administration (e.g. dose and dosing regimen errors).

1.2.2 Required Phase 4 Commitments N/A

1.2.3 Other Phase 4 Requests N/A

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The tedisamil atrial fibrillation/atrial flutter development program consisted of 9 studies involving an intravenous formulation of which four were labeled as phase 2 studies and five were labeled as phase 3 studies (refer to section 4.2). There were 2 additional studies of tedisamil involving an oral formulation intended for chronic use in patients with atrial fibrillation. The studies involving the oral formulation of tedisamil have not been reviewed in any detail.

The five phase 3 studies (3.112, 3.114, 3.116, 3.117, and 3.118) were designed very similarly (e.g. with respect to primary endpoint, dose and dosing regimen, population enrolled, etc) and thus they are amenable to pooling or an integrated analysis. Throughout this review, reference is made to an integrated review of safety and efficacy. The integrated review of safety pools data from all nine studies (five phase 3 studies and four phase 2 studies) while the integrated review of efficacy pools data from six studies (five phase 3 studies and one phase 2 study). Please refer to section 4.2 for some more details of the studies included in the integrated safety and efficacy analyses.

The study population consisted of subjects with hemodynamically stable atrial fibrillation or flutter. Approximately 47% of subjects presented with a first ever episode of arrhythmia ("new onset") while 53% presented with a recurrent episode ("paroxysmal"). Approximately 48% of subjects had an arrhythmia duration 48 hours or less. The mean pulse (heart rate) at baseline in the tedisamil development program was 98 beats per minute suggesting that most study subjects were not tachycardiac at the time of randomization. (As a side note, in one of the pivotal, dose ranging studies that formed the basis of approval of ibutilide, the mean heart rate at baseline was in the mid to upper 80's). The mean body mass index at baseline was 29 kg/m^2. The exclusion criteria required that if a study subject was on an antiarrhythmic drug prior to randomization he/she must have discontinued it for at least 5 half-lives.

1.3.2 Efficacy

Tedisamil is clearly effective as evidenced by its superiority over placebo and evidence of dose response (refer to section 6.1.4). The primary endpoint in each of the studies in the integrated efficacy analysis was the conversion from atrial fibrillation/atrial flutter to normal sinus rhythm (for at least 60 seconds) as measured by the percentage of subjects converted at any time within 2.5 hours after the start of infusion. This endpoint, in my view, is a surrogate endpoint. The sponsor did obtain agreement from the Division of Cardiovascular and Renal Drugs on this endpoint in a teleconference in January 2002. Assuming that this endpoint is still valid, tedisamil can be approved.

Tedisamil is effective in both men and women. However, tedisamil appears to be relatively less effective in women compared to men when administered the same mg/kg dosing regimen (refer to Figure 5). The rationale for this is not entirely clear. This phenomenon can not be explained by PK differences in the two sexes because when men and women are administered the same mg/kg dosing regimen, population PK analyses suggest that the plasma PK profiles are similar.

Tedisamil appears to be most effective in subjects with a duration $\leq$ 48 hours of their most recent atrial fibrillation episode. The effectiveness of tedisamil is much lower in subjects with a duration of their most recent episode of atrial fibrillation > 48 hours (refer to Table 46). The effectiveness of tedisamil is also much lower in converting subjects with baseline atrial flutter rhythm to normal sinus rhythm (refer to Table 47).

1.3.3 Safety

Tedisamil is proarrhythmic as would be expected from its pharmacologic activity. This feature is not unique to tedisamil but is also present with other Class III antiarrhythmics. It prolongs the corrected QT interval in a dose dependent manner. It also produces a dose-dependent increase in ventricular tachycardia (refer to Table 16). There are several well documented cases of Torsade de Pointes in association with tedisamil use (refer to Table 19). There were also several study subjects who experienced a ventricular arrhythmia that led to syncope and required DC cardioversion (please see narratives in section 7.1.2). Interestingly, tedisamil also appears to decrease heart rate. There was one subject (ID #43001) who experienced profound bradycardia and hypotension within 10 to 15 minutes of starting tedisamil requiring treatment with atropine. A few minutes thereafter, she also experienced a wide QRS arrhythmia and cardiac arrest that required resuscitation and mechanical ventilation. It appears this subject suffered anoxic brain injury as a result of the cardiac arrest and died 3 days after randomization. It appears that this the only case of death in which the pre-mortal events occurred in close temporal proximity to the study drug infusion.

1.3.4 Dosing Regimen and Administration

The sponsor proposes a rather complex dosing regimen (e.g. a sex-specific, weight adjusted, 2-step infusion) and one that could pre-dispose to medical errors.

In the proposed labeling, the sponsor has provided a table of volumes of tedisamil to administer based on a patient's weight and height. The volumes in the table are derived from the formulae in the table below. The table facilitates dose selection for a particular patient and prevents the prescribing physician from having to use a mathematical formula to derive a volume/dose of drug to administer. In my view, the proposed table is the simplest way to summarize dosing information for tedisamil (short of using a mathematical formula) and I do not have objections to using it.

$\leq$ 28 kg/m^2	Dose administered (mg) = actual weight (kg) * dose (mg/kg) Volume administered (mL) = Dose administered (mg) * Tedisamil concentrate (1 mL/2 mg)
> 28 kg/m^2	Dose administered (mg) = imputed weight (kg) * dose (mg/kg) *Imputed Weight (kg) = 28 kg/ m^2 * height^2 (m^2)* Volume administered (mL) is calculated as in the method above

The sponsor proposes a 2-step infusion administered over a 30 minute period. Half, the sex specific, weight adjusted dose would be administered over the first 10 minutes. The remaining half would be administered over the next 20 minutes. This two-step dosing regimen would require a health care provider to not only administer the appropriate sex specific dosing regimen but also to remember to turn down the infusion rate by 50% after 10 minutes. If a health care provider forgets to turn down the rate, a patient would be exposed to much higher plasma levels of tedisamil and the associated dose or concentration related side effects of tedisamil. It may be possible for the sponsor to simplify the dosing regimen and thereby reduce the risk of administration error by administering a "bolus" of study drug to achieve a targeted plasma concentration followed by a continuous infusion to maintain the target plasma concentrations.

I see no clear rationale for a sex specific dosing regimen (particularly when the dose administered is already adjusted for body weight). The potential for medical error could be reduced by having the same weight adjusted (mg/kg) dose administered to men and women. Presumably, the sponsor proposes a lower dose in females because of greater safety concerns in this subgroup. Figure 5 suggests that the incidence of TdP is greater in females compared to males at doses of 0.48 mg/kg and 0.64 mg/kg. However, it should be noted that there were relatively few cases of TdP observed overall and a relatively few female subjects exposed to doses above 0.32 mg/kg making estimates of the incidence of TdP unreliable at those doses. The QT data in Figure 15 suggest that there is very little difference between males and females in the Fridericia corrected QT interval change from baseline at various doses at the time of maximal plasma concentrations. The potential for drug error could be reduced by having a uniform, weight adjusted dose in males and females. Males could still receive clinical benefit of tedisamil by lowering the dose from 0.48 mg/kg to 0.32 mg/kg while lowering their risk of adverse events. If one were able to define a minimal, clinically relevant dose, further optimization of benefit and risk could be achieved with tedisamil.

In summary, in order to reduce the probability of drug administration error, I feel there should be a single dose approved for male and female subjects (e.g. 0.32 mg/kg). Another action that could be taken to reduce the probability of drug administration error would be to administer tedisamil as a slow bolus over 60 seconds to achieve a target concentration of around 880 ng/mL followed by a continuous 30-minute infusion to maintain this plateau plasma concentration. This latter regimen might reduce medical errors compared to a 2-step regimen where a health care provider would have to remember to turn down the infusion rate after 10 minutes.

1.3.5 Drug-Drug Interactions

Tedisamil appears to produce slowing of heart rate. This effect was much more pronounced in subjects who converted compared to those that did not convert. The heart rate slowing caused by tedisamil may be augmented by other drugs that also reduce heart rate (e.g. digoxin or beta-adrenergic blockers). Please refer to section 7.4.2.5. Prescribing physicians should be cautioned about the synergistic heart rate lowering produced by tedisamil and other treatments that decrease heart rate.

1.3.6 Special Populations

The sponsor proposes to contraindicate use of tedisamil in patients with severe renal impairment as defined by a GFR < 30 mL/min. No dose adjustment is proposed by the sponsor in patients with mild to moderate renal impairment. The sponsor's proposal appears reasonable as renal impairment does not markedly affect peak or plateau plasma level of tedisamil. The toxicity of tedisamil appears to be more closely related to plateau plasma level of tedisamil rather than area under the plasma concentration vs time curve. In addition, The QTcF versus time profile in subjects with moderate renal impairment and in subjects with "normal" renal function is shown Figure 16 and Figure 17. The QTcF versus time profiles in the two subpopulations is not too different.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Tedisamil sesquifumarate is a new molecular entity that blocks a variety of potassium (K^+) channels (I_{Kr}, I_{Ks}, I_{Kur}, I_{KACH}, I_{to}, and I_{KATP}) and has Class III anti-arrhythmic properties. The proposed trade name is PULZIUM®. The sponsor plans to supply tedisamil as a sterile intravenous (IV) solution to be administered in a hospital setting. The indication being sought by the sponsor is for the rapid conversion of atrial fibrillation or atrial flutter of recent onset to normal sinus rhythm.

The proposed dose is sex specific: 0.48 mg/kg in males and 0.32 mg/kg in females. The proposed dosing regimen is as an IV infusion administered over 30 minutes with half the dose being administered over the first 10 minutes and the remainder administered over the next 20 minutes. The full 30 minute infusion is to be administered regardless of whether the patient converts to normal sinus rhythm during the infusion.

During the pivotal clinical trials, for subjects who had an ideal body weight (IBW) $\leq$ 28 kg/m^2, the dose administered was calculated based on their actual body weight multiplied by the dose (in mg/kg). In subjects with an IBW > 28 kg/m^2, the body weight used for calculation of dose was the product of 28 kg/m^2 and height^2 (m^2).

2.2 Currently Available Treatment for Indications

Table 1 below is obtained from the 2001 ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. Three drugs from the table below are approved and labeled by the FDA for the acute conversion of atrial fibrillation and include dofetilide, ibutilide, and quinidine. Of the 3 currently approved drugs, 2 are data-driven approvals (ibutilide and dofetilide) while quinidine is a "grandfathered" drug.

Table 1: Drugs effective for cardioversion of atrial fibrillation (ACC/AHA/ESC guidelines)

Drug	Route of administration	Type of recommendation	Level of evidence	FDA approved
Dofetilide	Oral	I	A	Yes
Flecainide	Oral or IV	I	A	No
Ibutilide	IV	I	A	Yes
Propafenone	Oral or IV	I	A	No
Amiodarone	Oral or IV	IIa	A	No
Quinidine	Oral	IIb	B	Yes

Pharmacologic therapy is an alternative to direct current (DC) cardioversion for the conversion of atrial fibrillation to sinus rhythm. There are limited prospective, controlled, clinical trial data directly comparing the relative efficacy and safety of DC cardioversion versus pharmacologic therapy. While it is generally thought that DC cardioversion is more effective than

pharmacologic therapy, it is a relatively more uncomfortable method of cardioversion requiring pre-procedure sedation. In addition, there are other risks to consider such as the possibility of cutaneous burns.

2.3 Availability of Proposed Active Ingredient in the United States

Tedisamil has not been previously marketed in the U.S.

2.4 Important Issues With Pharmacologically Related Products

Other Class III antiarrhythmics that are potassium channel blockers include sotalol, dofetilide, ibutilide and amiodarone. These agents prolong the action potential duration and carry varying degrees of proarrhythmic risk.

2.5 Presubmission Regulatory Activity

Tedisamil was originally developed as an oral anti-anginal agent in patients with coronary artery disease. A complete phase 3 program was completed using the dihydrochloride salt formulation. However, the sponsor never submitted a formal new drug application for review by the FDA. Instead, the sponsor decided to pursue development of tedisamil as an anti-arrhythmic drug for conversion of recent onset atrial fibrillation/flutter to normal sinus rhythm. Meeting minutes from a teleconference between the Division and the Sponsor on January 23, 2002, revealed that the Division "agreed that the sponsor's proposed primary endpoint of conversion into NSR within 2.5 hours after initiating I.V. administration and the secondary endpoint of remaining in NSR at 24 hours or discharge [was] acceptable."

2.6 Other Relevant Background Information N/A

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No chemistry, manufacturing, and/or control issues have been identified as of the time that this review was completed. Please refer to the CMC review as this review will be completed at a later time relative to this review.

3.2 Animal Pharmacology/Toxicology

The pre-clinical data show that tedisamil prolongs the QT interval and is associated with Torsade de Pointes which is expected based its pharmacology. Since tedisamil was originally developed as a chronic therapy for angina, the sponsor has collected much more pre-clinical data than the Division is used to reviewing for a single use application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Information Withheld

Information Withheld

4.2 Tables of Clinical Studies

Table 2 below summarizes the five, phase 3 efficacy studies in the tedisamil IV atrial fibrillation development program. Each of the 5 studies was designed similarly with respect to the population enrolled, primary endpoint assessment, dosing regimen, etc. Each study was a randomized, double-blind, placebo-controlled, parallel group study. Consequently, pooling these studies as part of an integrated analysis of efficacy is reasonable. The integrated analysis of efficacy pools data from the 5 studies in the table below and one phase 2 study (Study 2.107) that is shown in Table 3.

Studies 3.116 and 3.118 in the table below were conducted in female subjects only. Study 3.117 was conducted in males only. Studies 3.112 and 3.114 were conducted predominantly in male subjects. Study 2.107 in Table 3 below included both male and female subjects but was limited to subjects with a duration of atrial fibrillation > 3 hours but < 48 hours (unlike the five phase 3 studies where the duration could be > 3 hours but less than 45 days).

During the conduct of studies 3.112 and 3.114, the tedisamil IV development program was temporarily halted by the sponsor to review safety data, specifically case reports of Torsade de pointes type arrhythmia. While these 2 studies eventually did resume, it was decided to continue the studies with only male subjects restricting doses to a maximum of 0.48 mg/kg. That may explain, in part, the higher proportion of males to females in studies 3.112 and 3.114.

Study 3.114 had 2 arms where subjects could receive an “extended” 50-minute infusion. If a subject did not convert within the 30 minutes post study drug initiation, an additional 0.16 mg/kg could be infused over 20 minutes (0.32 – 0.48 mg/kg arm) or an additional 0.24 mg/kg could be infused (0.48 – 0.72 mg/kg arm). Data from the extended “50-minute” infusion arms are not included in the integrated analyses of efficacy but are included in some of the integrated analyses of safety.

Table 2: Summary of the pivotal, phase 3 studies contributing to efficacy

Study ID (total Randomized)	Study dates (month/yr)	Top 3 enrolling countries	# subjects randomized to each study arm (note: dose of free base is reported in mg/kg)	Sex (F = female M = male)	Baseline Rhythm
3.112 (N =283)	10/02 – 3/04	Russia (N = 97), Ukraine (N = 89), Poland (N = 76)	Placebo (N = 72) Tedi 0.32 (N = 72) Tedi 0.48 (N = 73) Tedi 0.64 (N = 66)	F=38 M = 245	Afib = 244 Aflut = 39
3.114 (N = 296)	12/02 – 9/04	Ukraine (N = 137) Slovakia (N = 34) Israel (N = 32)	Placebo (N = 79) Tedi 0.16 (N = 61) Tedi 0.32 – 0.48 (N = 18) Tedi 0.32 (N = 60) Tedi 0.48 – 0.72 (N = 18) Tedi 0.48 (N = 60)	F = 20 M = 276	Afib = 263 Aflut = 33
3.116 (N = 367)	12/04 – 8/05	Ukraine (N = 77) Poland (N = 70) Slovakia (N = 60)	Placebo (N = 122) Tedi 0.24 (N = 122) Tedi 0.32 (N = 123)	F = 367	Afib = 329 Aflut = 38
3.117 (N = 123)	11/04 – 6/05	Poland (N = 40) Ukraine (N = 30) Czech Repub(N = 23)	Placebo (N = 62) Tedi 0.48 (N = 61)	M = 123	Afib = 100 Aflut = 23
3.118 (N = 155)	11/04 – 8/05	Bulgaria (N = 60) Hungary (N = 42) Poland (N = 35)	Placebo (N = 78) Tedi 0.32 (N = 77)	F = 155	Afib = 138 Aflut = 17

Table 3 below summarizes the phase 2 studies in tedisamil atrial fibrillation development program. The integrated analysis of safety pools the four phase 2 studies in the table below along with the five phase 3 studies summarized above. Study 2.111 and study 2.113 in the table below were prematurely terminated due to poor enrollment. The patient population in these 2 studies was different from the other listed studies in that they included post cardiac surgery patients. Study 2.102 was prematurely terminated for a suggested lack of efficacy and involved lower doses administered for a shorter duration compared to the other phase 3 studies.

Table 3: Summary of phase 2 studies

Study ID (total Rand)	Study dates (month/yr)	Top 3 enrolling countries	# subjects randomized(note: dose of free base is reported in mg/kg)	Sex (F = female M = male)	Baseline Rhythm	Other Notes
2.102 (N = 26)	8/98 – 8/99	United States (N = 26)	Placebo (N = 9) Tedi 0.16 (N = 9) Tedi 0.24 (N = 8)	F = 6 M = 20	Afib = 19 Aflut = 7	10-min infusion (not 30 min); DHCl formulation used
2.107 (N = 200)	4/00 – 7/02	United States (N = 94) Germany (N = 59) Canada (N = 27)	Placebo (N = 68) Tedi 0.32 (N = 74) Tedi 0.48 (N = 58)	F = 79 M = 121	Afib = 157 Aflut = 39	DHCl formulation used

Study ID (total Rand)	Study dates (month/yr)	Top 3 enrolling countries	# subjects randomized(note: dose of free base is reported in mg/kg)	Sex (F = female M = male)	Baseline Rhythm	Other Notes
2.111 (N = 17)	11/02 – 3/03	Russia (N = 8) Poland (N = 6) Germany (N = 2)	Placebo (N = 4) Tedi 0.32 (N = 5) Tedi 0.48 (N = 4) Tedi 0.64 (N = 4)	M = 17	Afib = 14 Aflut = 3	Study terminated early; population = post cardiac surgery
2.113 (N = 3)	2/03 – 3/03	Lithuania (N = 2) Slovakia (N = 1)	Placebo (N = 1) Tedi 0.48 – 0.72 (N = 2)	F = 1 M = 2	Afib = 2 Aflut = 1	Study terminated early; population = post cardiac surgery

The sponsor also conducted two phase 2 studies of an oral formulation of tedisamil in subjects with atrial fibrillation. I have not included either of these 2 studies in the table above and have not conducted a detailed review of these studies. Study 2.101 was a randomized, double-blind, placebo controlled study in subjects with chronic persistent atrial fibrillation involving the dihydrochloride formulation of tedisamil (100 or 150 mg orally twice daily). Study 2.103 was a 24 week, placebo-controlled extension study of Study 2.101.

4.3 Review Strategy

Rather than provide a separate summary for each study, this review focuses on providing an integrated review of efficacy and safety that pools data from multiple studies. It is reasonable to integrate the efficacy and safety data because the designs of the individual studies were similar (e.g. randomized, double-blind, multicenter, parallel group). In addition, the inclusion/exclusion criteria, population enrolled, study doses and dosing regimens administered were also generally similar.

While there were some differences in the baseline demographic features among individual studies there was, for the most part, balance between the treatment and placebo groups within a particular study.

4.4 Data Quality and Integrity

During the early stages of this review, there were a few issues that made me question the quality of the submission.

For instance, there was one case (Study 3.112, subject 27303) in whom the adverse event leading to study drug discontinuation after 25 minutes of infusion was reported in the electronic dataset as “Wide QRS Complex 140.1.” However, upon review of the CRF, it stated that study drug was “Premature[ly] stopped due to Ventricular tachycardia.”

There was another case (Study 3.116, subject 67406) in whom the adverse event leading to study drug discontinuation was reported in the electronic dataset as "Death." However, upon review of the CRF, it stated that the study drug infusion was terminated after 7 minutes due to QRS prolongation > 30%.

In addition, there was one CRF for a subject (Study 3.112, subject 23507) that discontinued the study drug infusion after 16 minutes due to a QT increase from baseline $\geq$ 20% and was not included in the original submission. The sponsor did eventually submit this CRF after an information request on February 9, 2007.

There was one dataset "HSDD" that contained Holter data that was incomplete. Specifically, in this dataset there were 20,000 or more rows with missing records. The sponsor did eventually submit a complete dataset after the deficiency was documented by the reviewer.

The sponsor, Solvay Pharmaceuticals, was concerned about the data from some sites in the Ukraine. Apparently, investigations by Ukranian authorities are still ongoing. The sponsor has conducted an analysis of the data which show that the overall efficacy and safety findings and conclusions are not markedly changed regardless of whether or not the data from those sites are included or not.

We have asked the Division of Scientific Investigations (DSI) to conduct a routine audit of selected sites.

4.5 Compliance with Good Clinical Practices

A sponsor representative signed a debarment certification stating that Solvay Pharmaceuticals did not use the services of any person debarred under Section 306 of the Federal FD&C Act in connection with NDA 22,123.

The pivotal phase 3 studies were conducted in accordance with the ICH consolidated guidelines for Good Clinical Practice (GCP) and the Code of Federal Regulations which originates from the ethical principles laid down in the Declaration of Helsinki. Written informed consent was to be obtained in all study subjects. Each of the study protocols describe procedures for Ethics Committee review and study subject informed consent.

4.6 Financial Disclosures

The sponsor provided financial disclosure information for "covered clinical studies" that included the 5 phase 3 studies (e.g. 3.112, 3.114, 3.116, 3.117, and 3.118).

A sponsor representative signed FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators). Box (1) of this form was checked. There were 3 principal investigators for whom certification was available but no disclosable information was provided: Dr. R. Zaliunas (site 421), Dr. R Jurgutis (site 423), and Dr. M Cinteza (site 451).

There was no certification or disclosable information provided for two principal investigators: Dr. V. Tseluyko (site 418) and Dr. G. Sojka (site 643).

The findings from the overall tedisamil program are robust with no single center/principal investigator or a group of principal investigators that are driving the study results.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

In this section, some key highlights with respect to tedisamil pharmacokinetics and clinical pharmacology are bulleted.

- After a two-step 30 minute IV infusion, tedisamil plasma concentrations decline in a multiexponential fashion. The PK can be described by a three-compartment model.
- The 2 IV salt formulations of tedisamil (dihydrochloride and sesquifumarate) are bioequivalent.
- Tedisamil AUC is observed to increase in a dose-proportional manner following IV administration over a dose range of 0.8 to 26 mg in healthy subjects and 0.16 to 0.64 mg/kg in Afib/Afl subjects.
- After single oral drug administration, the absolute bioavailability is 51-60%. The bioavailability increases by 50% after repeated oral dosing.
- The volume of distribution at steady state is 68-70 L in healthy subjects and 72-90 L in recent onset Afib/Afl subjects following a two-step 30-min IV infusion.
- The in vitro protein binding is approximately 96.5%.
- The metabolism of tedisamil is very limited. There is no *in vitro* evidence that human CYP450 enzymes contribute to the metabolism of tedisamil. Following IV administration of ^{14}C-tedisamil, about 3.4% of the radioactivity excreted in the urine is attributable to a single hydroxyl metabolite.
- Tedisamil does not induce CYP enzymes. Tedisamil strongly inhibits CYP2D6 and is a weaker inhibitor of CYP2C19 and CYP3A4.
- Tedisamil is a substrate for P-glycoprotein.
- Tedisamil is almost exclusively eliminated as unchanged drug via the renal route. Following IV administration, 83.5% of the radioactivity from a ^{14}C-tedisamil dose is recovered in the urine and 7.9% in the feces over a 96 hour collection period. Total clearance ranges from 204 to 267 mL/min in healthy subjects and 142-239 mL/min in Afib/Afl subjects following a two-step IV infusion. Renal clearance accounts for approximately 80% of the total clearance in healthy subjects. The elimination half-life ranges from 4.5 to 6.9 hours following IV administration in healthy subjects. Clearance is dose-independent.
- The effects of renal impairment on tedisamil PK were assessed in the phase 3 studies. The population PK data show that renal impairment does not markedly impact the plateau levels of tedisamil achieved during the 30 minute continuous infusion. Renal impairment

does affect the PK area under the curve (AUC). Toxicity with tedisamil is more closely related to the plateau (or Cmax) levels rather than the AUC levels. Consequently, dose adjustment in subjects with renal impairment does not seem too critical. Figure 1 below shows that the plateau concentrations (or Cmax) is not markedly affected by varying degrees of renal impairment.

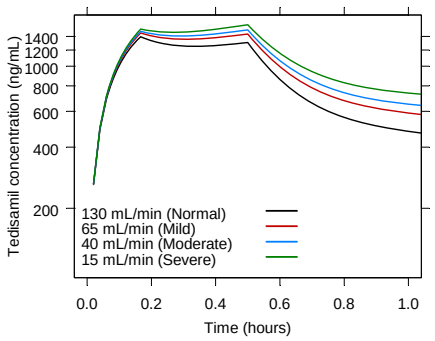

Figure 1: Simulated PK profile for renal impairment for an 80 kg subject receiving a 0.48 mg/kg dose

Source: Analysis by Christoffer Tornoe, FDA

- The effects of sex/gender on the PK of tedisamil have been investigated in the five phase 3 studies using population PK. Figure 2 below shows a simulated PK profile of a 0.48 mg/kg and 0.32 mg/kg dose infused over 30 minutes in males (dashed curve) and females (solid curve) respectively. The infusion was split in two with half the dose administered in the first 10 minutes and the remainder of the dose administered over the next 20 minutes. The figure below shows the plasma concentrations rapidly increase over the first 10 minutes and then achieve a "pseudo-plateau" during the next 20 minutes while the infusion rate has been cut in half. After the infusion is complete, the plasma concentrations begin to rapidly decline in a multi-exponential manner (refer to Figure 3 below).

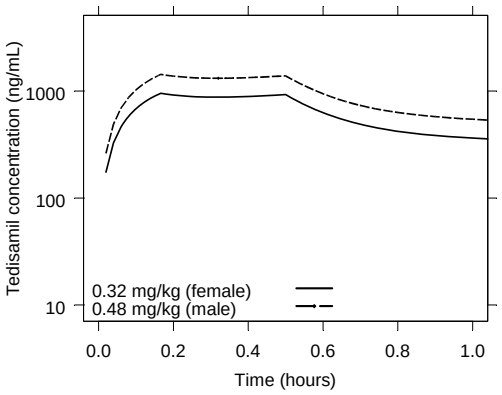

Figure 2: Simulated PK profile of tedisamil in males (upper curve) and females (lower curve)

Source: Christoffer Tornoe, FDA
Note: The simulated PK profile is based on a 30-minute infusion of tedisamil of 0.48 mg/kg in males and 0.32 mg/kg in females with half the dose administered over the first 10 minutes and the remainder of the dose administered over the next 20 minutes. The simulated PK profile represents an ideal subject (80 kg male or 75 kg female) with a CrCL = 87 mL/min.

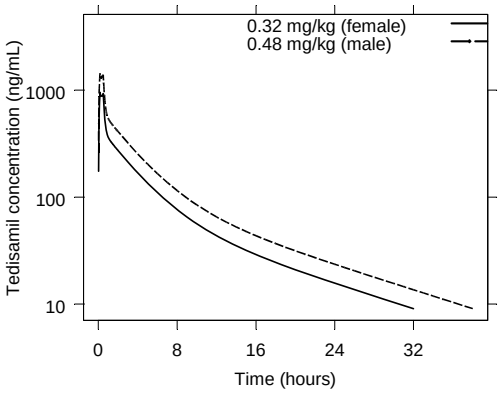

Figure 3: Simulated PK profile showing a rapid decline in plasma tedisamil concentrations

Source: Christoffer Tornoe, FDA

- It is worth noting that the simulated PK profile would be identical if male and female subjects were administered the same mg/kg tedisamil dosing regimen.
- Figure 4 below shows the "plateau" concentrations achieved with each dose/dosing regimen. The predicted "plateau" concentrations achieved with the 0.16, 0.24, 0.32, 0.48, and 0.64 mg/kg dose/regimen are 440, 660, 880, 1320, and 1760 ng/mL respectively.

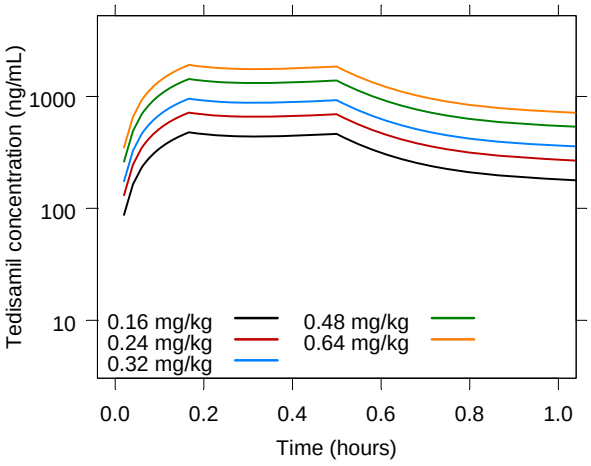

Figure 4: Predicted plasma levels at "plateau" with each dose/dosing regimen

Source: Christoffer Tornoe, FDA

5.2 Pharmacodynamics

The time course of tedisamil's effects on blood pressure, heart rate, and QT interval are discussed in other parts of this review. Please refer to sections 7.1.8 and 7.1.9 of this review for more details.

5.3 Exposure-Response Relationships

Exposure-response analyses with respect to efficacy and safety are presented in various parts of this review. In many parts of this review, I have used tedisamil dose (mg/kg) as a surrogate for exposure.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor's proposed indication is for "the rapid conversion of recent onset (3 hours to 45 days) atrial fibrillation (Afib) or atrial flutter (Afl) to normal sinus rhythm.

6.1.1 Methods

Please refer to sections 4.2 and 4.3 for further details. The sponsor has provided an integrated or pooled analysis of the data. An integrated analysis is reasonable for the reasons discussed above. There is consistency in the design of each of the individual studies that comprise the pooled analysis. There is also consistency in the primary efficacy results. In study 3.114, a few subjects underwent an extended 50-minute infusion of tedisamil. The data from these subjects have not been included in the integrated efficacy analyses.

6.1.2 General Discussion of Endpoints

Treatment of atrial fibrillation or atrial flutter includes either conversion to NSR (rhythm control) or control of ventricular rate (rate control). Conversion to NSR can be achieved with medication (pharmacologic conversion), electrical shocks (DC cardioversion) or a combination of both. The objectives of cardioversion are to: 1) restore the atrial contribution to ventricular filling/output; 2) regularize ventricular rate and 3) interrupt atrial remodeling.

The primary endpoint in each of the phase 3 studies used in the integrated efficacy analysis was the percentage of subjects that converted to NSR (for at least 60 seconds) at any time within 2.5 hours after the initiation of study drug. This endpoint, in my view, is a surrogate endpoint. Presumably the main reason to restore sinus rhythm acutely would be to relieve symptoms (e.g. palpitations due to a rapid heart rate or possibly to improve symptoms of shortness of breath or fatigue due to a lack of atrial contribution to ventricular filling) or to prevent heart failure. The sponsor did not collect data on symptom reduction or preventing adverse cardiovascular outcomes post study drug administration. Nevertheless, as discussed in section 2.5 above, the Division agreed to the sponsor's proposed primary endpoint.

The endpoint used in the tedisamil development program was qualitatively similar to the endpoint used in the ibutilide development program. In the major efficacy studies involving ibutilide, treatment success was defined as termination of arrhythmia (Afib or Afl) for **any** length of time prior to 1 hour following the end of infusion.

6.1.3 Study Design

The study designs for each of the six studies included in the integrated analysis of efficacy were generally similar. Each of the studies included the following design elements: double-blind, randomized, placebo-control, parallel group design.

The study drug was infused over 30 minutes in each of the six studies with half the dose being administered within the first 10 minutes and the remaining half being administered over the next 20 minutes. The ideal body weight was used to determine whether the dose administered was to be related to body weight or whether it was related to height. If IBW was $\leq$ 28 kg/m^2, the dose was a function of body weight in kg. If the IBW was > 28 kg/m^2, the dose was a function of height (please refer to section 2.1). The study drug infusion was not to be stopped when the subject converted to NSR during the infusion.

In the five phase 3 studies, the study population included subjects with a documented first ever or recurrent symptomatic episode of atrial fibrillation or flutter with a duration greater than 3 hours but less than 45 days. Subjects were also required to be hemodynamically stable prior to randomization. Please refer to the Appendix section 10.1.2 for a detailed inclusion/exclusion criteria list.

In study 2.107 (phase 2 study included in the integrated analysis of efficacy), subjects with a documented, symptomatic atrial fibrillation or flutter episode of greater than 3 hours but less than 48 hours were included – a subset of subjects in the remaining 5 studies.

6.1.4 Efficacy Findings

In this section, results from the pivotal studies are presented individually and also in an integrated analysis.

Table 4 below, summarizes the primary efficacy results from each of the 6 individual studies in the integrated analysis of efficacy. The table below shows a consistent and reproducible effect across each of the 6 studies. Note that study 2.107 was conducted primarily in North America and Western Europe. The results from this study are consistent with the results from studies the other five studies in the integrated efficacy analysis conducted predominantly in Eastern Europe and/or Russia. In Table 4 below (sponsor's analysis), study 3.112 did not include data from women. There were only a small number of women randomized in this study (N = 38). Dr. Valeria Freidlin has confirmed that the conclusions from the table below remain the same whether or not the female data from study 3.112 are included.

The primary efficacy results (% responders) in the table below were verified by Dr. Valeria Freidlin, FDA statistician.

Table 4: Summary of primary efficacy parameter for each individual study

Study	Overall Number Randomized/ Completed	Tedisamil dose infused (mg/kg)	NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion	Mean time to first conversion
S219.3.112	72/67	0.32	13/56 (23.2%), p = 0.0096	41.6 minutes
	73/62	0.48	28/51 (54.9%), p < 0.0001	37.9 minutes
	66/54	0.64	29/44 (67.4%), p < 0.0001	21.9 minutes
	72/65	Placebo	3/53 (5.7%)	45.0 minutes
S219.3.114	61/57	0.16	12/50 (24.0%), p = 0.057	33.1 minutes
	60/56	0.32	1551 (29.4%), p = 0.013	30.3 minutes
	60/51	0.48	14/45 (31.1%), p = 0.0089	18.5 minutes
	60/56	Placebo	5/51 (9.8%)	84.0 minutes
S219.3.116	122/115	0.24	10/106 (9.4%), p = 0.047	41.1 minutes
	123/115	0.32	23/107 (21.5%), p < 0.001	24.2 minutes
	122/112	Placebo	3/105 (2.9%)	88.7 minutes
S219.3.117	61/57	0.48	14/48 (29.2%) p=0.003	22.2 minutes
	62/57	Placebo	3/48 (6.3%)	92.7 minutes
S219.3.118	77/74	0.32	12/67 (17.9%), p=0.014	27.4 minutes
	78/73	Placebo	3/67 (4.5%)	88.7 minutes
S219.2.107	75/64	0.32	24/52 (46%), p < 0.001	34.8 minutes
	58/52	0.48	24/42 (57%), p < 0.001	34.2 minutes
	68/57	Placebo	4/46 (9%)	86.4 minutes

Source: Table 2.5.4-3 of NDA 22,123 (sponsor's analysis)

Figure 5 below shows the primary efficacy endpoint (% responders or converters) as a function of tedisamil dose. The data in the figure below are based on a pooled analysis of the ITT population in the 6 studies that form the integrated analysis of efficacy. The dose of 0.24 mg/kg was not studied in males while the dose of 0.16 mg/kg was not studied in females (this is the reason for the discontinuous male and female curves in the figure below). The figure shows clear evidence of dose response in both men and women. The figure also suggests that for any given dose, men tend to have a greater response compared to women. The analysis in the figure below includes 7 subjects (6 tedisamil, 1 placebo) who underwent DC cardioversion within the first 2.5 hours of initiation of study drug. The results and conclusion are not significantly changed by excluding these subjects.

It is worth noting that the acute conversion rate with ibutilide is around 45% at the approved dose based on approved labeling. The acute conversion rate with tedisamil (at the doses recommended for approval) is nominally lower at around 20% -40%. The ibutilide label states that the incidence of TdP requiring cardioversion was 1.7% where as with tedisamil TdP requiring cardioversion occurred with an incidence of 0.3%. The relative efficacy and safety of ibutilide and tedisamil can not be compared unless a head to head trial between the two drugs at equipotent doses is performed. Generally speaking, the overall benefit and risk profile of the two agents appears similar.

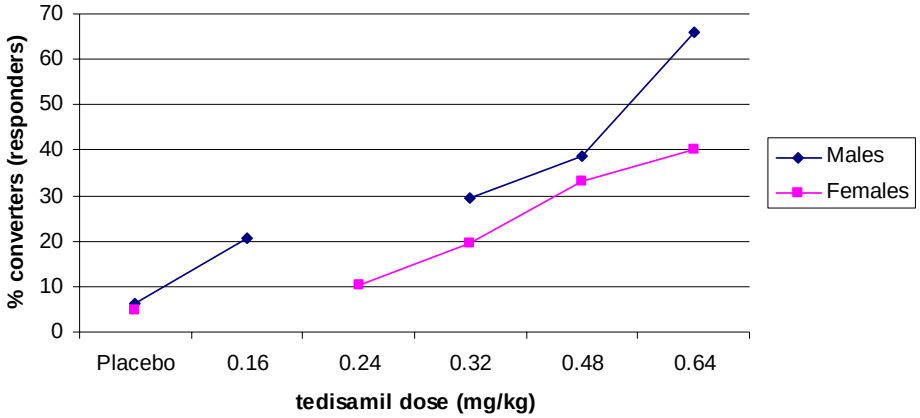

Figure 5: Integrated analysis of the primary efficacy variable by sex

Source: Analysis by Mehul Desai (Pooled analysis from studies 2.107, 3.112, 3.114, 3.116, 3.117, 3.118).

Table 5 below summarizes the response or "converter" rate in each individual dose group in each of the studies contributing to the integrated efficacy analysis. The estimate of tedisamil's effect can most precisely be assessed in the 0.32 mg/kg, 0.48 mg/kg, and placebo dose groups.

Table 5: Conversion rates by study and by dose

	Placebo	0.16 mg/kg	0.24 mg/kg	0.32 mg/kg	0.48 mg/kg	0.64 mg/kg
Study 2.107	6.8%			41.3%	50.0%	
Study 3.112	4.2%			19.7%	45.7%	61.7%
Study 3.114	8.8%	20.7%		27.6%	29.6%	
Study 3.116	5.1%		10.2%	20.0%		
Study 3.117	5.2%				25.4%	
Study 3.118	4.0%			15.8%		

A subgroup analysis of the primary efficacy endpoint is shown in section 10.1.11 of this review. In summary, the proportion of responders/converters was lower at each dose level in subjects with a longer duration (> 48 hours) of atrial fibrillation compared to subjects with a shorter duration (≤ 48 hours) of atrial fibrillation. The proportion of responders/converters was also lower in subjects with a predominant baseline rhythm of atrial flutter compared to those with a predominant baseline rhythm of atrial fibrillation.

6.1.5 Clinical Microbiology N/A

6.1.6 Efficacy Conclusions

Assuming that the endpoint is still valid, tedisamil is clearly effective as evidenced by superiority over placebo and evidence of dose response (refer to section 6.1.4). Tedisamil is effective in both men and women. However, tedisamil appears to be relatively less effective in women compared to men when administered the same mg/kg dosing regimen (refer to Figure 5). The rationale for this is not entirely clear. This phenomenon can not be explained by PK differences because when men and women are administered the same mg/kg dosing regimen, population PK analyses suggest that the plasma PK profiles are comparable in the two sexes.

Based on a subgroup analysis, tedisamil appears to be most effective in subjects with a duration of $\leq$ 48 hours of their most recent atrial fibrillation episode. The effectiveness of tedisamil is much lower in subjects with a duration of their most recent episode of atrial fibrillation > than 48 hours. Tedisamil appears to be much less effective in converting subjects with atrial flutter to normal sinus rhythm.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

A total of 13 deaths were reported in Afib/Afl subjects in the tedisamil program. Eleven deaths were included in the integrated safety database of the tedisamil IV studies and are shown in Table 6 below. Two deaths were reported in a phase 2 study involving the oral formulation (Study 2.101) and are shown in Table 7 below.

Of the 11 deaths occurring with the IV formulation of tedisamil, there were 2 deaths that occurred in subjects that were randomized but that did not receive study drug (subjects 90188 and 41401). In 3 cases, the deaths occurred in subjects randomized to placebo (subjects 90242, 22101, and 82711). Narratives from the remaining cases are described below. It appears that in only one case (Subject 43001), the death was possibly causally related to study drug.

The table below shows the AE preceding death as reported in the AEDD dataset and the study day the AE started (which is not necessarily the same as the day of death relative to the start of study medication). The day of death relative to start of study drug was not documented in the dataset.

Table 6: Deaths in the Afib/Afl program

Study ID	Site #	Country	Subj ID	Study drug	Age	Sex	Race	AE preceding death (PT)	Study day AE started
2.107	013	Germany	90188[a]	PLACEBO	86	M	WHITE	Right BBB, dyspnea, ST depression, PE, tachyarrhythmia	
2.107	061	US	90242	PLACEBO	70	M	WHITE	Pancreatic cancer	4
3.112	221	Czech Repub	22101	PLACEBO	74	M	WHITE	Ventricular fibrillation	14
3.114	414	Ukraine	41401[a,b]	TEDI 0.48 - 0.72 MG/KG	73	F	WHITE	Sudden death	
3.114	430	India	43001[b]	TEDI 0.32 - 0.48 MG/KG	80	F	ASIAN	Asystole, Electromechanical dissociation, hypotension	3
3.114	442	Slovakia	44203[b]	TEDI 0.32 MG/KG	72	M	WHITE	Acute MI	8
3.116	613	Ukraine	61304	TEDI 0.24 MG/KG	75	F	WHITE	PE	1
3.116	615	Ukraine	61508	TEDI 0.24 MG/KG	83	F	WHITE	Stroke	9
3.116	674	Poland	67406	TEDI 0.32 MG/KG	80	F	WHITE	Acute MI	4
3.118	825	Hungary	82506	TEDI 0.32 MG/KG	90	F	WHITE	Heart failure, Pneumonia	7
3.118	827	Hungary	82711	PLACEBO	85	F	WHITE	Stroke	6

[a]Deaths occurred before study drug infusion began
[b]Death occurred in subjects receiving the extended 50 minute infusion

Subject 43001 was an 80 year old Asian female who experienced bradycardia, asystole and low blood pressure resulting in a premature termination of study infusion within 15 minutes of its initiation. Approximately 10 minutes into the infusion, the subject experienced marked bradycardia and hypotension requiring atropine. Later during the infusion wide QRS complexes were noted possibly related to a wide QRS complex tachycardia. The subject underwent cardiopulmonary resuscitation and was intubated. On the same day, adverse events of acidosis (not otherwise specified), pulmonary edema, and hypoxic encephalopathy were reported. The subject was extubated 2 days post infusion but did not respond to further treatment and was declared dead. While a tabulation of deaths from the AEDD dataset revealed that the start date of the AE that led to death was day 3, a read of the narrative and case report form shows that this subject experienced serious AEs (e.g. asystole) starting within 15 minutes of study drug initiation that likely contributed to this subject's death.

Subject 61304 was a 75 year old white female who died of a pulmonary trunk embolus that was confirmed by autopsy. The death occurred about 10 hours post study drug initiation. This subject received 0.24 mg/kg of tedisamil.

Subject 61508 was an 83 year old white female, who died at home 1 week after suffering a cerebrovascular accident. The subject was discharged from the hospital in normal condition on the second day post infusion of study drug. Approximately 1 week later, the subject suddenly lost consciousness and experienced right sided hemiparesis. A cerebrovascular accident was diagnosed. This subject received 0.24 mg/kg of tedisamil.

Subject 44203 was a 72 year old white male who experienced an AE of acute MI about 1 week post study drug infusion. The MI led to the subject's hospitalization and ultimately to his death. This subject had a history of coronary artery disease and hypertension.

Subject 67406 was an 80 year old white female who died of an AE of acute MI. The subject was administered study drug but the infusion was terminated prematurely after 7 minutes due to QRS prolongation. The QRS prolongation resolved spontaneously later on that same day. The subject had normal sinus rhythm restored the first day after infusion via DC cardioversion. The subject was discharged from the hospital the same day. On the second day post study drug infusion, the subject developed sudden pain in the retrosternal region and was transferred to the hospital. Cardiac arrest occurred. An ECG showed asystole, resuscitation was started but was unsuccessful. This subject had a medical history of coronary artery disease, cardiac failure, MI and hypertension.

Subject 82506 was a 90 year old female who died of pneumonia and cardiac failure 7 days post study drug infusion. The subject had a history of hypertension, diabetes mellitus, ischemic heart disease, and heart failure.

Table 7 below lists deaths occurring with the oral formulation of tedisamil in study 2.101. Study 2.101 was a randomized, double-blind, placebo-controlled study of 24 weeks duration in subjects with chronic persistent atrial fibrillation.

Table 7: Deaths occurring with the oral formulation of tedisamil (study 2.101)

Study ID	Site #	Country	Subj ID	Study drug	Age	Sex	Race
2.101			21005	Tedi 120 mg bid	72	M	White
2.101			34005	Tedi 120 mg bid	79	F	White

Subject 34005 was a 79 y/o female with a past medical history of diabetes, hypertension, and coronary artery disease that received study drug for approximately 1 month (150 mg daily) starting 1/27/1998. The subject was to report to the clinic for a routine follow-up visit but did not show up because the subject's son reported that she was "weak and fatigued" and was experiencing diarrhea for an unknown duration. The subject's clinic visit was re-scheduled to 2/26/1998. Earlier that day, the clinical received a phone call from the subject's son stating that she had died at home. It is worth noting that this subject experienced "thumping in her chest" on 2/17/1998 leading to an Emergency room visit. At that time, the subject had a 12-lead ECG that showed the subject's rhythm to be normal sinus with no evidence of ischemic changes. Clinical lab studies were normal.

Subject 21005 was a 72 y/o male with a past medical history relevant for hypertension, diabetes, hyperlipidemia, and a 45 year smoking history. The subject received oral tedisamil at a dose of 150 mg daily for 8 to 9 days. He experienced a syncopal episode during church services and was found to be in pulseless ventricular fibrillation. Resuscitation was not successful.

7.1.2 Other Serious Adverse Events

Table 8 below summarizes the total # of subjects reporting at least one treatment emergent SAE (TESAE) by study. The SAE reporting rate was similar across the 9 studies in the integrated (pooled) safety analysis.

Table 8: TESAE incidence by study

Study ID	# of subjects reporting TESAE	Total # of subjects in "safety population"	TESAE incidence rate
All 9 studies	132	1401	9.4%
2.102	4	26	15.4%
2.107	17	180	9.4%
3.111	1	14	7.1%
3.112	24	272	8.8%
3.113	0	3	0%
3.114	22	279	7.9%
3.116	32	358	8.9%
3.117	11	117	9.4%
3.118	21	152	13.8%

Table 9 below shows the ten most frequently reported TESAEs in the integrated safety database using the MedDRA primary high level term (HLT). The analysis below combines all the tedisamil study doses into one group. The rationale for combining dose groups is that 1) there are too few subjects exposed at any dose level and 2) there are too few SAE's at a particular dose level for a MedDRA preferred (PT) term. A key limitation of this type of analysis is that information with respect to dose response is lost.

Although the total number of events was small, Table 9 below shows that the incidence of CNS hemorrhages and CVA was nominally higher in the tedisamil arm compared to the placebo arm. It is unlikely that any definitive conclusion can be made regarding this adverse event from the data in the table below.

Table 9: Treatment emergent SAEs (MedDRA high level term - HLT)

AEHLTP	TEDI N = 931	PLACEBO N = 470
# of subjects reporting at least 1 SAE	90 (9.7%)	42 (8.9%)
SUPRAVENTRICULAR ARRHYTHMIAS	33 (3.5%)	16 (3.4%)
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST	13 (1.4%)	7 (1.5%)
ISCHAEMIC CORONARY ARTERY DISORDERS	8 (0.9%)	2 (0.4%)
CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR ACCIDENTS	8 (0.9%)	1 (0.2%)
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	6 (0.6%)	3 (0.6%)
RATE AND RHYTHM DISORDERS NEC	5 (0.5%)	2 (0.4%)
VASCULAR HYPOTENSIVE DISORDERS	4 (0.4%)	3 (0.6%)
HEART FAILURES NEC	6 (0.6%)	0 (0.0%)
PULMONARY OEDEMAS	2 (0.2%)	2 (0.4%)
PAIN AND DISCOMFORT NEC	1 (0.1%)	2 (0.4%)

Table 10 below shows the ten most frequently reported treatment emergent SAEs in the integrated safety database using the MedDRA preferred term (PT). AEPFT in the table below refers to the MedDRA preferred term. There are too few events of a particular adverse event at any dose level to make any firm conclusions with respect to drug causality.

Table 10: Treatment emergent SAEs (MedDRA preferred term - PT)

AEPFT	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 - 0.48 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 - 0.72 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
Total # of subjects in safety sample	67	128	17	397	19	241	62	470
# of subjects reporting at least 1 SAE	5 (7.5%)	15 (11.7%)	4 (23.5%)	35 (8.8%)	1 (5.3%)	24 (10%)	6 (9.7%)	42 (8.9%)
ATRIAL FIBRILLATION	1 (1.5%)	6 (4.7%)	3 (17.6%)	7 (1.8%)	0 (0%)	10 (4.1%)	2 (3.2%)	12 (2.6%)
VENTRICULAR TACHYCARDIA	0 (0%)	1 (0.8%)	0 (0%)	2 (0.5%)	0 (0%)	3 (1.2%)	1 (1.6%)	2 (0.4%)
ATRIAL FLUTTER	0 (0%)	1 (0.8%)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.4%)	1 (1.6%)	3 (0.6%)
VENTRICULAR FIBRILLATION	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	1 (0.4%)	1 (1.6%)	4 (0.9%)
BRADYCARDIA	1 (1.5%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)	2 (0.4%)
HYPOTENSION	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	1 (0.4%)	1 (1.6%)	3 (0.6%)
MYOCARDIAL INFARCTION	1 (1.5%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	2 (3.2%)	2 (0.4%)
CEREBROVASCULAR ACCIDENT	1 (1.5%)	1 (0.8%)	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
PNEUMONIA	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	2 (0.8%)	0 (0%)	2 (0.4%)
CARDIAC ARREST	0 (0%)	1 (0.8%)	1 (5.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)

Narratives from selected subjects with serious adverse events are described below.

Subject 90229 was a 67 year old male subject that received study drug on April 16. On April 15, prior to receiving study drug, the subject received Lanoxin 0.5 mg and 0.25 mg IV. The subject experienced significant bradycardia with a continued pause requiring a bolus of Pronestyl followed by an IV drip. The subject also required placement of a pacemaker. By April 25, the event had resolved.

Subject 23803 was a 49 year old male that received 0.64 mg/kg of tedisamil IV. The study drug infusion was terminated after 12 minutes due to AEs of QT prolongation, ventricular extrasystoles, and ventricular tachycardia. The QT prolongation resolved on the same day while the events of ventricular extrasystoles and ventricular tachycardia were noted to resolve on the following day.

Subject 25825 was a 78 year old male that received 0.64 mg/kg of tedisamil IV. The study drug infusion was terminated prematurely because the subject developed a non-sustained, polymorphic ventricular tachycardia that led to syncope. This subject required DC cardioversion (2 shocks, each of 100 Joules) to restore normal sinus rhythm.

Subject 23405 was a 61 year old female that received a 0.48 mg/kg of tedisamil IV. Twenty minutes after the start of infusion, the subject developed ventricular tachycardia associated with hypotension and apnea. The subject also experienced loss of consciousness. The study drug infusion was prematurely stopped. The subject required DC cardioversion (1 x 150 Joules) and eventually regained consciousness.

Subject 25414 was a 64 year old female that received 0.64 mg/kg of tedisamil IV. She developed hypotension (60/40 mm Hg) 13 minutes after the start of the infusion leading to

termination of the infusion. Thirty one minutes after the start of infusion, the subject developed ventricular fibrillation requiring DC cardioversion.

Subject 41420 was a 54 year old male that received 0.48 mg/kg of tedisamil IV. Fourteen minutes after the start of infusion, the subject lost consciousness. An ECG showed ventricular fibrillation. The subject required DC cardioversion (a total of 4 shocks) to convert back into NSR. Per the Case Report Form, the infusion was not stopped after the occurrence of the arrhythmia but continued for the full 30 minutes.

Subject 41021 was a 54 year old male that received 0.32 mg/kg of tedisamil IV starting at 13:18. Approximately 11 minutes after the initiation of infusion, the subject experienced ventricular tachycardia with associated dizziness, loss of consciousness, and convulsions. The subject was successfully treated with DC cardioversion (100 J) and with amiodarone 150 mg IV. At 13:33, ventricular tachycardia recurred and sinus rhythm was again restored after DC cardioversion (100 J). At 13:35, ventricular tachycardia again recurred and was successfully treated with DC cardioversion (200 J) and amiodarone 150 mg IV.

Subject 42506 was a 65 year old male that received 0.32 mg/kg of tedisamil IV starting at 15:11 on February 11. Transitory episodes of ventricular tachycardia were noted on telemetry starting at 15:14 onwards. The subject experienced a total of 30 episodes of ventricular tachycardia. There was at least one episode that occurred more than 16 hours post study drug initiation.

Subject 41411 was a 76 year old female that received 0.32 -0 .48 mg/kg of tedisamil IV (extended infusion). She developed ventricular fibrillation 48 minutes post initiation of study drug (towards the end of the 50 minute infusion period). She had associated symptoms of dizziness. The arrhythmia was treated initially with a precordial thump. However, the arrhythmia recurred and was successfully treated with a lidocaine infusion.

Subject 84504 was a 73 year old female that received 0.32 mg/kg tedisamil IV on February 11. One to 3 hours post study drug infusion, the subject was noted to have "pauses" on the ECG tracing, along with bradycardia and a "nodus rhythm." These findings resolved spontaneously later on in the day. On February 12, the subject suffered from a cerebrovascular accident with associated motor aphasia and central facial nerve paralysis of the right side. This subject had been receiving "heparin-fraction, sodium salt 60 mg bid" subcutaneously from February 5 to 10, 60 mg qd subcutaneously from February 11 to 17th and 80 mg once daily from February 18.

7.1.3 Dropouts and Other Significant Adverse Events

According to the sponsor, there were a total of 28 subjects that dropped out due to adverse events from the 9 studies that form the integrated/pooled safety database. These 28 subjects include those that dropped out from the study while study drug was being infused and those subjects that dropped out from the study after completion of study drug infusion but before the 28 day safety follow-up. A total of 11 subjects dropped out from study 3.112. Six subjects each dropped out from studies 3.114 and 3.116. Three subjects dropped out from study 3.118. One subject each

dropped out from studies 2.102 and 2.107. No drop-outs were reported from studies 3.111, 3.113, and 3.117.

7.1.3.1 Overall profile of dropouts

Table 11 below shows the number (%) of subjects that dropped out in each study arm in the integrated safety database. Excluding the extended infusion arms (0.32 – 0.48 mg/kg and 0.48 – 0.72 mg/kg), there appears to be a dose-dependent increase in the incidence of subjects dropping out due to adverse events.

Table 11: Overall summary of drop-outs due to AEs

	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 - 0.48 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 - 0.72 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
Total # of subjects in safety sample	67	128	17	397	19	241	62	470
# of subjects that dropped out	1 (1.5%)	2 (1.6%)	2 (11.8%)	7 (1.8%)	0 (0%)	6 (2.5%)	5 (7.8%)	5 (1.1%)

Most of the study discontinuations occurred in subjects receiving tedisamil doses of 0.32 mg/kg or higher. There were multiple discontinuations for QT prolongation, ventricular tachycardia or Torsade de Pointes. There were also a few discontinuations for low blood pressure. More details of subjects that discontinued are provided in section 7.1.3.2.

7.1.3.2 Adverse events associated with dropouts

Table 12 below lists individual subjects that required pre-mature discontinuation of study drug infusion. In other words, study subjects experienced an adverse event or met a study withdrawal criteria while the study drug was being administered. Narratives from some of the subjects in the table below are discussed in section 7.1.2 above.

Table 12: Line listing of subjects dropping out due to an AE

STUDY ID	SITE #	COUNTRY	SUBJID	ARM	AGE	SEX	RACE	AE leading to discontinuation
3.112	234	Russia	23405	TEDI 0.48 MG/KG	61	F	WHITE	TORSADE DE POINTES, Hypotension, Apnea
3.112	234	Russia	23406	TEDI 0.32 MG/KG	64	F	WHITE	VENTRICULAR TACHYCARDIA
3.112	235	Russia	23507	TEDI 0.64 MG/KG	57	M	WHITE	QT > 20% INCREASE FROM BASELINE
3.112	238	Russia	23803	TEDI 0.64 MG/KG	49	M	WHITE	QT PROLONGATION AT ECG DURING INFUSION, VENTRICULAR ECTOPY SHORT RUNS OF VT
3.112	239	Russia	23901	TEDI 0.48 MG/KG	77	M	WHITE	QT INTERVAL INCREASE MORE THAN 550 MSEC (553 MSEC), MEASURED AFTER CONVERSION
3.112	239	Russia	23904	TEDI 0.64 MG/KG	47	M	WHITE	HYPOTENSION (85/65 MMHG) AND QT INTERVAL INCREASE TO GREATER THAN 550 MSEC (560MSEC)
3.112	240	Russia	24016	TEDI 0.48 MG/KG	75	M	WHITE	QT >20%
3.112	254	Ukraine	25414	TEDI 0.64 MG/KG	64	F	WHITE	DEVELOPMENT OF ARTERIAL HYPOTENSION DURING INFUSION
3.112	258	Ukraine	25825	TEDI 0.64 MG/KG	79	M	WHITE	VENTRICULAR TACHYCARDIA
3.112	273	Poland	27303	TEDI 0.48 MG/KG	72	M	WHITE	WIDE QRS COMPLEX 140.1.

STUDY ID	SITE #	COUNTRY	SUBJID	ARM	AGE	SEX	RACE	AE leading to discontinuation
3.114	410	Ukraine	41021	TEDI 0.32 MG/KG	54	M	WHITE	RECURRENT VENTRICULAR TACHYCARDIA; Syncope
3.114	412	Ukraine	41211	TEDI 0.48 MG/KG	47	M	WHITE	QT INT > 20 % OF BASELINE
3.114	414	Ukraine	41416	TEDI 0.48 MG/KG	77	M	WHITE	BRADYCARDIA
3.114	421	Lithuania	42101	TEDI 0.32 - 0.48 MG/KG	60	M	WHITE	INTERMITTENT LEFT AND RIGHT BUNDLE BRANCH BLOCK
3.114	430	India	43001	TEDI 0.32 - 0.48 MG/KG	80	F	ASIAN	HYPOTENSION WITH ATRIAL FIBRILLATION, BRADYCARDIA, ASYSTOLE, WIDE QRS
3.116	674	Poland	67406	TEDI 0.32 MG/KG	80	F	WHITE	QRS > 30%
3.116	684	Russia	68405	PLACEBO	79	F	WHITE	SEVERE ARTERIAL HYPOTENSION (BP 62/21)
3.118	806	Bulgaria	80607	TEDI 0.32 MG/KG	65	F	WHITE	BRADYCARDIA EXTRASYSTOLES

Table 13 lists subjects that were pre-maturely discontinued from the study. These subjects completed and tolerated the entire infusion period but were terminated sometime after completion of the study drug infusion but before completion of the 28 day safety follow-up.

Table 13: Subjects that dropped out of the study after completion of the study drug infusion

STUDY ID	SITE #	COUNTRY	SUBJID	ARM	AGE	SEX	RACE	AE leading to discontinuation
2.102	016	US	16006	TEDI 0.16 MG/KG	60	M	WHITE	
2.107	061	US	90242	PLACEBO	70	M	WHITE	PT. DIED PRIOR TO DAY 28
3.112	221	Czech Repub	22101	PLACEBO	74	M	WHITE	SEE ADVERS EVENT REPORT
3.114	442	Slovakia	44203	TEDI 0.32 MG/KG	72	M	WHITE	DEATH (Acute MI)
3.116	613	Ukraine	61304	TEDI 0.24 MG/KG	75	F	WHITE	DEATH DUE TO PULMONARY TRUNK THROMBOEMBOLISM
3.116	615	Ukraine	61508	TEDI 0.24 MG/KG	83	F	WHITE	STROKE
3.116	624	Ukraine	62401	PLACEBO	65	F	WHITE	LEFT CERVICAL HIP FRACTURE
3.116	676	Poland	67602	TEDI 0.32 MG/KG	76	F	WHITE	BRUISES DURING COLLECTING OF BLOOD SAMPLES
3.118	825	Hungary	82506	TEDI 0.32 MG/KG	90	F	WHITE	HEART FAILURE AND DEATH
3.118	827	Hungary	82711	PLACEBO	85	F	WHITE	SHOCK-DEATH

7.1.3.3 Other significant adverse events N/A

7.1.4 Other Search Strategies N/A

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In each of the studies, on all visits subjects were asked for adverse events using a standard phrase "how do you feel (since last visit)". The investigator was to record all adverse events in the CRF.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The MedDRA dictionary was used to code investigator reported AEs. The integrated safety database contains AE coding from 2 separate versions of MedDRA: version 5.1 and version 7.0. The AEs from study 2.107 only were coded using version 5.1. The remaining 8 studies in the integrated safety database were coded using MedDRA version 7.0.

7.1.5.3 Incidence of common adverse events

Table 14 below summarizes the total number of subjects reporting at least one TEAE by study. The data in the table below combine all tedisamil doses and placebo. There appears to be consistency in the incidence rate of TEAE in each the five phase 3 studies ranging from 54% to 75%. The TEAE incidence rate in study 2.107, a study conducted primarily in North America and Western Europe was slightly higher at 81.1%.

Table 14: TEAE incidence by study

Study ID	# of subjects reporting TEAE	Total # of subjects in "safety population"	TEAE incidence rate
All 9 studies	914	1401	65.2%
2.102	18	26	69.2%
2.107	146	180	81.1%
3.111	13	14	92.9%
3.112	204	272	75%
3.113	2	3	66.7%
3.114	151	279	54.1%
3.116	229	358	63.4%
3.117	71	117	60.7%
3.118	80	152	52.6%

Table 15 below shows the incidence of TEAE as a function of dose when all 9 studies are pooled. There appears to be evidence for dose response (excluding the subjects receiving extended infusions, 0.32-0.48 mg/kg and 0.48-0.72 mg/kg).

Table 15: TEAE incidence as a function of dose

	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 - 0.48 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 - 0.72 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
Total # of subjects in safety sample	67	128	17	397	19	241	62	470
# of subjects TEAE	32 (47.8%)	80 (62.5%)	12 (70.6%)	268 (67.5%)	12 (63.2%)	168 (69.7%)	49 (79%)	293 (62.3%)

7.1.5.4 Common adverse event tables

Table 16 below shows the 20 most frequently reported TEAE at the PT level. There are certain AE's that appear dose related including ventricular tachycardia, ventricular extrasystoles, supraventricular extrasystoles, sinus bradycardia, asthenia, and first degree AV block. The adverse event of "infusion site burning" appears to occur more frequently with tedisamil compared to placebo and occurs even at lowest studied dose of 0.16 mg/kg.

Table 16: TEAE (PT level)

AEPFT	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 - 0.48 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 - 0.72 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
Total # of subjects in "safety sample"	67	128	17	397	19	241	62	470
ATRIAL FIBRILLATION	8(11.9%)	20(15.6%)	4(23.5%)	48(12.1%)	2(10.5%)	35(14.5%)	21(33.9%)	62(13.2%)
VENTRICULAR TACHYCARDIA	0(0%)	6(4.7%)	2(11.8%)	24(6.0%)	4(21.1%)	29(12.0%)	15(24.2%)	28(6.0%)
HYPERTENSION	4(6%)	5(3.9%)	4(23.5%)	26(6.5%)	2(10.5%)	11(4.6%)	6(9.7%)	35(7.4%)
BRADYCARDIA	1(1.5%)	4(3.1%)	2(11.8%)	19(4.8%)	0(0%)	16(6.6%)	3(4.8%)	21(4.5%)
VENTRICULAR EXTRASYSTOLES	2(3.0%)	4(3.1%)	0(0%)	24(6.0%)	1(5.3%)	16(6.6%)	6(9.7%)	12(2.6%)
PALPITATIONS	0(0%)	4(3.1%)	0(0%)	19(4.8%)	1(5.3%)	13(5.4%)	0(0%)	12(2.6%)
ATRIAL FLUTTER	0(0%)	3(2.3%)	0(0%)	16(4.0%)	0(0%)	8(3.3%)	4(6.5%)	16(3.4%)
SUPRAVENTRICULAR EXTRASYSTOLES	1(1.5%)	2(1.6%)	0(0%)	16(4.0%)	0(0%)	9(3.7%)	6(9.7%)	13(2.8%)
HEADACHE	0(0%)	5(3.9%)	0(0%)	11(2.8%)	1(5.3%)	7(2.9%)	4(6.5%)	13(2.8%)
SINUS BRADYCARDIA	0(0%)	2(1.6%)	0(0%)	7(1.8%)	2(10.5%)	13(5.4%)	4(6.5%)	11(2.3%)
HYPOTENSION	2(3.0%)	2(1.6%)	1(5.9%)	9(2.3%)	2(10.5%)	4(1.7%)	3(4.8%)	10(2.1%)
ASTHENIA	0(0%)	1(0.8%)	0(0%)	14(3.5%)	0(0%)	9(3.7%)	3(4.8%)	4(0.9%)
DIZZINESS	0(0%)	4(3.1%)	0(0%)	9(2.3%)	0(0%)	5(2.1%)	2(3.2%)	11(2.3%)
DYSPNOEA	1(1.5%)	2(1.6%)	0(0%)	11(2.8%)	0(0%)	6(2.5%)	1(1.6%)	9(1.9%)
INSOMNIA	0(0%)	3(2.3%)	0(0%)	8(2.0%)	0(0%)	7(2.9%)	4(6.5%)	7(1.5%)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0(0%)	2(1.6%)	0(0%)	6(1.5%)	1(5.3%)	8(3.3%)	4(6.5%)	7(1.5%)
EXTRASYSTOLES	0(0%)	2(1.6%)	0(0%)	13(3.3%)	0(0%)	6(2.5%)	3(4.8%)	4(0.9%)
INFUSION SITE BURNING	2(3.0%)	6(4.7%)	0(0%)	5(1.3%)	1(5.3%)	5(2.1%)	4(6.5%)	2(0.4%)
NAUSEA	0(0%)	2(1.6%)	0(0%)	6(1.5%)	1(5.3%)	4(1.7%)	2(3.2%)	10(2.1%)
CHEST PAIN	0(0%)	0(0%)	0(0%)	9(2.3%)	1(5.3%)	3(1.2%)	0(0%)	9(1.9%)

Table 17 below compares the frequency of the top 5 commonly reported AEs as a function of sex/gender. The AE incidence rate does not appear markedly different between men and women.

Table 17: AE incidence in women and men for the top 5 reported TEAE's

		Tedisamil dose (mg/kg)					
Sex	MedDRA preferred term	0.16	0.24	0.32	0.48	0.64	placebo
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
M	ATRIAL FIBRILLATION	8 (12.1)		21 (12.2)	34 (16.4)	16 (30.8)	36 (15.6)
F	ATRIAL FIBRILLATION		20(16.4)	27 (12.0)	1 (2.9)	5 (50.0)	26 (10.9)
M	VENTRICULAR TACHYCARDIA	0 (0.0)		17 (9.9)	26 (12.6)	13 (25.0)	16 (6.9)
F	VENTRICULAR TACHYCARDIA		6 (4.9)	7 (3.1)	3 (8.8)	2 (20.0)	12 (5.0)
M	HYPERTENSION	4 (6.1)		9(5.2)	11(5.3)	5(9.6)	14(6.1)
F	HYPERTENSION		5 (4.1)	17 (7.6)	0 (0)	1 (10)	21 (8.8)
M	BRADYCARDIA	1 (1.5)		6 (3.5)	14 (6.8)	3 (5.8)	13 (5.6)
F	BRADYCARDIA		4 (3.3)	13 (5.8)	2 (5.9)	0 (0)	8 (3.3)
M	VENTRICULAR EXTRASYSTOLES	2 (3.0)		9 (5.2)	12 (5.8)	5 (9.6)	7 (3.0)
F	VENTRICULAR EXTRASYSTOLES		4 (3.3)	15 (6.7)	4 (11.8)	1 (10)	5 (2.1)

7.1.5.5 Identifying common and drug-related adverse events N/A

7.1.5.6 Additional analyses and explorations

Table 18 below shows TEAEs that occurred with an incidence of at least 2-fold higher on tedisamil compared to placebo. The table below pools data from tedisamil doses 0.32 mg/kg and 0.48 mg/kg, the proposed to be marketed doses in women and men respectively. The strongest signal for tedisamil-related adverse events occurs with adverse events of "Injection Site Pain," "Electrocardiogram QT prolonged," "Back Pain," "Hyperhidrosis," "Asthenia," and "Injection Site Burning."

Table 18: TEAEs with an incidence at least 2-fold higher greater on tedisamil compared to placebo

AEPFT	N(tedi) N = 638	% tedi	N(placebo) N = 470	% placebo
VENTRICULAR EXTRASYSTOLES	40	6.3	12	2.6
ASTHENIA	23	3.6	4	0.9
EXTRASYSTOLES	19	3.0	4	0.9
ELECTROCARDIOGRAM QT PROLONGED	13	2.0	1	0.2
INJECTION SITE PAIN	13	2.0	0	0
INFUSION SITE BURNING	10	1.6	2	0.4
BACK PAIN	9	1.4	1	0.2
HYPERHIDROSIS	9	1.4	0	0
PARAESTHESIA ORAL	7	1.1	2	0.4
ELECTROCARDIOGRAM ST SEGMENT ABNORMAL	6	0.9	2	0.4
INJECTION SITE BURNING	6	0.9	1	0.2
DYSGEUSIA	6	0.9	0	0
INFUSION SITE REACTION	6	0.9	0	0
DYSPEPSIA	5	0.8	1	0.2
BLOOD UREA INCREASED	4	0.6	1	0.2
HYPERTENSIVE CRISIS	4	0.6	1	0.2
INFUSION SITE PAIN	4	0.6	1	0.2
TACHYARRHYTHMIA	4	0.6	1	0.2
CARDIAC FAILURE CONGESTIVE	3	0.5	1	0.2
DIABETES MELLITUS	3	0.5	1	0.2
HAEMATURIA	3	0.5	1	0.2
HEPATIC ENZYME INCREASED	3	0.5	1	0.2
URINARY TRACT INFECTION	3	0.5	1	0.2
ACUTE MYOCARDIAL INFARCTION	3	0.5	0	0
ATRIOVENTRICULAR BLOCK SECOND DEGREE	3	0.5	0	0
ELECTROCARDIOGRAM Q WAVES	3	0.5	0	0
ELECTROCARDIOGRAM ST-T CHANGE	3	0.5	0	0
FLUSHING	3	0.5	0	0
HYPERURICEMIA	3	0.5	0	0
ISCHAEMIC STROKE	3	0.5	0	0
PAIN IN EXTREMITY	3	0.5	0	0
PARESTHESIA	3	0.5	0	0
RALES	3	0.5	0	0
RESPIRATORY TRACTION INFECTION VIRAL	3	0.5	0	0
THROMBOCYTOPENIA	3	0.5	0	0

Source: Analysis by Mehul Desai (combines AE data from 0.32 mg/kg and 0.48 mg/kg infusions)

7.1.6 Less Common Adverse Events

Table 19 below is the sponsor's tabulation of subjects that experienced a Torsade de Pointes adverse event in the integrated summary of safety (based on the development of tedisamil as an antiarrhythmic drug). The table shows that the sponsor identified a total of 12 cases of TdP of which 5 were sustained (requiring direct current cardioversion) and 7 were not sustained. There were a total of 6 cases in females and 6 in males. In most of the cases below, the occurrence of the TdP event was 11 to 48 minutes after initiation of study drug. In one case, the event occurred 18 hours post study drug initiation. Given that there is one case of TdP occurring 18 hours post study drug administration, the sponsor's proposal to monitor for 90 minutes post termination of study drug infusion seems inappropriate. Looking at the concomitant medication use in this subject, it does not appear that he received any confounding medications (except metoprolol) before or shortly after study initiation.

Table 19: Subjects experiencing Torsade de Pointes

STUDY ID	SUBJID	ARM	AGE	SEX	Description of TdP event; Time of onset relative to start of infusion	DC cardioversion needed?
3.112	23405	0.48 mg/kg	61	F	Sustained; 20 minutes	Yes
3.112	25414	0.64 mg/kg	64	F	Sustained; 30 minutes	Yes
3.112	25810	0.48 mg/kg	74	F	Non-sustained; 20 minutes	No
2.107	90644	0.48 mg/kg	87	F	Non-sustained; 45 minutes	No
3.114	41411	0.32 mg/kg + 0.16	76	F	Non-sustained; 45 minutes	No
3.118	80613	0.32 mg/kg	69	F	Non-sustained; 21 minutes	No
3.114	42301	0.48 mg/kg + 0.24	55	M	Non-sustained; 18 hours	No
3.112	22401	0.64 mg/kg	86	M	Non-sustained; 48 minutes	No
3.112	25825	0.64 mg/kg	79	M	Sustained; 15 minutes	Yes
3.114	42503	Placebo	67	M	Non-sustained; 4.5 hours	No
3.114	41021	0.32 mg/kg	54	M	Sustained; 11 minutes	Yes
3.114	41420	0.48 mg/kg	54	M	Sustained; 40 minutes	Yes

Source: Table 6 (page 27) of Sponsor's Risk Minimization Action Plan

Figure 6 below summarizes the incidence of TdP by sex in the integrated/pooled safety analysis. It is important to note that the figure below includes TdP events that were non-sustained and that did not require DC cardioversion. The incidence of TdP is rare at the doses proposed in labeling. The figure below shows the incidence of TdP increases relatively steeply in women at doses above 0.32 mg/kg. In men, there is a relatively steep increase in the incidence of TdP at doses above 0.48 mg/kg. It is important to note that there were relatively few cases of TdP observed overall and a relatively few female subjects exposed to doses above 0.32 mg/kg making estimates of the incidence of TdP unreliable at those doses. No firm conclusions about the differential risk of TdP in men and women should be made from the figure below.

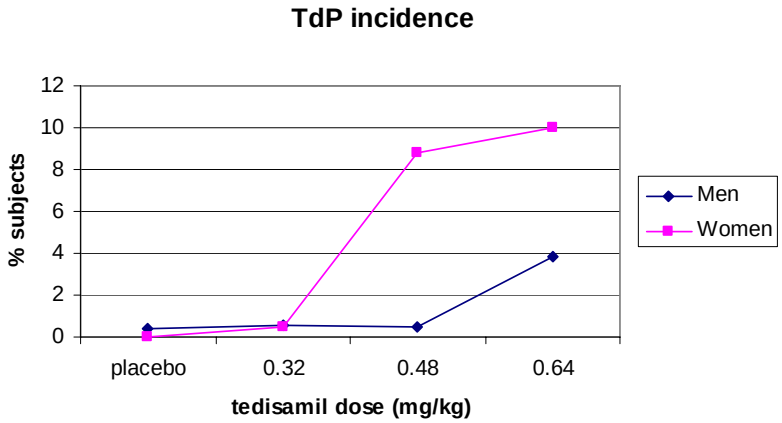

Figure 6: Incidence of TdP in women and men

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine laboratory tests (e.g. CBC, Chemistry labs) were performed at the screening visit, 24 hours post study drug initiation, and at the end of the 28 day safety follow-up period. Only selected studies and selected data are shown in this review. The sponsor's conclusion was that no laboratory parameters were significantly influenced by tedisamil. I have not seen any data in the sponsor's submission that refutes that conclusion.

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

In this section, I have included an analysis of laboratory data from what I believe are 2 representative studies of tedisamil. Please refer to section 4.2 of this review for a summary of the key studies in support of the atrial fibrillation indication. Study 3.116 was the largest study in the atrial fibrillation development program and was conducted in females only. Study 3.114 was also one of the larger studies in this development program and consisted of predominantly male subjects. The tables in section 7.1.7.3 below summarize the group mean data from these 2 studies.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Shown in Table 20 through Table 23 below are mean baseline (BL) values for the listed parameter and also the mean change from baseline to 24 hour post study drug initiation. Results of the safety labs that were collected at the 28 day follow-up visit are not included in this review. The data from the tables below do not suggest any clinically significant lab parameters changes from baseline based on group mean data.

Table 20: Changes from baseline in hematology parameters (Study 3.116)

	Tedi 0.24 N = 118		Tedi 0.32 N = 118		Placebo N = 119	
	BL value	Chg from BL	BL value	Chg from BL	BL value	Chg from BL
Hematocrit (V/V)	0.41	0	0.42	-0.01	0.41	-0.01
Platelet count (10^9/L)	245.09	-0.1	242.7	-3.15	237.26	2.91
WBC count (10^9/L)	7.08	0.03	6.98	0.11	7.14	-0.05

Table 21: Change from baseline in hematology parameters (Study 3.114)

	Tedi 0.16 N = 58		Tedi 0.32 N = 60		Tedi 0.48 N = 54		Placebo N = 75	
	Mean BL	Chg from BL	Mean BL	Chg from BL	Mean BL	Chg from BL	Mean BL	Chg from BL
Hct (V/V)	0.45	0	0.45	-0.02	0.44	-0.01	0.44	-0.01
Plt (10^9/L)	201.07	4.69	208.45	-6.91	212.34	-7.73	226.02	-3.08
WBC (10^9/L)	6.93	0.12	7.77	-1	7.19	-0.19	7.41	-0.54

Table 22: Changes from baseline in chemistry parameters (Study 3.116)

	Tedi 0.24 N = 118		Tedi 0.32 N = 118		Placebo N = 119	
	BL value	Chg from BL	BL value	Chg from BL	BL value	Chg from BL
ALBUMIN (g/L)	40.94	-1.17	40.65	-1.04	40.95	-1.59
ALK PHOS (IU/L)	84.90	-2.50	82.71	-3.37	86.40	-3.79
ALT (IU/L)	29.97	0.32	28.55	-0.45	35.00	0.46
AST (IU/L)	27.20	0.23	25.11	-0.06	30.11	0.04
CREATININE (mcmol/L)	82.33	3.07	79.05	3.90	78.41	2.26
CREATININE CL (mL/min)	73.65	-1.46	77.98	-2.18	83.77	-2.99
GGT (IU/L)	39.26	-0.56	39.12	-1.04	48.78	-2.46
GLUCOSE (mmol/L)	6.63	-0.03	6.82	0.17	6.53	0.52
MAGNESIUM (mmol/L)	0.93	-0.06	0.92	-0.05	0.93	-0.06
POTASSIUM(mmol/L)	4.26	0.09	4.28	0.05	4.36	-0.10
SODIUM (mmol/L)	141.10	0.04	140.68	-0.59	141.53	-0.88
T BILI (mcmol/L)	9.66	0.65	9.56	1.36	10.62	0.69

	Tedi 0.24 N = 118		Tedi 0.32 N = 118		Placebo N = 119	
	BL value	Chg from BL	BL value	Chg from BL	BL value	Chg from BL
TOTAL PROTEIN (g/L)	71.08	-1.29	70.15	-0.96	70.13	-1.79
UREA NITROGEN (mmol/L)	6.78	0.21	6.43	0.44	6.56	0.32
URICACID (mcmol/L)	379.48	-3.04	352.30	4.10	364.47	0.14

Table 23: Changes from baseline in chemistry parameters (Study 3.114)

	Tedi 0.16 N = 58		Tedi 0.32 N = 60		Tedi 0.48 N = 54		Placebo N = 75	
	Mean BL	Chg from BL	Mean BL	Chg from BL	Mean BL	Chg from BL	Mean BL	Chg from BL
ALBUMIN (g/L)	40.38	-0.91	39.89	-0.88	40	-1.48	40.39	-1.04
ALK PHOS (IU/L)	69.55	-0.74	75.34	-3	68.17	-1.48	85.5	-4.9
ALT (IU/L)	36.24	-1.08	38.39	-0.84	32.88	0.19	33.29	0.12
AST (IU/L)	27.84	1.42	36.04	-4.41	27.56	1.44	31.43	-1.73
CREATIN (mcmol/L)	90.77	0.91	91.68	1.95	92.63	1.35	90.51	-0.57
CREATININE CL (mL/min)	100.18	-2.83	99.66	-2.87	97.22	1.16	96.68	1.09
GGT (IU/L)	57.04	-3.6	65.18	-4.63	59.9	-0.38	79.79	-6.42
GLUCOSE (mmol/L)	6.46	-0.07	6.03	0.22	6.62	0.44	6.69	-0.19
MG (mmol/L)	0.85	0.01	0.87	-0.03	0.86	-0.03	0.87	-0.02
POTASSIUM(mmol/L)	4.43	0.05	4.42	-0.13	4.46	-0.06	4.35	0.02
SODIUM (mmol/L)	140.77	-0.46	140.36	-0.42	140.25	-0.29	140.37	-0.37
T BILI (mcmol/L)	11.02	-0.2	12.86	-0.97	13.98	-1.15	15.03	-1.45
TOTAL PROT (g/L)	70.79	-1.52	71.9	-2.66	71.85	-2.31	71.49	-2.33
UREA NIT (mmol/L)	6.75	0.53	6.43	0.42	6.76	0.34	6.37	0.28
URICACID (mcmol/L)	381.09	-1.78	404.51	-4.29	393.35	-13.94	388.45	-7.36

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Although not shown in this review, a visual analysis of the distributions of changes from baseline (from screening to 24 hours post study drug administration) in key hematology parameters (e.g. hematocrit, platelet count, and WBC count) and key chemistry parameters (e.g. albumin, alkaline phosphatase, ALT, AST, creatinine clearance, glucose, magnesium, potassium, and sodium) did not show any obvious differences between the tedisamil and placebo groups in study 3.116 or study 3.114.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

In the integrated analysis of safety, there were no subjects that terminated the study drug or that dropped out from the study due to a laboratory abnormality.

There was one case of a SAE consisting of elevated liver enzymes in a 75 year old female subject. This subject (ID # 73509) was enrolled in study 3.116 and received a dose of 0.32 mg/kg. On July 1, 2005, the day after the study drug infusion, the subject developed fever and

presented with elevated liver enzymes (alkaline phosphatase = 134 IU/L, ALT = 155 IU/L, AST = 269 IU/L, total bilirubin = 24 micromol/L). At the screening visit on June 30, the subject had liver enzymes within the normal range. The study subject was placed on antibiotics and had resolution of the fever on July 2 and resolution of elevated liver enzymes on July 5.

7.1.7.4 Additional analyses and explorations N/A

7.1.7.5 Special assessments N/A

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

There was a serial assessment of vital signs in the studies that form the integrated analysis of safety. Vital signs were collected at the following time points in most of the studies: 10 minutes pre-infusion and 0.5, 1, 2.5, and 24 hours post infusion. In study 2.107, vital sign assessment was relatively more intensive (10 minutes before infusion initiation, 0.5, 0.75, 1, 1.5, 2, 2.5, 4, 6, 8, and 24 hours post study drug initiation. Data from this single study are not shown in this review.

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

The vital sign data from all 9 safety studies were pooled and are presented in section 7.1.8.3.1 below. The data from subjects the relatively few subjects from study 3.114 that received the extended (50-minute) infusion are not included in the figures below.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Figure 7 below summarizes the group mean blood pressure in males at baseline and at various time points post initiation of study drug infusion. Tedisamil does appear to increase BP in males; however, there is no clear evidence of dose response.

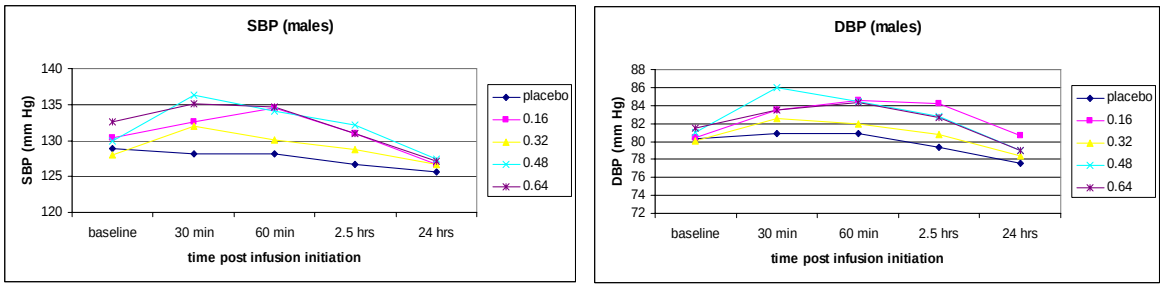

Figure 7: Mean SBP and DBP in males pre- and post study drug infusion.

Figure 8 below summarizes the group mean blood pressure in females at baseline and at various time points post initiation of study drug infusion. Similar to males, tedisamil appears to increase BP in females without evidence of dose response. Note that there were very few female subjects exposed to doses of 0.64 mg/kg and thus the data from this dose group may be less reliable relative to other dose groups.

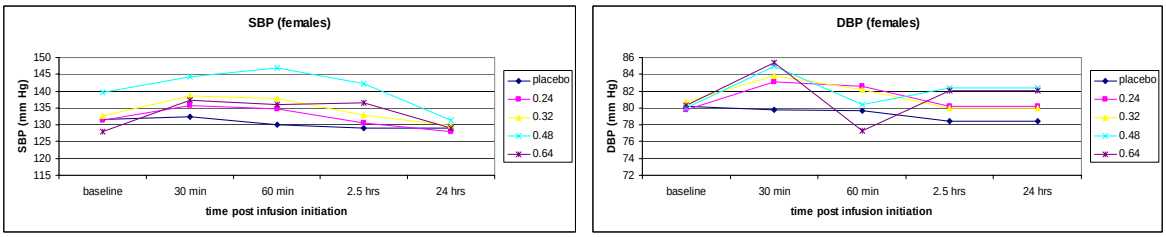

Figure 8: Mean SBP and DBP in females pre- and post study drug infusion

Figure 9 below shows the effect of tedisamil on pulse or heart rate change from baseline depending on whether subjects were classified as "converters" or "non-converters." Converters were defined as those subjects in the sponsor defined ITT population that converted to NSR within 2.5 hours of study drug initiation and that also were in NSR at 24 hours. Subjects not meeting this criterion were classified as "non-converters." The figure below shows that tedisamil produces a mean decrease in heart rate in "converters" but not in "non-converters." In converters, the effect on pulse is most pronounced in the first 30 to 60 minutes post study drug initiation. Thereafter the pulse drops significantly in the placebo arm for unclear reasons thus decreasing the separation between the study drug and placebo arms. While the effect is clearly greater on tedisamil compared to placebo, the question of whether there is a dose response is not as obvious.

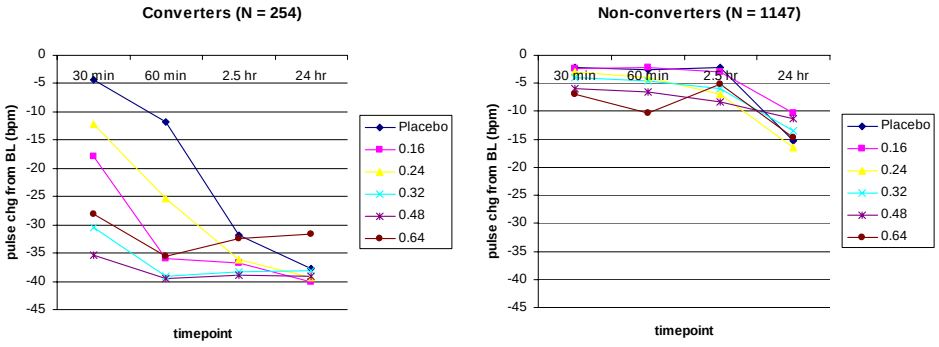

Figure 9: Mean Pulse change from pre-dose baseline in Converters vs Non-converters

Source: Analysis by Mehul Desai

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 24 below summarizes vital sign outlier data in the integrated analysis of safety. There was a higher incidence of subjects with a SBP ≤ 90 mm Hg and a decrease from baseline ≥ 20 mm Hg. There was also a higher incidence of subjects with a heart rate ≤ 50 bpm and a heart rate decrease from baseline ≥ 15.

Table 24: Outliers for vital sign data (SBP, DBP, and HR)

	Tedi (combined) N = 931	Placebo N = 470
SBP ≤ 90 mm Hg and decrease from baseline ≥ 20	14 (1.5%)	2 (0.4%)
SBP ≥ 180 mm Hg and increase from baseline ≥ 20	48 (5.2%)	16 (3.4%)
DBP ≤ 50 mm Hg and decrease from baseline ≥ 15	11 (1.2%)	7 (1.5%)
DBP ≥ 105 mm Hg and increase from baseline ≥ 15	57 (6.1%)	12 (2.6%)
HR ≤ 50 and HR decrease from baseline ≥ 15	88 (9.5%)	29 (6.2%)
HR ≥ 120 and HR increase from baseline ≥ 15	84 (9.0%)	46 (9.8%)

Source: Sponsor's analysis Table 2.7.4.4-3 from NDA 22,123

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Based on Table 12 in section 7.1.3.2, there were at least 5 subjects that pre-maturely discontinued the study drug infusion at least in part (or fully) due to hypotension. There were 3 subjects that pre-maturely discontinued the study drug infusion at least in part due to bradycardia.

7.1.8.4 Additional analyses and explorations N/A

7.1.9 Electrocardiograms (ECGs)

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

Twelve lead ECGs were serially collected in subjects post study infusion initiation at the following time points: Screening, -10 minutes prior to initiation of infusion, 10, 30, 45, 60, 90, 120, 150, 240, 360, 480, and 1440 minutes post infusion initiation.

In terms of preclinical results, in vivo studies in various species assessed the ECG and related effects on cardiac refractory periods over a wide dose range up to 8 mg/kg IV and 36 mg/kg orally. Tedisamil is more effective in increasing atrial versus ventricular action potentials in various animal species. Tedisamil increases the QT_c and ventricular refractory periods in rats, guinea pigs, ferrets, rabbits, cats, dogs, baboons, and monkeys. Tedisamil also reduced heart rates in a dose dependent manner in all species tested. Widening of QRS and PR intervals was restricted to higher dose groups. *In vitro* cardiac electrophysiologic studies show that tedisamil blocks human IKr with an $IC_{50} = 0.36$ μM. *In vitro* studies also show that tedisamil blocks voltage-dependent sodium channels and also causes slowing of AV and intraventricular conduction at higher concentrations (> 2 μM).

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

The ECG analyses presented in Figure 10 through Figure 13 below were pooled from the nine studies listed in section 4.2. Since tedisamil has effects on heart rate as discussed in section 7.1.8.3.1, only the QTc Fridericia data are presented in the figures below (the uncorrected QT and QTc Bazett's data are not shown). The data are sub-grouped by sex and also sub-grouped by whether subjects were "converters" or "non-converters." The rationale for sub-grouping by "converters" versus "non-converters" is that atrial fibrillation produces a noisy isoelectric baseline that makes it difficult to accurately measure the QT interval length. It is presumed that "converters" were more likely to be in NSR at various times of ECG capture. The "non-converter" subgroup includes subjects ITT population and also subjects in the safety population. It is worth noting again that the 0.16 mg/kg dose was investigated only in males while the 0.24 mg/kg dose was investigated only in females.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Figure 10 below shows the QTcF versus time profile in female subjects classified as "converters," (e.g. those subjects in the sponsor defined ITT population that were in NSR within 2.5 hours and in NSR at 24 hours). There is evidence for a dose dependent increase in QTcF

particularly at the 30 to 45 minute timepoint. The placebo and 0.32 mg/kg curves do not appear to merge together until the 720 minute timepoint.

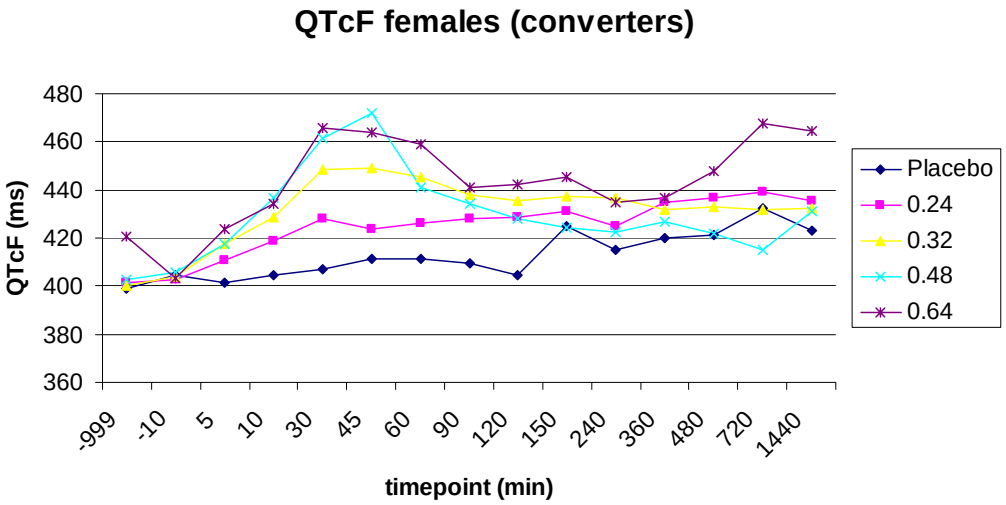

Figure 10: QTcF versus time profile in female "converters"

Figure 11 below shows the mean QTcF versus time profile in female, "non-converter" subjects. Included in the figure below are data from all female subjects that were classified as non-converters. The QTcF versus time profile is similar to that of "converters" particularly at the early timepoints (showing evidence of dose-dependent QTcF prolongation).

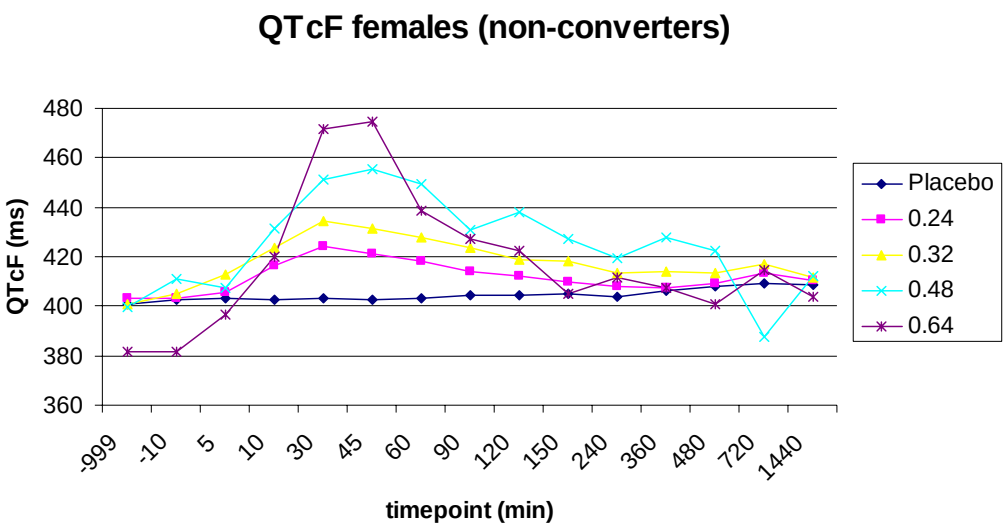

Figure 11: QTcF versus time profile in female "non-converters"

Figure 12 below shows the mean QTcF versus time profile in male "converters." Like in females, there is evidence for dose response at the 30 to 45 minute timepoint.

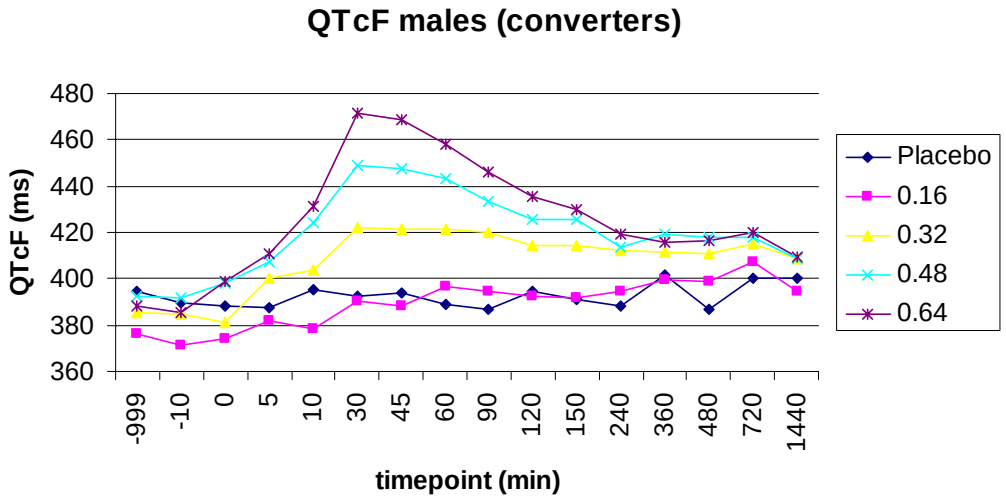

Figure 12: QTcF versus time profile in male "converters"

Figure 13 below shows the QTcF versus time profile in male, "non-converters." The figure below is generally similar to Figure 12 above except that the various curves appear to come together sooner in "non-converters" compared to "converters."

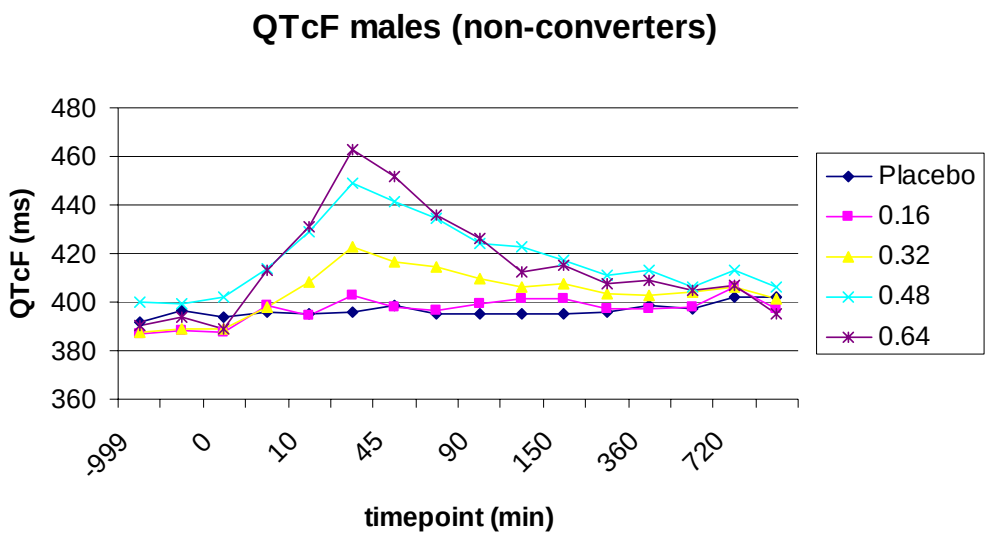

Figure 13: QTcF versus time profile in male "non-converters"

The data from the 4 figures above suggest that the sponsor's proposal for monitoring of subject's that will receive tedisamil is inadequate. The sponsor's proposal is that "monitoring should continue for the duration of the duration of PULZIUM therapy and for 1.5 hours thereafter." There is evidence that the curves for the 0.32 mg/kg dose in females and the 0.48 mg/kg dose in males are still sufficiently separated from placebo at the 120 minute post study drug initiation timepoint. Furthermore, as discussed in section 7.1.6, non-sustained, polymorphic ventricular tachycardia has been observed as late as 18 hours post study drug initiation. While the optimal duration of monitoring could be debated, it is likely that monitoring should be continued for more than 90 minutes post infusion termination.

The effects of tedisamil on QRS is much less pronounced than it is for effects on the QT interval. Figure 14 below shows the mean QRS values in the various treatment groups as a function of time. At baseline (time 0), the mean QRS values are not the same across different treatment groups. There does not appear to be evidence of a dose related increase in the QRS interval.

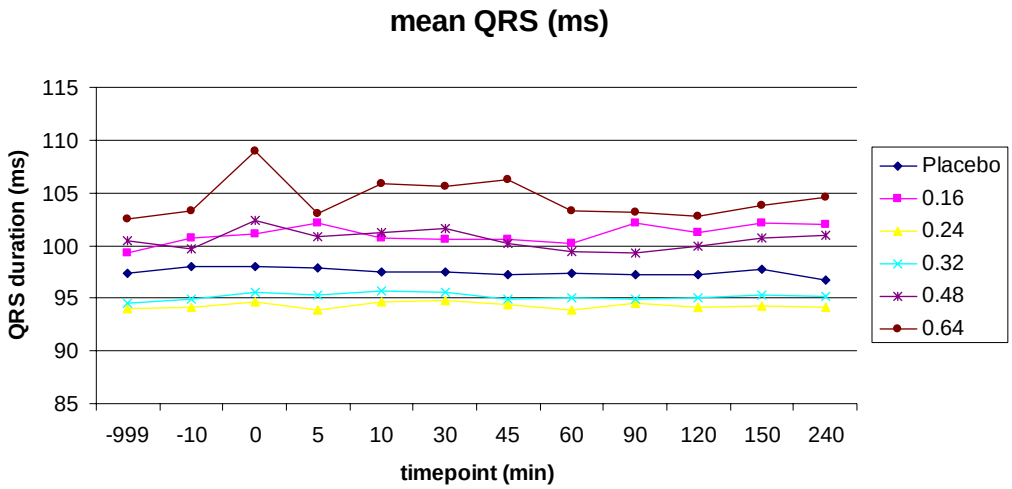

Figure 14: Effects of tedisamil on the QRS interval

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 25 below summarizes the number(%) of subjects that had QTcF changes from baseline > 60 ms. The table below assesses for outliers at the 120 minute time point post study drug initiation. This time point was chosen for analysis because it represents the time at which the sponsor recommends ECG monitoring terminated in the proposed labeling. The table below suggests that the 120 minute time point may be too early to stop ECG monitoring of subjects because many subjects still have QT changes from baseline exceeding 60 ms. QTcF changes from baseline > 60 ms were present in 3.5% of females at the 0.32 mg/kg dosing regimen and 8.3% of males at the 0.48 mg/kg dosing regimen.

The data in the table also suggest that subjects with mild to moderate degrees of renal impairment are not likely to need monitoring beyond what is needed for subjects with normal renal function (creatinine clearance > 90 mL/min).

Table 25: Number (%) of subjects with QTcF changes from BL > 60 ms (90 minutes post infusion termination)

Subgroup	Placebo	0.16	0.24	0.32	0.48	0.64
Females	Placebo (N = 207)	0.16 mg/kg (N = 1)	0.24 mg/kg (N = 96)	0.32 mg/kg (N = 199)	0.48 mg/kg (N = 33)	0.64 mg/kg (N = 9)
	1 (0.4%)		1 (1.0%)	7 (3.5%)	3 (9.1%)	3 (33.3%)
Males	Placebo (N = 217)	0.16 mg/kg (N = 57)	0.24 mg/kg (N = 6)	0.32 mg/kg (N = 163)	0.48 mg/kg (N = 180)	0.64 mg/kg (N = 49)
	0 ((0%)	1 (1.8)		8 (4.9%)	15 (8.3%)	10 (20.4%)

Subgroup	Placebo	0.16	0.24	0.32	0.48	0.64
CrCL ≥ 90 ml/min	Placebo (N = 174)	0.16 mg/kg (N = 28)	0.24 mg/kg (N = 23)	0.32 mg/kg (N = 151)	0.48 mg/kg (N= 95)	0.64 mg/kg (N = 34)
	0 (0%)	0 (0%)	1 (4.3%)	5 (3.3%)	7 (7.4%)	5 (14.7%)
CrCL ≥ 60, < 90 ml/min	Placebo (N = 157)	0.16 mg/kg (N = 23)	0.24 mg/kg (N = 45)	0.32 mg/kg (N = 133)	0.48 mg/kg (N= 86)	0.64 mg/kg (N = 22)
	0 (0%)	1 (4.3%)	0 (0%)	6 (4.5%)	6 (7.0%)	7 (31.8%)
CrCL ≥ 30, < 60 mL/min	Placebo (N = 73)	0.16 mg/kg (N = 4)	0.24 mg/kg (N = 31)	0.32 mg/kg (N = 65)	0.48 mg/kg (N= 26)	0.64 mg/kg (N = 2)
	0 (0%)	0 (0%)	1 (3.2%)	3 (4.6%)	5 (19.2%)	0 (0%)

Source: Analysis by Mehul Desai
Note: The data in the table above include both "converters" and "non-converters"

Table 26 below shows the number (%) of subjects with at least one QRS change from baseline > 30 ms. At higher tedisamil doses, there appear to be hints that there is greater QRS prolongation than at lower doses. However, the signal is not as pronounced as for QT effects of tedisamil.

Table 26: Number (%) of subjects with a QRS change from baseline > 30 ms

	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
QRS chg from BL > 30 ms	5 (7.5%)	7 (5.5%)	32 (8.1%)	23 (9.5%)	10 (16.1%)	31 (6.1%)

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

As shown in Table 12 above there were a total of 6 subjects that required premature termination of study drug infusion because of QT prolongation. Three subjects received doses of 0.48 mg/kg and 3 received doses of 0.64 mg/kg. All 6 subjects were male. Two subjects had a concomitant adverse event (in addition to QT prolongation). In one subject there were short runs of ventricular tachycardia and in another subjects there was hypotension associated with QT prolongation.

There were 3 subjects that had QRS prolongation that led, at least in part, to study drug discontinuation.

7.1.9.4 Additional analyses and explorations

Figure 15 below shows the QTcF change from baseline data at 30 minutes post infusion initiation (end of infusion). At the 30-minute timepoint, plasma concentrations of tedisamil are approximately at their highest level. As can be seen in the figures above in section 7.1.9.3.1, this is the time point where there is a maximal effect of tedisamil on the QT interval in both men and women. The data in the figure below show a dose dependent effect on the QTcF interval (change from BL) in both men and women. It is interesting to note that women and men have approximately the same QTcF changes from baseline at the 30 minute timepoint. This should be expected since the same weight adjusted dosing regimen given to women and men should produce a similar PK profile. What is less clear is the data in Figure 6 that shows a higher incidence of TdP in women compared to men at the 0.48 mg/kg and 0.64 mg/kg dosing regimen.

The incidence estimates of TdP may be unreliable in women at these doses due to few TdP events and few number of female subjects exposed to these dose levels.

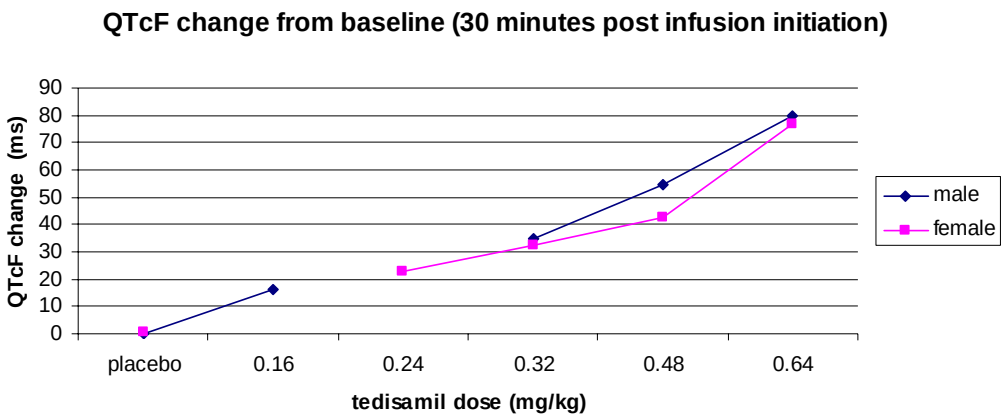

Figure 15: QTcF change from BL at the end of infusion as a function of dose

7.1.10 Immunogenicity N/A

7.1.11 Human Carcinogenicity N/A

7.1.12 Special Safety Studies N/A

7.1.13 Withdrawal Phenomena and/or Abuse Potential N/A

7.1.14 Human Reproduction and Pregnancy Data

There are no clinical data from the use of tedisamil in pregnant or lactating women. Safe use of tedisamil during pregnancy and lactation has not been established. In pregnant rats, tedisamil and/or its metabolites have been shown to cross the placenta and distribute into the fetus. Tedisamil is also excreted into the milk of lactating animals.

7.1.15 Assessment of Effect on Growth N/A

7.1.16 Overdose Experience

The sponsor reports no experience with accidental over-dosage. The sponsor reports that tedisamil is dialyzable based on in vitro data.

7.1.17 Postmarketing Experience N/A

7.2 Adequacy of Patient Exposure and Safety Assessments

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

7.2.1.1 Study type and design/patient enumeration

Please refer to section 4.2 for a listing of studies in the IV tedisamil, atrial fibrillation development program. Refer to section 6.1.3 for a summary description of the study designs of the key efficacy studies.

7.2.1.2 Demographics

Table 27 below contains demographic data from randomized subjects in the integrated safety population.

Table 27: Demographic data on the integrated safety population

	Tedi (combined) N = 931	Placebo N = 470
Mean ± SD age (years)	64.2 ± 11.5	64.5 ± 12.1
Age range (years)	26-91	20-92
Age (years) ≥ 65	495 (53.2%)	249 (53.0%)
Sex = Female	403 (43.3%)	239 (50.9%)
Race = White	911 (97.9%)	462 (98.3%)
Country = United States	91 (9.8%)	60 (12.8%)
Pre-dominant rhythm at randomization		
Atrial fibrillation	800 (85.9%)	408 (86.8%)
Atrial flutter	131 (14.1%)	62 (13.2%)
Duration of current episode		
3-48 hours	456 (49.0%)	221 (47.0%)
> 48 hours, 45 days	464 (49.8%)	242 (51.2%)

	Tedi (combined) N = 931	Placebo N = 470
Renal function		
Missing	32 (3.4%)	21 (4.5%)
< 30 mL/min	4 (< 1%)	5 (1.1%)
≥ 30 mL/min, < 60 mL/min	157 (16.9%)	85 (18.1%)
≥ 60 mL/min, < 90 mL/min	359 (38.6%)	167 (35.5%)
≥ 90 mL/min	379 (40.7%)	192 (40.9%)
Smoking status		
Current smoker	132 (14.2%)	64 (13.6%)
Former smoker	180 (19.3%)	82 (17.4%)
Never smoked	602 (64.7%)	314 (66.8%)
NYHA Class		
Missing	64 (6.9%)	34 (7.2%)
Class I	463 (49.7%)	232 (49.4%)
Class II	352 (37.8%)	173 (36.8%)
Class III	52 (5.6%)	31 (6.6%)

7.2.1.3 Extent of exposure (dose/duration)

Table 28 below shows the total number of male and female subjects randomized (and treated) in the pooled safety analysis. The vast majority of women (86.4%) randomized to tedisamil, received doses less than or equal to 0.32 mg/kg. The vast majority of men (87.3%) received doses of tedisamil less than or equal to 0.48 mg/kg. There were only a total of 62 subjects (10 females, 52 males) receiving a tedisamil dose of 0.64 mg/kg.

Table 28: Exposure to Tedisamil by dose and sex

	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 - 0.48 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 - 0.72 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
Total # of subjects in safety sample	67	128	17	397	19	241	62	470
Females	1	122	7	225	4	34	10	239
Males	66	6	10	172	15	207	52	231

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

As discussed in section 2.5, tedisamil was originally developed as an oral anti-anginal agent. There have been several randomized, placebo-controlled studies in subjects with coronary artery disease involving chronic, oral tedisamil administration. Safety information from chronic tedisamil administration may not be directly applicable to the setting in which single intravenous doses of tedisamil are administered for atrial fibrillation conversion. However, some data may be gleaned by focusing on adverse events that start within a short period of time after initiating oral tedisamil.

Table 29 below is derived from placebo-controlled studies in patients with coronary artery disease taking the oral formulation of tedisamil. The sponsor integrated or pooled data from studies 3101, 3108, 5013, 5024, 5027, and 5034. I have not reviewed any of these studies in

depth in this review. The COSTART body system and preferred term are shown in the left most column of the table. The data in the table show the number (%) of subjects dropping out due to an adverse event within 2 days of starting tedisamil. Similar to the IV tedisamil data, there is clear evidence of a dose dependent increase in drop-outs. There is also a dose dependent increase in the number of drop-outs due to cardiovascular (CV) and digestive system adverse events. There was 1 "sudden death" that occurred in a subject receiving the 200 mg bid dose. There were also 2 cases of myocardial infarctions – one at the 25 mg bid dose and one at the 200 mg bid dose. No myocardial infarctions were reported in the placebo group.

Table 29: Drop-outs due to AEs within 2 days of starting oral tedisamil

	Tedisamil dose (administered twice daily)							
	25 mg N = 75	50 mg N = 260	75 mg N = 157	100 mg N = 291	150 mg N = 74	200 mg N = 49	Total N = 830	Placebo N = 409
# with any AE	2 (2.7%)	4 (1.5%)	2 (1.3%)	10 (3.4%)	7 (9.5%)	14 (28.6%)	39 (4.7%)	3 (0.7%)
CV System	1 (1.3%)	3 (1.2%)	0	7 (2.4%)	4 (5.4%)	4 (8.2%)	19 (2.3%)	3 (0.7%)
Bradycardia	0	1 (0.4%)	0	2 (0.7%)	0	2 (4.1%)	5 (0.6%)	0
QT prolonged	0	0	0	1 (0.3%)	1 (1.4%)	1 (2.0%)	3 (0.4%)	0
Sudden Death	0	0	0	0	0	1 (2.0%)	1 (0.1%)	0
Digestive System	0	1 (0.4%)	1 (0.6%)	3 (1.0%)	5 (6.8%)	10 (20.4%)	20 (2.4%)	0
Diarrhea	0	0	1 (0.6%)	3 (1.0%)	4 (5.4%)	10 (20.4%)	18 (2.2%)	0

Source: Table 13.2.4.3.7a from information request submitted 4/26/2007

7.2.3 Adequacy of Overall Clinical Experience

If the exposures from the IV tedisamil program involving subjects with atrial fibrillation and the exposures from the oral tedisamil program involving subjects with coronary artery disease are totaled, the sponsor meets the ICH E1 criteria of 1500 patient exposures. However, this level of exposure may not be able to rule out the possibility of a small increase in risk of death or myocardial infarction if such a risk exists for tedisamil.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This appears adequate.

7.2.5 Adequacy of Routine Clinical Testing

This appears adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

While this appears adequate, one should refer to the Clinical Pharmacology/ Biopharmaceutics review for further details.

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

7.2.8 Assessment of Quality and Completeness of Data

Please refer to section 4.4 of this review for additional details on quality and completeness of data.

7.2.9 Additional Submissions, Including Safety Update N/A

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

As discussed elsewhere in this review, the potential for proarrhythmia exists with tedisamil. Cases of TdP have been reported with tedisamil which is not surprising based on the its pharmacologic activity. The relative risk of proarrhythmia with tedisamil relative to other approved agents for the conversion of atrial fibrillation to NSR can not be assessed because no comparative studies have been performed.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

This review provides a pooled or integrated analysis of safety and efficacy. Pooling data from the various phase 2 and/or phase 3 studies was rational for reasons cited elsewhere in this review.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Data on dose dependency for adverse events is shown in other parts of this review. In summary, there is evidence of dose dependence in the following measured parameters: QT prolongation, heart rate, and blood pressure. There is also evidence for dose dependency in the following adverse events: ventricular tachycardia, ventricular extrasystoles, infusion site burning/pain, first degree AV block.

7.4.2.2 Explorations for time dependency for adverse findings N/A

7.4.2.3 Explorations for drug-demographic interactions

Data on drug-gender/sex interactions with respect to efficacy and safety are presented in other parts of this review (e.g. section 6.1.4, 7.1.6, 7.1.8, 7.1.9).

7.4.2.4 Explorations for drug-disease interactions

Table 30 below shows the incidence of ventricular tachycardia as a function of baseline renal function. It does not appear that the risk of ventricular tachycardia or QT prolongation is affected by baseline creatinine clearance.

Table 30: Incidence of ventricular tachycardia as a function of creatinine clearance

Baseline Creatinine Clearance	Placebo	Tedisamil (pooled)
< 30 mL/min	0/5 (0%)	0/4 (0%)
≥ 30, <60 mL/min	4/85 (4.7%)	8/157 (5.1%)
≥ 60, < 90 mL/min	9/167 (5.4%)	39/359 (10.9%)
≥ 90	14/192 (7.3%)	30/379 (7.9%)

Table 31: Incidence of "Electrocardiogram QT prolonged" adverse event as a function of creatinine clearance

Baseline Creatinine Clearance	Placebo	Tedisamil (pooled)
< 30 mL/min	0/5 (0%)	0/4 (0%)
≥ 30, <60 mL/min	0/85 (0%)	2/157 (1.3%)
≥ 60, < 90 mL/min	1/167 (0.6%)	5/359 (1.4%)
≥ 90	0/192 (0%)	8/379 (2.1%)

Figure 16 below summarizes the time course of QTcF effects in subjects with moderate renal impairment (as defined by an estimated creatinine clearance ≥ 30 mL/min but less than 60 mL/min). The data in the figure below were derived using subjects in the integrated safety database (but excluding subjects receiving the extended infusion). Figure 17 below summarizes the time course of QTcF effects in subjects with normal renal function (as defined by an estimated creatinine clearance ≥ 90 mL/min). Based on the figures below, renal impairment does not appear to appreciably change the time course of QTcF effects of tedisamil. There were too few subjects with severe renal impairment studied in the development program to comment on the QTcF profile in this subgroup.

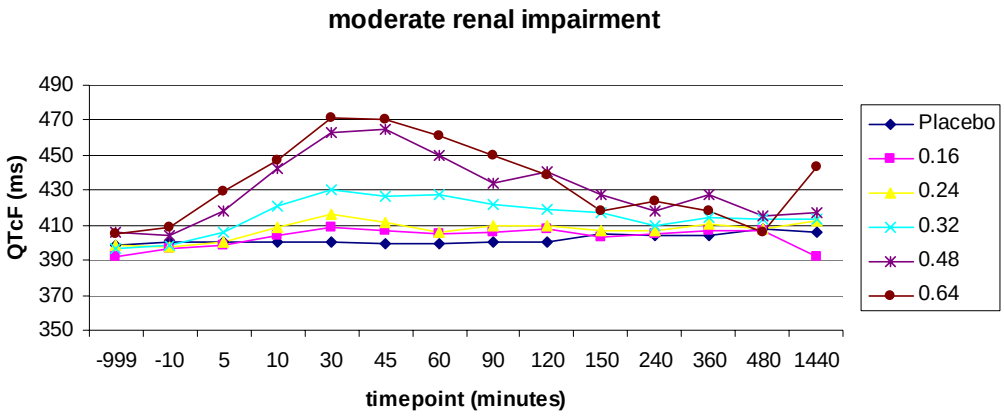

Figure 16: QTcF profile in subjects with moderate renal impairment

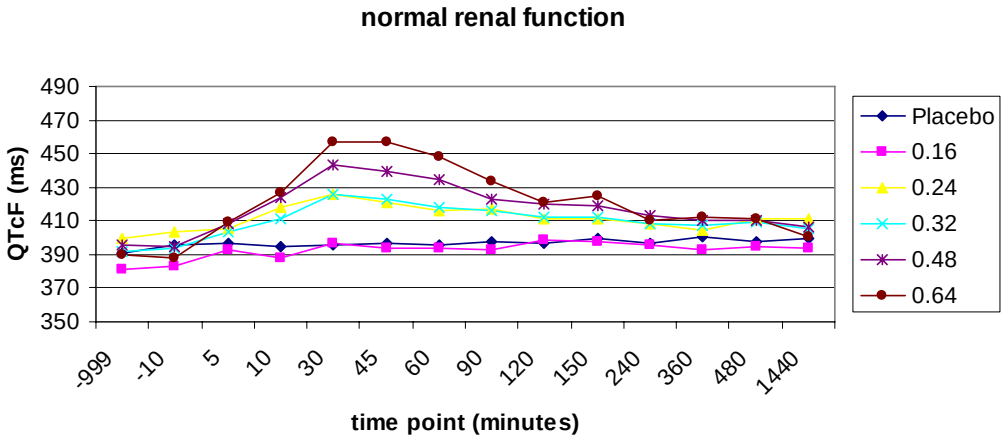

Figure 17: QTcF in subjects with "normal" renal function

7.4.2.5 Explorations for drug-drug interactions

No formal exploration for drug-drug interactions has been performed. The most commonly used drug prior to study drug initiation was digoxin (in 20% or fewer subjects).

Subject # 90229 was a 67 year old male subject that received study drug on April 16. On April 15, prior to receiving study drug, the subject received Lanoxin 0.5 mg and 0.25 mg IV. The subject experienced significant bradycardia with a continued pause requiring a bolus of Pronestyl followed by an IV drip. The subject also required placement of a pacemaker. By April 25, the

event had resolved. It is possible that the use of pre-study digoxin augmented the bradycardiac effects of tedisamil.

Subject #43001 experienced serious adverse events of bradycardia, hypotension, and cardiac arrest with 10 to 15 minutes post study drug initiation was reportedly receiving metoprolol and carvedilol prior to study drug administration. Like the case above, it is possible that the use of beta-blockers prior to study drug administration compounded the bradycardiac effects of tedisamil in this subject.

7.4.3 Causality Determination N/A

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor proposes a rather complex dosing regimen, one that could lead to medical errors if approved. The sponsor proposes a sex-specific, weight adjusted, 2-step infusion administered over a 30 minute period. Half, the sex specific, weight adjusted dose would be administered over the first 10 minutes. The remaining half would be administered over the next 20 minutes. This type of dosing regimen would require a health care provider to not only administer the appropriate sex specific dosing regimen but also to remember to turn down the infusion rate by 50% after 10 minutes. If the health care provider forgot to turn down the rate, a patient would be exposed to much higher plasma levels of tedisamil and the associated dose or concentration related side effects of tedisamil. I believe it is possible for the sponsor to simplify the dosing regimen in hopes of reducing medical errors by 1) administering the same weight adjusted dose in men and women and 2) administering a "bolus" of study drug to achieve a targeted plasma concentration followed by a continuous infusion to maintain the target plasma concentrations.

The sponsor proposes a dosing regimen that is both weight adjusted and sex specific. I see no clear rationale for both a weight-adjusted and sex specific dosing regimen. I believe that men and women should receive the same mg/kg dosing regimen. Presumably, the sponsor proposes a lower dose in females because of greater safety concerns in this subgroup. Figure 5 suggests that the incidence of TdP is greater in females compared to males at doses of 0.48 mg/kg and 0.64 mg/kg. However, it should be noted that there were relatively few cases of TdP observed overall and a relatively few female subjects exposed to doses above 0.32 mg/kg making estimates of the incidence of TdP unreliable at those doses. The QT data in Figure 15 suggest that there is little difference between males and females in the Fridericia corrected QT interval change from baseline at various doses at the time of maximal plasma concentrations. The potential for drug error could be reduced by having a uniform, weight adjusted dose in males and females. Males could still receive clinical benefit of tedisamil by lowering the dose from 0.48 mg/kg to 0.32 mg/kg while lowering their risk of adverse events. If one were able to define a minimal,

clinically relevant dose, further optimization of benefit and risk could be achieved with tedisamil.

The sponsor's proposed 2-step infusion produces a PK profile similar to that seen in Figure 2. It appears that the efficacy of tedisamil is related to the "pseudo-plateau" levels of tedisamil. The sponsor could reduce the risk of medical error by changing from a 2-step infusion to one in which a slow bolus is given over 1-2 minutes followed by a continuous infusion for approximately 30 minutes.

8.2 Drug-Drug Interactions

Tedisamil appears to produce slowing of heart rate. This effect was much more pronounced in subjects that converted compared to those that did not convert. The heart rate slowing caused by tedisamil may be augmented by other drugs that also reduce heart rate (e.g. digoxin or beta-adrenergic blockers). Please refer to section 7.4.2.5. Prescribing physicians should be cautioned about the synergistic heart rate lowering produced by tedisamil and other treatments that decrease heart rate.

8.3 Special Populations

The sponsor proposes to contraindicate use of tedisamil in patients with severe renal impairment as defined by a GFR < 30 mL/min. No dose adjustment is proposed by the sponsor in patients with mild to moderate renal impairment. The QTcF versus time profile in subjects with moderate renal impairment and in subjects with "normal" renal function is shown Figure 16 and Figure 17. The QTcF versus time profiles in the two subpopulations is not too different

8.4 Pediatrics N/A

8.5 Advisory Committee Meeting N/A

8.6 Literature Review N/A

8.7 Postmarketing Risk Management Plan

The sponsor has proposed a risk management plan for tedisamil. Elements of the risk management plan include tools such as a physician checklist (to ensure that the patient is suitable for treatment with tedisamil), an infusion bag sticker, an arrhythmia diagnostic guide, a dose guide and calculator, a QTc guide/calculator, a health care professional administration and monitoring guide, and a healthcare professional website.

It is important to note that ibutilide, an agent pharmacologically related to tedisamil and also indicated for the conversion of atrial fibrillation/flutter to normal sinus rhythm, is currently available in the U.S. without a risk management plan. Many elements or tools in the sponsor's proposed risk management plan are probably not needed as ibutilide is currently marketed without such a plan. However, if the sponsor and the Office of Surveillance and Epidemiology feel that a risk minimization plan is necessary, such a plan should focus on actions to minimize the likelihood of errors in drug administration (e.g. dose and dosing regimen errors).

8.8 Other Relevant Materials N/A

9 OVERALL ASSESSMENT

9.1 Conclusions

Pulzium® (tedisamil sesquifumarate) can be approved for use in patients with recent onset (≤48 hours duration) atrial fibrillation that is either newly diagnosed or paroxysmal. Tedisamil has been shown effective on the basis that it is superior to placebo and demonstrates evidence of dose response. Similar to other approved, Class III antiarrhythmic agents (e.g. ibutilide, dofetilide), tedisamil is proarrhythmic as would be expected based on its pharmacologic activity.

While tedisamil does not fill an unmet medical need, it would provide alternative therapeutic option to patients with a recent onset of atrial fibrillation. Based on the current available data, it can not be determined whether tedisamil possesses a unique safety or efficacy profile because there are no active control comparisons versus currently available therapy.

The data from the tedisamil development program do not convincingly support the efficacy of this drug in converting subjects with atrial flutter to normal sinus rhythm. The number of subjects with atrial flutter in the development program was quite small. The indication for tedisamil use should be limited to those with recent onset (≤ 48 hours) atrial fibrillation.

The approval of tedisamil should be conditional on the use of this compound health care professionals trained in the identification and treatment of acute ventricular arrhythmias and also in the setting of continuous ECG monitoring. The duration of monitoring should be continued for at least 6 to 8 hours. This proposed duration is longer than 90 minute monitoring duration proposed by the sponsor. The sponsor should also simplify the dose and dosing regimen as discussed in section 1.3.4.

9.2 Recommendation on Regulatory Action

Tedisamil can be approved provided the sponsor simplifies the dose and dosing regimen. While a weight adjusted dose is reasonable, there is no clear rationale for a sex specific dose. The same dose of 0.32 mg/kg could be administered to both males and females. The dosing regimen

should be simplified from its current two-step process. A bolus of tedisamil (over 1-2 minutes) followed by a continuous 30 minute infusion would probably decrease the likelihood of medication error compared to 2-step infusion where the health care provider would have to remember to reduce the infusion rate.

With respect to cardiac telemetry monitoring, the sponsor currently proposes to monitor subjects for 90 minutes post termination of infusion. In my opinion, this is too short a time to monitor.

9.3 Recommendation on Postmarketing Actions

Please refer to section 1.2.

9.4 Labeling Review

Please refer to section 10.3 for my preliminary labeling comments/suggestions.

9.5 Comments to Applicant N/A

10 APPENDICES

10.1 Pooled analysis of Phase 3 studies

The five phase 3 studies and the one phase 2 study (2.107) used in the integrated analysis of efficacy were designed similarly and thus amenable to integration or pooling. Throughout this review I have focused on providing an integrated analysis of the data. In the next two sections I provide a list of study objectives and inclusion/exclusion criteria common to each of the studies used in the integrated analysis.

10.1.1 Study objectives

Primary objective:

To demonstrate the superiority of a dose (or any dose in a multi-dose level study, if applicable) of tedisamil sesquifumarate to placebo in the rapid conversion to normal sinus rhythm (for at least 60 seconds), as measured by the percentage of subjects converted at any time within 2.5 hours after the start of infusion

Key secondary objectives:

- To determine the percentage of subjects converting to NSR at any time within 2.5 hours after the start of the intravenous infusion and in NSR at 2.5 hours after the initiation of the intravenous infusion of tedisamil sesquifumarate versus placebo.
- To determine the percentage of subjects converting to NSR at any time within 2.5 hours after the start of the intravenous infusion and in NSR at 24 hours after the initiation of the infusion of tedisamil sesquifumarate versus placebo.

10.1.2 Inclusion/exclusion criteria

There were some differences between individual studies in the pooled analysis. For example, some studies (e.g. 3.116 and 3.118) were done exclusively in women while some were done in men only.

Major inclusion criteria common to most of the studies in the pooled analysis:

1) Willing to sign informed consent
2) Age > 18 years

3) Subjects with documented (60 second rhythm strip) symptomatic atrial fibrillation (duration > 3 hours and < 45 days) at the time of randomization. (Study 2.107 was restricted to subjects with atrial fibrillation duration of > 3 hours but < 48 hours).
4) Subjects who are in no distress and hemodynamically stable

Major exclusion criteria common to most of the studies in the pooled analysis:

1) If women were eligible to participate in the study, any woman who is pregnant, lactating, or not using medically acceptable contraception. All women of child bearing potential who are not surgically sterilized must have a documented negative urine pregnancy test done at the screening visit and be practicing a medically acceptable contraceptive method for at least 3 calendar months prior to randomization.
2) Clinical evidence of hyperthyroidism
3) Demonstrated atrial or ventricular thrombus or vegetation during trans-esophageal echocardiogram
4) History of a cerebrovascular accident within six months prior to randomization
5) Congestive heart failure of NYHA functional Class IV
6) History of rheumatic heart disease (not applicable in studies 2.107, 3.112, and 3.114)
7) Acute coronary syndromes at the time of randomization
8) Known history and/or electrocardiographic evidence of ventricular pre-excitation
9) History of life-threatening ventricular arrhythmias including Torsade de Pointes
10) Previous electrocardiographic evidence of second or third degree AV block
11) Sick sinus syndrome (not applicable in studies 2.107, 3.112, and 3.114)
12) Ventricular rate < 50 bpm or > 200 bpm documented by 12-lead ECG
13) Myocardial infarction within 30 days prior to randomization
14) Cardiac surgery within 3 months prior to randomization
15) Need for external and internal pacemaker
16) Stent placement or PTCA within 30 days prior to randomization
17) Congenital long QT syndrome
18) QTc interval > 470 ms prior to randomization
19) Serum creatinine > 1.8 mg/dL
20) Serum potassium < 4.0 mEq/L
21) Serum Magnesium < 0.8 mmoL/L (not applicable in studies 2.107, 3.112, and 3.114)
22) Suspicion or evidence of digitalis intoxication
23) Concurrent treatment with antiarrhythmic drugs (except digitalis, diltiazem, or B-blockers), not discontinued for at least five half-lives before randomization. Sotalol is a disallowed medication.
24) Treatment with amiodarone within 3 months prior to randomization.
25) Participation in a previous tedisamil clinical study.
26) Severe valvular heart disease (not applicable in studies 2.107, 3.112, and 3.114)

10.1.3 Schedule of study procedures

Table 32 below summarizes the schedule of assessments from Study 3.118. It is representative of the schedule of assessments used in the other studies in the Integrated analysis of safety and efficacy.

There was a screening period for up to 48 hours prior to randomization. Study drug infusion was initiated at minute 0 and was continued until minute 30. There was a 24 hour observation period post study drug initiation. Holter monitoring was performed for a 24 hour period post study drug initiation. Study subjects were to have a safety follow-up 4 weeks after completion of the double-blind treatment period.

Table 32: Schedule of study assessments

SCHEDULE OF ASSESSMENTS

Assessment	Visit 1																	Safety Follow-up
	Screening Days	Baseline / Day 1 / Day 2															Monitoring in the hospital after 24-hour observation[5]	Days
		Minutes							Hours									
	Up to 48 hours	Baseline	-10	0[1]	5	10	30[2]	45	1	1.5	2	2.5	4	6	8	12	24		28
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
Demographic data	X																		
Medical History	X																		
Physical examination	X																X		X
Concomitant medication	X	X															X	X	X
12-lead ECG[3]	X	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X
Blood pressure, HR	X	X	X				X		X			X					X		X
Echocardiography	X																		
Laboratory assessment	X																X		X
Urine pregnancy test	X																		
Holter monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Telemetry			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Tedisamil PK sample[4]			X			X	X					X					X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Start of infusion
2 End of infusion
3 Additional recordings to be obtained at the time of conversion to normal NSR and the time of recurrence to atrial fibrillation / flutter during 24 hours post infusion
4 Additional sample to be drawn at the time when the infusion is prematurely stopped and at conversion (if possible)
5 Applicable to subjects only, who remain in the hospital after the 24 hour assessment.

10.1.4 Disallowed & Allowed Study medications

Medications that were disallowed included:

- Class I or Class III antiarrhythmic medications. In order to be included in the study these medications should have been discontinued for more than 5 half-lives prior to randomization.
- Amiodarone (was to have been discontinued for 3 months prior to randomization).
- Any potentially QT prolonging drugs (e.g. phenothiazines, tricyclic antidepressants, pentamidine, etc.).

Medications that were allowed include:

- Anticoagulants such as warfarin and other coumarin derivatives, heparin. Anticoagulation was to be undertaken at the discretion of the investigator following ACCP guidelines.
- Antihypertensive agents including potassium sparing diuretics (alone or combination with other diuretics), B-blockers, dihydropyridine calcium channel blockers, and diltiazem
- Acetylsalicylic acid
- Digoxin/digitoxin

10.1.5 Summary of key protocol amendments for studies 112, 114, 116, 117, and 118

10.1.5.1 Study 112 protocol amendments

Amendment 1 (28-June-2002):
Exclusion criteria regarding congestive heart failure subjects (originally Class III and Class IV) were changed so that only subjects with NYHA Class IV will be excluded.

Amendment 2 (26-August-2002):

- An internet address for an updated list of drugs that have the potential to prolong the QT interval was included in the protocol.
- There was also a change in the PK sample handling and work-up.

Amendment 3 (9-September-2002):
A secondary objective was added to the existing list of secondary endpoints. The new secondary objective dealt with the pharmacoeconomic evaluation of tedisamil.

Amendment 4 (30-September-2002):
This amendment added severe valvular heart disease and need for pacemaker as exclusion criteria.

Amendment 5 (22-May-2003):

- The protocol was amended to continue the study with male subjects only
- Continue with atrial fibrillation subjects only (excluding subjects with atrial flutter)
- "Sick sinus syndrome", "History of rheumatic heart disease", and "Serum Mg < 0.8 mmoL/L" were added as study exclusion criteria
- The number of ECGs collected in subjects that remain in the hospital beyond the 24-hour, post-infusion observation period was limited to one assessment per day.

Amendment 6 (27-August-2003):
Subjects with atrial flutter were re-allowed into the study (Amendment 5 excluded these subjects).

Amendment 7 (15-January-2004):
The 0.64 mg/kg tedisamil arm was terminated.

10.1.5.2 Study 114 protocol amendments

Amendments 1 through 6 were similar to the protocol amendments for Study 112

Amendment 7 (23-February-2004):
This amendment replaced the ECG interval QT by the QTc (calculated by Bazett's).

10.1.5.3 Study 116 protocol amendments

Amendment 1 (28-August-2003):
This amendment included subjects with atrial flutter in the study.

Amendment 2 (5-February-2004):
This amendment was applicable to Argentina only and changed the QTc cut-off exclusion from 470 ms to 450 ms.

Amendment 3 (13-September-2004):

- The 0.16 mg/kg arm of tedisamil was discontinued.
- To decrease the storage temperature for study medication
- The conditions for shipment of the PK samples were changed.

10.1.5.4 Study 117 protocol amendments

Amendment 1 (12-July-2004):
Replace the ECG interval QT by QTc (QTc calculated using Bazett's formula). Also the storage temperature for the study medication was decreased. Finally the conditions for shipment of study drug were modified.

10.1.5.5 Study 118 protocol amendments

Amendment 1 (12-July-2004):
The storage temperature for the study medication was decreased. Also, the conditions for shipment of study drug were modified.

10.1.6 Subject Disposition and Study populations (e.g. safety population, ITT)

Table 33 below summarizes the number of subjects screened, consented, and randomized, in the integrated safety and the integrated ITT population. The safety population consisted of subjects

that were randomized and received study drug. The ITT population consisted of subjects that were included in the safety sample of the respective study and who had at least some data on the primary efficacy parameter and who had not converted to NSR prior to initiation of study medication. The ITT population excluded subjects receiving the extended 50-minute infusion in Study 3.114.

Table 33 below shows that for the integrated analysis of efficacy, a total of 1424 subjects were randomized and 1297 were included in the ITT analysis. Thus about 9% of randomized study subjects were excluded from the ITT analysis. While this number may appear large for a clinical trial, in this specific case, given that tedisamil is highly effective, it may not be too much of a problem.

Table 33: Total # of subjects included in the Integrated Safety and Efficacy analyses

	Tedi (combined)	Placebo	Total
Integrated **safety analysis** that pools 9 studies (Study 2.102, 2.107, 3.111, 3.112, 3.113, 3.114, 3.116, 3.117, 3.118)			
Screened and consented			1619
All Randomized	974	495	1469
Safety Population (includes subjects randomized & that received study drug)	931	470	1401
Integrated **efficacy analysis** that pools 6 studies (Study 2.107, 3.112, 3.114, 3.116, 3.117, 3.118) excluding dose infusions greater than 30 minutes			
Screened and consented			1551
All Randomized			1424
Randomized AND did not receive study drug			66
Randomized and received 50 min infusion regimen (excluded from ITT)			50
Randomized but excluded from ITT for "other reasons"			11
Sponsor defined ITT population	859	438	1297

Source: Request for information received via email 3/14/2007

Table 34 below shows the number of randomized subjects not included in the ITT population in each of the individual studies comprising the integrated efficacy analysis. The table shows that there were relatively more subjects randomized but not included in the ITT population in studies 2.107 and 3.114 compared to studies 3.112, 3.116, 3.117, and 3.118. Given that there is a consistent efficacy of tedisamil across the individual studies that form the integrated analysis of efficacy, and that no individual study is driving the results of the integrated analysis makes the data from the table below reassuring.

Table 34: Total # of randomized subjects not included in the ITT analysis by study

Studies	Not dosed	Received 50-min infusion	"Other reason for exclusion"	Totals
2.107	21	0	6	27
3.112	11	0	0	11
3.114	16	50	2	68
3.116	9	0	2	11
3.117	6	0	0	6
3.118	3	0	1	4
All 6 studies				127

Source: Request for information received via email 3/14/2007

Table 35 below shows the number of subjects that prematurely terminated from the study. There were proportionately more subjects pre-maturely terminating from the study due to adverse events on tedisamil (pooled) relative to placebo. There was a dose dependent increase in drop-outs on tedisamil as shown in section 7.1.3.1.

Table 35: Disposition of study subjects

	Tedi (combined)	Placebo
Sponsor defined "ITT"	859	438
Subjects terminating "pre-maturely"	49 (5.7%)	20 (4.6%)
Adverse Event	20 (2.3%)	5 (1.1%)
Lack of efficacy	0	0
Lost to Follow-up	16 (1.9%)	9 (2.1%)
Withdrew consent	11 (1.3%)	4 (0.9%)
Administrative	1 (0.1%)	0
Protocol Violation	1 (0.1%)	2 (0.5%)
Subjects completing study	810	418

Source: Table 2.7.3.3-4 from NDA 22,123

10.1.7 Protocol Deviations

Protocol deviations were assessed in the 6 studies used for the integrated efficacy analysis (Study 2.107, 3.112, 3.114, 3.116, 3.117, 3.118). There were a total of 12 major protocol deviations. This would account for less than 1% of all randomized subjects in these studies.

Ten of the 12 major deviations occurred on tedisamil while 2 occurred on placebo.

Table 36 below shows that most of the major protocol deviations were from study 2.107.

Table 36: List of major protocol deviations

Study ID	Subject ID	Treatment Arm	Deviation type
S219.2.107	90066	TEDI 0.48 MG/KG	INTAKE OF FORBIDDEN CO-MEDICATION
S219.2.107	90180	TEDI 0.32 MG/KG	WRONG TREATMENT
S219.2.107	90181	TEDI 0.48 MG/KG	WRONG DOSING
S219.2.107	90249	PLACEBO	WRONG

Study ID	Subject ID	Treatment Arm	Deviation type
			TREATMENT
S219.2.107	90286	TEDI 0.48 MG/KG	INTAKE OF FORBIDDEN CO-MEDICATION
S219.2.107	90321	TEDI 0.48 MG/KG	WRONG DOSING
S219.2.107	90628	TEDI 0.48 MG/KG	WRONG DOSING
S219.2.107	90629	TEDI 0.48 MG/KG	WRONG DOSING
S219.2.107	90631	TEDI 0.48 MG/KG	WRONG DOSING
S219.3.112	27202	PLACEBO	INTAKE OF FORBIDDEN CO-MEDICATION
S219.3.114	41021	TEDI 0.32 MG/KG	INTAKE OF FORBIDDEN CO-MEDICATION
S219.3.114	41420	TEDI 0.48 MG/KG	INTAKE OF FORBIDDEN CO-MEDICATION

10.1.8 Baseline characteristics

Table 37 below summarizes baseline characteristics of study subjects in the integrated "ITT" population. The table shows that the 2 groups were balanced for the most part. However, there were nominally more female subjects in the placebo arm compared to the tedisamil arm.

Table 37: Baseline characteristics in the "ITT" population

	Tedi (combined) N = 859	Placebo N = 438
Mean (Std Dev) Age (years)	64.2 (11.6)	64.6 (12.2)
Age ≥ 65 years	461 (53.7%)	233 (53.2%)
Female	383 (44.6%)	227 (51.8%)
Race		
White	846 (98.5%)	432 (98.6%)
Mean (Std Dev)Body Mass Index (kg/m^2)	28.7 (4.86)	29.1 (5.22)
Mean (Std Dev) Pulse	97.9 (24.4)	97.7 (24.8)
Mean (Std Dev) Systolic BP (mm Hg)	131.1 (16.3)	130.2 (16.4)
Mean (Std Dev) Diastolic BP (mm Hg)	80.7 (10.2)	80.3 (10.6)
NYHA Class		
Class I	440 (51.2%)	219 (50.0%)
Class II	326 (38.0%)	164 (37.4%)
Class III	49 (5.7%)	30 (6.8%)
Class IV	0 (0%)	0 (0%)
Baseline Creatinine Clearance		
< 30 mL/min	3 (0.3%)	5 (1.1%)
≥ 30 - < 60 mL/min	148 (17.2%)	76 (17.4%)
≥ 60 - < 90 mL/min	331 (38.5%)	160 (36.5%)
≥ 90 mL/min	347 (40.4%)	176 (40.2%)

	Tedi (combined) N = 859	Placebo N = 438
Baseline uncorrected QT (msec)		
< 400 ms	750 (87.3%)	389 (88.8%)
≥ 400 – 470 ms	67 (7.8%)	29 (6.6%)
> 470 ms	1 (0.1%)	0

Source: Tables 2.7.3.3-8, 2.7.3.3-12 from NDA 22,123

Table 38 below summarizes the relevant atrial fibrillation/atrial flutter history in the "ITT" subjects. The tedisamil and placebo arms were similar at baseline. Approximately one-half of subjects presented to the study with a first ever reported episode of atrial fibrillation/flutter. Approximately one-half of subjects had an Afib/Afl duration of 48 hours or less.

Table 38: Atrial fibrillation/Atrial flutter medical history in the ITT population

	Tedi (combined) N = 859	Placebo N = 438
Number of subjects with first episode	412 (48%)	201 (45.9%)
Number of subjects with recurrent episode	447 (52%)	237 (54.1%)
Previously suffering from Afib	368 (82.3%)	194 (81.9%)
Previously suffering from Aflutter	29 (6.5%)	19 (8.0%)
Previously suffering from Afib & Aflutter	50 (11.2%)	23 (9.7%)
Mean Duration of Afib/Aflut (years)	4.2	3.9
Median Duration of Afib/Aflut (years)	2.9	2.7
Less than 1 attack/3 months	276 (61.7%)	152 (64.1%)
More than 1 attack/ 3 months	171 (38.3%)	85 (35.9%)
Shortest median duration of previous episode (days)	1	1
Longest median duration of previous episode (days)	3	3
Most recent episode terminated spontaneously	126 (28.2%)	72 (30.4%)
Most recent episode terminated by DC Cardioversion	100 (22.4%)	57 (24.1%)
Most recent episode terminated by pharmacologic conversion	219 (49.0%)	106 (44.7%)
Duration of Atrial fibrillation		
3-48 hours	419 (48.8%)	207 (47.3%)
>48 hrs – 45 days	438 (51.0%)	231 (52.7%)
> 45 days	0	0

Source: Table 2.7.3.3-17 from NDA 22,123.

Table 39 below summarizes the relevant medical history (other than atrial fibrillation/flutter) in "ITT" subjects. The two groups were similar with respect to baseline medical co-morbidities.

Table 39: Other relevant medical history

	Tedi (combined) N = 859	Placebo N = 438
Hypertension	561 (65.3%)	298 (68.3%)
Coronary Artery Disease	154 (17.9%)	90 (20.5%)
Myocardial Ischemia	151 (17.6%)	58 (13.2%)
Cardiac Failure	113 (13.2%0	54 (12.3%)
Atrial Fibrillation	91 (10.6%)	49 (11.2%)
Cholecystectomy	79 (9.2%)	41 (9.4%)

	Tedi (combined) N = 859	Placebo N = 438
Angina Pectoris	76 (8.8%)	43 (9.8%)
Diabetes Mellitus	75 (8.7%)	48 (11.0%)
Obesity	73 (8.5%)	45 (10.3%)
Hyperlipidemia	69 (8.0%)	44 (10.0%)

Source: Table 2.7.3.3-15 from NDA 22,123.

Table 40 below shows the relevant baseline characteristics or demographics by individual study. The data in the table below are based on an evaluation of the ITT population in each of the listed studies. There was some heterogeneity in the individual studies that comprise the integrated ITT population. Note that study 2.107 primarily enrolled subjects that had an Afib/Afl duration of 48 hours or less.

Table 40: Baseline characteristics by individual study

	Study 2.107	Study 3.112	Study 3.114	Study 3.116	Study 3.117	Study 3.118
Total # of "ITT" subjects	174	272	227	356	117	151
Mean ± SD age (yrs)	63.6 ± 13.8	61.0 ± 11.2	59.6 ± 12.1	68.2 ± 9.1	62.4 ± 11.6	70.9 ± 9.7
Age (years)						
< 65	79 (45.4%)	163 (59.9%)	146 (64.3%)	111 (31.2%)	64 (54.7%)	40 (26.5%)
≥ 65	95 (54.6%)	109 (40.1%)	81 (35.7%)	245 (68.8%)	53 (45.3%)	111 (73.5%)
Afib/Afl duration (hours)						
≤ 48	172 (98.9%)	138 (50.7%)	90 (39.6%)	118 (33.1%)	67 (57.3%)	42 (27.8%)
> 48	2 (1.1%)	134 (49.3%)	136 (59.9%)	238 (66.9%)	50 (42.7%)	109 (72.2%)
Predominant BL rhythm						
Afib	139 (79.9%)	233 (85.7%)	199 (87.7%)	318 (89.3%)	96 (82.1%)	135 (89.4%)
Aflut	35 (19.6%)	39 (14.3%)	28 (12.3%)	38 (10.7%)	21 (17.9%)	16 (10.6%)
Arrhythmia history						
1st episode	64 (36.8%)	113 (41.5%)	138 (60.8%)	165 (46.3%)	57 (48.7%)	76 (50.3%)
Recurrent episode	110 (63.2%)	159 (58.5%)	89 (39.2%)	191 (53.7%)	60 (51.3%)	75 (49.7%)
BL Creat CL (mL/min)						
Unknown	25 (14.4%)	5 (1.8%)	11 (4.8%)	5 (1.4%)	2 (1.7%)	3 (2.0%)
< 30	0 (0%)	1 (0.4%)	0 (0%)	3 (0.8%)	1 (0.9%)	3 (2.0%)
≥ 30, < 60	18 (10.3%)	22 (8.1%)	26 (11.5%)	95 (26.7%)	12 (10.3%)	51 (33.8%)
≥ 60, < 90	55 (31.6%)	105 (38.6%)	70 (30.8%)	154 (43.3%)	45 (38.5%)	62 (41.1%)
≥ 90	76 (43.7%)	139 (51.1%)	120 (52.9%)	99 (27.8%)	57 (48.7%)	32 (21.2%)
NYHA Class						
Unknown	4 (2.3%)	1 (0.4%)	2 (0.9%)	28 (7.9%)	12 (10.3%)	22 (14.6%)
Class 1	111 (63.8%)	182 (66.9%)	118 (52.0%)	131 (36.8%)	61 (52.1%)	56 (47.9%)
Class 2 and 3	59 (33.9%)	89 (32.7%)	107 (47.1%)	197 (55.3%)	44 (37.6%)	73 (48.3%)

10.1.9 Use of medications prior to randomization and in the first 24 hours post randomization

Table 41 below summarizes the most commonly used drugs prior to study-drug initiation. Medications used in more than 5% of subjects are reported in the table below. The use of various medications was balanced at baseline as shown in the table below based on pooling of studies in the integrated analysis of efficacy. The most commonly used medication prior to study drug initiation was digoxin with a frequency of about 20%.

It is interesting to note that in a population of subjects such as the one studied in this development program (with nearly 50% of subjects having intermittent atrial fibrillation) the use of anticoagulation was very low. The use of warfarin at baseline occurred in less than 4% of study subjects. Guidelines suggest a population like this should be chronically anticoagulated.

Table 41: Summary of commonly (> 5%) used medications prior to start of study

Drug name (generic)	N(TEDI)	% TEDI	N(PLAC)	% PLAC
# of subjects in the ITT population	859		438	
# of subjects taking at least 1 medication	673 (	78.3	330	75.3
DIGOXIN	163	19.0	91	20.8
METOPROLOL	145	16.9	68	15.5
VERAPAMIL	106	12.3	49	11.2
POTASSIUM	89	10.4	50	11.4
PROPAFENONE	91	10.6	38	8.7
SOTALOL	69	8.0	34	7.8
AMIODARONE	65	7.6	37	8.4
ATENOLOL	57	6.6	33	7.5
PROPRANOLOL	61	7.1	29	6.6
HEPARIN	48	5.6	27	6.2

Source: Analysis by Mehul Desai

Table 42 below shows that there was some heterogeneity in the use of certain medications across studies. There was no single medication used in more than 30% of subjects in any of the individual studies.

Table 42: Commonly used medications prior to start of study by individual study

	Study 2.107	Study 3.112	Study 3.114	Study 3.116	Study 3.117	Study 3.118
Total # ITT subjects	174	272	227	356	117	151
DIGOXIN	24 (13.8%)	56 (20.6%)	45 (19.8%)	74 (20.8%)	13 (11.1%)	42 (27.8%)
METOPROLOL	28 (16.1%)	46 (16.9%)	22 (9.7%)	64 (18.0%)	23 (19.7%)	30 (19.9%)
VERAPAMIL	12 (6.9%)	21 (7.7%)	54 (23.8%)	48 (13.5%)	9 (7.7%)	11 (7.3%)
POTASSIUM	11 (6.3%)	35 (12.9%)	21 (9.3%)	41 (11.5%)	15 (12.8%)	16 (10.6)
PROPAFENONE	13 (7.5%)	17 (6.3%)	17 (7.5%)	50 (14.0%)	9 (7.7%)	23 (15.2%)
SOTALOL	27 (15.5%)	27 (9.9%)	12 (5.3%)	21 (5.9%)	10 (8.5%)	6 (4.0%)
AMIODARONE	11 (6.3%)	30 (11.0%)	23 (10.1%)	18 (5.1%)	5 (4.3%)	15 (9.9%)
ATENOLOL	7 (4.0%)	32 (11.8%)	13 (5.7%)	22 (6.2%)	5 (4.3%)	11 (7.3%)
PROPRANOLOL	0 (0%)	30 (11.0%)	18 (7.9%)	34 (9.6%)	6 (5.1%)	2 (1.3%)
HEPARIN	16 (9.2%)	16 (5.9%)	20 (8.8%)	18 (5.1%)	2 (1.7%)	3 (2.0%)

Source: Analysis by Mehul Desai

Table 43 below summarizes the most commonly used medications newly started after the start of study drug infusion or taken before the start of the study and continued to be taken after the start of study treatment. Medications taken by more than 10% of subjects in the tedisamil arm are shown. The data in the table below are derived from the integrated ITT analysis population.

Table 43: Medications newly taken after start of study treatment or cont'd after start of study treatment

	N(TEDI)	% tedi	N(PLAC)	% placebo
ACETYLSALICYLIC ACID	430	50.1	203	46.3
METOPROLOL	347	40.4	174	39.7
WARFARIN	243	28.3	134	30.6
AMIODARONE	245	28.5	118	26.9
ENALAPRIL	223	26.0	109	24.9
HEPARIN-FRACTION	212	24.7	89	20.3
DIGOXIN	175	20.4	101	23.1
ACENOCOUMAROL	173	20.1	101	23.1
HEPARIN	162	18.9	88	20.1
POTASSIUM	143	16.6	88	20.1
FUROSEMIDE	127	14.8	82	18.7
HYDROCHLOROTHIAZIDE	111	12.9	86	19.6
PROPAFENONE	123	14.3	74	16.9
ATENOLOL	115	13.4	60	13.7
BISOPROLOL	116	13.5	55	12.6
SIMVASTATIN	101	11.8	52	11.9
SOTALOL	85	9.9	52	11.9
ISOSORBIDE DINITRATE	97	11.3	39	8.9

Source: Analysis by Mehul Desai

As with the use of medications before study drug initiation, there was heterogeneity between individual studies in the use of various medications post study drug initiation (data is not shown in this review).

10.1.10 Secondary endpoint analyses and Subgroup Analyses

Before showing data on the effect of tedisamil on sustaining NSR at **both** 2.5 hours and 24 hours post study drug initiation, I would like to show data on the number of subjects receiving DC cardioversion and/or prohibited medication in the 24 hour period after study drug initiation. Table 44 below shows that the number (%) of subjects requiring DC cardioversion was higher on placebo compared to tedisamil (as would be expected). The table also shows that the number of subjects requiring DC cardioversion and/or prohibited medication during the first 24 hours was also higher on placebo compared to tedisamil.

Table 44: Number (%) of subjects DC cardioversion and/or a prohibited medication(1st 24 hours)

	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
Total # of subjects in ITT	58	118	388	235	60	438
# of subjects requiring DC cardioversion in 1st 24 hours	7(12.1%)	23(19.5%)	78(20.1%)	50(21.3%)	12(20%)	123(28.1%)
# of subjects requiring DC cardioversion ***and/or*** receiving a prohibited medication in the 1st 24 hours	10(17.2%)	29(24.6%)	116(29.9%)	88(37.4%)	19(31.7%)	177(40.4%)

Source: Analysis by Mehul Desai

Table 45 below suggests that the effects of tedisamil seen early (at 2.5 hours) are sustained at 24 hours post study drug initiation. The first row in the table below is the total number of subjects in the integrated ITT population. In the second row are subjects excluded from the original, integrated ITT population because they underwent DC cardioversion and/or received a prohibited antiarrhythmic medication at any time in the first 24 hours post study drug initiation. The third row shows the number of subjects in the modified ITT population (subtracting subjects in row 2 from those subjects in row 1). The fourth row shows the number of subjects in NSR at any time within the first 2.5 hours and in NSR at 24 hours. Note that the denominator for Row 4 is Row 3.

Table 45: Number (%) of subjects in NSR at 2.5 hours AND 24 hours post study drug

	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
# of subjects in the integrated ITT population	58	118	388	235	60	438
# of subjects excluded from integrated ITT population because of DC cardioversion and/or a prohibited medication in the first 24 hours	10	29	116	88	19	177
Modified ITT (# of subjects in the ITT sample that did not undergo DC cardioversion ***and/or*** did not receive a prohibited medication within 24 hours)	48	89	272	147	41	261
In NSR (at least 60 seconds) at any time within 2.5 hours **and** in NSR at 24 hours after the start of Study drug infusion	9(18.8%)	12(13.5%)	79(29.0%)	69(46.9%)	28(68.3%)	19(7.3%)

Source: Analysis by Mehul Desai

Table 46 below shows a subgroup analysis of the primary efficacy endpoint – specifically the number (%) of subjects that were responders. Subgroup analysis is shown for age, concomitant beta blocker use, NYHA Class, and duration of most recent episode of atrial fibrillation. Subgroup analysis was not done for race or baseline rhythm since there were very few non-white subjects and few subjects with atrial flutter at baseline. The data in the table below reflect pooling of 5 studies (3.112, 3.114, 3.116, 3.117, 3.118).

Subjects with a duration of Afib/Afl > 48 hours were clearly less responsive to tedisamil compared to subjects with a duration of Afib $\leq$ 48 hours.

Table 46: Subgroup analysis of primary efficacy endpoint - N(%) of subjects that converted

	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
< 65 years	8 (23.5%)	4 (12.1%)	28 (20.3%)	36 (36.7%)	25 (69.4%)	9 (5.0%)
≥ 65 years	4 (16.7%)	8 (9.4%)	37 (19.9%)	25 (30.1%)	10 (45.5%)	11 (5.6%)
Concomitant beta blocker	10 (24.4%)	8 (8.5%)	45 (18.4%)	39 (32.8%)	23 (60.5%)	17 (5.9%)
No Concomitant beta-blocker	2 (11.8%)	4 (16.7%)	20 (25.3%)	22 (35.5%)	12 (60.0%)	3 (3.3%)
NYHA Class 1	10 (33.3%)	1 (2.6%)	36 (23.7%)	38 (37.6%)	28 (70.0%)	11 (6.0%)
NYHA Class II/III	2 (7.1%)	11 (15.1%)	26 (17.8%)	21 (29.2%)	7 (38.9%)	8 (4.7%)
Duration ≤ 48 hours	11 (37.9%)	10 (27.8%)	43 (35.5%)	44 (50.6%)	22 (68.8%)	17 (11.4%)
Duration > 48 hours	1 (3.4%)	2 (2.4%)	22 (10.8%)	17 (18.3%)	13 (50.0%)	3 (1.3%)

Source: Various Tables from 2.7.3.3-46 through 2.7.3.3-63 from NDA 22,123. The data on the subgroup response in subjects with a predominant baseline rhythm of atrial fibrillation or atrial flutter was derived by Mehul Desai.

Table 47 shows a subgroup analysis of the primary efficacy endpoint based on the predominant rhythm at baseline. The data in the table below reflect a pooling on the 5 phase 3 studies and 1 phase 2 study (2.107). The likelihood of a favorable response (conversion to NSR at 2.5 hours) is greater in subjects with a baseline rhythm of atrial fibrillation compared to those with a baseline rhythm of atrial flutter. It is important to note that only about 10%-20% of subjects in the overall tedisamil program had a baseline rhythm of atrial flutter and thus any conclusions about the safety and/or efficacy in this subgroup should be made with caution.

Table 47: N(%) converters as a function baseline rhythm

	N(TEDI 0.16 MG/KG)	N(TEDI 0.24 MG/KG)	N(TEDI 0.32 MG/KG)	N(TEDI 0.48 MG/KG)	N(TEDI 0.64 MG/KG)	N(PLACEBO)
Predominant BL rhythm = Afib	12 (24%)	10 (9.4%)	90 (26.5%)	82 (42.5%)	33 (64.7%)	21 (5.5%)
Predominant BL rhythm = Aflut	0 (0%)	2 (16.7%)	2 (4.2%)	7 (16.7%)	4 (44.4%)	3 (5.2%)

Source: Analysis by Mehul Desai

10.1.11 Additional analyses

Table 48 below summarizes the number of subjects receiving a prohibited anti-arrhythmic medication during the first 24 hours following study drug infusion. There were 5 subjects that received a prohibited medication during the first 2.5 hours post study drug initiation. Of these 5 subjects, 4 received tedisamil and 1 received placebo.

Table 48: Subjects receiving a prohibited antiarrhythmic during the first 24 hours following infusion

Drug	Tedisamil Dose mg/kg						
	0.16	**0.24**	**0.32**	**0.48**	**0.64**	**Combined tedisamil**	**Placebo**
N	58	118	388	235	60	859	438
AMIODARONE		4 (3.4%)	19 (4.9%)	17 (7.2%)	4 (6.7%)	44 (5.1%)	18 (4.1%)
ANTIARRHYTHMICS, CLASS I AND III	0	0	0	1 (0.4%)	0	1 (0.1%)	0
CORDICHIN	0	0	0	1 (0.4%)	0	1 (0.1%)	0
DOFETILIDE	0	0	1 (0.3%)	2 (0.9%)	0	3 (0.3%)	3 (0.7%)
FLECAINIDE	0	0	0	1 (0.4%)	0	1 (0.1%)	3 (0.7%)
IBUTILIDE	0	0	1 (0.3%)	4 (1.7%)	0	5 (0.6%)	13 (3.0%)
IPRATROPIUM	0	0	0	1 (0.4%)	0	1 (0.4%)	0
LIDOCAINE	0	0	0	2 (0.9%)	2 (3.5%)	4 (0.5%)	0
PRAJMALIUM	0	0	0	0	0	0	1 (0.2%
PROCAINAMIDE	0	0	1 (0.3%)	1 (0.4%)	0	2 (0.2%)	2 (0.2%)
PROPAFENONE	3 (5.2%)	5 (4.2%)	16 (4.1%)	12 (5.1%)	3 (5.0%)	39 (4.5%)	25 (5.7%)
QUINIDINE	0	0	5 (1.3%)	4 (1.7%)	0	9 (1.0%)	4 (0.9%)
SOTALOL	0	0	10 (2.6%)	8 (3.4%)	4 (6.7%)	22(2.6%)	14 (3.2%)
	3 (5.2%)	9 (7.6%)	53 (13.7%)	54 (23.0%)	13 (21.7%)	132 (15.4%)	83 (17.2%)

Source: Table 2.7.3.3-24 from NDA 22,123

Table 49 below compares and contrasts "converters" and "non-converters." "Converters" were subjects that converted to NSR at any time within 2.5 hours post study drug initiation. "Non-converters" did not convert to NSR within this prespecified period of time. Of the total 1297 subjects in the sponsor defined ITT analysis, 266 (20%) were "converters" and 1031 (80%) were "non-converters". "Converters" were more likely than "non-converters" to have received tedisamil. "Converters" were more likely than "non-converters" to be in NSR at 24 hours. "Converters" were also more likely than "non-converters" to have a baseline Afib/Afl duration of 48 hours or less. "Converters" also experienced fewer DC cardioversions in the first 24 hours post study drug initiation compared to "non-converters." There was similar frequency of use of a prohibited medication (e.g. dofetilide, ibutilide, amiodarone, sotalol, etc.) in the 24 hours post study drug initiation in "converters" and "non-converters."

Table 49: Comparison of "converters" and "non-converters" at 2.5 hours post study drug infusion

	NSR at 2.5 hours (N = 266)	Not NSR at 2.5 hours (N = 1031)
How many on tedisamil?	242 (91.0%)	617 (59.8%)
How many in NSR at 24 hours?	254 (95.5%)	332 (32.2%)
Afib/Afl duration ≤ 48 hours	203 (76.3%)	424 (41.1%)
Subjects receiving DC cardioversion in first 24 hours	12 (4.5%)	281 (27.3%)
Subjects receiving prohibited medication in first 24 hours	35 (13.2%)	165 (16.0%)

Source: Analysis by Mehul Desai

Of the 1031 "non-converters" at 2.5 hours, 634 (61.5%) did not subsequently receive either DC cardioversion or some other antiarrhythmic agent within 24 hours of study drug administration. Of these 634 subjects, 533 remained "non-converters" at 24 hours. This data suggest that the study investigators saw no urgency to treat these subjects. This also suggests that subjects were not so uncomfortable with the symptoms of atrial fibrillation that they were demanding some type of treatment from study investigators.

10.2 Review of Individual Study Reports

N/A

10.3 Line-by-Line Labeling Review

On the following page is the sponsor's proposed labeling along with my recommended changes.

Page 82 redacted for the following reason:
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Page 83 redacted for the following reason:
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Page 84 redacted for the following reason:
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Mehul Desai
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MEDICAL OFFICER

CLINICAL PHARMACOLOGY

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	22-123
Category	1S
Brand Name (proposed)	Pulzium
Generic Name	Tedisamil sesquifumarate
Applicant	Solvay Pharmaceuticals Inc.
Submission Date(s)	12/18/2006 and 08/09/2007
Clinical Pharmacology Reviewer	Robert O. Kumi, Ph.D.
Clinical Pharmacology Team Leader	Patrick Marroum, Ph.D.
Pharmacometrics Reviewer	Christoffer Tornoe, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
OCP Division	1
OND Division	Cardiovascular and Renal Drug Products
Submission Type; Code	N_000
Formulation; Strength(s)	Solution for IV administration, 20 mg/ 10 mL
Class/Indication	Anti-arrhythmic/ rapid conversion of recent onset (3 h to 45 days) atrial fibrillation or atrial flutter, to normal sinus rhythm

Briefing Level: Required Office Level for NME
Briefing Date: 09/06/2007
Briefing Attendees: C. Garnett, N. Stockbridge, S. Lemtouni, T. Marciniak, E. Fromm, T. Fadiran, T. Ong, E. Mishina, M. Mehta, A. Parekh, R. Uppoor, J. Lazor, S. Targum, M. Blank and Drug Saety Representative

1. Executive Summary

Solvay Pharmaceuticals Inc, submitted NDA 22-123- Pulzium (Tedisamil Sesquifumarate IV Solution) on December 18, 2006 pursuant to Section 505 (b) of the Federal Food, Drug and Cosmetic Act and to 21 CFR §314.50. Pulzium is proposed for rapid conversion of recent onset (3 h to 45 days) atrial fibrillation or atrial flutter, to normal sinus rhythm. Tedisamil is primarily a class III anti-arrhythmic agent. Pharmacologically it is characterized as a multiple potassium (I_{Kr}, I_{Ks}, I_{Kur}, I_{to}, I_{KACH}, I_{KATP}) and above 2 μM also sodium current (I_{Na}) blocker with predominant atrial activity.

Pulzium will be marketed as a 20 mg/10 mL solution for IV administration. The proposed dosage regimen is a single two-step 30 minute infusion (half over 10 min and remainder over 20 min) but the actual dosage is dependent on sex:

- AF/AFL in Males: 0.48 mg/kg
- AF/AFL in Females: 0.32 mg/kg

Numerous clinical and non-clinical studies were conducted to support the Pulzium NDA including five pivotal trials with the to-be-marketed formulation in the target patient population, over 40 clinical pharmacology (pharmacokinetic studies), and over 10 *in vitro* studies. The clinical studies were conducted in healthy subjects and various patient groups including patients with the AF/AFL, coronary artery and ischemic heart disease. Tedisamil was administered intravenously as well as orally; however, most of the studies were via the oral route. In the clinical studies both tedisamil salt forms, tedisamil sesquifumarate and tedisamil dihydrochloride, were administered.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 22-123. The CPB information provided in NDA 22-123 is acceptable. However, the applicant should adequately address the following:

Comments to Applicant

- Please characterize tedisamil's PGP transport *in vitro* with respect to Papp (apparent permeability coefficient) using at least two PGP inhibitors
- Reach agreement on labeling (Please refer to the attached, revised label in Section 4.1), particularly with regard to drug-drug interactions. The sponsor has not adequately addressed tedisamil's CYP2D6 inhibition potential: An in vivo drug-drug interaction study with tedisamil and a sensitive CYP2D6 substrate was not conducted.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Biopharmaceutics Findings

Over 40 studies were included in the clinical pharmacology and biopharmaceutics development program for the use of tedisamil in patients with atrial fibrillation (AF) or atrial flutter (AFL). In these studies tedisamil was administered by the oral and intravenous route, as a dihydrochloride or sesquifumarate salt. Five pivotal clinical studies provided data for a population PK/PD analysis. Additionally, tedisamil was evaluated in over 10 *in vitro* studies. Studies included in NDA 22-123 are presented in Appendix 4.1; not all of the submitted studies were reviewed because they were not required for evaluation of the proposed formulation or indication.

Key Clinical Pharmacology and Biopharmaceutics Findings and Information

1. General Pharmacokinetics (ADME)

- A three-compartment pharmacokinetic (PK) model with first-order elimination adequately described the time-course of the observed tedisamil concentrations following a two-step IV infusion over 30 minutes of 0.16 mg/kg to 0.72 mg/kg in patients with AF or AFL.
- Systemic clearance is dose-independent; this translated into dose proportional increase in area under the curve (AUC) following IV administration over the tedisamil dose range of 0.8 to 26 mg in healthy subjects and 0.16 to 0.72 mg/kg in AF/AFL subjects.

Absorption/absolute bioavailability

Tedisamil *absolute oral bioavailability* (BA) following administration of the dihydrochloride (DHCl) is approximately 60 %.

Distribution

- *In vitro* plasma protein binding is approximately 93 % at therapeutic concentrations, and exhibits concentration dependent binding at supra-therapeutic concentrations.
- The volume of distribution at steady-state (Vss) ranges from 68 to 70 L in healthy subjects and from 72 to 90 L in AF/AFL subjects.
- Body weight is a significant covariate for tedisamil volume of distribution.

Metabolism and P-glycoprotein

In vitro information

- CYP enzymes do not contribute to the metabolism of tedisamil.
- Tedisamil is a strong inhibitor of CYP2D6, inhibits CYP2C19 and CYP3A4 to a limited extent, but does not inhibit other CYP enzymes *in vitro*.
- Tedisamil does not appear to be an inducer of CYP enzymes.
- Tedisamil passes through membranes at an intermediate rate and is a substrate for the human P-glycoprotein (PGP) transporter. The PGP-mediated transport of tedisamil is inhibited *in vitro* by verapamil.

In vivo information

- No clinically significant drug-drug interactions were found in the population PK analysis (beta blockers, verapamil and other agents) of IV administered tedisamil.
- No clinically significant drug-drug interactions were found when atenolol, digoxin, warfarin, nifedipine, isosorbide dinitrate, or glibenclamide were administered with oral tedisamil. However, coadministration of oral tedisamil and verapamil led to a clinically significant increase (77 %) in tedisamil exposure.

Properties of metabolites

Only one metabolite was identified in man, the M1 or 11-hydroxy tedisamil (KC 11233). This metabolite is 2- to 3- fold less active than tedisamil and accounts for < 4 % of tedisamil exposure

Excretion (Elimination)

- Tedisamil is almost exclusively eliminated as unchanged drug via the renal route. Upon IV administration, 83.5% of the radioactivity from a 14C-tedisamil dose is recovered in urine and 7.9% is recovered in the feces over a period of 96 h. The metabolism of tedisamil is very limited. An average of 3.4% of the total radioactivity recovered from the urine is attributable to a single hydroxy metabolite.
- Following a single IV infusion of tedisamil, total clearance (CL) ranges from 204 to 267 mL/min in healthy subjects, with renal clearance (ranging from 183 to 201 mL/min) accounting for approximately 80% of total clearance. CL ranges from 142 to 239 mL/min in AF/AFL subjects.

2. Exposure Response (PK/PD) of tedisamil

General PD Characteristics

- Alters electrophysiological measures: generally increases QT and QTc, PR- and RR- and QRS- intervals and decreases T-wave amplitude
- Decreases heart rate (bradycardic effect)

QT analysis

- The population PK/PD relationship between QTcF and tedisamil concentrations was adequately described by a linear model.
- Tedisamil was found to increase the QTc change from baseline with a mean predicted change from baseline QTc of 32 and 38 msec at the mean observed male and female tedisamil C_{max} of 954 and 1317 ng/mL, respectively.
- The mean QTcF is predicted to return to normal 8 hours after tedisamil dosing of 0.32 and 0.48 mg/kg.

Exposure-Efficacy

- The probability of converting to normal sinus rhythm within 2.5 hours after start of the tedisamil infusion is correlated with tedisamil Cmax.
- Atrial fibrillation patients with their most recent onset of AF episode less than 8 hours from tedisamil dosing had significantly higher response rates (60%) compared to patients with duration of the most recent episode >8 hours (20%).

- Patients with atrial fibrillation have higher response rates compared to atrial flutter patients at similar tedisamil exposure.
- Male patients have higher response rates compared to females at similar tedisamil exposure. The Applicant's proposed dose for males is higher (0.48 mg/kg) than that for females (0.32 mg/kg) based on a reported difference in the incidence of Torsades de Pointes (TdP) at the 0.48 mg/kg dose.

Exposure-Safety

- The probability of developing tachycardia, bradycardia, extrasystoles, AV block, hypertension, and TdP increases with increasing tedisamil Cmax
- Females appear to be more likely to develop TdP compared to males at similar tedisamil exposure.

3. Special/Sub-Populations (Population PK Covariate Analyses)

- Creatinine clearance is a significant covariate for tedisamil clearance with a 10 % and 350 % higher Cmax and AUC, respectively, in patients with severe renal impairment compared to patients with normal renal function.
- PK of IV tedisamil in AF/AFL subjects is not influenced by gender, smoking status, congestive heart failure (CHF) grade according to the New York Heart Association (NYHA) classification, albumin level and total protein level.
- The effect of race and hepatic function was not adequately evaluated.

4. Formulation

The tedisamil SQF formulation proposed for marketing is bioequivalent with the DHCL formulation when given as 26 mg free base using a two-step 30-min IV infusion.

Signatures

Clinical Pharmacology Reviewer: _____

Pharmacometrics Reviewer _____

Team Leader Concurrence

Pharmacometrics _____

Clinical Pharmacology _____

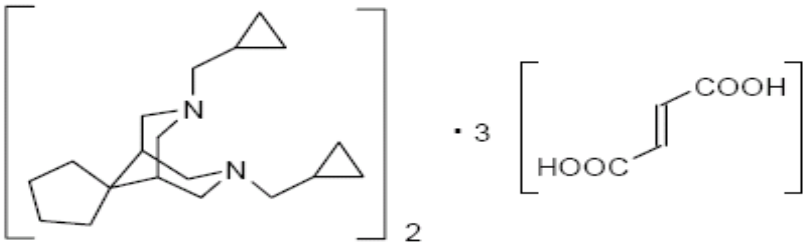
2 Question Based Review

2.1 What are the general attributes of tedisamil?

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

Tedisamil sesquifumarate is formulated as a solution for IV administration. Additional characteristics of tedisamil are as follows:

Chemical Name 3,7-bis(cyclopropylmethyl)-3,7- diazaspiro [bicyclo [3.3.1]nonane-9,1'-cyclopentane] (2E)-but-2-enedioate (2:3)
Molecular Weight 288.48 Da (free base) and
Molecular Formula $[C_{19}H_{32}N_2]_2 \cdot 3 [C_4H_4O_4]$
Structural Formula



Appearance white to off-white crystals or crystalline powder
Solubility soluble in water and freely soluble in methanol

Formulation Information

The final IV solution is described as a 20 mg/10 mL clear, colorless aqueous liquid. The drug product is a sterile solution for IV application which has to be diluted prior to use. The composition of the to-be-marketed formulation is presented in Table 1.

Table 1: Composition of tedisamil sesquifumarate solution

Component	Theoretical Quantity (mg) per Unit	Function	Reference
Tedisamil (as Tedisamil sesquifumarate)	20.0 (32.07)	Active ingredient	SOLID 0000050497
Sodium chloride	90.0	Tonicity adjustment	Ph.Eur.[1] / USP-NF[1,2]
Water for injections	to 10052 (= to 10 ml)	Solvent	Ph.Eur.[1] / USP-NF[1,2]

[1] current edition
[2] NF = National Formulary of the United States

2.1.2 Proposed Mechanism of Action and Indication

Tedisamil has been developed as a class III anti-arrhythmic agent for the rapid conversion of AF or AFL of recent onset (3 h to 45 days) to normal sinus rhythm (NSR). Pharmacologically it was characterized as a multiple potassium (I_{Kr}, I_{Ks}, I_{Kur}, I_{to}, I_{KACH}, I_{KATP}) and above 2 µM also sodium current (I_{Na}) blocker with predominant atrial activity.

2.1.3 Proposed Administration Route and Dosage

Pulzium is intended for intravenous administration using a 20 mg/10 mL solution. The proposed dosage regimen is a single two-step 30 minute infusion (half over 10 min and remainder over 20 min) but the actual dosage is dependent on sex:

- AF/AFL in Males: 0.48 mg/kg
- AF/AFL in Females: 0.32 mg/kg

2.2 What are the general clinical pharmacology characteristics of tedisamil?

2.2.1. Design features of clinical studies used to support dosing in AF/AFL patients

The key design features of the clinical studies used to support dosing in the target population (AF/AFL) are summarized in Table 2.

Table 2: Key design features of the primarily clinical and clinical pharmacology studies supporting proposed indication

Study	Salt	Route of Admin	Dose (free base)	Total Number of Subjects ITT Population		Subject Type
Phase II Studies						
2.102	DHCL	IV	0.16 mg/kg (10 minute) 0.24 mg/kg (10 minute) Placebo	26 Subjects	20 M 6 F	M & F Sustained (3-90 days) Afib/Afl
2.107	DHCL	IV	0.32 mg/kg (30 minute) 0.48 mg/kg (30 minute) Placebo	175 Subjects	108 M 67 F	M & F Recent onset Afib/Afl
Phase III Studies (Pivotal)						
3.112	SQF	IV	0.32 mg/kg (30 minute) 0.48 mg/kg (30 minute) 0.64 mg/kg (30 minute) Placebo	272 Subjects	236 M 36 F	M & F Recent onset Afib/Afl
3.114 (post-amendment 5)	SQF	IV	0.16 mg/kg (30 minute) 0.32 mg/kg (30 minute) 0.48 mg/kg (30 minute) Placebo	227 Subjects	227 M	M Only Recent onset Afib/Afl
3.116	SQF	IV	0.24 mg/kg (30 minute) 0.32 mg/kg (30 minute) Placebo	356 Subjects	356 F	F Only Recent onset Afib/Afl
3.117	SQF	IV	0.48 mg/kg (30 minute) Placebo	117 Subjects	117 M	M Only Recent onset Afib/Afl
3.118	SQF	IV	0.32 mg/kg (30 minute) Placebo	151 Subjects	151 F	F Only Recent onset Afib/Afl

2.2.2 Clinical response variables (endpoints) for efficacy and safety

There was one primary clinical response variable and multiple secondary variables:

- Primary Efficacy Variable: percentage of subjects that converted to NSR (for at least 60 seconds) at any time within 2.5 hours after the initiation of the infusion of study drug.
- Secondary Efficacy Variables- The percentages of subjects that converted to NSR (for at least 60 seconds) at any time
    - within 2.5 hours and who were in NSR at 2.5 hours after start of infusion, at 24 hours after start of infusion and at hospital discharge.
    - Time to first conversion to NSR.
    - Dose-and concentration-response relationships.
    - Direct current (DC) cardioversion energy.

The selected primary parameter appears acceptable as it is consistent with that used for other agents with a similar indication.

The safety and tolerability of tedisamil SQF versus placebo was determined by physical examination, electrocardiogram (ECG), 24-hour Holter monitoring, vital signs, laboratory evaluations and adverse events (AEs).

2.2.3 Identification and measurement of tedisamil concentrations in plasma

Tedisamil appeared to be adequately identified and measured in most studies. Tedisamil was measured by an array of validated assays. These assays employed HPLC with electrochemical detection and LC/MS/MS. Please refer to Analytical Section (2.6) for additional assay information.

2.2.4 Tedisamil Exposure-Response (Information Extracted from Pharmacometrics Consult Review by Christoffer Tornoe, Ph.D.)

2.2.4.1 Is there evidence of exposure-efficacy (Exposure- Effectiveness Assessment)?

There is clear evidence of an exposure-response (conversion to normal sinus rhythm within 2.5 hours of tedisamil dosing) relationship for tedisamil using Cmax as the exposure variable (Figure 1). Tedisamil was found to be most effective in patients with recent onset of AF/AFL episode (i.e. less than 48 hours from initiation of tedisamil dosing) compared to patients with AF/AFL for more than 48 hours with an odd-ratio of 5.4 (95% CI 3.8-7.6). Tedisamil was also found to be more effective in AF patients compared to AFL patients with an odds-ratio of 3.2 (95% CI 1.7-6.0). Finally, tedisamil was also found to be more effective in males compared to females under similar tedisamil exposure with an odds-ratio of 1.5 (95% CI 1.1-2.1).

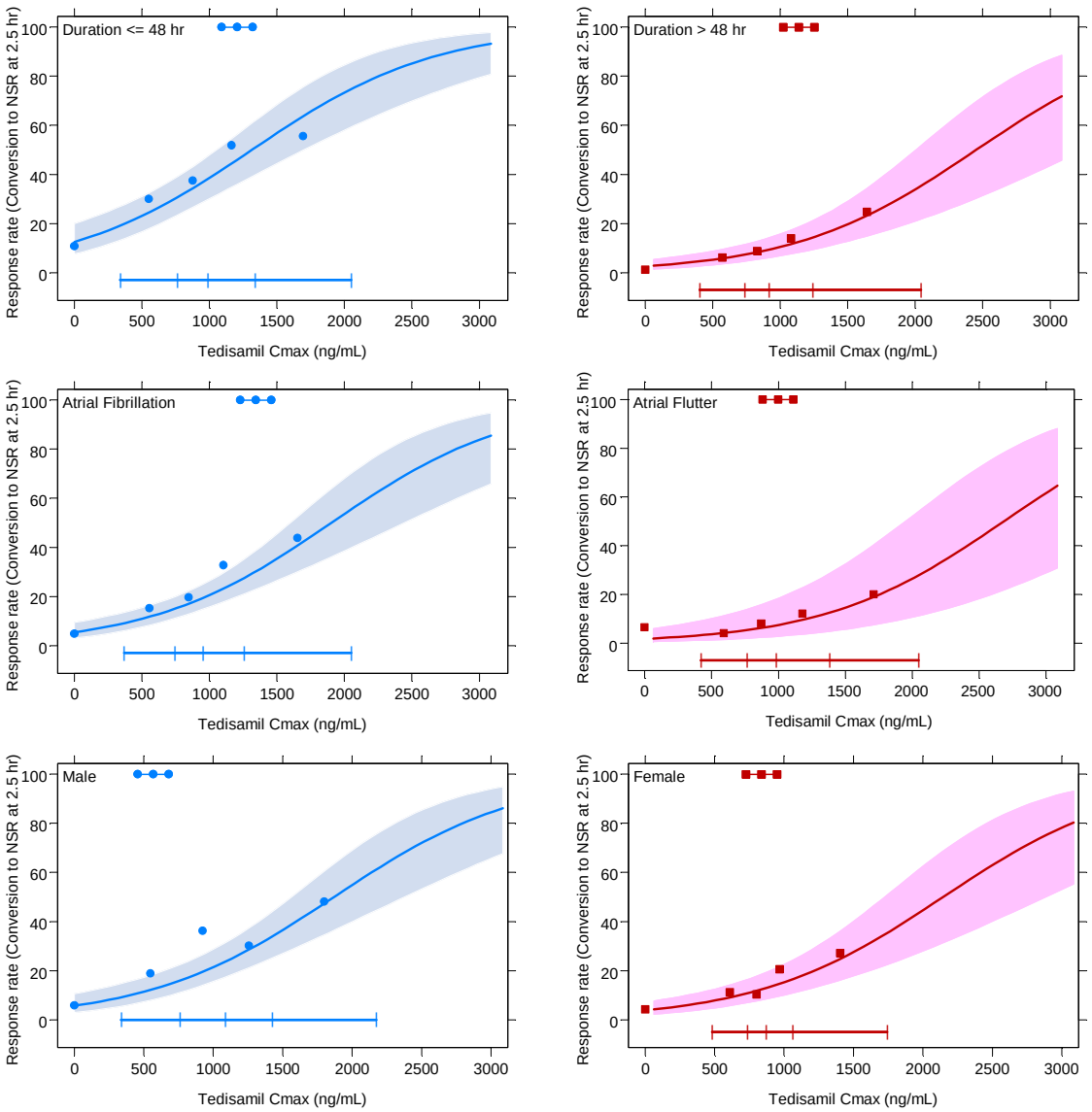


Figure 1. Exposure-response relationship for **(Top)** Duration of most recent Afib/Aflut episode (duration ≤ 48 hrs (left) and > 48 hrs (right)), **(Middle)** Diagnosis (Afib (left) and Aflut (right)), and **(Bottom)** Gender (males (left) and females (right)). The solid colored lines are the predicted response rates and the associated 95% CI is shown as a shaded colored area. The dots represent the mid-quartile tedisamil 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.

Duration of the most recent atrial fibrillation episode (<48 or >48 hr) was found to be the most important demographic covariate for response. A total of 631 (Active:Placebo N=434:197) out of 1006 atrial fibrillation patients had information about how many hours since the start of their most recent atrial fibrillation episode.

As seen in Figure 2, patients with most recent Afib episode <8 hours from the tedisamil dose had a tedisamil response rate of 60% (placebo response of 20%) whereas the tedisamil response rate in patients with >8 hours duration was around 20% (placebo response 2-6%).

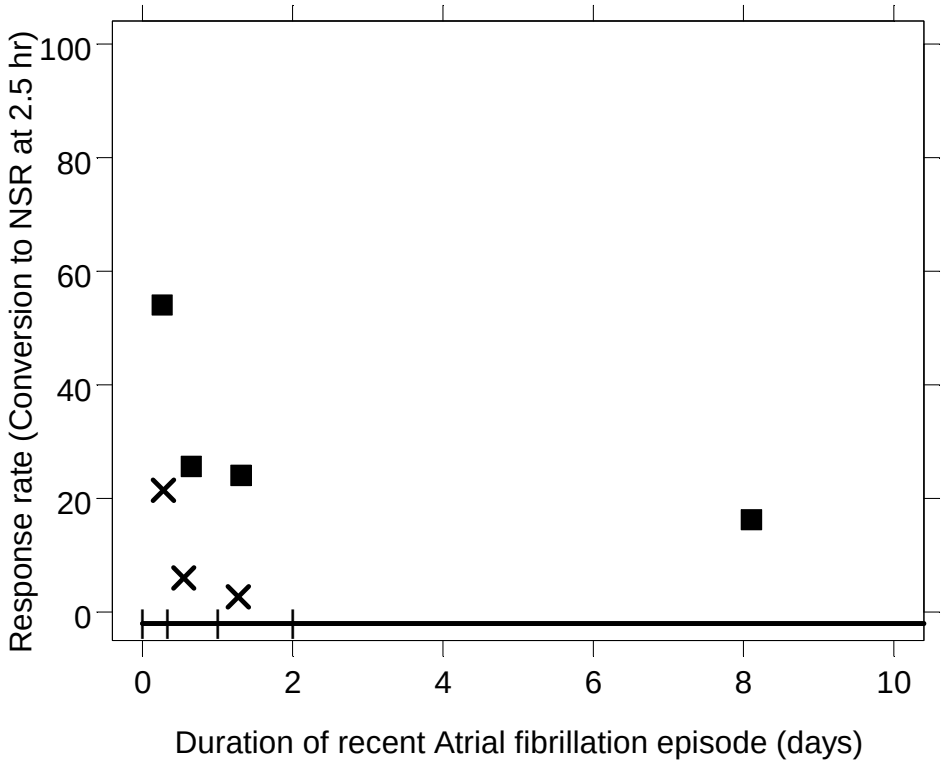


Figure 2. Response rate vs. duration of most recent Afib episode at the median duration of most recent Afib episode within each bin, i.e. 0-8 hr (Active:Placebo N=37:14), 8-24 hr (Active:Placebo N=113:56), 24-48 hr (Active:Placebo N=102:41), and 48 hr-45 days (Active:Placebo N=182:0). Solid squares (tedisamil) and cross (placebo).

2.2.4.2 Is there evidence of an exposure-safety relationship? (Exposure-Safety Assessment)
The probability of developing tachycardia, bradycardia, extrasystoles, AV block, hypertension, and Torsades de Pointes was found to increase with increasing tedisamil peak concentration (Figure 3). Gender (sex) was the only identified significant covariate for tachycardia where females have lower probability of tachycardia compared to males at similar exposure.

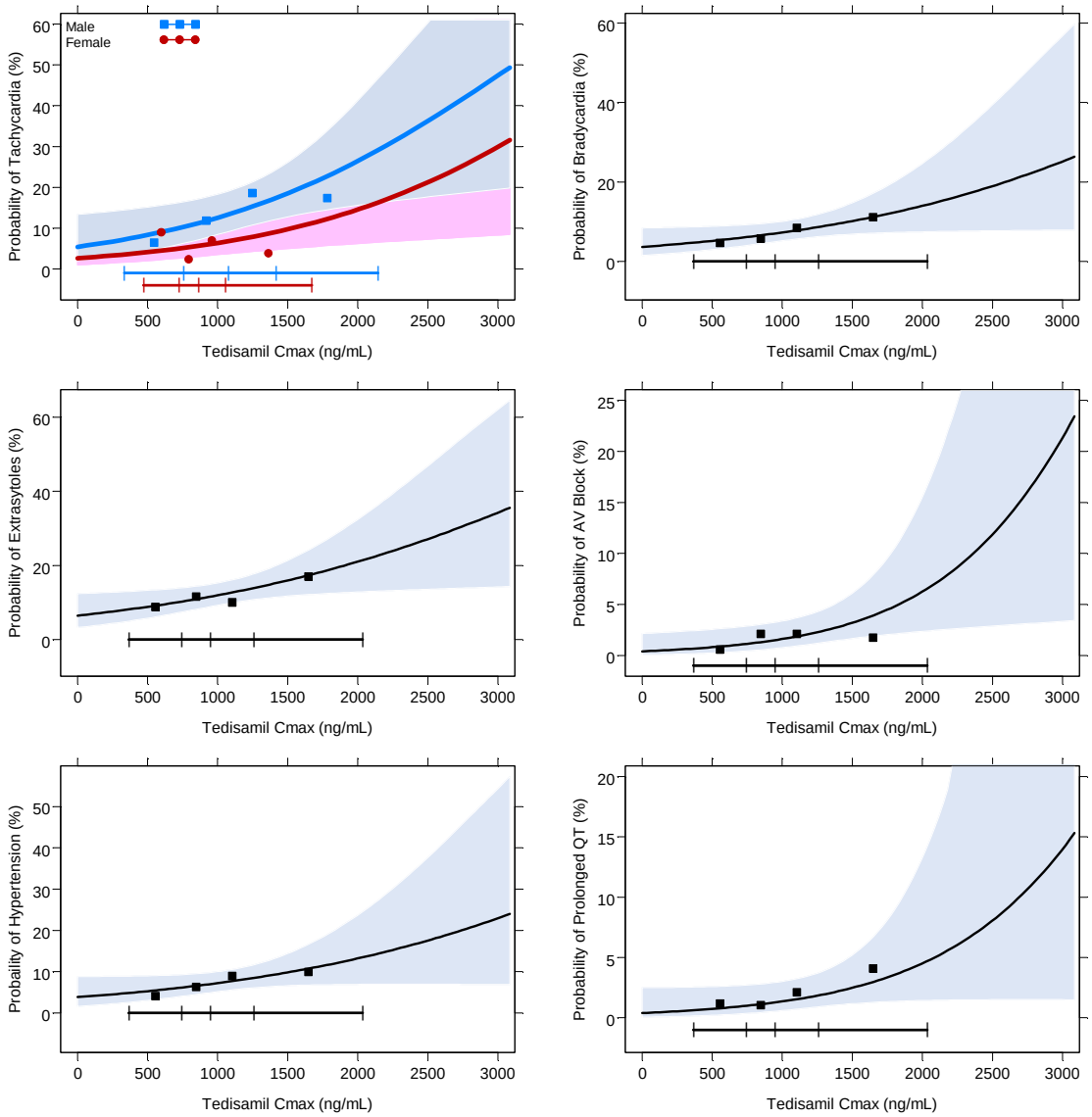


Figure 3. Exposure-safety analysis. Relationship between tedisamil peak concentration and tachycardia (top left), bradycardia (top right), extrasystoles (middle left), and AV block (middle right), hypertension (bottom left 3), and prolonged QT (bottom right).

The probability of torsade de pointes was also found to be related to tedisamil C_{max} and ΔQTcF (change from baseline) at time of maximum concentration (see Figure 4).

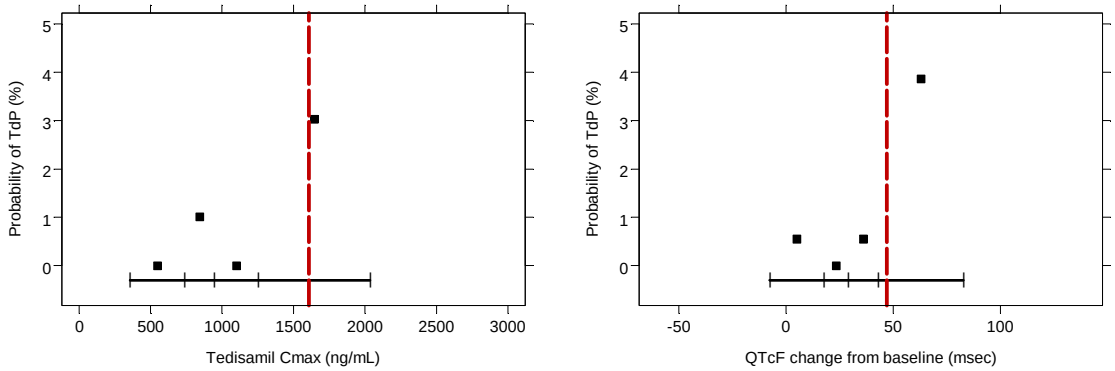


Figure 4. Relationship between probability of Torsade de Pointes and tedisamil C_{max} (left) and QTcF change from baseline at C_{max} (right).

Classification and regression tree (CART) analysis was performed in S-PLUS to estimate a break point in tedisamil C_{max} and ΔQTcF which maximally distinguishes the risk of TdP in two groups. The risk of torsade de points increases from 0.5 to 18% for female and 1 to 3% for male patients with C_{max}>1607 ng/mL compared to patients with C_{max}<1607 ng/mL. Similarly for ΔQTcF, the risk of TdP increases from 0.4 to 6% for females and 1 to 3% for males with ΔQTcF > 47 msec compared to patients with ΔQTcF <47 msec (see Figure 5).

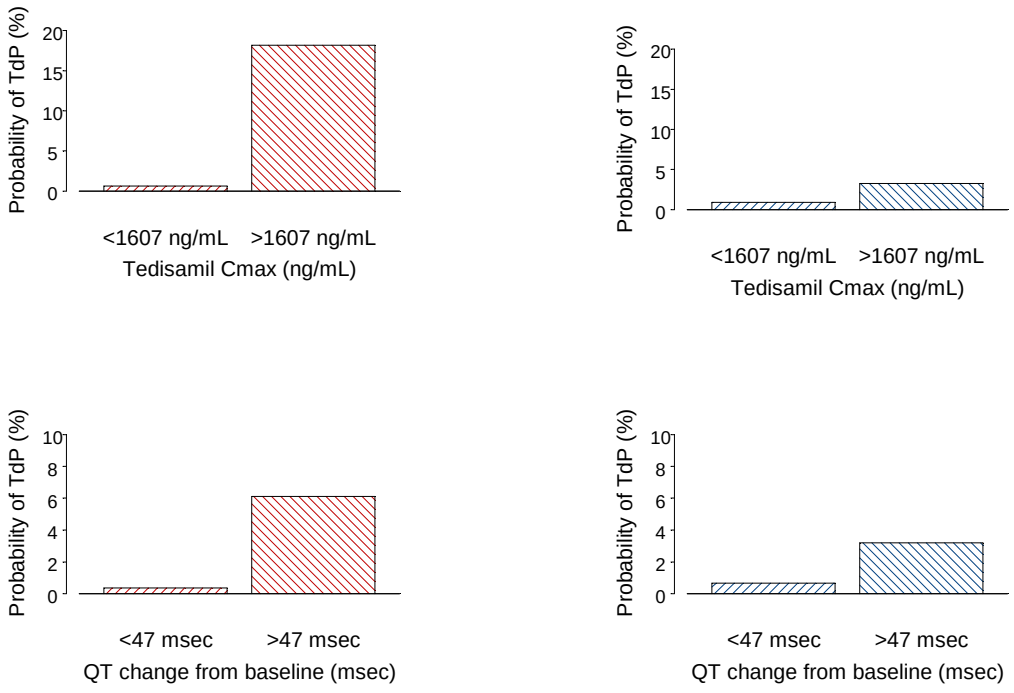


Figure 5. Probability of Torsade de Pointes for females (left) and males (right) with Cmax above and below 1607 ng/mL (top) and ΔQTcF above and below 47 msec.

2.2.4.3. Does tedisamil prolong the QT interval?

Tedisamil was found to prolong the QT interval with a mean predicted QT change from baseline of 32 and 38 msec at the mean observed female and male tedisamil Cmax of 954 and 1317 ng/mL, respectively (see Figure 6).

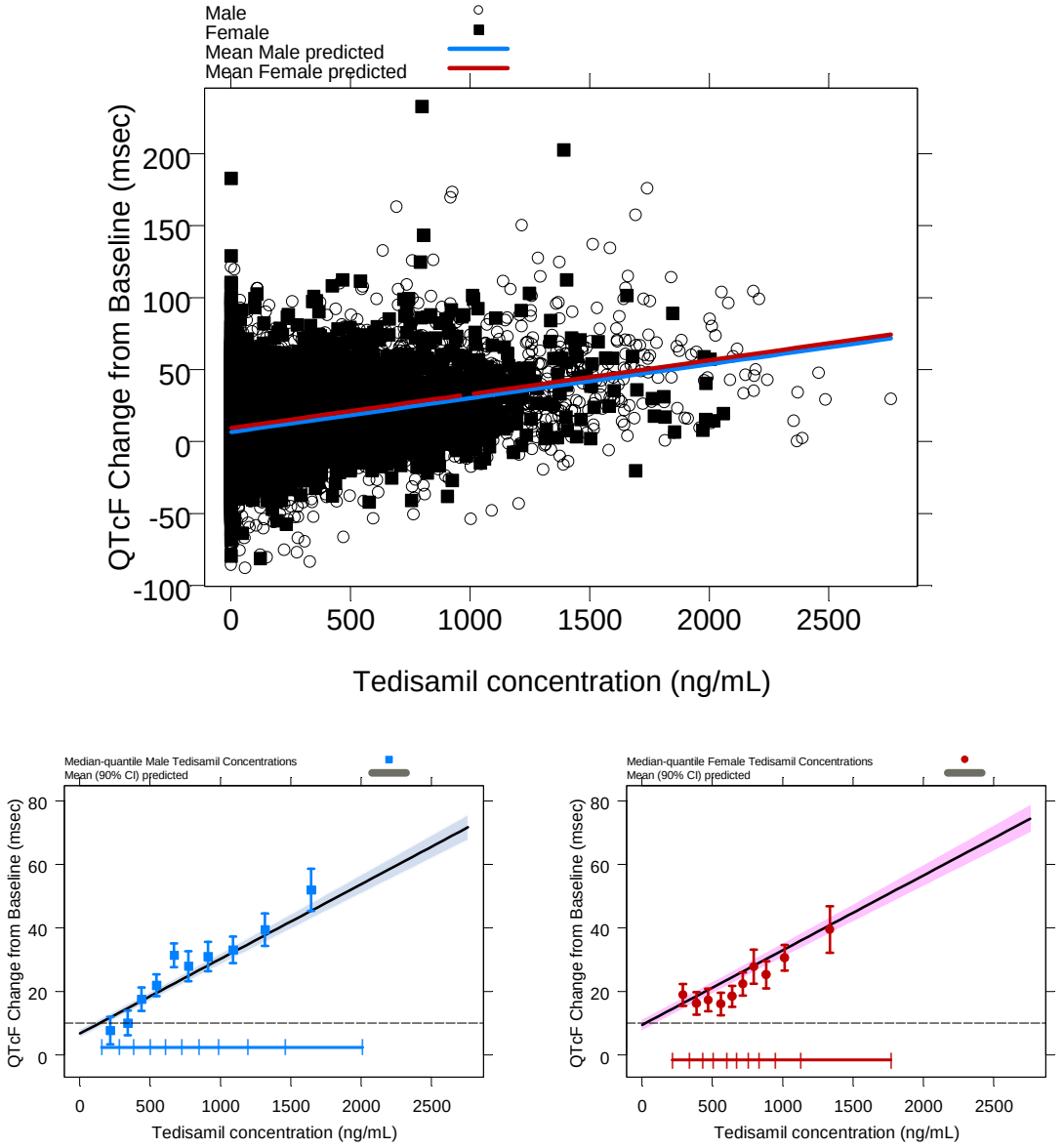


Figure 6. **(Top)** ΔQTcF (Change from Baseline) vs. tedisamil concentrations. **(Bottom)** Median-quantile tedisamil concentrations and associated 90% CI together with the population predictions with 90% confidence interval. The horizontal bars show the quantile range for males (blue) and females (red).

The mean QTcF prolongation is predicted to return to normal 8 hours after tedisamil dosing of 0.32 and 0.48 mg/kg. The 90 minutes of ECG monitoring proposed by the sponsor should therefore be extended until return to pre-dose baseline which on average is 8 hours postdose (see Figure 7).

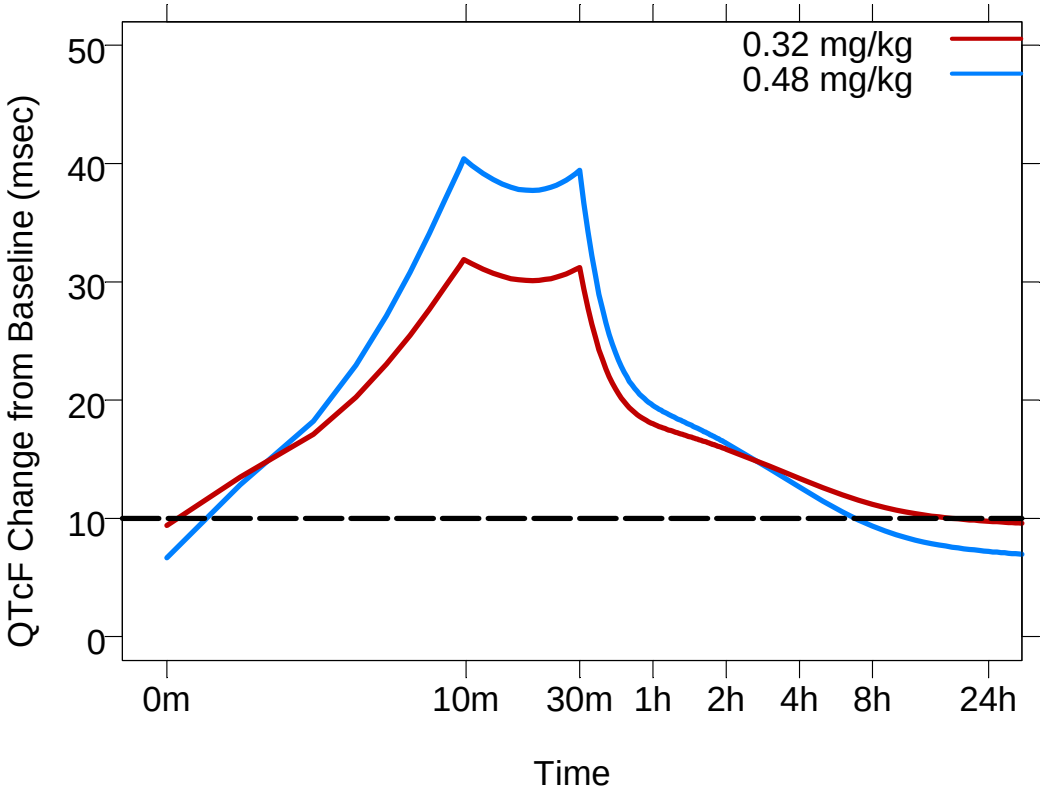


Figure 7. Population mean predicted QTcF change from baseline vs. log-time for a typical 80 kg subject with CrCL=87 mL/min receiving 0.32 (female, red), 0.48 (male, blue) dose.

QT prolongation was also observed in several clinical pharmacology studies (healthy volunteers) and was of similar magnitude to that observed in patients.

2.2.4.5 *Acceptability of applicant's proposed dosage regimen*

The Applicant has proposed different dosing in males and females and does not recommend dose adjustment in patients with mild and moderate renal impairment. Each of these groups is addressed in turn.

Is gender specific dosing (female=0.32 mg/kg, male=0.48 mg/kg) justified?

The proposed gender specific dosing regimen (0.32 mg/kg for females and 0.48 mg/kg for males) is acceptable only if the medical reviewer can confirm the higher probability of TdP for females compared to males at the same dose. Otherwise, the tedisamil dosing regimen for males and females should be 0.48 mg/kg.

The selection of 0.48 mg/kg for males and 0.32 mg/kg for females was based on observed data from the tedisamil studies where the incidence of TdP was found to be 0.5% (CI: 0.0 to 2.5) in males for the dose of 0.48 mg/kg and 0.4% (CI: 0.0 to 2.5) in females for the dose of 0.32 kg/kg, respectively. No gender differences in tedisamil exposure were identified and efficacy data suggest that females need higher tedisamil doses to obtain similar response rates (conversion to normal sinus rhythm within 2.5 hrs) as males.

Should doses be adjusted for renal impairment?
A dose adjustment for mild and moderate renal impairment is not needed. Tedisamil clearance was found to decrease with decreasing creatinine clearance (CLcr). However, renal impairment does not significantly influence the peak tedisamil concentration (Cmax) which is the exposure variable most related to both tedisamil efficacy and safety. It is noted that patients with mild and moderately impaired renal function were included in pivotal clinical trials and these patients had an acceptable safety profile compared to patients with normal renal function. Applicant adequately suggests to exclude patients with severe renal impairment since these patients were not studied in the pivotal tedisamil studies.

2.2.5 Pharmacokinetic characteristics of tedisamil and its major metabolites

Tedisamil pharmacokinetics (PK) were determined following oral and IV administration in healthy subjects and in patients with various forms of cardiac disease. The most relevant PK information for the proposed indication was obtained from IV administration studies in the pivotal clinical trials (Pharmacometrics Consult: Population PK analyses) and studies in healthy volunteers. Tedisamil is intended for single administration.

2.2.5.1 *Tedisamil pharmacokinetic measures*

Tedisamil PK measures following single IV administration of tedisamil in two Phase I studies and in the pivotal trials of tedisamil dihydrochloride are presented in Table 3, Table 4, Table 5 and Table 6. It should be noted that the Population PK (POPPK) results obtained by the Applicant were considered reasonable by the Pharmacometrics (PM) Reviewer; although the PM Reviewer had recommendations to improve the applicant's modeling (See PM Review in Appendix, Section 4). Both sets of POPPK results (Applicant and PM Reviewer's) are presented to complement each other.

Table 3: Mean (CV %) PK Measures following IV administration of tedisamil sesquifumarate as a two-step infusion in healthy volunteers (n = 18, per treatment)

Study	S219.1.116	S219.1.117	S219.1.117
Formulation	DHCl	SQF	DHCl
Dose	0.32 mg/kg	26 mg*	26 mg*
PK Measures			
Cmax (ng/mL)	905 (33)[GM]	945 (24.3)	944 (20.8)
$AUC_{0\text{-inf}}$ (hr ng/mL)	1821 (35.7)	1810 (17.9)	1870 (21.3)
Vss (L)	68.0 (42.7)	69.5 (23.2)	69.3 (24.7)
CL (L/hr)	16.02 (37.3)	14.82 (19.2)	14.58 (22.3)
$T_{1/2\ (hr)}$	5.5 (26.0)	6.3 (23.2)	6.9 (34.0)

^ Tmax reported as median and (range)
* mean weight in study was 77.12 and median weight was 75.70, thus based on average weight the dose was 0.337 mg/kg and based on median weight the dose was 0.343 mg/kg
[GM] value reported is a geometric mean, rather than an arithmetic mean

Table 4: Tedisamil PK Parameter Estimates Obtained from Population PK Modeling (Per Pharmacometrics Review)

Parameter	Unit	Population parameters		Inter-individual variability	
		Estimate	%RSE	Estimate (CV%)	%RSE
Fixed-Effects Parameters					
CL	[L/hr]	10.3	1.546	32.1	6.66
Q_1	[L/hr]	42.9	1.38	*	-
Q_2	[L/hr]	3.67	6.89	*	-
V_1	[L]	8.20	3.12	63.9	10.0
V_2	[L]	32.6	2.99	46.0	7.5
V_3	[L]	37.7	4.14	*	-

Table 5: Tedisamil population mean predicted Cmax and AUC for a typical 80 kg patient with CLcr = 87 mL/min (Per Pharmacometrics Review)

Tedisamil dose	Population Mean C_{max} (ng/mL)	Population Mean AUC_{0-48} (ng*hr/mL)
0.16 mg/kg	479	1289
0.24 mg/kg	718	1933
0.32 mg/kg*	957	2578
0.48 mg/kg**	1436	3867
0.64 mg/kg	1914	5156

*Proposed female dose
**Proposed male dose

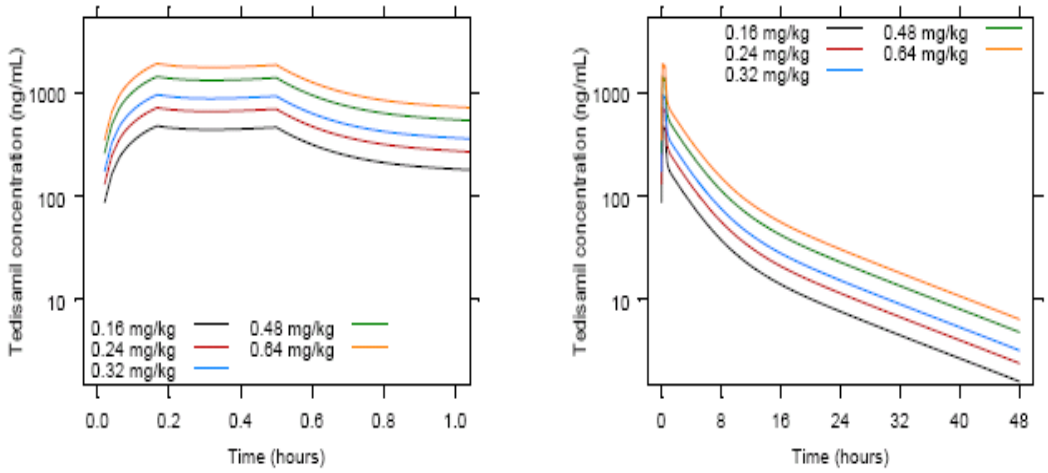
Table 6: Tedisamil PK Parameter Estimates in AF/AFL Patients Obtained from Population PK Modeling (Per Applicant)

Dose of Free Base (mg/kg)	N	Cmax (ng/mL)	AUC(0-inf) (ng*h/mL)	CL (mL/min)	Vss (L)
0.16	58	480 (33.4)	1194 (42.5)	13.26 (51.0)	89.7 (30.2)
0.24	116	793 (23.2)	2252 (39.3)	8.52 (36.4)	71.8 (23.0)
0.32	323	975 (30.3)	2899 (53.1)	10.26 (49.7)	78.2 (32.5)
0.48	196*	1337 (29.1)	3883 (40.5)	11.82 (36.6)	85.4 (26.4)
0.64	60	1849 (27.3)	4712 (30.8)	11.88 (36.6)	78.9 (22.5)
0.72	17	n/a	n/a	14.34 (44.2)	90.3 (27.8)

* n = 180 for Cmax and AUC_{0-inf}

The population mean predicted tedisamil concentration-time profiles for a typical 80 kg subject receiving different tedisamil doses are illustrated in Figure 8.

Figure 8: Population mean predicted tedisamil concentration-time profiles for a typical 80 kg subject receiving different tedisamil dose (left panel in first hour and right panel over 48-hour period)



2.2.5.2 *Pharmacokinetic Comparisons: Normal Volunteers vs. AF/AFL Patients*

PK in patients with AF/AFL differed from those in healthy subjects; this was most evident in CL estimates. At the proposed doses CL in healthy volunteers was ~ 15 L/hr vs. ~12 L/hr at most doses in AF/AFL patients. The reason for the difference is unclear, but may be due to differences in cardiac output.

2.2.5.3 *Characteristics of drug transport*

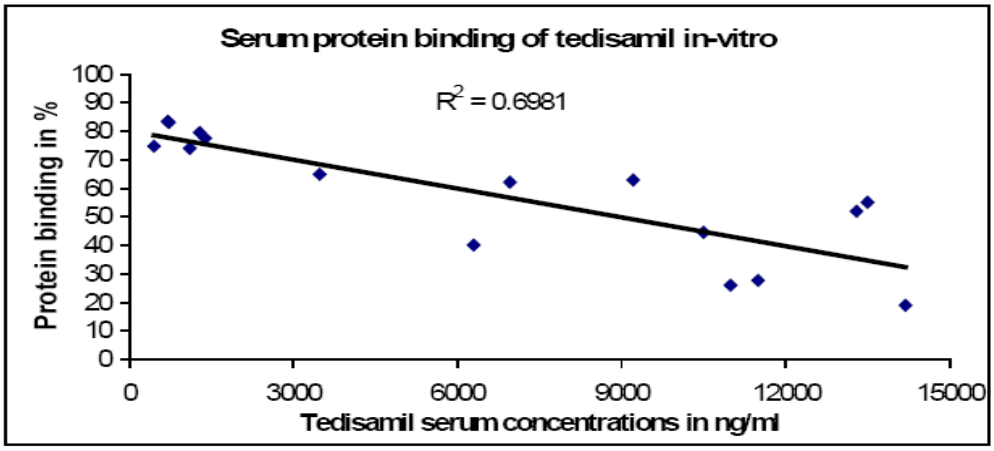
Tedisamil is a PGP substrate therefore its transport characteristics are likely to be altered in the presence of potent PGP inhibitors or inducers, as well as in the presence of other PGP substrates (see Drug-Drug Interactions). No relative Papp (apparent permeability) were provided and no comparison to established PGP substrates were provided therefore it is not possible to characterize tedisamil's degree of sensitivity as a PGP substrate.

2.2.5.4 *Distribution of tedisamil*

Following IV administration of tedisamil to patients, Vss was ~ 80 L.

The plasma protein binding of tedisamil was between 90 and 97 % at anticipated therapeutic concentrations (Cmax ~ 1000 ng/mL) and binding was concentration independent in that range. However, binding was concentration-dependent at concentrations exceeding 1000 ng/mL. Alpha-1 acid glycoprotein appeared to account for the majority of the plasma protein binding of tedisamil.

Figure 9: Dependence of tedisamil Plasma protein binding on tedisamil concentration



2.2.5.5 *Mass Balance Information*

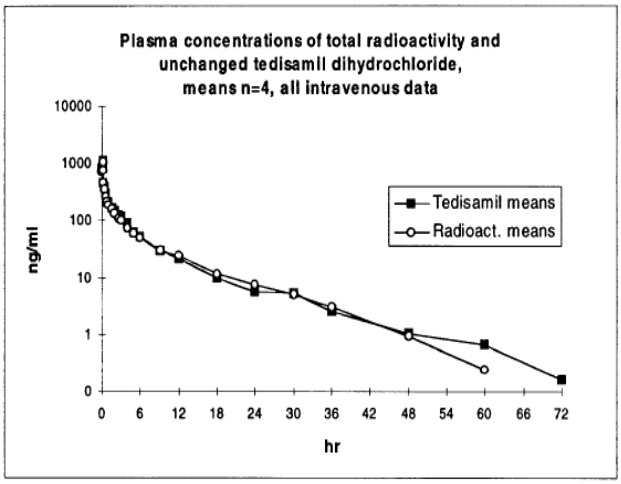
Overall, the mass balance results suggest that the primary route of drug elimination is renal with a minor contribution by metabolism. Results from the mass balance study are summarized in the following table.

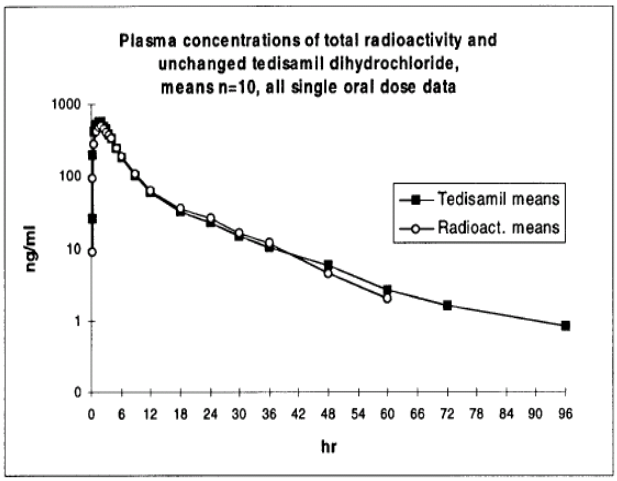
Table 7: Mean ± SD tedisamil total radioactivity measures (96 hours post dose) following IV (22.74 mg containing 96.2 µCi) and oral (100 mg containing 96.39 µCi) administration of tedisamil DHCL

Route	Recovery (% Dose)	
Renal	83.5 ± 8.1	37.7 ± 5.9
Fecal	7.9 ± 2.3	48.3 ± 7.9
Total	91.4 ± 8.2	85.9 ± 8.3

After single dose administration of radiolabeled tedisamil to healthy volunteers recovery was almost complete (~ 90 %) following both routes of administration. The plots of total radioactivity and unchanged tedisamil were almost identical (Figure 10) indicating that tedisamil was not biotransformed appreciably.

Figure 10: Plasma concentration-time profiles of total radioactivity with unchanged tedisamil following IV (left) or oral (right) administration of radio-labeled tedisamil

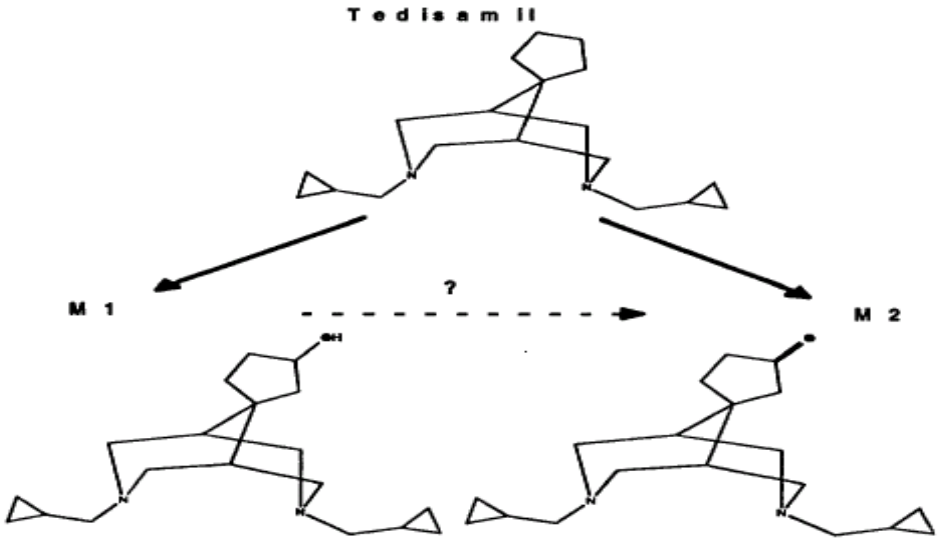




The only identified metabolite accounted for

less than 4 % of the total radioactive dose and corresponded to previously identified hydroxy metabolite, M1, depicted below. It should be noted no metabolites were detected following oral administration and that metabolism was greater in animals than man.

Figure 11: Metabolic pathways of tedisamil based on animal data (only M1 formed in man) *



* The two main tedisamil metabolites in animals, KC11233 (11-hydroxy tedisamil) or M1 and KC11756 (11-keto tedisamil) or M2, have some activity (about 2 - 3 times less than tedisamil) in animal experiments (guinea pig right atria and ventricular papillary muscles, and anesthetized rats).

2.2.5.6 *Metabolism*

In vitro system

In vitro studies with human microsomes and human hepatocyte system indicated that tedisamil was not metabolized appreciably by any of the major CYP pathways. No metabolites were identified in the *in vitro* studies.

In Vivo Systems

In vivo the hydroxy metabolite of tedisamil accounted for less than four percent of total radioactivity (mass balance study) and the metabolite was not monitored in clinical studies. This lack of monitoring seems acceptable due to limited metabolite exposure and minimal activity.

2.2.5.7 *Excretion and Elimination*

As reported previously in the mass balance findings, following IV administration tedisamil is cleared primarily via renal mechanisms. No half-life estimation is available in patients. Overall, tedisamil concentrations appeared to decline in a bi- to triphasic manner after achieving Cmax by both oral and IV routes.

2.2.5.8 *Degree of Linearity/Nonlinearity in dose-concentration relationship*

Based on the evaluation of tedisamil's PK profile across doses), tedisamil exhibits a linear dose-concentration relationship and dose-independent PK.

2.2.5.9 *Inter and intra-subject variability in tedisamil PK*

There was moderate to high inter-subject variability in tedisamil PK (see Table 4 and Table 6) following IV administration as evidenced by the CV (%); the CV range was approximately between 30 and 60 %. Intrasubject variability was 28.3 %.

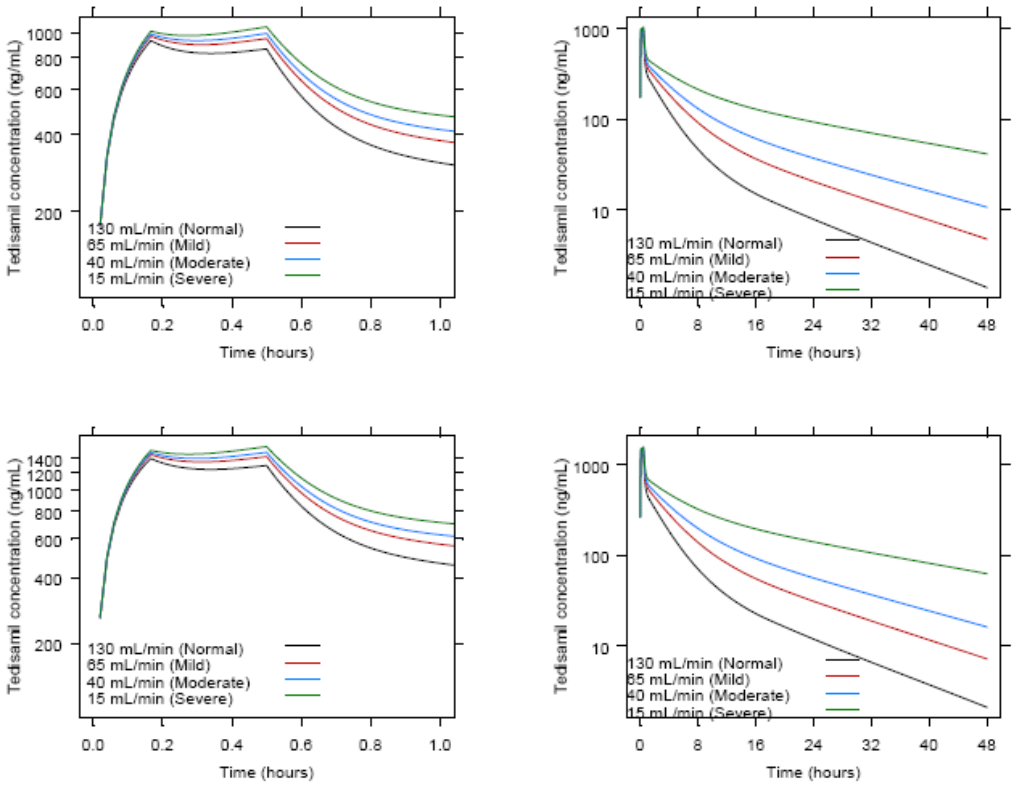
2.3 What Intrinsic Factors Affect Tedisamil Exposure-Response?

Tedisamil exposure appeared to be affected primarily by renal function (insufficiency) per Pharmacometrics Review. Other intrinsic factors, including age, gender, weight, were evaluated using Population Pharmacokinetic Analyses but had a minimal impact on tedisamil exposure or clearance.

Renal Insufficiency

Tedisamil clearance was found to decrease with decreasing creatinine clearance (CLcr). However, the degree of renal impairment does not significantly influence tedisamil Cmax which is the exposure variable most related to both tedisamil efficacy and safety. The plasma concentration-time profiles for patients with normal and impaired renal function are depicted in Figure 12.

Figure 12: Effect of Renal Function on tedisamil concentrations (top row for 0.32 mg/kg dose and bottom row for 0.48 mg/kg dose)



Patients with normal renal function and those with mild and moderate renal insufficiency were included in the pivotal clinical trials; whereas, patients with severe renal impairment were excluded.

Hepatic Insufficiency
The effect of impaired hepatic function was not been assessed in this NDA. This omission appears acceptable in light of the minimal role of metabolism, hepatic or otherwise.

Age and Weight
Based on the final PK model neither age nor weight impacted tedisamil clearance; however, these two covariates are indirectly accounted for in the PK model that included a measure of renal function (creatinine clearance or CRCL). The relationship between age and weight and CRCL is:

$$CRCL = \frac{(140 - Age) \cdot Weight}{72 \cdot Serum\ Creatinine} (\cdot 0.85\ for\ female)$$

Gender
No gender differences in tedisamil exposure were identified based on the Population PK modeling analyses.

Race
Effects of race could not be adequately evaluated in NDA 22-123.

2.4 What Extrinsic Factors Affect Tedisamil Exposure Response?

2.4.1 Drug-drug Interactions

The main extrinsic factor that may influence the tedisamil exposure-response is concomitantly administered drugs. However, the impact of this factor is unlikely to have a major effect during tedisamil therapy because tedisamil is intended for single (acute) use and has limited susceptibility to the usual drug interaction pathway.

2.4.1.1 *CYP Substrate Status*

As indicated in the metabolism section, tedisamil is not metabolized by CYP enzymes. Therefore the impact of concomitant administration of CYP inhibitors or inducers is of limited consequence.

2.4.1.2 *PGP substrate status*

Tedisamil appears to be a PGP substrate thus there is a potential for tedisamil exposure to be altered by PGP inhibitors or inducers.

In vitro, verapamil, a PGP inhibitor, impeded transport of tedisamil as shown by the decrease in PGP factor, whereas verapamil did not influence passive transport of tedisamil. The applicant should have conducted the study with another PGP inhibitor as recommended in the Drug Interaction Guidance to confirm the PGP substrate status of tedisamil. Additionally, the Applicant should have provided an estimate of Papp to characterize tedisamil's PGP substrate status.

Table 8: Effect of PGP transport (PK1 LLC MDR cells) on tedisamil in the absence and presence of verapamil after 3.5 hr incubation

Treatment	PGP factor(+/- SD)
tedisamil	27.2 +/- 5.3
tedisamil + 1 µg/ml verapamil	16.1 +/- 3.6
tedisamil + 10 µg/ml verapamil	3.8 +/- 0.7

PGP factor = PGP factor = T% bottom-> top / T% top-> bottom in a standardized time. (Per Applicant PGP factors range from 1, suggesting no PGP transport to about 100 for very strong PGP substrates

In vivo, when verapamil was coadministered with oral tedisamil, tedisamil exposure increased by approximately 77 %, suggesting that verapamil altered tedisamil PK via PGP inhibition. Generally, one expects a greater magnitude of PGP interaction following oral administration due to PGP presence in the gut, however, PGP is found in many other parts of the body as well. In the population PK analyses, administration of verapamil with IV tedisamil resulted in a smaller apparent increase in tedisamil exposure (i.e. tedisamil exposure decreased 13 %: clearance is inversely related to exposure) in tedisamil exposure that was not considered clinically significant. In this Reviewer's opinion the conclusions from the POPPK study do not rule out the potential interaction between PGP inhibitors and inducers, because POPPK studies are often underpowered to accurately quantify the magnitude of a drug interaction.

2.4.1.3 *CYP Induction and Inhibition Potential*

Tedisamil does not appear to induce common CYP enzymes, particularly CYP3A, but there was no definitive information regarding CYP1A2. Tedisamil is a potent inhibitor of

CYP2D6, has limited inhibition towards CYP3A and CYP2C19, and does not inhibit the other common CYP enzymes.

Induction Potential

Induction potential was evaluated in two studies, but only one of the studies was considered reliable. Data demonstrating tedisamil's lack of inducing activity is summarized in Table 9.

Table 9: Evaluation of Tedisamil's Induction Potential

Enzyme	**Substrate**	**Inducer**	**Comment**
CYP1A	Ethoxyresorufin deethylase activity	3-methylcholanthrene	8.8 to 15-fold increase in activity
CYP2B6	Pentoxyresorufin dealkylase	Phenobarbital	Negligible increase
CYP3A	Nifedipine oxidase activity	Rifampin	2.5 – 6.1-fold increase inactivity
Enzyme	**Substrate**	**Inducer**	**Comment**
CYP1A	Ethoxyresorufin deethylase activity	Tedisamil	1.2 to 2.5-fold increase in activity
CYP3A	Nifedipine oxidase activity	Tedisamil	1.5 to 2 -fold increase in activity

The main limitation associated with the study that yielded unreliable results was the use of hepatocytes from a single donor; thus, the spectrum of metabolic activity was not adequately represented (contrary to Guidance recommendation). The induction evaluation did not adequately address potential CYP1A2 induction by tedisamil. It should be noted that in principle, the presence or absence of induction potential is not too relevant for a drug that is administered once, as induction usually requires multiple doses. Consequently the assessment of induction potential is not too critical for Pulzium.

Tedisamil inhibited the activity of CYP2C19, CYP3A and CYP2D6 at therapeutic tedisamil concentrations as shown in Table 10). The data suggest that tedisamil will increase the exposure of CYP2D6 substrates. No specific study was conducted with tedisamil (oral or IV) to evaluate the effect of tedisamil on a CYP2D6 substrate.

Table 10: CYP Isoform Activity for Assessment of Tedisamil's Inhibition Potential (Tedisamil 1 - 100 µM)

CYP isoform	**inhibitor**	**Metabolite Activity monitored**	**Specific activity Pmol/min/mg/protein**	**Percent Vehicle Control**
CYP2C19	Vehicle control	0.801 ± 0.0632	53.4 ± 4.21	100
	Tedisamil	0.544 ± 0.707	36.2 – 47.1	67.9 – 88.2
CYP2D6	Vehicle control	0.615 ± 0.0273	82.0 ± 3.64	100
	tedisamil	0.0688 – 0.120	9.17 – 16.0	11.2 – 19.5
CYP3A4	Vehicle control	8.67 ± 0.210	1157 ± 28.0	100
Testosterone	Ketoconazole	0.393 ± 0.007	52.3 ± 0.938	4.53
Testosterone substrate	Vehicle control	4.96 ± 0.0756	440 ± 6.72	100
	Tedisamil	7.42 – 8.87	989 - 1183	85.5 - 102
Midazolam substrate	Vehicle control	3.69 ± 0.0481	491 ± 6.42	100
	Tedisamil	2.63 – 3.56	351 - 474	71.5 – 96.5

2.4.1.4 *PGP Inhibition Potential (Role of PGP Transporters)*

No *in vitro* information was provided to determine if tedisamil is a PGP inhibitor, however, an *in vivo* study with digoxin, a sensitive PGP substrate, indicated that tedisamil is not a PGP inhibitor.

2.4.1.5 ***In vivo studies with medications that are likely to be administered in AF/AFL patients and that serve as metabolic or transporter probes (substrates/inhibitors/ inducers)***

Apart from the interaction between oral tedisamil and verapamil, no clinically significant PK (PD) drug-drug interactions appeared to occur when tedisamil (IV or oral) was coadministered with likely comedications.

Drug-drug interaction studies were conducted with tedisamil and the following compounds: verapamil, digoxin, glibenclamide, warfarin, atenolol, isosorbide dinitrate and nifedipine. The listed drugs are those in which oral tedisamil was administered and the studies were reviewed. Additional drug-drug interaction information is available from the pivotal clinical trials and this information was reviewed as part of the Pharmacometrics consult

Is a Dosage Adjustment Based on Drug Interaction Needed for Tedisamil?

In this Reviewer's opinion, no specific dosage adjustments appear to be needed for tedisamil because tedisamil has a low propensity to undergo drug-drug interactions. However, due to tedisamil's PGP status, careful and extended monitoring as well as appropriate interventions should be in place for adverse events when potent PGP inhibitors are coadministered. The information regarding the verapamil-tedisamil interaction should be included in the label, especially in light of the significant interaction following oral administration. It is unclear if the findings from the population PK analyses are definitive, as the population PK study findings may not have yielded accurate quantitative estimates due to under-powering.

Is Dosage Adjustment/contraindication or staggered administration needed for concomitant medications?

CYP2D6 Substrates

The Applicant has indicated that caution should be employed when a CYP2D6 substrate needs to be taken with tedisamil. Although this recommendation is reasonable in an emergency room setting, where clinical monitoring is employed, it may pose an unknown risk to patients. Consequently, this Reviewer recommends a more cautions approach as described as follows. To remove this contraindication or dosing restriction (staggering), the applicant should conduct a study with IV tedisamil and at least one sensitive CYP2D6 substrate.

When tedisamil is administered with CYP2D6 substrates the following may be needed:

- ***Dose reduction/adjustment***: since tedisamil is likely to increase the substrates exposure; however, this adjustment can not be readily facilitated due to the lack of information with these substrates.
- ***Staggered administration***: tedisamil concentrations should be well below K_I (0.107 μM or ~ 30 ng/mL) for CYP2D6 inhibition thereby limiting the potential for interaction; based on the plasma concentration-time profile simulations, the delay should be ~ 24 hr

- ***Contraindication:*** the pharmacodynamic impact of the interaction is unknown and may pose unacceptable risks to patients; in this case an alternative treatment to tedisamil may be sought

Class I and III Anti-arrhythmic
The applicant indicates that there is a lack of experience with co administration of tedisamil with Class I and III anti-arrhythmic thus coadministration of these agents with tedisamil is not permitted. This recommendation appears reasonable.

Drugs that Cause QT Prolongation
The Applicant does not recommend coadministration of tedisamil with drugs that prolong QT. This recommendation also appears reasonable as tedisamil causes QT prolongation.

Reviewer Note on Feasibility of Contraindication/Staggered Administration
This Reviewer acknowledges the fact that the preceding proposals may be challenging or not practical clinically. However, the unknown potential risks caused by the drug-drug interactions may not be acceptable since there are alternative treatment modalities available and some of the adverse effects are not readily reversible.

2.4.1.6 Mechanistic basis for PD drug-drug interactions between tedisamil and comedications
There is a potential for additive to synergistic pharmacodynamic effects between tedisamil, an anti-arrhythmic agent, and other drugs used in patients with cardiac disease or drugs that interact with potassium channels.

In all clinical studies tedisamil caused QT prolongation suggesting that coadministration of tedisamil with other drugs that cause QT prolongation is not advisable or should be conducted with extreme caution. There was no interaction between glibenclamide, a drug that interacts with potassium channels, and tedisamil.

2.4.2 Unaddressed Potential Drug Interactions
As mentioned previously this application does not adequately address the potential interaction between CYP2D6 substrates and tedisamil. In the absence of this evaluation CYP2D6 substrates should be contraindicated or coadministered on a staggered schedule.

2.5 What are the General Biopharmaceutics Characteristics of Tedisamil Formulations?

2.5.1 Bioequivalence (BE) between tedisamil dihydrochloride (DHCl) and sesquifumarate (SQF)

Pulzium, IV solution (tedisamil sesquifumarate), the proposed market formulation was used in the pivotal clinical trials, thus no BE information was required. However, the applicant conducted a BE study to link the clinical information obtained with a previously studied, alternative salt form, tedisamil DHCl. The DHCl salt was BE (Table 11) to the SQF salt and exhibited similar PD (Table 12) characteristics, thus in general data obtained with tedisamil DHCl are applicable to tedisamil on the whole.

Table 11: Tedisamil Expo sure Comparison- Tedisamil SQF vs. Tedisamil DHCl

	Ratio (%)	90% CI (%)
AUC_{0-t}	98	95-102
$AUC_{0-t'}$	98	94-102
AUC_{0-inf}	98	94-102
C_{max}	100	91-109

Descriptive statistics for derived ECG variables are summarized in Table 12.

Table 12: Descriptive statistics of ECG parameters following tedisamil administration

		Treatment A (N=18)		Treatment B (N=18)	
		Mean	SD	Mean	SD
Heart rate	$AUC_{(0-8)}$ (h*bpm)	474	60	468	54
	$AUC_{(0-8)\ corrected}$ (h*bpm)	-11	27	-27	31
	Maximum decrease (bpm)	13	3	14	2
QT-interval	$AUC_{(0-8)}$ (h*ms)	3258	217	3259	183
	$AUC_{(0-8)\ corrected}$ (h*ms)	153	73	176	88
	Maximum increase (ms)	88	21	88	22
QTc-interval	$AUC_{(0-8)}$ (h*ms)	3221	173	3205	152
	$AUC_{(0-8)\ corrected}$ (h*ms)	106	75	79	83
	Maximum increase (ms)	65	17	60	25

Notes: sesquifumarate = treatment A; dihydrochloride = treatment B; corrected values are pre-dose corrected.

2.6 What Analytical Methods were used in the Tedisamil Development Program?

Overall, the performance of the bioanalytical methods used to identify and measure tedisamil levels was acceptable (the assays satisfy the criteria for accuracy precision, and specificity) per Bioanalytical Guidance. The analytical methods used in the clinical pharmacology and efficacy/safety studies are summarized in Table 13 and Table 14.

Sample stability was also demonstrated under various conditions including long-term storage, freeze-thaw, sample-handling, sample transport and with autosampler. Generally low, mid and high QC samples were present and these QC samples were adequate with respect to their relevant values to points on the standard curve.

Table 13:- Summary of bioanalytical studies associated with clinical pharmacology studies and efficacy/safety clinical studies (per Applicant) for tedisamil

Assay Method	Site	Matrix	Assay Range (ng/mL)	Internal Standard	Sample Preparation	Analytical Technique
T01	Solvay, DE	Plasma	10 – 1000	KC 7507	L/L	GC-NFID
T02	LAB, DE1	Plasma	0.5 - 200	Gallopamil	L/L	HPLC-EC
T03	Solvay, US	Plasma	0.5 – 200	Bertosamil	L/L	HPLC-EC
T16	Solvay, US	Urine	250 – 250,000	Bertosamil	L/L	HPLC-EC
T04	Solvay, US	Plasma	2.5 – 2500	Bertosamil	L/L	HPLC-EC
T05	Covance, UK	Plasma	0.5 – 200	Gallopamil	L/L	HPLC-EC
T06	Covance, UK	Urine	50 – 2500	Gallopamil	L/L	HPLC-EC
T07	XenoBiosis, NL	Plasma Urine	0.5 – 200 50 – 2500	Gallopamil2	L/L	HPLC-EC
T08	XenoBiosis, NL	Serum	0.5 – 200	Gallopamil2	L/L	HPLC-EC
T09	XenoBiosis, NL	Dialysate	0.2 – 200	Gallopamil2	L/L	HPLC-EC
T10	Covance, UK	Plasma	1 – 200	Gallopamil	L/L	LC-MS
T11	Solvay, DE	Plasma Urine	1 - 1000	Bertosamil	L/L	LC-MS/MS
T12	Solvay, US	Plasma	2.5 – 2500	Bertosamil	L/L	LC-MS/MS
T13	MDS, CH	Plasma	1.06 – 1060	Gallopamil2	L/L	LC-MS/MS
T14	MDS, CH	Plasma	2 – 2000	D4-tedisamil	Protein precipitation	LC-MS/MS
T15	MDS, CH	Urine	100 – 100,000	D4-tedisamil	"Dilute & shoot"	LC-MS/MS

Table 14: Bioanalytical Method Validation - Other Compounds

Assay Method	Analyte	Site	Matrix	Assay Range (ng/mL)
V1	Verapamil	TNO, NL	Plasma	2 - 200
N1	Norverapamil	AAI, DE	Plasma	2.5 - 200
A1	Atenolol	Corning Hazleton, UK3	Plasma	5 - 500
D1	Digoxin	PTRL Europe GmbH, DE	Serum Urine	0.1 – 5 0.2 10 – 250
G1	Glibenclamide	Cephac, FR	Plasma	2 – 1000
S1	d,l-Sotalol	Analytical Solutions, US	Plasma Urine	25 – 10,000 3000 – 100,000

3 Detailed Labeling Recommendations

Based on the Clinical Pharmacology and Biopharmaceutics Review, the following changes were made to the applicant's original labeling proposal. These changes apply to the Clinical Pharmacology and Dosage and Administration sections of the label.

The applicant's proposed labeling is acceptable with the noted recommendations (please refer to the relevant sections of attached label.

4 Appendices

4.1 Proposed labeling with revised text (Reviewer recommended shown as track changes or comments- highlighted/underlined)

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4.2 Individual Study Reviews

4.2.1 A double-blind, randomized, two way cross-over study to assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of tedisamil sesquifumarate in comparison to tedisamil dihydrochloride after single intravenous administration in healthy male volunteers (S219.1.117, 2003).

STUDY/PROTOCOL #	S219.1.117
INVESTIGATOR	K.M. Eckl, M.D.
STUDY SITE	Pharm PlanNet Contract Research GmbH, Mönchengladbach, Germany
STUDY PERIOD	10/2001 – 11/2001
REPORT LOCATION	Module 5 Volumes 90 - 93

Objectives (per applicant):

1. To describe the pharmacokinetics and pharmacodynamics of tedisamil during and following a two-step infusion scheme.
2. To assess the safety and tolerability of tedisamil sesquifumarate in comparison to tedisamil dihydrochloride during and following a two-step infusion scheme in healthy male volunteers.
3. To determine the local tolerability of tedisamil sesquifumarate in comparison to tedisamil dihydrochloride during and following a two-step infusion scheme in healthy male volunteers.

Study Design

This was a single-center, double-blind, randomized, two-way cross-over study in healthy male volunteers. Each subject participated in two study sessions separated by a washout period of one week. The treatments administered in a randomized order were:

- Treatment A: a single i.v. dose of 26 mg tedisamil as sesquifumarate
- Treatment B: a single i.v. dose of 26 mg tedisamil as dihydrochloride

A single dose of 26 mg tedisamil as sesquifumarate (SQF) was infused i.v. over 30 minutes, with half the dose infused over 10 minutes and half the dose infused over the remaining 20 minutes (treatment A). Similarly, a single dose of 26 mg tedisamil as dihydrochloride (DHCl) was infused i.v. over 30 minutes, with half the dose infused over 10 minutes and half the dose infused over the remaining 20 minutes (treatment B).

Reviewer Note

The dose evaluated in this study differs from that proposed (0.32 mg/kg and 0.48 mg/kg in females and males, respectively) for anti-arrhythmic activity.

Formulation

- Tedisamil sesquifumarate (test), 2 mg/mL solution (tedisamil free base) ; Batch number 1020250/0001
- Tedisamil dihydrochloride (reference), 1.59 mg/mL solution (tedisamil free base); Batch number 1017540-0001

Pharmacokinetic (PK) sampling times

PK blood samples were drawn at 30 minutes pre-infusion, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90 minutes and 2, 4, 6, 8, 12, 18, 24 hours after start of infusion.

Pharmacokinetics

The following pharmacokinetic measures were determined: Cmax, tmax, AUC_{0-t}, $AUC_{0-t'}$, AUC_{0-inf}, λ_z, $t_{1/2}$, CL, MRT, and Vss.

Bioanalytical methods

Tedisamil concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 15.

Table 15: Performance of Tedisamil Assay in Bioavailability Study

Parameter	Measure	Reviewer Comment
Linearity	Range: 1 – 1000 ng/mL; $R^2 > 0.994$	Satisfactory
CV (%) as a Measure of Between day Precision	< 11 %	Satisfactory
Relative Bias (%) as Accuracy Measure	-7.7 to -1.3	Satisfactory
LLOQ	1 ng/mL	Satisfactory
Specificity	Chromatograms provided that demonstrate specificity	Satisfactory

The Cmax and AUC variables did not show statistically significant differences between the treatments.

Pharmacodynamics

ECG heart rate, QT-interval, QTc-interval; $AUC_{(0-8)}$, pre-dose corrected $AUC_{(0-8)}$

Safety Endpoints

Safety and tolerability were assessed by measuring electrocardiogram (ECG), pulse rate, blood pressures, hematology, blood chemistry, urinalysis, local tolerability and adverse events. Adverse events included laboratory assessments (hematology, clinical chemistry, and urinalysis), vital signs, physical examination, ECG and local tolerability.

Statistics

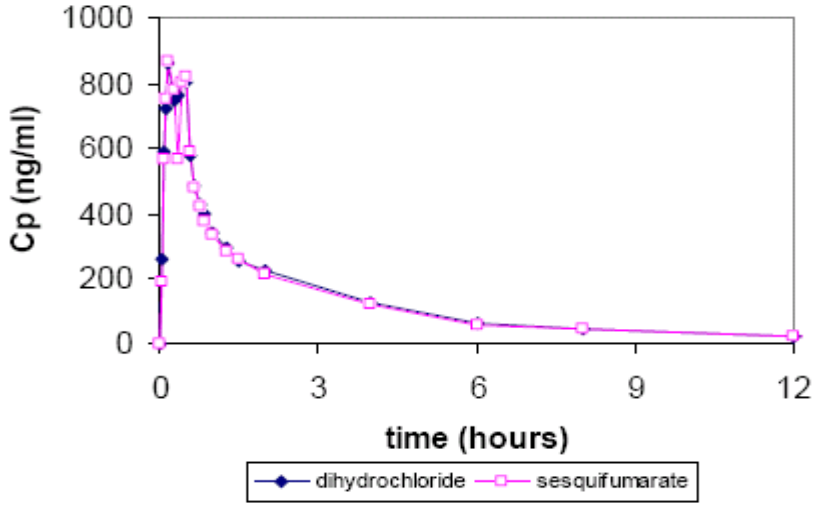
Standard descriptive statistics were obtained for PK, PD and safety variables; additionally ANOVA were used in PK analysis.

RESULTS AND DISCUSSION

Plasma Concentrations

The geometric mean plasma concentration-time profiles for both tedisamil treatments are depicted in Figure 13.

Figure 13: Tedisamil plasma concentration-time profiles (geometric mean) for dihydrochloride and sesquifumarate salts



Relative Bioavailability Assessment

PK measures obtained following administration of the two tedisamil formulations are summarized in Table 16.

Table 16: PK Measures following administration of tedisamil sesquifumarate and tedisamil hydrochloride

Treat-ment	N	t_{max} h	C_{max} ng/ml	AUC_{0-t} ng/ml.h	$AUC_{0-t'}$ ng/ml.h	AUC_{0-inf} ng/ml.h	CL ml/min	MRT h	V_{ss} l	λ_z 1/h	$t_{1/2}$ h
A	18	0.238	918	1720	1720	1780	243	4.68	67.8	0.115	6.34
B	18	0.282	923	1760	1760	1820	237	4.81	67.3	0.110	6.86

Note: sesquifumarate = treatment A; dihydrochloride = treatment B

The intersubject variability associated with each treatment was < 25 %.

As shown in Table 17, there were no significant differences in tedisamil exposure after administration of tedisamil SQF and DHCl. Consequently the two formulations are bioequivalent.

Table 17: Tedisamil Exposure Comparison- Tedisamil SQF vs. Tedisamil DHCl

	Ratio (%)	90% CI (%)
AUC_{0-t}	98	95-102
$AUC_{0-t'}$	98	94-102
AUC_{0-inf}	98	94-102
C_{max}	100	91-109

Pharmacodynamic Results

Descriptive statistics for derived ECG variables are summarized in Table 18.

Table 18: Descriptive statistics of ECG parameters following tedisamil administration

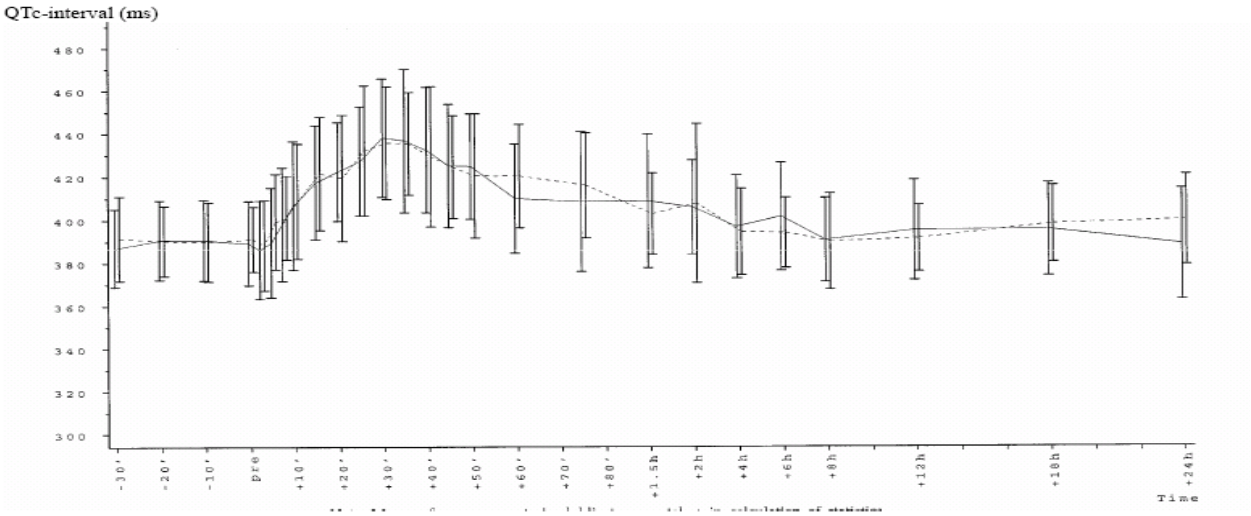
		Treatment A (N=18)		Treatment B (N=18)	
		Mean	SD	Mean	SD
Heart rate	$AUC_{(0\text{-}8)}$ (h*bpm)	474	60	468	54
	$AUC_{(0\text{-}8)\ corrected}$ (h*bpm)	-11	27	-27	31
	Maximum decrease (bpm)	13	3	14	2
QT-interval	$AUC_{(0\text{-}8)}$ (h*ms)	3258	217	3259	183
	$AUC_{(0\text{-}8)\ corrected}$ (h*ms)	153	73	176	88
	Maximum increase (ms)	88	21	88	22
QTc-interval	$AUC_{(0\text{-}8)}$ (h*ms)	3221	173	3205	152
	$AUC_{(0\text{-}8)\ corrected}$ (h*ms)	106	75	79	83
	Maximum increase (ms)	65	17	60	25

Notes: sesquifumarate = treatment A; dihydrochloride = treatment B; corrected values are pre-dose corrected.

Both treatments exhibited a similar mean decrease of heart rate and similar mean increases of QT-and QTc-intervals.

The temporal relationship for QTc is depicted in Figure 14.

Figure 14: ECG derived measures following administration of tedisamil SQF and DHCl



Note: Means of measurements in duplicate were taken in calculation of statistics.
Solid lines display means under tedisamil sesquifumarate, dotted lines display means under tedisamil dihydrochloride.

The median time-point to maximum changes of the ECG measures were comparable:

- Decrease in heart rate- 0.46 hours (treatment A) vs. 0.58 hours (treatment B).
- Increase of QT was 0.5 hours for both treatments
- Increase of QTc was 0.58 hours for both treatments

However, it should be noted that for maximal heart rate the modal time was slightly different from median time values: for SQF the mode occurred at 0.42 hr and for DHCL at 0.33 hr.

Overall the PK and PD findings suggest tedisamil SQF performs similarly to tedisamil DHCl.

Applicant's Safety Summary

In this study no deaths or other serious adverse events were reported. Treatment-emergent signs and symptoms (TESS) were reported in 28% (n=5) of the subjects while on treatment A and 39% (n=7) of the subjects while on treatment B. All adverse events were of mild or moderate intensity. The most frequently reported adverse events were headache (18%, n=3) on treatment A and pain (22%, n=4) on treatment B, respectively. Local tolerability was similar among both treatment groups.

No clear differences in laboratory measurements were observed between the two treatments with respect to mean values or shifts with respect to normal ranges. None of the individual laboratory abnormalities were considered clinically significant by the investigator. The mean SBP and DBP showed a slight increase following treatment, which lasted about two hours. The mean pulse rate decreased slightly for about one hour. There were no marked differences between the two treatments and there were no clinically significant ECG abnormalities as judged by the investigator.

Recommendations/Conclusions

The following PK information generated in is acceptable for labeling purposes, as appropriate.

- In both treatments similar mean plasma concentration-time profiles were observed.
- The mean pharmacokinetic parameters of both treatments were comparable
- Pharmacodynamic properties of single i.v. doses of tedisamil sesquifumarate and tedisamil dihydrochloride -as assessed by ECG heart rate, QT-interval and QTc-interval- were similar.

Mean (CV %) PK Measures following IV administration of tedisamil sesquifumarate as a two-step infusion (26 mg) in healthy volunteers

PK Measures	Value
Tmax (hr)	0.238
Cmax (ng/mL)	918
AUC_{0-t} (h·ng/mL)	1720
Vss (L)	67.8
CL (mL/min)	243
$T_{1/2\ (hr)}$	6.34

^ Tmax reported as median and (range)

4.2.2 The pharmacokinetics and metabolism of ^{14}C-tedisamil dihydrochloride in healthy male volunteers (K.219.5020)

PROTOCOL #	Study no. K.219.5020
INVESTIGATOR	Prof. Dr. H.-P. Breuel
STUDY SITE	Institute for Clinical and Experimental Medicine, Prague, Czech Republic
STUDY PERIOD	1994
Report Location	Module 5 Volumes 41 and 42

Objectives (per applicant)

To determine the pharmacokinetics of radioactivity following single oral and intravenous drug administration of ^{14}C-tedisamil dihydrochloride.

To determine rate and extent of absorption, extent of renal and fecal excretion, total recovery and mass balance after single oral and intravenous drug administration.

To determine the metabolism in plasma and urine samples.

To determine rate and extent of absorption, the extent of renal and fecal excretion and mass balance of radioactivity at tedisamil dihydrochloride steady state; tedisamil dihydrochloride was given as a first ^{14}C-labelled dose, followed by bid administration of the unlabelled compound, followed by a second ^{14}C-labelled dose.

Study Design

This was a two-part, randomized two period crossover study in healthy volunteers (n = 14). In Part A subjects received a single oral and intravenous dose or radio-labeled tedisamil dihydrochloride (DHCL); in Part B subjects received multiple oral doses of labeled and non-labeled tedisamil. The IV and oral doses were as follows:

- IV- 22.74 mg ^{14}C-tedisamil DHCL in 10 mL of solution over 10 minutes
- Oral- 100 mg ^{14}C-tedisamil DHCL

CYP2D6 metabolic status was evaluated.

Reviewer Note on Content of Review

This review focuses on Part A information, particularly following IV administration, as this information is most relevant in the submitted NDA. Oral data can be used in conjunction with IV data to provide an absolute bioavailability estimate and estimate differences in disposition between parenteral and oral routes. It should be noted that the dihydrochloride salt form is not the to-be-marketed salt form.

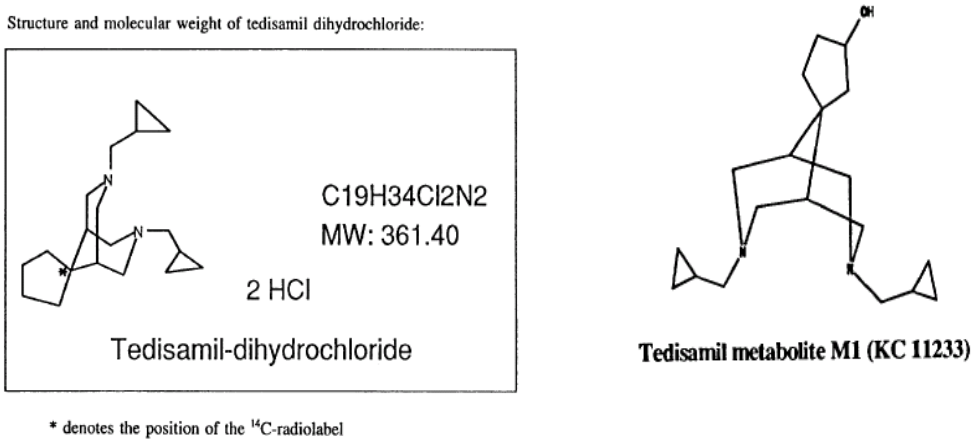
Formulation/Drugs

Tedisamil dihydrochloride capsules containing 100 mg and 96.39 µCi, batch 020 P, lot no. 007 VP
Tedisamil dihydrochloride capsules containing 100 mg unlabelled, batch 054 N, lot no. 007 VP
Tedisamil dihydrochloride ampoules 10 ml, containing 22.74 mg and 96.2 µCi, batch 015 P, lot 007VP

The formulations were manufactured by Kalie-Chemie Pharma GmbH, Hannover.

The structures of tedisamil and its hydroxy metabolite are depicted in Figure 15.

Figure 15 : Stuctures of Tedisamil and Its Primary Metabolite , M1



* denotes the position of the ^{14}C-radiolabel

Blood Sampling

Blood samples were collected at predose and 3, 6, 10, 15, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 18, 24, 30, 36, 48, 60, 72, and 96 h post dose.

Urine Sampling

Urine samples were collected over the following intervals: predose and 0-3, 3-6, 6-12, 12-24, 24-36, 48-72 and 72-96 h post dose.

Feces Sampling

All excreted feces were collected over the entire course of the study.

Bioanalytical Assay

Samples were analyzed by liquid scintillation counting and unchanged tedisamil was measured by HPLC with electrochemical detection. The HPLC assay performance was acceptable with the following characteristics: CV < 19 %, relative bias ranging from -5.3 to – 1.1, for plasma and CV < 8 %, relative bias ranging from -4.8 to + 0.9 for urine. The linear ranges were 50 to 2500 ($R^2 > 0.994$) and 0.5 to 200 ($R^2 > 0.993$) for urine and plasma, respectively.

Pharmacokinetic Methods

The following PK measures were determined: Cmax, Tmax, AUC and $t_{1/2}$. Metabolic profiling was also conducted: two metabolites were available as reference material.

Statistical Methods

After correcting for dose AUC data were log-transformed and 95 % confidence intervals calculated according to the two-sided one-sample test.

RESULTS

CYP2D6 Metabolic Status

The sponsor indicates that CYP2D6 genotyping was conducted for all 14 subjects. One subject (#12) was a poor metabolizer. Based on Exon5, all subjects were homozygous extensive metabolizers; whereas, based on Intron3/Exon4 the majority of subjects were extensive metabolizers (n = 9), the remaining subjects were heterozygous extensive metabolizer status (n =4).

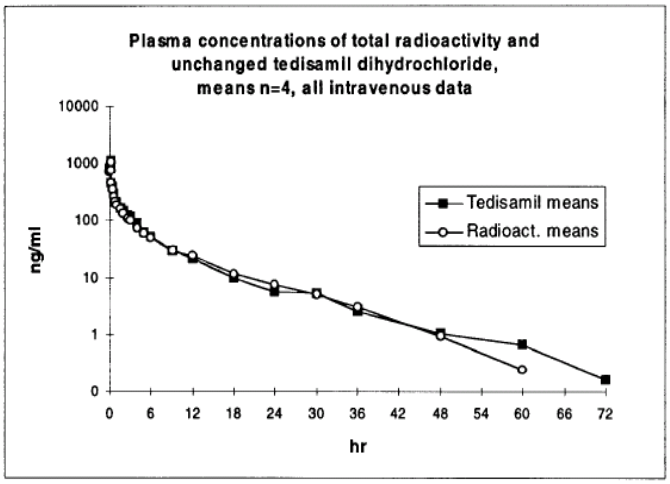
Reviewer Note

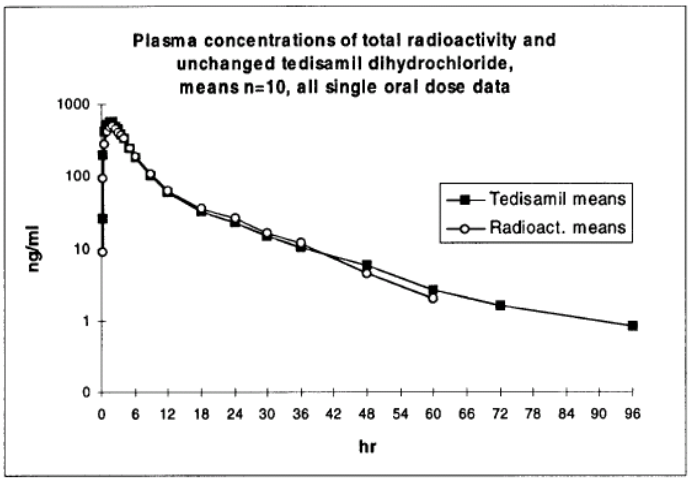
The metabolic status does not have a bearing on PK results as tedisamil is not metabolized by CYP2D6, furthermore the data indicate metabolism of tedisamil was non-existent or minimal in this study.

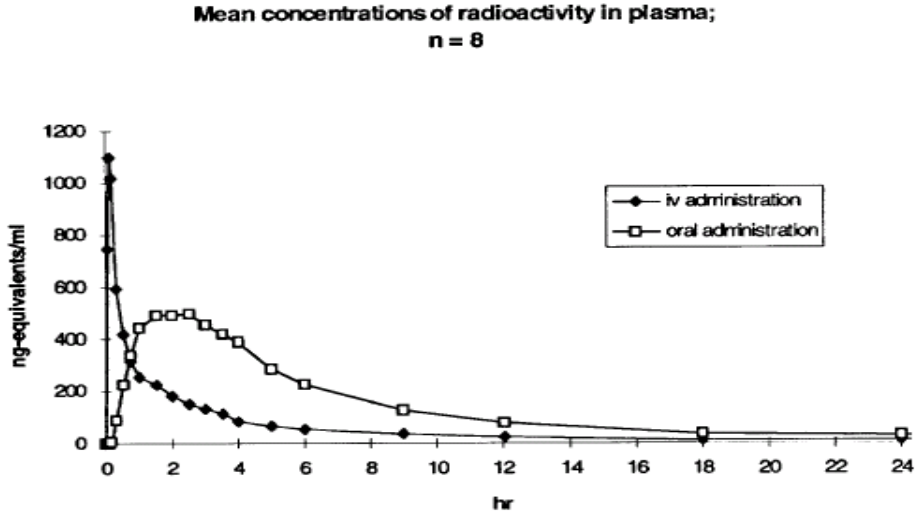
Oral and IV Plasma Pharmacokinetics

The mean (± SD) plasma concentration-time profiles of radioactivity, following IV and oral administration of tedisamil are shown in Figure 16.

Figure 16: Plasma concentration-time profiles of total radioactivity (bottom), and total radioactivity and total radioactivity with unchanged tedisamil following IV (top left) or oral (top right) administration of radio-labeled tedisamil







The profiles suggest that tedisamil is minimally metabolized following IV as well as oral administration. It is noted that there were only four subjects in the IV cohort in which total radioactivity as well as unchanged tedisamil were measurable; however, the oral data has more data points (n = 10) and provides additional supportive evidence that tedisamil is minimally metabolized. In general, metabolism is expected to be greater following oral administration as a result of first pass effects and other GI related phenomena.

Table 19 provides a summary of PK measures based on total radioactivity over 96 hours. The data indicate that recovery was fairly extensive following IV administration and renal elimination is the main pathway by which tedisamil is excreted from the body. Potentially, excretion was not complete when the study was stopped.

Table 19: Mean ± SD Pharmacokinetic parameters of tedisamil total radioactivity measures following administration of IV (22.74 mg containing 96.2 µCi) and oral (100 mg containing 96.39 µCi) tedisamil DHCL

		22.74 mg intravenous n=8	100 mg oral n=8
Cmax	(ng/ml)	1176 ± 170	581 ± 132
Tmax	(h)	0.14 ± 0.04	1.59 ± 0.73
AUC(0-Tlast)	(ng*h/ml)	1521 ± 358	3914 ± 812
AUC(0-inf)	(ng*h/ml)	1581 ± 387	4049 ± 839
t1/2	(h)	11.45 ± 2.21	11.61 ± 2.87
CL, CL/f	(ml/min)	254 ± 69	428 ± 95
Clren	(ml/min)	215 ± 73	159 ± 30
Vz, Vz/f	(l)	245 ± 52	421 ± 95
Recovery	(% dose)		
renal		83.5 ± 8.1	37.7 ± 5.9
fecal		7.9 ± 2.3	48.3 ± 7.9
total		91.4 ± 8.2	85.9 ± 8.3

The absolute bioavailability of tedisamil DHCL is ~ 60 % (tabulated below), this is based on total radioactivity measurements. It should be noted that 95 % confidence intervals (CIs) rather then 90 % CIs (recommended) were estimated.

Part A n=8	Geometric means		Mean ratio	p *	shortest CI **
	iv	oral			
AUC normalized	68	40	59 %	0.001	51-68 %

* p-value of the two-sided one sample t-test

** conventional 95 % confidence interval according to the one sample t-test

Metabolites and metabolite profiling

Only a single metabolite was found in the urine following IV administration and this metabolite accounted for 3.6 % of the total radioactive dose. This metabolite's retention time was identical

to metabolite, M1 that had previously been identified. No metabolite was detected in urine following oral administration.

Applicant's safety summary

The study treatments were well tolerated. Tedisamil altered some ECG parameters in a manner consistent with its anti-arrhythmic properties.

Recommendations/Conclusions

The following information from the study is acceptable for labeling, as needed

- The total recovery of radioactivity was 91 % after IV administration.
- Approximately 84 % and 8 % of the administered IV dose of ^{14}C- was excreted in urine and feces, respectively
- Tedisamil did not appear to be appreciably metabolized following IV or oral administration; the only identified metabolite accounted for less than 4 % of the total radioactive dose and corresponded to previously identified hydroxy metabolite, M1.
- The absolute bioavailability for orally administered tedisamil DHCl is ~ 60 %.

4.2.3 A double-blind, placebo-controlled, randomized, single iv dose, two periods cross-over study to assess the safety, tolerability, pharmacodynamics and pharmacokinetics during and following a two step infusion of tedisamil in healthy male subjects (S219.1.116, 2001)

PROTOCOL #	S219.1.116
INVESTIGATOR	K.M. Eckl, M.D.
STUDY SITE	Pharm PlanNet Contract Research GmbH, Mönchengladbach, Germany
STUDY PERIOD	16 Nov 1999- 14 Dec 1999
REPORT LOCATION	Module 5 Volumes 87 - 89

Objectives (per applicant)

1. To assess safety and tolerability of tedisamil in healthy male subjects during and following a two step infusion scheme .
2. To examine the correlation between plasma concentrations of tedisamil and the pharmacodynamic variables QT, QTc, and heart rate, calculated from the RR-interval, using the PK/PD model and to compare these results with results gained from a previous simulation study.

Reviewer Note on Review Content
This review focuses on PK information; PK/PD information were not reviewed in detail since PK/PD characteristics of volunteers differ from those of patients (Refer to Pharmacometrics Consult)

Study Design

This was a single center, double-blind, placebo-controlled, randomized, single IV dose, two period cross-over study. Subjects were randomly allocated to either treatment sequence Tedisamil-Placebo or Placebo-Tedisamil. One day per period, at which an infusion over a total duration of 30 minutes was administered. Half the dose was infused over the first 10 minutes and the remaining half over 20 minutes. The total tedisamil dose was 0.4 mg/kg. Both drug administrations were separated by a wash-out period of one week.

Formulations

Tedisamil dihydrochloride Strength: 2 mg/ml Batch No: 104R

Pharmacodynamics (PD)

Twelve-lead 12-lead ECG was taken at several time points to explore the PD effects (QT and QTc) of tedisamil during and following infusion.

Pharmacokinetics

The following pharmacokinetic parameters were determined: AUC(0-inf), AUC(0-t), Cmax, Tmax, t1/2, λz, Vss, CL, and MRT

Bioanalytical methods

Tedisamil concentrations were determined using a validated liquid chromatography- with mass spectrometry (LC-MS) method. The assay performance was acceptable as illustrated in Table 20.

Table 20: Performance of Tedisamil Assay in Two-step Infusion Study

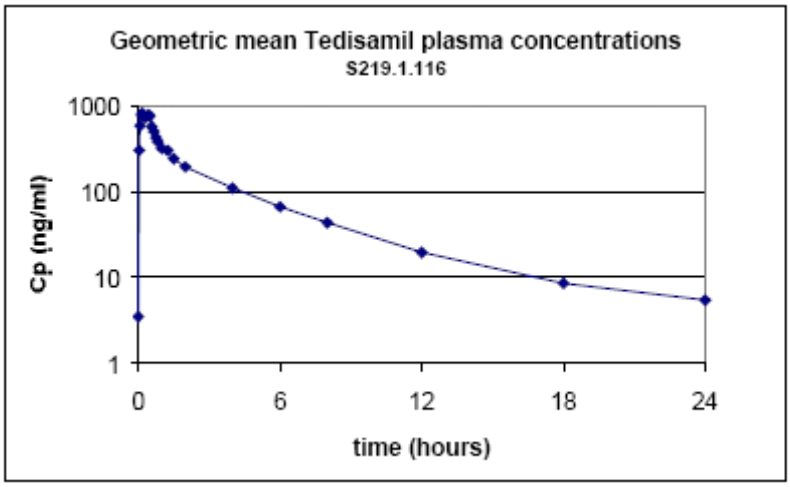
Parameter	Value	Reviewer Comment
Linearity	Range: 1 to 200 ng/mL; $R^2 > 0.982$	Satisfactory
CV (%) as Measure of Between day Precision	< 13 %	Satisfactory
Relative Bias as Measure of Accuracy	-6.5 to +4.0	Satisfactory
LLOQ	1 ng/mL	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Results

Pharmacokinetics

The tedisamil plasma concentration-time profile following a two-step infusion is depicted in the following figure.

Figure 17: Tedisamil plasma concentration-time profiles following two step IV infusion (0.4 mg/kg)



Tedisamil PK measures are presented in Table 21.

Table 21: PK Measures following Two-step infusion

PK Measure	Type of Mean	Tedisamil	90% confidence interval	
			Lower	Upper
AUC(0-inf) (ng*h/ml)	Geometric Mean (CV)	1715 (36)	1554	2088
AUC(0-t) (ng*h/ml)	Geometric Mean (CV)	1670 (36)	1512	2042
Cmax (ng/ml)	Geometric Mean (CV)	905 (33)	826	1086
t1/2 (h)	Arithmetic Mean (SD)	5.5 (1.4)	4.88	6.04
λz (1/h)	Arithmetic Mean (SD)	0.1334 (0.0281)	0.1219	0.1449
Tmax (min)	Median (Range)	12.5 (5-75)	13	26.5
MRT (h)	Arithmetic Mean (SD)	4.22 (0.56)	3.99	4.45
Vss (L)	Arithmetic Mean (SD)	85.2 (36.4)	70.3	100.1
CL (ml/min)	Geometric Mean (CV)	315 (37)	284	386

Tmax ranged between 5 and 75 minutes after start of infusion and showed a median value of 12.5 minutes.

The report indicates that the best-fitting pharmacokinetic model was the three-compartment constant infusion model.

Pharmacodynamics

Table 22 and Table 23 provide a summary of ECG measures.

Table 22: Derived Parameters of ECG intervals

Parameter	Derived Parameter	Tedisamil Arith. Mean (SD)	Placebo Arith. Mean (SD)
QT Interval (ms)	Maximum	474.2 (39.2)	416.9 (19.4)
	Maximum Increase	76.0 (22.4)	18.0 (11.5)
QTc Interval (ms)	Maximum	455.9 (30.0)	421.9 (21.5)
	Maximum Increase	61.1 (30.3)	27.0 (13.9)
Heart Rate (bpm)	Minimum	49.2 (7.0)	52.7 (4.8)
	Maximum Decrease	10.6 (3.8)	6.4 (3.4)

Table 23: Statistical analyses of derived ECG intervals

Parameter	Derived Parameter	Estimate (Tedisamil-Placebo)	95% C. I.	
			lower	upper
QT Interval (ms)	Maximum	58.4	46.4	70.4
	Maximum Increase	57.9	44.7	71.1
QTc Interval (ms)	Maximum	34.0	16.7	51.2
	Maximum Increase	34.1	16.1	52.1
Heart Rate (bpm)	Minimum	- 4.01	- 5.96	- 2.06
	Maximum Decrease	4.22	2.04	6.39

The ECG data indicate that relative to placebo:

- tedisamil increased the QT and QTc interval
- tedisamil decreased heart rate

Each of the above comparisons were statistically significant ($p<0.002$). These findings are consistent with tedisamil's role as anti-arrhythmic.

Applicant's Safety Summary

The following adverse events were judged as probably related to the study drug:

- injection site reaction (mild and moderate),
- pain at injection site
- paresthesia (mild)

Overall, a two-step infusion with 0.4 mg tedisamil dihydrochloride per kg body weight was well tolerated. No clinically relevant findings were observed in parameters of hematology, clinical chemistry, urinalysis and vital signs. Nevertheless there was a small increase in the arithmetic mean of systolic and diastolic blood pressure in the first four hours after dosing and a decrease in pulse rate in the first hour after dosing in the tedisamil group and almost no change in the placebo group.

Recommendations/Conclusions

Pharmacokinetics

- Tedisamil PK may be described by a three-compartment constant infusion model
- This study provides estimates of PK measures (see Table below) in healthy volunteers at a dose that is intermediate to that proposed as an anti-arrhythmic

PK Measure	Type of Mean	Tedisamil	90% confidence interval	
			Lower	Upper
AUC(0-inf) (ng*h/ml)	Geometric Mean (CV)	1715 (36)	1554	2088
AUC(0-t) (ng*h/ml)	Geometric Mean (CV)	1670 (36)	1512	2042
Cmax (ng/ml)	Geometric Mean (CV)	905 (33)	826	1086
t1/2 (h)	Arithmetic Mean (SD)	5.5 (1.4)	4.88	6.04
λz (1/h)	Arithmetic Mean (SD)	0.1334 (0.0281)	0.1219	0.1449
Tmax (min)	Median (Range)	12.5 (5-75)	13	26.5
MRT (h)	Arithmetic Mean (SD)	4.22 (0.56)	3.99	4.45
Vss (L)	Arithmetic Mean (SD)	85.2 (36.4)	70.3	100.1
CL (ml/min)	Geometric Mean (CV)	315 (37)	284	386

Pharmacodynamics

- Tedisamil increases QT and QTc interval by a maximum of ~ 50 and 30 ms, respectively, relative to placebo
- Tedisamil decreases heart rate by a maximum of ~ 4 bpm, relative to placebo

4.2.4 In vitro metabolism studies using rate and human hepatocytes following three consecutive repeated periods of 24 hour incubations(K.219.6022, 1998)

PROTOCOL #	K.219.6022
AUTHOR	H. Fritsch
STUDY SITE	Solvay Pharmaceuticals, Hannover, Germany
STUDY PERIOD	January to May, 1996
REPORT LOCATION	Module 4 Volume 18

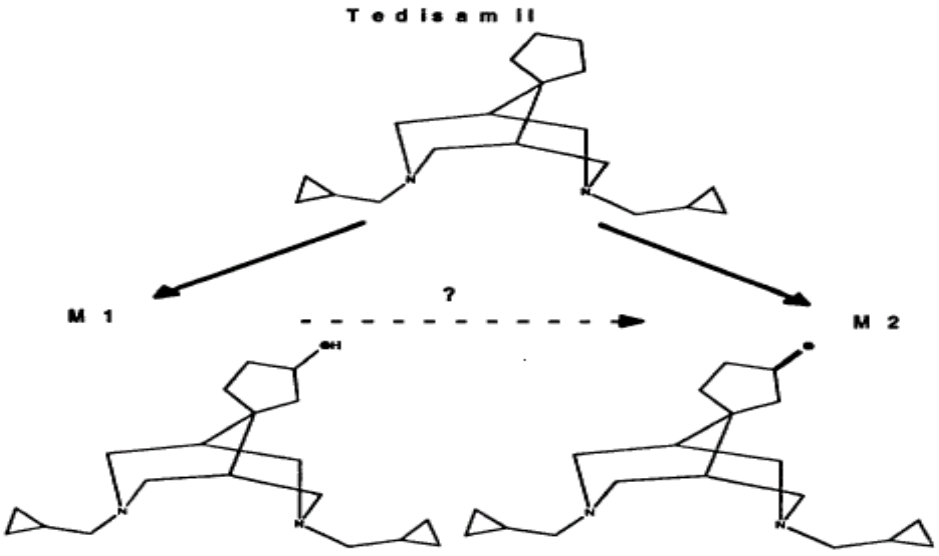
Reviewer Note on Information Reviewed and Review Content
This review focuses on the human hepatocyte information. The applicant indicates that this report is an amendment to Report K.219.6013.

Experimental Conditions (Method)

Various concentrations (1, 3, 10, 30, and 100 μM) of tedisamil were incubated with rat and human hepatocytes for 24 hours. The supernatants were tested for tedisamil metabolism. Tedisamil was added to the culture medium after the 24 hr period on two occasions to determine metabolism at 48 and 72 hours, as was done for the initial 24 hour period. Human hepatocytes were isolated from five different donors. Concentrations were determined by HPLC.

Drugs/Formulations

- Tedisamil: lot No. A9-4/M from Kali-Chemi Pharma
- Metabolite 1, M1 (KC11233) and Metabolite 2, M2 (SG2030-SG1014) were synthesized by Kali-Chemie Pharma



Based on the rat hepatocyte data and previously obtained information two putative tedisamil metabolites have been identified.

RESULTS

In a control experiment, metabolism was shown to be stable in culture medium, (Table 24) indicating that the medium did not cause metabolism or degradation of tedisamil

Table 24: Control experiments with tedisamil in culture medium

tedisamil µM	M1 %	M2 %	Tedisamil %
1	0.0	0.0	100.0
3	0.0	0.0	100.0
10	0.0	0.0	100.0
30	0.0	0.0	100.0
Blank 80 µl	0.0	0.0	0.0
Blank 40 µl	0.0	0.0	0.0
Blank15 µl	0.0	0.0	0.0
Blank 5 µl	0.0	0.0	0.0

Tedisamil was not metabolized by human donors as shown in Table 25.

Table 25: Metabolism of Tedisamil by Human Hepatocytes*

Donor ID n°.	incubation time	M1 %	M2 %	Tedisamil %
2	0-24 h	0	0	100
2	24-48h	0	0	100
2	48-72h	0	0	100
6	0-24 h	0	0	100
6	24-48h	0	0	100
6	48-72h	0	0	100
7	0-24 h	0	0	100
7	24-48h	0	0	100
7	48-72h	0	0	100
10	0-24 h	0	0	100
10	24-48h	0	0	100
10	48-72h	0	0	100
11	0-24 h	0	0	100
11	24-48h	0	0	100
11	48-72h	0	0	100

* structures of the two putative metabolites are depicted in the Appendix.

Conclusions/Recommendations

Tedisamil was not metabolized by human hepatocytes, indicating hepatic metabolism plays no or only a minor role in tedisamil elimination.

4.2.5 In vitro metabolism studies with microsomes isolated from human, rat, dog, mouse, hamster, rabbit, rhesus monkey, and cynomologus monkey liver (Study K.219.6023)

PROTOCOL #	K.219.6022
AUTHOR	Dr. H. Fritsch
STUDY SITE	Solvay Pharmaceuticals, Hannover, Germany
STUDY PERIOD	June to October, 1995
REPORT LOCATION	Module 4 Volume 18

Reviewer Note on Information Reviewed

This review focuses on the human microsome information. This report is an amendment to Report K.219.6013.

Experimental Conditions (Method)

Frozen human liver microsomes were obtained from Natutec, Germany. Standard procedures for evaluating in vitro metabolism were adopted including: microsomes (1 mg total protein), addition of NADPH-generating system. The tedisamil concentration was 10 nmol. Concentrations were determined by HPLC.

Drugs/formulations

Compound name	Source
Tedisamil (KC-8857)	Kali-Chemie Pharma Lot: A9-4/M purity > 98 %
[cyclopentane-1-^{14}C]Tedisamil * 2HCl (KC-11-8857)	Amersham, CFQ 8255 purity > 98.4 %
Metabolite M1 (KC11233)	Kali-Chemie Pharma purity > 98 %
Metabolite M2 ((SG2030-SG1014)	Kali-Chemie Pharma

RESULTS

Tedisamil was not metabolized by liver microsomes isolated in human male and female human donors as shown in Table 26.

Table 26: Individual data from metabolism study with human liver microsomes incubated with tedisamil for 60 minutes

			M1	tedisamil	mean area %	mean area %	specific activity mean
species	sex	microsomes	(µV*min)	(µV*min)	M1	tedisamil	pmol/min/mg
donor 7	male	+ NADPH	0	488678			
	male	+ NADPH	0	433650	0	100	**0**
	male	- NADPH	0	439286		100	0
donor 15	male	+ NADPH	0	430623			
	male	+ NADPH	0	425932	0	100	**0**
	male	- NADPH	0	414043		100	0
donor 16	female	+ NADPH	0	411335			
	female	+ NADPH	0	407903	0	100	**0**
	female	- NADPH	0	400623		100	0

CONCLUSIONS/RECOMMENDATIONS

Tedisamil was not metabolized by human liver microsomes, indicating CYP enzymes play a negligible role in tedisamil elimination.

4.2.6 Biotransformation studies of KC 8857 in rat and human hepatocytes (Study K.219.6028)

PROTOCOL #	K.219.6028
STUDY SITE	BIOPREDIC Rennes, France
STUDY PERIOD	November 1998
REPORT LOCATION	Module 4 Volume 19

Reviewer Note on Information Reviewed

This review focuses on the human hepatocyte information. There were two sets of studies conducted: 1) addressing morphological changes and viability of cells and 2) addressing induction potential. Only the induction studies were reviewed as these are pertinent to current procedures to assess drug interaction potential.

Experimental Conditions (Method)

CYP induction ability of KC 8857 (tedisamil) was evaluated in human hepatocytes (three donors) and compared to reference inducer compounds, 3-methylcholanthrene, phenobarbital, 16α-pregnenolone and rifampin. Reagents and compounds were obtained from commercially available sources or as gifts from various companies. Human hepatocytes were obtained from donors (2, 10 and 11 in induction test); the characteristics of the donors are in the appendix.

The timeline for the experiment is depicted as follows.

Time synopsis

t : preparation and seeding of cells
T : incubation with test compound or reference compounds
↑ : addition of medium containing test compound or reference compounds
↓ : collection of the supernatants for metabolite analysis
• : morphological observations
* : assays for cellular enzyme activities

Drug Products (Treatments)

The characteristics of the test compound are tabulated as follows

Test compound	L or NL	Supplier	Date of supply	Batch number	Quantity NL: mg L: MBq	Specific activity (MBq/mmole))	Storage Tempera-ture (°C)	Storage Particular conditions
KC 8857	NL	KALI CHEMIE PHARMA	22th September 1994	A15/M	10 000	W.O.	+ 4	in the dark
^{14}C-KC 8857	L	KALI CHEMIE PHARMA	22th September 1994	N.K.	18.5	1998	- 20	in the dark

L : labelled ; NL : non labelled
W.O. : without object ; N.K. : not known

The range of tedisamil concentrations was 3 x 10^{-6} to 3 x 10^{-4} M for human hepatocytes.

Reviewer Note on Characteristics of Liver Donors
No information was given in terms of the use of drugs (e.g. use of enzyme inducers) before donation.

The following CYP probe substrates and inducers were used:*

Enzyme	Substrate	Inducer	Comment
CYP1A	Ethoxyresorufin deethylase activity	3-methylcholanthrene at 5 x 10^{-6} M	Satisfactory^
CYP2B	Pentoxyresorufin dealkylase activity	Phenobarbital at 3 x 10^{-3} M	Acceptable
CYP3A	Nifedipine oxidase activity	Rifampin at 5 x 10^{-5} M	Acceptable

* the current guidance indicates that CYP3A (co-induced with CYP2C, CYP2B and P-gp) and CYP1A2 should be evaluated.
^ the scientific literature reports the sue of the Applicant's system, but this approach is not reported in FDA guidance

Reviewer Note on Enzyme Systems
Standard *in vitro* drug-drug interaction conditions were used for the experiment. It is noted that the CYP1A enzyme system is not considered in the current drug interaction guidance. The guidance specifies investigation of CYP1A2 vs. CYP1A Additionally, per the Guidance there was no need to evaluate CYP2B as a distinct enzyme system as it is co-induced with CYP3A. It should be noted that this study was conducted prior to issuance of the current drug interaction guidance.

RESULTS

The applicant indicates that there was a high degree of inter-individual variability in drug metabolizing activity, both at the beginning and end of incubation in the control cultures.

The study results are presented in Table 27.

Table 27: Evaluation of Tedisamil's Induction Potential

Enzyme	Substrate	Inducer	Comment
CYP1A	Ethoxyresorufin deethylase activity	3-methylcholanthrene at 5 x 10^{-6} M	8.8 to 15-fold increase in activity
CYP2B6	Pentoxyresorufin dealkylase	Phenobarbital at 3 x 10^{-3} M	Negligible increase
CYP3A	Nifedipine oxidase activity	Rifampin at 5 x 10^{-5} M	2.5 – 6.1-fold increase inactivity
Enzyme	**Substrate**	**Inducer**	**Comment**
CYP1A	Ethoxyresorufin deethylase activity	Tedisamil	1.2 to 2.5-fold increase in activity
CYP3A	Nifedipine oxidase activity	Tedisamil	1.5 to 2 -fold increase in activity

Overall, the data suggest that tedisamil does not induce CYP3A or CYP1A activity. The utility of the CYP2B system was not established. However, based on the current Guidance CYB2B6 is not likely to be induced, since it is co-induced with CYP3A.

Recommendations/Conclusions

- Tedisamil does not induce CYP3A activity.
- Tedisamil does induce CYP1A activity, but it is unknown if tedisamil would induce CYP1A2 activity

It should be noted that since tedisamil is only given as a single dose for the proposed indication, its potential inducing ability is limited; most compounds that are inducers require multiple administrations to affect induction. Therefore induction potential is not an issue from a clinical point of view.

APPENDIX

Characteristics of Human Liver Donors

Cell origin	Freezing	Viability (Trypan blue exclusion test, %)	
		After isolation	After freezing, thawing and purification on a Percoll cushion
Donor 2	Yes	81	95
Donor 10	No	81	W.O.
Donor 11	No	91	W.O.

W.O. : without object

Study designation	Age (years)	Sex	Liver (L) or biopsy (B)	Particular information
Donor 1	73	W	B*	Benign tumour
Donor 2	41	M	B*	Liver metastasis
Donor 3	48	W	B*	Liver metastasis
Donor 6	64	M	B*	Liver metastasis
Donor 7	64	M	B*	Liver metastasis
Donor 10	63	W	L	Trauma to head
Donor 11	48	W	L	Intracerebral hemorrhage

W : woman ; M : man

* : cells were isolated from the non tumoral area of the biopsy.

4.2.7 Determination of the Induction Potential of Tedisamil Sesquifumarate on the Activities of CYP1A2, CYP2C9, and CYP3A4 in Cryopreserved Human Hepatocytes (K.219.6030, 2003)

PROTOCOL #	1023/ K.219.6030
STUDY DIRECTOR	Aruna Koganti, Ph.D.
STUDY SITE	In Vitro Technologies, Inc. Baltimore, MD 21227
STUDY PERIOD	March 2003
REPORT LOCATION	Module 4 Volume 19

Study Design

Standard procedures for in vitro metabolism studies were used. Cryopreserved human hepatocytes were obtained from a single organ donor* (see Appendix for characteristics of donor). Tedisamil sesquifumarate was incubated with the hepatocytes for two days. Subsequently a selective substrate for each CYP isoform was added to the incubation system. The formation of the selective metabolite from its substrate was measured by HPLC. Tedisamil concentrations were 10, 30, and 100 µM (based on salt concentration). Rifampin (CYP3A) and omeprazole (CYP1A2) were used as positive controls to ensure system suitability.

Reviewer Note on Study Design Limitations

Use of a single donor is not optimal, as this will not account for inter-individual in drug metabolizing ability. Consequently the results from this study will only have qualitative value and should not be considered definitive.

The following table summarizes the CYP enzymes and substrates evaluated in this study.

Table 28: CYP450 Enzyme substrates and inhibitors (per Applicant's report)

CYP isoform	Isoform-selective substrate	Substrate concentration
CYP1A2	Phenacetin	150 µM
CYP2C9	Tolbutamide	50 µM
CYP3A4	Testosterone	125 µM

- **Phenacetin O-deethylase (CYP1A2)-** based on measuring acetaminophen (metabolite); parent and metabolite were analyzed by an ultraviolet (UV) detector.
- **Tolbutamide methyl-hydroxylase (CYP2C9)-** based on measuring hydroxymethyl-tolbutamide (metabolite); parent and metabolite were detected by fluorescence.
- **4.3 Testosterone 6β-hydroxylase (CYP3A4)-** based on measuring, 6β-hydroxytestosterone (metabolite); parent and metabolite were analyzed by a UV detector.

Compounds

- Tedisamil sesquifumarate salt (molecular weight = 462.59; batch no. WRM02K420)
- CYP enzyme substrates and inhibitors were obtained from commercial sources

RESULTS

The data obtained from the experiments designed to evaluate the induction potential of tedisamil sesquifumarate are presented in the preceding three tables. The rifampin and omeprazole positive controls functioned appropriately indicating that the test system was suitable. In all systems tedisamil had similar activity as the vehicle control (Table 29) indicating, it was not an inducer at the tested tedisamil concentrations (10, 30, and 100 μM based on salt concentration).

Table 29: Assessment of CYP activity to evaluate Tedisamil Induction Potential

		Metabolite Formation	Specific Activity μM/min/million cells	Percent of Vehicle Control
	CYP1A2 Evaluation (acetaminophen formation from phenacetin)			
acetonitrile	Vehicle Control	1.21 ± 0.185	23.1 ± 3.53	100
omeprazole	Positive Control	7.66 ± 1.17	146 ± 22.2	633
Tedisamil	10 μM Tedisamil	1.20 ± 0.116	22.8 ± 2.22	99.1
Tedisamil	30 μM tedisamil	0.977 ± 0.058	18.6 ± 1.10	80.8
tedisamil	100 μM Tedisamil	0.883 ± 0.013	16.8 ± 0.249	73.0
	CYP2C9 evaluation (hydroxymethyl tolbutamide formation form tolbutamide)			
acetonitrile	Vehicle Control	0.622 ± 0.451	8.88 ± 0.644	100
Tedisamil	10 μM Tedisamil	0.657 ± 0.0237	9.39 ± 0.338	106
Tedisamil	30 μM tedisamil	0.620 ± 0.0389	8.86 ± 0.555	100
tedisamil	100 μM Tedisamil	0.578 ± 0.001	8.26 ± 0.137	93.0
	CYP3A evaluation (6-beta-hydroxy testosterone formation)			
acetonitrile	Vehicle Control	5.24 ± 0.236	150 ± 6.73	100
rifampin	Positive control	32.0 ± 1.48	913 ± 42.4	609
Tedisamil	10 μM Tedisamil	5.57 ± 0.107	159 ± 3.07	106
Tedisamil	30 μM tedisamil	5.78 ± 0.253	165 ± 7.23	110
tedisamil	100 μM Tedisamil	6.76 ± 0.290	193 ± 8.30	129

Recommendations/Conclusions

The findings form this study are not definitive due to the use of hepatocytes from only one subject. Additional information will be needed to support the conclusion that tedisamil does not induce the main CYP enzymes. With this caveat in place, this induction study suggests that tedisamil does not induce the major CYP enzymes.

APPENDIX

Characteristics of Donor

In Vitro Technologies lot no. QKR was a 35-year-old Caucasian male who died of a seizure. Urinalyses and blood chemistries were within normal limits. Serologies were negative, including cytomegalovirus. The donor had a history of a seizure disorder, possible alcoholism, and a subdura hema. The donor had a history of alcohol use (one to three beers per day for 17 years), tobacco use (one pack per day for 15 years) and drug use (unknown, non-intravenous drug use 10 years prior to death). No chronic medications were listed.

4.2.8 Determination of the Inhibitory Potential of Tedisamil Sesquifumarate on the Activities of CYP450 Isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in Human Liver Microsomes (K.219.6031, 2004)

PROTOCOL #	1022 (K.219.6031)
Study Director	Aruna Koganti, Ph.D.
STUDY SITE	In Vitro Technologies, Inc., Baltimore, MD 21227
STUDY PERIOD	March 2004
REPORT LOCATION	Module 4 Volume 19

Study Design

Standard procedures for in vitro metabolism studies were used. Microsomes were pooled from at least 10 human donors. The formation of the selective metabolite from its substrate was measured by high performance liquid chromatography (HPLC). Microsomes were pre-incubated with 1, 3, 10, 30, and 100 μM (based on salt concentration) tedisamil sesquifumarate in an NADPH regenerating system and liver microsomes. CYP enzyme substrates and inhibitors were obtained from commercial sources.

The following table* summarizes the CYP enzymes and substrates evaluated in this study.

CYP isoform	**Isoform-selective substrate**	**Activity monitored**	**Substrate concentration**	**Selective Inhibitor**
CYP1A2	Phenacetin	O-Deethylase	150 μM	Furafylline
CYP2A6	Coumarin	7-hydroxylase	8 μM	None
CYP2C9	Tolbutamide	Methyl-Hydroxylase	250 μM	None
CYP2C19	S-Mephenytoin	4´-hydroxylase	100 μM	None
CYP2D6	Dextromethorphan	O-Demethylase	8 μM	Quinidine
CYP2E1	Chlorzoxazone	6-hydroxylase	50 μM	None
CYP3A4	Testosterone	6β-Hydroxylase	50 μM	ketoconazole
CYP3A4	Midazolam	hydroxylation	10 μM	None

Reviewer Note on Enzymes System

The experimental conditions were not optimal, with respect to including a positive control for all CYP enzymes. However, each study included a vehicle control, which provides some degree of assay sensitivity as vehicle control should produce any changes.

Data Interpretation

Per applicant, the following interpretations were made for percent activity of the Vehicle control: > 85 % means no inhibition, 50 to 85 % means slight inhibition and < 50 % of vehicle control means significant inhibition.

Results

Ketoconazole and furafylline demonstrated significant inhibition towards CYP3A (4.53 % of vehicle control) and CYP1A2 (21.7 % of vehicle control), respectively as expected. Results of the inhibition evaluation are summarized in Table 30.

Table 30: CYP Isoform Activity for Vehicle Control, Positive Control and Tedisamil (1 - 100 µM)

CYP isoform	inhibitor	Metabolite Activity monitored	Specific activity Pmol/min/mg/protein	Percent Vehicle Control
CYP1A2	Vehicle control	4.96 ± 0.0756	440 ± 6.72	100
	Positive control	1.07 ± 0.0484	95.5 ± 4.30	21.7
	Tedisamil	5.18 – 5.76	460 - 512	104 - 116
CYP2A6	Vehicle control	0.547 ± 0.0183	72.9 ± 2.44	100
	Tedisamil	0.479 – 0.543	63.8 – 72.4	87.5 – 99.3
CYP2C9	Vehicle Control	2.91 ± 0.0862	388 ± 11.5	100
	tedisamil	2.59 – 2.79	346 - 372	89.1 - 96
CYP2C19	Vehicle control	0.801 ± 0.0632	53.4 ± 4.21	100
	Tedisamil	0.544 ± 0.707	36.2 – 47.1	67.9 – 88.2
CYP2D6	Vehicle control	0.615 ± 0.0273	82.0 ± 3.64	100
	tedisamil	0.0688 – 0.120	9.17 – 16.0	11.2 – 19.5
CYP2E1	Vehicle control	2.10 ± 0.0617	280 ± 8.23	100
	Tedisamil	1.76 – 1.87	235 – 249	84.0 – 89.1
CYP3A4	Vehicle control	8.67 ± 0.210	1157 ± 28.0	100
Testosterone	Ketoconazole	0.393 ± 0.007	52.3 ± 0.938	4.53
Testosterone substrate	Vehicle control	4.96 ± 0.0756	440 ± 6.72	100
	Tedisamil	7.42 – 8.87	989 - 1183	85.5 - 102
Midazolam substrate	Vehicle control	3.69 ± 0.0481	491 ± 6.42	100
	Tedisamil	2.63 – 3.56	351 - 474	71.5 – 96.5

Tedisamil sesquifumarate at the evaluated concentrations of 1, 3, 10, 30, and 100 µM did not inhibit CYP1A2, CYP2A6, CYP2C9, or CYP2E1 activity. Moderate inhibition of CYP2C19 activity by 3, 10, 30, and 100 µM tedisamil sesquifumarate was observed. Conflicting results were obtained for CYP3A4 activity:

- no significant inhibition at all concentrations per 6β-hydroxytestosterone formation; however, at the two high concentrations of tedisamil sesquifumarate
- moderate inhibition of CYP3A4 activity was observed per 1-hydroxymidazolam formation.

The tedisamil concentrations at which CYP3A inhibition was observed are higher than anticipated therapeutically, thus inhibition of CYP3A is not likely to occur in vivo. CYP2D6 inhibition was observed at all tedisamil concentrations indicating that tedisamil is a CYP2D6 inhibitor . Lower tedisamil concentrations (re-incubations with varying substrate concentrations) were investigated to determine how potent an inhibitor tedisamil is.

The results from the CYP2D6 re-incubations (lower tedisamil concentrations) are summarized in Table 31. When lower tedisamil concentrations were tested the IC50 of tedisamil sesquifumarate for inhibition of CYP2D6 activity was 0.0841 µM. Additional investigations determined the Ki value for inhibition of CYP2D6 enzyme activity by tedisamil sesquifumarate to be 0.107 µM. Using I/Ki considerations, tedisamil is likely a potent CYP2D6 inhibitor.

Table 31: CYP2D6 Activity for Positive Control , Vehicle Control and Tedisamil (0.003 - 1.0 µM)

CYP isoform	inhibitor	Metabolite Activity monitored	Specific activity Pmol/min/mg/protein	Percent Vehicle Control
CYP2D6	Vehicle control	0.524 ± 0.00426	69.9 ± 0.567	100
	Positive control	0.0502 ± 0.0003	6.70 ± 0.0472	9.59
Dextromethorphan 8 µM	Tedisamil	0.071 – 0.508	9.47 – 67.7	13.6 – 96.9
	Vehicle control	0.461 ± 0.008	123 ± 2.04	100
	Positive control	0.0501 ± 0.0003	13.4 ± 0.0827	10.9
	Tedisamil	0.0926 – 0.487	24.7 - 130	20.1 - 106
Dextromethorphan 75 µM	Vehicle control	1.86 ± 0.0586	497 ± 15.6	100
	Tedisamil	0.662 – 1.86	176 - 495	35.5 – 99.6
Dextromethorphan 300 µM	Vehicle control	3.21 ± 0.0302	857 ± 8.05	100
	Tedisamil	2.05 – 3.12	546 - 865	63.7 - 101

Recommendations/Conclusions

The in vitro inhibition results indicate that tedisamil:

- does not inhibit CYP1A2, CYP2A6, CYP2C9, or CYP2E1 activity
- is a weak inhibitor of CYP2C19 and CYP3A
- is a potent CYP2D6 inhibitor

Based on these findings, at least one in vivo study should be conducted with a sensitive CYP2D6 substrate to determine the magnitude of inhibition by tedisamil or restrictive labeling language should be employed.

4.2.9 Tedisamil: Effect of verapamil on human p-glycoprotein mediated transport of tedisamil in PK 1 LLC MDR cells in vitro (H219.6.002)

PROTOCOL or Report #	H219.6.002
Author	H.G.Keizer and R.J.Vonk
STUDY SITE	The Netherlands
STUDY PERIOD	March 2004
REPORT LOCATION	Module 5 Volume 28

Study Design

In this study the effect of verapamil on p-glycoprotein mediated transport of tedisamil in vitro was investigated. The transport of tedisamil was studied in a tissue culture system in which two compartments are separated by a monolayer of PK1 LLC MDR cells* , expressing the human MDR1 gene product p-glycoprotein. Both basolateral to apical (b->a) and apical to basolateral (a->b) transport of the compound were evaluated. A reference compound SOBA 20593994, a good substrate for p-glycoprotein (per Applicant), was used as reference and as positive control for activity of p-glycoprotein. The effect of verapamil on the transport of tedisamil and SOBA 20593994 was studied by adding 1 or 10 µg/ml of verapamil to the transport experiments. Two parameters were calculated from these transport studies both in the presence or absence of verapamil: (1) The mean percentage of compound transported from a->b and b->a after 3.5 hours of incubation (= passive membrane passage), and (2) the ratio of these percentages (= P-gp factor) as a measure of P-gp mediated transport. Tedisamil and SOBA 20593994 samples were analyzed using a LC/MS system.

*The cells used in this study are PK1 LLC MDR cells. The PK1 LLC MDR cells are transgenic cells of pig origin and express the human p-glycoprotein, the gene product of the MDR1 gene. These cells were originally obtained from Prof. P.Borst, The Netherlands Cancer Institute in Amsterdam.

Reviewer Note on Study Design

The approach adopted is acceptable; however, the control compound employed is not ideal as it's PGP status is not known with respect to well established PGP substrates such as digoxin or quinidine. It is noted that an additional PGP study (H.219.6033: Module 4 Volume 19) was conducted using another putative PGP substrate. This reviewer did not review that study in detail because it lacked a PGP inhibitor, such as verapamil, that would provide some validation of the PGP substrate status of the reference compound or tedisamil.

Neither of the two PGP studies evaluates the PGP inhibitor status of tedisamil.

Analyses

The applicant conducted the following calculations to define tedisamil PGP properties:

- T% = percentage transported compound = conc. top/ (conc. top + conc. bottom) x 100% (compound added to the bottom compartment: for passive diffusion, percent = 50 % and > 50 % indicates active transport)
- M% = membrane transport at time point= M% = (T% top-> bottom + T% bottom-> top) / 2 (per applicant range of values is 0 %, suggesting no membrane passage to 40 % for free passage)

- P-gp factor = P-gp factor = T% bottom-> top / T% top-> bottom in a standardized time. (per applicant P-gp factors range from 1, suggesting no P-gp transport to about 100 for very strong P-gp substrates

Reviewer Note on Applicant's Analyses

The sponsor's analyses appear reasonable, however are not consistent with FDA current practices; FDA recommends calculation of apparent permeability for a quantitative estimate of P-gp susceptibility. It appears the sponsor's calculations will yield qualitative (relative estimates) of P-gp transport activity. The applicant should provide Papp estimations including the raw data used to derive the estimations. This raw data should include the following: V_r (volume of medium in the receiver chamber), C_0 (concentration of the test drug in the donor chamber), S (surface area of monolayer), and dC/dt (linear slope of the drug concentration in the receptor chamber with time after correcting for dilution).

Test Compounds

Tedisamil (batch SOBA 20641611) was the test compound used in this study. All amounts and concentrations of tedisamil in this report are expressed as ng compound (free base) per /ml.

Results

Reviewer Note

Only summary data were provided, thus the data could not be verified. Furthermore, the applicant did not use standard calculations, including determination of apparent permeability. The applicant will be asked to provide data in the appropriate format to facilitate a thorough review. It is noted that the sponsor did not propose the inclusion of PGP information in the label. Due to the limitations in the report, this review will not provide recommendations.

The summary data indicate that recoveries of SOBA 20593994 and tedisamil were acceptable (above 80%). The P-gp factors and passive membrane passage data (M %) for tedisamil (n = 3) and for the reference compound (n = 2) in the absence or presence of verapamil are shown in Table 32.

Table 32: Effect of PGP transport on tedisamil in the absence and presence of verapamil after 3.5 hr incubation

Compound	P-gp factor (+/- SD)	Passive membrane passage (%) (+/- SD)
tedisamil	27.2 +/- 5.3	20.1 +/- 0.8
tedisamil + 1 µg/ml verapamil	16.1 +/- 3.6	19.8 +/- 0.4
tedisamil + 10 µg/ml verapamil	3.8 +/- 0.7	17.7 +/- 2.4
SOBA 20593994 (positive control)	6.8 +/- 0.6	33.2 +/- 1.3
SOBA 20593994 + 1 µg/ml verapamil	2.8 +/- 0.6	34.0 +/- 1.1
SOBA 20593994 + 10 µg/ml verapamil	1.6 +/- 0.2	33.5 +/- 3.8

According to the applicant, the positive control data were as expected. As shown in the table under P-gp factor, verapamil at 1 or 10 µg/ml dose dependently inhibited p-glycoprotein mediated transport of both the reference control compound and of tedisamil. In principle, when a

P-gp inhibitor is present, the transport of a P-gp substrate is reduced, thereby decreasing the value of the P-gp factor.
The passive membrane passage of both the reference control compound and tedisamil was not clearly influenced by the addition of verapamil to the transport study. This lack of effect on passive transport may be expected as verapamil affects P-gp transport, not passive transport

Recommendations/Conclusions

The following list of deficiencies was identified for this study:

1. absence of raw data and failure to calculate standard P-gp parameter, apparent permeability
2. absence of established P-gp substrate; the reference substrate appears to have a large passive diffusion component, with less P-gp sensitivity than tedisamil
3. use of only one P-gp inhibitor, verapamil: verapamil lacks inhibitor specificity, therefore the use of multiple inhibitors is recommended to determine whether the efflux activity observed in vitro is related to P-gp.
4. lack of evaluation of P-gp inhibitory status of tedisamil

Despite the study limitations there is some evidence to suggest that tedisamil is a P-gp substrate, based on the interaction with verapamil: transport of tedisamil was reduced in the presence of verapamil. Additional information, such as an in vivo study with a well-established P-gp inhibitor should be obtained to confirm the P-gp substrate status of tedisamil. A study should also be conducted to determine if tedisamil is a P-gp inhibitor; this could be an in vitro study and/or in vivo study with a known P-gp substrate, such as digoxin.

Appendix

Table A: PGP Data

testcondition	% transport (recovery)		P-gp factor (K')	% Mean membrane passage
	top to bottom	bottom to top		
T control 1	1.3 (104%)	37.7 (111%)	24.3 (18.0)	19.6
T control 2	1.7 (90%)	40.4 (111%)	24.0 (19.3)	21.0
T control 3	1.1 (89%)	38.0 (102%)	33.3 (18.5)	19.6
T+ vpl 1 µg/ml 1	2.7 (104%)	35.9 (112%)	13.1 (16.6)	19.3
T+ vpl 1 µg/ml 2	2.5 (100%)	37.4 (103%)	15.0 (17.4)	19.9
T+ vpl 1 µg/ml 3	1.9 (103%)	38.3 (111%)	20.1 (18.2)	20.1
T+ vpl 10 µg/ml 1	7.0 (93%)	27.7 (127%)	3.9 (8.6)	17.4
T+ vpl 10 µg/ml 2	10.2 (103%)	30.2 (112%)	3.0 (10.1)	20.2
T+ vpl 10 µg/ml 3	5.8 (93%)	25.3 (101%)	4.4 (9.8)	15.5
S control 1	8.7 (99%)	56.0 (107%)	6.4 (23.6)	32.3
S control 2	8.3 (95%)	59.8 (110%)	7.2 (25.8)	34.1
S + vpl 1 µg/ml 1	16.3 (126%)	53.3 (113%)	3.3 (18.6)	34.8
S + vpl 1 µg/ml 2	19.4 (111%)	47.1 (116%)	2.4 (13.7)	33.2
S+ vpl 10 µg/ml 1	22.5 (77%)	39.2 (103%)	1.7 (8.0)	30.8
S +vpl 10 µg/ml 2	30.7 (103%)	41.8 (105%)	1.4 (6.0)	36.2

% transport, % recovery (in brackets) were determined as described in methods section. P-gp factor (with K' in brackets), and membrane passage were determined from %transport data at 3.5 hours after dosing. T= tedisamil, S= positive contol, vpl= verapamil. For controls 0.1% DMSO was added in stead of verapamil (in DMSO).

4.2.10 A double-blind, semi-randomized, placebo-controlled, four period cross-over study on the potential pharmacokinetic and pharmacodynamic interaction between verapamil and tedisamil in healthy male and female volunteers (S2191110)

PROTOCOL #	S2191110
INVESTIGATOR	Prof. A. F. Cohen, M.D. and Dr. J. Burggraaf,
STUDY SITE	Centre for Human Drug Research, Zernikedreef 10 2333 CL Leiden, The Netherlands
STUDY PERIOD	02/1998 – 08/1998
REPORT LOCATION	Module 5 Volumes 71 - 77

Rationale for Drug-Drug Interaction Study

Background Information on Study Drugs (Verapamil and Tedisamil)

	Verapamil	Tedisamil
Indication	Calcium Channel Blocker; For the treatment of angina, arrhythmias, and essential hypertension.	Anti-arrhythmic, potassium channel blocker that was studies for antianginal activity
Metabolites	Twelve metabolites have been identified in plasma, mostly in trace amounts. The major metabolite is norverapamil.	A hydroxy metabolite, M1 has been identified in man.
Metabolic/Elimination Pathway	First-pass effect; Predominantly biotransformed by CYP3A4, however CYP1A2 and members of the CYP2C family are also involved in the metabolism. 70% is excreted in the urine as metabolites.	Does not appear CYP enzymes are involved; primarily renally excreted as unchanged drug
CYP Inhibitory Potential	Predominantly CYP3A4.	Strong CYP2D6 inhibitor with limited CYP2C19 and CYP3A inhibition
Highest Recommended Dose/Studied Dose	Available in sustained release (SR) and immediate release (IR) formulations. The dose can range from 80 – 480 mg/day depending on the indication and can be titrated. The dose studied was 180 mg and is considered an intermediate therapeutic dose in angina pectoris or anti-arrhythmic	The proposed IV dose is 0.32 or 0.48 mg/kg dependent on sex The oral tedisamil dose 100 mg BID was anticipated as an effected dose in angina pectoris

Objectives (per applicant)

Primary objective

To determine the effect of concurrent administration of tedisamil and verapamil on cardiac function by measuring the PR interval.

Secondary objectives

- To determine the effect of concurrent administration of tedisamil and verapamil on cardiac function by measuring RR, QRS, QT, QTc and cardiac output.
- To assess a potential mutual interaction on pharmacokinetic parameters between tedisamil and verapamil.

Safety and tolerance

To evaluate the safety and tolerability of tedisamil when given in combination with verapamil.

Reviewer Note on Review Content
This review focuses solely on the PK interaction information; PD information is available from the pivotal clinical trials that are more likely to reflect clinical situations. It is noted that the sponsor conducted a PK/PD analyses as well that will not be reviewed.

Study Design

This was a single center, double-blind, semi-randomized, multiple oral dose, placebo controlled, four-period crossover study in healthy volunteers. Ten subjects completed the study. The four treatments were:

- 100 mg tedisamil dihydrochloride (DHCl) and placebo BID
- 180 mg verapamil DHCl and placebo BID
- 100 mg tedisamil DHCl and 180 mg verapamil DHCl BID
- Placebo capsules BID

There were four treatment periods that were subdivided into Periods 1/2 and Periods 3/4:

Periods 1 and 2
On days 1 and 2 either tedisamil or verapamil monotherapy was administered twice daily and the monotherapies were administered only in the morning of Day 3

Periods 3 and 4
On Days 1 and 2 received combination therapy twice daily and once in the morning on Day 3.

Reviewer Note on Verapamil Dose
The verapamil dose was not the highest approved dose which is contrary to the recommendation in the Drug Interaction Gudiance. Use of doses lower than the maximum dose may not yield maximal potential inhibition thereby not providing optimal drug interaction information.

Pharmacokinetic sampling times

Blood samples were collected at predose and 0.5 , 1, 2, 3, 4, 6, 9, 12 , 15, 24, 30 and 36 h post dose.

Formulation

- Tedisamil dihydrochloride capsule, 100 mg; Batch No. 025T; Lot No. 001VU and 018VU
- Placebo capsule; Batch No. 024T and 031 T; Lot No. 001VU and 018VU
- Verapamil dihydrochloride retard capsules (Verahexal®) 180 mg; Batch No. 058T, 001U and 028 U; Lot No. 001VU and 018VU

Bioanalytical methods

The concentrations of tedisamil, verapamil and norverapamil were determined by validated bioanalytical methods.

Tedisamil Assay
Tedisamil concentrations were determined by a method employing liquid/liquid extraction and liquid chromatography with mass spectroscopic detection. The assay performance was acceptable as illustrated in Table 33.

Verapamil and Norverapamil Assay

Verapamil and norverapamil were determined by liquid chromatography with fluorescence detection. The assay performance was acceptable as illustrated in Table 33.

Table 33: Performance of Tedisamil, Verapamil and Norverapamil Assays

Parameter	Measure	Reviewer Comment
	Tedisamil Assay	
Linearity	Range: 1 to 200 ng/mL; $R^2 > 0.992$	Satisfactory
CV (%) Measure of Between day Precision	< 11 %	Satisfactory
Relative Bias (%) Accuracy Measure	-4 to + 2.6	Satisfactory
LLOQ	2.5 ng/mL	Satisfactory
Specificity	Chromatograms provided that demonstrate specificity	Satisfactory
	Verapamil	
Linearity	Range: 2 to 200 ng/mL; $R^2 > 0.990$	Satisfactory
CV (%) Measure of Between day Precision	< 20 %	Satisfactory
Relative Bias (%) Accuracy Measure	+ 4 to + 21 %	Satisfactory
LLOQ	2.5 ng/mL	Satisfactory
Specificity	No direct measure of specificity	Cannot be assessed
	Norverapamil Assay	
Linearity	2.5 to 200 ng/mL; $R^2 > 0.999$	Satisfactory
CV (%) Measure of Between day Precision	< 5 %	Satisfactory
Relative Bias (%) Accuracy Measure	- 0.2 to + 0.6	Satisfactory
LLOQ	2.5 ng/mL	Satisfactory
Specificity	No direct measure of specificity	Cannot be assessed

Pharmacokinetics

The following pharmacokinetic parameters were determined:
Ctrough, Cmax, Tmax, t ½ , AUC(0-12), AUC(0-Tlast), and AUC(0-inf)

Statistical methods

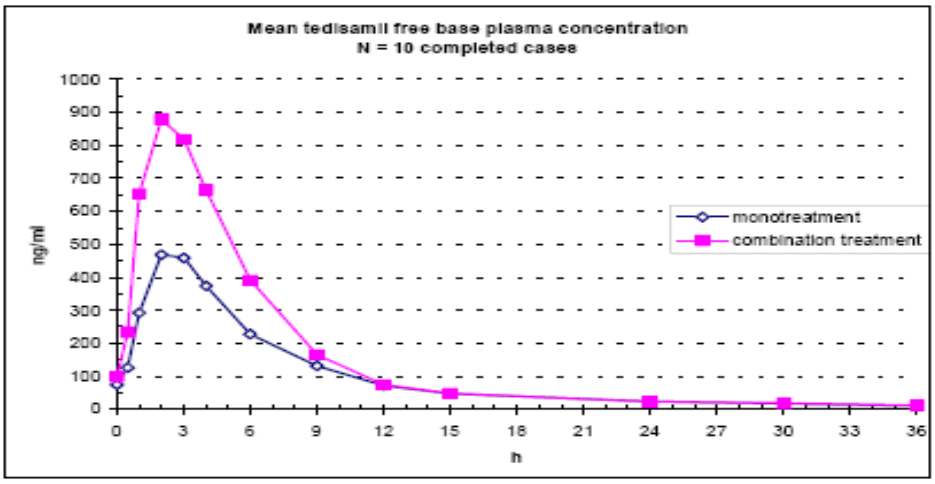
Standard pharmaco-statistical methods were used to evaluate drug-drug interactions. The monotherapy treatments were the reference treatments and test treatment was combination therapy.

RESULTS

Pharmacokinetics

The mean plasma concentration-time profiles of tedisamil under mono and combination treatment conditions after 3 days administration is depicted in the following figure.

Figure 18: Mean tedisamil plasma concentration-time profile following administration of tedisamil+/- verapamil



The tedisamil PK measures (mean ± SD, as well as estimates and 90 % confidence intervals for the treatment ratios) are summarized in Table 34.

Table 34: Tedisamil PK measures following oral administration of tedisamil +/- verapamil

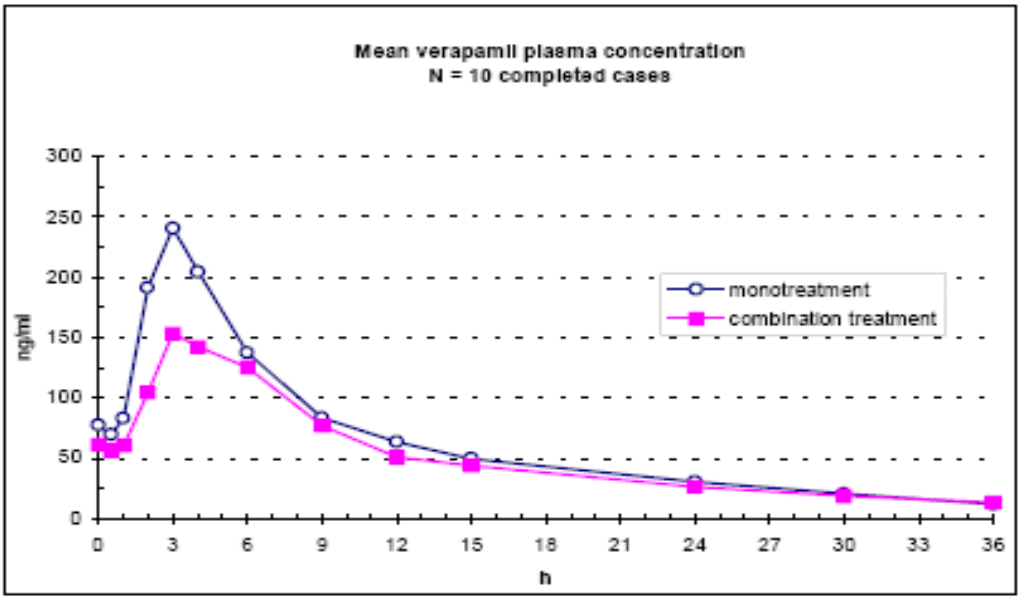
		Monotreatment	Combination treatment	Ratio [%]	90 % CI [%]
Ctrough	(ng/ml)	74.6 ± 29.3	99.3 ± 39.5	134	92 – 195
Cmax	(ng/ml)	532.9 ± 137.5	937.3 ± 185.5	178	157 – 202
Tmax	(h)	2.9 ± 1.3	2.6 ± 0.8	-0.5*	0.555**
t½	(h)	10.9 ± 3.3	10.7 ± 2.4	100	82 – 122
AUC(0-Tlast)	(ng*h/ml)	3526 ± 1018	5585 ± 907	163	139 – 191
AUC(0-inf)	(ng*h/ml)	3702 ± 999	5779 ± 962	159	137 – 186
AUC(0-12h)	(ng*h/ml)	2853 ± 819	4901 ± 777	177	151 – 208

* median difference
** p-value for the signed rank test

In comparison to the mono-treatments, the combined administration of tedisamil and verapamil led to an increase of the tedisamil AUC over the dose interval (AUC(0-12h)) by 77 %. This finding suggests that verapamil alters tedisamil PK, most likely tedisamil bioavailability via PGP interaction. Verapamil is a PGP inhibitor and tedisamil is a PGP substrate.

The mean plasma concentration-time profiles of verapamil under mono and combination treatment conditions after 3 days administration is depicted in the following figure.

Figure 19: Verapamil Plasma concentration-time profile following administration of verapamil +/- tedisamil



The verapamil PK measures (mean ± SD, as well as estimates and 90 % confidence intervals for the treatment ratios) are summarized in the following table.

Table 35: Verapamil PK measures in drug interaction study

		Monotreatment	Combination treatment	Ratio [%]	90 % CI [%]
Ctrough	(ng/ml)	77.2 ± 32.2	60.6 ± 24.8	82	64 – 104
Cmax	(ng/ml)	251.2 ± 135.6	178.0 ± 104.4	72	61 – 86
Tmax	(h)	3.1 ± 0.7	3.7 ± 1.0	0.5*	0.313**
t½	(h)	9.7 ± 1.3	11.1 ± 3.0	112	102 – 124
AUC(0-Tlast)	(ng*h/ml)	2304 ± 1042	1811 ± 856	81	69 – 96
AUC(0-inf)	(ng*h/ml)	2473 ± 1113	2040 ± 1040	84	71 – 99
AUC(0-12h)	(ng*h/ml)	1550 ± 757	1165 ± 481	79	68 – 92

* median difference
** p-value for the signed rank test

The mean plasma concentration-time profiles of norverapamil under mono and combination treatment conditions after 3 days administration are depicted in Figure 20.

Norverapamil PK measures obtained following mono-therapy and combination therapy are presented in Table 36.

Figure 20: Norverapamil plasma concentration-time profile following administration of verapamil +/- tedisamil

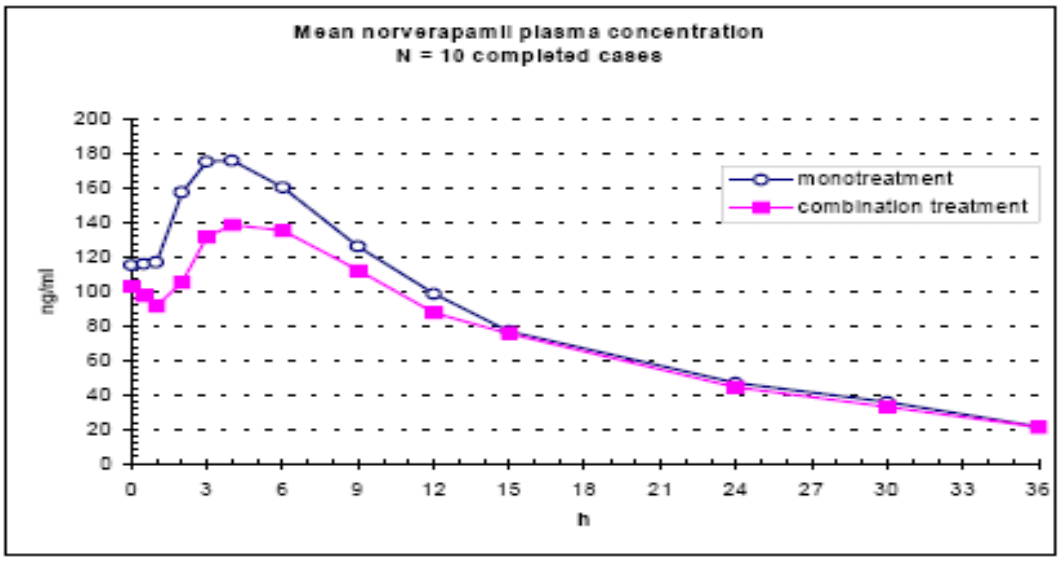


Table 36: Norverapamil PK measures in drug interaction study

		Monotreatment	Combination treatment	Ratio [%]	90 % CI [%]
Ctrough	(ng/ml)	115.3 ± 36.0	102.8 ± 26.3	92	76 – 110
Cmax	(ng/ml)	182.4 ± 48.9	144.6 ± 36.0	80	71 – 90
Tmax	(h)	3.4 ± 0.5	4.9 ± 1.9	1.1*	0.023**
t½	(h)	10.9 ± 2.1	10.8 ± 2.8	98	86 – 112
AUC(0-Tlast)	(ng*h/ml)	2910 ± 963	2486 ± 808	87	75 – 101
AUC(0-inf)	(ng*h/ml)	3265 ± 1131	2854 ± 1122	88	75 – 103
AUC(0-12h)	(ng*h/ml)	1706 ± 517	1381 ± 364	83	72 – 94

* median difference
** p-value for the signed rank test

The data in indicate that overall tedisamil did not significantly affect verapamil or norverapamil PK, although tedisamil presence tended to decrease verapamil's exposure. The reason for this trend is unclear but may be in part due to competition for P-gp or renal excretion (verapamil and tedisamil are highly renally excreted).

Applicant's Safety Summary

There was a comparable percentage of adverse events in combination treatment and verapamil alone (~ 90 %). The most frequently reported treatment emergent adverse events were diarrhea and headache under either treatment. None of the treatment emergent adverse events were

classified as severe. No deaths occurred and no serious adverse event was reported during the course of the study. Four subjects were withdrawn from the study due to adverse events.

RECOMMENDATIONS/CONCLUSIONS

- Tedisamil PK are altered when tedisamil is co-administered with verapamil; the interaction appears to be due to P-gp inhibition: Tedisamil AUC is increased by 77 % whereas half-life is not affected suggesting an alteration in bioavailability, rather than clearance.
- Neither verapamil nor norverapamil PK were altered when verapamil was coadministered with tedisamil

These findings are based on orally administered tedisamil and may not have accurate quantitative value with respect to IV tedisamil. Typically the most significant PGP interactions (greatest magnitude) occur in the gut, although P-gp is located in other tissues. Consequently evaluation of the effect of a potent P-gp inhibitor on IV tedisamil is recommended.

4.2.11 Pharmacokinetic Determination of Tedisamil and Atenolol in Human Plasma Samples from a 3-Periods (Single and Double Blind) Study of Tedisamil Dihydrochloride in Combination with Atenolol Versus Tedisamil and Atenolol Alone. Investigating Safety (K.219.5028, 1995)

PROTOCOL #	K.219.5028
INVESTIGATOR	Prof. Dr. P. Jallion
STUDY SITE	Hopital St. Antoine, Paris, France
STUDY PERIOD	October 1994- March 1995
REPORT LOCATION	Module 5 Volumes 78 - 81

Rationale for Drug-Drug Interaction Study

Background Information on Study Drugs (Atenolol and Tedisamil)

	Atenolol	Tedisamil
Indication	Beta blocker; Used in the management of hypertension. Also used in angina pectoris and acute myocardial infarction	Anti-arrhythmic, potassium channel blocker that was studies for antianginal activity
Metabolites	Minor urinary hydroxylated metabolite has been identified	A hydroxy metabolite, M1 in man
Metabolic/Elimination Pathway	Metabolism only plays a minor role; absorbed portion eliminated primarily renally.	Does not appear CYP enzymes are involved; primarily renally excreted as unchanged drug
CYP Inhibitory Potential	N/A	Strong CYP2D6 inhibitor with limited CYP2C19 and CYP3A inhibition
Highest Recommended Dose/Studied Dose	Initial dose is 50 mg once daily and may be increased to 100 mg daily.	The proposed IV dose is 0.32 or 0.48 mg/kg dependent on sex. The oral tedisamil dose 100 mg BID was anticipated as an effected dose in angina pectoris

Objective (per applicant)

Primary

To assess the bradycadic effects of tedisamil, atenolol and the combination under steady state conditions at rest and during sub maximal exercise versus baseline (placebo)

Secondary

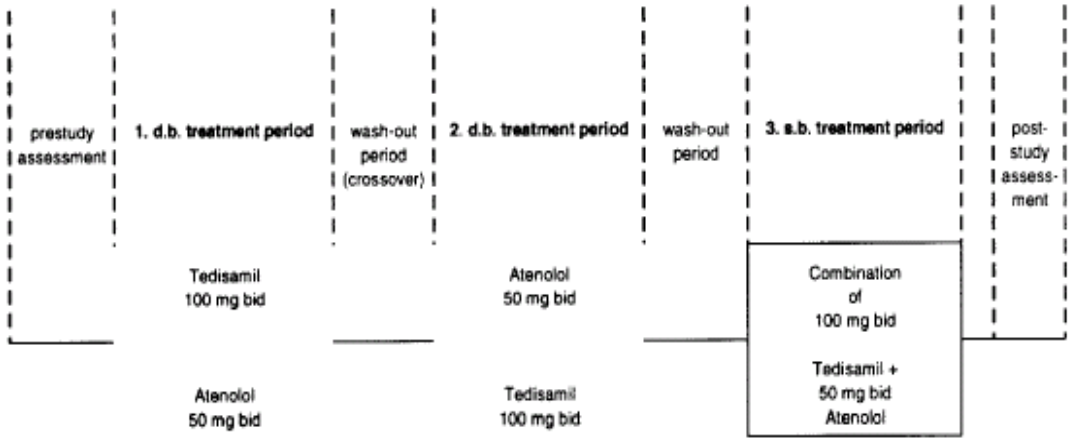
- to assess the QT- and QT_c-prolongation of each therapy regimen at rest and under exercise conditions in comparison to baseline
- to assess the safety and tolerance of the combination in comparison to each of the monotherapies
- to determine the pharmacokinetic parameters of tedisamil and atenolol, given alone and in the combination treatment
- to assess the blood pressure under atenolol and tedisamil as well as the combination treatment.

Reviewer Note on Review Content

This review focuses on the PK results.

Study Design

This was a three period, double blind cross over study in healthy male volunteers. The study design and course are depicted in the following figure.



Subjects were assigned to one of two parallel treatment groups as shown in figure and there were three treatment periods: first two treatment periods were double-blind (d.b) and last treatment was single blind (s.b.). Additional dosing details are tabulated below.

Period / day	Visit	Morning dose	Evening dose
I / 1 I / 2-5 I / 6	2 3-6 7	placebo 50 mg A or 100 mg T 50 mg A or 100 mg T	placebo 50 mg A or 100 mg T
II / 1 II / 2-5 II / 6	8 9-12 13	placebo 50 mg A or 100 mg T 50 mg A or 100 mg T	placebo 50 mg A or 100 mg T
III / 1 III / 2-5 III / 6	14 15-18 19	placebo 50 mg A and 100 mg T 50 mg A and 100 mg T	placebo 50 mg A and 100 mg T

Formulations

- Tedisamil dihydrochloride 100 mg capsule (Kali-Chemie), batch number 005 P.
- Placebo capsule (Kali-Chemie), batch number 007 P
- Atenolol 50 mg tablet, Cuxanorm® 50 (TAD Cuxhaven); batch number 029 P

Blood sampling for Genotyping

Blood samples were taken during the prestudy examination for CYP2D6 genotyping.

Pharmacokinetic sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- Day 1 at predose
- Day 6 at 0 h (prior to morning dose) and 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 h post dose.

Pharmacodynamics

The main pharmacodynamic parameter was change in heart rate at a comparable workload within each trial period. This parameter was analyzed after baseline adjustment. Additionally, QT analyses were performed with baseline corrections.

Bioanalytical methods

Tedisamil Assay

Tedisamil concentrations were determined using a validated HPLC with electrochemical detection method. The assay performance was acceptable as shown in Table 37.

Atenolol Assay

Atenolol concentrations were determined using a validated HPLC with fluorescence detection method. The assay performance was acceptable as shown in Table 37.

Table 37: Performance of Tedisamil and Atenolol Assays

Parameter	Measure	Reviewer Comment
	Tedisamil	
Linearity	Range: 0.5 – 200 ng/mL; $R^2 > 0.995$	Satisfactory
CV as measure of Between day Precision	< 24 %	Acceptable*
Relative Bias as Measure of Accuracy	-0.9 to + 7.0	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms provided demonstrating specificity	Satisfactory
	Atenolol	
Linearity	Range: 0.5 – 200 ng/mL; $R^2 > 0.993$	Satisfactory
CV as Measure of Between day Precision	< 6 %	Satisfactory
Relative Bias as Measure of Accuracy	0 to + 3.5	Satisfactory
LLOQ	5.0 ng/mL	Satisfactory
Specificity	Chromatograms provided demonstrating specificity	Satisfactory

* The low QC sample had CV = 23.7, whereas the remaining QC samples had CV < 10 %.

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined after each treatment: Cmax, Ctrough, Tmax, AUC (0-12, 0-t and 0 – inf), and $t_{½}$

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Tedisamil alone was the reference treatment and tedisamil + atenolol was the test treatment. However, in contrast to the recommended 90 % confidence interval, the 95 % confidence interval was calculated. Pharmacodynamic measures were also analyzed using standard statistical approaches.

Results

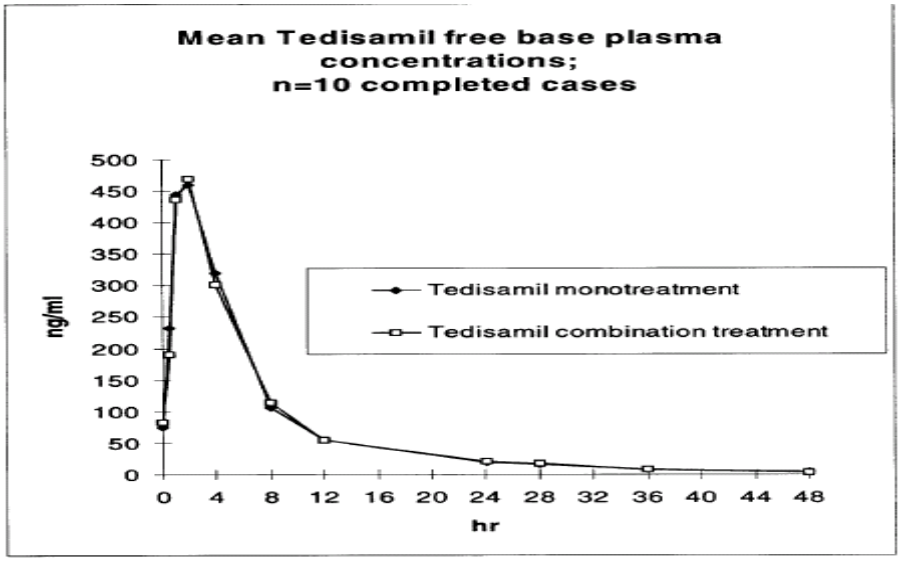
Genotyping

Neither atenolol nor tedisamil are CYP2D6 substrates, thus the utility of the CYP2D6 information is unclear. The genotyping assay indicated that nine subjects were extensive metabolizers (Subjects 1, 4, 5, 7, 8, 10, 12, 13 and 14) and two subjects were poor metabolizers (subjects 3 and 11). Genotyping was not done in Subject 6.

Tedisamil Pharmacokinetics

The mean tedisamil plasma concentration time profiles following administration of tedisamil alone and tedisamil co-administered with atenolol are depicted in Figure 21.

Figure 21: Tedisamil plasma concentration-time profile following administration of tedisamil +/- atenolol



Tedisamil PK were not altered when atenolol was coadministered with tedisamil.

Table 38: Tedisamil PK measures and statistics in atenolol drug interaction study (n = 10 subjects)

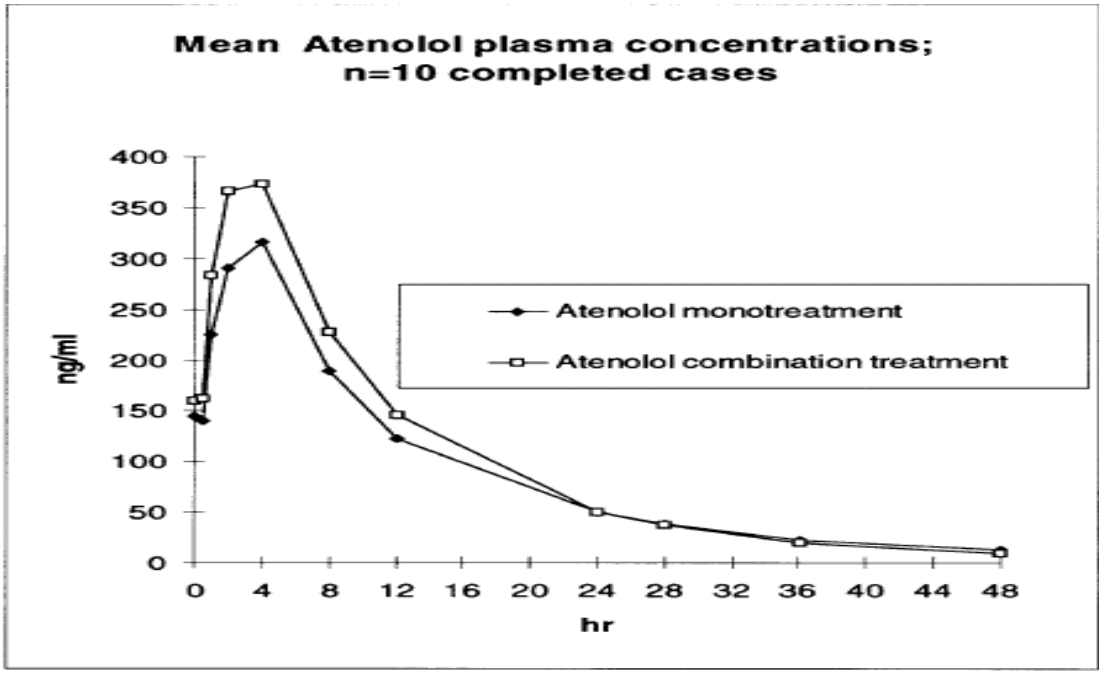
	Geometric means		Ratio (%)	p	shortest CI (%)
	mono-treatment	combination treatment			
trough (ng/ml)	67.36	60.25	89	0.740	43-187
Cmax (ng/ml)	532	494	93	0.492	73-118
AUC(0-12h) (ng*h/ml)	2448	2436	99	0.958	80-124
AUC(0-Tlast) (ng*h/ml)	3112	3055	98	0.856	78-123
AUC(0-inf) (ng*h/ml)	3209	3112	97	0.765	77-121
t1/2 (h)	11.72	9.82	84	0.083	68-103

p = p-value of the two-sided one sample t-test;
shortest CI = conventional 95%-confidence interval according to the one sample t-test;

Atenolol Pharmacokinetics

The mean atenolol plasma concentration time profiles following administration of tedisamil alone and tedisamil co-administered with atenolol are depicted in the following figure.

Figure 22: Atenolol plasma concentration-time profile following administration of atenolol +/- tedisamil



The atenolol PK measures from the drug interaction study are summarized in Table 39.

Table 39: Atenolol PK measures in drug interaction study

	Geometric means		Ratio (%)	p	shortest CI (%)
	mono-treatment	combination treatment			
trough (ng/ml)	126.64	156.04	123	0.274	82-185
Cmax (ng/ml)	347	400	115	0.023	102-130
AUC(0-12h) (ng*h/ml)	2621	3149	120	0.003	109-133
AUC(0-Tlast) (ng*h/ml)	4222	4841	115	0.017	103-127
AUC(0-inf) (ng*h/ml)	4435	5019	113	0.029	102-126
t1/2 (h)	11.70	10.07	86	0.147	70-107

p = p-value of the two-sided one sample t-test;
shortest CI = conventional 95%-confidence interval according to the one sample t-test;

Co-administration of tedisamil and atenolol led to a 15 – 20 % increase in atenolol AUC and Cmax, which does not appear to be clinically significant.

Applicant's Safety Summary

There were no serious adverse events (SAEs) or deaths in this study. The most frequently reported AEs included aesthenia, headache, and diarrhea; the number of patients with these adverse events tended to increase in the combination therapy relative to monotherapy. There were no pathological changes in ECG parameters. There was a decrease in systolic and diastolic blood pressure during atenolol alone treatment and the combination treatment.

Recommendations/Conclusions

1. mean tedisamil PK were not altered when tedisamil was co-administered with atenolol
2. mean atenolol exposure was increased by approximately 15 % when atenolol was coadministered with tedisamil. This magnitude of interaction does not seem clinically significant to warrant dosage adjustment. The mechanism of interaction is unclear, but is unlikely due to CYP2D6 inhibition.
3. This study does not address the impact of CYP2D6 inhibition by tedisamil because atenolol is not a CYP2D6 substrate.

4.2.12 Open, randomized, three-period crossover study of multiple oral doses of tedisamil dihydrochloride and digoxin (Lenoxin-mite) investigating possible pharmacokinetic interactions in steady state in healthy male and female volunteers (S2191101, 1997)

PROTOCOL #	S2191101
INVESTIGATOR	R.A. Theodor, MD
STUDY SITE	PHAROS GmbH Germany
STUDY PERIOD	June – August 1995
REPORT LOCATION	Module 4 Volumes 60 - 63

Rationale for Drug-Drug Interaction Study

Background Information on Study Drugs (Digoxin and Tedisamil)

	Digoxin	Tedisamil
Indication	Cardiac Glycoside; Inhibits sodium/potassium ATPase; For the treatment of mild to moderate heart failure, and control of ventricular response rate in patients with chronic atrial fibrillation.	Anti-arrhythmic, potassium channel blocker that was studies for antianginal activity
Metabolites	3 β-digoxigenin, 3-keto- digoxigenin, and their glucuronide and four sulfate conjugates.	A hydroxy metabolite, M1 in man
Metabolic Pathway	Not dependent on CYP450; Substrate of P-glycoprotein (PGP)	Does not appear CYP enzymes are involved; primarily renally excreted as unchanged drug
CYP Inhibitory Potential	Does not inhibit or induce CYP450.	Strong CYP2D6 inhibitor with limited CYP2C19 and CYP3A inhibition
Highest Recommended Dose/Studied Dose	Available in tablets, capsules, elixir, and injection. The dose can range from 125 to 500 mcg depending on the indication and can be titrated.	The proposed IV dose is 0.32 or 0.48 mg/kg dependent on sex. The oral tedisamil dose 100 mg BID was anticipated as an effected dose in angina pectoris

Objectives (per applicant)

To determine peak plasma concentration and the area under the curve of the dose interval at steady state of tedisamil dihydrochloride and digoxin following mono- and combination treatment of both drugs.

To determine trough level, time of peak plasma concentration, terminal rate constant, half-life and the amount renally excreted over the dose interval at steady state of tedisamil dihydrochloride and digoxin following mono- and combination treatment of both drugs.

Study Design

This was a multiple dose, open, randomized study. There were three study periods where:

- Tedisamil was given on Day 1 as a single 50 mg dose followed by 50 mg BID for five days and a single dose on the sixth day
- Digoxin was administered initially as a loading dose, 0.25 mg BID over two days, followed by 0.125 mg BID over the next five days and a single dose on the sixth day.
- Both tedisamil and digoxin were administered: digoxin given by procedure above (loading followed by maintenance- Day 1 and 2); subsequently tedisamil was initiated with digoxin

maintenance dose (Day 3) and both drugs administered BID from Day 3 to Day 7 and only the morning dose on Day 8.

Reviewer Note on Review Content
This review focuses on the PK findings.

Pharmacokinetics Blood Sampling

Tedisamil and Digoxin Monotherapy

- Days 1 to 5: predose samples
- Day 6: predose and post dose at 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 18, 24, 30, 26 and 48 hours post dose

Combination Therapy

Predose samples on Days 1 to 5 for tedisamil

- Days 1 and 2: predose samples for digoxin only as tedisamil was not coadministered
- Days 3 to 7: predose samples
- Day 8: predose and post dose at 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 18, 24, 30, 26 and 48 hours post dose; additionally samples were taken at 72 and 96 hours for digoxin only

Urine Sampling

Urine was sampled over 0-12 hours on the sixth day of concomitant administration

Pharmacokinetics

The following PK measures were estimated on Day 6 of treatment:

Cmax, Tmax, AUC(0-12h), Ctrough, t½, Ae(0-12h), CL/f, CLren, Vz/f

Formulation

- Tedisamil dihydrochloride capsule, 50 mg. Batch number 017P
- Digoxin tablet; Batch number F 1519A

Statistical Analyses

Drug-drug interactions were evaluated by standard phamaco-statistical procedures. The test treatment was tedisamil/digoxin and the reference treatments were tedisamil or digoxin alone.

Assay

Digoxin and tedisamil concentrations in plasma and urine samples were determined by validated bioanalytical procedures.

Tedisamil Assay

The tedisamil assay performance was acceptable as demonstrated in Table 40 .

Table 40: Tedisamil Assay Performance Characteristics

Parameter	Measure	Reviewer Comment
	Tedisamil by HPLC with electrochemical detection (plasma)	
Linearity	Range is 1.0 to 200 ng/mL; $R^2 > 0.980$	Satisfactory
CV (%) as measure of Between day Precision	< 7 %	Satisfactory
Relative Bias (%) as Accuracy Measure	+ 4.4 to + 14.6 %	Satisfactory
LLOQ	1 ng/mL	Satisfactory
Specificity	Chromatograms provided that demonstrate specificity	Satisfactory
	Tedisamil by HPLC with electrochemical detection (urine)	
Linearity	Range is 50 – 4000 ng/mL $R^2 > 0.999$	Satisfactory
CV (%) as measure of Between day Precision	< 3%	Satisfactory
Relative Bias (%) as Accuracy Measure	-3.8 to + 0.3	Satisfactory
LLOQ	50 ng/mL	Satisfactory
Specificity	Chromatograms provided that demonstrate specificity	Satisfactory

Digoxin Assay

Overall the digoxin assay performance appeared acceptable as shown in Table 41. The digoxin assay was a modified form of a commercially available RIA kit (Amerlex Digoxin ^{125}I RIA from Johnson and Johnson). However, it should be noted that tedisamil interfered with the digoxin assay when tedisamil concentration was relatively high (> 10,000 ng/mL) and digoxin concentration was low (0.10 ng/mL). The interference was manifested in the form of increased apparent digoxin concentration (67 % bias); according to the applicant the interference is due to cross-reactivity with the digoxin antibody.

Table 41: Digoxin Assay Performance Characteristics

Parameter	Measure	Reviewer Comment
	Digoxin by RIA for plasma	
Linearity	Effective Range: 0.00 to 5.00 ng/mL	Satisfactory
CV (%) as Measure of Between day Precision		Satisfactory
Relative Bias as Accuracy Measure	-2.1 to + 3.1	Satisfactory
LLOQ	0.10 ng/mL	Satisfactory
Specificity	No direct measure of specificity is available	Cannot be assessed
	Digoxin by RIA for urine*	
Limit of detection	Effective Range is 0.00 to 500 ng/mL	Satisfactory
CV (%) as Measure of Between day Precision	< 30 %	^Unacceptable
Relative Bias as Accuracy Measure	-16.5 to +1.0	Satisfactory
LLOQ	10 ng/mL	Satisfactory
Specificity.	No direct measure of specificity is available	Cannot be assessed

* It appears there are typos in the report: the cited calibration range is 0 to 5 ng/mL, but QC samples were from 10 to 250 ng/mL and LOQ is 10.0 ng/mL.

^ CV associated with QC samples was 9.0, 26.6 and 29.7 %: frequently with RIA and other non-specific assays relatively high CVs are obtained.

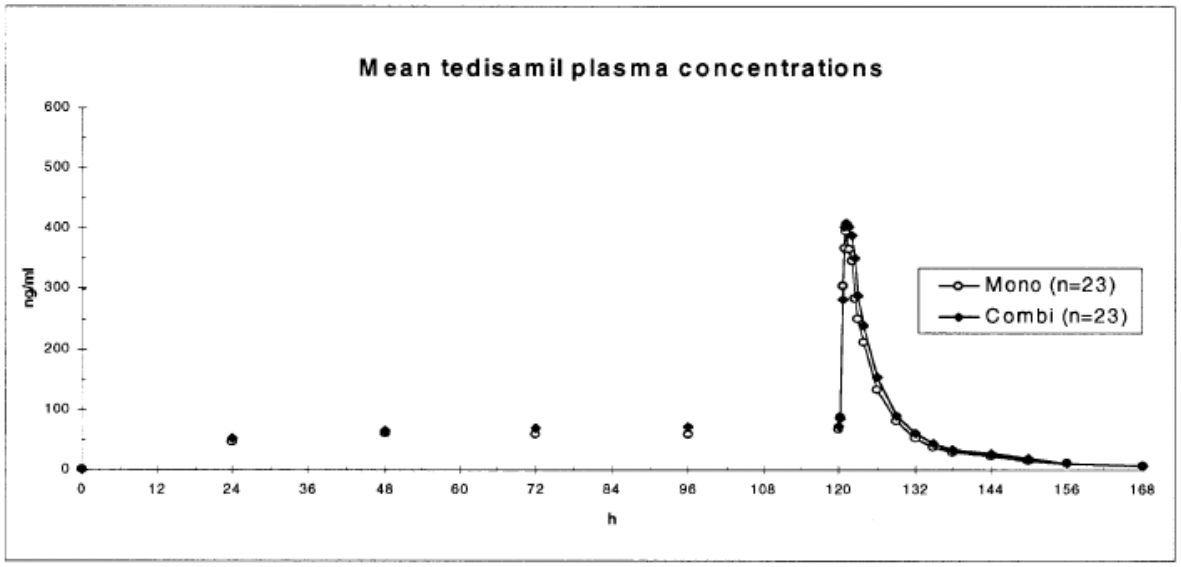
Reviewer Note on Interference

The impact of the observed interference appears manageable. As noted by the Applicant, the interference can be avoided by limiting the dilute of digoxin containing samples; typically, tedisamil concentrations will not exceed 10,000 ng/mL.

Results

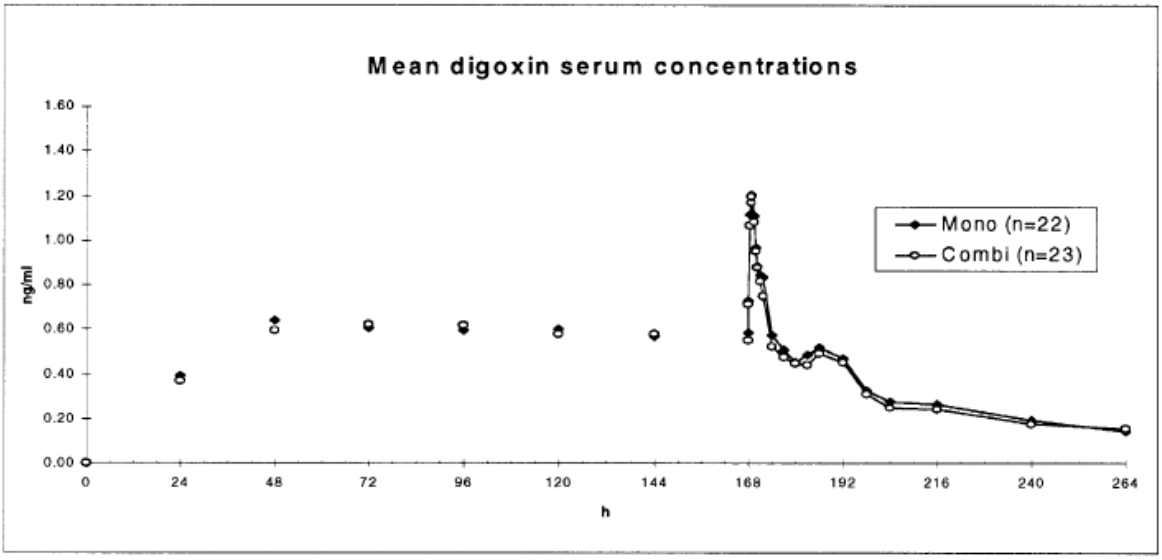
The mean tedisamil plasma concentration time profiles during mono and combination treatment are depicted in Figure 23.

Figure 23: Tedisamil plasma concentration time profile in digoxin-tedisamil interaction study



The mean digoxin plasma concentration time profiles during mono and combination treatment are depicted in Figure 24.

Figure 24: Digoxin plasma concentration-time profile in drug interaction study



The tedisamil (Table 42) and digoxin (Table 43) PK results are tabulated below.

Table 42: Tedisamil PK measures in tedisamil-digoxin drug interaction study (n =23)

		Monotreatment			Combination treatment			Ratio	90 % CI
Ctrough	(ng/ml)	65.47	±	20.51	71.88	±	18.48	112 %	101-124 %
Cmax	(ng/ml)	425.29	±	96.94	462.17	±	102.28	109 %	102-117 %
Tmax	(h)	1.07	±	0.47	1.08	±	0.45		
AUC(0-12h)	(ng*h/ml)	2000	±	412	2241	±	318	113 %	107-120 %
t½(h)	(h)	12.18	±	3.57	11.90	±	3.02	98 %	91-106 %
CL/f	(ml/min)	348	±	77	303	±	48	88 %	83-94 %
Clren	(ml/min)	154	±	36	138	±	44	86 %	78-95 %
Vz/f	(l/kg)	5.38	±	2.04	4.56	±	1.29	87 %	79-95 %
Ae(0-12h)	(% dose)	45.7	±	14.5	45.6	±	14.5	97 %	86-111 %

Tmax : p= 0.968 signed rank test

Table 43: Digoxin PK Measures in Digoxin-Tedisamil drug interaction study (n = 22)

		Monotreatment			Combination treatment			Ratio	90 % CI
Ctrough	(ng/ml)	0.59	±	0.16	0.55	±	0.14	94 %	89-99 %
Cmax	(ng/ml)	1.28	±	0.30	1.26	±	0.27	98 %	92-105 %
Tmax	(h)	0.90	±	0.30	0.94	±	0.35		
AUC(0-12h)	(ng*h/ml)	8.29	±	1.93	7.86	±	1.75	95 %	90-100 %
t½(h)	(h)	63.11	±	22.35	57.31	±	22.75	91 %	76-109 %
CL/f	(ml/min)	263	±	55	278	±	60	106 %	100-112 %
Clren	(ml/min)	141	±	34	135	±	39	95 %	85-107 %
Vz/f	(l/kg)	21.12	±	9.26	19.65	±	7.93	96 %	79-117 %
Ae(0-12h)	(% dose)	54.1	±	11.2	49.8	±	14.4	90 %	80-102 %

Tmax : p= 0.593 signed rank test

The data indicate that tedisamil and digoxin PK were not altered by either drug. The Ctrough data (Table 44 and Table 49) suggest that PK steady state was achieved for both drugs.

Table 44: mean predose tedisamil plasma concentrations during monotherapy and combination therapy

Tedisamil Troughs

	Day 1 / 3	Day 2 / 4	Day 3 / 5	Day 4 / 6	Day 5 / 7	Day 6 / 8
Mono-treatment	0	45.64 ± 16.01	59.43 ± 19.69	57.98 ± 21.75	58.34 ± 18.99	65.47 ± 20.51
Combination treatment	0	52.11 ± 18.07	63.68 ± 18.47	68.92 ± 22.48	69.73 ± 15.87	71.88 ± 18.48

Digoxin Troughs

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Mono-treatment	0	0.39 ± 0.10	0.64 ± 0.12	0.60 ± 0.18	0.60 ± 0.14	0.60 ± 0.17	0.57 ± 0.15	0.59 ± 0.16
Combination treatment	0	0.37 ± 0.10	0.60 ± 0.18	0.62 ± 0.19	0.62 ± 0.17	0.58 ± 0.15	0.58 ±0.15	0.55 ± 0.14

Safety

According to the applicant, overall, tedisamil monotherapy and combination therapy with digoxin were well tolerated. There were no deaths and no serious adverse events (SAEs) during

the study. The most frequent treatment emergent AEs were headache and diarrhea. The frequency or severity of occurrence of these adverse events was comparable during combination treatment and monotherapy.

CONCLUSIONS/RECOMMENDATIONS

There is no pharmacokinetic interaction between orally administered tedisamil and digoxin. This finding suggests that tedisamil is not a PGP inhibitor.

4.2.13 A double-blind, randomized, placebo controlled, parallel group study investigating possible pharmacodynamic and pharmacokinetic interactions of tedisamil dihydrochloride and glibenclamide in type II non-insulin-dependent diabetes mellitus (S2191107, 1998)

PROTOCOL #	S2191107
INVESTIGATOR	Prof. Dr. H.-P. Breuel, Pharmacon Research, Berlin, Germany
STUDY SITE	Federal Republic of Germany / Czech Republic
STUDY PERIOD	October 1996 - September 1997
REPORT LOCATION	Module 5 Volumes 64 - 66

Rationale for Drug-Drug Interaction Study

Background Information on Study Drugs (and Tedisamil)

	glibenclamide	tedisamil
Indication/Mechanism of Action	Used in diabetes treatment/ local potassium channel blocker (ATP-dependent) in pancreatic beta cells	Anti-arrhythmic, potassium channel blocker that was studies for antianginal activity
Metabolites	Two active metabolites: 4-trans-hydroxyglibenclamide (M1) and 3-cis-hydroxyglibenclamide (M2)	A hydroxy metabolite, M1 in man
Metabolic/Transport Pathway	CYP3A is major metabolic pathway with minor contribution from CYP2C19. PGP substrate and inhibitor.	Does not appear CYP enzymes are involved; primarily renally excreted as unchanged drug
CYP Inhibitory Potential	None reported	Strong CYP2D6 inhibitor with limited CYP2C19 and CYP3A inhibition
Highest Recommended Dose/Studied Dose	Dosage usually initiated at 2.5 to 5 mg daily. The usual maintenance dose is between 1.25 and 20 mg	The proposed IV dose is 0.32 or 0.48 mg/kg dependent on sex. The oral tedisamil dose 100 mg BID was anticipated as an effected dose in angina pectoris

Objectives (per applicant)

Primary Objective

To determine and compare the average glucose concentration over six hours following glibenclamide monotreatment and glibenclamide/tedisamil combination treatment.

Secondary Objectives

- To determine average concentrations of glucose, insulin and the connecting peptide (C-peptide) over 24 hours following glibenclamide monotreatment and glibenclamide/ tedisamil combination treatment.
- To determine the minimum glucose concentration over 24 hours following glibenclamide monotreatment and glibenclamide/tedisamil combination treatment.
- To determine trough plasma concentration, peak plasma concentration, time to peak plasma concentration and the area under the curve of glibenclamide over the glibenclamide dose interval following glibenclamide monotreatment and glibenclamide/tedisamil combination treatment.

- To determine trough plasma concentration, peak plasma concentration, time to peak plasma concentration and the area under the curve of tedisamil over the tedisamil dose interval following glibenclamide/ tedisamil combination treatment.

Safety and tolerance
To evaluate the safety and tolerability of the combination of glibenclamide and tedisamil in type II diabetic subjects.

Study Design

This was a double-blind, randomized, placebo controlled study in patients with Type II non-insulin dependent diabetes mellitus. On day 1, all subjects received placebo BID. Thereafter, subjects were randomized to one of two treatment groups. Treatment was started at a dose regimen of 50 mg BID tedisamil or placebo from the morning of day 2 until the morning of day 7. From the evening of day 7 until the evening of day 21, subjects were continued on placebo or tedisamil 100 mg BID. The dose of Glibenclamide was variable according to individual needs. The daily dose, however, had to be $\geq$ 3.5 mg taken as once daily dose in the morning or BID and had to be kept constant throughout the study.

Formulations

- Tedisamil dihydrochloride and placebo capsules with the following batch information:

		Placebo	Tedisamil 50 mg	Tedisamil 100 mg
Vol. 01 - 04	batch no.	061R	010 R	137 R
Vol. 05 - 17; 21 - 27	batch no.	102 R	010 R	081 S
Vol. 18 - 20; 28 - 36	batch no.	009 T	010 T	017 T

- Glibenclamide tablets (commercially available; no additional information provided)

Sampling Plan for pharmacodynamics and pharmacokinetics

PD Sampling
Blood samples for the analysis of glucose, insulin and c-peptide: On day 1 and 21, blood samples were taken as follows: pre-breakfast (within 5 minutes before breakfast) and post breakfast at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 hours (lunch), 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12 hours (dinner), 12.5, 13, 13.5, 14, 14.5, 15, 16, 24 hours (prior to breakfast day 2 or day 22).

PK Blood Sampling
Blood samples for analysis of glibenclamide were taken on day 1 and 21 as follows: predose (within 15 minutes prior to dosing) and post dose at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 hours (prior to glibenclamide evening dose, if this dose is required), 24 hours (prior to glibenclamide morning dose day 2 or day 22).

Blood samples for analysis of tedisamil were taken on day 21 as follows: predose (within 15 minutes prior to dosing) and post dose at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 hours (prior to the tedisamil evening dose).

Pharmacodynamics

The following pharmacodynamic measures were diabetes related markers were evaluated:

Glucose:	Caverage(0-6h), Caverage (0-24h); Cmin;
Insulin:	Caverage(0-6h), Caverage (0-24h);
C-peptide:	Caverage(0-6h), Caverage (0-24h);

Pharmacokinetics

The following PK measures were determined for the compounds.

- Glibenclamide: Ctrough, Cmax, Tmax, AUC(0-12h) and AUCnorm*
- Tedisamil: Ctrough, Cmax, Tmax and AUC(0-12h)

AUCnorm* was defined as the AUC(0-12h)/body weight.

Tedisamil

Tedisamil was measured in plasma using a validated HPLC method with electrochemical detection. The assay performance was acceptable as shown in Table 45.

Glibenclamide

Glibenclamide was measured in plasma by a validated HPLC method with fluorimetric detection. The assay performance was acceptable as shown in Table 45.

Table 45: Tedisamil and Glibenclamide Assay Performance Characteristics

Parameter	Measure	Reviewer Comment
	Tedisamil	
Linearity	Range: 1- 200 ng/mL; $R^2 > 0.992$	Satisfactory
CV (%) as measure of Between day Precision	< 10 %	Satisfactory
Relative Bias (%) as Measure of Accuracy	-2 to +5.2 %	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms provided to demonstrate specificity	Satisfactory
	Glibenclamide	
Linearity	Range: 2 – 1000 ng/mL; R^2 not provided	Satisfactory
CV (%) as measure of Between day Precision	< 15 %	Satisfactory
Relative Bias (%) as Measure of Accuracy	- 5 to +8.1 %	Satisfactory
LLOQ	2.00 ng/ml	Satisfactory
Specificity	Chromatograms provided to demonstrate specificity	Cannot be assessed

Statistical methods:

The primary parameter, $Cave_{(0-6h)}$ for glucose was analyzed after baseline adjustment, i.e. the difference between day 21 (after three weeks of double-blind treatment) and day 1 (baseline). The tedisamil/glibenclamide combination treatment was to be proven to cause at least no clinically relevant drop in blood glucose compared to the glibenclamide monotreatment, i.e. one-sided equivalence was to be demonstrated (one-sided t-test at the 5% level).

The secondary pharmacodynamic parameters and the pharmacokinetic parameters were analyzed exploratively.

RESULTS

Pharmacodynamics

The mean data means ± SD and p-values of glucose, insulin and C-peptide are presented in Table 46.

Table 46: Pharmacodynamic/statistical results of glucose, insulin and C-peptide

Measure	**Placebo Treatment** (n=16) Difference Day 21 - Day 1 Means ± SD	**Tedisamil 100 mg BID** (n=15) Difference Day 21 - Day 1 Means ± SD	**p-value**
Glucose (mmol/l)			
Cave (0-6 h)	-0.06 ± 1.74	-0.75 ± 2.20	0.038[1]
Cave (0-24 h)	0.19 ± 1.22	-0.49 ± 1.67	0.165[2]
Cmin	0.06 ± 1.07	-0.29 ± 1.91	0.431[2]
Insulin (µU/ml)			
Cave (0-6 h)	8.80 ± 28.77	-4.39 ± 20.72	0.445[2]
Cave (0-24 h)	-0.66 ± 13.14	-0.65 ± 11.42	0.964[2]
C-peptide (pmol/l)			
Cave (0-6 h)	156 ± 418	105 ± 457	0.7932
Cave (0-24 h)	60 ± 272	146 ± 238	0.5722

1 p-value for testing the null-hypothesis that there is a drop of at least 2 mmol/l in blood glucose under glibenclamide/tedisamil treatment compared with glibenclamide/placebo treatment;
2 two-sided t-test for treatment differences

Overall, the pharmacodynamic data indicate that there is no effect of tedisamil on glucose and insulin metabolism in non-insulin-dependent diabetics. For the primary parameter Cave (0-6h), there was less than a 2 mmol/L drop in blood glucose: comparison of combination treatment to glibenclamide alone. In essence the combination treatment did not significantly alter the PD characteristics of glibenclamide. It should be noted that there was high variability in PD measures which may have obscured potential differences; this variability may be due to intrinsic inter-patient variability and the use of different glibenclamide doses.

Glibenclamide Pharmacokinetics

Plasma exposure measures of glibenclamide on day 1 and 21 are shown in Table 47.

Table 47: Table Pharmacokinetic/statistical results of glibenclamide

	Placebo Treatment (n=15)	**Tedisamil 100 mg BID** (n=14)	**p-value**
	Difference Day 21 - Day 1 Means ± SD	Difference Day 21 - Day 1 Means ± SD	
Ctrough (ng/ml)	-8.09 ± 28.45	-0.74 ± 34.03	0.742[1]
Cmax (ng/ml)	-22.59 ± 76.23	-4.69 ± 83.87	0.903[1]
Tmax (h)	0.14 ± 1.42	0.18 ± 2.01	0.894[2]
AUC (0-12 h) (ng*h/ml)	-92 ± 223	-69 ± 151	0.908[1]
AUC (norm) (ng*h/ml/kg-BW/mg-dose)	-0.13 ± 0.31	-0.15 ± 0.32	0.905[1]

1 two-sided t-test for treatment differences
2 two-sided Wilcoxon test

The sponsor notes that some patients did not have quantifiable Ctrough values below (limit of quantification): subjects 10, 14, 20, 25, 34 and 35 (tedisamil treatment) and subjects 6, 18, 28 and 36 (placebo). Therefore these trough values were equal to zero, but a Ctrough value was

imputed (half the lower limit of quantification, i.e. 1.00 ng/ml.) to carry out mathematical operations.

Overall, the data indicate that there is no effect of tedisamil on the pharmacokinetics of glibenclamide in non-insulin-dependent diabetics. As noted previously for PD data, the PK data were highly variable; this variability appears due to different glibenclamide doses and potential inter-patient variability.

Tedisamil Pharmacokinetics

Plasma PK measures of tedisamil free base is shown in Table 48 .

Table 48: Pharmacokinetic results of tedisamil free base

PK Measures		Day 21 Means ± SD
Ctrough (ng/ml)	N=13	154.7 ± 6.2
Cmax (ng/ml)	N=15	1034 ± 418
Tmax (h)	N=15	1.73 ± 0.80
AUC (0-12 h) (ng*h/ml)	N=13	5056 ± 2238

Safety

Treatment emergent adverse events were more frequent in the tedisamil arm relative to placebo (62.5% in tedisamil vs. 18.8% in placebo). The most frequently reported treatment emergent adverse event was diarrhea in 7/16 subjects under tedisamil (43.8 %). None of the treatment emergent adverse events were classified as severe. No deaths and no serious adverse events were reported during the course of the study. There were no withdrawals due to treatment emergent adverse events.

Conclusions

1. Tedisamil does not affect glucose and insulin levels in type II non-insulin-dependent diabetics.
2. Tedisamil has no influence on the pharmacokinetics of glibenclamide in type II non-insulin-dependent diabetics.
3. Glibenclamide does not appear to change the pharmacokinetics of tedisamil in type II non-insulin-dependent diabetics.

4.2.14 A double-blind, randomized, placebo-controlled, two-period crossover study investigating the effects of multiple oral doses of tedisamil on the pharmacodynamics and pharmacokinetics of warfarin in healthy male and female volunteers (S219.1.108, 1998)

PROTOCOL #	S219.1.108
INVESTIGATOR	Prof. F. O. Müller and Dr. M. V. Middle,
STUDY SITE	South Africa Clinical Trials George East, Republic of South Africa
STUDY PERIOD	June – Aug, 1997
REPORT LOCATION	Module 5 Volumes 66 - 70

Rationale for Drug-Drug Interaction Study

Background Information on Study Drugs (Warfarin and Tedisamil)

	warfarin	tedisamil
Indication/Mechanism of Action	Anticoagulant used for several indications including	Anti-arrhythmic, potassium channel blocker that was studies for antianginal activity
Metabolites	Several metabolites formed including hydroxylated and reduced (alcohol) species. These metabolites have minimal activity.	A hydroxy metabolite, M1 in man
Metabolic Pathway	Undergoes stereo-selective metabolism (S-isomer is five times as active as R-isomer and primarily responsible for clinical effectiveness). Multiple CYP enzymes but CYP2C9 appears predominant	Does not appear CYP enzymes are involved; primarily renally excreted as unchanged drug
CYP Inhibitory Potential	None reported	Strong CYP2D6 inhibitor with limited CYP2C19 and CYP3A inhibition
Highest Recommended Dose/Studied Dose	Dose titrated to achieve adequate anticoagulation based on international normalized ratio	The proposed IV dose is 0.32 or 0.48 mg/kg dependent on sex. The oral tedisamil dose 100 mg BID was anticipated as an effected dose in angina pectoris

Objectives (per applicant)

Major

To determine the effect of multiple oral doses of tedisamil on the pharmacodynamics of a single oral dose of warfarin by measuring prothrombin time.

Secondary objectives

- To determine tedisamil plasma concentrations following multiple oral doses of tedisamil and a single oral dose of warfarin.
- To determine the effect of multiple oral doses of tedisamil on the pharmacokinetics of a single oral dose of warfarin by measuring R- and S-warfarin plasma concentrations.

Safety and tolerance

To evaluate the safety and tolerability of tedisamil alone and given in combination with warfarin.

Study Design

This was a double-blind, randomized, placebo-controlled, two-period crossover trial in healthy volunteers. Tedisamil or placebo were given for seven days, with a wash-out period in-between of 14 days. On Day 4 of tedisamil and of placebo treatment, a single dose of warfarin was given. The tedisamil dihydrochloride dose was 100 mg BID and the warfarin* sodium dose was 25 mg.

* Prior to receiving placebo or tedisamil, subjects participated in one warfarin "priming" session three weeks before the first treatment period (Day -21). In this "priming" session, a single oral dose of 25 mg warfarin sodium was given. According to the applicant the "priming" dose neutralizes the greater pharmacodynamic response after administration of a first single oral dose of warfarin compared to consecutive administrations.

Formulation

- Characteristics of Tedisamil capsules

  Manufacturer: Solvay Pharmaceuticals GmbH, Germany;
  Batch No.: 017T;
  Lot No.: 019VT;
- Characteristics of placebo capsules

  Manufacturer: Solvay Pharmaceuticals GmbH, Germany;
  Batch No.: 009T;
  Lot No.: 019VT;
- Characteristics of Warfarin tablets

  Manufacturer: Boots Pharmaceuticals (Pty) Ltd, Republic of South Africa;
  Trade name: Coumadin 5®;
  Lot No.: 2G;

Bioanalytical methods

Tedisamil Assay

Tedisamil concentrations were determined by a validated HPLC method with electrochemical detection.

Table 49: Performance of Tedisamil Assay

Parameter	Measure	Reviewer Comment
Linearity	Range: 1- 200 ng/mL; $R^2 > 0.992$	Satisfactory
Between day Precision	< 10 %	Satisfactory
Accuracy	-1.3 to + 5.2	Satisfactory
LLOQ	1 ng/mL	Satisfactory
Specificity	Representative chromatograms demonstrated specificity	Satisfactory

Warfarin Assay

R- and S-Warfarin concentrations were not determined due to the lack of PD interactions.

Pharmacokinetic Blood Sampling

Day 4 / Day 25:

PK of tedisamil

before the 8:00 h drug administration, (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h post drug administration (Day 4)

PK of warfarin

before the 8:00 h drug administration (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 30, 36, 48, 60, 72 and 96 h post drug administration (Day 4)

Pharmacodynamic Blood Sampling

Day 4 / Day 25:
before the 8:00 h drug administration (0 h) and at 4, 8, 10, 12, 24, 30, 36, 48, 60 and 72 h after the 8:00 h drug administration on Day 4

Pharmacokinetics

No PK evaluation was done for warfarin due to the lack of PD interaction. However, the following pharmacokinetic parameters were determined for tedisamil

- Cmax (ng/ml): maximum plasma concentration from the measured data;
- Tmax (h): time of maximum plasma concentration from the measured data;
- AUC(0-12) (ng*h/ml): area under the plasma concentration-time curve using the trapezoidal rule from time of administration until the end of the dose interval.

Activity/Pharmacodynamics

The pharmacodynamic effect, prothrombin time was determined using a commercially available kit (Dade Innovin®). The following prothrombin time related parameters were determined:

- PT AUC(0-96h) area under the prothrombin time curve using the trapezoidal rule from time of administration until the 96 h after dosing;
- PT 48h prothrombin time at 48 h from the measured data.

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PD drug-drug interaction. The reference treatment was warfarin alone and the test treatment was warfarin + tedisamil.

Reviewer Note on PD Statistical Analyses
INR is the most commonly used warfarin PD measure, however results for INR were not provided.

Results

Pharmacodynamic Results

Prothrombin times following the administration of warfarin on Day 4 / 25 are summarized in Table 50.

Table 50: Arithmetic means ± SD, ratios of geometric means, p-values and 90%- confidence intervals of prothrombin time (n = 17 completers)

PD Measure	Tedisamil Mean ± SD	Placebo Mean ± SD	Ratio %	p-value *	90% CI %
PT AUC(0-96h)	1200 ± 228	1152 ± 201	104	0.026	101 - 107
PT 48h	16.1 ± 3.9	15.5 ± 4.9	104	0.194	99 - 110

* p-value of the two-sided one sample t-test;

For the primary efficacy parameter, the p-value of 0.026, indicates a treatment difference. However, the 90 % confidence interval of the area under the prothrombin-time curve as well as of the 48 h measurement were fully within the acceptance interval of 80 to 125 %. Thus, overall the pharmacodynamics of warfarin in the presence of tedisamil as assessed by prothrombin time measurements is equivalent to the pharmacodynamics of warfarin alone.

Reviewer Note

The applicant decided not to determine warfarin pharmacokinetics due to a lack of PD effect. determined. This exclusion appears reasonable; although the lack of an observed PD effect after a single dose may not rule out the possibility of a PD interaction upon multiple dosing.

Pharmacokinetic Results

Mean ± SD pharmacokinetic data of tedisamil free base are presented in Table 51.

Table 51: Table: Pharmacokinetic results of tedisamil on Day 4/25 (N = 18)

Cmax in ng/ml	866 ± 299
Tmax in h	1.31 ± 0.55
AUC (0-12 h) in ng*h/ml	4089 ± 1213

Safety per Applicant

Overall, the treatments were well tolerated. There were no deaths or serious adverse events during the course of the study. The most frequently reported treatment emergent adverse events with tedisamil were abnormal ECG (7/18 = 38.9%), prolongation of QT interval (3/18 = 16.7%), inversion of T-wave (4/18 = 22.2%) and diarrhea (4/18 = 22.2%).

4.2.15 Open, uncontrolled study investigating safety and tolerability combination of tedisamil 100mg bid and nifedipine retard 20mg bid or isosorbide dinitrate retard 20mg bid in patients remaining symptomatic on treatment with calcium antagonists or long acting nitrates (K.219.5023E2,1998)

PROTOCOL #	K.219.5023E2
INVESTIGATOR	PD Dr. V. Mitrovic (chief investigator) and Dr. M. Keck, Fachklinik
STUDY SITE	Mitrovic and Keck, Germany
STUDY PERIOD	July 1997 – July 1998
REPORT LOCATION	Module 4 Volumes 115 - 117

Rationale for Drug-Drug Interaction Study

Table 52: Background Information on Study Drugs (Nifedipine and Isosorbide Dinitrate and Tedisamil)

	Nifedipine/ Isosorbide Dinitrate (ISDN)	tedisamil
Indication/Mechanism of Action	Nifedipine: Calcium channel blocker used as antihypertensive and for angina ISDN: treatment of heart failure	Anti-arrhythmic, potassium channel blocker that was studies for antianginal activity
Metabolites	Nifedipine: Numerous metabolites ISDN: major circulating metabolites are pyruvate and methyltriazolophthalazine	A hydroxy metabolite, M1 in man
Metabolic Pathway	Nifedipine: Extensively metabolized; appears to be metabolized by CYP3A ISDN: metabolism is main route, via acetylation, ring oxidation and conjugation	Does not appear CYP enzymes are involved; primarily renally excreted as unchanged drug
CYP Inhibitory Potential	Nifedipine: CYP3A (Ki = 10 -22 μM) and PGP inhibitor	Strong CYP2D6 inhibitor with limited CYP2C19 and CYP3A inhibition
Highest Recommended Dose/Studied Dose	Nifedipine: Usual maintenance dose is 30 to 60 mg QD (initial 30 mg) and is titrated ISDN: each tablet in combination product (BIDIL) contains 20 mg ISDN and is initiated at a dose of 1 tablet TID; the dose should not exceed 2 tablets TID	The proposed IV dose is 0.32 or 0.48 mg/kg dependent on sex. The oral tedisamil dose 100 mg BID was anticipated as an effected dose in angina pectoris

Objectives (per applicant)

Primary objective:
To investigate the hemodynamic effects of the combinations of tedisamil 100 mg BID with nifedipine retard 20 mg BID or isosorbide dinitrate or ISDN retard 20 mg BID on cardiac output at rest after single oral dose administration and under steady state conditions.

Secondary objectives:

- to evaluate the other hemodynamic effects of tedisamil 100 BID on top of nifedipine retard 20 mg BID or ISDN retard 20 mg BID during rest and exercise after acute administration and under steady state conditions in patients with coronary artery disease.

- to evaluate the safety and tolerability of tedisamil 100 mg BID when added to established treatment with either nifedipine retard 20 mg BID or ISDN retard 20 mg BID as revealed by spontaneously reported adverse events, physical examinations, surface ECGs, Holter-ECGs, blood pressure, heart rate and laboratory tests.

Study Design

This was an open, uncontrolled study in patients remaining symptomatic on either a calcium antagonists (nifedipine retard 20 mg BID) or a long-acting nitrate (ISDN retard 20 mg BID). Tedisamil was given at a dose of 100 mg BID in combination with nifedipine or ISDN after a prestudy assessment and washout of antianginal agents. Cardiac output and heart rate were determined for only up to 2 hours post dose.

Reviewer Note

This study was conducted as part of an extension study; there were no PK determined in this study, although PK sampling was originally envisaged. It should be noted that when this study was conducted tedisamil was being considered as an antianginal agent, not as an anti-arrhythmic. This review highlights some of the PD findings.

Results

The results for the primary efficacy variable, Cardiac output at rest, and heart rate are presented in the following section.

<u>Effect of Tedisamil on Cardiac output at rest</u>

The data in Table 53 indicate that:

- the combination of nifedipine and tedisamil did not affect cardiac output under resting conditions after the first dose or after 6 days of dosing,
- the combination of ISDN and tedisamil decreased cardiac output at 30 minutes after the first dose, but did not alter cardiac output at other time points
- on Day 6, the combination of ISDN and tedisamil decreased cardiac output at 30 minutes and time points beyond after the first dose

Table 53: Changes in cardiac output at rest

			Cardiac Output			Δ baseline[1)]			
			N	$\bar{x}$	SD	N	$\bar{x}$	SD	p-value
Nifedipine retard (N = 16)	Day 1	baseline	16	5.28	1.35				
		30 min post	15	5.49	1.40	15	0.11	0.91	0.635
		1 h post	15	5.38	1.47	15	0.09	1.17	0.639
		2 h post	15	5.18	1.49	13	-0.11	1.17	0.337
	Day 6	pre (12 h post)	13	4.99	0.83	13	0.00	0.72	0.906
		30 min post	13	4.82	1.24	13	-0.17	0.98	0.292
		1 h post	11	5.11	1.11	11	0.24	1.07	0.850
		2 h post	12	4.70	0.99	12	-0.28	0.69	0.170
ISDN retard (N = 28)	Day 1	baseline	27	5.04	1.70				
		30 min post	26	4.69	1.11	25	-0.52	1.36	0.043
		1 h post	27	4.86	1.00	26	-0.30	1.69	0.657
		2 h post	27	4.63	1.23	26	-0.52	1.62	0.137
	Day 6	pre (12 h post)	22	4.89	1.21	22	-0.29	1.65	0.394
		30 min post	21	4.44	1.05	21	-0.78	1.72	0.032
		1 h post	22	4.35	0.99	22	-0.83	1.55	0.003
		2 h post	20	4.10	0.80	20	-1.12	1.52	<0.001

[1)] mean of individual changes

Effect of Tedisamil on Heart Rate at rest

Under combination therapy with tedisamil and either nifedipine retard or ISDN retard, baseline heart rate (88.9 bpm and 81.9 bpm, respectively) was decreased statistically significantly (Table 54) after the first dose and under steady state conditions, except for the predrug (12 hours post drug) value. The maximal mean effects occurred at 2 hours post dose, which was the last measured time point. Thus it is unknown, if heart rate would have continued to decrease after the 2-hour time point.

Table 54: Changes in Baseline Heart Rate Under Resting conditions

			Δ Rest			
			N	$\bar{x}$	SD	p-value
Nifedipine retard (N = 16)	Day 1	30 min post	16	-10.8	9.4	<0.001
		1 h post	15	-15.8	8.3	<0.001
		2 h post	15	-17.9	10.7	<0.001
	Day 6	pre (12 h post)	14	1.4	11.0	0.537
		30 min post	14	-9.6	8.8	0.002
		1 h post	13	-11.1	12.3	0.006
		2 h post	13	-16.6	12.1	<0.001
ISDN retard (N = 28)	Day 1	30 min post	25	-5.8	8.5	0.001
		1 h post	26	-12.2	9.6	<0.001
		2 h post	26	-14.2	9.2	<0.001
	Day 6	pre (12 h post)	22	0.3	5.5	0.862
		30 min post	21	-8.7	8.0	<0.001
		1 h post	22	-13.4	8.9	<0.001
		2 h post	22	-15.5	7.3	<0.001

Generally, the effects under exercise conditions were smaller than the effects at rest (data not included for this review).

Safety Results (per Applicant)

The most common adverse event of tedisamil 100 mg BID in combination with nifedipine retard 20 mg BID and ISDN retard 20 mg BID was diarrhea, occurring in 18.8% (3/16) and 21.4% (6/28) patients, respectively. There were no deaths during the course of the study. Two patients had a serious adverse event:

- Patient 2010 (male, 43 years old), treated with tedisamil and nifedipine retard, experienced an acute posterior wall myocardial infarction on day 6 of the treatment period.
- Patient 2007, a 77 year old female with a prolonged QTc value and frequent bradycardic episodes in the 24-hour Holter ECG at baseline, developed hypokalemia under treatment with tedisamil and ISDN retard. A severe ventricular arrhythmia, (Torsade de Pointes) occurred, on the first study day. Study medication was judged to be highly probably related to this event and discontinued.

No clinically relevant shifts from normal values before to abnormal after adding tedisamil were observed in the hematology or urinalysis values.

Other significant safety findings include:

- The mean resting pulse decreased significantly under tedisamil treatment combined with nifedipine retard and ISDN
- Under both combination treatments mean heart rate was statistically significantly reduced on day 6
- The mean maximum QT interval under treatment increased statistically significantly by ~ 40 ms ($p < 0.001$) with tedisamil on top of nifedipine retard and ISDN retard. The QTc interval increased under both treatments by 25 ms ($p = 0.003$ for nifedipine retard and $p < 0.001$ for ISDN retard).
- In the 24-hour Holter ECG, no signs for pro-arrhythmic effects could be detected.

4.2.16 Single, intravenous, rising dose, open study of tedisamil dihydrochloride (KC 8857) investigating hemodynamics in patients with documented ischemic heart disease (K.219.5005, 1992)

PROTOCOL #	K.219.5005,
INVESTIGATOR	Dr. med. V. Mitrovic
STUDY SITE	Bad Nauheim, Germany
STUDY PERIOD	No directly stated, but completed prior to 1992 (report date)
STUDY REPORT	Module 5 Volumes 93 and 94

Objective

- To assess the hemodynamic effects of tedisamil after IV administration to ischemic heart disease (IHD) patients
- To investigate the bradycardic proportions of tedisamil during rest and exercise in IHD patients

Reviewer Note on Review Content

This review focuses on the PK information; IHD patients are not included in the target disease population. Initially tedisamil was being developed for IHD and angina, but the proposed indication is as an anti-arrhythmic.

Study Design

This was a single center, single, intravenous, rising dose, open label study in patients with IHD (n = 32). All patients received a single dose of tedisamil hydrochloride IV over a 10-minute infusion time. The four tedisamil dose groups were: 0.1, 0.2, 0.3 and 0.4 mg/kg.

Formulation

	Tedisamil		
Dosage form Strength	Ampoule 10 mg/5 ml		
Batch No. Lot No. Expiry date	042H 042VK 10/Dec/90	091K 079VK 18/Dec/91	003L 019VL 18/Jan/92
Pharmaceu- tical Manu- facturer	Kali-Chemie Pharma GmbH Hannover		

PK Blood Sampling

Blood samples were drawn prior to infusion, at 10 minutes (end of infusion) and 30 minutes, and 1, 2, 4, and 24 hours post infusion.

Reviewer Note on Blood sampling

The blood sampling does not appear sufficient to fully characterize the plasma concentration time profile; however, the adopted schedule will allow an approximate estimate of some PK measures. The applicant notes that the limited blood sampling renders the findings from this study as preliminary; this assessment appears reasonable.

PK Analyses

The following PK measures were estimated: Cmax, AUC, Tmax, k, CL, Vz and $t_{1/2.}$

Assay

Tedisamil concentrations were measured by a validated thermospray ionization tandem mass spectrometric method*.

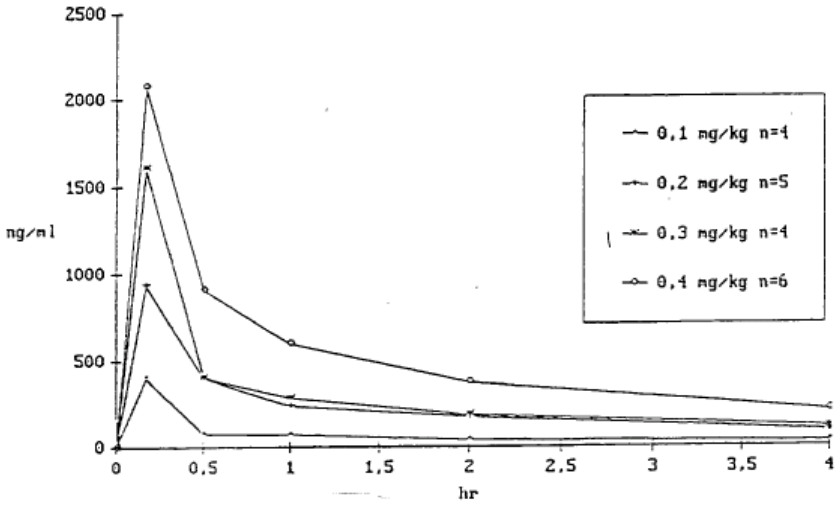
Parameter	Measure	Reviewer Comment
Linearity	Range: 1 to 1000 ng/mL	Satisfactory
CV (%) As Measure of Between day Precision	< 13 %	Satisfactory
Relative Bias as Measure of Accuracy	-1.9 to + 0.9	Satisfactory
LLOQ	1 ng/mL	Satisfactory
Specificity	Chromatograms were not provided	Cannot be assessed

* this method was abandoned as drug development progressed.

RESULTS

The plasma concentration-time profiles of tedisamil in IHD patients are depicted in Figure 25. Tedisamil plasma concentrations declined bi-exponentially after reaching a peak.

Figure 25: Mean tedisamil plasma concentration-time profiles in IHD patients



The following PK measures were estimated in patients with IHD (Table 55). The sponsor indicates that data from several patients were excluded due to missing or unclearly labeled blood samples.

Table 55: Table: Pharmacokinetic results of tedisamil on Day 4/25 (N = 18)

	0.1 mg/kg n=4	0.2 mg/kg n=5	0.3 mg/kg n=4	0.4 mg/kg n=6
Cmax [ng/ml]	405 ± 160	938 ± 440	1611 ± 437	2079 ± 949
Tmax [h]	0.17 ± 0.00	0.17 ± 0.00	0.17 ± 0.00	0.17 ± 0.00
AUC(0-Tlast) [ng×h/ml]	661 ± 182	2010 ± 932	2704 ± 1000	4655 ± 2083
AUC(0-∞) [ng×h/ml]	733 ± 240	2175 ± 1044	2940 ± 1079	5081 ± 2354
t½ [h]	7.85 ± 2.30	6.81 ± 0.59	7.42 ± 0.86	7.23 ± 1.09
Cl [ml/min]	165 ± 47.9	139 ± 47.6	166 ± 49.3	125 ± 48.6
Vz [l]	108 ± 33.5	80.4 ± 22.6	108 ± 40.2	78.6 ± 35.6

The PK data suggest that tedisamil exhibits approximately linear kinetics in patients with IHD.

Safety Findings per Applicant

Treatment emergent adverse events were more common in the highest two dose groups than the lower dose groups. These events included “tingling lips”, feel of warmth during infusion and taste perversion. All the events were mild in intensity and stopped after cessation of drug infusion.

Conclusions/Recommendations

Based on the clearance estimates, tedisamil exhibits approximately linear kinetics following IV infusion over doses of 0.1 to 0.4 mg/kg in patients with IHD.

4.2.17 Tedisamil Dihydrochloride: Studies on Protein Binding (K.219.6007)

Study/ PROTOCOL #	K.219.6007
STUDY SITE	Kalie-Chemie AG, Hannover, Germany
STUDY PERIOD	09/1998 – 12/1998
Authors	H.J. Hausleiter and G. Achtert
REPORT LOCATION	Module 4 Volume 16

Objectives

- To determine the proportion of tedisamil dihydrochloride bound to human serum
- To determine the proportion of drug bound to human serum albumin

Materials and Methods

Standard procedures for determining plasma protein binding were employed. Protein binding was assessed by ultrafiltration. Human serum was obtained from healthy volunteers from a blood bank (Medizinische Hochschule, Hannover). Human serum albumin was obtained from Sigma. The test product was ^{14}C-labelled tedisamil dihydrochloride. An initial experiment was conducted to determine the equilibration time (times evaluated: 0.25 hr to 11 hr); the 1 hr equilibration time was selected on the basis of this experiment. For the experiment with human serum proteins, tedisamil concentration ranged from 50 to 5000 ng/mL or 0.138 to 13.759 µM . For the human serum albumin determination, the buffer contained 30, 300 and 636 µM (physiological albumin concentration) with the same tedisamil concentration range.

RESULTS

The results form the equilibration time experiment are presented in Table 56. These data were obtained at the lowest tedisamil concentration evaluated and may not represent an optimal condition, if tedisamil has concentration-dependent protein binding. However, a 1 hr incubation period appears reasonable from a practical standpoint.

Table 56: Influence of incubation time on protein binding of 50 ng/mL tedisamil (mean± sd; N = 3)

Incubation time [h]	Percentage of bound drug
0.25	91.1 ± 0.6
1	91.6 ± 0.3
2	92.1 ± 0.4
3	90.5 ± 2.1
6	88.5 ± 1.8
11	90.0 ± 0.2

The binding of tedisamil to human serum proteins is summarized in the following table.

Table 57: Tedisamil Protein Binding to Human Serum Proteins (mean± sd; N = 3)

Concentration of tedisamil [µM/l]	Percentage of bound drug
0.138	86.2 ± 2.2
0.276	89.8 ± 1
1.376	89.8 ± 0.6
2.752	88.3 ± 0.6
13.759	62.5 ± 0.4

The data demonstrate that tedisamil plasma protein binding is fairly constant over the 50 to 1000 ng/mL concentration range, but shows concentration dependency between 1000 and 5000 ng/mL. According to the applicant the 50 to 1000 ng/mL represents the range of plasma concentrations that will be achieved following oral administration.

Binding of tedisamil to different concentrations of serum albumin are summarized in Table 58.

Table 58: Binding of tedisamil to varying concentrations of human serum albumin

	Degree of Binding		
Tedisamil Concentration (µM)	636 µM serum albumin	300 µM serum albumin	30 µM serum albumin
0.138	32.9 ± 3.7	18.4 ± 3.5	10.1 ± 1.4
0.276	33.2 ± 0.5	20.2 ± 1.6	6.5 ± 2.7
1.376	26.1 ± 1.9	16.9 ± 1.4	7.2 ± 3.2
2.752	22.0 ± 6.1	14.2 ± 1.5	6.4 ± 0.5
13.759	20.0 ± 11.0	12.2 ± 4.4	1.5 ± 2.2

The data show a concentration dependency with respect to albumin concentration and tedisamil concentration. Based on the human serum data, constant binding was obtained up to 2.752 µM tedisamil concentration, thus one would expect binding to serum albumin to remain constant and close to 80 % over the stated tedisamil range, if serum albumin was the main binding component. Due to the relatively low binding under the various serum concentration, it appears that serum proteins, other than albumin are likely to contribute to the tedisamil binding characteristics.

Conclusions/Recommendations

1. Tedisamil is bound approximately 88 % by serum proteins at therapeutic concentrations, and exhibits concentration dependent binding at concentrations > 1000 ng/mL
2. Serum albumin does not appear to contribute significantly to tedisamil's binding to serum proteins

4.2.18 Tedisamil: In vitro binding to plasma proteins in rat, dog and human (S0219.7.007X)

Study/ PROTOCOL #	K219.7.007X
STUDY SITE	Covance Laboratories Limited, UNITED KINGDOM
STUDY PERIOD	09/1998 – 12/1998
REPORT LOCATION	Module 4 Volume 16

Objective

To determine the extent of in vitro binding of Tedisamil to plasma proteins in rat, dog and human samples.

Reviewer Note on Review Content

This review focuses on the binding information obtained in human plasma at relevant tedisamil concentrations.

Materials and Methods

Standard procedures for determining plasma protein binding were employed. Protein binding was assessed by equilibrium dialysis. Non-specific binding and equilibration time were determined by equilibrium dialysis at a nominal concentration of 100 ng/mL over 0, 0.5, 1, 2, 4 and 6 hours. The equilibration time for tedisamil was determined as 4 hours, and subsequent plasma protein binding experiments were conducted for this length of time. Initially binding was determined at nominal concentrations of 100, 10,000 and 100,000 ng/mL. However following evaluation of the initial results, six concentrations were subsequently investigated (nominal concentrations 50, 200, 800, 2000, 5000 and 10,000 ng/mL). In addition, an investigation of the binding of tedisamil to human a1-acid glycoprotein was included in the study. Solutions of alpha1-acid glycoprotein in phosphate buffered saline (20 µM, 0.8 mg/mL), were spiked with tedisamil at each concentration (50, 200, 800, 2000, 5000 and 10,000 ng/mL, nominal) and subjected to equilibrium dialysis. Buffer and protein compartment samples of each dialysis cell were analyzed using liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). Pooled plasma from three human male volunteers (in house by Covance) were used. Alpha-1 acid glycoprotein was obtained form Sigma. Tedisamil (Batch no. WAS01370) was obtained from Solvay Pharmaceuticals.

RESULTS

Non-specific binding to the equilibrium dialysis equipment was approximately 40% in the absence of plasma proteins.

The binding of tedisamil to human serum proteins is summarized in the table.

Table 59: Tedisamil Plasma Protein Binding

Matrix	Nominal spiked concentration (ng/mL)	Actual spiked concentration (ng/mL)	Mean protein binding (%)
Human plasma	10,000	11,145	45.73
	5,000	5,573	62.62
	2,000	2,229	81.59
	800	892	93.42
	200	223	96.28
	50	56	96.48
α1-Acid glycoprotein	10,000	11,145	19.59
	5,000	5,573	40.34
	2,000	2,229	70.81
	800	892	87.04
	200	223	93.88
	50	56	94.80

The data from human plasma demonstrate that tedisamil plasma protein binding is fairly constant over the 50 to 800 ng/mL concentration range, but shows concentration dependency at concentrations above 800 ng/mL. This suggests that some sort of saturation phenomenon occurs at tedisamil concentrations > 800 ng/mL

Tedisamil plasma protein binding appears closely related to alpha-acid glycoprotein binding, especially at concentrations between 50 and 800 ng/mL: on average ~ 94 % plasma protein binding occurred and ~ 90 % alpha-acid glycoprotein binding occurred.

Conclusions/Recommendations

Tedisamil is bound approximately 94 % by plasma proteins at therapeutic concentrations and the binding appears mainly due to alpha-acid glycoprotein. There is concentration-dependent binding at concentrations > 800 ng/mL.

4.2.19 Dialysability and protein binding of tedisamil in vitro S2191114 .

Study/ PROTOCOL #	S2191114
STUDY SITE	Pharmacon GmbH, Berlin Germany
STUDY PERIOD	09/1998 – 12/1998
INVESTIGATOR/Site	Prof. Dr. H.-P. Breuel, M.D.
Location	Module 5 Volume 27

Objectives

- To determine the in-vitro dialysability of a therapeutically relevant concentration of tedisamil from human plasma.
- To determine the in-vitro dialysability of toxic concentrations of tedisamil from human plasma up to 10.000 ng/ml, which is 5-fold the upper therapeutic concentration.
- To determine the in-vitro protein binding of tedisamil from a therapeutically relevant concentration up to toxic levels.

Reviewer Note on Review Content
This report was not reviewed in detail because the utility of the results was unclear. Some highlights from the study follow.

Utility of Dialysis Information
According to the report, the analysis of tedisamil in dialysate turned out to be difficult. This difficulty was encountered mainly due to tedisamil's chemical structure: tends to cause chelate formation, especially in strong ionogenic fluids. This is applicable to dialysate, which contains a high calcium concentration. The compositions of the dialysis solutions were as follows

Component	Amount	Component	Amount
Sodium	140 mmol/l	Potassium	3 mmol/l
Calcium	1.75 mol/l	Magnesium	0.5 mmol/l
Osmolality	293 mosmol/kg	Chloride	112 mmol/l
Bicarbonate	32 mmol/l		

The following dialysers were evaluated (tabulated below).

Dialyser	Membrane	KUF*	Urea clearance**	Creatinine clearance**	Vitamin B12 clearance**	Manufacturer
F6	polysulphone low flux	5.5	179 ml/min	160 ml/min	60 ml/min	Fresenius Germany
F60	polysulphone high flux	40	186 ml/min	172 ml/min	118 ml/min	Fresenius Germany
BK-1,3P	polymethyl metacrylate	26	182 ml/min	172 ml/min	98 ml/min	Toray Japan

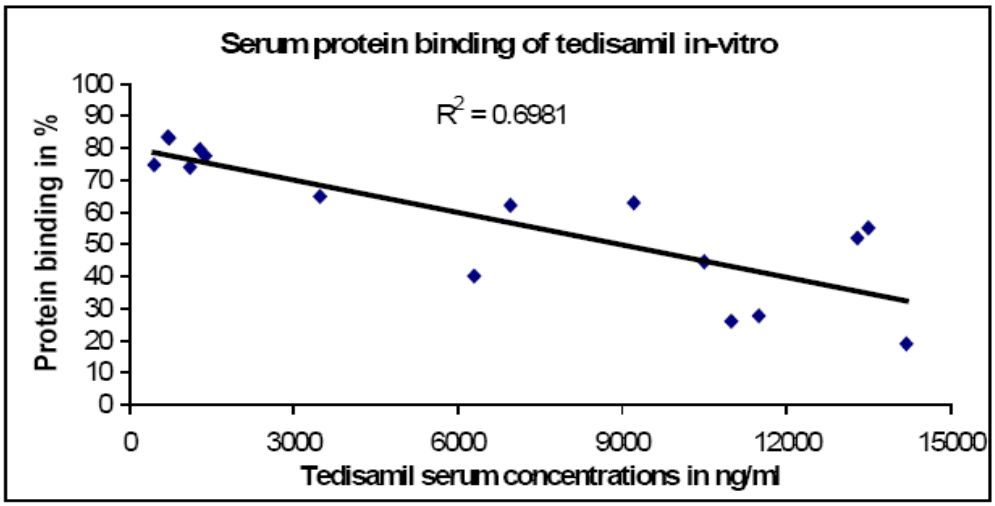
* Ultrafiltration coefficient: in ml per torr per hour.
** Dialysis with plasma flow rate of 200 ml/min and dialysis solution flow rate of 500 ml/min.

The applicant indicates that there were highly variable recoveries in the experiments because the methods used were not identical (differences in constitution of dialysates). Therefore, the data

from the dialysate analyses in this study should be interpreted only qualitatively. This reviewer agrees with the applicant's assessment. Furthermore, it is not clear that the in vitro results will be applicable to the in vivo results.

In vitro protein binding of tedisamil

Following incubation of tedisamil with varying tedisamil concentrations, there was an inverse concentration dependent decrease in binding. This relationship is depicted in the following figure: binding ranged from ~ 80 to 40 % for low to high tedisamil concentrations.



Recommendations/Conclusions

- The utility of in vitro dialysis information is unclear; a study should be conducted in human subjects to determine if tedisamil can be dialyzed.
- In-vitro protein binding is concentration dependent; therapeutic concentrations are ~ 80 % bound, whereas supra-therapeutic concentrations are ~ 40 % bound.

4.3 Pharmacometric Review

PHARMACOMETRICS REVIEW

NDA:	22-123
Drug name:	Pulzium (tedisamil sesquifumarate)
Indication:	Atrial Fibrillation/Flutter
Proposed Regimen (Sponsor):	0.48 mg/kg IV (males) 0.32 mg/kg IV (females)
Applicant:	Solvay Pharmaceuticals
OCP Reviewer	Robert O. Kumi, 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

Executive Summary

The pharmacokinetics of tedisamil was evaluated in 1169 patients with atrial fibrillation or flutter from five pivotal tedisamil studies. A three-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed tedisamil concentrations following a two-step IV infusion over 30 minutes of 0.16 mg/kg to 0.72 mg/kg.

Body weight was found to be significant covariate for tedisamil pharmacokinetics while gender was not. Gender specific tedisamil dosing (0.32 mg/kg for females and 0.48 mg/kg for males) is therefore not justified based on tedisamil exposure.

Renal impairment affects the area under the tedisamil concentration-time curve (AUC) but not the peak tedisamil concentration (C_{max}) which was found more correlated with efficacy (conversion to normal sinus rhythm within 2.5 hr after tedisamil dosing) and safety (tachycardia, bradycardia, extrasytoles, AV block, hypertension, prolonged QT, and Torsade de Pointes) compared to AUC. Dose adjustment for renal impairment is therefore not needed.

No clinical significant drug-drug interactions were identified in the population PK analysis of IV administered tedisamil.

Tedisamil was found to prolong the QT interval with a mean predicted QT change from baseline of 32 and 38 msec at the mean peak tedisamil concentration (C_{max}) of 954 and 1317 ng/mL after tedisamil doses of 0.32 and 0.48 mg/kg, respectively. ECG monitoring should be continued for 8 hours postdose until the QTcF is within normal limits. Gender was identified as a significant covariate for intercept in the concentration-QTcF analysis where females were found to have a higher intercept compared to males, (9.4 vs. 6.7 msec).

Logistic regression analyses were performed using efficacy and safety data from evaluable patients in the pivotal tedisamil studies. The analyses indicate that higher C_{max} significantly increases the probability of conversion to normal sinus rhythm within 2.5 hours after tedisamil dosing. Patients with the duration of their most recent Afib/Aflut episode within 8 hours of tedisamil dosing had 60% response rate compared to > 8 hrs of 20%. Males were found to be 1.5 times more likely to convert compared to females at similar exposure.

Logistic regression analyses for safety indicated that the probability of the tachycardia, bradycardia, extrasystoles, AV block, hypertension, prolonged QT, and Torsade de

Pointes (TdP) increases with increasing C_{max}. Gender was only identified as a significant covariate for tachycardia where females have lower probability of tachycardia compared to males at similar exposure.

The risk of TdP was also found to be correlated with exposure and QTcF change from baseline. Patients with tedisamil C_{max} above 1607 ng/mL or patients with QTcF change from baseline above 47 msec are at a significant higher risk of TdP compared to patients <1607 ng/mL and 47 msec.

The gender specific dosing proposed by the sponsor was based on early phase 3 (study S219.3.112) data suggesting that females have higher probability of TdP compared to males at similar exposure. This gender effect on TdP was not statistically significant in a logistic regression analysis with pooled data from the five pivotal studies.

The proposed gender specific dosing regimen (0.32 mg/kg for females and 0.48 mg/kg for males) is only acceptable if the medical reviewer can confirm the higher probability of TdP for females compared to males. Based on exposure, efficacy, and safety analysis, females should at least get the male dose of 0.48 mg/kg to get similar efficacy and safety profiles.

Question Based Review

Is gender specific dosing (female=0.32 mg/kg, male=0.48 mg/kg) justified?
The selection of 0.48 mg/kg for males and 0.32 mg/kg for females was based on observed data from the tedisamil studies where the incidence of TdP was found to be 0.5% (CI: 0.0 to 2.5) in males for the dose of 0.48 mg/kg and 0.4% (CI: 0.0 to 2.5) in females for the dose of 0.32 kg/kg, respectively.

No gender differences in tedisamil exposure were identified and efficacy data suggest that females need higher tedisamil doses to obtain similar response rates (conversion to normal sinus rhythm within 2.5 hrs) as males.

Should doses be adjusted for renal impairment?
Tedisamil clearance was found to decrease with decreasing creatinine clearance (CrCL). However, renal impairment does not significantly influence the peak tedisamil concentration (C_{max}) which is the exposure variable most related to both tedisamil efficacy and safety. It therefore appears reasonable not to suggest a dose adjustment for renal impairment. Sponsor adequately suggests to exclude patients with severe renal impairment since these patients were not studied in the pivotal tedisamil studies.

Is there evidence of exposure-response?
There is clear evidence of an exposure-response (conversion to normal sinus rhythm within 2.5 hours of tedisamil dosing) relationship for tedisamil using C_{max} as the exposure variable. Tedisamil was found to be most effective in patients with recent onset of Atrial fibrillation/flutter (Afib/Aflut) episode (i.e. less than 48 hours from initiation of tedisamil dosing) compared to patients with Afib/Aflut for more than 48 hours with an odd-ratio of 5.4 (95% CI 3.8-7.6). Tedisamil was also found to be more effective in Atrial fibrillation patients compared to Atrial flutter patients with an odds-ratio of 3.2 (95% CI 1.7-6.0). Finally, tedisamil was found to be more effective in males compared to females under similar tedisamil exposure with an odds-ratio of 1.5 (95% CI 1.1-2.1).

Patients with onset of Atrial fibrillation less than 8 hours since the start of their most recent episode had a significant higher response rate of 60% compared to the response rate of Atrial fibrillation patients with >8 hours duration with a response rate in the range of 20%.

Does tedisamil prolong the QT interval?

Tedisamil was found to prolong the QT interval with a mean predicted QT change from baseline of 32 and 38 msec at the mean observed female and male tedisamil C_{max} of 954 and 1317 ng/mL, respectively. The mean QTcF is predicted to return to normal within 8 hours after tedisamil dosing of 0.32 and 0.48 mg/kg, respectively.

Is there evidence of exposure-safety relationship?

The probability of developing tachycardia, bradycardia, extrasystoles, AV block, hypertension, prolonged QT, and Torsade de Pointes was found to increase with increasing tedisamil peak concentration. Gender was only identified as a significant covariate for tachycardia where females have lower probability of tachycardia compared to males at similar exposure.

Are claims based on the population PK/PD analysis acceptable?

The influence of verapamil on tedisamil clearance when co-administered with tedisamil was not found clinical significant (less than 5% reduction in tedisamil CL) in the population PK analysis.

7 DRUG INTERACTIONS

~~Upon I.V. administration of tedisamil using a two-step 30 min infusion in Afib/Afl subjects, co-administration of verapamil is associated with a 13% decrease in tedisamil clearance.~~ No significant PD interaction could be observed between verapamil and tedisamil in healthy subjects and Afib/Afl subjects.

Recommendations

The Pharmacometrics Staff in Office of Clinical Pharmacology finds that the NDA is acceptable.

The exposure, efficacy, and safety (excluding Torsade de Pointes) data analysis do not warrant gender specific dosing of tedisamil as suggested by the sponsor (i.e. 0.32 mg/kg for females and 0.48 mg/kg for males).

The sponsor's dosing recommendations were based on early phase 3 data (study S219.3.112) where the incidence of TdP was found to be similar in females (0.4% (CI: 0.0 to 2.5) at the dose of 0.32 mg/kg) compared to males (0.5% (CI: 0.0 to 2.5) at the dose of 0.48 mg/kg). This gender effect on TdP was not statistically significant in a logistic regression analysis with data pooled from the five pivotal studies.

Given the discrepancy between the sponsor's safety summary data (10 TdP events) and the raw safety data (2 TdP events), the validity of these summary statistics is pending on the medical reviewer's assessment of these TdP cases.

The proposed gender specific dosing regimen (0.32 mg/kg for females and 0.48 mg/kg for males) is only acceptable if the medical reviewer can confirm the higher probability of TdP for females compared to males. Based on exposure, efficacy, and safety analysis, females should at least get the male dose of 0.48 mg/kg to get similar efficacy and safety profiles.

Introduction

Background

Tedisamil is a potassium channel blocking agent with Class-III antiarrhythmic properties development as an antiarrhythmic agent for the conversion of atrial fibrillation or flutter to normal sinus rhythm (NSR).

Aims of Analysis

The primary objectives of this analysis are:

- To characterize the population PK of tedisamil in subjects with recent onset atrial fibrillation or flutter
- To characterize the tedisamil concentration-QT relationship in subjects with recent onset atrial fibrillation or flutter;
- To evaluate the relationship between tedisamil exposure and the primary efficacy variables and the most common adverse effect of the drug.

Sponsor's Population PK Analysis

Studies

Studies S219.3.112, S219.3.114, S219.3.116, S219.3.117, and S219.3.118 were multi-center, double-blind, randomized, placebo-controlled parallel design trials in subjects with recent onset atrial fibrillation or flutter. The studies were designed to evaluate the efficacy and safety of an IV tedisamil sesquifumarate infusion versus a placebo infusion in the rapid conversion of recent onset atrial fibrillation or flutter to normal sinus rhythm (NSR). Serial blood samples and ECG measurements were collected in all subjects to characterize the population PK and PK/PD of tedisamil.

Study S219.3.112 was originally planed to enroll 212 subjects with recent onset atrial fibrillation. After Amendment 5, the target enrollment was 248 subjects with recent onset atrial fibrillation in male subjects only. In addition, subjects with atrial flutter could have been enrolled within the scope of the study. The study terminated as soon as the planned number of the atrial fibrillation subjects had been reached. Following the screening and baseline assessments, eligible subjects were randomized to either 0.32 mg/kg, 0.48 mg/kg, or 0.64 mg/kg tedisamil free base treatment, or placebo, which was infused intravenously over 30 minutes, with one-half of the dose infused during the first 10 minutes and the second half of the dose infused over the remaining 20 minutes (two-step infusion procedure).

Study S219.3.114 was originally planned to enroll 90 subjects with recent onset atrial fibrillation. After Amendment 5, the target enrollment was 212 subjects with atrial fibrillation in male subjects only. In addition, subjects with atrial flutter could have been enrolled within the scope of the study. The study terminated as soon as the planned number of atrial fibrillation subjects had been reached. Following the screening and baseline assessments, eligible subjects were randomized to either 0.32 mg/kg or 0.48 mg/kg tedisamil free base treatment, or placebo, which was infused intravenously over 30 minutes, with one-half of the dose infused during the first 10 minutes and the second half of the dose infused over the remaining 20 minutes. Subjects, who did not convert to NSR within the 30 minutes infusion period, may have had their infusion extended for another 20 minutes. Consequently, these subjects received a total dose of 0.48 mg/kg if randomized to the 0.32 mg/kg treatment or 0.72 mg/kg if randomized to the 0.48 mg/kg treatment. After Amendment 5, the dose was limited to 0.16 mg/kg, 0.32 mg/kg, and 0.48 mg/kg tedisamil free base, or placebo, each infused over 30 minutes, with half of the dose during the first 10 minutes and the second half of the dose infused over the remaining 20 minutes. The extended regimen over 50 minutes was removed.

Study S219.3.116 was planned to enroll 330 female subjects with recent onset atrial fibrillation (110 subjects per treatment group). In addition, subjects with recent onset atrial flutter could have been enrolled within the scope of the study. The study terminated as soon as the planned number of atrial fibrillation subjects had been reached. Following the screening and baseline assessments, eligible subjects were randomized to either 0.24 mg/kg or 0.32 mg/kg tedisamil free base treatment, or placebo, which was infused intravenously over 30 minutes, with one-half of the dose infused during the first 10

minutes and the second half of the dose infused over the remaining 20 minutes (two-step infusion procedure).

Study S219.3.117 was planned to enroll 100 male subjects with recent onset atrial fibrillation (50 subjects per treatment group). In addition, subjects with recent onset atrial flutter could have been enrolled within the scope of the study. The study terminated as soon as the planned number of atrial fibrillation subjects had been reached. Following the screening and baseline assessments, eligible subjects were randomized to either 0.48 mg/kg tedisamil free base treatment or placebo, which was infused intravenously over 30 minutes, with one-half of the dose infused during the first 10 minutes and the second half of the dose infused over the remaining 20 minutes (two-step infusion procedure).

Study S219.3.118 was planned to enroll 140 female subjects with recent onset atrial fibrillation (70 subjects per treatment group). In addition, subjects with recent onset atrial flutter could have been enrolled within the scope of the study. The study terminated as soon as the planned number of atrial fibrillation subjects had been reached. Following the screening and baseline assessments, eligible subjects were randomized to either 0.32 mg/kg tedisamil free base treatment or placebo, which was infused intravenously over 30 minutes, with one-half of the dose infused during the first 10 minutes and the second half of the dose infused over the remaining 20 minutes (two-step infusion procedure).

Pharmacokinetic, Efficacy, and Safety Assessments

For studies S219.3.112, S219.3.114, and S219.3.116, blood samples were collected at predose (-10 minutes) and 5, 10, and 30 minutes after the initiation of the infusion and/or immediately after the infusion was prematurely stopped, at 45 minutes, and 1, 1.5, 2, 2.5, 4, 6, 8, 12, and 24 hours after the start of the infusion, at conversion to the sinus rhythm (if possible), and at hospital discharge. For study S219.3.117, blood samples were collected predose (-10 minutes) and at 10 and 30 minutes after the initiation of the infusion and/or immediately after the infusion was prematurely stopped, at 2.5 and 24 hours after the start of the infusion, at conversion to the sinus rhythm (if possible), and at hospital discharge. For study S219.3.118, blood samples were collected predose (-10 minutes) and at 5, 10, and 30 minutes after the initiation of the infusion and/or immediately after the infusion was prematurely stopped, at 2.5 and 24 hours after the start of the infusion, at conversion to the sinus rhythm (if possible), and at hospital discharge.

A 24-hour Holter ECG was started 10 minutes before start of the study drug infusion. The Holter tapes were collected, transferred to Spacelabs Medical Data, and analyzed for the identification of the first conversion into NSR of at least 60 seconds as well as the assessment of maintenance of NSR, in case of conversion, up to 24 hours after the start of the infusion. The Holter ECGs were analyzed for arrhythmias according to specific Holter analysis definitions. Ventricular events were coded according to a predefined coding system. The Holter data were primarily used for assessing the occurrence of conversions as well as the time to conversion. In the event that the Holter data were of poor quality or lacking, the 120 seconds rhythm strips were used for the assessment of the efficacy variables.

In addition, to document conversion from atrial fibrillation or flutter to NSR, 12-lead ECGs, including 120 seconds rhythm strip (3 or 6 leads), were obtained at 10 minutes prior to the infusion, and 5, 10, 30, 45, 60 minutes, 1.5, 2, 2.5, 4 (except for Studies S219.3.117 and S219.3.118), 6, 8 (except for Studies S219.3.117 and S219.3.118), 12, and 24 hours after initiation of infusion. In addition, a 12-lead ECG, including a 120 seconds rhythm strip, was performed at any time of conversion to NSR (if applicable) and if the subject reverted to atrial fibrillation or flutter from NSR within 24 hours after the initiation of infusion. Blinded reviews of 12-lead ECGs to adjudicate the clinical endpoint (conversion to NSR) were performed centrally according to standard guidelines.

Data

Pharmacokinetic Data

The combined bioanalytical database from the five studies contained 11,041 concentration records from 1,173 subjects, from which 10,421 concentration records from 777 tedisamil treated subjects were used for creating the PK database, and the remaining 620 concentration records from 396 placebo subjects were excluded. Of the 10,421 tedisamil concentration records, 1,279 concentration records were initially excluded from the dataset as follows: 1,062 samples associated with LLOQ, 90 samples associated with predose concentration above LLOQ, 41 samples considered to be outliers, 48 samples associated with non-matching dosing information between the bioanalytical and clinical databases, and 38 samples associated with duplicated samples drawn at the same time (ie, the duplicated samples specified as being collected at conversion to NSR or hospital discharge were excluded). Four subjects (ie, Subject Numbers 21601, 41211, 67406, 77102) were excluded from the PK dataset due to the exclusion criteria. Therefore, the final full PK dataset included 9,142 evaluable concentration records from 773 tedisamil treated subjects (58 subjects received 0.16 mg/kg, 117 subjects received 0.24 mg/kg, 324 subjects received 0.32 mg/kg, 197 subjects received 0.48 mg/kg, 60 subjects received 0.64 mg/kg, and 17 subjects received 0.72 mg/kg tedisamil). All placebo subjects were also included in the full PK dataset.

Of the 773 tedisamil treated subjects, 79% of subjects (611 subjects: 157 subjects from Study S219.3.112, 160 subjects from Study S219.3.114, 187 subjects from Study S219.3.116, 47 subjects from Study S219.3.117, and 60 subjects from Study S219.3.118) were split into the index dataset. Even though the index PK dataset included 611 subjects, tedisamil treated subject 48003 did not provide any concentrations. Thus, 610 subjects with 7,242 concentrations were included in the index PK dataset used for PK model development. The index PK dataset also included 314 placebo treated subjects (ie, 79% of a population of 396 placebo treated subjects with 56, 59, 94, 46, and 59 subjects from studies S219.3.112, S219.3.114, S219.3.116, S219.3.117, and S219.3.118, respectively). The placebo treated subjects did not contribute any information into the PK model development.

The remaining 21% of subjects (162 subjects: 43 subjects from Study S219.3.112, 42 subjects from Study S219.3.114, 49 subjects from Study S219.3.116, 12 subjects from Study S219.3.117, and 16 subjects from Study S219.3.118) were split into the validation dataset.

The validation dataset contained 1,900 concentration records. During the validation of the final PK model, 1 additional observation from Subject 27604 in the validation dataset was associated with an absolute value of WRES=111.01 and was identified for exclusion as a PK outlier. Even though the validation PK dataset included 162 tedisamil treated subjects, subjects 48103 and 62507 did not provide any concentrations. Therefore, the final validation dataset used in PK model validation included 1,899 concentrations from 160 tedisamil treated subjects. The validation PK dataset also included 82 placebo treated subjects (ie, 21% of a population of 396 placebo treated subjects with 15, 15, 24, 12, and 16 subjects from studies S219.3.112, S219.3.114, S219.3.116, S219.3.117, and S219.3.118, respectively). The placebo treated subjects did not contribute any information into the PK model validation.

Pharmacodynamic Data

Upon completion of the population PK analysis, an index PK/PD dataset was created for the same 611 tedisamil and 314 placebo treated subjects included in the index PK dataset. The model predicted tedisamil concentrations at the collection time of QTc Fredericia was set as independent variable, and the observed QTc Fredericia intervals was set as the dependent variable. The model predicted tedisamil concentrations for placebo subjects were set to missing. Even though Subject 48003 did not provide any tedisamil concentrations, predicted tedisamil concentrations for Subject 48003 were obtained from the final PK model.

A total of 660 individual predicted concentrations (from 571 subjects) were less than the LLOQ cutoff value of 2 ng/mL; thus, they were set equal to zero. A total of 13,271 QTc Fredericia intervals were available in the index PK/PD dataset. Of these, 2,479 QTc Fredericia intervals were excluded from the dataset as follows: 950 QTc Fredericia intervals due to time matched excluding PK records (ie, if corresponding observed concentration time points were excluded, the respective QTc Fredericia interval was also excluded), 629 intervals taken greater than 24 hours after the start of infusion, 522 intervals associated with subjects undergoing DC conversion, and 378 intervals taken greater than 24 hours after the start of infusion and associated with DC conversion. Twenty-five (25) subjects (ie, 16 tedisamil and seven placebo treated subjects) with all QTc Fredericia intervals being the excluded intervals were also excluded in the index PK/PD dataset. In summary, the final index PK/PD dataset included 10,792 QTc Fredericia intervals from 900 subjects (ie, 7,296 and 3,496 QTc Fredericia intervals from 595 and 305 tedisamil and placebo treated subjects, respectively).

Similarly to the creation of the index PK/PD dataset, the same 162 tedisamil and 82 placebo treated subjects in the validation PK dataset were included in the validation PK/PD dataset. Even though tedisamil treated Subjects 48103 and 62507 did not provide any tedisamil concentrations, predicted tedisamil concentrations for Subjects 48103 and 62507 were obtained from the final PK model. A total of 172 individual predicted concentrations (from 144 subjects) were less than the LLOQ cutoff value of 2 ng/mL and were set equal to zero. Three tedisamil and five placebo treated subjects (Subjects 27304, 27604, 48011, 68101, 69806, 72903, 95902, and 82401) did not contribute any QTc Fredericia intervals.

A total of 3,424 QTc Fredericia intervals were available in the validation PK/PD dataset. Of these, 617 QTc Fredericia intervals were excluded from the dataset as follows: 235 QTc Fredericia intervals due to time matched excluding PK records (ie, if corresponding observed concentration time points were excluded, the respective QTc Fredericia interval was also excluded), 96 intervals taken greater than 24 hours after the start of infusion and associated with DC cardioversion, 156 intervals taken greater than 24 hours after the start of infusion, and 130 intervals associated with DC conversion. All QTc Fredericia intervals were excluded, per the exclusion criteria, for four subjects (ie, Tedisamil treated Subject Numbers 40503, 69802, 69804, and Placebo Subject Number 82511) from the validation PK/PD dataset. In summary, the final validation PK/PD dataset included 2,807 QTc Fredericia intervals from 232 subjects (ie, 1,912 and 895 QTc Fredericia intervals from 156 and 76 tedisamil and placebo treated subjects, respectively).

Study Populations

The studies were conducted in male and female subjects older than 18 years old with recent onset atrial fibrillation or flutter. The subjects had to be in no distress and in hemodynamically stable condition. Summary statistics of the PK population in the index dataset is shown in Table 60.

Table 60 Summary Statistics of Demographics and Other Baseline Characteristics of the Pharmacokinetic Population.

Variable	N (%)	Mean (SD)	Median	Min – Max
Age (years)	610	64.7 (11.2)	66.0	26.0 – 91.0
Weight (kg)	610	81.3 (15.6)	80.0	45.0 – 140
BMI (kg/m^2)	610	28.4 (4.72)	28.3	18.4 – 52.1
LBM (kg)	610	56.1 (9.61)	55.3	34.7 – 84.6
Protein (g/dL)	610	71.2 (6.09)	71.0	49.0 – 96.0
Albumin (g/dL)	610	40.6 (3.90)	40.0	25.0 – 52.0
CRCL (mL/min)	610	85.5 (31.0)	82.0	24.4 – 223
Gender Male Female	 332 (54.4%) 278 (45.6%)	NA	NA	NA
Smoking Smoker Non-smoker	 182 (29.8%) 428 (70.2%)	NA	NA	NA
NYHA Class I Class II and III Missing	 296 (48.5%) 284 (46.6%) 30 (4.9%)	NA	NA	NA

BMI: body mass index; LBM: lean body mass; CRCL: creatinine clearance; NYHA: New York Heart Association; Smoker includes subjects who had history of smoking or current smokers; NA: not applicable; SD: standard deviation;

Supporting data: *Appendix 8.5.3.1, page 10579, Appendix 8.5.3.2, page 10582*

Methods

Population PK Analysis

Structural Models

Tedisamil concentration-time data were analyzed by nonlinear mixed-effects modeling to develop a base structural population PK model. If the run time allowed, the first-order condition estimation (FOCE) method with interaction was to be used. The base model was identified by comparing different structural PK models (eg, 1-, 2-, and 3-compartment models).

Inter-Individual Variability

Random effects (between-individual variability on the PK parameters) assumed a log-normal distribution

$$P_j = \theta \exp(\eta_i)$$

where P is the parameter of interest, i is the i^{th} subject, θ is the estimate of the population mean and η_i is the deviation from the population mean for the i^{th} subject under the assumption that $\eta \sim N(0,\omega_\theta^2)$. For a 1-compartment model, random effects were initially modeled on clearance (CL). For 2- and 3-compartment models, random effects were initially modeled on CL and V1 with diagonal 2 x 2 covariance matrix. Additional random effects were then added or removed from the model sequentially. Addition or removal of model terms was based on whether the models were nested or non-nested, all other things being equal, eg, precision of standard error of the parameter estimates, unbiasedness of residual plots, and precision of estimation of the variability associated with the random effects. If multiple random effects were included in the model, a diagonal covariance matrix for the random effects was initially used.

Once the base model was identified, individual subject PK parameters for which random effects were included in the model were calculated by the posterior conditional estimation (POSTHOC) technique of NONMEM. Correlation between PK parameters was evaluated graphically using a matrix plot and via modeling by adding a covariance term between the random effects. In the event that the base model included multiple random effects, Spearman's rank correlation coefficient between PK parameters was calculated. If any Spearman's rank correlation coefficient was significant at the 0.1 level, a covariance term between the random effects of PK parameters showing significant correlation was to be added to the covariance matrix of the base model.

Intra-Individual Variability

Initially, residual error was modeled as a proportional error

$$Y_{ij} = C_{ij}(1+\varepsilon_{ij})$$

where Y is the observed concentration for the i^{th} subject's j^{th} concentration, C_{ij} is the predicted concentration, and ε_{ij} is the residual proportional error term under the assumption that $\varepsilon \sim N(0,\sigma_\varepsilon^2)$. Concentrations might have been log-transformed in the model if large residual variability was identified. In which case, residual error was to be modeled as follows

$$log\ Y_{ij} = \log C_{ij} + \varepsilon_{ij}$$

where $\log Y_{ij}$ is the observed concentration for the i^{th} patient's j^{th} concentration, Cij is the predicted concentration, and εij is the residual error term under the assumption $\varepsilon \sim N(0,\sigma_\varepsilon^2)$.

Once the random effects covariance matrix was determined, the data set was examined for outliers by examining weighted residuals. Data points with weighted residuals determined to be outside the bulk of the data were considered outliers and excluded from modeling. The model was to be re-fitted and the individual subject PK characteristics recalculated. At this point, further outlier exclusion was not to be done.

Once the random effects covariance matrix was determined and all outliers were excluded, the residual error model was further evaluated. The additive and proportional error model (APEM)

$$Y_{ij} = C_{ij}(1+\varepsilon_{1,ij}) + \varepsilon_{2,ij}$$

and the additive error model

$$Y_{ij} = C_{ij}(1+\varepsilon_{1,ij}) + \varepsilon_{2,ij}$$

Covariate Models

A scatter plot correlation matrix was developed to examine the dependency among covariates. For covariates that were continuous in nature, scatter plots of PK parameter estimates against covariates overlaid with a LOESS smoother were used to help identify functional relationships. For covariates that were categorical in nature, box and whisker plots of PK parameters for each of the groups were used to identify differences between groups. If several correlated covariates (eg, BMI and body surface area (BSA)) were statistically significant, the one with the largest coefficient of determination to the PK parameter of interest was to be tested in the covariate model. Covariates were added to the base model incrementally and tested by NONMEM to determine if they were indeed statistically significant. A p-value of 0.01 was used as the criteria for statistical significance. A change in objective function value (OFV) of 6.635 points was considered significant for addition of 1 model parameter or 1 degree of freedom. Covariates that are continuous in nature were entered into the model in a mean centered manner

$$P_i = \theta_0 + \theta_1*(X_1-M(X_1))$$

where P_i is the i^{th} parameter, θ_0 is the intercept, θ_1 is the slope relating the covariate, X1, to the PK parameter, and $M(X_1)$ is the mean of X_1. Centering of covariates had a number of advantages including: reduced numerical instability in the parameter estimates when there are high correlations among the parameters, the extended least-squares algorithm is least likely to terminate with rounding errors, and more meaningful estimates in that the θ_0 represents the population mean parameter estimate at the mean of X_1, while θ_1 represents the rate of change in the parameter per unit change in X_1.

If the scatter plot between the covariate and the PK parameter indicated a log-linear or exponential relationship, a multiplicative model was used

$$P_i = \theta_0\left[\frac{X_1}{M(X_1)}\right]^{\theta_1}$$

or

$$P_i = \theta_0 + exp[\theta_1*(X_1-M(X_1))]$$

Combinatory linear and multiplicative models may have been developed as needed.

Categorical covariates were entered into the model using dummy variables (0 or 1) using a fractional change model. For the linear model with a dichotomous covariate

$$P_i = \theta_0 * (1 + \theta_1 * X_1)$$

where $1 + \theta_1$ is the fractional multiplier for X_1. Thus when $X_1 = 1$, $P_i = \theta_0 \cdot (1 + \theta_1)$. When $X_1 = 0$, $P_i = \theta_0$.

If run time allowed, the FOCE method with interaction was to be used during the covariate screening process. Covariates that demonstrated significant population PK model improvement were considered for the next step of covariate model development. The covariate model demonstrating the greatest improvement in the population PK model was incorporated into the base population PK model and remaining candidate covariates were re-evaluated incrementally. This process was repeated until none of the remaining candidate covariates provided significant improvement to the population PK model.

Population PD Analysis

Structural Models

Tedisamil concentration-effect data were analyzed by nonlinear mixed-effects modeling to develop PK/PD models for QTc Fredericia intervals. Electrocardiogram measurements recorded in the presence of any disallowed anti-arrhythmic agent (ie, class I, III, or sotalol) or other allowed anti-arrhythmic agents (ie, beta blockers or diltiazem) were evaluated for exclusion from the PK/PD modeling. All models were minimized under FOCE method with interaction. Because diurnal variations in QTc Fredericia intervals have been reported, the PK/PD model would be the sum of diurnal variation and drug effects.

A linear-quadratic model was used to model placebo effect in QTc Fredericia intervals in subjects randomized to placebo:

$$E_{Placebo} = E_0 + A_1 * Time + A_2 * Time^2$$

where $E_{Placebo}$ is the measured QTc Fredericia interval in subjects randomized to placebo, E_0 is the baseline QTc Fredericia interval, and A_1 and A_2 are the slopes of the linear and quadratic terms, respectively, between measured QTc Fredericia interval and time.

Significance of the linear and quadratic terms was tested by sequentially removing these terms one at a time. A significance level of 0.01 was used. If deemed appropriate, additional structural models, such as a cosine function, were to be tested.

$$E_{Placebo} = E_0 + A * \cos(Time - T) * 2\pi / 24)$$

where A is the amplitude of the circadian variation in measured QTc Fredericia interval in subjects randomized to placebo and T is the time of maximum increase from baseline. QTc Fredericia intervals from subjects randomized to placebo and tedisamil were then to be combined for the characterization of the full PK/PD model containing both the diurnal variation model identified in the first step and a drug effect model,

$$E = E_{Placebo} + E_{Tedisamil}$$

The PK component of the drug effect model was then set to the individual concentrations predicted under the final PK model identified during the population PK analysis.

Concentrations predicted to be below the lower limit of quantification of the assay were set to 0 and included in the PK/PD modeling. Models tested for identification of the base structural drug effect model were:

Linear model: $E_{Tedisamil} = Slope * C$

Power model: $E_{Tedisamil} = Slope * C^{\lambda}$,

Emax model: $$E_{Tedisamil} = \frac{E_{\max} * C}{EC_{50} + C}$$

Sigmoid-Emax model: $$E_{Tedisamil} = \frac{E_{\max} * C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

where $E_{Tedisamil}$ is the measured QTc Fredericia interval in subjects randomized to tedisamil, C is the predicted tedisamil plasma concentration, eC_{50} is the concentration producing 50% effect, λ is the power parameter, and γ is the sigmoidicity factor.

Exposure-Response Analysis

An analysis of the relationship between model predicted tedisamil exposure parameters C_{max} and $AUC_{0\text{-}inf}$ and primary efficacy endpoint (responder or non-responder) was conducted. For each subject, C_{max} and $AUC_{0\text{-}inf}$ were computed via non-compartmental analysis using predicted tedisamil concentrations under the final PK model. Responders were defined as subjects who converted to NSR for at least 60 seconds by 2.5 hours after the initiation of the study drug infusion. Descriptive statistics of predicted Cmax and $AUC_{0\text{-}inf}$ were summarized across responders and non-responders. The exposure-efficacy relationship was evaluated by logistic regression analysis with a level of significance of 0.05. Exposure data were log transformed using a base of two (Log2). This transformation was selected for the exposure covariates for computational convenience to yield a simple interpretation in terms of odds of response for doubling exposure (ie, when exposure is doubled, change in efficacy parameter = exp[coefficient for Exposure]. In addition, for the responders, the time to conversion to NSR was plotted against predicted C_{max} and $AUC_{0\text{-}inf}$. The exposure-time to conversion to NSR relationship was evaluated by linear regression analysis with a level of significance of 0.05.

The top five AEs most frequently reported by subjects randomized to receive tedisamil were selected to evaluate the relationship between tedisamil exposure and the incidents of AEs. Subjects experiencing a particular AE were coded as 1, otherwise the subjects were coded as 0. The relationship between the occurrence of any of these AEs and predicted systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) was analyzed by logistic regression analysis with a significance level of 0.05. The exposure data were log transformed with a base of two (Log 2). The following AEs were evaluated: tachycardia (including ventricular tachycardia, supraventricular tachycardia, tachycardia, and sinus tachycardia), bradycardia (including sinus bradycardia, bradycardia not-otherwise-specified (NOS), bradycardia), extrasystoles (including ventricular extrasystoles, supraventricular extrasystoles, extrasystoles NOS, and extrasystoles), hypertension (including hypertension NOS, hypertension, and accelerated hypertension), hypotension (including hypotension and hypotension NOS), elevation of GGT, 1st degree AV block, prolongation of QT interval, and TdP. Similar analyses were performed o determine

whether the occurrence of increased GGT or 1st degree AV block was related to predicted C_{max} and $AUC_{0\text{-}inf}$. The relationships between tedisamil exposure and the other two AEs (QT prolongation and TdP) were also analyzed through graphically comparison, but no statistical test was performed due to the low incident (<2%).

Results

Population PK Analysis

Base PK Model

Evaluation of the objective function value (OFV) and precision of parameter estimates suggested the data was adequately described by a three-compartment model with an additive and proportional error model and inter-individual variability on CL, V_1, Q_2, and V_2.

Covariate PK Model

Covariates tested on PK parameters were age (as continuous and age group (<65 versus ≥65 years)), weight, BMI, LBM, sex, smoking status, NYHA classification of congestive heart failure, clinical laboratory measurements including total protein level, albumin level, CRCL (as continuous and CRCL group (as CRCL≤60 versus CRCL>60 mL/min)), and concomitant medications. Concomitant medications included beta-blockers, diuretics, inhibitors/substrates of organic anion and cation renal transporters, vasodilators12, ACE-inhibitors, digoxin, and verapamil.

In summary, the final covariate model resulting from forward addition and backward elimination, performed with FOCEI method, contained the following:

- Power mean normalized relationship between CRCL and CL,
- Linear mean normalized relationship between LBM and V_1,
- Power mean normalized relationship between CRCL and V_2,
- Fractional change relationship between AGE and Q_2,
- Fractional change relationship between the co-administration of verapamil and CL,
- Fractional change relationship between the co-administration of a beta-blocker and V_2, and
- Linear mean normalized relationship between BMI and CL.

Final PK Model

The PK parameter estimates of sponsor's final PK model are shown Table 61.

Table 61 Sponsor's Final PK Model Parameter Estimates.

Model Parameters	Parameter	Estimate	SE	RSE (%)	95% CI
Objective Function Value	OFV	66750.696			
Clearance, CL (L/h)	θ (1)	10.4	0.205	2.0	10.0 – 10.8
CL = (θ(1) * (CRCL/87) $^{\theta(7)}$ * FCM03	θ(7)	0.766	0.0389	5.1	0.690 – 0.842
FCM03=1 if not on Verapamil FCM03=θ(11) if on Verapamil * FCMCC	θ(11)	0.869	0.0257	3.0	0.819 – 0.919
FCMCC=1 if not on ACE-inhibitor	θ(12)	1 FIXED			
FCMCC=θ(12) if on ACE-inhibitor + (BMI-28) * θ(14)	θ(14)	-0.116	0.0279	24.1	-0.171 – -0.0613
Central Volume, V1 (L)	θ(2)	7.92	0.230	2.9	7.47 – 8.37
V1= θ(2) + (LBM-56) * θ(8)	θ(8)	0.145	0.0197	13.6	0.106 – 0.184
Q2 Prevent Theta	θ(3)	34.4	1.27	3.7	35.6 – 40.6
Intercompartment Clearance, Q2 (L/h)	θ(3) + Q3	38.1			
Q2 = (θ(3) + Q3) * FAGE FAGE=1 if AGE >= 65 FAGE=θ(10) if AGE < 65	θ(10)	1.24	0.0535	4.3	1.14 – 1.34
Peripheral Volume, V2 (L)	θ(4)	30.7	1.05	3.4	28.6 – 32.8
V2 = θ(4) * (CRCL/87) $^{\theta(9)}$ * FCMCG	θ(9)	0.326	0.0519	15.9	0.224 – 0.428
FCMCG=1 if not on beta-blocker FCMCG=θ(12) if on beta-blocker	θ(13)	1.12	0.0343	3.1	1.05 – 1.19
Intercompartment Clearance, Q3 (L/h)	θ(5)	3.73	0.0779	2.1	3.58 – 3.88
Peripheral Volume, V3 (L)	θ(6)	35.5	0.755	2.1	34.0 – 37.0
Between-Subject Variability, CL	η(2)	0.129 CV = 37.1%	0.00716	5.6	0.115 – 0.143
Between-Subject Variability, V1	η(1)	0.294 CV = 58.5%	0.0207	7.0	0.253 – 0.335
Between-Subject Variability, Q2	η(4)	0.144 CV = 39.4%	0.0115	8.0	0.121 – 0.167
Between-Subject Variability, V2	η(3)	0.246 CV = 52.8%	0.0173	7.0	0.212 – 0.280
Off-Diagonal Correlation, CL and V1		0.0838 Cor = 0.430	0.0101	12.1	0.0640 – 0.104
Off-Diagonal Correlation, CL and Q2		0.0239 Cor = 0.175	0.00778	32.6	0.00865 – 0.0391
Off-Diagonal Correlation, CL and V2		0.117 Cor = 0.657	0.00943	8.1	0.0985 – 0.135
Off-Diagonal Correlation, V1 and V2		0.122 Cor = 0.454	0.0149	12.7	0.0928 – 0.151
Off-Diagonal Correlation, Q2 and V2		0.0877 Cor = 0.466	0.0111	12.2	0.0659 – 0.109
Residual Variability, Proportional	ε(1)	0.0518 CV = 22.8%	0.000560	1.1	0.0507 – 0.0529
Residual Variability, Additive	ε(2)	7.39 SD = 2.72	0.573	7.8	6.27 – 8.51

The goodness-of-fit graphs of sponsor's final PK model are shown in Figure 26.

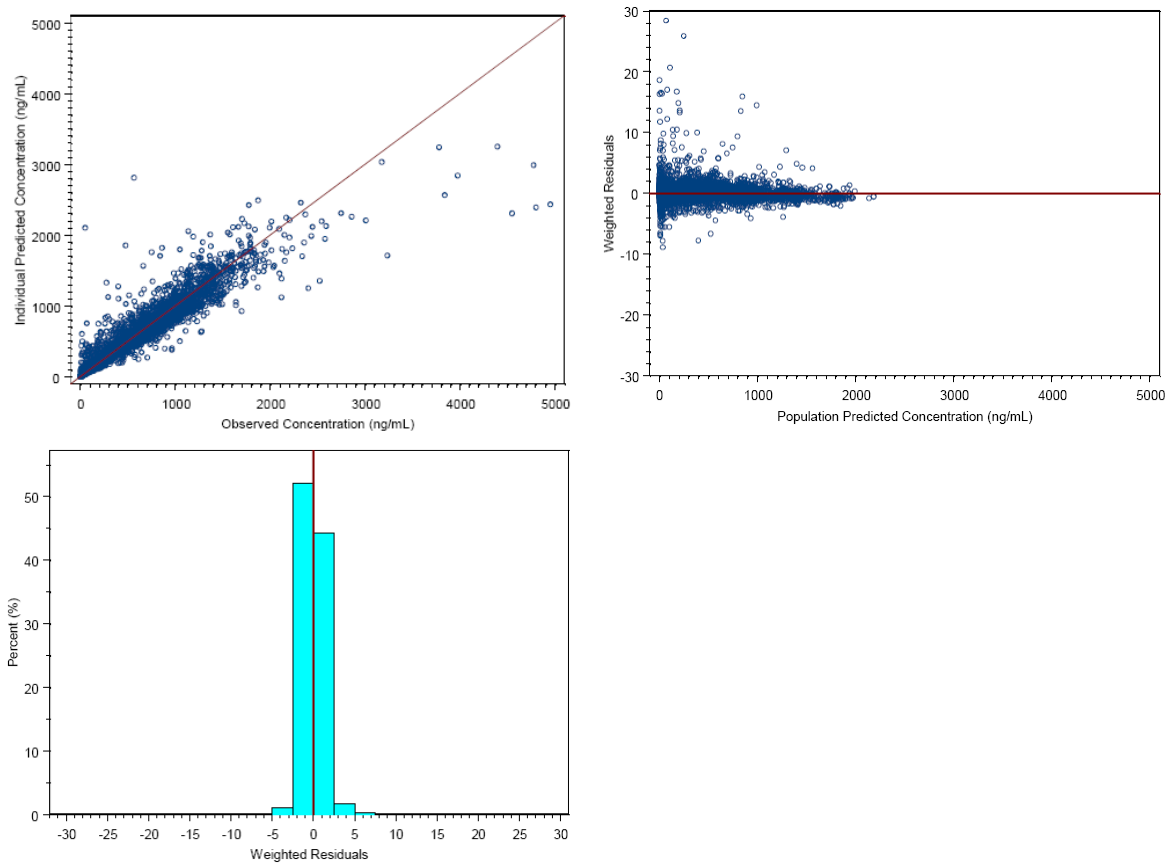


Figure 26 Goodness-of-fit graphs for sponsor's final PK model. Observations vs. individual predicted (top left), weighed residuals vs. population predicted (top right), histogram of weighted residuals (bottom left). The solid red line is the line of unity/identity.

Population PD Analysis

The observed tedisamil concentration-QTcF relationship prior and following conversion to NSR is shown in Figure 27 along with the QTcF vs. clock time and time after dose for placebo subjects. The concentration-QTcF relationship seems to be non-linear while there is no indication of a diurnal relationship between QTcF and clock time but perhaps a weak positive placebo effect as time after dose increases.

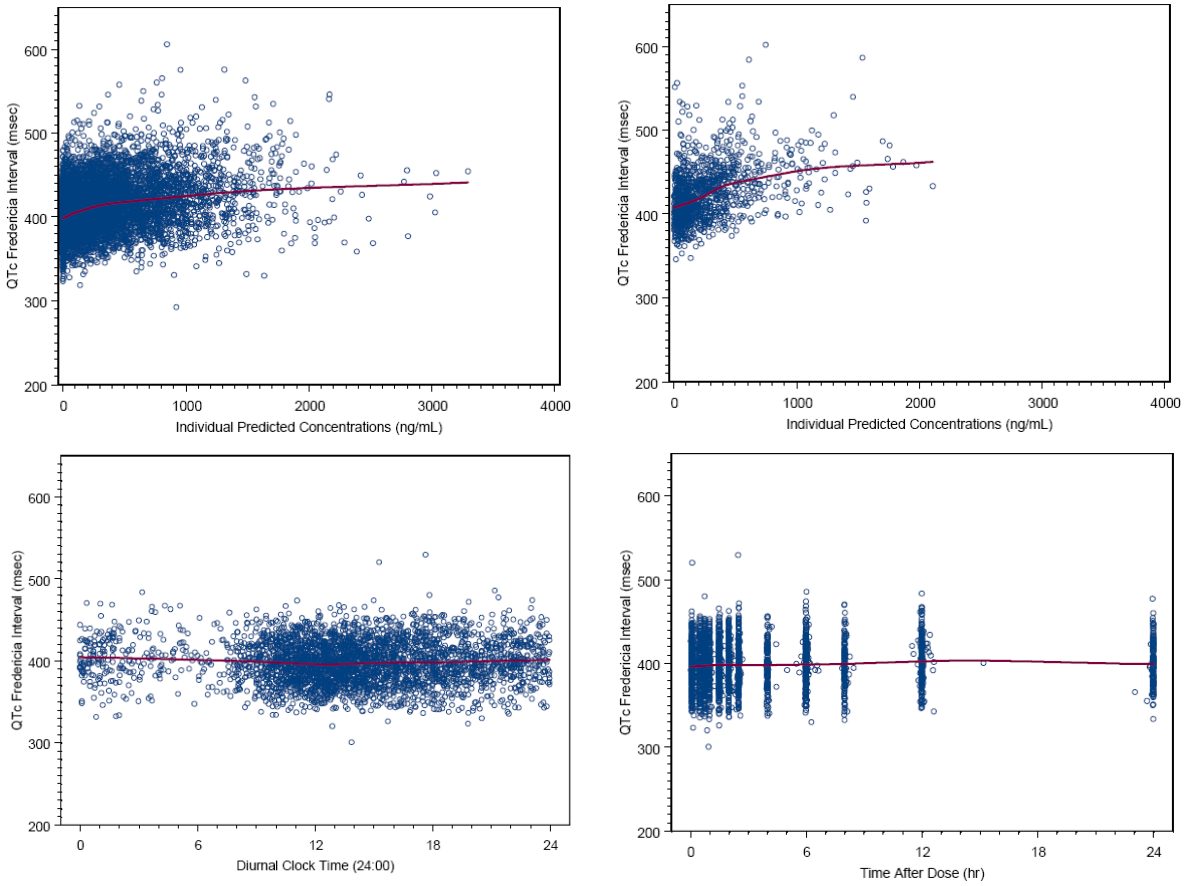


Figure 27. QTc Fredericia intervals versus individual predicted tedisamil concentrations in subjects who received tedisamil, prior to (Top Left) and following (Top Right) conversion to normal sinus rhythm, QTc Fredericia intervals versus clock time in placebo subjects (Bottom Left), and QTc Fredericia intervals versus time after first dose in placebo subjects (Bottom Right).

Base PD Model

The E_{max} PK/PD model was used as the base model for further model evaluation. Inter-individual variability parameters were modeled for baseline, E_{max}, and EC_{50} parameters. The inter-individual variability estimate for E_{max} was modeled as an additive error model while the inter-individual variability estimate for the baseline and EC_{50} parameters was modeled as an exponential error model. Residual error was modeled as a proportional error model. Due to minimal diurnal or placebo effect observed in the graphical analysis, combination E_{max} and diurnal or placebo effect models ($E = E_{Diurnal} + E_{Tedisamil}$ or $E = E_{Placebo} + E_{Tedisamil}$) were not tested.

Covariate PD Modeling

Covariates tested on the PD parameters associated with tedisamil effect included age (as continuous and age group (<65 versus ≥65 years)), weight, LBM, BMI, sex, total tedisamil dose administered, dose group, smoking status, potassium level, CRCL (as continuous and CRCL group (CRCL≤60 versus CRCL>60 mL/min)), conversion to NSR by 2.5 hours after the initiation of the study drug infusion, NYHA classification of congestive heart failure, type of arrhythmia (fibrillation or flutter), duration of atrial fibrillation or flutter (≤ 48 hr versus > 48 hr), and whether it was a recurrent episode or first episode. Potential drug/drug interactions with digoxin, beta-blockers, and anti-arrhythmic drugs were also examined. These covariates were also tested on the baseline ECG measurements with the exception of the tedisamil dose.

In summary, the identified significant PD model parameter-covariates relationships were:

- Total administered tedisamil dose on Emax using a linear model centered around the mean total dose.
- Age on baseline using a power model centered around the mean age.
- Potassium level on baseline using a linear model centered around the mean potassium level.
- Beta-blocker on baseline parameterized as fractional change.
- Type I, IA, IB, IC, or III Anti-arrhythmic on Baseline parameterized as fractional change.

Final PD Model

The PD parameter estimates of sponsor's final PD model are shown Table 62.

Table 62 Sponsor's Final PD Model Parameter Estimates.

Model Parameters	Parameter	Estimate	Standard Error	RSE (%)	95% CI
Objective Function Value	OFV	73187.695			
Baseline (msec)	θ(1)	397	1.12	0.282	395 – 399
Baseline = θ(1) * (AGE/65)^θ(5) * FCMG * FCMQ	θ(5)	0.0577	0.00926	16.0	0.0396 – 0.0758
+ θ(6) * (KION - 4.4)	θ(6)	-6.77	1.31	19.4	-9.34 – -4.20
FCMG = θ(7), if subject did take a beta-blocker, FCMG = 1, if subject did not take a beta-blocker	θ(7)	1.01	.00300	0.297	1.00 – 1.02
FCMQ = θ(8), if subject did take a Type I, IA, IB, IC, or III AA, FCMQ = 1, if subject did not take a Type I, IA, IB, IC, or III AA	θ(8)	1.01	.00441	0.437	1.00 – 1.02
Emax (msec)	θ(2)	24.9	1.82	7.31	21.3 – 28.5
Emax = θ(2) + θ(4) * (DOS2–18,500)	θ(4)	0.00103	0.000128	12.4	0.000779 – 0.00128
EC50 (ng/mL)	θ(3)	315	49.1	15.6	219 – 411
Between-Subject Variability, Baseline	η(1)	0.00323 CV = 5.69%	0.000166	5.14	0.00290 – 0.00356
Between-Subject Variability, Emax	η(2)	510 SD = 22.6	75.5	14.8	362 – 658
Residual Variability	ε(1)	0.00140 CV = 3.74%	0.0000535	3.82	0.00130 – 0.00150

Notes: Emax = maximum effect; EC50 = concentration producing 50% maximum effect;
BSV = between subject variability; SE=standard error; RSE= residual standard error;
CI = confidence interval; θ = theta; η = eta (BSV); ε = epsilon (residual variability);
OFV= objective function value;
Data were modeled using FOCE/I;
η(1)- exponential error model, η(2) – additive error model; ε(1)- proportional error model.
CV= (exp[η(1)]-1)½ for an exponential between-subject variability error model;
SD= η(x)½ for an additive between-subject variability error model;
CV= ε(1)½ * 100 for residual error;
RSE = SE/ Estimate* 100.
The 95% confidence interval (CI) was calculated as Estimate ± 1.96 * SE.
DOS2 = total tedisamil administered dose (mcg).
AGE = subject's age (years).
FCMG = fractional change code for beta-blocker
KION = potassium level (mEq/L)
AA = anti-arrhythmic

Supporting data: *Appendix 8.4.2.5.2, page 10163* and *Table 80, page 422*

The goodness-of-fit graphs of sponsor's final PD model are shown in.

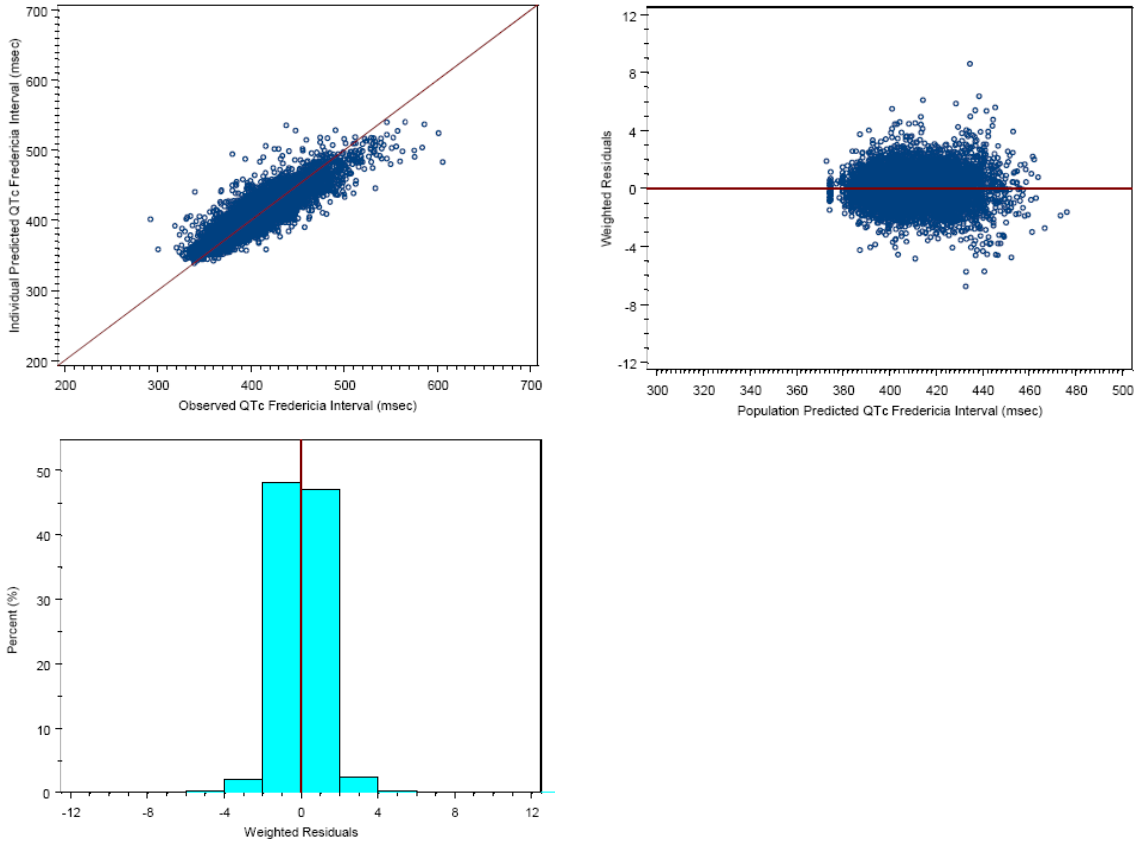


Figure 28 Goodness-of-fit graphs for sponsor's final PD model. Observations vs. individual predicted (top left), weighed residuals vs. population predicted (top right), histogram of weighted residuals (bottom left). The solid red line is the line of unity/identity.

Change from baseline in QTcF was further estimated for each subject in the full dataset using POSTHOC estimation under the final PK/PD covariate model. The mean values of the model predicted changes from baseline in QTcF intervals suggested females had slightly lower mean values than males as shown in Table 63.

Table 63. Model predicted change from baseline in QTcF for tedisamil treated subjects.

	Male				Female			
Change from baseline [a]	N	Mean (SD)	Median	Range	N	Mean (SD)	Median	Range
30 ± 5 minutes	347	29.4 (19.6)	28.8	-31.3 – 97.8	283	22.2 (14.1)	21.5	-22.5 – 74.6
60 ± 5 minutes	359	22.3 (15.9)	21.8	-20.0 – 80.9	293	16.8 (12.0)	15.5	-19.3 – 75.4
2.5 ± 0.5 hours	380	18.3 (13.6)	17.2	-15.3 – 69.2	299	13.8 (10.1)	12.4	-15.2 – 66.2
4 ± 0.5 hours	311	14.5 (11.9)	12.6	-12.8 – 57.1	195	10.5 (9.41)	8.69	-11.7 – 58.9
6 ± 0.5 hours	341	12.0 (9.52)	10.7	-10.1 – 43.1	267	8.62 (7.08)	7.05	-8.46 – 49.0
8 ± 0.5 hours	290	9.02 (7.72)	7.50	-8.06 – 35.0	190	6.41 (6.37)	4.78	-6.72 – 41.0
12 ± 1 hours	336	6.14 (5.51)	5.04	-5.39 – 24.1	260	4.58 (4.18)	3.33	-5.11 – 28.9
24 ± 1 hours	237	2.60 (2.95)	1.62	-2.04 – 18.8	193	2.28 (2.29)	1.43	-0.18 – 13.3

[a]Change from baseline in QTc Fredericia was estimated for each subject in the full dataset (ie, index and validation dataset combined) using POSTHOC estimation under the final PK/PD covariate model (Model QTCF-COV-544, *Table 39, page 128*). Supporting data *Appendix 8.5.11.2, page 10713*

Exposure-Response Relationship

Model predicted systemic exposure parameters ($AUC_{0\text{-}inf}$ and C_{max}) were calculated using WinNonlin for each subject. The calculations were based on individual tedisamil concentrations predicted with the final population PK model. Only subjects who received two-infusion regimens were included in the analysis. Subjects 48003, 48103, and 62507 who did not provide tedisamil concentrations in the full PK dataset were also excluded from the analysis.

Descriptive statistics of C_{max} and $AUC_{0\text{-}inf}$ broken down by treatment arm and sex are summarized in Table 64. Mean values of C_{max} and $AUC_{0\text{-}inf}$ increased proportionally with increasing dose.

Table 64. Tedisamil exposure by treatment arm.

PK parameter	Treatment Arm	Sex	N	Mean	SD	Median	Minimum	Maximum
C_{max} (ng/mL)	0.16 mg/kg [a]	Male	58	480	160	488	227	1336
	0.24 mg/kg [b]	Female	116	793	184	772	327	1306
	0.32 mg/kg	Male	122	934	333	886	287	2713
		Female	201	1000	268	965	423	2698
		Both	323	975	295	944	287	2713
	0.48 mg/kg	Male	169	1319	381	1278	544	2952
		Female	11	1622	423	1493	930	2443
		Both	180	1337	389	1302	544	2952
	0.64 mg/kg	Male	50	1829	502	1756	762	3572
		Female	10	1948	534	1807	1530	3405
		Both	60	1849	505	1767	762	3572
$AUC_{0\text{-}inf}$ (ng/mL*hr)	0.16 mg/kg	Male	58	1194	508	1098	355	3101
	0.24 mg/kg	Female	116	2252	885	2078	1001	5790
	0.32 mg/kg	Male	122	2397	1067	2113	561	8023
		Female	201	3203	1695	2725	951	10264
		Both	323	2899	1538	2519	561	10264
	0.48 mg/kg	Male	169	3802	1554	3436	1158	8392
		Female	11	5130	1387	5064	2652	7598
		Both	180	3883	1573	3506	1158	8392
	0.64 mg/kg	Male	50	4645	1460	4238	1300	8766
		Female	10	5045	1446	5040	3055	7438
		Both	60	4712	1453	4320	1300	8766

N = number of subjects; SD = standard deviation; C_{max} = maximum concentration; $AUC_{0\text{-}inf}$ = area under the curve from zero to infinity;
[a] Only male subjects were included in 0.16 mg/kg treatment group;
[b] Only female subjects were included in 0.24 mg/kg treatment group;
Supporting data: *Appendix 8.5.11.6,*

Descriptive statistics of C_{max} and $AUC_{0\text{-}inf}$ in responders and non-responders are summarized in Table 65. Responders were defined as subjects with atrial fibrillation who converted to NSR for at least 60 seconds within 2.5 hours of the start of study drug infusion. Mean predicted $AUC_{0\text{-}inf}$ values for responders were 8% higher compared to non-responders. Likewise, mean C_{max} values for responders were 24% higher than non-responders.

Table 65. Tedisamil exposure stratified by responder and non-responder.

PK parameter	Responder?	N	Mean	SD	Median	Minimum	Maximum
C_{max} (ng/mL)	Yes	171	1251	541	1127	227	3572
	No	566	1011	420	931	230	3264
$AUC_{0\text{-}inf}$ (ng/mL*hr)	Yes	171	3241	1610	2968	355	8766
	No	566	2993	1660	2547	506	10264

N = number of subjects; SD = standard deviation; C_{max} = maximum concentration; $AUC_{0\text{-}inf}$ = area under the curve from zero to infinity.

Results of the logistic regression analysis did not show a statistically significant relationship between predicted $AUC_{0\text{-}inf}$ and the primary efficacy endpoint (ie, converting to NSR at any time within 2.5 hours after the start of infusion of tedisamil). However, a statistically significant relationship between C_{max} and the primary efficacy endpoint was found in both male and female subjects ($p<0.01$). Table 66 presents the p-values of the statistically significant relationships. The odds-ratio for C_{max} was 2.30 for all male and female subjects combined, suggesting that doubling the model predicted tedisamil C_{max} increased the odds of responding to tedisamil by a factor of 2.30. Female subjects appeared to have a higher oddsratio for responding to tedisamil than male subjects (ie, 2.59 versus 1.91, respectively) when the model predicted tedisamil C_{max} doubled.

Table 66. Statistically significant relationship between tedisamil exposure and conversion to normal sinus rhythm.

Exposure	Sex	N	Odds-ratio[a]	95% CI of odds-ratio	p-values
Cmax	Male	399	1.91	(1.37, 2.67)	0.0001
	Female	338	2.59	(1.35, 4.97)	0.0043
	Both	737	2.30	(1.69, 3.12)	<.0001

[a] Odds-ratio: odds-ratio for doubling the exposure. When exposure is doubled, the odds of responding to tedisamil is increased by a factor equal to the odds-ratio.
Notes: Results are based on a logistic regression with LOG2 exposure parameter as a continuous covariate.
Supporting Documentation: *Appendix 8.5.10.2.1,page 10704*

The time to conversion to NSR in responders was plotted against predicted C_{max} and $AUC_{0\text{-}inf}$ in Figure 29. Although there was a tendency for shorter time to normalization of sinus rhythm with increasing predicted C_{max}, the relationship was not found to be statistically significant.

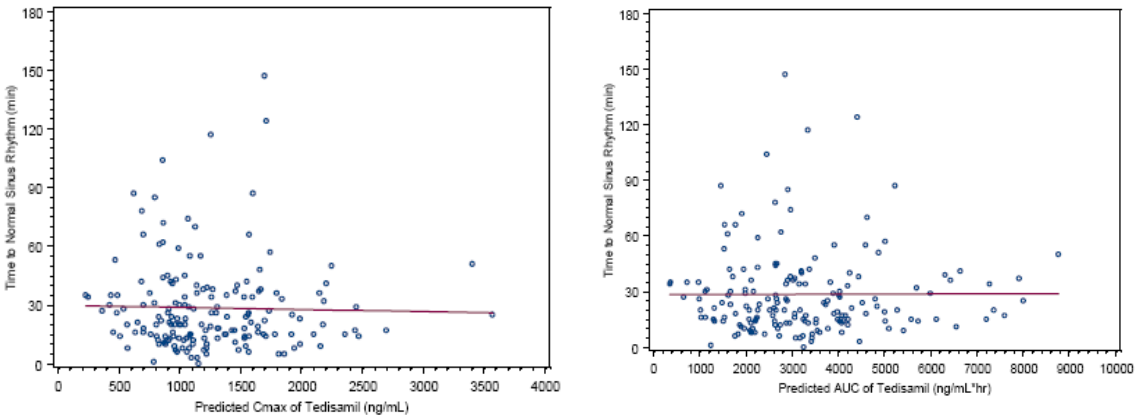


Figure 29. Time to conversion to normal sinus rhythm over predicted C_{max} (left) and $AUC_{0\text{-}inf}$ (Right) in responders.

Exposure-Safety Relationship

The relationship between model predicted systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) to tedisamil and the occurrence of any of the AEs most frequently reported by subjects randomized to receive tedisamil (ie, tachycardia [79 events, 10.7%], bradycardia [57 events, 7.7%], hypertension [56 events, 7.6%], hypotension [17 events, 2.3%], extrasystoles [92 events, 12.5%], increased GGT [15 events, 2.0%], and AV block [15 events, 2.0%]) were evaluated via logistic regression analysis.

Statistically significant relationships ($p<0.05$) between model predicted tedisamil $AUC_{0\text{-}inf}$ and the incidents of tachycardia, bradycardia, and AV block were observed. The odds-ratio for $AUC_{0\text{-}inf}$ was 1.57 for tachycardia, 1.74 for bradycardia, and 2.39 for AV block, suggesting that doubling the model predicted $AUC_{0\text{-}inf}$ increased the odds of experiencing tachycardia by a factor of 1.57, bradycardia by a factor of 1.74, and AV block by a factor of 2.39.

Statistically significant relationships between model predicted C_{max} and the incidents of extrasystoles, tachycardia, bradycardia, and AV block were also observed. The odds-ratio for C_{max} was 1.58 for extrasystoles, 2.53 for tachycardia, 1.83 for bradycardia, and 2.96 for AV block, suggesting that doubling the model predicted tedisamil C_{max} increased the odds of experiencing extrasystoles by a factor of 1.58, tachycardia by a factor of 2.53, bradycardia by a factor of 1.83, and AV block by a factor of 2.96.

No statistical significant relationship was observed between either C_{max} or $AUC_{0\text{-}inf}$ and the other two AEs (hypertension and hypotension) at $\alpha=0.05$. Table 67 presents the p-values and odds-ratios of the statistically significant relationships and Figure 30 visualizes the relationships.

Table 67. Statistically significant relationship between tedisamil exposure and adverse event.

Adverse event	Exposure	Odds-ratio[a]	95% CI of odds-ratio	p-values
Extrasystoles	Cmax	1.58	(1.09, 2.28)	0.0156
Tachycardia	AUC	1.57	(1.14, 2.15)	0.0053
	Cmax	2.53	(1.67, 3.81)	<.0001
Bradycardia	AUC	1.74	(1.20, 2.51)	0.0035
	Cmax	1.83	(1.16, 2.90)	0.0097
AV Block	AUC	2.39	(1.17, 4.89)	0.0167
	Cmax	2.96	(1.23, 7.08)	0.0151

[a] Odds-ratio: odds-ratio for doubling the exposure. When exposure is doubled the odds of experiencing the adverse event is increased by a factor equal to the value of the odds-ratio.
Notes: Results are based on a logistic regression with LOG2 exposure parameter as a continuous covariate.
Supporting Documentation: *Appendix 8.5.10.2.2, page 10705.*

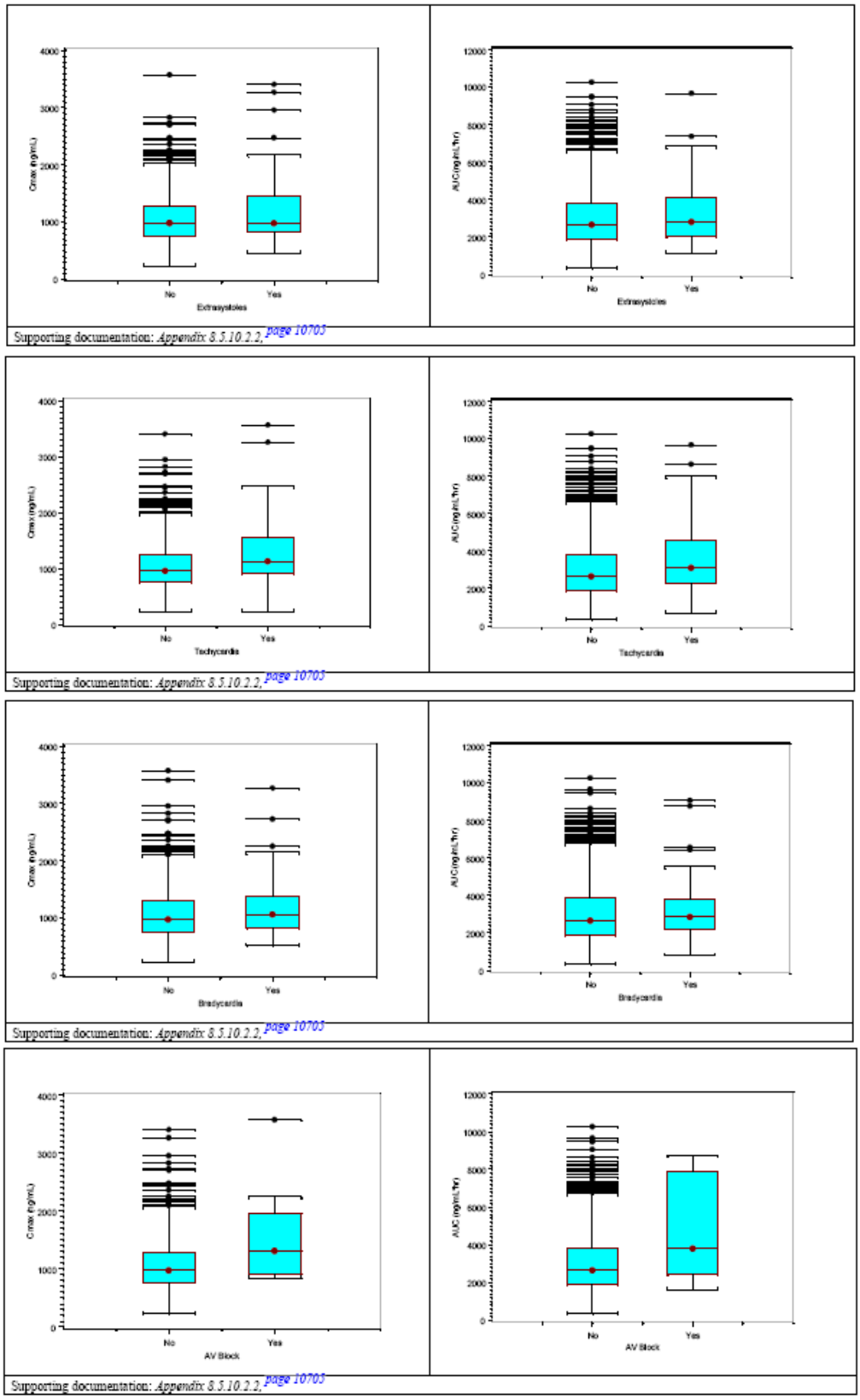


Figure 30. Relationship between Tachycardia (Top), Bradycardia (Middle), and AV block (Bottom) and model predicted pharmacokinetic parameters (C_{max} and $AUC_{0\text{-}inf}$).

Upon review of the Holter data, ten subjects (five females and five males) including two subjects who received a three-step infusion regimen of tedisamil were reported to experience Torsade de Pointes (TdP). Most of the TdP incidents occurred within 48 minutes after start of infusion except for Subject 42301 for which the incident occurred 18 hours after start of infusion. Table 68 summarizes the exposure parameter $AUC_{0\text{-}inf}$ and C_{max} of these subjects.

Table 68. Exposure parameters in subjects who experienced Torsade de Pointes.

Subject ID	Study	Dose[a] (mg/kg)	Gender	AUC0-inf[b] (ng/mL * hr)	Cmax[b] (ng/mL)
22401	S219.3.112	0.64	Male	4911	2219
23405	S219.3.112	0.48	Female	7598	2443
25414	S219.3.112	0.64	Female	3984	1643
25810	S219.3.112	0.48	Female	3587	1493
25825	S219.3.112	0.64	Male	8004	3572
41021	S219.3.114	0.32	Male	1967	884
41411	S219.3.114	0.32+0.16	Female	3025	960
41420	S219.3.114	0.48	Male	6310	1225
42301	S219.3.114	0.48+0.24	Male	5850	3003
80613	S219.3.118	0.32	Female	2259	960

Graphical observation suggested higher mean values of the model predicted Cmax and $AUC_{0\text{-}inf}$ in subjects who experienced TdP compared with those who did not experience TdP as shown in Figure 31 . However, the number of TdP events was too low (ie, 1.36% of the population analyzed) to further evaluate the exposure-response relationship of TdP cases.

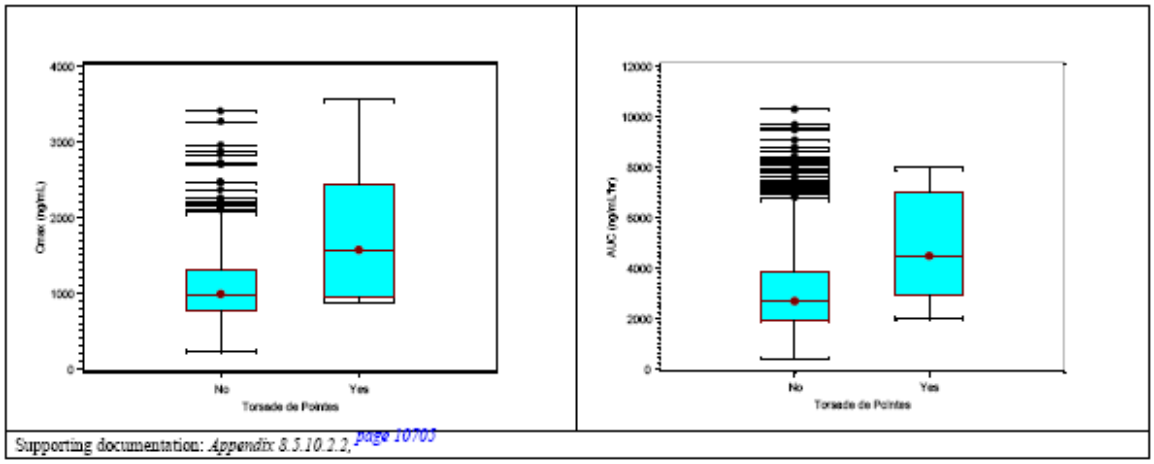


Figure 31. Relationship between Torsade de Pointes and model predicted pharmacokinetic parameters (C_{max} and $AUC_{0\text{-}inf}$).

Twelve subjects (one female and eleven males) who received tedisamil were reported to experience prolonged QT intervals. Table 69 summarizes the exposure parameter $AUC_{0\text{-}inf}$ and C_{max} of these subjects.

Table 69. Exposure parameters in subjects with prolonged QT intervals.

Subject ID	Study	Dose[a] (mg/kg)	Gender	AUC0-∞[b] (ng/mL * hr)	Cmax[b] (ng/mL)
23507	S219.3.112	0.64	Male	3986	2102
23803	S219.3.112	0.64	Male	3081	1860
23901	S219.3.112	0.48	Male	3780	1223
23904	S219.3.112	0.64	Male	1300	762
23914	S219.3.112	0.48	Male	3375	1551
24011	S219.3.112	0.48	Male	2835	1000
24013	S219.3.112	0.32	Male	2667	1568
24016	S219.3.112	0.48	Male	1542	1570
25414	S219.3.112	0.64	Female	3984	1643
42504	S219.3.114	0.48	Male	2871	1262
42510	S219.3.114	0.32	Male	3291	1042
95906	S219.3.117	0.48	Male	1870	666

Graphical observation suggested higher mean values of the model predicted C_{max} and $AUC_{0\text{-}inf}$, in subjects who experienced prolonged QT intervals compared with those who

did not experience prolonged QT intervals as shown in Figure 32. However, the number of QT prolongation events was too low (i.e., 1.63% of the population analyzed) to further evaluate the exposure-response relationship of QT prolongation cases.

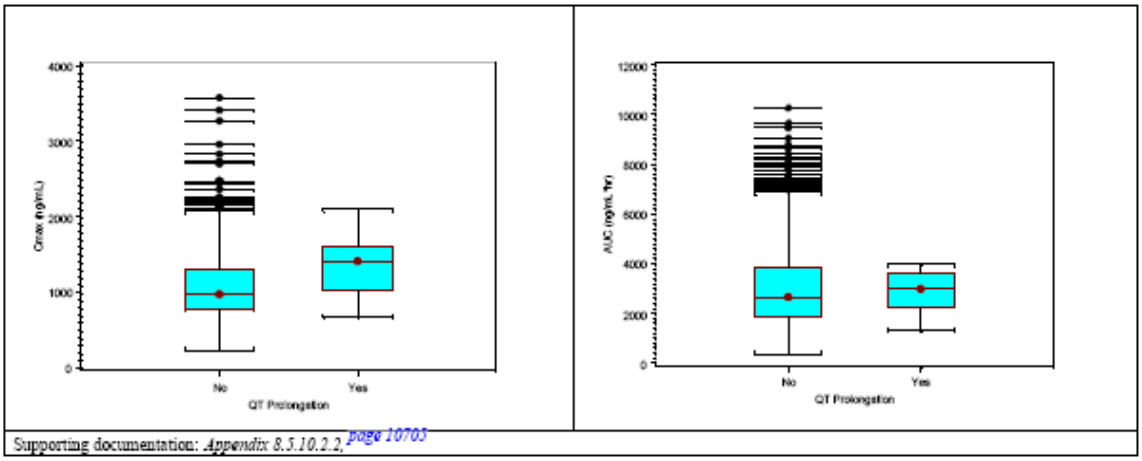


Figure 32. Relationship between QT prolongation and model predicted pharmacokinetic parameters (C_{max} and $AUC_{0\text{-}inf}$).

Sponsor's Conclusions

Pharmacokinetic Conclusions

- The population PK of tedisamil, following a two- or three-step intravenous infusion over 30 to 50 minutes at doses of 0.16 mg/kg to 0.72 mg/kg, in subjects with recent onset atrial fibrillation or flutter was adequately described by a three-compartment model.
- The population PK analysis indicated the following significant relationships:
  - Tedisamil CL decreased as CRCL decreased by a power function with an exponent power of 0.766. Tedisamil CL also decreased as BMI increased by a linear function with a slope of -0.166 (L/hr)/(kg/m^2). Co-administration of verapamil decreased tedisamil CL by 13.1%.
  - Tedisamil V_1 increased as LBM increased by a linear function with a slope of 0.145 L/kg.
  - Subjects younger than 65 years of age had 24% higher tedisamil Q_2 than those older than 65 years of age.
  - Tedisamil V_2 increased as CRCL increased by a power function with an exponent power of 0.326.
  - Co-administration of beta-blocker increased tedisamil V_2 by 12%.

- The population PK analysis indicated that the PK of tedisamil was not influenced by weight, gender, smoking status, CHF grade according to the NYHA classification, albumin level, total protein level, or co-administration of ACE-inhibitors, diuretics, vasodilators, digoxin, and substrates or inhibitors of organic anion and cation renal transporters.

Pharmacodynamic Conclusions

- The population PK/PD relationship between QTc Fredericia intervals and tedisamil concentrations was adequately described by a simple baseline maximum effect model. The population predicted values of the PD parameters were 397 msec for baseline QTc Fredericia, 24.9 msec for E_{max}, and 315 ng/mL for EC_{50}.
- The population PK/PD analysis indicated the following significant relationships:
  - Emax of QTc Fredericia increased as total tedisamil administered amount increased by a linear function with a slope of 1.03 msec/mg.
  - Baseline QTc Fredericia increased as age increased by a power function with an exponent power of 0.0577 and as potassium level decreased by a linear function with a slope of -6.77 msec/(mEq/L). Coadministration of beta-blockers or anti-arrhythmic agents class I or III decreased baseline QTc Fredericia by 1%.

- Weight, BMI, LBM, gender, smoking status, CRCL, CHF grade according to the NYHA classification, type of arrhythmia, whether the episode lasted $\leq$ 48 hrs or more, whether or not conversion to NSR occurred within 2.5 hrs after initiation of the infusion of study drug, whether it was a recurrent episode or first episode, or coadministration of digoxin or verapamil were not found to be statistically significant covariates on the PD of tedisamil.

Exposure-Response Conclusions

- The exploratory analysis indicated the odds of responding to tedisamil increased by a factor of 2.30 for each two-fold increase in the value of C_{max}. While doubling the model predicted tedisamil $AUC_{0\text{-}inf}$ was not found to increase the odds of responding to tedisamil. No statistically significant relationship was observed between the model predicted tedisamil C_{max} or $AUC_{0\text{-}inf}$ and the time to conversion to NSR.
- The exploratory analysis indicated the odds of experiencing extrasystoles, tachycardia, bradycardia, and AV block increased by a factor of 1.58, 2.53, 1.83, and 2.96, respectively, for each two-fold increase in the C_{max} value. The odds of experiencing tachycardia, bradycardia, and AV block increased by a factor of 1.57, 1.74, and 2.39, respectively, for each two-fold increase in the $AUC_{0\text{-}inf}$ value. No statistically significant relationship was observed between the model predicted tedisamil exposure (C_{max} or $AUC_{0\text{-}inf}$) and the incidents of hypertension and hypotension.
- Graphical evaluation of the relationship between the model predicted tedisamil exposure and incidents of TdP suggested a higher mean value of the model predicted tedisamil C_{max} or $AUC_{0\text{-}inf}$ in subjects who experienced TdP. Higher mean value of the model predicted C_{max} and slightly higher mean value of the model predicted $AUC_{0\text{-}inf}$ was also observed in subjects who experienced QT prolongation.

Reviewer's Comments on Sponsor's Analysis

- Population PK/PD analysis comments:
  - Sponsor performed a very comprehensive PK/PD data analysis using data from all phase III studies. The approach was to divide the PK/PD data into an index data set used for building the PK/PD model and a validation data set to check the predictive performance of the model. However, the sponsor did not pool all the data into a combined data set for final analysis thereby not utilizing all the data to derive the final PK/PD parameter estimates.
  - Selection of demographic covariate effects on PK/PD parameters was purely driven by statistical principles and testing without considering the physiological understanding of the system. The identified significant covariate effects on PK/PD are therefore questionable.
  - Creatinine Clearance was found to be a covariate for tedisamil clearance but no dose adjustment was suggested for renal impairment in the proposed label. It is unclear to what extent renal impairment influences the C_{max} and/or AUC.
  - No gender effect was identified to influence the PK of tedisamil, i.e. the same dose of e.g. 0.32 mg/kg would result in the same exposure in females and males. The proposed tedisamil dose of 0.32 and 0.48 mg/kg for females and males, respectively, do not appear to be derived by differences in the PK.
  - Neither did the sponsor find any gender specific parameters in the tedisamil concentration-QTcF analysis.
  - The predicted power of the PK/PD model when trying to predict the parameters in the validation data was not overwhelming (not shown) and the goodness-of-fit graphs indicate some model misspecifications, i.e. both the PK model and the E_{max} PK/PD model seem to underpredict the observed PK and QT effects of tedisamil, respectively (see Figure 26 and Figure 28).

- Exposure-Response for Efficacy comments:
  - Exposure-response analysis using logistic regression showed a statistically significant relationship between C_{max} and the primary efficacy endpoint (i.e. subjects with atrial fibrillation who converted to NSR for at least 60 seconds within 2.5 hours of the start of study drug infusion) in both male and female subjects. Female subjects appeared to have a higher odds-ratio for responding to tedisamil than male subjects (i.e. 2.59 versus 1.91, respectively). It is however difficult to determine whether different dosing regimens between males and females are warranted by different odds-ratios due to the fact that males and females had different intercept estimates. Furthermore, a discrepancy in responder status was found for 17 patients in the poppkpd.xpt file compared to the reported results in the individual study reports.
  - The sponsor did not investigate/address differences in the exposure-response relationship between subjects with a duration ≤48 and >48 hours

of their most recent atrial fibrillation episode since tedisamil appears less effective in the latter group of patients. Furthermore, no analysis was performed investigating differences between patients with atrial fibrillation and atrial flutter.

- The sponsor concluded that there appeared to be a correlation between time to conversion and C_{max} but it was not statistical significant. It is unknown whether the sponsor used parametric hazard modeling thereby corrected for underlying covariates such as duration of their most recent onset of atrial fibrillation/flutter when testing the statistical significance between time to conversion and tedisamil exposure.

- Exposure-Response for Safety comments:
  - Sponsor concluded that the odds of experiencing extrasystoles, tachycardia, bradycardia, and AV block increased with increasing tedisamil exposure. Graphical evaluation of the relationship between tedisamil exposure and incidents of TdP and QT prolongation suggested a higher mean value of tedisamil exposure in subjects who experienced TdP and QT prolongation. Sponsor did not investigate gender differences in the exposure-safety analyses. Again, it is difficult to determine whether a different dosing regimen for males and females is justified based on safety findings and odds-ratios.

The identified deficiencies in sponsor's analysis are addressed in the reviewer's analysis.

Reviewer's Analysis

The data, studies, and methods described in Sponsor's analysis in Sections 0-0 are identical to those used for the reviewer's analysis.

Population PK Analysis

Base Model

One-, two-, and three-compartment PK models were tested and similar to the sponsor, a three-compartment model was found to best describe the observed tedisamil concentration-time profiles. Unlike the sponsor, an additive residual error model on the log scale corresponding to a proportional residual error model on the normal scale was found to be most appropriate to obtain homogeneity of the residual error variance.

The PK parameter estimates for the reviewer's base tedisamil PK model using all available data are shown in Table 70.

Table 70 Reviewer's Base PK Model Parameter Estimates.

		Population parameters		Inter-individual variability	
Parameter	**Unit**	**Estimate**	**%RSE**	**Estimate (CV%)**	**%RSE**
CL	[L/hr]	9.83	1.64	41.6	6.36
Q_1	[L/hr]	42.9	4.18	-	-
Q_2	[L/hr]	3.88	6.29	-	-
V_1	[L]	8.29	4.23	67.2	5.08
V_2	[L]	31.7	2.45	48.2	7.50
V_3	[L]	37.7	3.77	-	-
Proportional residual error	[-]	28.4	3.14	-	-

Covariate Model

PK parameter-covariate relationships for the base PK model are shown in Figure 47 - Figure 49. The three PK parameters with inter-individual variability (CL, V_1, and V_2) are discussed in the following.

Tedisamil Clearance

Creatinine clearance was identified as the most significant covariate for tedisamil clearance (see Figure 33). After correcting for creatinine clearance, the inter-individual variability in clearance was no longer correlated with body weight or age since the Cockcroft-Gault formula for calculating creatinine clearance already includes both age body weight, i.e.

$$CRCL = \frac{(140 - Age) \cdot Weight}{72 \cdot Serum\ Creatinine} (\cdot 0.85\ \ for\ \ female)$$

Body weight and age are therefore indirectly covariates for tedisamil clearance even though it does not appear directly in the final PK model.

Co-administration of beta-blockers (447 out of 1169 patients), verapamil (71 out of 1169 patients) and ACE inhibitors (398 out of 1169 patients) were found to statistically significant covariates for tedisamil clearance (see Figure 47) but all with less than 10% reduction in clearance.

Since tedisamil is a known substrate for PgP, co-administration of verapamil (a known PgP inhibitor) was used in the final model as a covariate for tedisamil clearance (see Figure 33).

Tedisamil volume of distribution

Body weight was found to be a covariate for the central and peripheral volume of distribution (see Figure 33).

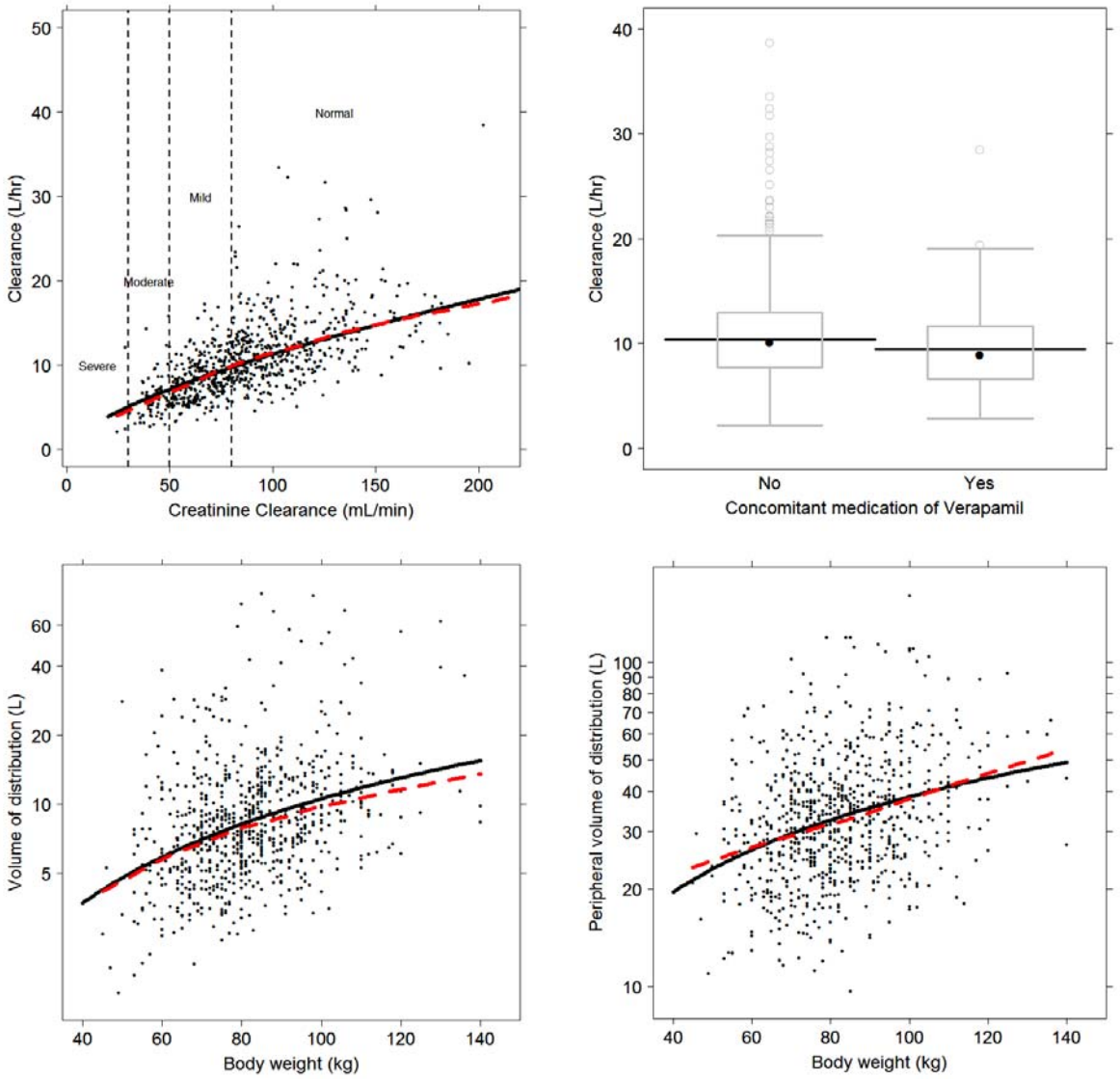


Figure 33 Identified covariate-PK parameter relationships. (Top Left) Creatinine clearance influence on tedisamil clearance, (Top Right) Co-administration of verapamil influence on tedisamil clearance, (Bottom Left) Body weight influence on central volume of distribution, and (Bottom Right) Body weight influence on peripheral volume of distribution. The solid black lines are the model predictions and the dotted red lines are the smoothing local regression.

Final PK Model

The PK parameter estimates for the reviewer's final tedisamil PK model using all available data are shown in Table 71 and the goodness-of-fit graphs are shown in Figure 50-Figure 54.

Table 71 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]	10.3	1.546	32.1	6.66
Q_1	[L/hr]	42.9	1.38	*	-
Q_2	[L/hr]	3.67	6.89	*	-
V_1	[L]	8.20	3.12	63.9	10.0
V_2	[L]	32.6	2.99	46.0	7.5
V_3	[L]	37.7	4.14	*	-
Inter-individual off-diagonal covariance					
CL-V_1				0.122	10.8
CL-V_2				0.103	7.82
V_1-V_2				0.152	12.5
Covariate-relationships					
CL-CrCL exponent	[-]	0.659	9.03	*	-
V_1-WT exponent	[-]	1.14	39.3	*	-
V_2-WT exponent	[-]	0.738	16.8	*	-
Verapamil CL reduction	[%]	-4.6	3.51	*	-
Intra-Individual Variability					
Proportional error	[%]	28.3	3.21	-	-

*Not estimated

PK Simulations

The population mean predicted tedisamil concentration-time profiles for a typical 80 kg subject receiving different tedisamil doses are illustrated in Figure 34 and the population mean predicted maximum plasma concentration and AUC are shown in Table 72.

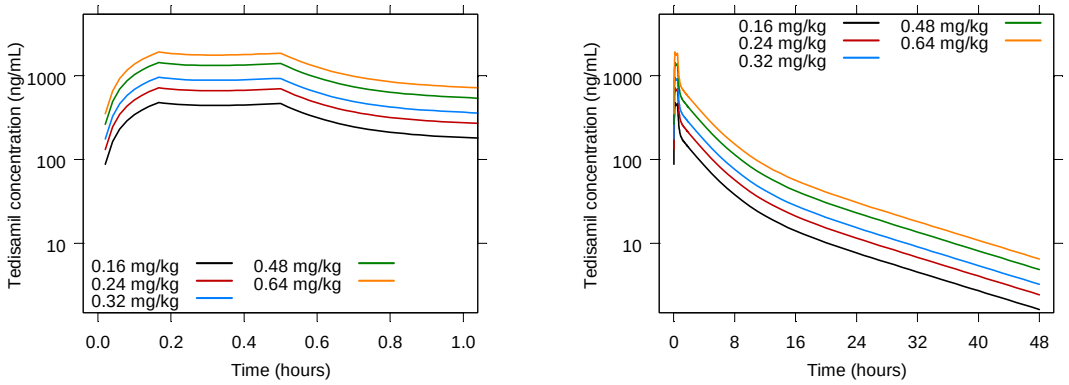


Figure 34 Population mean predicted tedisamil concentration-time profiles. (Left) Tedisamil concentration-time profiles between 0-1 hour (Left) and 0-48 hours (Right) after start of infusion for a typical 80 kg subject receiving 0.16 (black), 0.24 (red), 0.32 (blue), 0.48 (green), and 0.64 mg/kg (orange) dose.

Table 72 Population mean predicted C_{max} and AUC for a typical 80 kg patient with CrCL=87 mL/min.

Tedisamil dose	Population Mean Predicted C_{max} (ng/mL)	Population Mean Predicted AUC_{0-48} (ng*hr/mL)
0.16 mg/kg	479	1289
0.24 mg/kg	718	1933
0.32 mg/kg*	957	2578
0.48 mg/kg**	1436	3867
0.64 mg/kg	1914	5156

*Proposed female dose
**Proposed male dose

Similar C_{max} and AUC between males and females given the same dose are predicted since no gender differences were identified in the covariate PK analysis.

Effect of Body Mass Index on Cmax

The sponsor's proposed tedisamil dosing regimen is based on body weight for patients with BMI<28 kg/m^2. For patients with BMI>28 kg/m^2, the dose is based on an imputed weight (=28 kg/m^2 * height^2 m^2) corresponding to lean body mass.

Figure 35 shows that the proposed dosing regimen seems adequate since C_{max} appear to be within the same range (250-3000 ng/mL) for patients with BMI above and below 28 kg/m^2.

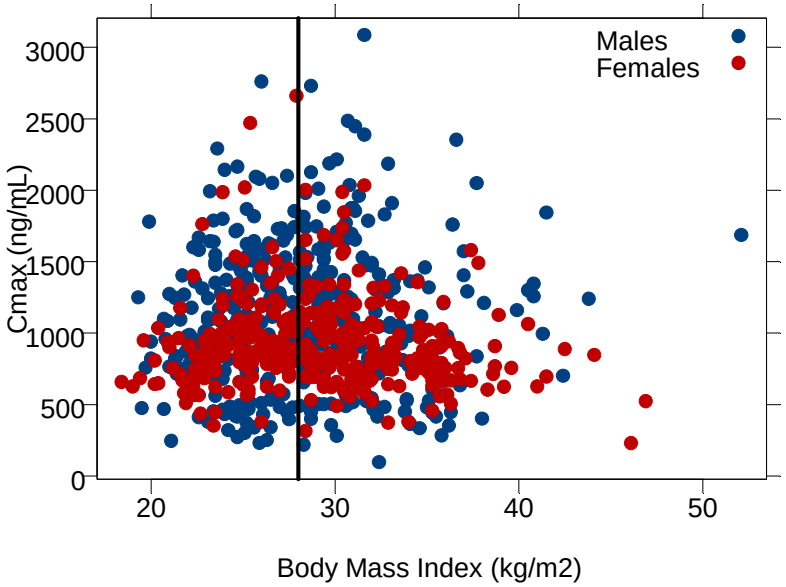


Figure 35. Model predicted C_{max} vs. BMI (vertical black line is BMI=28 kg/m2).

Effect of Renal Impairment

The tedisamil concentration-time profile for different degrees of renal impairment is shown in Figure 36 for a typical 80 kg subject receiving 0.32 (top) and 0.48 (bottom) mg/kg dose. It is seen that the impact of renal impairment is on the area under the concentration-time curve (AUC) and not the peak tedisamil concentration (C_{max}). It therefore seems reasonable not to suggest a dose adjustment for renal impairment since C_{max} is the exposure variable most related to both efficacy and safety as shown in sponsor's analysis.

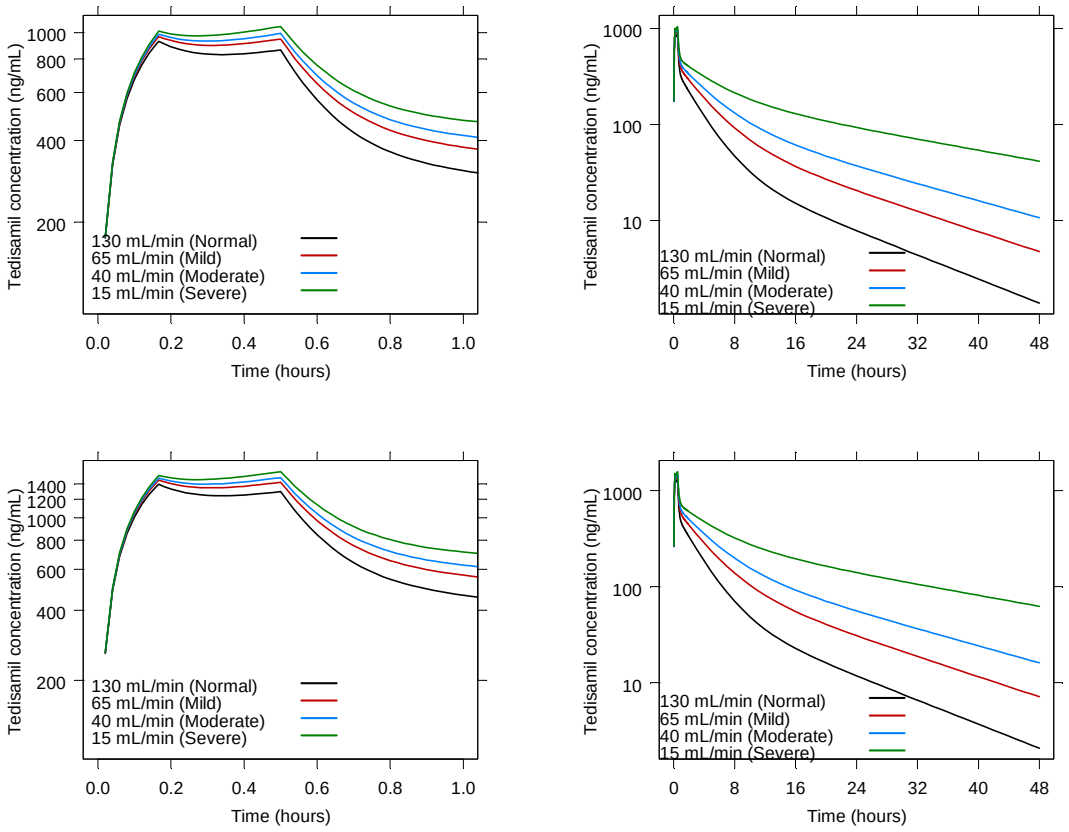


Figure 36 Effect of renal impairment on tedisamil concentrations. (Left) Tedisamil concentration-time profiles between 0-1 hour (Left) and 0-48 hours (Right) after start of infusion for a typical 80 kg subject receiving 0.32 (top) and 0.48 (bottom) mg/kg dose. Normal (black), mild (red), moderate (blue), and severe (green) renal impairment.

The corresponding population predicted C_{max} and AUCs are shown in Table 73. It is noticed that renal impairment has a substantial influence on AUC but not on C_{max}.

Table 73 Population mean predicted C_{max} and AUC for a typical 80 kg patient with CrCL=130 (Normal), 65 (Mild), 40 (Moderate), and 15 (Severe) mL/min receiving 0.32 mg/kg or 0.48 mg/kg tedisamil dose.

Tedisamil dose	CrCL	Population Mean C_{max} (ng/mL)	Population Mean AUC_{0-48} (ng*hr/mL)
0.32 mg/kg	130 (Normal)	929	1894
	65 (Mild)	967	2938
	40 (Moderate)	986	3942
	15 (Severe)	1011	6654
0.48 mg/kg	130 (Normal)	1393	2841
	65 (Mild)	1451	4407
	40 (Moderate)	1479	5913
	15 (Severe)	1516	9981

Concentration-QTcF Analysis

QT Corrections

The different QTc correction methods vs. RR are shown in Figure 37. The Fridericia correction (QTcF) appears to undercorrect for the heart rate effect while the Bazett correction method (QTcB) overcorrects. However, QTcF was found to be the best correction method for the concentration-QT analysis.

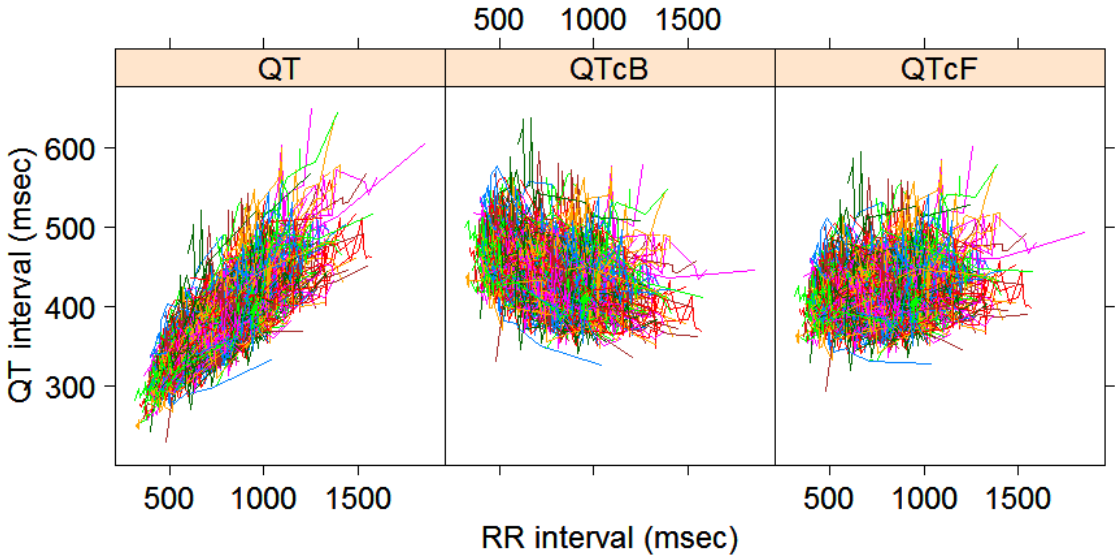


Figure 37 Relationship between QT, QTcB, and QTcF and RR interval. Each line represents data from one patient.

Base Concentration-QTcF Model

The mean QTcF change from baseline (ΔQTcF) over time for different tedisamil dose groups are shown in Figure 39 with a mean ΔQTcF of 30 and 50 msec for 0.32 and 0.48 mg/kg at t_{max}=30 minutes.

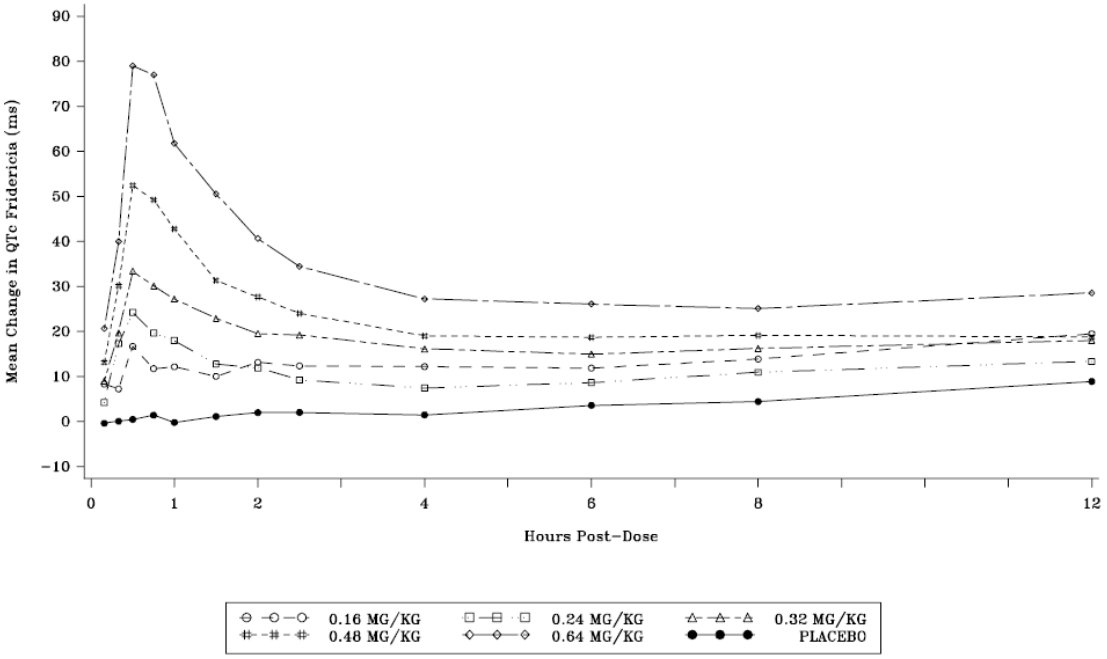


Figure 38 Mean change from baseline in QTcF (source Figure 2.7.4.4-3 in sponsor's submission).

Subjects who had converted to normal sinus rhythm would be expected to have a marked heart rate slowing. Therefore, the concentration-QTcF analysis was performed only on measurements before conversion to normal sinus rhythm. However, the analysis is still confounded by the fact that all patients at baseline were in atrial fibrillation/flutter in whom QT measurements are difficult to substantiate.

Linear, log-linear, and E_{max} models were initially tested with the linear model fitting the data best.

The parameter estimates from the concentration-QTcF analysis can be found in Table 74.

Table 74 Reviewer's Base Concentration-QTcF Linear Model Parameter Estimates.

		Population parameters		Inter-individual variability
Parameter	**Unit**	**Estimate**	**RSE (%)**	**SD**
Intercept	[msec]	7.43	9.03	13.6
Slope	[msec/(µg/mL)]	23.9	3.69	16.7
Residual error (SD)	[msec]	17.4	2.25	-

Covariate Concentration-QTcF Model

Baseline QTcF was identified as a significant covariate on intercept and slope while sex was a significant covariate for intercept (see Figure 39).

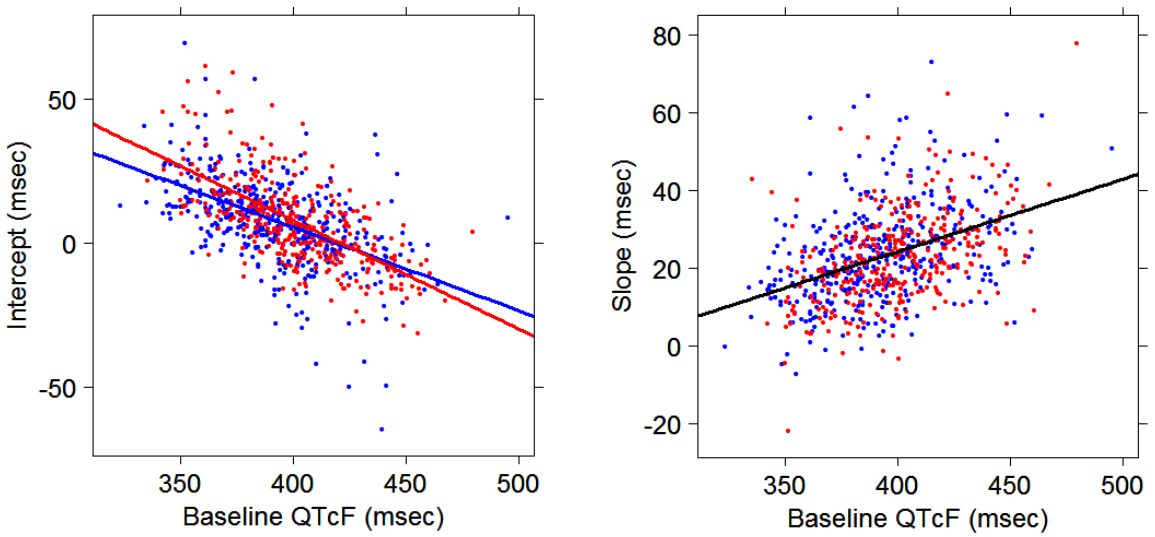


Figure 39 Relationship between (left) intercept and baseline QTcF, and (Right) slope and baseline QTcF. The solid lines (red=female, blue=male, black=combined) represent the population estimates and the dots (red=female, blue=male) are the individual estimates.

Final Concentration-QTcF Model

The parameter estimates from the final concentration-QTcF analysis are shown in Table 75 and the goodness-of-fit graphs are shown in Figure 40.

Table 75 Reviewer's Final Concentration-QTcF Linear Model Parameter Estimates.

		Population parameters		Inter-individual variability
Parameter	**Unit**	**Estimate**	**RSE (%)**	**SD**
Intercept male	[msec]	6.67	13.1	
Additional female intercept	[msec]	2.73	44.3	13.7
Base QTcF-Intercept (Centered around mean 396 msec)	[-]	-0.289	12.4	-
Concentration-Slope	[msec/µg/mL]	23.5	3.64	15.9
Base QTcF-Slope (Centered around mean 396 msec)	[1/µg/mL]	0.187	18.5	-
Residual error (SD)	[msec]	17.4	-	-

The population mean predicted ΔQTcF at mean C_{max} of 954 and 1317 ng/mL is 32 and 38 msec for females and males receiving 0.32 and 0.48 mg/kg, respectively (see Figure 40).

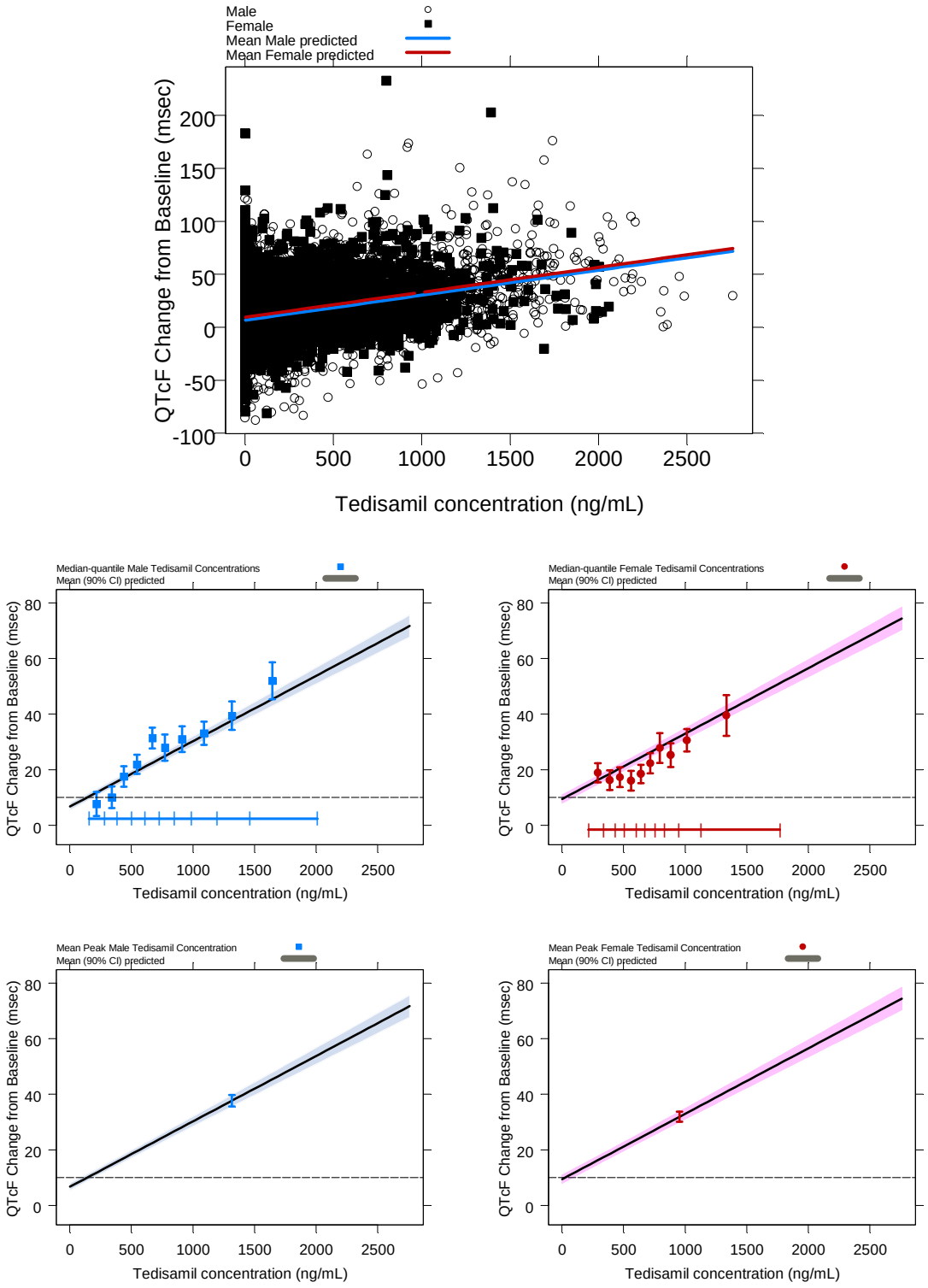


Figure 40. **(Top)** ΔQTcF (Change from Baseline) vs. tedisamil concentrations. **(Middle)** Median-quantile tedisamil concentrations and associated 90% CI together with the population predictions with 90% confidence interval. The horizontal bars show the quantile range for males (blue) and females (red). **(Bottom)** Population predictions and associated 90% CI at mean male (blue) and female (red) peak tedisamil concentrations.

The population mean predicted QT prolongation-time profiles for a typical 80 kg subject with CrCL=87 mL/min receiving different 0.32 and 0.48 mg/kg tedisamil doses are illustrated in Figure 41.

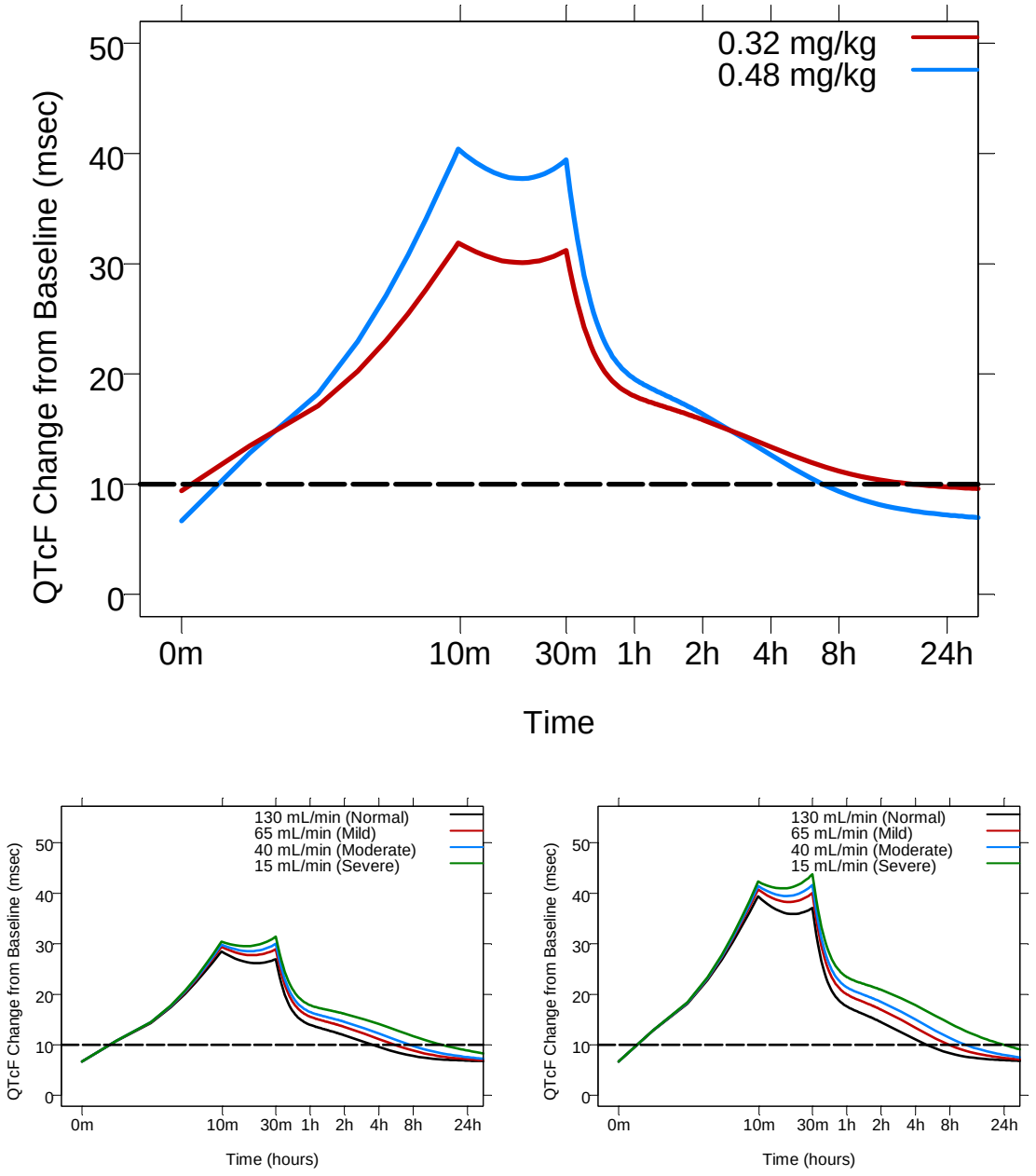


Figure 41. Population mean predicted QT prolongation-time profiles **(Top)** for a typical 80 kg subject and CrCL=87 mL/min receiving 0.32 (female, red), 0.48 (male, blue) dose, **(Bottom)** for typical patients with different degrees of renal impairment receiving **(Left)** 0.32 (female) and **(Right)** 0.48 (male) mg/kg.

It takes approx. 8 hours before the typical patient's QTcF is back to normal after having received a tedisamil dose of 0.32 and 0.48 mg/kg, respectively.

Exposure-Response Analysis

The exposure-response analysis was performed using the individual predicted C_{max} concentration and AUC as the exposure parameter and the response was conversion to normal sinus rhythm at 2.5 hr after start of the tedisamil infusion.

The probability of having conversion to normal sinus rhythm was modeled using a logistic regression model of the general form

$$\text{logit}(\Pr(Conv \le 2.5hr)) = \alpha_{Intercept} + \beta_0 \cdot Cov + \beta_1 \cdot Exposure$$

where Exposure is C_{max} or $AUC_{0\text{-}2.5}$ centered around the median value and Cov is any potential covariate.

C_{max} was found to be better exposure parameter than $AUC_{0\text{-}2.5}$ for the exposure-response analysis. The exposure-response analysis parameter estimates are shown in Table 76 and visualized in Figure 42.

The tedisamil C_{max} was the most significant covariate followed by the duration of the most recent episode (≤48 hr or >48 hr), the diagnosis (Atrial fibrillation or flutter), and last gender (male or female). Based on the exposure-response results, females should have gotten a higher dose to obtain similar efficacy to males.

Table 76 Reviewer's Exposure-Response (Conversion to normal sinus rhythm at 2.5 hr) Logistic Response Parameter Estimates.

Parameter	Covariate	Estimate	RSE (%)	P-value	Odds Ratio (95% CI)
$\alpha_{Intercept}$	Median C_{max} (950 ng/mL), Duration>48hr, Atrial Flutter, and Female	-3.44	10.1	<0.0001	-
β_{Cmax}	$\frac{C_{max} - \overline{C}_{max}}{1000}$	1.48	10.1	<0.0001	4.4 (3.3-5.9)
$\beta_{Duration}$	Duration ≤48hr	1.68	10.7	<0.0001	5.4 (3.8-7.6)
$\beta_{Diagnosis}$	Atrial Fibrillation	1.17	27.3	0.0003	3.2 (1.7-6.0)
β_{Gender}	Male	0.413	42.9	0.0201	1.5 (1.1-2.1)

The odds of responding to tedisamil (conversion to normal sinus rhythm within 2.5 hrs) increased by a factor of 4.4 with a doubling of the mean observed exposure (C_{max}) from 1000 to 2000 ng/mL. The conversion to normal sinus rhythm increases by a factor 5 for patients with their most recent episode of Afib/Aflut less than 48 hours before tedisamil dosing compared to > 48 hrs. Atrial fibrillation patients had an odds ratio of 3.2 compared to atrial flutter patients and males were found 1.5 more likely to convert compared to females.

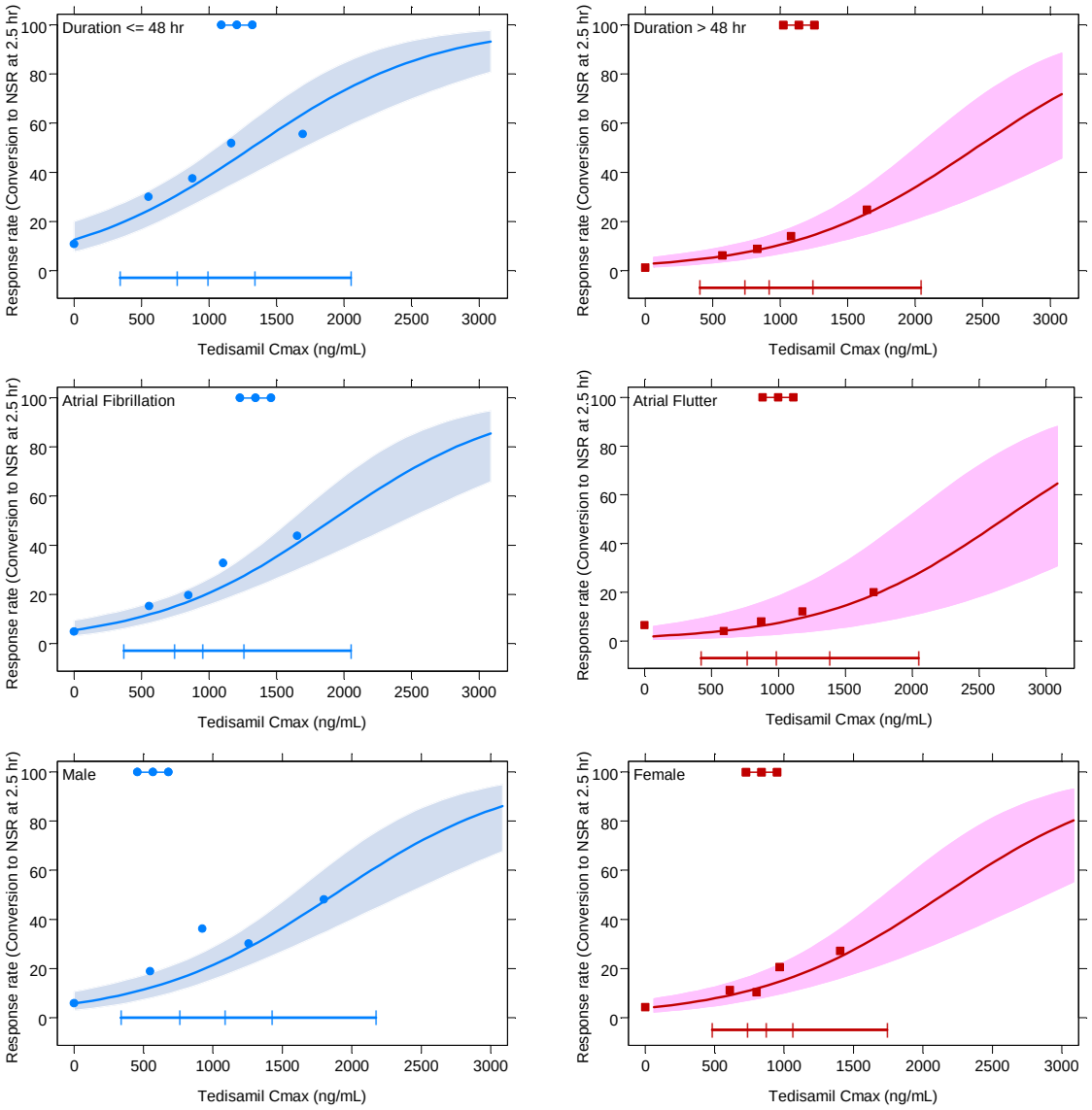


Figure 42. Exposure-response relationship for **(Top)** Duration of most recent Afib/Aflut episode (duration ≤ 48 hrs (left) and > 48 hrs (right)), **(Middle)** Diagnosis (Afib (left) and Aflut (right)), and **(Bottom)** Gender (males (left) and females (right)). The solid colored lines are the predicted response rates and the associated 95% CI is shown as a shaded colored area. The dots represent the mid-quartile tedisamil 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.

Duration of the most recent atrial fibrillation episode (<48 or >48 hr) was found to be the most important demographic covariate for response. A total of 631 (Active:Placebo N=434:197) out of 1006 atrial fibrillation patients had information about how many hours since the start of their most recent atrial fibrillation episode.

As seen in Figure 43, patients with most recent Afib episode <8 hours from the tedisamil dose had a tedisamil response rate of 60% (placebo response of 20%) whereas the tedisamil response rate in patients with >8 hours duration was around 20% (placebo response 2-6%).

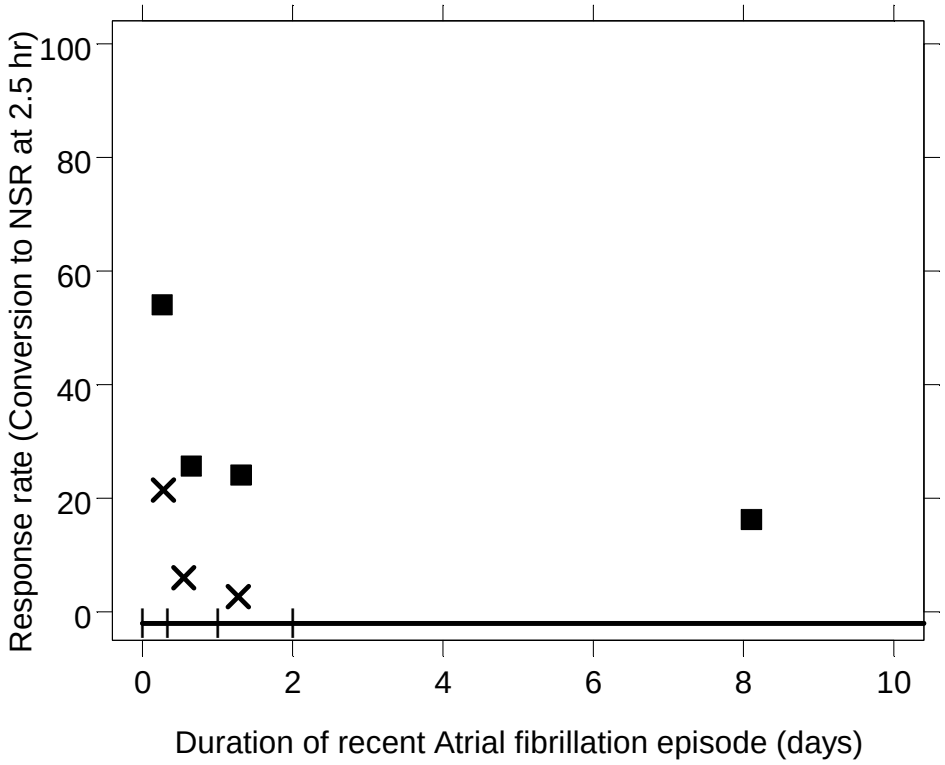


Figure 43. Response rate vs. duration of most recent Afib episode at the median duration of most recent Afib episode within each bin, i.e. 0-8 hr (Active:Placebo N=37:14), 8-24 hr (Active:Placebo N=113:56), 24-48 hr (Active:Placebo N=102:41), and 48 hr-45 days (Active:Placebo N=182:0). Solid squares (tedisamil) and cross (placebo).

Exposure-Safety Analysis

The probability of tachycardia [79 events, 10.7%], bradycardia [57 events, 7.7%], extrasystoles [92 events, 12.5%], AV block [15 events, 2.0%], hypertension [56 events, 7.6%], prolonged QT [13 events, 1.8%], and Torsade de Pointes [10 events, 1.4%] was found to be correlated with tedisamil peak concentration (see Table 77 and Figure 44 and Figure 55 for gender goodness-of-fit plots).

Table 77 Reviewer's Exposure-Safety (Tachycardia, Bradycardia, Extrasystoles, AV Block, Hypertension, Prolonged QT, and Torsade de Pointes) Logistic Response Parameter Estimates.

AE	Parameter	Covariate	Estimate	RSE (%)	P-value	Odds Ratio (95% CI)
Tachycardia	$\alpha_{Intercept}$	Median C_{max} (950 ng/mL) and female	-2.74	8.27	<0.0001	-
	β_{Cmax}	$\frac{C_{max}-\overline{C}_{max}}{\overline{C}_{max}}$	0.92	27.8	0.0003	2.5 (1.5-4.1)
	β_{Gender}	Male	0.75	36.7	0.0066	2.1 (1.2-3.6)
Bradycardia	$\alpha_{Intercept}$	Median C_{max} (950 ng/mL)	-2.58	5.80	<0.0001	-
	β_{Cmax}	$\frac{C_{max}-\overline{C}_{max}}{\overline{C}_{max}}$	0.73	40.0	0.0124	2.1 (1.2-3.6)
Extrasystoles	$\alpha_{Intercept}$	Median C_{max} (950 ng/mL)	-2.03	5.84	<0.0001	-
	β_{Cmax}	$\frac{C_{max}-\overline{C}_{max}}{\overline{C}_{max}}$	0.67	35.8	0.0053	2.0 (1.2-3.1)
AV block	$\alpha_{Intercept}$	Median C_{max} (950 ng/mL)	-4.18	7.68	<0.0001	-
	β_{Cmax}	$\frac{C_{max}-\overline{C}_{max}}{\overline{C}_{max}}$	1.40	34.1	0.0033	4.1 (1.6-10.4)
Hypertension	$\alpha_{Intercept}$	Median C_{max} (950 ng/mL)	-2.59	5.79	<0.0001	-
	β_{Cmax}	$\frac{C_{max}-\overline{C}_{max}}{\overline{C}_{max}}$	0.67	43.9	0.0227	2.0 (1.1-3.5)
Prolonged QT	$\alpha_{Intercept}$	Median C_{max} (950 ng/mL)	-4.35	7.98	<0.0001	-
	β_{Cmax}	$\frac{C_{max}-\overline{C}_{max}}{\overline{C}_{max}}$	1.24	43.6	0.0220	3.4 (1.2-9.9)
Torsade de Pointes	$\alpha_{Intercept}$	Median C_{max} (950 ng/mL)	-4.98	9.23	<0.0001	-
	β_{Cmax}	$\frac{C_{max}-\overline{C}_{max}}{\overline{C}_{max}}$	2.15	25.4	<0.0001	8.6 (2.9-25.2)

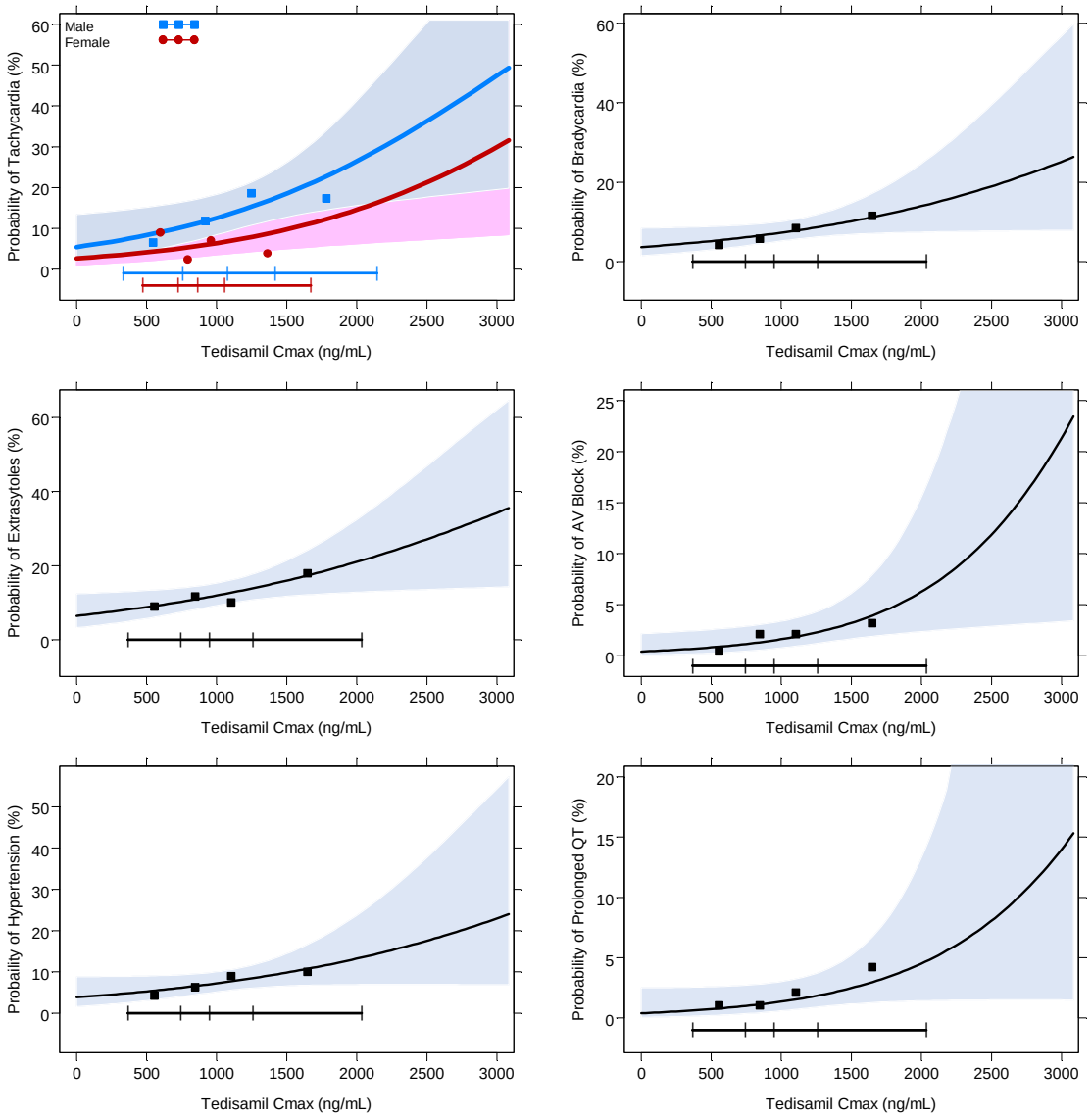


Figure 44. Exposure-safety analysis. Relationship between tedisamil peak concentration and tachycardia (top left), bradycardia (top right), extrasytoles (left 2. row), and AV block (right 2. row), hypertension (left 3. row), and prolonged QT (right 3. row).

The probability of torsade de pointes was also found to be related to tedisamil C_{max} and ΔQTcF (change from baseline) at time of maximum concentration.

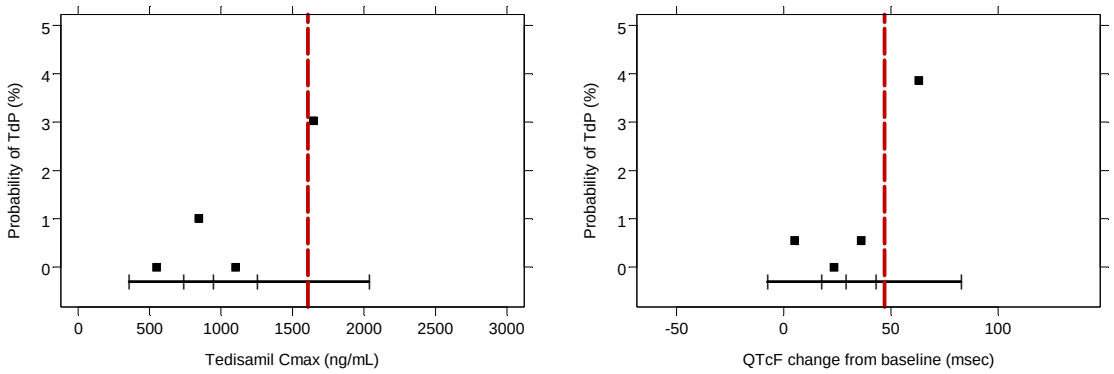


Figure 45. Relationship between probability of Torsade de Pointes and tedisamil C_{max} (left) and QTcF change from baseline at C_{max} (right).

Classification and regression tree (CART) analysis was performed in S-PLUS to estimate a break point in tedisamil C_{max} and ΔQTcF which maximally distinguishes the risk of TdP in two groups. The risk of torsade de points increases from 0.5 to 18% for female and 1 to 3% for male patients with C_{max}>1607 ng/mL compared to patients with C_{max}<1607 ng/mL. Similarly for ΔQTcF, the risk of TdP increases from 0.4 to 6% for females and 1 to 3% for males with ΔQTcF > 47 msec compared to patients with ΔQTcF <47 msec (see Figure 46).

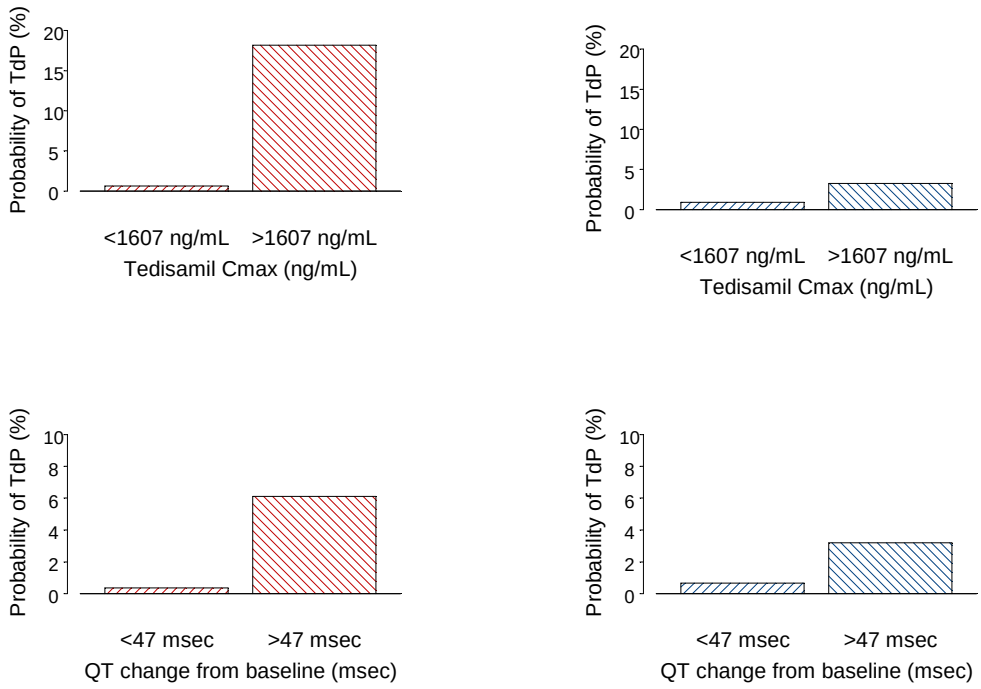


Figure 46. Probability of Torsade de Pointes for females (left) and males (right) with Cmax above and below 1607 ng/mL (top) and ΔQTcF above and below 47 msec.

Pharmacometric Review Conclusions

The overall conclusions for the Pharmacometric review are:

Pharmacokinetic Conclusions

- A three-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed tedisamil concentrations following a two-step IV infusion over 30 minutes of 0.16 mg/kg to 0.72 mg/kg in patients with atrial fibrillation or flutter.
- Creatinine clearance was found to be a significant covariate for tedisamil clearance with a 10% and 350% higher C_{max} and AUC, respectively, in patients with severe renal impairment compared to patients with normal renal function.
- Body weight was identified as a significant covariate for tedisamil volume of distribution.
- Gender was not found to influence tedisamil PK.
- No significant drug-drug interactions were found in the population PK analysis of IV administered tedisamil.

QT analysis Conclusions

- The population PK/PD relationship between QTcF and tedisamil concentrations was adequately described by a linear model.
- Tedisamil was found to increase the QTcF change from baseline with a mean predicted change from baseline QT of 32 and 38 msec at the mean observed female and male tedisamil C_{max} of 954 and 1317 ng/mL, respectively.
- The QTcF is predicted to return to normal 8 hours after drug administration.

Exposure-Response Conclusions

- The exposure-response analysis indicated that the probability of converting to normal sinus rhythm within 2.5 hours after start of the tedisamil infusion is correlated with tedisamil C_{max}.
- Patients with their most recent onset of Afib episode less than 8 hours from tedisamil dosing had significant higher response rates (60%) compared to patients with duration of the most recent episode >8 hours (20%).
- Patients with Atrial fibrillation have higher response rates compared to Atrial flutter patients at similar tedisamil exposure.
- Male patients have higher response rates compared to females at similar tedisamil exposure.

Exposure-Safety Conclusions

- The probability of developing tachycardia, bradycardia, extrasystoles, AV block, hypertension, prolonged QT, and Torsade de Pointes was found to increase with increasing tedisamil peak concentration. Females were not found to be more likely to develop TdP compared to males at similar tedisamil exposure.

Appendices

Covariate-PK Parameter Relationships for Base PK Model

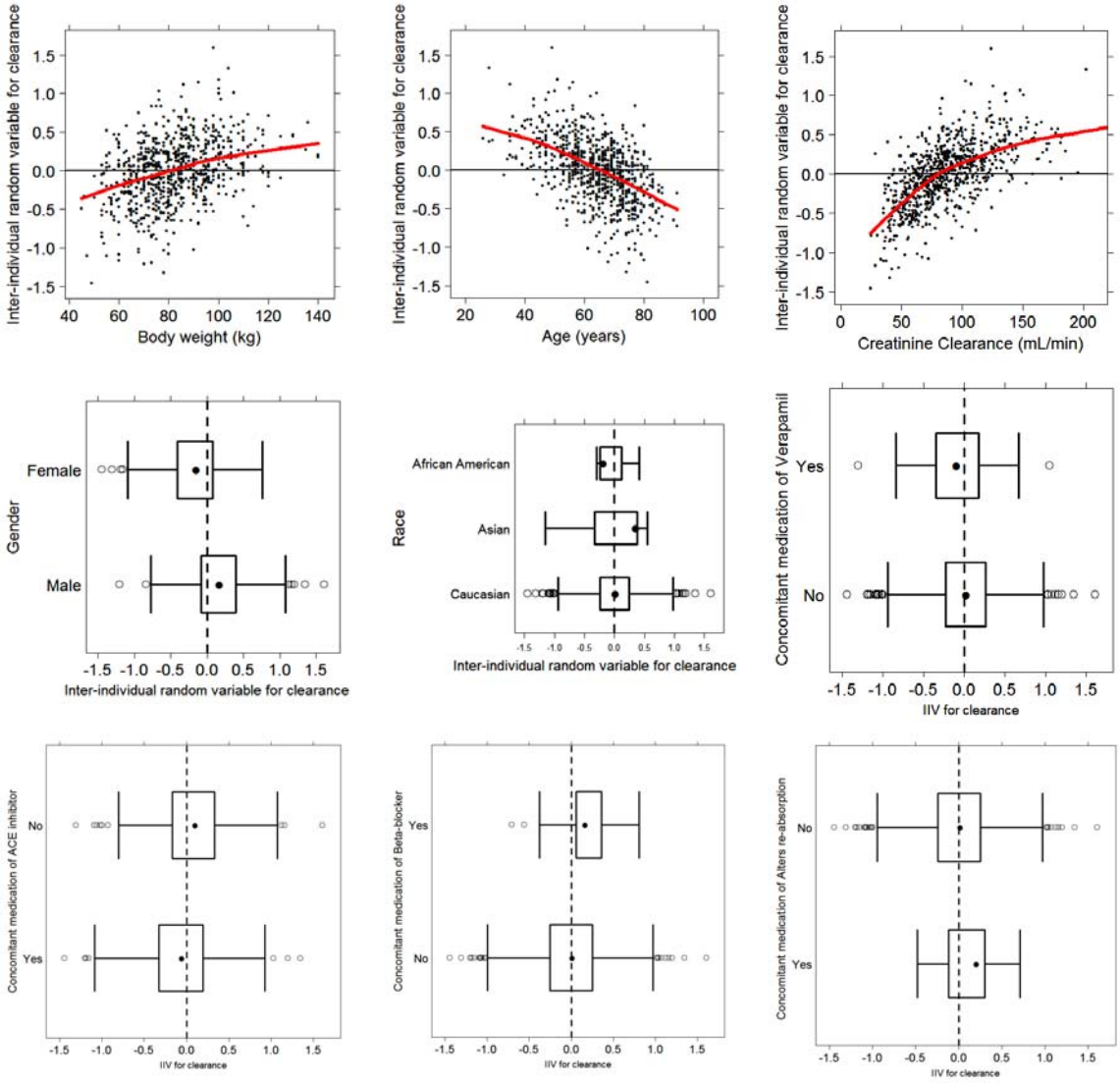


Figure 47 Graphical analyses of clearance-covariate relationships from base PK model.

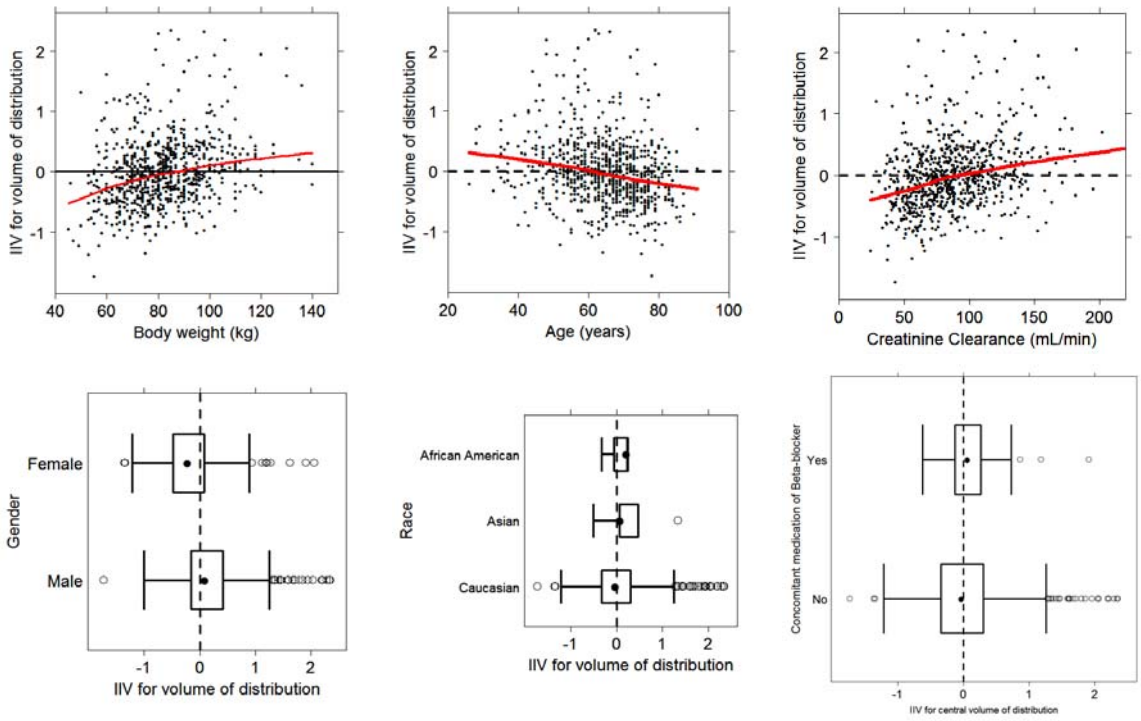


Figure 48 Graphical analyses of volume of distribution-covariate relationships from base PK model.

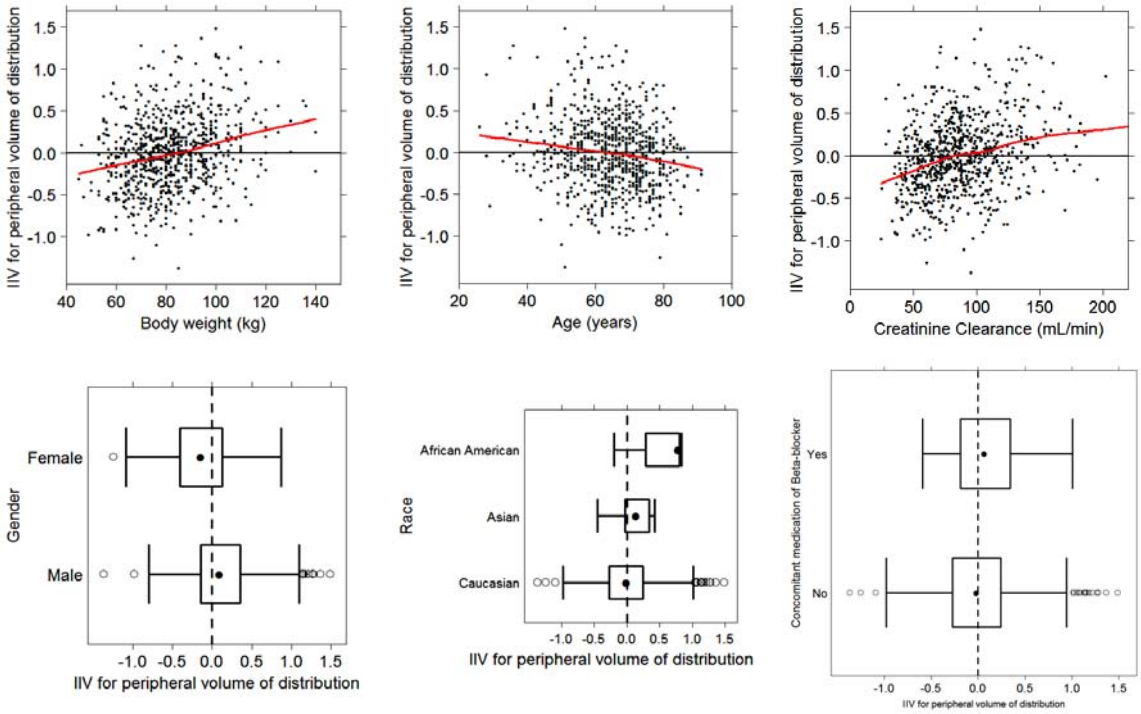


Figure 49 Graphical analyses of peripheral volume of distribution-covariate relationships from base PK model.

Goodness-Of-Fit Graphs for Reviewer's Final PK Model

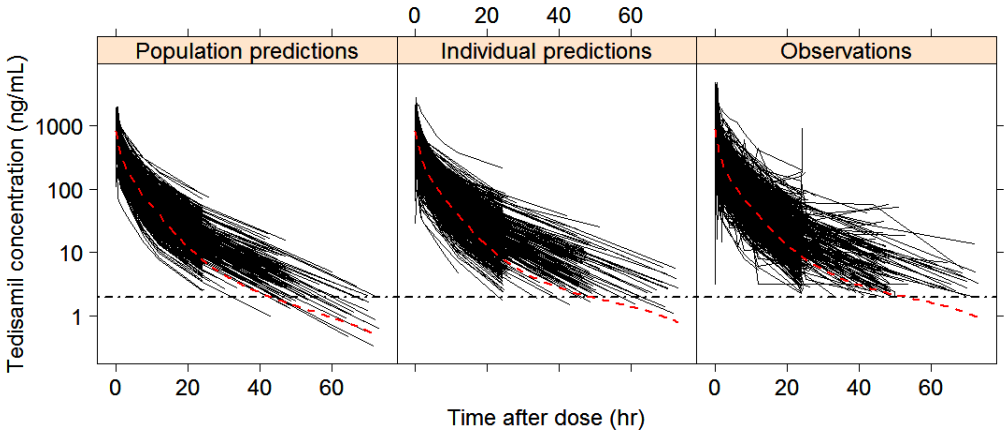


Figure 50 Tedisamil concentration-time profiles for population predicted (left), individual predicted (middle), and observed (right) tedisamil concentrations for reviewer's final PK model. The dotted black line is the LLOQ of 2 ng/mL and the dotted red line is a smoothing regression line.

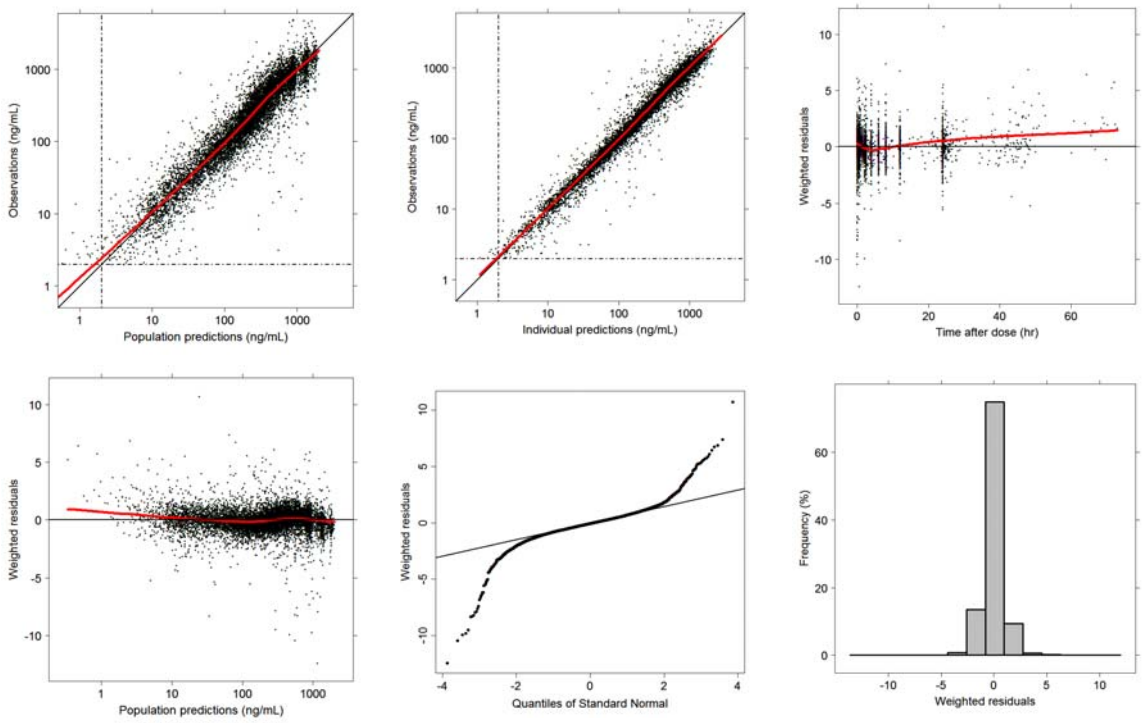


Figure 51 Goodness-of-fit graphs for reviewer's final PK model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the solid red line is a smoothing regression line.

Covariate-PK Parameter Relationships For Final PK Model

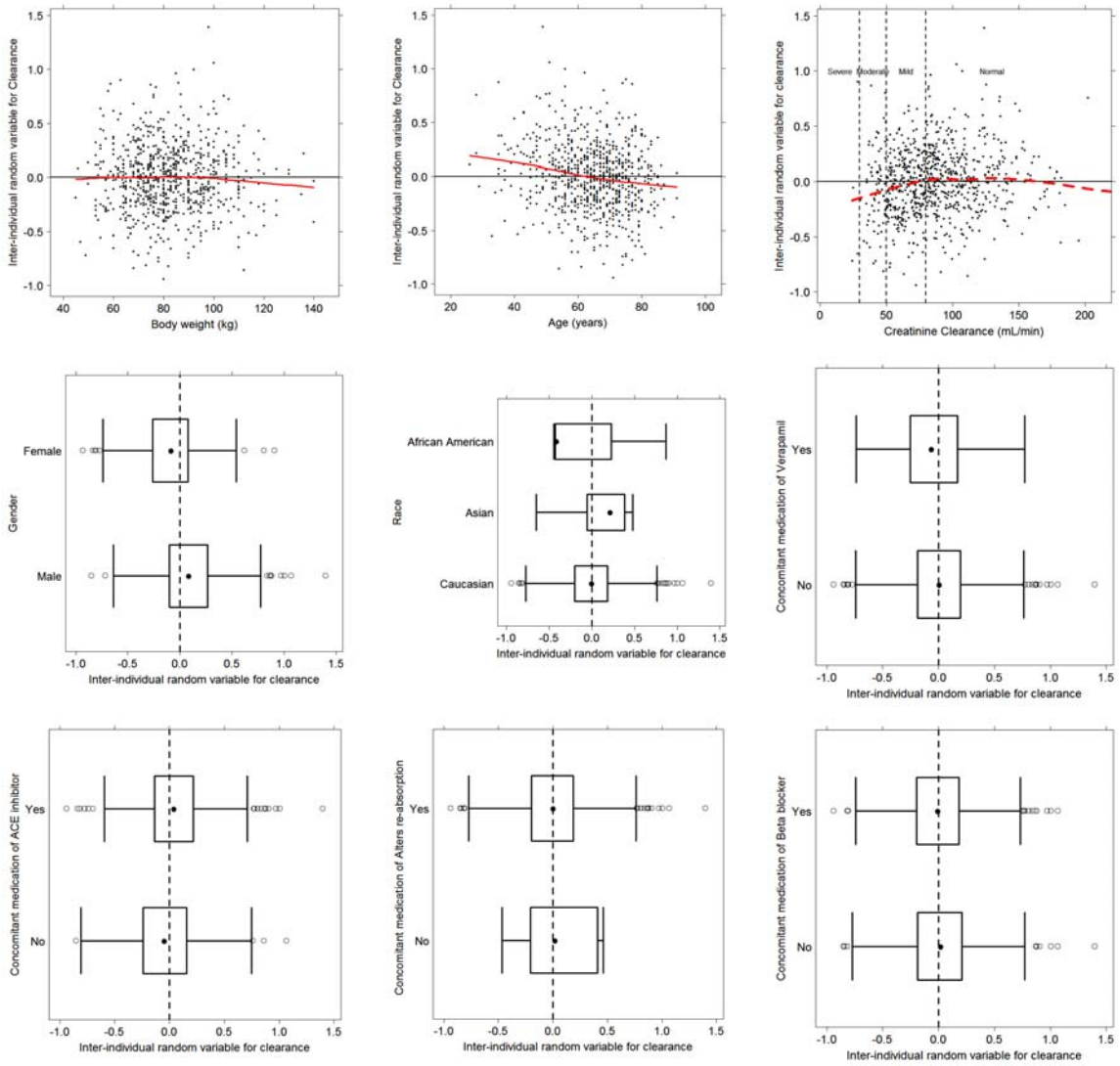
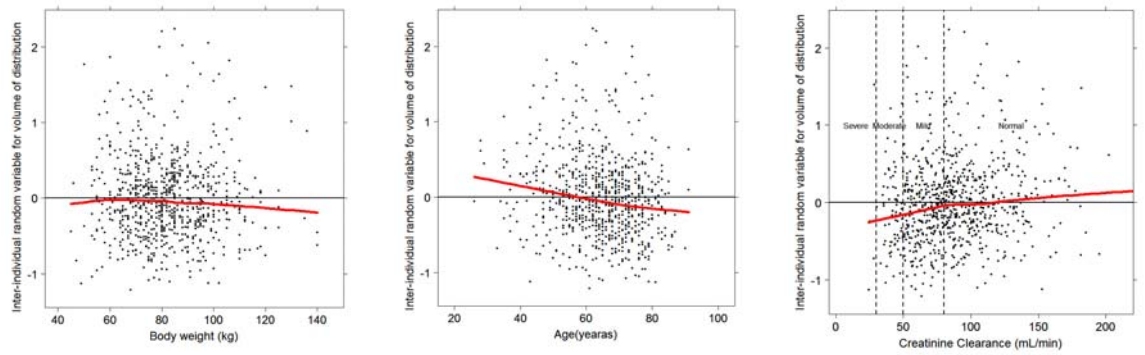


Figure 52 Graphical analyses of inter-individual variability in clearance-covariate relationships from final PK model.



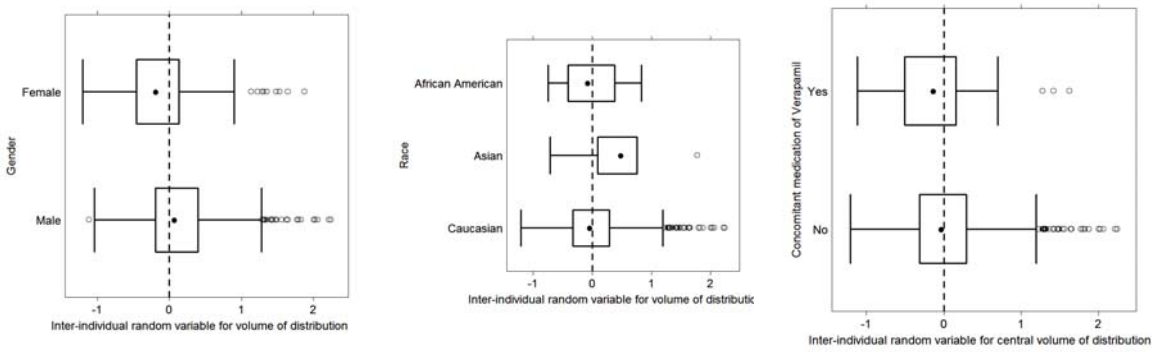


Figure 53 Graphical analyses of inter-individual variability in volume of distribution-covariate relationships from final PK model.

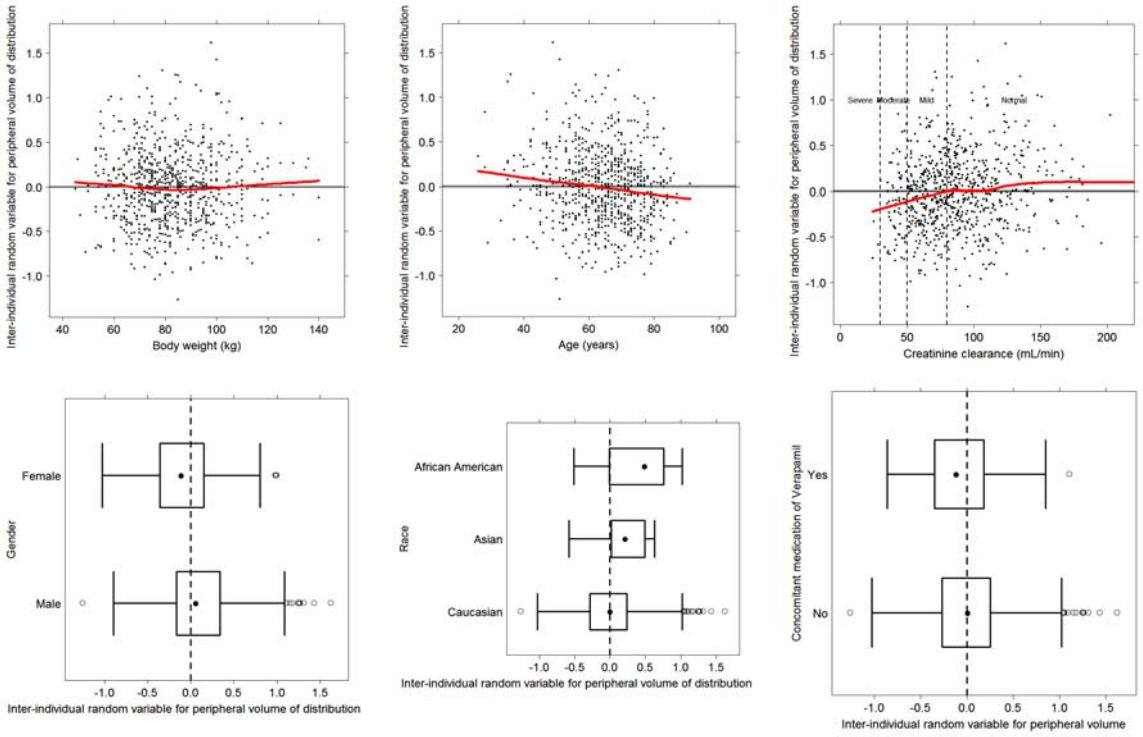


Figure 54 Graphical analyses of inter-individual variability in peripheral volume of distribution-covariate relationships from final PK model.

Exposure-Safety Gender Goodness-of-Fit Plots

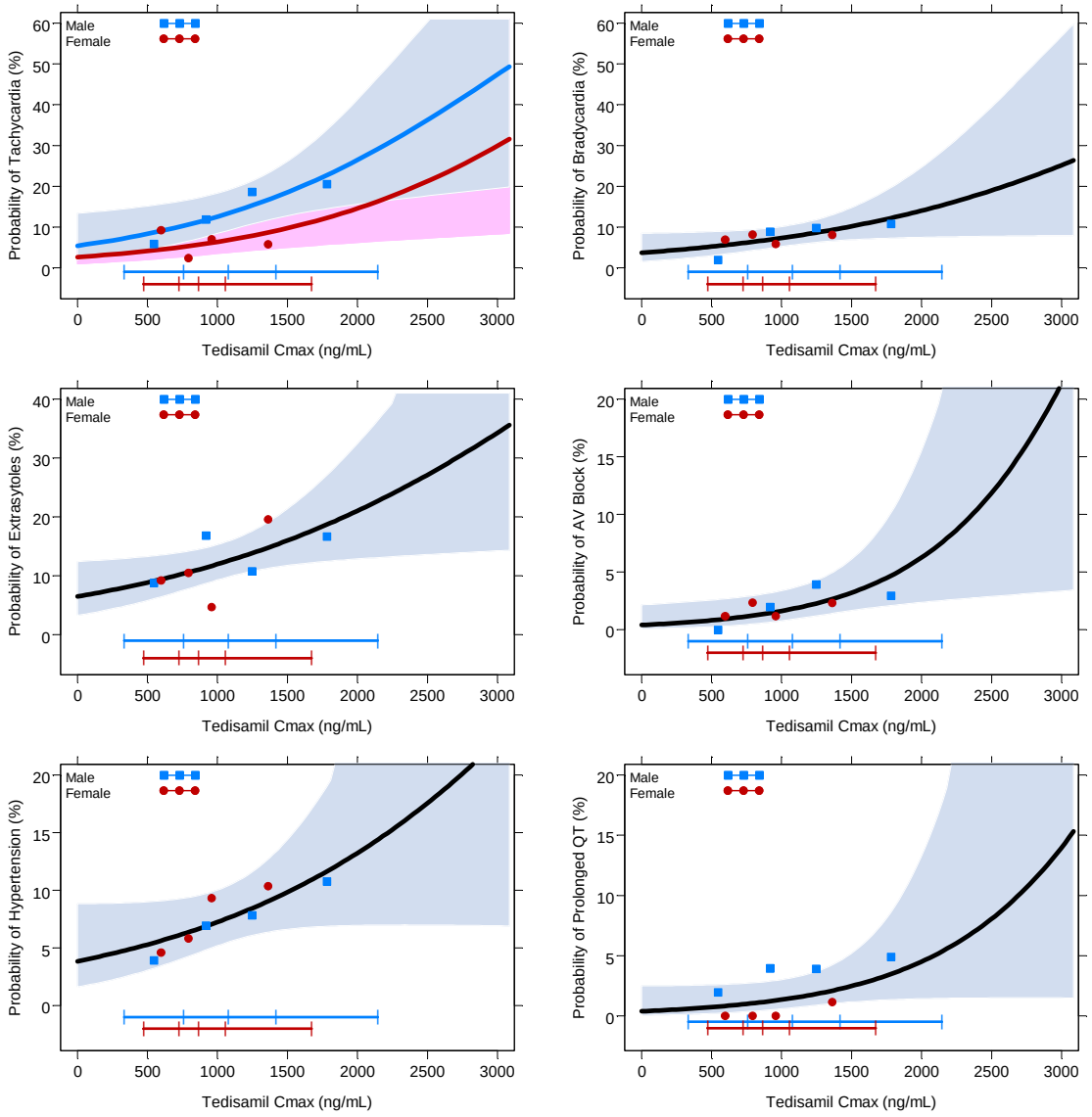


Figure 55. Exposure-safety analysis. Relationship between tedisamil peak concentration and tachycardia (top left), bradycardia (top right), extrasytoles (left 2. row), and AV block (right 2. row), hypertension (left 3. row), and prolonged QT (right 3. row).

4.4 Filing Criteria and OCP Filing/Review Form

NDA 22-123 Tedisamil Sesquifumarate: Evaluation of Clinical Pharmacology Refusal to File (RTF) Criteria

Criteria for Refusal to File (RTF)

1. Has the Applicant submitted bioavailability data satisfying the CFR requirements?

Yes, it appears so.

2. Has the Applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?

No; study not needed as to-be-marketed IV formulation used in pivotal trials.

3. Are the clinical pharmacology and biopharmaceutical sections of the NDA organized in a manner to allow substantive and effective review?

Yes. Submission follows CTD format; although some of the links in EDR are not functional.

4. Are the data sets presented in a readable and accessible form?

Yes, however, minimal datasets were provided (for only population pharmacokinetic/ pharmacodynamic studies (n = 5). Will ask Applicant for datasets from other clinical pharmacology/PK biopharmaceutic studies.

5. Has the Applicant provided information on the metabolic fate of the drug and the activities of the circulating moieties?

Yes. A mass balance study was conducted (both via oral and IV administration)

6. Did the Applicant submit data to allow the evaluation of the validity of the analytical assay?

Yes. Assay reports are available (randomly sampled studies).

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-123	**Brand Name**	Pulzium (proposed)
DCP (I, II, III)	I	**Generic Name**	Tedisamil sesquifumarate
Medical Division	Cardiovascular and Renal	**Drug Class**	Anti-arrhythmic
OCP Reviewer	Robert Kumi	**Indication(s)**	Rapid Conversion of Atrial fibrillation/Flutter to Normal Sinus Rhythm
OCP Team Leader	Patrick Marroum	**Dosage Form**	Solution for IV dosing
		Dosing Regimen	Males:
Date of Submission	12/18/2006	**Route of Administration**	Intravenous (infusion)
Estimated Due Date of CPB Review	09/? Last possible from clinical	**Applicant**	Solvay
PDUFA Due Date	10/19/07 (if standard clock)	**Priority Classification**	To be determined
Division Due Date			

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		Both IV and oral route
Isozyme characterization:	x	9		Microsomes/Hepatocytes etc
Blood/plasma ratio:				
Plasma protein binding:	x	3		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	7		IV studies cited/additional oral
multiple dose:				
Patients-				
single dose:	x	1		Ischemic heart disease
multiple dose:	x	4		Oral formulation only
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	3		Also studied in population PK analysis
In-vivo effects of primary drug:	x	5		Also studied in population PK analysis
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	x	1		Age effect study
renal impairment:	x	2		Single dose and multiple dose study

hepatic impairment:				
PD:				
Phase 2:	x	4h , 6cd, 3hs, 8cads		h- healthy, single dose cd- cardiac disaesa single dose hs- healhty supplemental after multiple doses cads- coronary artery disease supplemental Three different formulations, including to-be-marketed one used
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	5[a]		[a] population PK/PD source
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	x	1		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		6		
Bioequivalence studies -				
traditional design; single / multi dose:		1SD , 2MD		Single dose, multiple dose
replicate design; single / multi dose:				
Food-drug interaction studies:	x	2		Evaluated for IR and ER products
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Total Number of Studies		52		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	Sufficient information to review, however will need additional data/information as outlined in comments to be sent to firm
Comments to be sent to firm?		1. Please provide control streams used in population PK/PD analysis. 2. Please provide SAS code used to generate PK/PD data. 3. Please provide all available PK/PD data generated in PK, PD and biopharmaceutic studies.
QBR questions (key issues to be considered)	• Is there clinically significant QT prolongation associated with tedisamil administration? • Is there a need for different dosing in males and females?	

NOTES:

1. Pharmacometrics consult will be required; if feasible, I (primary reviewer, depending on my workload) would like to conduct the phamacometrics review with guidance/support from pharmacometrics
2. The majority of the oral studies do not need to be reviewed
3. Several bioanalytical assays were used, and studies were conducted in multiple countries.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Kumi
11/9/2007 10:22:28 AM
BIOPHARMACEUTICS

Please sign ASAP (by noon today).

Christoffer Tornoe
11/9/2007 12:04:51 PM
BIOPHARMACEUTICS

Yaning Wang
11/9/2007 12:08:23 PM
BIOPHARMACEUTICS

Patrick Marroum
11/9/2007 12:53:42 PM
BIOPHARMACEUTICS

STATISTICAL REVIEW

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-123

Drug Name: Pulzium® (tedisamil)
Indication(s): Conversion of Afib/Aflut to NSR
Applicant: Solvay
Date(s): Letter Date: 18-December-2006
PDUFA Goal Date: 18-October-2007
Review Priority: Standard

Biometrics Division: DB1
Statistical Reviewer: Valeria Freidlin, Ph.D.
Concurring Reviewers: James Hung, Ph.D.

Medical Division: Cardio-Renal
Clinical Team: Mehul Desai, M.D.

Project Manager: Russell Fortney

Keywords: multiplicity, Bonferroni-Holm procedure.

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Pulzium® (tedisamil) is effective in patients with recent onset atrial fibrillation. Tedisamil has been shown statistically significantly superior to placebo relative to the primary endpoint. As the number of subjects with atrial flutter was quite small, there was no convincing support for the efficacy in subjects with atrial flutter. The indication for tedisamil use should be limited to those with recent onset atrial fibrillation.

1.2 Brief Overview of Clinical Studies

The tedisamil atrial fibrillation/atrial flutter development program includes five phase 3 studies (3.112, 3.114, 3.116, 3.117, and 3.118). Of the five phase 3 studies, this reviewer used three studies (3.112, 3.114 and 3.116) as the pivotal studies. This reviewer used study 3.116 as an additional third pivotal study because the first two studies (3.112 and 3.114) mostly had male patients and study 3.116 had 367 female patients.
The other two phase 3 studies (3.117 and 3.118) were considered as supportive.

1.3 Statistical Issues and Findings

This reviewer agrees with the statistical methods used by the sponsor. The primary efficacy results in the five phase 3 studies (3.112, 3.114, 3.116, 3.117, and 3.118) were verified and confirmed by this reviewer.
Most of the centers were small and no single center carried a study.
This reviewer was concerned that some of the centers were re-used in the different phase 3 studies. The matter was complicated by the fact that the same center had different IDs in different studies. As some of the centers were reused, this reviewer examined the data (using the date of birth and other demographic characteristics) to check whether some patients were used in more than one of the phase 3 studies. The result of this investigation was negative: no patient was reused in different phase 3 studies.

2. INTRODUCTION

2.1 Overview

Table 1 below, summarizes the three phase 3 pivotal studies of tedisamil IV for atrial fibrillation. Each of the 3 studies was designed similarly with respect to the population enrolled, primary endpoint assessment, statistical methods, etc. Each study was a randomized, double-blind, placebo-controlled, parallel group study.

Study 3.116 in the table below was conducted in female subjects only. Studies 3.112 and 3.114 were conducted predominantly in male subjects. During the conduct of studies 3.112 and 3.114, the tedisamil IV development program was temporarily halted by the sponsor to review safety data, specifically case reports of Torsades de pointes type arrhythmia. While these 2 studies

eventually did resume, it was decided to continue the studies with only male subjects restricting doses to a maximum of 0.48 mg/kg. That may explain, in part, the higher proportion of males to females in studies 3.112 and 3.114.

Table 1: Summary of the pivotal phase 3 studies

Study ID (total Randomized)	Study dates (month/yr)	Top 3 enrolling countries	# subjects randomized to each study arm (dose in mg/kg)	Sex (F = female M = male)	Baseline Rhythm
3.112 (N =283)	10/02 – 3/04	Russia (N = 97), Ukraine (N = 89), Poland (N = 76)	Placebo (N = 72) Tedisamil 0.32 (N = 72) Tedisamil 0.48 (N = 73) Tedisamil 0.64 (N = 66)	F=38 M = 245	Afib = 244 Aflut = 39
3.114 (N = 296)	12/02 – 9/04	Ukraine (N = 137) Slovakia (N = 34) Israel (N = 32)	Placebo (N = 79) Tedisamil 0.16 (N = 61) Tedisamil 0.32 – 0.48 (18) Tedisamil 0.32 (N = 60) Tedisamil 0.48 – 0.72 (N = 18) Tedisamil 0.48 (N = 60)	F = 20 M = 276	Afib = 263 Aflut = 33
3.116 (N = 367)	12/04 – 8/05	Ukraine (N = 77) Poland (N = 70) Slovakia (N = 60)	Placebo (N = 122) Tedisamil 0.24 (N = 122) Tedisamil 0.32 (N = 123)	F = 367	Afib = 329 Aflut = 38

Supporting Phase 3 studies

Table 2 below shows two supporting phase 3 studies (3.117 and 3.118). Each of the 2 supporting studies was designed similarly to other phase 3 studies with respect to the population enrolled, primary endpoint assessment, dosing regimen, etc. Each study was a randomized, double-blind, placebo-controlled, parallel group study. Study 3.118 in the table below was conducted in female subjects only. Study 3.117 was conducted in males only.

Table 2. Supporting phase 3 studies

Study ID (total Randomized)	Study dates (month/yr)	Top 3 enrolling countries	# subjects randomized to each study arm (dose in mg/kg)	Sex (F = female M = male)	Baseline Rhythm
3.117 (N = 123)	11/04 – 6/05	Poland (N = 40) Ukraine (N = 30) Czech Repub(N = 23)	Placebo (N = 62) Tedisamil 0.48 (N = 61)	M = 123	Afib = 100 Aflut = 23
3.118 (N = 155)	11/04 – 8/05	Bulgaria (N = 60) Hungary (N = 42) Poland (N = 35)	Placebo (N = 78) Tedisamil 0.32 (N = 77)	F = 155	Afib = 138 Aflut = 17

2.2 Data Sources

The sponsor has submitted a paper NDA. Electronic copies of the reports and SAS datasets can be found at the following link: \\CDSESUB1\N22123\N_000\2006-12-18.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The primary efficacy population was the ITT population. Subjects who underwent DC cardioversion within 2.5 hours after the start of the study drug infusion were to be excluded from the analysis.

The primary efficacy endpoint in every phase 3 study was the percentage of subjects converted to NSR (for at least 60 seconds) at any time within 2.5 hours after the study drug infusion. Pair-wise comparisons of frequencies of conversion were made between tedisamil and placebo groups using the Pearson chi-square statistic. The Bonferroni-Holm multiple comparison procedure determined if p-values were significant.

Table 3 below, shows the primary efficacy results in each of the 3 pivotal studies.

Table 3: Summary of primary efficacy results in each individual pivotal study

Study	**Overall number of subjects with A/fib who did not undergo DC cardioversion within 2.5 hours after the start of study drug infusion**	**Tedisamil dose infused** (mg/kg)	**Proportion of patients with NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion**
3.112	56	0.32	13/56 (23.2%), p=0.0096*
(males only)	51	0.48	28/51 (54.9%), p<0.001*
	43	0.64	29/43 (67.4%), p<0.001*
	53	Placebo	3/53 (5.7%)
3.114	50	0.16	12/50 (24.0%), p=0.057
	51	0.32	15/51 (29.4%), p=0.013*
	45	0.48	14/45 (31.1%), p=0.0089*
	51	Placebo	5/51 (9.8%)
3.116	106	0.24	10/106 (9.4%), p=0.047*
	107	0.32	23/107, (21.5%), p<0.001*
	105	Placebo	3/105 (2.9%)

* Significant difference compared to placebo using the Bonferroni-Holm procedure.
Source: Sponsor's Table 2.5.4-3 (confirmed by the statistical reviewer)

In Table 3 above (sponsor's analysis), study 3.112 did not include data from females. There were only a small number of females randomized in this study. This reviewer has confirmed that the conclusions from Table 3 remain the same whether or not the female data from study 3.112 are included (see Table 4 below).

Table 4: Primary efficacy results for pivotal study 3.112 including both males and females

Study	**Overall number of subjects with A/fib**	**Tedisamil dose infused** (mg/kg)	**Proportion of patients with NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion**
3.112	61	0.32	14/61 (23.0%), p=0.0040*
(males and females)	60	0.48	30/60 (50.8%), p<0.001*
	51	0.64	31/51 (63.3%), p<0.001*
	61	Placebo	3/61 (4.9%)

* Significant difference compared to placebo using the Bonferroni-Holm procedure.

Table 5 below shows the primary efficacy results from two supporting phase 3 studies.

Table 5: Summary of primary efficacy results for two supporting phase 3 studies

Study	**Overall number of subjects with A/fib who did not undergo DC cardioversion within 2.5 hours after the start of study drug infusion**	**Tedisamil dose infused** (mg/kg)	**Proportion of patients with NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion**
3.117	48 48	0.48 Placebo	14/48 (29.2%) , p=0.0033* 3/48 (6.3%)
3.118	67 67	0.32 Placebo	12/67 (17.9%), p=0.014* 3/67 (4.5%)

* Significant difference compared to placebo using the Bonferroni-Holm procedure.
Source: Sponsor's Table 2.5.4-3 (confirmed by the statistical reviewer)

3.2 Evaluation of Safety

Integrated analysis of safety found a total of 13 deaths in Afib/Afl subjects in the tedisamil program. Two deaths were in Phase 2 studies and involved oral formulation. Of the 11 deaths occurring with the IV formulation of tedisamil, there were 2 deaths that occurred in subjects that were randomized but that did not receive study drug. In 3 cases, the deaths occurred in subjects randomized to placebo. The most prevalent AEs were arrhythmias and cardiac arrest. The rates were similar in the tedisamil and placebo groups.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Tedisamil is effective in both men and women. However, tedisamil appears to be relatively less effective in women compared to men when administered the same mg/kg dosing regimen (compare the results of studies 3.112, 3.114 and 3.117 mostly in males with the results of studies 3.116 and 3.118 in females in Tables 3-5).

The effectiveness of tedisamil is much lower in subjects with baseline atrial flutter as compared to subjects with baseline atrial fibrillation. This may be explained by the small number of subjects with atrial flutter in the studies.

Tedisamil appears to be most effective in subjects with duration of $\leq$ 48 hours of their most recent atrial fibrillation episode. The effectiveness of tedisamil is much lower in subjects with a duration of their most recent episode of atrial fibrillation > than 48 hours.

5. SUMMARY AND CONCLUSIONS

Tedisamil is effective as evidenced by statistically significant superiority over placebo in the three pivotal phase 3 studies and two supporting Phase 3 studies. The primary endpoint in each of the phase 3 studies was the conversion from atrial fibrillation/atrial flutter to normal sinus rhythm (for at least 60 seconds) as measured by the percentage of subjects converted at any time within 2.5 hours after the start of infusion. The sponsor did obtain agreement from the Division of Cardiovascular and Renal Drugs on this endpoint in a teleconference in January 2002.

5.1 Statistical Issues and Collective Evidence

There were no statistical issues in this submission.

5.2 Conclusions and Recommendations

Tedisamil is effective as evidenced by statistically significant superiority over placebo in the three pivotal phase 3 studies and two supporting phase 3 studies. Safety of tedisamil is a matter of clinical judgment of the medical division.

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/s/

Valeria Freidlin
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James Hung
6/15/2007 01:03:16 PM
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THOMAS A. MARCINIAK, M.D.
MEDICAL TEAM LEADER, DCRDP

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Secondary Review

NDA:	22-123
Drug:	tedisamil sesquifumarate 2 mg/mL IV solution (Pulzium®)
Indication:	conversion of atrial fibrillation and flutter
Sponsor:	Solvay Pharmaceuticals, Inc.
Review date:	November 13, 2007
Reviewer:	Thomas A. Marciniak, M.D. Medical Team Leader

Recommendation and Conclusions

I recommend that tedisamil be approvable for the indication of conversion of recent onset atrial fibrillation pending the results of a clinical study demonstrating the safety and efficacy of a simplified dosing and administration scheme. Tedisamil clearly has some efficacy in converting recent onset atrial fibrillation to sinus rhythm. However, the difference in success rates (sinus rhythm without additional conversion attempts at 24 hours) between tedisamil at the proposed to-be-marketed doses (0.32 mg/kg in women and 0.48 mg/kg in men) and placebo is modest (about 30%, but lower in women and in patients whose onset is more than two days in the past). Benefit at 24 hours for patients with atrial flutter is not established. Tedisamil has the potential for fatal toxicity, both through the pro-arrhythmic Torsades de Pointes/ventricular tachycardia route and through the bradycardia/hypotension route. Both of these toxicities begin to manifest themselves at the proposed to-be-marketed dosages. Because of the complex dosing and administration scheme, errors in dosing could contribute to excess toxicity or reduced efficacy. In addition to testing a simplified dosing and administration scheme, the new clinical study must also address some unanswered safety issues, e.g., what is the interaction with rate-reduction drugs such as beta blockers and whether tedisamil has a pro-embolic effect. The study must also enroll reasonable numbers of blacks.

Materials Used in Review

1. NDA 22-123 submissions
2. Clinical Review by Mehul Desai, M.D., dated June 19, 2007
3. Statistical Review by Valeria Freidlin, Ph.D., dated June 15, 2007
4. Pharmacology/Toxicology Review by James Willard, Ph.D., dated August 10, 2007
5. Chemistry Review by David J. Claffey, PhD, dated September 10, 2007
6. RiskMAP Review by OSE Tedisamil Risk Management Team, dated October 29, 2007
7. Clinical Pharmacology and Biopharmaceutics Review by Robert Kumi, Ph.D., and Christopher Tornoe, Ph.D., dated November 9, 2007

Background

Tedisamil is a multiple potassium channel blocker, hence a Vaughan Williams class III anti-arrhythmic, that the sponsor proposes for the conversion of atrial fibrillation and flutter (afib/flut) of recent onset (3 hours to 45 days). The sponsor originally developed it as an oral agent for the chronic treatment of angina pectoris. However, the sponsor abandoned that indication and focused on afib/flut conversion by the intravenous (IV) route. The clinical development program for the IV formulation includes nine studies, four labeled as phase 2 and five as phase 3. The reason for the large number of phase 3 studies is that the sponsor modified the initial phase 3 studies because of concerning cases of Torsades de Pointes (TdP) in women at higher dosages and added gender-specific trials, one in men and two using lower dosages in women. The sponsor is proposing a lower dosage for women (0.32 mg/kg) than for men (0.48 mg/kg).

Chemistry

The chemistry reviewer, Dr. Claffey, recommends that the application is approvable from a chemistry, manufacturing, and controls viewpoint. He does note some deficiencies regarding limits, package labeling, and fumarate component to be resolved prior to approval—please see his review for details. Otherwise, perhaps of clinical relevance is that the pH of the drug product solution is rather acidic (3.4), but it is just inside the acceptable pH range for an IV administered product.

Pre-Clinical Pharmacology and Toxicology

The pharmtox reviewer, Dr. Willard, recommends that tedisamil is approvable from a pharmtox perspective. He notes that it blocks IKr, IKs, IKur, Ito and IKATP, as well as Ca^{++} dependent K^{+} channels, and the protein kinase A Cl^{-} channel. It prolongs the cardiac action potentials and the QT interval and slows heart rate. He hypothesizes that its primary pharmacodynamic action as a non-specific K channel blocker is responsible for both its efficacy (conversion of atrial fibrillation) and its toxicity (QTc prolongation leading to Torsades de Pointes and other arrhythmias, bradycardia). He also notes that its ability to block potassium channels extends beyond cardiac tissue, so that it prolongs nerve action potentials and produces seizures. He believes that respiratory depression producing mortality in some of the toxicity studies was due to a central nervous system effect of potassium channel blockade. Other than these consequences of ion channel blockade, he comments that tedisamil displays little ancillary toxicity. He does have the following recommendations:

- The sponsor should investigate the interactions between tedisamil and other QT prolonging drugs and with other bradycardic agents, i.e., beta blockers.
- The label should include warnings that tedisamil is a potent blocker of CYP2D6, a P450 enzyme responsible for the metabolism of many neurologically active drugs that also frequently contribute to QT prolongation.

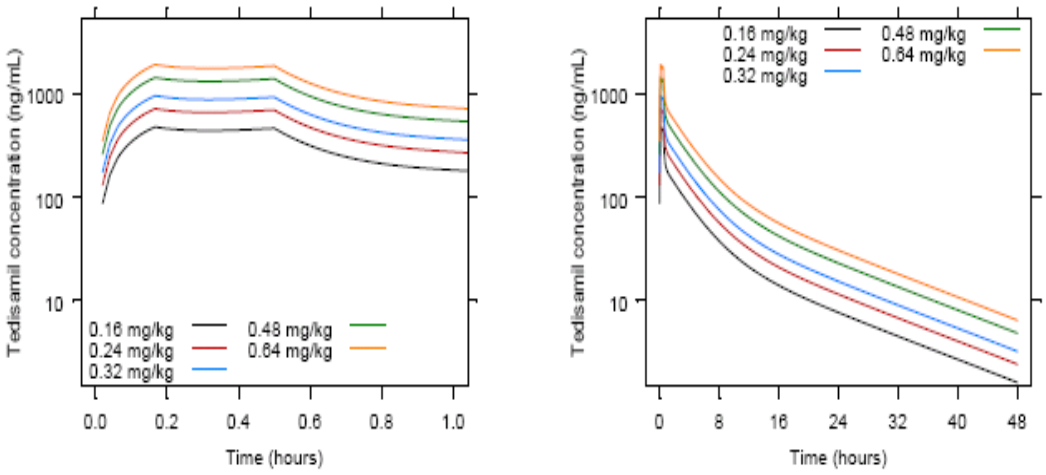
Clinical Pharmacology

The clinical pharmacology and biopharmaceutics (CPB) reviewers, Drs. Kumi and Tornoe, find the CPB data acceptable except for characterizing better PGP transport and

revising drug interaction labeling, particularly regarding inadequate addressing of CYP2D6 inhibition. The most relevant observations from their review are the following:

- A three-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed tedisamil concentrations following a two-step IV infusion over 30 minutes of 0.16 mg/kg to 0.72 mg/kg with dose-proportionality for this range. Body weight is a significant covariate for volume of distribution. The sponsor justifies the two-step infusion based on "the most promising PK data". Dr. Tornoe's estimates of population mean predicted tedisamil concentration-time profiles for a typical 80 kg subject are shown in Figure 1.

Figure 1: Clinical Pharmacology Reviewer's Concentration-time Profiles (80 kg Subject)



COMMENT: While the sponsor may find it promising to have a nice-looking plateau of drug levels, we do not know how such a plateau relates to either efficacy or toxicity. The downside is that producing the plateau does necessitate a relative complex administration methodology, with a change in infusion rate at 10 minutes of a 30 minute total infusion. See the RiskMAP Review by the OSE Tedisamil Risk Management Team for a discussion of the issue of a complex dosing and administration scheme.

- Tedisamil is almost exclusively eliminated as unchanged drug via the renal route. Only one metabolite was identified in man, 11-hydroxy tedisamil. This metabolite is 2- to 3- fold less active than tedisamil and accounts for < 4 % of tedisamil exposure. Creatinine clearance is a significant covariate for tedisamil clearance, with a 10% higher C_{max} and 350% higher AUC in patients with severe renal impairment compared to patients with normal renal function.

- Tedisamil is a strong inhibitor of CYP2D6 and a substrate for PGP. Otherwise CYP interactions are slight and no clinically significant drug interactions were identified except coadministration of oral tedisamil and verapamil led to a 77% increase in oral tedisamil exposure.

- Tedisamil generally increases QT and QTc, PR- and RR- and QRS- intervals, decreases T-wave amplitude, and decreases heart rate. The population PK/PD relationship between QTcF and tedisamil concentrations was adequately described by a linear model. Tedisamil increases the QTc change from baseline with a mean predicted change from baseline QTc of 32 and 38 msec at the mean observed male and female C_{max} of 954 and 1317 ng/mL, respectively. The mean QTcF is predicted to return to normal eight hours after dosing of 0.32 and 0.48 mg/kg.

  COMMENT: The Drs. Kumi and Tornoe recommend that the label specifies that the monitoring time following drug administration be eight hours, corresponding to the time for QTcF to normalize, rather than the 1.5 hours proposed by the sponsor.

- The most important covariate for predicting conversion rate is duration of the episode. Please see Efficacy, Time from Onset below for the analysis.

- The probability of developing tachycardia, bradycardia, extrasystoles, AV block, hypertension, and TdP was found to increase with increasing tedisamil peak concentration. The risk of TdP increases from 0.5 to 18% for female and 1 to 3% for male patients with C_{max}>1607 ng/mL compared to patients with C_{max} <1607 ng/mL.

Efficacy

Both the primary clinical reviewer, Dr. Desai, and the statistical reviewer, Dr. Freidlin judge tedisamil to be effective as evidenced by superiority to placebo in converting recent onset atrial fibrillation to sinus rhythm, at least per the definition of the primary endpoint in the pivotal studies (sinus rhythm of at least 60 seconds duration within 2.5 hours of study drug administration.) The sponsor's summary of the pivotal trial results, quoted by Dr. Desai in his review, is shown in Table 1.

Table 1: Sponsor's Summary of Primary Efficacy Parameter and Mean Time to First Conversion for the Individual Efficacy Studies

Study	Overall Number Randomized/ Completed	Tedisamil dose infused (mg/kg)	NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion	Mean time to first conversion
S219.3.112	72/67	0.32	13/56 (23.2%), p = 0.0096	41.6 minutes
	73/62	0.48	28/51 (54.9%), p < 0.0001	37.9 minutes
	66/54	0.64	29/44 (67.4%), p < 0.0001	21.9 minutes
	72/65	Placebo	3/53 (5.7%)	45.0 minutes
S219.3.114	61/57	0.16	12/50 (24.0%), p = 0.057	33.1 minutes
	60/56	0.32	1551 (29.4%), p = 0.013	30.3 minutes
	60/51	0.48	14/45 (31.1%), p = 0.0089	18.5 minutes
	60/56	Placebo	5/51 (9.8%)	84.0 minutes
S219.3.116	122/115	0.24	10/106 (9.4%), p = 0.047	41.1 minutes
	123/115	0.32	23/107 (21.5%), p < 0.001	24.2 minutes
	122/112	Placebo	3/105 (2.9%)	88.7 minutes
S219.3.117	61/57	0.48	14/48 (29.2%) p=0.003	22.2 minutes
	62/57	Placebo	3/48 (6.3%)	92.7 minutes
S219.3.118	77/74	0.32	12/67 (17.9%), p=0.014	27.4 minutes
	78/73	Placebo	3/67 (4.5%)	88.7 minutes
S219.2.107	75/64	0.32	24/52 (46%), p < 0.001	34.8 minutes
	58/52	0.48	24/42 (57%), p < 0.001	34.2 minutes
	68/57	Placebo	4/46 (9%)	86.4 minutes

At first glance the p values in the fourth column of Table 1 appear very reassuring that tedisamil is effective in converting atrial fibrillation/flutter to normal sinus rhythm (NSR); the percentage conversion rates in the fourth column are less reassuring that the conversion is a real clinical benefit. However, a closer examination of Table 1 reveals another problem: The denominators (total 1089) in the fourth column used to calculate the conversion rates are substantially lower (about 21% lower) than the numbers randomized (total 1370) in the second column. Some of the reasons for the discrepancy (difference of 221) are the following:

- The efficacy analyses (column 4) only include atrial fibrillation patients while the randomized numbers (column 2) also include patients with baseline atrial flutter (184) and with missing baseline rhythm (4).
- Study 112 excludes women (38) from the efficacy analysis but includes both genders in the randomized numbers.
- The efficacy analyses also exclude patients (6 tedisamil, 1 placebo) who underwent electrical cardioversion within 2.5 hours.
- For the 59 other patients excluded from the efficacy analyses, 51 did not take study medication, four had a negative time to conversion, and four had no post-baseline efficacy data. These patients are distributed between tedisamil and placebo roughly the same as the overall randomization ratio (about 2:1). The four patients with negative time to conversion and 38 of the others converted to sinus rhythm prior to receiving study drug (about 3%). Many of the cases lack follow-up data on rhythm but, for the ones that have data, all remained in sinus rhythm at the later times. The other patients who did not take study medication typically had study exclusions (prolonged QTc, abnormal lab value) not detected prior to randomization.

COMMENT: Of the above exclusions, the exclusions of atrial flutter patients and women in Study 112 are reasonable (although the former exclusion likely restricts the indication to patients with baseline atrial fibrillation.) Excluding patients who underwent electrical cardioversion within 2.5 hours is inappropriate; these patients should be counted as failures. Regarding the other 59 exclusions, I would include them in the primary analysis to maintain the randomization.

Hence I believe that the most meaningful analysis includes the usual true ITT, i.e., randomized, numbers in the denominators for the conversion rates. The numerators should include the successes, i.e., the numbers of patients who converted (or spontaneously reverted) to NSR and who did not have another conversion intervention (i.e., either electrical or chemical conversion.) I would include the spontaneous reverters as successes in the numerator to maintain the numbers randomized in the denominators. I would count as failures, i.e., exclude from the numerator, any patients having a second conversion attempt prior to the endpoint time regardless of whether the patients is in NSR at any time. The rate by this definition might be considered a success rate reflecting the rate of patients who practically benefited from the treatment (plus the few who didn't really need it.)

In addition to the ITT conversion rate or success rate, there are several other efficacy issues that must be addressed to support approval and labeling (as well as the major concerns regarding safety that I address in the next section). My additional efficacy issues are the following:

- *What is the rate of sinus rhythm maintained at 24 hours without additional chemical or electrical conversion attempts?*
- *How do the conversion rates compare for baseline atrial flutter vs. baseline atrial fibrillation?*
- *How do the conversion rates vary by time since onset of the atrial fibrillation?*
- *Is the differential dosing by gender, body weight, and BMI well justified?*

Because these efficacy issues affect both approvability and labeling, I address each of them below.

Success Rates at 2.5 Hours

I show the placebo-subtracted success rates at any time within 2.5 hours (the primary endpoint time) for the ITT cases with atrial fibrillation, by study and dose, in Table 2. In this table I count patients who spontaneously converted to sinus rhythm prior to study drug administration as successes and patients who also received electrical cardioversion are counted as failures. Because study participation varied by gender, I include the numbers of patients by gender.

Table 2: Reviewer's Placebo-Subtracted Success Rates within 2.5 Hours for the ITT Cases with Atrial Fibrillation

				dose									
				0.16		0.24		0.32		0.48		0.64	
study	F	M	placebo	%	p	%	p	%	p	%	p	%	p
107	64	93	15%					33%	<0.001	42%	<0.001		
112	0	213	7%					17%	0.014	45%	<0.001	56%	<0.001
114	0	213	15%	13%	0.09			17%	0.04	18%	0.03		
116	329	0	6%			4%	0.2	15%	0.001				
117	0	100	8%							24%	0.003		
118	138	0	7%					12%	0.037				

COMMENT: Table 2 confirms that tedisamil has efficacy compared to placebo in converting atrial fibrillation to sinus rhythm at least for a short time. However, the placebo-subtracted success rates are not impressive, reaching 42-45% only in two studies at the highest dose proposed for marketing. This limited benefit must be weighed against the risk. Also, examination of subgroups for varying efficacy and safety is justified.

Success Rates at 24 Hours

I show the placebo-subtracted success rates at 24 hours for the ITT cases with atrial fibrillation, by study and dose, in Table 3. For this table I counted patients who received

electrical conversion or other chemical conversion as failures regardless of whether they remained in sinus rhythm.

Table 3: Reviewer's Placebo-Subtracted Success Rates at 24 Hours for the ITT Cases with Atrial Fibrillation

				dose									
				0.16		0.24		0.32		0.48		0.64	
study	F	M	placebo	%	p	%	p	%	p	%	p	%	p
107	64	93	28%					16%	0.07	17%	0.08		
112	0	213	20%					11%	0.2	31%	0.001	35%	<0.001
114	0	213	22%	10%	0.3			15%	0.09	16%	0.07		
116	329	0	15%			6%	0.2	11%	0.05				
117	0	100	18%							14%	0.1		
118	138	0	10%					9%	0.1				

COMMENT: The spontaneous rates of conversion in the placebo group are higher at 24 hours than at 2.5 hours such that, while the conversions on drug at 2.5 hours are largely maintained, the differences between the drug and placebo groups are diminished. At the highest proposed to-be-marketed dose 30% or fewer of the patients benefited compared to the 96% of patients who were given study drug and were at risk of adverse effects.

Flutter

I show the placebo-subtracted success rates at any time within 2.5 hours (the primary endpoint time) for the ITT cases with atrial flutter, by study and dose, in Table 4 and the success rates at 24 hours in Table 5. I calculated these rates the same as those for atrial fibrillation in Table 2 and in Table 3.

Table 4: Reviewer's Placebo-Subtracted Success Rates within 2.5 Hours for the ITT Cases with Atrial Flutter

		dose									
		0.16		0.24		0.32		0.48		0.64	
study	placebo	%	p	%	p	%	p	%	p	%	p
107	0%					9%	0.3	20%	0.09		
112	0%					0%		25%	0.1	50%	0.018
114	0%	0%				0%		13%	0.4		
116	23%			-6%	0.7	-15%	0.3				
117	17%							-8%	0.6		
118	0%					0%					

Table 5: Reviewer's Placebo-Subtracted Success Rates at 24 Hours for the ITT Cases with Atrial Flutter

		dose									
		0.16		0.24		0.32		0.48		0.64	
study	placebo	%	p	%	p	%	p	%	p	%	p
107	0%					9%	0.3	7%	0.3		
112	22%					-11%	0.5	3%	0.9	28%	0.3
114	17%	8%	0.7			17%	0.5	-4%	0.8		

		dose									
		0.16		0.24		0.32		0.48		0.64	
116	23%			10%	0.6	8%	0.7				
117	25%							-25%	0.08		
118	38%					-38%	0.04*				

COMMENT: While the number of patients with baseline atrial flutter is low (177), the conversion rates appear to be lower than with baseline atrial fibrillation. There is no evidence of a beneficial impact at 24 hours for the proposed to-be-marketed doses.

Time from Onset

I show the placebo-subtracted success rates at 24 hours for the ITT cases with atrial fibrillation of duration 3-48 hours in Table 6, of duration 3-45 days in Table 7, and the clinical pharmacology reviewer's analysis of conversion rates at 2.5 hours by duration of atrial fibrillation in Figure 2.

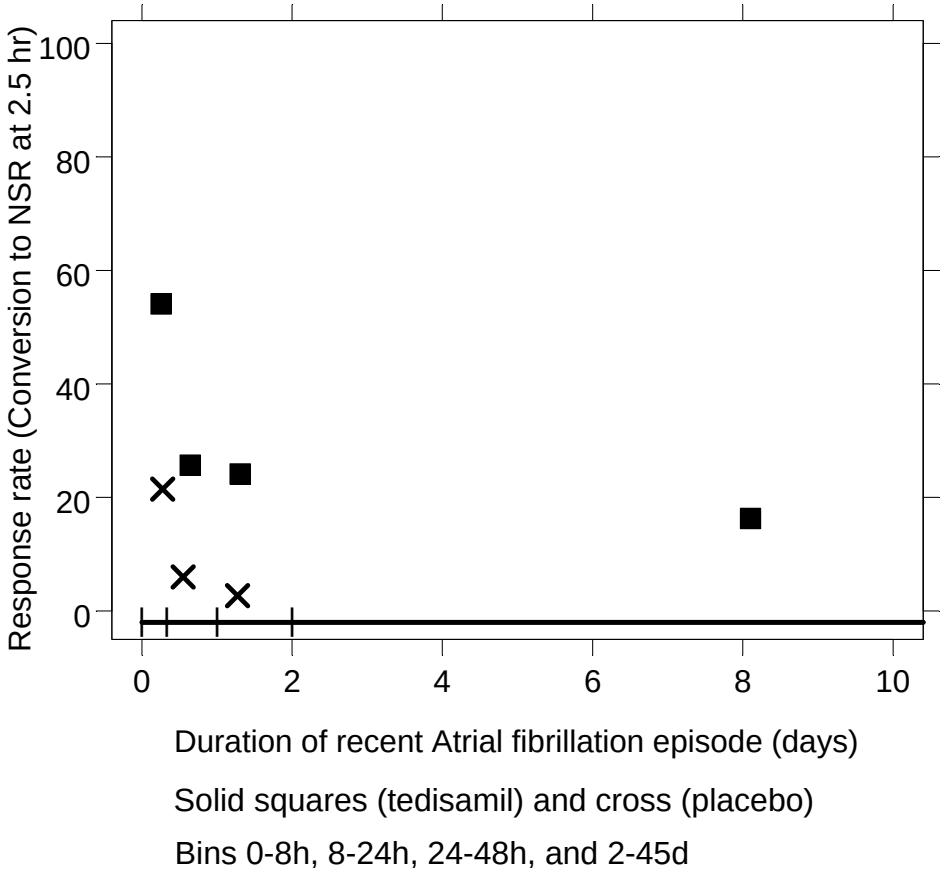
Table 6: Reviewer's Placebo-Subtracted Success Rates at 24 Hours for the ITT Cases with Atrial Fibrillation Duration 3-48 Hours

study	n	placebo	dose				
			0.16	0.24	0.32	0.48	0.64
107	140	28%			17%	17%	
112	109	34%			21%	32%	25%
114	84	55%	1%		20%	5%	
116	102	42%		11%	3%		
117	55	26%				34%	
118	36	39%			11%		

Table 7: Reviewer's Placebo-Subtracted Success Rates at 24 Hours for the ITT Cases with Atrial Fibrillation Duration 2-45 Days

study	n	placebo	dose				
			0.16	0.24	0.32	0.48	0.64
107	2	0%			0%	0%	
112	95	4%			6%	26%	43%
114	115	0%	4%		15%	16%	
116	217	1%		4%	13%		
117	41	0%				4%	
118	100	0%			6%		

Figure 2: Clinical Pharmacology Reviewer's Conversion Rates at 2.5 Hours by Duration of Atrial Fibrillation



COMMENT: Both the tables and the figure demonstrate that conversion rates decrease as the duration of the atrial fibrillation episode, the time from onset, increases. The modest benefit of 30-40% increase in conversion rate decreases to 10-20% with atrial fibrillation durations greater than 48 hours. Because the risks do not decrease correspondingly, the risk-benefit analysis is less favorable for the longer durations.

Dosing

The sponsor is proposing a complicated dosing scheme for tedisamil based on gender, weight, and height. The proposed labeling includes four pages of tables for clinicians to use to calculate the dosage. The sponsor justifies the dosing by gender, proposed 0.48 mg/kg for men and 0.32 mg/kg for women, based on high rates of TdP in women at dosages exceeding 0.32 mg/kg (see Safety, Pro-Arrhythmic Activity below—but this dosing scheme is based on limited data, i.e., two cases of sustained TdP in 55 women treated at the higher dosages.) In the clinical studies the sponsor dosed on a weight (mg/kg) basis for subjects with a body mass index (BMI) of ≤ 28 kg/m^2. For patients with a BMI index of above 28, the sponsor based dosing on a maximum BMI of 28 and the height, i.e., an adjusted "weight" of 28 x height squared (in m^2). The sponsor justifies this latter adjustment by stating that tedisamil is hydrophilic and wanting to avoid

overdosing in patients with excess fat. The sponsor incorporated this latter adjustment into the label dosing tables.

One important question regarding the proposed dosing is whether efficacy differs by gender with the lower dosing in women. The sponsor claims that "In the integrated data, subgroup analysis by gender revealed that the 0.32 mg/kg dose gave similar response rates in men and women. The dose response seen for the ITT population in doses ranging from 0.16 to 0.64 mg/kg, was also seen in the male subgroup but could not be confirmed in women due to the low numbers at the higher treatment doses." The sponsor's observation regarding the 0.32 mg/kg dosing is not inconsistent with the results shown in Table 2 and in Table 3. However, the comparison is across studies in those tables. I show the success rates by gender at 24 hours for the evaluable atrial fibrillation cases in the two studies enrolling both genders (including 31 women in Study 112 excluded from the other efficacy analyses) in Table 8.

Table 8: Reviewer's Success Rates by Gender at 24 Hours for the Atrial Fibrillation Cases in the Studies Enrolling Both Genders

study	sex	placebo	dose		
			0.32	0.48	0.64
107	F	25%	32%	35%	
	M	31%	50%	52%	
112	F	13%	20%	11%	29%
	M	23%	30%	51%	59%

The Table 8 results suggest that women have a lower conversion rate at any given dose than men. However, conversion rates are affected by other factors, such as time from onset. I believe another useful analysis is to do a multivariate analysis such as the logistic regression shown in Table 9.

Table 9: Reviewer's Logistic Regression of Success Rates at 24 Hours for the ITT Cases with Atrial Fibrillation

```
Logistic regression                                   Number of obs   =       1146
                                                      LR chi2(10)     =     332.46
                                                      Prob > chi2     =     0.0000
Log likelihood = -533.98738                           Pseudo R2       =     0.2374

------------------------------------------------------------------------------
success @24h | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        dose |   10.94291   4.538988     5.77   0.000     4.853606    24.67181
        male |   1.949292   .7207877     1.81   0.071     .9443417    4.023693
         age |   .9853856   .0066652    -2.18   0.030     .9724083    .9985361
      weight |   .9763074   .0052401    -4.47   0.000     .9660908     .986632
onset 3-45 d |   .0890485   .0167029   -12.89   0.000     .0616547    .1286135
   Study 112 |   1.584564   .4473153     1.63   0.103     .9112118    2.755498
   Study 114 |   1.772238    .506967     2.00   0.045     1.011643    3.104682
   Study 116 |   2.131841    .714196     2.26   0.024     1.105581     4.11073
   Study 117 |   .8799506   .3003148    -0.37   0.708     .4507702    1.717756
   Study 118 |   1.648361   .6638035     1.24   0.215     .7486333    3.629407
------------------------------------------------------------------------------
```

COMMENT: Both the results in the two studies enrolling both genders and the logistic regression suggest that efficacy is lower in women at any dose level. The logistic regression also suggests that weight is still a significant factor affecting success rates,

calling into question the sponsor's truncation of dosing for BMI > 28. It also confirms that time since onset of the current episode is a very important factor affecting success rates, with an estimated odds ratio of about 11 for recent onset (3-48 hours) compared to longer duration (3-45 days.) I discuss how safety relates to dosing in the next section.

Safety

The major safety issue for tedisamil is its proarrhythmic activity. Tedisamil is a multiple potassium channel blocker, including blocking I_{Kr}, that prolongs the QTc interval in a dose-related fashion. Tedisamil administration has been associated with several well-documented cases of Torsades de Pointes (TdP). Tedisamil also produces bradycardia. While the bradycardia is mild (estimated 11-14 bpm at C_{max} for 0.32 mg/kg in healthy volunteers), bradycardia was the initial event in the one patient whose death is linked to events initiated during the infusion.

Total exposure to drug was reasonable (931) in the integrated safety database—at least for whites. Because 98% of the patients were white (only 9 patients were black in the safety population), reliable data on effects in other races is lacking. Conversely, because atrial fibrillation rates increase dramatically with age, the elderly are well represented—52% of the patients were 65 or older. While total exposure was reasonable, several different dosing levels and regimens were used, randomization among the trials varied from 1:1 to 3:1, and (unusually) some trials were gender-specific. I show the gender distributions by study and placebo/drug in Table 10.

Table 10: Reviewer's Exposure by Study and Gender in the Integrated Safety Database

	placebo		tedisamil	
study	F	M	F	M
102	3	6	3	14
107	26	35	45	74
111	0	3	0	11
112	9	62	27	174
113	1	0	0	2
114	7	67	11	194
116	118	0	240	0
117	0	58	0	59
118	75	0	77	0
Subtotal	239	231	403	528
Total	470		931	

COMMENT: Because the two genders were studied in different trials, I believe that any safety analysis that lumps all trial data together without differentiating by gender may be misleading. Hence all analyses that I present below include differentiation by gender.

Pro-Arrhythmic Activity

The sponsor provided in advisory committee materials the summary of possible TdP events shown in Table 11**.**

Table 11: Sponsor's Adjudicated Torsade-like Events by Dose - Integrated Safety Dataset

Dose	Total no. of subjects [a]	No. of TdPs		% of subjects with Adjudicated Events	95% CI [b]
		Polymorphic and nonsustained VT	Polymorphic and sustained VT		
Male					
> 0.48 mg/kg[c]	67	2	1	4.5	0.9; 12.5
0.48 mg/kg[d]	217 [d]	0	1	0.5	0.0; 2.5
0.32 mg/kg	172	0	1	0.6	0.0; 3.2
0.16 mg/kg	66	0	0	0.0	0.0; 5.4
Placebo	231	1	0	0.4	0.0; 2.4
Female					
> 0.32 mg/kg[e]	55	3[f]	2	9.1	3.0; 20.0
0.32 mg/kg	225	1	0	0.4	0.0; 2.5
0.24 mg/kg	122	0	0	0.0	0.0; 3.0
Placebo	239	0	0	0.0[g]	0.0; 1.5

While Table 11 appears to justify not exceeding dosages of 0.48 mg/kg in men and 0.32 mg/kg in women, it also may imply that arrhythmia rates at or below these dosages are low. However, if one considers all potentially dangerous ventricular arrhythmic events (reported ventricular tachycardia, fibrillation, or cardiac arrest) on study day one, one gets the rates of events shown in Table 12.

Table 12: Reviewer's Rates of Ventricular Tachycardia, Fibrillation, or Cardiac Arrest on Day 1 by Dose and Gender, Safety Population

	F		M	
dose	subjects	%	subjects	%
placebo	239	2.9%	231	5.6%
0.16	1	0.0%	66	0.0%
0.24	122	3.3%	6	0.0%
0.32	225	3.1%	172	7.6%
0.32-0.48	7	28.6%	10	10.0%
0.48	34	8.8%	207	11.1%
0.48-0.72	4	0.0%	15	20.0%
0.64	10	20.0%	52	23.1%

COMMENT: While the majority of the events included in Table 12 were non-sustained ventricular tachycardias, they were reported by investigators as adverse events. Note that, except for the low numbers for the 0.32-0.48 and 0.24 (in men) doses, the rates are slightly higher in men than women (although this small difference may reflect the different enrollment by gender in the studies.) The rates in the placebo group likely do not reflect simple "placebo" treatment because, even though I selected day one event rates, other treatments were used in placebo patients. Regardless, it is clear that event rates are increased in men at the proposed to-be-marketed dose of 0.48 mg/kg.

Bradycardia and Hypotension

The other worrisome adverse event for tedisamil is bradycardia, perhaps leading to AV block and hypotension. The one death in the development program likely related to tedisamil use had pre-terminal events starting with bradycardia. Dr. Desai's summary of the events leading to death in this patient is as follows: An 80-year-old Asian female experienced bradycardia, asystole and low blood pressure resulting in a premature termination of study infusion within 15 minutes of its initiation. Approximately 10 minutes into the infusion, the subject experienced marked bradycardia and hypotension requiring atropine. Later during the infusion wide QRS complexes were noted possibly related to a wide QRS complex tachycardia. The subject underwent cardiopulmonary resuscitation and was intubated. On the same day, adverse events of acidosis (not otherwise specified), pulmonary edema, and hypoxic encephalopathy were reported. The subject was extubated two days post infusion but did not respond to further treatment and was declared dead.

I show the rates of bradycardia, bradycardia and hypotension, and AV block on day 1 by dose and gender in Table 13.

Table 13: Reviewer's Rates of Bradycardia, Bradycardia & Hypotension, and AV Block on Day 1 by Dose and Gender, Safety Population

dose	F			M		
	bradycardia	bradycardia & hypotension	AV block	bradycardia	bradycardia & hypotension	AV block
0	1.3%	0.0%	0.0%	2.6%	0.0%	0.4%
0.16	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
0.24	2.5%	0.0%	2.5%	0.0%	0.0%	0.0%
0.32	4.0%	0.4%	0.9%	2.3%	0.0%	1.7%
0.32-0.48	14.3%	14.3%	0.0%	10.0%	0.0%	0.0%
0.48	11.8%	0.0%	8.8%	8.2%	0.5%	1.0%
0.48-0.72	25.0%	25.0%	25.0%	13.3%	6.7%	0.0%
0.64	0.0%	0.0%	0.0%	5.8%	3.8%	3.8%

About 73% of patients received concomitant beta blocker therapy. Perhaps not surprisingly, these adverse events appear to be more frequent in patients with concomitant beta blocker use. I show the rates of bradycardia and hypotension on day one by dose, gender, and beta blocker use in Table 14.

Table 14: Reviewer's Rates of Bradycardia & Hypotension on Day One by Dose, Gender and Beta Blocker Use, Safety Population

dose	F		M		Both	
	No BB	BB	No BB	BB	No BB	BB
0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
0.16			0.0%	0.0%	0.0%	0.0%
0.24	0.0%	0.0%			0.0%	0.0%
0.32	0.0%	0.6%	0.0%	0.0%	0.0%	0.3%
0.32-0.48	0.0%	20.0%	0.0%	0.0%	0.0%	8.3%
0.48	0.0%	0.0%	1.4%	0.0%	1.2%	0.0%

dose	F		M		Both	
	No BB	BB	No BB	BB	No BB	BB
0.48-0.72	0.0%	33.3%	0.0%	11.1%	0.0%	16.7%
0.64	0.0%	0.0%	0.0%	5.4%	0.0%	4.9%

BB = beta blocker use

COMMENT: The rates of bradycardia and AV block in women are increased even at the ineffective dose of 0.24 mg/kg. They may be increased for men as low as 0.32 mg/kg and are clearly increased for both genders at the proposed to-be-marketed doses (0.32 mg/kg for women and 0.48 mg/kg for men). The events are also associated with beta blocker use and with the abandoned two dosage, 50-minute dosing regimen. Because one death (in a patient with concomitant beta blocker use) is linked to these events, I am concerned about the risk/benefit tradeoff for tedisamil at the proposed to-be-marketed doses.

Other Adverse Events

There are three other types of adverse events that I consider noteworthy:

- Infusion site burning or pain on day 1 was more common with tedisamil, reaching about 8% in the 0.64 mg/kg groups vs. <1% in the placebo groups. This may be due to the low pH of the drug product.
- Seizures were rare, occurring in two patients (one placebo and one tedisamil 0.48) at one site and both in association with DC cardioversion on day 1. One patient in a tedisamil 0.32 group had an "epilepsy paroxysm" on day 14, but that event would appear totally unrelated to drug treatment because of its timing.
- Dr. Desai's notes in his review that strokes appeared to be more frequent in the tedisamil groups but he is unable to provide an explanation or interpretation. I agree that attribution for these events is difficult (because the times of occurrence are scattered and usually delayed days from drug administration), but I found the following thromboembolic events in the two weeks following study drug administration: 8:2 MIs (tedisamil:placebo, but note that randomization was about 2:1), 1:1 pulmonary emboli, 1:0 limb thrombosis, and 9:0 strokes, for an overall ratio of 19:3. These events are distributed by dose group and gender as shown in Table 15.

Table 15: Reviewer's Thromboembolic Event Rates in the Two Weeks following Administration by Dose and Gender

dose	F	M	Both
0	0.8%	0.4%	0.6%
0.16	0.0%	1.5%	1.5%
0.24	1.6%	0.0%	1.6%
0.32	3.6%	1.2%	2.5%
0.32-0.48	0.0%	0.0%	0.0%
0.48	0.0%	1.0%	0.8%
0.48-0.72	0.0%	0.0%	0.0%
0.64	10.0%	5.8%	6.5%

COMMENT: While I can only speculate on whether there is a real association between tedisamil use and thromboembolic events and a cause for it, the results in Table 15 are concerning to me because there is a suggestion of a dose-response. The highest rates in the 0.64 group are from one study (112), and the placebo group in that study had no events. I am concerned that many or most of these events may be embolic events that are related to atrial thrombi and could be related to a differential effect of tedisamil. I could not relate these events to the use of heparin or warfarin—most are associated with heparin use because higher risk patients are more likely to receive heparin or heparin may have been started as a treatment for the event. At least these event rates should remind us that conversion of atrial fibrillation is associated with clinically significant rates of adverse events other than electrical ones.

Risk Minimization Action Plan (RiskMAP)

The sponsor has proposed an education-based RiskMAP incorporating reminder tools and an evaluation plan to manage the risks associated with tedisamil. The Office of Surveillance and Epidemiology (OSE) has completed a thorough review of this plan. They have concluded that medication errors due to a complex dosing and administration regimen are very concerning and warrant further deliberation. They believe that the increased risk for dosing/administration error can be best mitigated by simplifying and improving the dosing regimen and the product label. They recommend that approval of tedisamil should be contingent upon simplifying the dosage and administration regimen and addressing the recommendations outlined below. At this time, they are unable to determine if a RiskMAP is warranted (or provide a meaningful review) until the dosing and administration regimen is established.

COMMENT: I share OSE's concerns about the complexity of the dosing and administration regimen. In addition to the complex (and not well justified) dosing scheme by gender, weight, and height discussed under Efficacy, Dosing above, the administration scheme involves a change in infusion rate: Half of the dose is to be administered in the first 10 minutes and the other half in the last 20 minutes. The sponsor's justification for this administration scheme is based on pharmacokinetic considerations (see Clinical Pharmacology above). Dr. Desai's suggestion that the sponsor change the regimen to a slow bolus plus a constant infusion seems preferable. However, the sponsor would have to test such a change in regimen in a clinical trial.

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