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Solvay Pharmaceuticals

Tedisamil Injection 20 mg/10 mL

NDA No. 22-123

Indication: Rapid conversion of recent onset (3 hours – 45 days) atrial fibrillation or atrial flutter to normal sinus rhythm

Briefing Book for Advisory Committee

Cardiovascular and Renal Drugs FDA Advisory Committee Meeting
December 12, 2007

AVAILABLE FOR PUBLIC DISCLOSURE
WITHOUT REDACTION

Solvay Pharmaceuticals Inc,
901 Sawyer Road,
Marietta, GA 30062

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LIST OF ABBREVIATIONS

AEs	Adverse Event(s)
AFib	Atrial Fibrillation
AFl	Atrial Flutter
AOC	Adjudication and Oversight Committee
AUC	Area Under the Curve
AV	Atrioventricular
ATP	Adenosine Triphosphate
b.i.d.	Twice daily dosing
BMI	Body mass index
bpm	beats per minute
BP	Blood pressure
bw	body weight
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CL	Clearance
CrCL	Creatinine Clearance
DBP	Diastolic Blood Pressure
DC	Direct Current (cardioversion)
DHCL	Dihydrochloride
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
F	Female
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gamma-GT	Gamma Glutamyl Transferase
GFR	Glomular Filtration Rate
HCP	Health Care Professional
HLT	High Level Term
ICD	Implantable Cardiac Devices
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IHD	Ischemic Heart Disease
IR	Immediate release
ISS	Integrated Summary of Safety
ITT	Intent-To-Treat
IV	Intravenous
LBM	Lean Body Mass
M	Male
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities

mg	milligram
mg/kg	milligram per kilogram
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
mL	milliliter
NEC	Not Elsewhere Classified
NOS	Not Otherwise Specified
NSR	Normal Sinus Rhythm
NS-PVT	Non-sustained Polymorphic Ventricular Tachycardia
NYHA	New York Heart Association
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
QT	QT-interval of the ECG
QTc	Heart rate corrected QT interval of the ECG
QTcB	QTc Bazett
QTcF	QTc Fridericia
QRS	Q wave, R wave and S wave complex
RR	RR interval of the ECG
SAEs	Serious Adverse Events
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
S-PVT	Sustained Polymorphic Ventricular Tachycardia
SQF	Sesquifumarate
SVE	Supraventricular Extrasystoles
SVT	Supraventricular tachycardia
TEAE	Treatment Emergent Adverse Events
TESAE	Treatment Emergent Serious Adverse Events
TdP	Torsade de pointes
U.S.	United States
VT	Ventricular Tachycardia

1 Executive Summary

1.1 Overview

Solvay Pharmaceuticals submitted a United States (U.S.) New Drug Application (NDA) for Tedisamil Injection 20 mg/10 ml (Tedisamil) to the U.S. Food and Drug Administration (FDA) in December 2006. Tedisamil is a Class III antiarrhythmic agent for the proposed indication:

> *The rapid conversion of recent onset (3 hours to 45 days) atrial fibrillation (AFib) or atrial flutter (AFl) to normal sinus rhythm*

The clinical development program for intravenous (IV) tedisamil included two Phase II studies and seven Phase III studies in subjects with AFib or AFl. In this program, 1401 AFib/AFl subjects were treated: 931 subjects received IV tedisamil and 470 subjects received placebo. Based on experience during the clinical program, a gender-specific dosing regimen is being recommended to produce the most favorable benefit/risk balance for this compound:

- AFib/AFl in Males: 0.48 mg/kg administered intravenously using a two-step, 30-minute infusion regimen.
- AFib/AFl in Females: 0.32 mg/kg administered intravenously using two-step, 30-minute infusion regimen.

The benefits of tedisamil include rapid and sustained conversion to normal sinus rhythm (NSR), which has been demonstrated across several important subject subgroups including populations: over age 65 years; with mild to moderate renal impairment; with congestive heart failure (New York Heart Association [NYHA] Class II/III); using beta-blocking agents; with AFib/AFl of longer than 48 hours in duration; and with recurrent AFib/AFl episodes. Safety has been demonstrated at the recommended doses.

Tedisamil treatment requires appropriate selection of patients, careful calculation of dose, and administration in a monitored in-hospital setting. Solvay is committed to implementing a Risk Minimization Action Plan (Risk MAP) to reinforce the labeling instructions and help assure optimal patient outcomes in clinical practice.

1.2 Disease Background

Atrial fibrillation is the most common, clinically relevant arrhythmia with an overall prevalence that increases with age.[1] This common sustained cardiac rhythm disorder results in a substantial mortality and morbidity from stroke, thromboembolism, heart failure and impaired quality of life.[2,3] Atrial fibrillation affects an estimated 2.3 million adults in the United States, with more than 160,000 new cases diagnosed each year.[4]

In the Framingham study, the lifetime risks at age >40 years for developing atrial fibrillation were 26% for men and 23% for women.[5,6] As women tend to live longer than men, and because the disease is more prevalent in older people,[4] the disease burden on women is high and growing.

The symptoms of atrial fibrillation (e.g., palpitation, presyncope, fatigue, dyspnea) are primarily caused by fast ventricular rates, which can be controlled by using atrio-ventricular node blocking drugs (rate control) or by converting atrial fibrillation to sinus rhythm (rhythm control). Restoration of sinus rhythm reduces the need for the use of atrio-ventricular node blocking drugs for rate control, decreases chances of thromboembolism, prevents tachycardia-related cardiomyopathy, and lessens atrial mechanical dysfunction and electrophysiological remodeling.[8]

1.3 Unmet Medical Need

There is no one single best approach to treating AFib/AFl. Physicians today select from several treatment strategies and options and tailor their treatment to the individual patient's medical needs and personal expectations. Cardioconversion to NSR by direct electric current (DC) is very effective. The potential drawbacks of DC cardioversion include the need for anesthesia, risk of aspiration, pain, skin burning, pulmonary edema, pacemaker malfunction, thromboembolism, and adverse cardiac effects such as sinus arrest and ventricular fibrillation.[9,10] In addition, patient anxiety related to the procedure is frequently a consideration. Pharmacological cardioversion, while typically less effective than DC cardioversion, has the advantages of generally being simpler and convenient, free of the anesthesia requirement, and being feasible if the patient has recently eaten (recent post-prandial state). The potential disadvantages include drug-related side effects and limited effects in patients with AFib/AFl of long duration.

The drugs used for rhythm control in recent onset atrial fibrillation patients are Class IA (e.g., quinidine, procainamide, disopyramide), Class IC (e.g., flecainide, propafenone), and Class III (e.g., ibutilide, dofetilide, sotalol, amiodarone) antiarrhythmic agents, both by oral and intravenous routes.[10,11] Some of these agents are used "off-label" for conversion of atrial fibrillation or flutter in that they have not been approved by FDA for this use. In general, these drugs work by prolonging atrial refractoriness. Both Class I and Class III agents have significant proarrhythmic effects, which are intensified in patients with structural heart disease. These agents individually may cause other severe adverse effects.[12-18]

Due to the limitations of Class I and III antiarrhythmic agents currently available, there is unmet medical need for a drug with a well-characterized efficacy and safety profile, predictable pharmacokinetics, a sustained effect, efficacy in atrial fibrillation of longer duration, well-characterized proarrhythmic potential, and good tolerability in patients with cardiac disease. Tedisamil, a Class III antiarrhythmic agent, provides such pharmacological alternative to fill this unmet medical need.

Of particular note, there are well documented differences in QT between males and females.[19] Women tend to have longer QT intervals between puberty and at least 55 years of age, perhaps due to lower parasympathetic tone, or estrogen- or metabolic-related changes. They are more susceptible to malignant arrhythmias than men, and there is an increased incidence of Torsades de Pointes (TdPs) among women when treated with Class III antiarrhythmics, which is a consistent finding with all Class III agents approved for atrial fibrillation.[20,21,22] The reason for the female predominance in drug-induced TdP remains unclear. These gender-based differences have been investigated in the tedisamil AFib/AFl development program.

1.4 Mechanism of Action and Clinical Pharmacology

Tedisamil is a multiple potassium channel blocker which blocks the rapid (IK_r), slow (IK_s) and ultra-rapid (IK_{ur}) components of the delayed rectifier current, the transient outward current (Ito) and the ATP sensitive (IK_{ATP}), and the acetylcholine-activated (IK_{ACH}) potassium currents, two of them (IK_{ur} and IK_{ACH}) being atria specific. Tedisamil is a Class III antiarrhythmic drug that prolongs the cardiac action potential duration and refractory period, and at higher concentrations (10 times that required to block IK_r) also possesses sodium channel blocking properties in animal and human cardiac tissue preparations. Prolongation by tedisamil of the cardiac action potential duration and refractory period is seen predominantly in the atria compared to the ventricles.

Tedisamil clinical pharmacology has been characterized in Phase I studies and in clinical studies in AFib/AFl subjects. Key findings include the following:

- After intravenous administration, plasma concentrations decline in a multiexponential fashion. The elimination half-life of tedisamil is 4.5-6.9 hours following IV administration. Time of peak plasma concentration (T_{max}) shows a median value of 12.5 min when tedisamil is administered using the proposed two-step 30-min IV infusion.
- Tedisamil pharmacokinetics is linear and is not affected by gender or by congestive heart failure (NYHA Class I-III).
- Tedisamil metabolism is very limited. Elimination is almost exclusively as unchanged drug via the renal route.
- Tedisamil is associated with a dose-dependent QT/QTc prolongation which is not dependent on gender.
- Tedisamil clearance decreases in AFib/AFl subjects with moderate renal impairment, with no substantial effect on C_{max} following a single dose short infusion. The safety profile and the magnitude of QTc effects are similar in subjects with moderate renal impairment when compared to subjects with normal renal function. Dose adjustments in subjects with mild to moderate renal impairment are not needed for single dose short infusions of tedisamil.
- The volume of distribution of tedisamil increases with lean body mass (LBM). This is reflected in the recommended dosing regimen for tedisamil.
- The small decrease in tedisamil clearance following co-administration of tedisamil and verapamil does not affect the relationship between tedisamil exposure and QT in AFib/AFl subjects. Coadministration of tedisamil with verapamil does not necessitate a dosing adjustment.
- Tedisamil is a strong inhibitor of CYP 2D6. Caution should be exercised for co-administration with other drugs metabolized by CYP2D6, such as Type 1C antiarrhythmics (e.g., propafenone, flecainide, encainide), antidepressants (e.g., paroxetine, imipramine) and beta-blocking agents (e.g., metoprolol, carvedilol).

1.5 Clinical Development Program

Tedisamil was initially developed as an oral anti-angina compound in subjects with chronic stable angina pectoris. Given the antiarrhythmic profile of tedisamil and the availability of a variety of antianginal agents for first and second line treatment of chronic stable angina pectoris, it was considered appropriate to focus further development efforts on rapid conversion of AFib/AFl to NSR. Subsequently, work on the angina indication was discontinued and the development program was refocused to conversion of AFib/AFl to NSR.

Phase II studies with tedisamil in AFib/AFl subjects began in June 1998. Study S219.2.102 was designed to determine the percentage of AFib/AFl subjects who converted and remained in NSR at one hour after the start of a 10-minute infusion of tedisamil at 0.16 mg/kg and 0.24 mg/kg. This study was discontinued due to slow recruitment and lack of efficacy. Based on pharmacokinetic and pharmacodynamic (PK/PD) modeling, the dose and infusion regimen were adapted in subsequent studies.

The tedisamil doses were increased to include doses of 0.32 mg/kg and greater and the infusion time was lengthened to 30 minutes utilizing a two-step infusion process (half the dose in the first 10 mins and the other half in the remaining 20 mins). These doses and the revised infusion regimen were tested in a Phase II "proof of principle" study (S219.2.107), which enrolled subjects who had an AFib/AFl episode of ≤48 hour duration. This study showed efficacy in both doses compared to placebo. The rate of conversion within 2.5 hours was 46.2% (24/52) for 0.32 mg/kg and 57.1% (24/42) for 0.48 mg/kg tedisamil compared to 8.7% (4/46) for placebo.

Phase III studies, using the two-step, 30-minute infusion regimen, began in November 2002. Following several reports of serious events in female subjects, Solvay decided to suspend the studies in March 2003 after consultation with the program's drug safety monitoring board (the Adjudication and Oversight Committee - AOC). A thorough investigation showed that arrhythmic events in female subjects occurred at doses of tedisamil 0.48 mg/kg and higher. Following a review of available data and consultation with the FDA and Medicines and Healthcare Products Regulatory Agency (MHRA), the antiarrhythmia program was revised to adopt a dose-finding strategy separated by gender. The two studies investigating doses above 0.32 mg/kg were amended to enroll only male subjects and three gender-specific Phase III studies were added to the program (one male and two female gender-specific studies). A total of 931 AFib/AFl subjects were exposed to IV tedisamil and 470 AFib/AFl subjects were exposed to placebo in the antiarrhythmia program (Table 4-1). The numbers of subjects exposed to the recommended doses were 207 males at 0.48 mg/kg and 225 females at 0.32 mg/kg, compared to 231 males and 239 females exposed to placebo.

Efficacy of tedisamil in the AFib/AFl population is based on results from five multicenter, randomized, double-blind, placebo-controlled, parallel, Phase III studies conducted in subjects with recent onset (3 hours – 45 days) of AFib/AFl. Three studies were primarily in males and two studies were in females only. All five studies had the same study design and differed only in the tedisamil doses tested and the gender of subjects enrolled. Efficacy data were compared across studies and then integrated for subgroup analyses.

Key inclusion and exclusion criteria -- Subjects had to have documented AFib or AFl for at least 3 hours but not more than 45 days as a first or recurrent episode, be hemodynamically stable (SBP > 90mmHg, DBP <105mmHg), and be at least 18 years of age. Anticoagulation was to be undertaken at the discretion of the investigator, according to current guidelines.

The exclusion criteria included:

- Congestive heart failure of NYHA functional Class IV
- Clinical evidence of hyperthyroidism
- History of life-threatening ventricular arrhythmias including TdP
- Myocardial infarction (MI) within 30 days before randomization
- Cardiac surgery within three months before randomization
- Congenital long QT syndrome
- QTc interval >470 msec prior to randomization
- Serum creatinine >1.8 mg/dL (159 mmol/L) or serum potassium <4.0 mEq/L (<4.0 mmol/L)

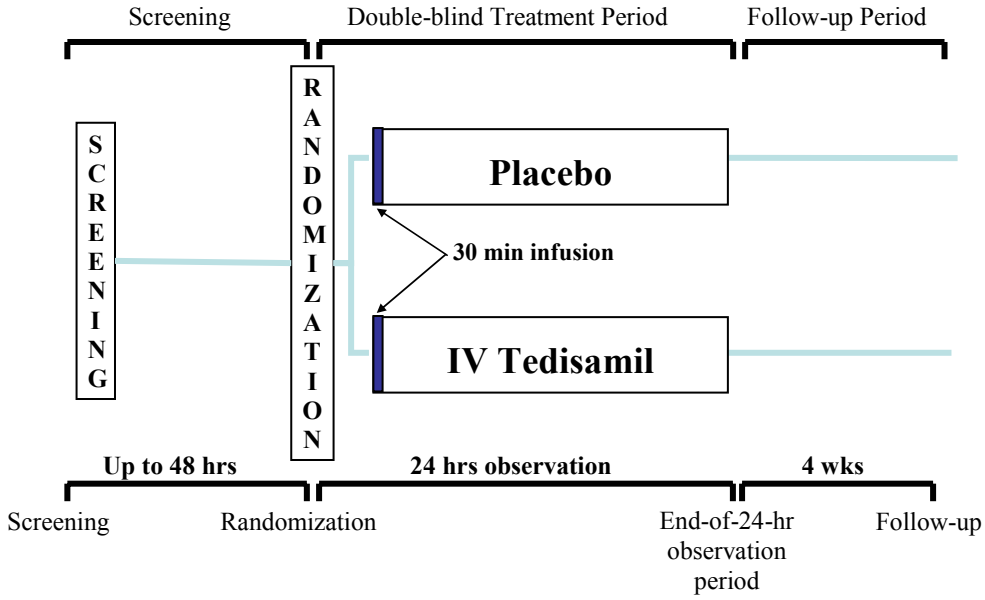
Concurrent treatment with antiarrhythmic drugs (except for digitalis, diltiazem, or beta-blocking agents) was not allowed. Subjects could not have been treated with amiodarone in the three months before randomization.

If entry criteria were met, subjects were randomized to receive one of the doses of tedisamil or placebo. Subjects were hospitalized for study drug infusion and monitored for 24 hours by Holter electrocardiogram (ECG), which was started 10 minutes before the start of the study drug infusion. The Holter tapes were analyzed centrally (by a specialized contract research organization) to identify the primary endpoint of conversion to NSR (for at least 60 sec), and in the case of conversion, to assess maintenance of NSR for 24 hours.

The Holter tapes were also analyzed to assess tedisamil's proarrhythmic potential. This analysis was a supplement to the more traditional reporting of adverse events (AEs) by the investigators. Ventricular tachycardia events were coded by prespecified definitions (see Section 6.8.1) and adjudicated by the AOC as non-sustained monomorphic, non-sustained polymorphic, sustained monomorphic, sustained polymorphic, and Torsade-like. (A copy of the AOC Charter is provided in Appendix 1.) In addition, a 12-lead ECG, including 120 sec rhythm strips, was administered at regularly scheduled intervals.

The study design for the five Phase III studies is shown in Figure 1-1 and described in detail in Section 5.2.

Figure 1-1 Schematic for Study Design of Pivotal Studies in Tedisamil Clinical Development Plan



Efficacy Parameters

The primary efficacy parameter was the percentage of subjects who converted to NSR for at least 60 seconds at anytime within 2.5 hours after the initiation of the study drug infusion.

Secondary efficacy parameters included the percentage of subjects achieving the primary endpoint (ie, conversion to NSR within 2.5 hrs) and who were:

- in NSR at 2.5 hours after start of infusion
- in NSR at 24 hours
- remaining in NSR for 24 hours (analyzed only with integrated efficacy dataset)
- in NSR at hospital discharge.

Time to conversion (time from start of infusion to first conversion to NSR) was also a secondary efficacy parameter.

Subject Demographics

Subjects participating in the IV tedisamil studies were almost exclusively Caucasian with 98% classified as white. In the integrated safety dataset, the tedisamil groups consisted of 759 males (528 tedisamil; 231 placebo) and 642 females (403 tedisamil; 239 placebo) (Table 4-1). The female population tended to be older (by ~8 years), more likely to have more severe congestive heart failure (NYHA Class II/III), and have an arrhythmia episode of greater than 48 hours duration. A summary of the baseline characteristics for the efficacy dataset for the individual Phase III studies is provided in Section 5.3 and for the integrated safety dataset in Appendix 2.

Overall, medical history and use of concomitant medication were comparable across studies, across the dose groups, and between treatment groups (tedisamil vs. placebo). The main categories of medical conditions were vascular disorders and cardiac conditions. The major classes of concomitant medications taken, anti-thrombotic agents, beta-blocking agents and cardiac therapy, are consistent with this population. In addition to those medications, tedisamil was used during the studies with a broad range of concomitant medications, including calcium antagonists, nitrates, lipid-lowering agents, hypoglycemics, hormone replacement therapy, diuretics, acetylsalicylic acid, NSAIDS, H_2 antagonists, and ACE-inhibitors. When compared by gender, females took a wider variety of concomitant medications than males.

1.6 Efficacy Summary

Five multicenter, randomized, double-blind, placebo-controlled Phase III studies demonstrate the efficacy of tedisamil in subjects with recent onset (3h – 45 days) AFib/AFl. Integrated Phase III efficacy analyses from the five Phase III studies included data from 580 male subjects (403 in tedisamil groups and 177 in placebo groups) and 543 female subjects (341 in tedisamil groups and 202 in placebo groups (Table 5-1). Tedisamil dose groups were 0.16, 0.24, 0.32, 0.48, or 0.64 mg/kg. Efficacy results for the integrated data were consistent with the individual studies for both the primary and secondary efficacy parameters.

Efficacy Data from Individual Phase III Studies

All studies met their primary objective and demonstrated efficacy of tedisamil compared to placebo at the recommended doses of 0.48 mg/kg for males (three studies) and 0.32 mg/kg for females (two studies), thus demonstrating reproducibility of results (as shown in Table 1-1). The rates of conversion to NSR in the three male studies of 0.48 mg/kg were 52.9%, 31.1%, and 29.2%, compared to 5.7%, 9.8%, and 6.3%, respectively, for placebo. In the two female studies, the rates of conversion for 0.32 mg/kg tedisamil were 21.5% and 17.9%, compared to 2.9% and 4.5% for placebo.

Table 1-1 Summary of Primary Efficacy from Individual Studies

Study	Tedisamil Dose mg/kg	NSR for at least 60 sec at any time within 2.5 h after start of study drug infusion AFib ITT[a] n/N (%)	P-value[b]	Confidence Interval
Phase III Male Studies				
S219.3.112[c]	0.32 **0.48** 0.64 Placebo	13/56 (23.2%) **27/51 (52.9%)** 29/43 (67.4%) 3/53 (5.7%)	0.0096 **<0.0001** <0.0001	2.1, 33.0 **29.0, 65.6** 43.1, 80.4
S219.3.114 (Post Amend)[d]	0.16 0.32 **0.48** Placebo	12/50 (24.0%) 15/51 (29.4%) **14/45 (31.1%)** 5/51 (9.8%)	0.057 0.013 **0.0089**	-3.3, 31.7 1.4, 37.8 **2.1, 40.5**
S219.3.117	**0.48** Placebo	**14/48 (29.2%)** 3/48 (6.3%)	**0.003**	**8.3, 37.5**
Phase III Female Studies				
S219.3.116	0.24 **0.32** Placebo	10/106 (9.4%) **23/107 (21.5%)** 3/105 (2.9%)	0.047 **<0.0001**	-0.8, 13.9 **9.0, 28.3**
S219.3.118	**0.32** Placebo	**12/67 (17.9%)** 3/67 (4.5%)	**0.014**	**3.0, 23.9**

[a] Predefined primary efficacy analysis in the individual studies was performed using AFib ITT sample.
[b] Comparison between tedisamil dose group and placebo.
[c] Study S219.3.112 included 36 female subjects, which were not included in these results; they are included in the integrated Phase III efficacy dataset and its female subgroup.
[d] Study S219.3.114 was amended to enroll only male subjects.

In addition, tedisamil's effect was sustained, with the vast majority of subjects who converted within 2.5 hours remaining in NSR for at least 24 hours (representing at least 92% of those who converted in the initial 2.5 hours). The percentages of converters who were in NSR at 24 hours were 92.6%, 100%, and 100% for males in the 0.48 mg/kg tedisamil group in the three male studies and 95.6% and 91.7% for females in the 0.32 mg/kg tedisamil group in the two female studies.

Tedisamil's effect was rapid. The mean time to conversion at the recommended dose (0.48 mg/kg) in the three male studies was 37.7, 18.5, and 22.2 mins compared to 45.0, 84.0, and 92.7 mins, respectively, for the placebo groups. In females at the recommended dose (0.32 mg/kg), the mean time to conversion with tedisamil was 24.2 and 27.4 mins compared to 88.7 mins with placebo in both studies.

Integrated Efficacy Data

Based on the integrated efficacy dataset of the five Phase III studies, at the recommended doses, 34.5% of males (at 0.48 mg/kg) and 18.3% of females (at 0.32 mg/kg) converted to NSR within 2.5 hours (vs. 6.2% and 4.5% in the respective placebo groups). Table 1-2 shows the percentage of converters for males who received 0.48 mg/kg and for females who received 0.32 mg/kg compared to those who received placebo for all subjects by duration of episode

(≤48 hours or >48 hours). A higher percentage of subjects converted to NSR if the duration of arrhythmic episode was ≤48 hours than if the subjects had their current episode for longer than 48 hours. This finding is consistent with clinical experience, where AFib/AFl of longer duration is more difficult to cardioconvert.

Table 1-2 Percentage Conversion within 2.5 Hrs in Subjects with AFib/AFl – Integrated Phase III Efficacy Dataset by Recommended Dose and Duration of Episode

Gender	Tedisamil Dose Group	% Conversion to Normal Sinus Rhythm (NSR) for at least 60 secs within 2.5 hrs Duration AFib/AFl					
		3 Hours to 45 Days		≤ 48 Hrs		>48 Hrs	
		Tedisamil	Placebo	Tedisamil	Placebo	Tedisamil	Placebo
Male Subjects	0.48 mg/kg	(N=171)[a] 34.5% p <0.0001; CI: 20.5, 36.3	(N=177) 6.2%	(N=82) 52.4% p<0.0001 CI: 26.5, 52.6	(N=89) 12.4%	(N=88)[a] 18.2% p<0.0001 CI: 10.6, 28.1	(N=88) 0.0%
Female Subjects	0.32 mg/kg	(N=202) 18.3% p <0.0001; CI: 7.6, 20.0	(N=201)[a] 4.5%	(N=71) 32.4% p=0.0022 CI: 8.8, 36.2	(N=60) 10.0%	(N=131) 10.7% P=0.0041 CI: 2.3, 14.7	(N=141)[a] 2.1%

Note: Dose listed is recommended therapeutic dose. CI describes comparison of treatment group versus placebo.
Percentages are based on the total number of subjects in the ITT sample, Phase III grouping, who did not undergo DC cardioversion within 2.5 hours after the start of study drug infusion.
[a] Excludes one subject who had DC cardioconversion within 2.5 hours.

Based on the integrated efficacy data, tedisamil at the recommended doses was also effective across other subgroups. Subject age (<65; ≥65 years), NYHA status (Class I; Class II/III), concomitant use of beta-blocking agents, first episode or recurrent episode, and renal status (CrCL <60; ≥60 mL/min) did not affect the efficacy of tedisamil at those doses (Table 5-7 for males and Table 5-8 for females).

Tedisamil's effect was sustained in subjects who converted within the 2.5 hours. Table 1-3 shows that at the recommended doses, 53 of the 59 (89.8%) males who converted at 2.5 hours with 0.48 mg/kg tedisamil, and 32 of 37 (86.5%) females who converted at 2.5 hours with 0.32 mg/kg tedisamil remained in NSR at 24 hours. This was also true for the very small number of placebo subjects who converted to NSR within 2.5 hours.

Tedisamil reduced the time to conversion. The mean time to conversion to NSR for male subjects who received 0.48 mg/kg was 28.6 mins compared to 75.7 mins for placebo males. The mean time to conversion for female subjects who received the 0.32 mg/kg was 25.1 mins compared to 92.1 mins for placebo females (Table 5-10).

Table 1-3 Results from the Secondary Efficacy Parameters for Recommended Dose by Gender

Gender; Tedisamil Dose	Secondary Efficacy Parameter Conversion within 2.5 hours and:			
	In NSR at 2.5 hrs n (%)[a]	In NSR at 24 hrs n (%)[a]	Remaining In NSR at 24 hrs n (%)[a]	In NSR at Hospital Discharge n (%)[a]
Male				
0.48 mg/kg	57/59 (96.6%)	56/59 (94.9%)	53/59 (89.8%)	47/59 (79.7%)
Placebo	10/11 (90.9%)	10/11 (90.9%)	10/11 (90.9%)	9/11 (81.8%)
Female				
0.32 mg/kg	36/37 (97.3%)	35/37 (94.6%)	32/37 (86.5%)	30/37 (81.1%)
Placebo	9/9 (100%)	8/9 (88.9%)	8/9 (88.9%)	7/9 (77.8%)

[a] Denominator is the number of converters from the Primary Efficacy Parameter i.e., the number converting to NSR for at least 60 secs within 2.5 hrs of infusion; subjects who required DC cardioconversion during these time points were excluded from analysis.

A summary of the efficacy results from the individual studies and from the integrated Phase III efficacy dataset are provided in Section 5.3.

1.7 Safety Summary

The safety profile of tedisamil, when administered at the gender-specific recommended doses, appears to be comparable to that reported in the literature for other Class III antiarrhythmic medications.[13,15,25-32] No additional safety concerns were identified.

The integrated safety dataset consists of data collected on 931 AFib/AFl subjects exposed to tedisamil and 470 placebo AFib/AFl subjects enrolled in nine clinical studies (two Phase II and seven Phase III studies).

Adverse Events

A summary of treatment-emergent adverse events (TEAEs) are summarized in the following paragraphs. These events were collected and reported by the investigators in the standard manner for clinical trials.

TEAEs: Treatment-emergent adverse events (TEAEs) were reported for a similar percentage of subjects in the tedisamil and placebo groups (66.9% vs. 61.9% for males; 66.5% vs. 62.8% for females). In most cases TEAEs were transient, and mild or moderate in severity. The most commonly occurring TEAEs were cardiac disorders, which were reported in a dose-dependent pattern. The percentage of subjects reporting cardiac disorders at the recommended dose (0.48 mg/kg) in males was 48.3% with tedisamil versus 42.0% with placebo, and at the recommended dose (0.32 mg/kg) in females was 40.4% with tedisamil versus 28.0% with placebo (Table 6-10 for males and Table 6-11 for females).

Ventricular tachycardia (VT) and bradycardia were the most commonly reported cardiac TEAEs in both male and female subjects. The incidence of VTs reported as TEAEs was slightly higher in the male tedisamil subjects (11.6%) than the male placebo subjects (6.9%), but the incidence was similar in the female treatment groups (4.7% vs. 5.0%). At the

recommended doses, the incidence of VT was 12.6% in males (0.48 mg/kg) and 3.1% in females (0.32 mg/kg). Bradycardia reported as a TEAE was not different between the tedisamil and placebo male subjects (4.5% vs. 5.6%), and only slightly higher in the tedisamil female subjects than the placebo female subjects (5.2% vs. 3.3%).

The most commonly occurring non-cardiac TEAEs in males at the recommended dose were headache (reported by 2.9% of tedisamil subjects vs. 2.2% placebo subjects), infusion site burning (2.4% vs. 0.4%), injection site pain (2.4% vs. 0.0%), hypotension (1.4% vs. 0.9%), and oral paraesthesia (1.9% vs. 0.4%). In females at the recommended dose, the most common were headache (3.6% vs. 3.3%), hypotension (2.2% vs. 3.3%), and dizziness (1.8% vs. 1.7%). Infusion site burning, injection site pain, and oral paraesthesia were reported by 0.9%, 1.3%, and 0.9% of females at the recommended dose (vs. 0.4%, 0.0%, and 0.4%, respectively, with placebo). Except for injection/infusion site reactions and oral paraesthesia, no meaningful difference was observed between tedisamil and placebo (see Table 6-6).

TESAEs: Treatment-emergent serious adverse events (TESAEs) were reported for 9.7% of tedisamil and 8.9% of placebo subjects. Cardiac disorders were the most common type of TESAEs. The incidence of cardiac TESAEs was comparable between the combined tedisamil and placebo groups in males at the recommended dose of 0.48 mg/kg (6.8% vs. 6.1%). There was no apparent dose response pattern in males. In females, the incidence of cardiac TESAEs at the recommended dose of 0.32 mg/kg was 5.3% compared to 4.2% with placebo. The most commonly reported cardiac TESAE was atrial fibrillation, which was reported for 4.3% of males at the recommended dose of tedisamil compared to 3.0% of placebo males, and for 1.3% of females at the recommended dose compared to 2.1% of placebo females (see Table 6-12 and Table 6-13).

Deaths: Eleven deaths (4 males and 7 females) occurred in the IV tedisamil antiarrhythmia program. Two of the 11 subjects were randomized, but died before receiving treatment. The other nine deaths are included in the integrated safety dataset and occurred at an equal rate in both treatment groups: 0.64% (6/931 tedisamil and 3/470 placebo subjects). The majority of deaths were cardiac related and none were considered related to study drug. (Table 6-9 in Section 6.5 provides a brief description of these deaths.)

Discontinuations due to TEAEs: The number of subjects who terminated from the study due to a TEAE was low and they were distributed evenly across dose groups. Discontinuations due to a TEAE at the recommended doses were: 4 (1.9%) of 207 tedisamil males (vs. 0.9% in placebo) and 5 (2.2%) of 225 tedisamil females (vs. 1.3% in placebo) (see Table 6-14 and Table 6-15).

ECG Measurements

Mean QTc Bazett (QTcB) values increased in a dose-dependent manner in the tedisamil groups, reaching a maximum at 30 minutes after start of infusion. QTcB values had generally stabilized at 2.5 hours after the initiation of infusion and the majority of maximum QT values occurred during the initial 2.5 hours from baseline. The incidence of QTcB measurements ≥550 msec was generally low, with a higher incidence at the higher dose groups.

Holter data were analyzed to evaluate tedisamil for proarrythmia events. The Holter tapes were centrally analyzed for arrhythmias according to specific definitions. All events of 3 or more abnormal/aberrant ventricular complexes with a rate of >100 bpm were defined as single episodes of adjudicated VT, coded (as monomorphic or polymorphic, sustained or non-sustained, or Torsade-like) and adjudicated by the AOC according to predefined categories (see Appendix 1).

Adjudicated Torsade-like VTs, as assessed by the AOC based on Holter analysis, were reported for 12 subjects, 10 tedisamil subjects and 2 placebo subjects. However, one of the placebo subjects (female) experienced a Torsade-like VT as a result of a non-synchronized DC cardioversion and was excluded from consideration. Another Torsade-like VT was identified from an ECG reading in a female (at 0.48 mg/kg tedisamil) for which no Holter data was available, but which was reported as an adverse event as "drug-induced prolonged QT syndrome with non-sustained polymorphic ventricular tachycardia". Therefore, the accurate count of adjudicated Torsade-like VTs in the arrhythmia studies was 11 (1.2%) tedisamil subjects and 1 (0.2%) placebo subject. Of these 12 adjudicated TdPs, seven were classified as non-sustained and five sustained polymorphic VTs. The latter all received DC cardioversion. Only in two cases was the adjudicated TdP actually reported as an adverse event of TdP (i.e., as a TEAE) by the investigator; one female case in the 0.48 mg/kg dose group, and one female case in the 0.64 mg/kg dose group.

A dose relationship was observed in the incidence of the adjudicated Torsade-like events, with increases occurring at doses >0.48 mg/kg in males and >0.32 mg/kg in females, as shown in Table 1-4. For males in the recommended dose group (0.48 mg/kg), 1 adjudicated Torsade-like event (0.5%) was occurred; for females in the recommended dose group (0.32 mg/kg tedisamil), 1 adjudicated Torsade-like event (0.4%) occurred. With placebo, one (0.4%) male subject and no (0.0%) female subject experienced an adjudicated Torsade-like event. Also worth noting is that most (10/12) adjudicated Torsade-like events occurred within 50 minutes after initiation of infusion; the other two occurred at 4.5 and 18 hours after initiation of infusion (see Section 6.8.3). All sustained Torsade-like events occurred within 40 minutes after the start of infusion. DC cardioconversion was applied to the subjects who experienced a sustained, polymorphic, Torsade-like VT, and NSR was achieved. Subjects who had non-sustained polymorphic VTs, including Torsade-like events, did not require DC cardioconversion.

Table 1-4 Adjudicated Torsade-like Events by Dose - Integrated Safety Dataset

Dose	Total no. of subjects[a]	No. of Adjudicated Torsade-like Events		% of subjects with Adj. Torsade-like 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	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 [f]	239	0	0	0.0[g]	0.0; 1.5

[a] Incidence and confidence intervals (CIs) are not given for 0.24 mg/kg for males and 0.16 mg/kg for females due to small numbers; no adjudicated Torsade events occurred at these doses.
[b] Clopper-Pearson confidence interval
[c] Doses included: 0.64 mg/kg and 0.48-0.72 mg/kg
[d] Including 10 male subjects on 0.32-0.48 mg/kg
[e] Doses included: 0.32-0.48 mg/kg, 0.48 mg/kg, 0.64 mg/kg and 0.48-0.72 mg/kg
[f] One of these 3 subjects was diagnosed from an ECG reading, while the others were all identified by Holter analysis.
[g] One female placebo subject had a non-synchronized DC-induced Torsade-like event and was not included in this summary.

Safety in Subgroups

Safety was assessed in subgroup populations including subjects over age 65 years, with congestive heart failure (NYHA Class II/III), using beta-blocking agents; and with renal impairment. Tedisamil was found to have a favorable safety profile as follows:

- No clinically relevant differences between tedisamil and placebo were observed at the recommended doses in the incidence of TEAEs or TESAEs in subjects <65 and ≥65 years of age.

- In patients with NYHA Class I and in NYHA Class II/III, no meaningful differences were observed between tedisamil and placebo in the incidence of TEAEs at the recommended doses. Therefore, tedisamil is recommended for use in male and female subjects who are categorized up to NYHA Class III. (NYHA Class IV was excluded from the clinical studies and therefore no safety information is available.)

- Tedisamil can be used in patients with mild to moderate renal impairment (<60 mL/min) without dose adjustment. Subjects with severe renal impairment (<30 mL/Min) were excluded from the efficacy studies and use in this population is contraindicated.

- For subjects not taking concomitant beta-blocking agents, a slightly higher rate of TESAEs in tedisamil treated male subjects was observed in comparison to placebo subjects. This phenomenon was not observed in female subjects. Otherwise, the occurrence of adverse events was comparable in the tedisamil and placebo groups at the recommended doses, whether or not the subject was receiving concurrent beta-blocking agents.

1.8 Benefit/Risk Assessment

As noted above, there is clearly an unmet medical need for treatment alternatives to provide rapid, effective restoration of NSR in patients with AFib/AFl. When used according to the label recommendations, tedisamil's clinical benefits are significant and directly address the areas of unmet medical need. The clinical program has evaluated tedisamil in both male and female populations, and has allowed for an appropriate characterization of the efficacy and safety profile in each, leading to a gender-specific dosing regimen that produces the most favorable benefit/risk ratio of this compound:

- AFib/AFl in Males: 0.48 mg/kg
- AFib/AFl in Females: 0.32 mg/kg
- Dosage regimen for both genders is a two-step, 30-minute IV infusion (half of the dose over 10 min and remainder over 20 min)

At the recommended doses, the benefits of tedisamil include:

- Conversion to NSR at recommended doses
- Rapid conversion to NSR
- Sustained conversion, i.e., remaining in NSR for 24 hours and at hospital discharge
- The benefits of tedisamil use are seen across subgroups. It should be noted that tedisamil has:
  - Efficacy in patients over 65 years of age
  - Efficacy in AFib of longer duration (up to 45 days)
  - Efficacy in congestive heart failure (through NYHA III)
  - Adequate safety data in males and females, including subjects over age 65 years
  - Tolerability, with a low incidence of AEs and discontinuations
  - Safety when used in subjects with mild to moderate renal impairment (no dose adjustment needed)
- Hepatic impairment not expected to have a significant effect on tedisamil elimination
- Can be administered concurrently with a broad range of medications, with very limited potential for drug interactions, because tedisamil is not metabolized in humans

The risks associated with tedisamil are similar to those already identified for other Class III antiarrhythmics. Solvay has clearly and completely disclosed these risks in the proposed labeling and in the recommended dosage regimen. Moreover, these risks will be further minimized by gender-specific doses and the implementation of the RiskMAP.

The risks associated with tedisamil are cardiovascular in nature and include:

- TdPs
- Other types of ventricular arrhythmias
- Bradycardia
- Hypotension

The level of risk may be altered if patient selection, dose calculation, or drug administration is inappropriate or incorrect.

Tedisamil must be administered in a setting that allows for continuous ECG monitoring for at least 2 hours (i.e. the 30 minute infusion period and the following 1.5 hours). This is important for the early identification and treatment of potential life-threatening ventricular arrhythmias, particularly polymorphic sustained ventricular tachycardia.

In summary, with careful selection of patients and adherence to the recommended doses and infusion regimen, the benefits of tedisamil treatment outweigh the risks. A Risk Minimization Action Plan (RiskMAP) has been developed to reinforce correct use according to the label and help health care professionals use tedisamil properly.

1.9 Risk Minimization Action Plan

As with other Class III antiarrhythmic drugs with pro-arrhythmic potential, the greatest concern about tedisamil use is the risk of TdP. However, other cardiac risks exist, including ventricular tachycardia and bradycardia. Risks of tedisamil use can be minimized with appropriate dosing and administration consistent with the proposed product label. A RiskMAP has been developed to reinforce correct use according to the label and help health care professionals achieve the following objectives:

- Appropriate patient selection
- Correct dose and administration
- Treatment in appropriate setting (in hospital with ECG monitoring)
- Monitoring for 2.0 hours

The Risk MAP achieves these objectives via a targeted education and outreach program to health care professionals who are likely to use tedisamil. Several reminder systems will be provided to encourage correct, while avoiding unsafe, product usage. These reminders include:

- Algorithm checklist for appropriate prescribing with a focus on patient selection and identification of necessary assessments prior to use (e.g. checking electrolytes prior to administration)
- Detailed gender-specific dosage guides (included in the label and in additional materials, including a dose guide and calculator)
- Administration and monitoring requirement guide (designed to be posted in the patient care area)

The RiskMAP is described in more detail in Section 8.

1.10 Conclusions

Tedisamil is a Class III antiarrhythmic agent indicated for the restoration of NSR in subjects with AFib/AFl. The efficacy and safety of tedisamil has been established during a comprehensive clinical development program that has led to a gender-specific dosage regimen to produce the most favorable risk/benefit relationship for the product.

Tedisamil provided rapid (within 30 minutes) and sustained (through 24 hours) restoration of NSR for a significant proportion of the population. This effect remained consistent across a range of subgroups, including gender, age, concomitant use of beta-blocking agents, NYHA class, first and recurrent arrhythmia episodes, and in mild to moderate renal impairment. Tedisamil was more effective in AFib subjects and in subjects whose current arrhythmic episode was 48 hours or less in duration. Subjects continued on rate control agents (digoxin, beta-blocking agents) throughout the studies and multiple other drugs were used concomitantly without causing drug interactions.

Safety data for tedisamil did not reveal any unexpected safety findings compared to other drugs in the class. It was well-tolerated by various subgroups including subjects with congestive heart failure (NYHA I-III), and mild or moderate renal insufficiency. The most common TEAEs were cardiac disorders, which were also the most common cause of study withdrawal. As with other Class III antiarrhythmics, tedisamil can cause QT prolongation, and TdP is a concern. In the clinical program, the risk of adjudicated Torsade-like events at the recommended doses was 0.5% or less for both males and females. The proposed labeling calls for two hours of ECG monitoring from the initiation of the infusion to enable early identification and treatment of potential life-threatening ventricular arrhythmias, particularly sustained polymorphic ventricular tachycardia, should it occur.

The tedisamil RiskMAP has been developed to increase the care devoted to patient selection, help make dosing more accurate, and generally improve compliance with the requirements related to administration and monitoring. The end result is expected to be close alignment between product usage and product labeling, effectively minimizing the risk to patients.

In conclusion, considering the efficacy and safety profile, the positioning of tedisamil in the armamentarium of treatments for arrhythmia, and the risk management plan, tedisamil shows a positive risk/benefit balance and merits approval for the proposed indication:

> *The rapid conversion of recent onset (3 hours to 45 days) atrial fibrillation (AFib) or atrial flutter (AFl) to normal sinus rhythm.*

2 Background

Atrial fibrillation is the most common, clinically relevant arrhythmia with an overall prevalence that increases with age.[1] This common sustained cardiac rhythm disorder results in a substantial mortality and morbidity from stroke, thromboembolism, heart failure and impaired quality of life.[2,3] Atrial fibrillation affects an estimated 2.3 million adults in the United States, with more than 160,000 new cases diagnosed each year.[4]

In the Framingham study, the lifetime risks at age >40 years for developing atrial fibrillation were 26% for men and 23% for women.[5,6] As women tend to live longer than men, and because the disease is more prevalent in older people,[4] the disease burden on women is high and growing.

In most patients, atrial fibrillation can be easily recognized from the surface electrocardiogram with the presence of rapid, irregular fibrillatory waves, and irregular ventricular response. Electrocardiogram tracings between atrial fibrillation and atrial flutter greatly overlap.

The symptoms in atrial fibrillation (palpitation, presyncope, fatigue, dyspnea) are primarily caused by fast ventricular rates, which can be controlled by using the atrio-ventricular node blocking drugs (rate control) or by converting atrial fibrillation to sinus rhythm (rhythm control). Restoration of sinus rhythm reduces the need for the use of atrio-ventricular node blocking drugs for rate control, decreases chances of thromboembolism, prevents tachycardia-related cardiomyopathy, and lessens atrial mechanical dysfunction and electrophysiological remodeling.[8]

There is no one single best approach to treating AFib/AFl. Physicians today select from several treatment strategies and options and tailor their treatment to the individual patient's medical needs and personal expectations. Cardioversion to NSR by direct electric current (DC) is very effective. The potential drawbacks of DC cardioversion include the need for anesthesia, risk of aspiration, pain, skin burning, pulmonary edema, pacemaker malfunction, thromboembolism, and adverse cardiac effects such as sinus arrest and ventricular fibrillation.[9,10] In addition, patient anxiety related to the procedure, is frequently a consideration. Pharmacological cardioversion, while typically less effective than DC cardioversion, has the advantages of generally being simpler and convenient, free of the anesthesia requirement, and being feasible in recent post-prandial state. The potential disadvantages include drug-related side effects and limited effect in atrial fibrillation of longer duration.

The drugs used for rhythm control in recent onset atrial fibrillation patients include Class IA (e.g., quinidine, procainamide, disopyramide), Class IC (e.g., flecainide, propafenone), and Class III (e.g., ibutilide, dofetilide, sotalol, amiodarone) antiarrhythmic agents, both by oral and intravenous routes.[10,11] Some of these agents are used "off-label" for conversion of atrial fibrillation or flutter in that they have not been approved by FDA for this use. In general, all these drugs work by prolonging atrial refractoriness. Both Class I and Class III agents have significant proarrhythmic effects, which are intensified in patients with congestive heart failure.

Class IC antiarrhythmic drugs, flecainide and propafenone, are generally considered to be better than Class IA agents for the cardioversion of atrial fibrillation because of their higher success rates and favorable adverse effect profile.[12,13] These drugs do not prolong the repolarization phase of the cardiac action potential and thus, do not precipitate TdPs. Nonetheless, Class IC drugs prolong the depolarization, which may result in transient widening of the QRS complex and conduction disturbances. Due to this mechanism, these agents are contraindicated in patients with structural heart disease.

Among Class III drugs (e.g., ibutilide and dofetalide), the potential concern is prolongation of the QT interval and an incidence of 3-6% of TdP, which should preclude the use of these agents outside a monitored environment.[14,15] Efficacy of sotalol for conversion of atrial fibrillation appears to be modest and not proven through clinical studies.[16] Amiodarone is approved for life-threatening ventricular arrhythmias and is often used off-label for conversion of atrial fibrillation, but is associated with a number of adverse effects, the most important of which is organ toxicity. Amiodarone and dofetilide are the only antiarrhythmic considered safe and effective in patients with moderate-to-severe left ventricular dysfunction. However amiodarone should be used cautiously due to the risk of organ toxicity such as pulmonary fibrosis, hepatic and thyroid dysfunction, and neurological and dermatological effects that may develop at high doses after extended long-term use.[17,18]

Due to the limitations of Class I and III antiarrhythmic agents currently available, there is unmet medical need for a drug with a well-characterized efficacy and safety profile, predictable pharmacokinetics, a sustained effect, efficacy in atrial fibrillation of longer duration, well-characterized proarrhythmic potential, and good tolerability in patients with cardiac disease.

Of particular note, there are well documented differences in QT between males and females.[19] Women tend to have longer QT intervals between puberty and at least 55 years of age, perhaps due to lower parasympathetic tone, or estrogen- or metabolic-related changes. They are more susceptible to malignant arrhythmias than men, and there is an increased incidence of TdP among women when treated with Class III antiarrhythmics, which is a consistent finding with all Class III agents approved for atrial fibrillation.[20,21,22] The reason for the female predominance in drug-induced TdP remains unclear. These gender-based differences have been investigated in the tedisamil AFib/AFl development program.

3 Clinical Pharmacology

The current application is for IV administration of tedisamil, and therefore, this section focuses on studies that evaluated the PK/PD of IV tedisamil in healthy subjects. Data from a population PK/PD meta-analysis of five Phase III studies of IV tedisamil in subjects with AFib/AFl administered IV tedisamil is also included in this section. Finally, data from the oral tedisamil program for the angina indication will also be discussed where relevant to the IV tedisamil AFib/AFl indication.

Two salt formulations of tedisamil have been used in the development program. The tedisamil sesquifumarate (SQF) formulation proposed for marketing is bioequivalent with the dihydrochloride (DHCL) formulation and was used in the Phase III program.

3.1 Mechanism of Action

Tedisamil is a multiple potassium channel blocker which blocks the rapid (IK_r), slow (IK_s) and ultra-rapid (IK_{ur}) components of the delayed rectifier current, the transient outward current (Ito) and the ATP sensitive (IK_{ATP}), and the acetylcholine-activated (IK_{ACH}) potassium currents, two of them (IK_{ur} and IK_{ACH}) being atria-specific. Tedisamil is a Class III antiarrhythmic drug that prolongs the cardiac action potential duration and refractory period, and at higher concentrations (10 times that required to block IK_r) also possesses sodium channel blocking properties in animal and human cardiac tissue preparations. Prolongation by tedisamil of the cardiac action potential duration and refractory period is seen predominantly in the atria compared to the ventricles.

3.2 Basic Pharmacokinetic Characteristics

After IV administration, tedisamil plasma concentrations decline in a multiexponential fashion. The PK of tedisamil can be described by a three-compartment model. Tedisamil exposure (area under the curve, AUC) increases proportionally with dose over the tedisamil dose range of 0.01 to 0.32 mg/kg in healthy subjects and 0.16 to 0.64 mg/kg in AFib/AFl subjects. Systemic clearance (CL) is dose-independent, ranging from 204 to 267 mL/min in healthy subjects and 142 to 239 mL/min in AFib/AFl subjects. The volume of distribution (Vss) ranges from 68 to 70 L in healthy subjects and 72 to 90 L in AFib/AFl subjects. The elimination half-life ($t_{½}$) of tedisamil ranges from 4.5 to 6.9 h. Time of peak plasma concentration (T_{max}) shows a median value of 12.5 min when tedisamil is administered using the two-step 30-min IV infusion.

The pharmacokinetic parameters calculated from the PK meta-analysis at the recommended doses during a two-step 30-min IV infusion regimen are given in Table 3-1.

Table 3-1 Pharmacokinetic Parameters at the Recommended Doses in AFib/AFl Subjects (meta-analysis)

Dose	Number of subjects	AUC (ng·h/mL)	C_{max} (ng/mL)
Females: 0.32 mg/kg (50 % in 10 min, 50 % in 20 min)	201	3203	1000
Males: 0.48 mg/kg (50 % in 10 min, 50 % in 20 min)	169	3802	1319

3.3 Basic Pharmacodynamic Characteristics

After IV administration, tedisamil is associated with dose-dependent QT/QTc prolongation and mild bradycardia. These effects closely follow the time course of tedisamil plasma concentrations. At a dose level of 0.32 mg/kg in healthy male subjects, the maximum placebo corrected QTcB prolongation was 34 msec. The placebo corrected heart rate reduction was 4 bpm.

In AFib/AFl subjects, the observed maximum QTcB prolongation is 41 msec in male subjects at a dose of 0.48 mg/kg and 25 msec in female subjects at a dose of 0.32 mg/kg.

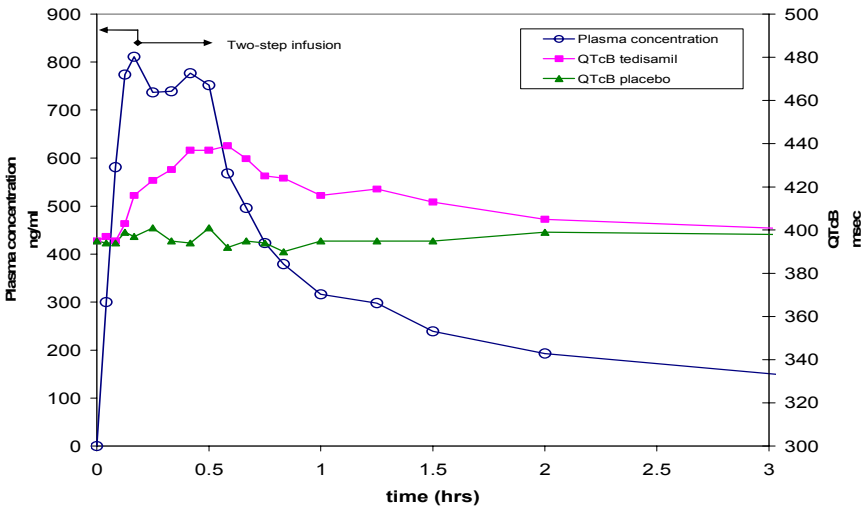
3.4 Two-Step Infusion Regimen

The infusion regimen used in the Phase III program was designed using PK/PD modeling, processing data generated in two healthy volunteer studies. QT/QTc prolongation was chosen as the major pharmacodynamic parameter for PK/PD modeling, as it was regarded as a surrogate for the pharmacodynamic action of tedisamil and a surrogate for safety.

The PK/PD modeling process identified the two-step infusion regimen with a starting dose high enough to ensure a relevant and stable QT/QTc prolongation versus baseline over at least 30 minutes, and with a maximum dose level that is not expected to lead to a maximum absolute QT value exceeding 550 msec in the majority of subjects.

The correlation between plasma concentrations of tedisamil and QT/QTcB in healthy male subjects during a two-step, 0.32 mg/kg 30-min infusion regimen was examined. The expected pharmacodynamic action, i.e. a prolongation of QT and QTc interval was observed over a time period of 2 hours after the start of the infusion. The mean plasma concentration and mean QTcB curves over time are shown in Figure 3-1.

Figure 3-1 Two-Step Infusion Regimen (0.32 mg/kg) in Healthy Male Volunteers: Plasma Concentration and QTcB– Time Profile (Study S219.1.116)



3.5 Population Pharmacokinetics/Pharmacodynamics

A meta-analysis evaluating data collected across five Phase III studies was carried out to further define the PK/PD characteristics of IV tedisamil in AFib/AFl subjects. The QTc Fridericia (QTcF) was taken as the PD parameter. A total of 9,141 tedisamil concentrations from 770 subjects with recent onset AFib/AFl were included in the population PK meta-analysis. Serial PK sampling was obtained from subjects enrolled in studies S219.3.112, S219.3.114, and S219.3.116. Sparse PK sampling at multiple timepoints was done in studies S219.3.117 and S219.3.118. A total of 13,599 QTcF measurements from 1,132

subjects (i.e., 4,391 QTcF measurements from 381 placebo-treated subjects and 9,208 QTcF measurements from 751 tedisamil-treated subjects) were included in the population PK/PD analysis.

The following factors were identified to significantly influence tedisamil clearance or volume of distribution: renal function (as estimated by creatinine clearance, CrCL), lean body mass (LBM), and co-administration of verapamil.

- The increase in volume of distribution with lean body mass is consistent with the recommended consideration of weight in dosing tedisamil (see Section 3.6).
- Tedisamil CL decreases by 42% in AFib/AFl subjects with moderate renal impairment compared with subjects with normal renal function or mild renal impairment. As C_{max} is not affected by the decreased clearance in moderate renal impairment this does not warrant a dosing adjustment (see Section 3.8).
- Co-administration of tedisamil and verapamil is associated with a 13% decrease in tedisamil CL in AFib/AFl subjects, without significant effect on QTcF. This does not warrant a dosing adjustment (see Section 3.9).

The PK of IV tedisamil in AFib/AFl subjects is not influenced by gender, smoking status, severity of congestive heart failure based on NYHA classification, albumin level, total protein level, or the concomitant use of ACE inhibitors, diuretics, vasodilators, digoxin, and substrates or inhibitors of organic anion and cation renal transporters.

PK/PD modeling has shown that the total tedisamil dose is the only factor identified to significantly influence the relationship between tedisamil exposure and QTcF. The effect of tedisamil on QTcF is not influenced by demographics or clinical covariates.

3.6 Body Size

In the Phase III program dosing was done on a mg/kg basis. Since distribution of the non-lipophilic drug tedisamil is limited to total body water, the actual body weight was only used for subjects with a BMI up to 28 kg/m^2. For overweight and obese subjects (BMI > 28 kg/m^2) dosing was based on a body weight associated with a fixed BMI of 28 kg/m^2 (e.g. for a person with a BMI of 33 kg/m^2 and a height of 1.85 m, dosing was based on a body weight of $28*1.85^2 = 96$ kg). This is consistent with the observed increase in volume of distribution with lean body mass in the meta-analysis.

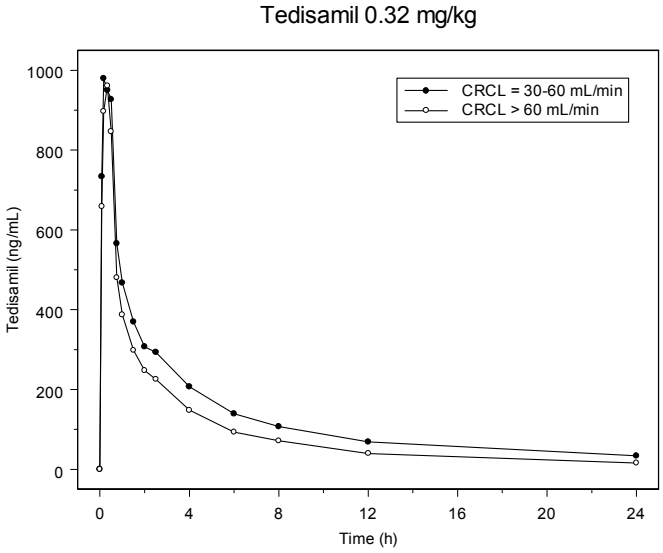
3.7 Age and Gender

The meta-analysis did not reveal any effect of gender on the pharmacokinetics of tedisamil. In clinical studies, tedisamil C_{max} was only slightly higher (3-6 %) in subjects ≥65 y compared to those <65 y. AUC was 11-19 % higher in subjects ≥65 y compared to those <65 y. The meta-analysis did not reveal any effect of age as such on the main pharmacokinetic parameters, namely clearance and volume of distribution. The increased exposure in the elderly is likely related to their reduced renal function, which was identified as a significant covariate affecting tedisamil clearance.

3.8 Elimination

Tedisamil is almost exclusively eliminated as unchanged drug via the renal route. Upon IV administration, about 97 % of the dose excreted in the urine was attributed to the parent compound. Hepatic impairment would not be expected to have a significant effect on tedisamil elimination. Tedisamil CL decreases by 42% in AFib/AFl subjects with moderate renal impairment (30≤CrCL<60 mL/min) compared with subjects with normal renal function or mild renal impairment (CrCL≥60 mL/min). As expected from a drug administered as a single dose short infusion, C_{max} is not affected by the decreased clearance in moderate renal impairment. This is illustrated in Figure 3-2 in which the average PK profile following a two-step 30-min IV infusion in AFib/AFl subjects with normal renal function or mild renal impairment and subjects with moderate renal impairment at a 0.32 mg/kg dose level is depicted. Similar results were observed at the 0.48 mg/kg dose level.

Figure 3-2 Average PK Profile Following a 2-Step, 30-min, IV Infusion of Tedisamil in Normal and Renally Impaired Subjects at a Dose Level of 0.32 mg/kg (meta-analysis)



The safety profile and the magnitude of QTc effects are similar in subjects with moderate renal impairment when compared to subjects with normal function. No dosing adjustment is proposed in AFib/AFl subjects with mild or moderate renal impairment. Tedisamil should not be administered in subjects with severe renal impairment; such subjects were not studied in the tedisamil clinical development program.

3.9 Drug Interaction Potential

The metabolism of tedisamil is very limited. There is no *in vitro* evidence that the human cytochrome P450 (CYP) isoenzymes contribute to the metabolism of tedisamil. Consequently, it is unlikely that significant changes in tedisamil exposure would occur from a CYP-related drug interaction.

Tedisamil is a strong inhibitor of CYP 2D6. Tedisamil is not an inducer of CYP isoenzymes *in vitro*. Based on observations from the Phase III studies in AFib/AFl subjects, there is no evidence for any relevant drug interaction issues with co-administration of tedisamil with beta-blocking agents that are metabolized by CYP2D6, such as carvedilol or metoprolol. In general caution should be exercised for co-administration with beta-blocking agents and other drugs metabolized by CYP2D6 such as Type 1C antiarrhythmics (e.g., propafenone, flecainide, encainide) and antidepressants (e.g., paroxetine, imipramine).

Tedisamil is a substrate for the human P-glycoprotein (Pgp) transporter. The Pgp-mediated transport of tedisamil is inhibited *in vitro* by verapamil. Upon IV administration, co-administration of tedisamil and verapamil is associated with a 13% decrease in tedisamil CL in AFib/AFl subjects, without a relevant effect on the QT interval. Coadministration of tedisamil with verapamil does not necessitate a dosing adjustment.

The *in vitro* protein binding of tedisamil is 96.5%. No significant PK/PD interaction was observed upon co-administration of oral tedisamil with warfarin, suggesting a lack of displacement of protein-bound tedisamil by warfarin, and vice-versa.

No significant PK/PD interaction exists between oral/IV tedisamil and digoxin and between oral tedisamil and glibenclamide.

4 Clinical Development Program for Atrial Fibrillation/Atrial Flutter

4.1 Overview of Studies

Tedisamil was initially developed as an oral anti-angina compound in subjects with chronic stable angina pectoris. Given the antiarrhythmic profile of tedisamil and the availability of a variety of antianginal agents for first and second line treatment of chronic stable angina pectoris, it was considered appropriate to focus further development efforts on rapid conversion of AFib/AFl to NSR. Subsequently, work on the angina indication was discontinued and the development program was refocused to conversion of AFib/AFl to NSR.

The primary objective of the antiarrhythmia clinical development program was to detect a difference between any dose of tedisamil and placebo on the ability to convert atrial fibrillation/flutter to NSR.

Phase II studies with tedisamil in AFib/AFl subjects started in June 1998. Study S219.2.102 was designed to determine the percentage of AFib/AFl subjects who converted and remained in NSR at one hour after the initiation of a 10-min infusion of tedisamil at 0.16 mg/kg and 0.24 mg/kg. It was discontinued following slow recruitment and lack of efficacy. Based on PK/PD modeling, the dose and infusion regimen were adapted in subsequent studies.

The tedisamil doses were increased to 0.32 mg/kg and 0.48 mg/kg, and the infusion time was lengthened to 30 minutes utilizing a two-step infusion regimen (half the dose in the first 10 mins and the other half in the remaining 20 mins). (See Section 3.4 for the rationale for this change.) These doses and the revised infusion regimen were tested in a Phase II "proof of

principle" study (S219.2.107), which enrolled subjects who had an AFib/AFl episode of ≤48 hour duration. This study showed efficacy in both doses compared to placebo. The rate of conversion within 2.5 hours was 46.2% (24/52) for 0.32 mg/kg and 57.1% (24/42) for 0.48 mg/kg tedisamil compared to 8.7% (4/46) for placebo.

Phase III studies, using the two-step infusion regimen, began in November 2002. Following several reports of serious events in female subjects, Solvay decided to suspend the studies in March 2003 after consultation with the AOC. A thorough investigation showed that arrhythmic events in female subjects, occurred at doses of tedisamil 0.48 mg/kg and higher. Following a review of available data and consultation with the FDA and MHRA, the antiarrhythmia program was revised to adopt a dose-finding strategy separated by gender. The following modifications were made to the clinical development plan:

- Study S219.3.112 was amended to exclude females.
- S219.3.114 was amended to exclude females and to adapt the dose; the option to extend the infusion to 50 minutes was deleted, eliminating the extended doses of "0.32-0.48 mg/kg" and "0.48-0.72 mg/kg".
- Three gender-specific studies were added: Study S219.3.117 enrolled only male subjects, and Studies S219.3.116 and S219.3.118 enrolled only female subjects.
- In addition, the post-cardiac surgery studies S219.3.111 and S219.3.113 were terminated due to low enrollment.

A total of nine clinical studies have been conducted for IV tedisamil as an antiarrhythmic: two Phase II studies and seven Phase III studies. The numbers of subjects who received study drug in these studies are summarized by dose in Table 4-1. These nine studies provide information on the safety of tedisamil. A total of 1401 subjects received study drug in these studies (931 received tedisamil and 470 received placebo). This is defined as the integrated safety dataset.

Table 4-1 Overview of Clinical Studies for IV Tedisamil Antiarrhythmia Project

Study	Total subjects treated (n)			Tedisamil dose group (n)							Combined Tedisamil	Placebo (n)
				IV Tedisamil (mg/kg)								
	Safety Population[a]	Male	Female	0.16	0.24	0.32	0.32-0.48 [b]	0.48	0.48-0.72 [b]	0.64		
Phase II												
S219.2.102 [c]	26	20	6	9	8	-	-	-	-	-	17	9
S219.2.107	180	109	71	-	-	65	-	54	-	-	119	61
Phase III post-cardiac surgery[d]												
S219.3.111[d]	14	14	0	-	-	5	-	4	-	2	11	3
S219.3.113[d]	3	2	1	-	-	-	-	-	2	-	2	1
Phase III												
S219.3.112	272	236	36	-	-	71		70	-	60	201	71
S219.3.114 (Post Amend)[b]	228	228	0	58	-	59	-	54	-	-	171	57
S219.3.114 (Pre Amend)[b]	51	33	18	-	-		17	-	17	-	34	17
S219.3.116	358	0	358	-	120	120	-	-	-	-	240	118
S219.3.117	117	117	0	-	-		-	59	-	-	59	58
S219.3.118	152	0	152	-	-	77	-	-	-	-	77	75
Total IV	**1401[e]**	**759**	**642**	**67**	**128**	**397**	**17**	**241**	**19**	**62**	**931**	**470**

[a] Safety Population included all subjects who received any amount of study drug.

[b] Study S219.3.114 was amended to exclude females and removed the option to extend the infusion to 50 minutes, Prior to the amendment, subjects who received an initial dose of 0.32 mg/kg and were still not in NSR, received an extended dose of 0.16 mg/kg over the next 20 mins giving a total dose of 0.48 mg/kg over 50 mins (noted as "0.32-0.48 mg/kg" dose). Subjects who received an initial dose of 0.48 mg/kg using and were still not in NSR, received an extended dose of 0.24 mg/kg over the next 20 mins giving a total dose of 0.72 mg/kg over 50 mins (noted as "0.48 mg/kg – 0.72 mg/kg" dose).

[c] Phase II Study used 10 min IV infusion

[d] Post-cardiac surgery studies were terminated due to low enrollment.

[e] This number includes the 931 tedisamil subjects and 470 placebo subjects who were in the integrated safety dataset.

5 Clinical Efficacy

5.1 Efficacy Overview

Seven Phase III studies were conducted. The two studies in subjects treated after cardiac surgery (S219.3.111 and S219.3.113) were terminated early due to low enrollment, and therefore, were not included in efficacy analyses. Efficacy assessments of tedisamil are based on the five gender-specific multicenter, randomized, double-blind, placebo-controlled, Phase III studies that evaluated the efficacy of IV tedisamil in subjects with a recent onset (3 hours – 45 days) episode of AFib/AFl:

- Studies S219.3.112, S219.3.114, and S219.3.117 in males; and
- Studies S219.3.116 and S219.3.118 in females.

The primary objective of these clinical studies was to detect a difference between any dose of tedisamil and placebo in converting atrial fibrillation to NSR. Study drug (tedisamil or placebo) was administered as a two-step 30-min infusion, with half of the dose given during the first 10 minutes and the remaining dose given over the next 20 minutes.

The efficacy population was based on the "full analysis set" as described in the International Conference on Harmonisation (ICH) guidelines E-9 (*Statistical Principles for Clinical Trials*) and is referred to in this briefing document and in the NDA as the AFib/AFl ITT sample. It consisted of all treated subjects who:

- Had post-baseline efficacy data (Holter and/or ECG recording available), and
- Did not convert to NSR before the initiation of the study drug infusion.

In the individual studies, randomization was stratified by type of arrhythmia (AFib or AFl). The primary efficacy analyses were performed on the AFib subjects (AFib ITT). In addition, analyses were done on the combined population of AFib and AFl subjects (AFib/AFl ITT). Efficacy results from the integrated Phase III efficacy dataset focus on the AFib/AFl ITT.

As shown in Table 5-1, 27 subjects randomized to tedisamil (22 males; 5 females) and 15 randomized to placebo (8 males; 7 females) were not treated and are excluded from the efficacy and safety populations. Four subjects were excluded from ITT analyses across the five studies. Reasons for being excluded were 1) conversion before start of infusion (n=3) and no post-baseline efficacy data (n=1).

Table 5-1 Overview of Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Studies of IV Tedisamil

Male Studies Population Sample	**S219.3.112[a]**				**S219.3.114 (Post Amendment 5)**				**S219.3.117**		**Combined**	
	Tedisamil			**Placebo**	**Tedisamil**			**Placebo**	**Tedisamil**	**Placebo**	**Tedisamil**	**Placebo**
	0.32 mg/kg	**0.48 mg/kg**	**0.64 mg/kg**		**0.16 mg/kg**	**0.32 mg/kg**	**0.48 mg/kg**		**0.48 mg/kg**			
Randomized	72	73	66	72	61	60	60	60	61	62	453	194
- No study drug	*1*	*3*	*6*	*1*	*3*	*1*	*6*	*3*	*2*	*4*	*22*	*8*
Safety	71	70	60	71	58	59	54	57	59	58	431	186
- Conversion before start of infusion	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*1*	*0*
AFib/AFl ITT - Males - Females	65 (56/9) 6 (5/1)	59 (51/8) 11 (9/2)	50 (44/6) 10 (7/3)	62 (53/9) 9 (8/1)	58 (50/8)	58 (52/6)	54 (46/8)	57 (51/6)	59 (48/11)	58 (48/10)	403 (347/56) 27 (21/6)	177 (152/25) 9 (8/1)
AFib ITT - Males	56	51	44	53	50	52	46	51	48	48	347	152

[a] Before amendment, the study randomized 29 AFib females and 7 AFl females.

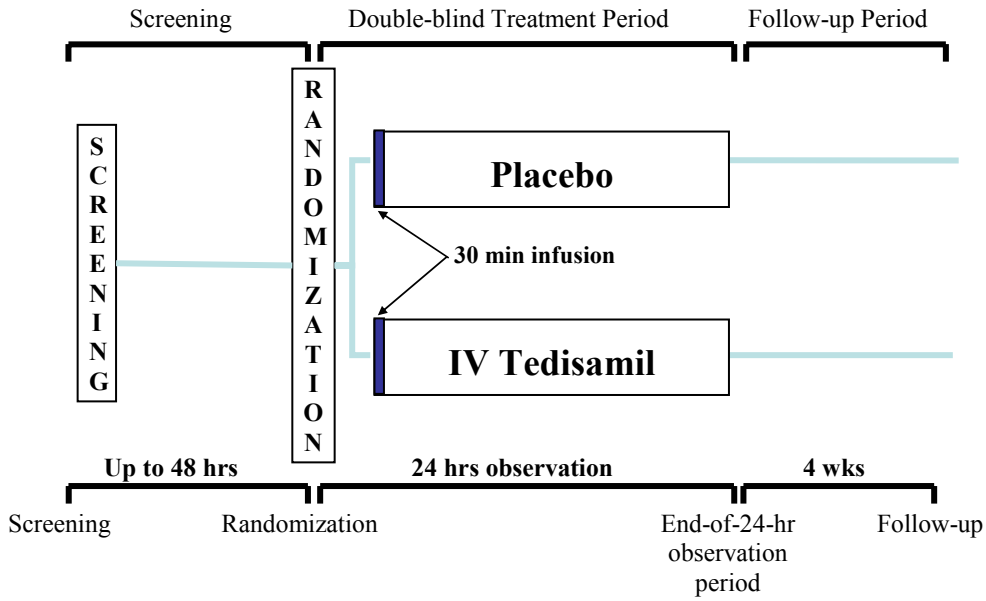
Female Studies Population Sample	**S219.3.116**			**S219.3.118**		**Combined**	
	Tedisamil		**Placebo**	**Tedisamil**	**Placebo**	**Tedisamil**	**Placebo**
	0.24 mg/kg	**0.32 mg/kg**		**0.32 mg/kg**			
Randomized	122	123	122	77	78	322	200
- No study drug	*2*	*3*	*4*	*0*	*3*	*5*	*7*
Safety [a]	120	120	118	77	75	317 [a]	193 [a]
- Conversion before start of infusion	*1*	*0*	*0*	*1*	*0*	*2*	*0*
- No post-baseline efficacy data	*1*	*0*	*0*	*0*	*0*	*1*	*0*
AFib/AFl ITT - Females	118 (106/12)	120 (107/13)	118 (105/13)	76 (67/9)	75 (68/7)	314 (280/34)	193 (173/20)
AFib ITT - Females	106	107	105	67	68	280	173

[a] The integrated safety dataset included 27 tedisamil and 9 placebo female subjects exposed in Study S219.3.112, for a total safety female population of 344 in the combined tedisamil group and 202 in the placebo group. In the integrated dataset, 202 female subjects received the recommended dose of 0.32 mg/kg tedisamil.

5.2 Study Design

The study design used in all the Phase III studies is shown in Figure 5-1.

Figure 5-1 Schematic for Study Design of the Phase III Studies in the Tedisamil Clinical Development Plan



Subjects for enrollment were screened from the investigator's practice and referral base. At screening, subjects were to be in AFib or AFl as documented by 12-lead ECG (120 second rhythm strip with at least 60 seconds of an evaluable recording).

The Phase III studies had the same inclusion/exclusion criteria, except for subject gender. All subjects had to have documented AFib or AFl for at least 3 hours but not more than 45 days as a first or recurrent episode, be hemodynamically stable (SBP > 90mmHg, DBP <105mmHg), and be at least 18 years of age. Anticoagulation was to be undertaken at the discretion of the investigator, according to current guidelines.

The main exclusion criteria included:

- Congestive heart failure of NYHA functional Class IV
- Clinical evidence of hyperthyroidism
- History of life-threatening ventricular arrhythmias including TdPs
- MI within 30 days before randomization
- Cardiac surgery within three months before randomization
- Congenital long QT syndrome
- QTc interval >470 msec prior to randomization

- Serum creatinine >1.8 mg/dL (159 mmol/L) or serum potassium < 4.0 mEq/L (< 4.0 mmol/L)

Concurrent treatment with antiarrhythmic drugs (except for digitalis, diltiazem, or beta-blocking agents) was not allowed. Subjects could not have been treated with amiodarone in the three months before randomization.

If entry criteria were met at baseline, subjects were randomized to receive one of the doses of tedisamil or placebo. Subjects were hospitalized for study drug infusion and 24-hour telemetry.

Study drug was administered by a two-step, 30-min infusion. The infusion was completed whether or not the subject converted to NSR. Other antiarrhythmic drugs were allowed after 24 hours after the start of infusion. Doses of tedisamil ranged from 0.16 to 0.64 mg/kg (see Section 3.6).

Subjects were hospitalized for at least 24 hours after the start of the infusion and monitored for safety. If clinically indicated, the investigator could restore NSR immediately or at any time during the study by DC cardioversion. To avoid interference with the primary endpoint, DC cardioconversion within 2.5 hours after initiation of the infusion was discouraged.

A Holter tape was started 10 minutes before start of study drug infusion and continued for 24 hours. The Holter tapes were analyzed centrally to document the first conversion into NSR (for at least 60 sec) and to monitor rhythm for 24 hours. The Holter tapes were also analyzed for arrhythmias according to specific Holter analysis definitions and ventricular events were coded according to a predefined coding system (as described in Section 6.8.1). These codes were adjudicated by an independent AOC (its charter is provided in Appendix 1). In addition, 12-lead ECGs, including 120 sec rhythm strips, were obtained at regularly scheduled intervals.

Efficacy Parameters

The primary efficacy parameter was the percentage of subjects who converted to NSR for at least 60 seconds at anytime within 2.5 hours after the initiation of the infusion of study drug.

Secondary efficacy parameters included the percentage of subjects achieving the primary endpoint (i.e., converting to NSR within 2.5 hours) and who were:

- in NSR at 2.5 hours after start of infusion
- in NSR at 24 hours
- remaining in NSR for 24 hours (analyzed only with integrated efficacy dataset)
- in NSR at hospital discharge.

Time to conversion (time from start of infusion to first conversion to NSR) was also a secondary efficacy parameter.

5.3 Demographics and Baseline Characteristics

The demographics and baseline characteristics for the AFib/AFl ITT sample from the individual studies are summarized by dose in Table 5-2 for the predominately male studies and in Table 5-3

for the female-specific studies. Within the gender-specific studies, subjects had similar baseline characteristics in the tedisamil and placebo groups. Between genders, there were some notable differences. Female subjects tended to be older, were more likely to have more severe congestive heart failure (Class II/III; NYHA class IV subjects were excluded), and more likely to have an arrhythmic episode >48 hr.

Overall, medical history and use of concomitant medication were comparable within the male studies and within the female studies, across dose groups and treatment groups (tedisamil vs. placebo). The main categories of medical conditions were vascular disorders and cardiac conditions. The major classes of concomitant medications taken, anti-thrombotic agents, beta-blocking agents and cardiac therapy, are consistent with this population. In addition to those medications, tedisamil was used during the studies with a broad range of concomitant medications, including calcium antagonists, nitrates, lipid-lowering agents, hypoglycemics, hormone replacement therapy, diuretics, acetylsalicylic acid, NSAIDS, H_2 antagonists, and ACE-inhibitors. When compared by gender, females took a wider variety of concomitant medications than males.

Table 5-2 Baseline Characteristics of AFib/AFl ITT in Predominately Male Studies

Baseline Characteristic	AFib/AFl ITT									
	S219.3.112[a]				S219.3.114				S219.3.117	
	Tedisamil			Placebo	Tedisamil			Placebo	Tedisamil	Placebo
	0.32 mg/kg N=71	0.48 mg/kg N=70	0.64 mg/kg N=60	N=71	0.16 mg/kg N=58	0.32 mg/kg N=58	0.48 mg/kg N=54	N=57	0.48 mg/kg N=59	N=58
Age, mean y	60.4	62.6	60.1	60.8	60.7	59.2	61.4	57.1	64.4	60.4
Age range y	33, 86	35, 87	35, 86	21, 81	26, 91	29, 79	36, 84	20, 82	37, 85	30, 88
Race, White %	100%	100%	98.3%	98.6%	100%	98.3%	98.1%	98.2%	96.6%	100%
BMI, mean kg/m^2	28.65	27.90	28.64	28.77	28.56	28.38	28.52	27.76	27.57	28.96
SBP, mmHg	132.5	133.4	131.4	131.9	130.4	129.4	131.5	127.1	129.0	131.2
DBP, mmHg	81.9	81.7	81.6	81.5	80.7	82.1	81.1	79.8	82.9	82.8
Pulse, bpm	96.9	101.4	97.8	102.8	99.0	95.3	97.7	99.8	91.3	93.5
NYHA I, %	67.6%	60.0%	66.7%	73.2%	51.7%	50.0%	50.0%	56.1%	55.9%	48.3%
NYHA II, %	31.0%	34.3%	28.3%	25.4%	39.7%	43.1%	38.9%	35.1%	28.8%	39.7%
NYHA III, %	0%	5.7%	5.0%	1.4%	8.6%	5.2%	9.3%	8.8%	3.4%	3.4%
1st episode, %	35.2%	47.1%	48.3%	36.6%	58.6%	51.7%	74.1%	59.6%	49.2%	48.3%
Recurrent episode, %	64.8%	52.9%	51.7%	63.4%	41.4%	48.3%	25.9%	40.4%	50.8%	51.7%
Duration AFib (males only)	n=56	n=51	n=44	n=53	n=50	n=52	n=46	n=51	n=48	n=48
3 - 48 h	46.4%	54.9%	61.4%	52.8%	52.0%	34.6%	45.5%	62.7%	47.9%	66.7%
>48 h - 45 d	53.6%	45.1%	38.6%	47.2%	48.0%	65.4%	55.6%	37.3%	52.1%	33.3%

[a] Data include 36 females.

Table 5-3 Baseline Characteristics of AFib/AFl ITT in Female Studies

Baseline Characteristic	AFib/AFl ITT [a]				
	S219.3.116			S219.3.118	
	Tedisamil		Placebo	Tedisamil	Placebo
	0.24mg/kg N=118	0.32mg/kg N=120	N=118	0.32 mg/kg N=76	N=75
Age, mean y	68.7	68.2	67.7	69.9	71.9
Age range y	47, 85	39, 87	42, 87	43, 91	50, 92
Race, White %	99.2%	99.2%	100%	98.7%	100%
BMI, mean kg/m^2	29.33	29.16	30.44	28.76	29.41
SBP, mmHg	131.3	133.3	132.4	132.2	129.4
DBP, mmHg	80.0	81.1	81.3	79.6	79.1
Pulse, bpm	97.8	97.0	96.0	95.3	95.3
NYHA I, %	33.1%	43.3%	33.9%	31.6%	42.7%
NYHA II, %	50.0%	45.0%	46.6%	38.2%	32.0%
NYHA III, %	11.9%	3.3%	9.3%	11.8%	14.7%
1^{st} episode, %	53.4%	41.7%	44.1%	51.3%	49.3%
Recurrent episode, %	46.6%	58.3%	55.9%	48.7%	50.7%
Duration of AFib	n=106	n=107	n=105	n=67	n=68
3 - 48 h	30.2%	34.6%	30.5%	28.4%	23.5%
>48 h - 45 d	69.8%	65.4%	69.5%	71.6%	76.5%

[a] Integrated Phase III efficacy dataset sample size includes 36 females (27 tedisamil and 9 placebo) that were enrolled in Study 219.3.112 and were included in the female subgroup of the Phase III integrated efficacy database.

5.4 Statistical Methodology

The primary efficacy parameter was the percentage of subjects who converted to NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion.

Determination of conversion to NSR was based on the Holter rhythm data. Where Holter rhythm data were not available then ECG rhythm strip data were used instead.

The primary analysis was done on the AFib ITT sample.

For the primary parameter, pairwise comparisons of frequencies of conversion were made between each active treatment group and placebo using the (Pearson) chi-square statistic. The statistical null hypothesis was that for each of the active treatment groups, the underlying difference in the percentage of subjects who converted as compared to the placebo group was equal to zero.

Subjects who underwent DC cardioversion within 2.5 hours after the start of study drug infusion were excluded from the analyses. In studies where subjects underwent DC cardioversion within 2.5 hours after the start of study drug infusion, an additional analysis was performed on the primary efficacy parameter where subjects who underwent DC cardioversion within 2.5 hours after the start of study drug infusion were considered as non-converters. Similar results to the primary analyses were observed in these sensitivity analyses.

For the primary analysis, the Bonferroni-Holm multiple comparison procedure was used to adjust for multiple doses tested versus placebo in studies S219.3.112, S219.3.114 and S219.3.116. The significance level in the individual studies was set to α=0.05.

In addition, two-sided confidence intervals for the differences between each active treatment group and placebo in the percentage of subjects converting to NSR were obtained using the normal approximation to the binomial distribution.

5.5 Efficacy Results from Individual Clinical Trials

5.5.1 Primary Efficacy Results from Individual Clinical Trials

Table 5-4 and Table 5-5 provide tabular summaries of the percentage of male and female subjects who converted to NSR (for at least 60 sec) at any time within 2.5 hours after the start of the study drug infusion for the AFib ITT and the AFib/AFl ITT samples.

Figure 5-2 and Figure 5-3 graphically show the placebo-corrected point estimates and confidence intervals (CIs) associated with the confirmatory analyses by individual study and dose for the male and female studies.

Across the three male studies, a statistically significant increase in the rate of conversion to NSR within 2.5 hrs was observed in tedisamil doses 0.32 mg/kg and higher. At the recommended dose of 0.48 mg/kg, the conversion rates in the three studies were 52.9%, 31.1% and 29.2% compared with placebo rates of 5.7%, 9.8%, and 6.3%, respectively.

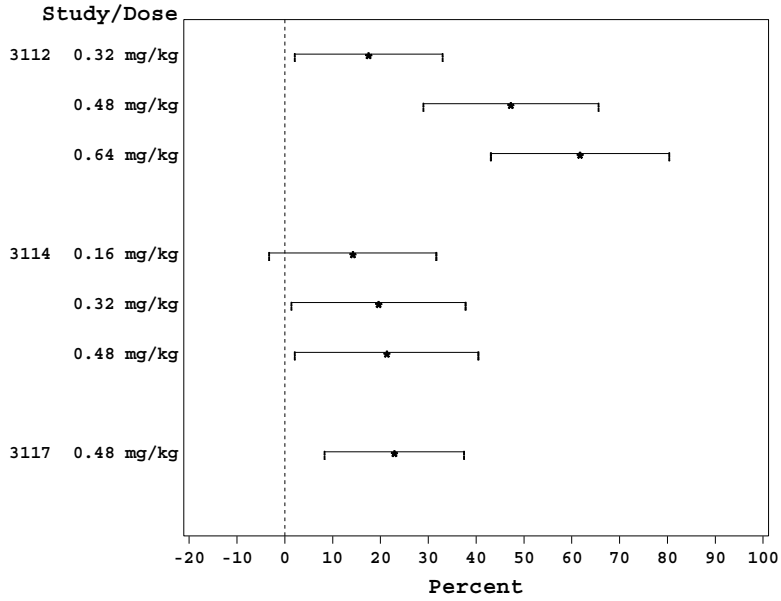
In the two female studies, tedisamil at the 0.32 mg/kg dose significantly increased the rate of conversion within 2.5 hrs (21.5% and 17.9%) compared with placebo (2.9% and 4.5%).

Table 5-4 Summary of Primary Efficacy Parameter for Individual Studies – Male Studies

Study	Tedisamil dose (mg/kg)	NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion AFib ITT Subjects [a]	NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion AFib/AFl ITT Sample [a]
S219.3.112 [b]	0.32	13/56 (23.2%) p=0.0096 CI [2.1, 33.0]	13/65 (20.0%) p=0.0101 CI [4.1, 26.3]
	0.48	27/51 (52.9%) p< 0.0001 CI [29.0, 65.6]	29/59 (49.2%) p <0.0001 CI [30.5, 58.1]
	0.64	29/43 (67.4%) p< 0.0001 CI [43.1, 80.4]	32/49 (65.3%) p <0.0001 CI [46.1, 74.8]
	Placebo	3/53 (5.7%)	3/62 (4.8%)
S219.3.114 (Post Amendment)	0.16	12/50 (24.0%) p=0.057 CI [-3.3, 31.7]	12/58 (20.7%) p=0.072 CI [-0.8, 24.7]
	0.32	15/51 (29.4%) p=0.013 CI [1.4, 37.8]	15/57 (26.3%) p= 0.014 CI [4.0, 31.1]
	0.48	14/45 (31.1%) p=0.0089 CI [2.1, 40.5]	15/53 (28.3%) p=0.0080 CI [5.4, 33.7]
	Placebo	5/51 (9.8%)	5/57 (8.8%)
S219.3.117	0.48	14/48 (29.2%) p=0.0033 CI [8.3, 37.5]	15/59 (25.4%) p=0.0024 CI [7.8, 32.7]
	Placebo	3/48 (6.3%)	3/58 (5.2%)

[a] Predefined primary efficacy analysis in the individual studies was performed using AFib ITT sample.
[b] Study S219.3.112 randomized 36 females that are not included in these results; those females are included in the integrated Phase III efficacy dataset and counted in the female subgroup of integrated analyses.

Figure 5-2 Difference Vs Placebo in Percentage of Conversion to NSR within 2.5 Hrs by Study – AFl ITT - Male



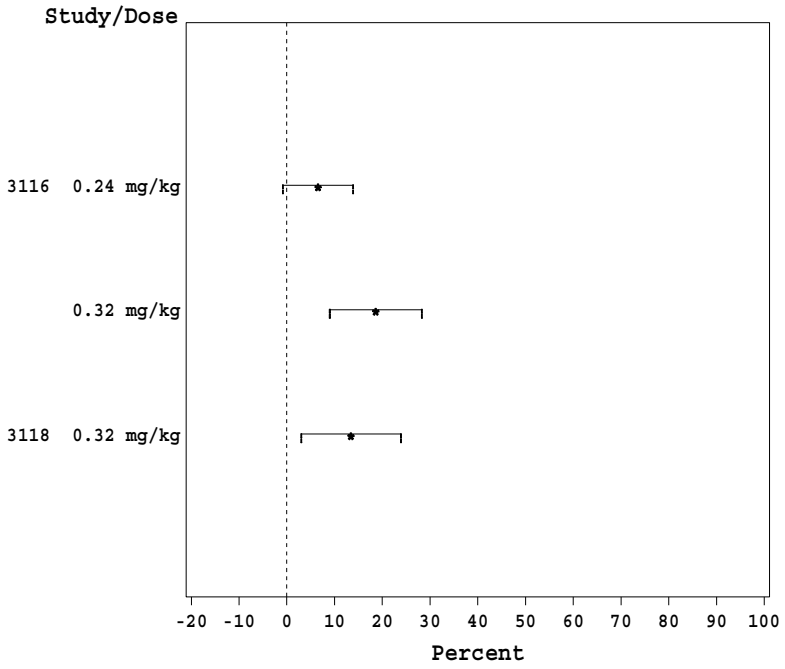
The figure shows, by individual study, placebo-corrected point estimates and confidence intervals associated with the confirmatory analysis.

Table 5-5 Summary of Primary Efficacy Parameter for Individual Studies – Female Studies

Study	Tedisamil dose (mg/kg)	NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion AFib ITT Subjects [a]	NSR for at least 60 seconds at any time within 2.5 hours after the start of study drug infusion AFib/AFl ITT Population [a]
S219.3.116	0.24	10/106 (9.4%) p=0.047 CI [-0.8, 13.9]	12/118 (10.2%) p=0.14 CI [-1.7, 11.8]
	0.32	23/107 (21.5%) p< 0.0001 CI [9.0, 28.3]	24/120 (20.0%) p=0.0005 CI [6.7, 23.1]
	Placebo	3/105 (2.9%)	6/118 (5.1%)
S219.3.118	0.32	12/67 (17.9%) p=0.014 CI [3.0, 23.9]	12/76 (15.8%) p=0.017 CI [2.4, 21.1]
	Placebo	3/67 (4.5%)	3/74 (4.1%)

[a] Predefined primary efficacy analysis in the individual studies was performed using AFib ITT sample.

Figure 5-3 Difference Vs Placebo in Percentage of Conversion to NSR within 2.5 Hrs by Study – AFl ITT - Females



The figure shows, by individual study, placebo-corrected point estimates and confidence intervals associated with the confirmatory analysis.

5.5.2 Secondary Efficacy Results in Individual Clinical Trials

The major secondary efficacy parameters of the percentage of converters in NSR at 24 hours and the time to conversion are summarized by dose for each of the Phase III studies in Table 5-6. At the recommended doses, at least 92.6% of the males (0.48 mg/kg) and 91.7% of the females (0.32 mg/kg) who converted within 2.5 hours remained in NSR at 24 hours. This was also true for the very small number of placebo subjects who had converted within 2.5 hours. The time to conversion decreased with increasing doses of tedisamil and conversion was more rapid with all doses of tedisamil compared with placebo in all male and female studies.

Table 5-6 Percentage of Converters in NSR at 24 Hrs and Time to Conversion by Individual Study

Study	Tedisamil dose mg/kg	% of converters in NSR at 24 hours AFib ITT Subjects [a] n (%)	Time to Conversion Mins (SD)
Phase III Male Studies			
S219.3.112	0.32 0.48 0.64 Placebo	13/13 (100) 25/27 (92.6) 27/29 (93.1) 3/3 (100)	41.6 (40.8) 37.7 (26.5) 21.9 (14.3) 45.0 (10.6)
S219.3.114 (Post Amendment)	0.16 0.32 0.48 Placebo	11/12 (91.7) 15/15 (100) 14/14 (100) 5/5 (100)	33.1 (12.2) 30.3 (29.3) 18.5 (12.2) 84.0 (65.1)
S219.3.117	0.48 Placebo	14/14 (100) 3/3 (100)	22.2 (20.1) 92.7 (28.6)
Phase III Female Studies			
S219.3.116	0.24 0.32 Placebo	10/10 (100) 22/23 (95.6) 3/3 (100)	41.1 (24.5) 24.2 (16.2) 88.7 (55.2)
S219.3.118	0.32 Placebo	11/12 (91.7) 3/3 (100)	27.4 (20.9) 88.7 (44.2)

[a] Predefined primary efficacy analysis in the individual studies was performed using AFib ITT sample.

5.5.3 Efficacy Conclusions from Individual Clinical Trials

Five Phase III multicenter, randomized, double-blind, placebo-controlled studies evaluated the efficacy of tedisamil in subjects with recent onset (3 hr – 45 days) AFib/AFl episode (3 in males; 2 in females).

Primary Efficacy Parameter

- All five Phase III studies consistently demonstrated, compared to placebo, the superiority of tedisamil dose at 0.32 mg/kg or higher for conversion to NSR within 2.5 hours. Results from these studies demonstrated the reproducibility of the efficacy results for the recommended doses of 0.48 mg/kg in males and 0.32 mg/kg in females.
- The rate of conversions to NSR in the placebo group within 2.5 hours was consistent within the gender-specific studies, further supporting the reproducibility of the study results (5.7% - 9.8% in males; 2.9% - 4.5% in females).

- At the recommended dose of 0.48 mg/kg for males, the rates of conversion were 52.9%, 31.1% and 29.2%, compared with placebo rates of 5.7%, 9.8%, and 6.3%, respectively.
- At the recommended dose of 0.32 mg/kg for females, the rates of conversion were 21.5% and 17.9%, compared with placebo rates of 2.9% and 4.5%.

Secondary Efficacy Parameters

- Tedisamil's effect was sustained. A vast majority of both male and female subjects who converted remained in NSR for at least 24 hours (representing at least 92% of those who converted in the initial 2.5 hours). The percentages of converters who were in NSR at 24 hours were 92.6%, 100%, and 100% for males in the 0.48 mg/kg tedisamil group in the three male studies and 95.6% and 91.7% for females in the 0.32 mg/kg tedisamil group in the two female studies.
- Tedisamil's effect was rapid. The mean time to conversion at the recommended dose for males (0 .48 mg/kg) ranged across the studies from 18.5 -37.7 mins compared to a range of 45.0 – 92.7 mins in the placebo groups. In females at the recommended dose (0.32 mg/kg), the mean time to conversion was 24.2 and 27.4 mins compared to 88.7 mins with placebo in both studies.

5.6 Efficacy Results from Integrated Efficacy Data

An integrated Phase III efficacy analyses were performed on the AFib/AFl ITT sample from the five Phase III studies: 580 male subjects (403 in tedisamil groups and 177 in placebo groups) and 543 female subjects (341 in tedisamil groups and 202 in placebo groups) (Table 5-1). Tedisamil dose groups were 0.16, 0.24, 0.32, 0.48, or 0.64 mg/kg.

Demographic and baseline characteristics for the individual Phase III studies were provided earlier in Table 5-2 and Table 5-3 for male and female studies.

5.6.1 Integrated Statistical Methodology

The five Phase III studies had very similar study designs (including placebo control), inclusion/exclusion criteria, procedures, and assessments, and predefined primary and secondary efficacy parameters, and therefore, were suitable for integration. The conversion rates on placebo were comparable across studies, ranging from 2.9 to 9.8%.

For the primary parameter, stratified estimates of difference between each active treatment group and placebo in proportions of subjects converting to NSR and associated unadjusted 95% confidence intervals were derived, with study as stratum. Subjects who underwent DC cardioversion within 2.5 hours after the start of study drug infusion were excluded from the analysis. These analyses were performed on the integrated efficacy dataset as well as on subgroups.

The following subgroups were defined:

- Gender
- Age (<65 and ≥ 65 years of age)
- Predominant rhythm (atrial fibrillation versus atrial flutter)

- Concomitant use of beta-blocking agents (yes/no)
- NYHA classification (I, II or III)
- Duration of arrhythmic episode (≤ 48 hours, >48 hours)
- Type of episode (first or recurrent)
- Creatinine clearance (<60 and ≥ 60 ml/min)

5.6.2 Primary Efficacy Results from Integrated Phase III Efficacy Dataset

Results from the analysis of the integrated Phase III efficacy dataset for the primary efficacy parameter were as follows:

- Tedisamil was significantly different from placebo in restoring NSR within 2.5 hours in subjects with AFib/AFl at doses 0.32 mg/kg, 0.48 mg/kg, and 0.64 mg/kg in males (23.0%, 34.5%, and 65.3% conversion vs. 6.2% with placebo) and at 0.32 mg/kg in females (18.3% vs. 4.5% with placebo).
- There was a dose response pattern in males and females with the conversion rate increasing with increasing dose of tedisamil.

Subgroup analyses were performed based on age (<65; ≥65 y); type of arrhythmia (AFib; AFl); duration of episode (≤48; and >48 hr); use of beta-blocking agents (yes; no); NYHA Class (I; II/III), first episode versus recurrent episode; and renal status (CrCL <60 mL/min; ≥60 mL/min). The results of the subgroup analyses for males at the recommended dose of 0.48 mg/kg are provided in Figure 5-4, followed by Table 5-7, which provides the actual percentages and sample sizes. The results of the subgroup analyses for females at the recommended dose of 0.32 mg/kg are provided in Figure 5-5, followed by Table 5-8. These results support the following conclusions at the recommended doses:

- Subjects <65 years and those ≥65 years had similar conversion rates.
- Tedisamil was effective at restoring NSR in AFib and AFl male subjects and in AFib female subjects.
- A higher percentage of subjects converted to NSR if the duration of arrhythmic episode was ≤ 48 hours than if the subjects had their current episode for longer than 48 hours, but both had conversion rates that were statistically significantly different from placebo.
- Concomitant treatment with beta-blocking agents did not interfere with the efficacy of tedisamil in either males or females.
- NYHA classification status (I or II/III) did not alter the efficacy of tedisamil in either males or females. (Subjects with NYHA IV were excluded from the study.)
- Whether the subject was experiencing a first AFib/AFl episode or a recurrent episode, tedisamil was effective at restoring NSR.
- Conversion rates to NSR with tedisamil were similar in males who had CrCL <60 mL/min and subjects who had CrCL ≥60 mL/min, and both subgroups were significantly higher than placebo. Likewise, the conversion rates were similar in

females between the CrCL subgroups, but due to the small number of females with CrCL <60 mL/min the difference from placebo did not reach significance.

Figure 5-4 Primary Efficacy Parameter: Placebo-Corrected % Converters to NSR within 2.5 Hrs by Subgroups for Recommended Dose 0.48 mg/kg Tedisamil - Male AFib/AFl ITT

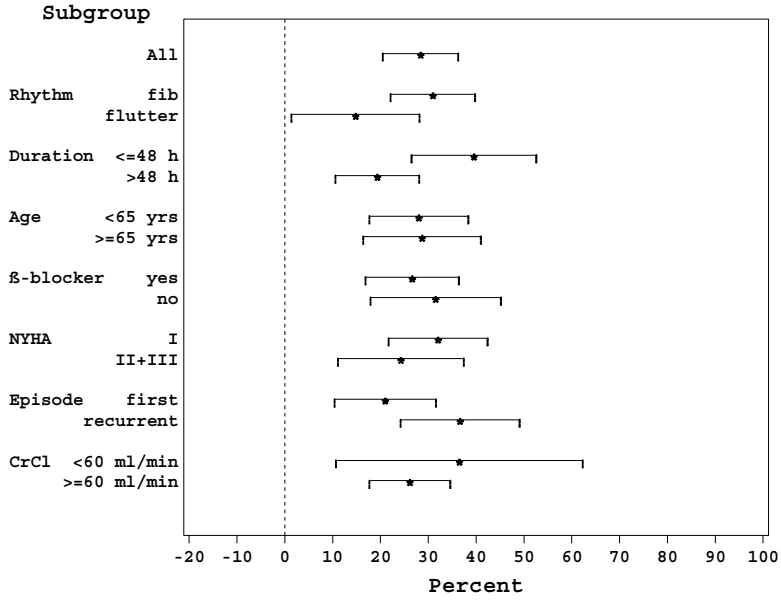


Table 5-7 Rate of Conversion to NSR within 2.5 Hrs by Subgroup for Males at Recommended Dose (0.48 mg/kg) –AFib/AFl ITT

Subgroup		Tedisamil 0.48 mg/kg	Placebo	Difference from Placebo		
				Estimate	Confidence Intervals Lower	Upper
All		59/171[a] (34.5 %)	11/177 (6.2 %)	28.4	20.5	36.3
Rhythm	fib	55/144 (38.2 %)	11/152 (7.2 %)	31.0	22.1	39.8
	flutter	4/27 (14.8 %)	0/25	14.8	1.4	28.2
Duration	≤ 48 hrs	43/82 (52.4 %)	11/89 (12.4 %)	39.6	26.5	52.6
	> 48 hrs	16/88 (18.2 %)	0/88	19.4	10.6	28.1
Age	< 65 yrs	34/95 (35.8 %)	8/116 (6.9 %)	28.1	17.7	38.4
	≥ 65 yrs	25/76 (32.9 %)	3/61 (4.9 %)	28.7	16.4	41.0
ß-blocking agents	yes	38/112 (33.9 %)	9/124 (7.3 %)	26.7	16.9	36.4
	no	21/59 (35.6 %)	2/53 (3.8 %)	31.6	17.9	45.2
NYHA	I	37/100 (37.0 %)	6/105 (5.7 %)	32.1	21.7	42.4
	II+III	20/63 (31.7 %)	5/67 (7.5 %)	24.3	11.1	37.4
Episode	first	29/99 (29.3 %)	6/83 (7.2 %)	21.0	10.4	31.6
	recurrent	30/72 (41.7 %)	5/94 (5.3 %)	36.7	24.2	49.1
CrCL	< 60 ml/min	10/23 (43.5 %)	1/17 (5.9 %)	36.5	10.7	62.3
	≥ 60 ml/min	46/141 (32.6 %)	10/154 (6.5 %)	26.2	17.7	34.6

Note: Subject numbers in individual subgroups may not equal the overall subject number due to missing data.

[a] One subject who underwent DC cardioversion within 2.5 hours after the start of study drug infusion was excluded from analysis.

Figure 5-5 Primary Efficacy Parameter: Placebo-Corrected % Converters to NSR within 2.5 Hrs by Subgroups for Recommended Dose 0.32 mg/kg Tedisamil - Female AFib/AFl ITT

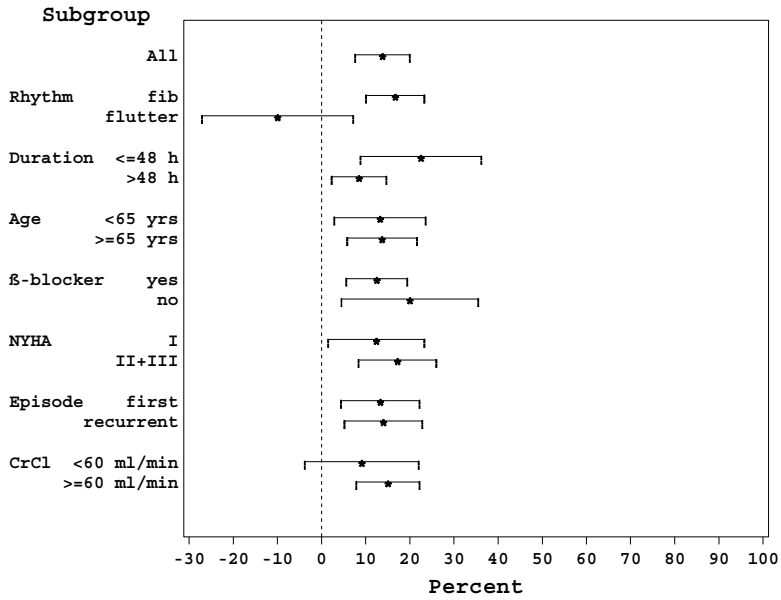


Table 5-8 Rate of Conversion to NSR within 2.5 Hrs by Subgroup for Females at Recommended Dose (0.32 mg/kg) – AFib/AFl ITT

Subgroup		Tedisamil 0.32 mg/kg	Placebo	Difference from Placebo		
				Estimate	Confidence Intervals	
					Lower	Upper
All		37/202[a] (18.3 %)	9/201[a] (4.5 %)	13.8	7.6	20.0
Rhythm	AFib	36/179 (20.1 %)	6/180 (3.3 %)	16.7	10.1	23.3
	AFl	1/23 (4.3 %)	3/21 (14.3 %)	-10.0	-27.1	7.2
Duration	≤ 48 hrs	23/71 (32.4 %)	6/60 (10.0 %)	22.5	8.8	36.2
	> 48 hrs	14/131 (10.7 %)	3/141 (2.1 %)	8.5	2.3	14.7
Age	< 65 yrs	9/61 (14.8 %)	1/65 (1.5 %)	13.3	2.9	23.6
	≥ 65 yrs	28/141 (19.9 %)	8/136 (5.9 %)	13.7	5.8	21.6
ß-blocking	yes	28/162 (17.3 %)	8/163 (4.9 %)	12.5	5.6	19.4
agents	no	9/40 (22.5 %)	1/38 (2.6 %)	20.0	4.5	35.5
NYHA	I	15/77 (19.5 %)	5/78 (6.4 %)	12.4	1.5	23.3
	II+III	20/101 (19.8 %)	3/103 (2.9 %)	17.2	8.4	26.0
Episode	first	15/90 (16.7 %)	3/94 (3.2 %)	13.3	4.4	22.2
	recurrent	22/112 (19.6 %)	6/107 (5.6 %)	14.0	5.2	22.8
CrCL	< 60 ml/min	11/59 (18.6 %)	5/56 (8.9 %)	9.1	-3.8	22.0
	≥ 60 ml/min	25/140 (17.9 %)	4/142 (2.8 %)	15.1	7.9	22.2

Note: Subject numbers in individual subgroups may not equal the overall subject number due to missing data.
[a] The total number of subjects include 6 female subjects in the 0.32 mg/kg tedisamil group and 9 female subjects in the placebo group who received study drug in Study 219.3.112 and did not have DC conversion within 2.5 hours.

5.6.3 Secondary Efficacy Results from Integrated Phase III Efficacy Dataset

NSR Status at Various Timepoints

Secondary efficacy parameters included the percentage of subjects who achieved the primary efficacy endpoint (i.e., converting to NSR within 2.5 hours) and who were:

- in NSR at 2.5 hours after start of infusion
- in NSR at 24 hours
- remaining in NSR for 24 hours
- in NSR at hospital discharge.

The secondary efficacy results for males and females are summarized in Table 5-9. Tedisamil's effect was sustained in subjects who converted to NSR within the 2.5 hours. At the recommended dose 0.48 mg/kg, of the 59 males who converted, 53 (89.8%) remained in NSR for 24 hours. At the recommended dose 0.32 mg/kg, of the 37 females who converted, 32 (86.5%) remained in NSR for 24 hours. This was also true for the very small number of placebo subjects who had converted within 2.5 hours.

Table 5-9 Results from Secondary Efficacy Parameters for Recommended Doses

Tedisamil (mg/kg)	# Subjects that converted within 2.5 hours/ total number in AFib/AFl ITT	Secondary Efficacy Parameter AFib/AFl ITT Conversion within 2.5 hours and:			
		In NSR at 2.5 hours n (%)	In NSR at 24 hrs n (%)	Remaining in NSR for 24 hrs n (%)	In NSR at Hospital Discharge n (%)
Males					
0.48 mg/kg	59/171	57 (96.6%)	56 (94.9%)	53(89.8%)	47 (79.7%)
Placebo	11/177	10 (90.9%)	10 (90.9%)	10 (90.9%)	9 (81.8%)
Females					
0.32 mg/kg	37/202	36 (97.3%)	35 (94.6%)	32 (86.5%)	30 (81.1%)
Placebo	9/201	9 (100%)	8 (88.9%)	8 (88.9%)	7 (77.8%)

Note: Denominator is the number of converters from the Primary Efficacy Parameter, i.e., the number converting to NSR for at least 60 secs within 2.5 hours of infusion.

Time to Conversion

The mean time to first conversion to NSR was analysed using summary statistics. The results demonstrated that the effect of tedisamil was rapid. For those subjects who converted within 2.5 hours, conversion to NSR generally occurred within 30 minutes from start of infusion. The results from the analysis of the mean time to first conversion to NSR demonstrated that:

- Tedisamil significantly reduces time to conversion to NSR for subjects compared with placebo in both males and females, as shown in Table 5-10. For males who received the recommended dose of 0.48 mg/kg, the mean time to conversion was 28.6 mins in the tedisamil group compared with 75.7 mins in the placebo group.

- The mean time to conversion to NSR for females who received the recommended dose of 0.32 mg/kg was 25.1 mins in the tedisamil group compared with 92.1 min in the placebo group.
- Tedisamil reduced the mean time to first conversion in subjects with AFib/AFl at the recommended doses for males and females irrespective of :
  - Age (<65 or ≥65)
  - Whether subjects were receiving concomitant beta-blocking agents or not
  - NYHA classification
  - Duration of arrhythmic episode

Table 5-10 Time to Conversion to NSR – Integrated Phase III Efficacy Dataset, by Dose and Gender

	Tedisamil Dose	Placebo
Males	**0.48 mg/kg**	
Total Subjects in ITT AFib/AFl	172	177
Subjects who converted, n	59	11
Time to NSR (mins)		
Mean (SD)	28.6 (22.8)	75.7 (47.8)
Median	21.0	60.0
Min, Max	0, 124	0, 144
Females	**0.32 mg/kg**	
Total Subjects in ITT AFib/AFl	202	202
Subjects who converted, n	37	9
Time to NSR (mins)		
Mean (SD)	25.1 (17.4)	92.1 (44.6)
Median	20.0	94.0
Min, Max	3, 74	36, 148

Note: Subjects who underwent DC cardioconversion within 2.5 hours after the start of study drug infusion were excluded from this "time to NSR" analysis. Subjects not converting to NSR within 2.5 hours were excluded from this "time to NSR" analysis.

5.6.4 Conclusions from Integrated Phase III Efficacy Dataset

Results for the integrated efficacy data were consistent with results from the individual studies and demonstrated that tedisamil is effective in achieving rapid conversion to NSR within 2.5 hours and that NSR is sustained in tedisamil-converted subjects for at least 24 hours.

Primary Efficacy Parameter

- Tedisamil was effective at restoring NSR in AFib/AFl subjects within 2.5 hours of study drug infusion compared to placebo at doses of 0.48 mg/kg in males and at 0.32 mg/kg in female subjects.
- Analysis by type of rhythm showed that tedisamil was effective at restoring NSR within 2.5 hours irrespective of gender in AFib subjects.
- Duration of AFib/AFl episodes: Tedisamil at doses of 0.32 mg/kg and above showed significant efficacy in restoring NSR in subjects with AFib/AFl within 2.5 hours, irrespective

of whether the subject's qualifying arrhythmic episode was ≤48 hours or >48 hours in duration. A higher percentage of both male and female subjects converted to NSR within 2.5 hours if the duration of arrhythmic episode was ≤ 48 hours.

- Tedisamil's effect was observed in other subgroups: age (<65 or ≥65), NYHA classification Class I; Class II/III), concomitant use of beta-blocking agents (yes; no), first episode or recurrent episode, and renal status (CrCL <60; ≥60 mL/min).

Secondary Efficacy Parameters

- The effect of tedisamil was sustained within the majority of subjects who converted within 2.5 hours remaining in NSR for at least 24 hours. At the recommended doses, 89.8% of tedisamil male converters and 86.5% of tedisamil female converters remained in NSR for 24 hours.
- Tedisamil significantly reduced the mean time to first conversion to NSR in both males and females. The mean time to conversion for male subjects who received 0.48 mg/kg was 28.6 mins compared to 75.7 mins for placebo males. The mean time to conversion for female subjects who received the 0.32 mg/kg was 25.1 min compared to 92.1 min for placebo females.

5.7 Efficacy Summary and Conclusions

Five multicenter, randomized, double-blind, placebo-controlled, Phase III studies demonstrate the efficacy of tedisamil in subjects with recent onset (3h – 45 days) AFib/AFl. All studies met their primary objective and demonstrated efficacy of tedisamil compared to placebo at the recommended doses of 0.48 mg/kg for males and 0.32 mg/kg for females, thus demonstrating reproducibility of results. At the recommended dose of 0.48 mg/kg, a total of 171 tedisamil and 177 placebo male subjects were evaluated; and at the recommended dose of 0.32 mg/kg, a total of 202 tedisamil and 201 placebo female subjects were evaluated.

Tedisamil's effect was sustained, with the vast majority of subjects who converted within 2.5 hours remaining in NSR for at least 24 hours. At the recommended doses, 90% of males and 87% of females who had converted within 2.5 hours remained in NSR for at least 24 hours. Tedisamil significantly reduced the mean time to first conversion to NSR in both males and females. The mean time to conversion for male subjects who received 0.48 mg/kg was 28.6 mins compared to 75.7 mins for placebo males. The mean time to conversion for female subjects who received the 0.32 mg/kg was 25.1 min compared to 92.1 min for placebo females.

Subgroup analyses showed that subjects <65 years and those ≥65 years had similar conversion rates. NYHA classification status (I and II/III), concomitant use of beta-blocking agents, or mild to moderate renal impairment did not affect the efficacy of tedisamil at those doses. Also similar efficacy was observed in subjects with a first AFib/AFl episode and subjects who had a recurrent episode. A higher percentage of subjects converted to NSR if the duration of arrhythmic episode was ≤48 hours than if the subjects had their current episode for longer than 48 hours. This finding is consistent with clinical experience, where AFib/AFl of longer duration is more difficult to cardioconvert.

The data from the efficacy analysis support the use of tedisamil for the rapid conversion to NSR in subjects with AFib/AFl of recent onset (3 hrs-45 days) at dose of 0.48 mg/kg in males and 0.32 mg/kg female.

6 Clinical Safety

6.1 Exposure

Tedisamil for the treatment of AFib/AFl is intended to be administered as a single infusion. The number of subjects who have received an infusion of IV tedisamil is shown in Table 6-1. A total of 1137 subjects, which included healthy volunteers, symptomatic non-CAD subjects, AFib/AFl subjects, and subjects with other cardiovascular conditions, were exposed to IV tedisamil in the clinical development program. The integrated safety dataset consists of data from the 931 AFib/AFl subjects exposed to tedisamil in Phase II and Phase III studies (and the 470 placebo AFib/AFl subjects in those same studies). In addition, 206 subjects were exposed to IV tedisamil outside the Phase II/III AFib/AFl program.

The number of subjects exposed to each dose of tedisamil is provided in Table 6-3 as part of the integrated safety dataset discussion.

Table 6-1 Summary of Overall Exposure to IV Tedisamil

IV Tedisamil Studies	Subject Type	Dose Range	Duration	No of Subjects
AFib/AFl	**AFib/AFl subjects**	**0.16-0.72 mg/kg**	**Single Dose**	**931**
Non-AFib/AFl				
Phase I	Healthy Volunteers/Symptomatic Non-CAD subjects	1-30 mg/day	Single Dose	123[a]
Angina	CAD subjects with stable Angina	0.08-0.32 mg/kg	Single Dose	70 [a,b]
Other Cardiac Disorders	Subjects with IHD and CHF	0.3-0.5 mg/kg	Single Dose	13 [a,b]
Total Non-AFib/AFl				**206**
Total Exposed to IV Tedisamil				**1137**

[a] The other 206 (1137 minus 931) subjects not integrated were not AFib/AFl subjects (eg, healthy volunteers, subjects with other types of cardiac disorders). The 70 CAD subjects and the 13 subjects with ischemic heart disease (IHD) and congestive heart failure (CHF) were included in the integrated summary of safety written for the angina program, which is discussed in Section 0.2. The safety data from the Phase I studies of IV tedisamil were reviewed individually by study and findings were consistent with those reported for IV tedisamil. The most common TEAEs were injection site pain, headache, and asthenia.
[b]These subjects were included in the integrated summary of safety written for the angina program, which is discussed in Section 0.2.

There were 2391 subjects exposed to oral tedisamil, which include the large pool of subjects who participated in the earlier angina clinical program. Those subjects are summarized in Table 6-2. Included in that count, were subjects who may have received both single and multiple doses of tedisamil or both oral and IV doses of tedisamil. Safety observations from those subjects that may be relevant to exposure of a single infusion of IV tedisamil in the AFib/AFl population are addressed in Section 6.12.2.

Table 6-2 Summary of Overall Exposure to Oral Tedisamil

Tedisamil Oral	Subject Type	Dose Range	Duration	No of Subjects
Phase I Studies	Healthy Volunteers/Symptomatic Non-CAD subjects	10-200 mg Tedisamil 25-200 mg b.i.d.	Single Dose Sum of exposure days: 2255	510[a]
Angina ISS Studies	CAD subjects with stable Angina	25-200 mg b.i.d	Mean exposure days: 114.7	1668
Other Cardiac Disorders Studies	Subjects with IHD and CHF	50-100 mg b.i.d	Range 1-100 days	32
Angina post ISS Studies	CAD subjects with stable Angina	50-100 mg b.i.d	Range 3-449 days	109
AFib/AFl Studies	AFib/AFl subjects	80-120 mg b.i.d	Range 1-214 days	98
Total Exposed to Oral Tedisamil				**2391[b]**

[a] Includes subjects who were exposed to both multiple and single oral doses of tedisamil.
[b] Includes subjects who were exposed to both multiple and single oral doses of tedisamil and 26 subjects exposed to both oral and IV formulations.

6.2 Safety Measurements in the IV Tedisamil Studies

Adverse Events

A treatment emergent AE (TEAE) was defined as any AE with onset date on or after the start of study medication and up through 42 days from last study drug intake. The existence of, or change in, an AE could have been concluded based on the necessity to administer a concomitant medication, from a spontaneous report by the subject, from a physical examination, or from special tests such as ECGs, laboratory assessments or other study-specified tests (source of AE). Each AE was evaluated for duration, severity, seriousness, and causal relationship to the investigational drug.

ECG collection

A standard supine 12-lead ECG at a paper speed of 25 mm/sec and an amplitude of 10 mV/mm was recorded at all specified time points. For data capture, ECG intervals (RR, PQ, QRS, and QT) were centrally evaluated. In all studies, continuous Holter ECG monitoring was performed for 24 hours, beginning 10 minutes before the start of infusion.

Holter tapes (24 h) were analyzed for arrhythmias according to specific Holter analysis definitions. Ventricular events were coded according to a predefined coding system assessed by the AOC. All events of 3 or more abnormal/aberrant ventricular complexes with a rate of > 100 beats per minute were defined as a single episode of VT. Events were grouped by morphology, i.e. polymorphic ventricular tachycardia (poly-VT), monomorphic ventricular tachycardia (mono-VT) and by duration, i.e. sustained (>30 seconds) or non-sustained. (See Section 6.8.1 for more details on the coding of VTs.)

Laboratory Evaluations
Blood and urine samples for routine laboratory testing were obtained at screening, 24 hours post infusion or upon early termination from the study, and at the follow-up visit scheduled at 4 weeks post infusion.

Vital signs were monitored by change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse. Physical examinations were conducted at screening, end of hospitalization (24 hours after start of infusion), and at the follow-up visit. Weight and height were measured with the subjects wearing normal indoor clothes but without shoes.

6.3 Integrated Safety Dataset

Safety data from the nine IV tedisamil Phase II and Phase III studies identified previously in Table 4-1 were included in an integrated safety dataset. The integrated safety dataset consisted of 1401 subjects, of which 931 subjects received a single infusion of IV tedisamil and 470 subjects received placebo. Integrated safety data were grouped according to treatment doses.

The number of subjects in each dose group is shown in Table 6-3 by gender and within gender by subgroups of interest (age; beta-blocker use; NYHA Class; and renal status).

The demographics and baseline characteristics for subjects in the integrated safety dataset (n=1401) were very similar to those for subjects enrolled in the five Phase III studies, which were summarized by study in Section 5.3. A summary of the integrated safety dataset baseline characteristics is provided in Appendix 2.

In the integrated safety dataset, the tedisamil groups consisted of 759 males (528 tedisamil; 231 placebo) and 642 females (403 tedisamil; 239 placebo). Subjects were almost exclusively Caucasian with 98% classified as white, 0.8% Black/African American, 0.6% Asian, 0.6% other, and 0.1% native Hawaiian or other Pacific Islander. Ages ranged from 26 to 91 years for subjects treated with tedisamil and 20 to 92 years for subjects who received placebo. The average age for males was 60.8 years for tedisamil and 60.3 years for placebo. For females the average age was 68.7 years for tedisamil subjects and 68.6 years for placebo. The female population tended to be older (by ~8 years), more likely to have more severe congestive heart failure (NYHA Class II/III), and have an arrhythmia episode of greater than 48 hours duration.

Table 6-3 Integrated Safety Dataset, Number of Subjects in Male and Female Subgroups

Dose mg/kg	0.16 Tedisamil	0.24 Tedisamil	0.32[a] Tedisamil	0.32-0.48 Tedisamil	0.48[a] Tedisamil	0.48-0.72 Tedisamil	0.64 Tedisamil	Combined Tedisamil	Placebo
Number of subjects									
All Subjects N	67	128	397	17	241	19	62	931	470
Male Subjects N	66	6	172	10	207	15	52	528	231
Age < 65	38 (57.6%)	2 (33.3%)	106 (61.6%)	8 (80.0%)	119 (57.5%)	11 (73.3%)	35 (67.3%)	319 (60.4%)	144 (62.3%)
Age >= 65	28 (42.4%)	4 (66.7%)	66 (38.4%)	2 (20.0%)	88 (42.5%)	4 (26.7%)	17 (32.7%)	209 (39.6%)	87 (37.7%)
Beta-Blocking Agents=Yes	45 (68.2%)	4 (66.7%)	121 (70.3%)	7 (70.0%)	137 (66.2%)	9 (60.0%)	37 (71.2%)	360 (68.2%)	158 (68.4%)
Beta-Blocking Agents=No	21 (31.8%)	2 (33.3%)	51 (29.7%)	3 (30.0%)	70 (33.8%)	6 (40.0%)	15 (28.8%)	168 (31.8%)	73 (31.6%)
NYHA Classification I	30 (45.5%)	--	113 (65.7%)	4 (40.0%)	123 (59.4%)	3 (20.0%)	37 (71.2%)	310 (58.7%)	137 (59.3%)
NYHA Classification II/III	28 (42.4%)	--	55 (32.0%)	6 (60.0%)	74 (35.7%)	11 (73.3%)	15 (28.8%)	189 (35.8%)	83 (35.9%)
Creatinine Clearance <60ml/min	5 (7.6%)	0 (0.0%)	12 (7.0%)	0 (0.0%)	23 (11.1%)	2 (13.3%)	2 (3.8%)	44 (8.3%)	26 (11.3%)
Creatinine Clearance >=60ml/min	59 (89.4%)	6 (100.0%)	154 (89.5%)	10 (100.0%)	177 (85.5%)	12 (80.0%)	47 (90.4%)	465 (88.1%)	191 (82.7%)
Female Subjects N	1	122	225	7	34	4	10	403	239
Age < 65	0 (0.0%)	33 (27.0%)	69 (30.7%)	1 (14.3%)	8 (23.5%)	2 (50.0%)	4 (40.0%)	117 (29.0%)	77 (32.2%)
Age >= 65	1 (100.0%)	89 (73.0%)	156 (69.3%)	6 (85.7%)	26 (76.5%)	2 (50.0%)	6 (60.0%)	286 (71.0%)	162 (67.8%)
Beta-Blocking Agents=Yes	0 (0.0%)	97 (79.5%)	181 (80.4%)	5 (71.4%)	20 (58.8%)	3 (75.0%)	4 (40.0%)	310 (76.9%)	187 (78.2%)
Beta-Blocking Agents=No	1 (100.0%)	25 (20.5%)	44 (19.6%)	2 (28.6%)	14 (41.2%)	1(25.0%)	6(60.0%)	93 (23.1%)	52 (21.8%)
NYHA Classification I	0 (0.0%)	40 (32.8%)	91(40.4%)	3 (42.9%)	12 (35.3%)	3 (75.0%)	4 (40.0%)	153 (38.0%)	95 (39.7%)
NYHA Classification II/III	0 (0.0%)	74 (60.7%)	108 (48.0%)	4 (57.1%)	22 (64.7%)	1(25.0%)	6 (60.0%)	215 (53.3%)	121 (50.6%)
Creatinine Clearance <60ml/min	0 (0.0%)	39 (32.0%)	63 (28.0%)	4 (57.1%)	8 (23.5%)	2 (50.0%)	1(10.0%)	117 (29.0%)	64 (26.8%)
Creatinine Clearance >=60ml/min	1 (100.0%)	81(66.4%)	154 (68.4%)	3 (42.9%)	23 (67.6%)	2 (50.0%)	9 (90.0%)	273 (67.7%)	168 (70.3%)

Note: Subject numbers in individual subgroups may not equal the overall subject number due to missing data.

6.4 Adverse Events

6.4.1 Overall Summary of Adverse Events

An overview of adverse events is provided by dose in Table 6-4 for male subjects and in Table 6-5 for female subjects.

Nine deaths (3 males and 6 females) were reported among the 1401 subjects (tedisamil 931; placebo 470) who were included in the IV tedisamil integrated safety dataset. An additional 2 deaths occurred in subjects randomized but not treated. These deaths are discussed in detail in Section 6.5.

TEAEs and TESAEs were reported by a comparable percentage of subjects in the combined tedisamil and placebo groups for males and for females. In most cases, the TEAEs were transient, and mild or moderate in severity.

Table 6-4 Overview of Adverse Events by Dose – Integrated Safety Dataset - Males

Number of Subjects with at least one of the following:	Stat	Tedisamil (mg/kg) 0.16 N=66	0.24 N=6	0.32 N=172	0.32-0.48 N=10	0.48 N=207	0.48-0.72 N=15	0.64 N=52	Combined Tedisamil N=528	Placebo N=231
Death [a]	n (%)	0	0	1 (0.6)	0	0	0	0	1 (0.2)	2 (0.9)
SAE	n (%)	5 (7.6)	1 (16.7)	16 (9.3)	1 (10.0)	21 (10.1)	1 (6.7)	4 (7.7)	49 (9.3)	21 (9.1)
TESAE		5 (7.6)	1 (16.7)	15 (8.7)	1 (10.0)	19 (9.2)	1 (6.7)	4 (7.7)	46 (8.7)	20 (8.7)
Discontinued study due to TEAE	n (%)	1 (1.5)	0	2 (1.2)	1 (10.0)	4 (1.9)	0	3 (5.8)	11 (2.1)	2 (0.9)
TEAE	n (%)	32 (48.5)	4 (66.7)	122 (70.9)	6 (60.0)	140 (67.6)	9 (60.0)	40 (76.9)	353 (66.9)	143 (61.9)
Severe TEAE	n (%)	4 (6.1)	1 (16.7)	10 (5.8)	1 (10.0)	12 (5.8)	2 (13.3)	3 (5.8)	33 (6.3)	11 (4.8)

Table 6-5 Overview of Adverse Events by Dose - Integrated Safety Dataset - Females

Number of Subjects with at least one of the following:	Stat	Tedisamil (mg/kg) 0.16 N=1	0.24 N=122	0.32 N=225	0.32-0.48 N=7	0.48 N=34	0.48-0.72 N=4	0.64 N=10	Combined Tedisamil N=403	Placebo N=239
Death [a]	n (%)	0	2 (1.6)	2 (0.9)	1 (14.3)	0	0	0	5 (1.2)	1 (0.4)
SAE	n (%)	0	14 (11.5)	21 (9.3)	3 (42.9)	5 (14.7)	0	3 (30.0)	46 (11.4)	23 (9.6)
TESAE		0	14 (11.5)	20 (8.9)	3 (42.9)	5 (14.7)	0	2 (20.0)	44 (10.9)	22 (9.2)
Discontinued study due to TEAE	n (%)	0	2 (1.6)	5 (2.2)	1 (14.3)	1 (2.9)	0	1 (10.0)	10 (2.5)	3 (1.3)
TEAE	n (%)	0	76 (62.3)	146 (64.9)	6 (85.7)	28 (82.4)	3 (75.0)	9 (90.0)	268 (66.5)	150 (62.8)
Severe TEAE	n (%)	0	5 (4.1)	10 (4.4)	2 (28.6)	7 (20.6)	0	2 (20.0)	26 (6.5)	15 (6.3)

Note(s) TEAEs are defined as AEs with start date beyond or equal to first day of study treatment but within 42 days after last study drug intake (for SAEs within 42 days). This includes AEs that worsened during treatment. TEAEs leading to study termination are obtained from the AE form (Led to study termination: yes). Severe = Severity reported as "severe" or missing. Death is defined as a fatal outcome of an (S) AE

[a] Of a total of 11 deaths, the 2 deaths in subjects who did not receive study medication were excluded from the integrated safety dataset; therefore, 9 deaths (3 males and 6 females) were included in the integrated safety dataset.

Summary of subjects with at least 1 TEAE

The number of subjects reporting at least 1 TEAE ranged from 48.5% (0.16 mg) to 76.9% (0.64 mg) in male subjects and from 62.3% (0.16 mg) to 90.0% (0.64 mg) in female subjects. The most common type of TEAEs reported were cardiac disorders, which are discussed separately in Section 6.5.

The incidences of non-cardiac disorders of special interest are summarized in Table 6-6 for males and Table 6-7 for females and are briefly discussed in the following paragraphs. Selection of the TEAEs of special interest was based on experience with tedisamil in the angina program.

Gastrointestinal disorders

The gastrointestinal disorders considered to be of special interest were diarrhea and oral hypoaesthesia. Diarrhea was reported by comparable percentage of tedisamil and placebo subjects in both the male and female populations. Oral hypoaesthesia was reported by 3 (0.6%) tedisamil-treated male subjects. No cases of oral hypoaesthesia were reported for placebo-treated males or any females.

General Disorders and Administration Site Conditions

Injection/infusion site reactions were reported more frequently in the tedisamil group than the placebo group in both male and female populations, and were the most commonly reported TEAEs judged to be related to treatment. Infusion site burning was reported for 3.2% of tedisamil-treated males (vs. 0.4% placebo) and 1.5% of tedisamil-treated females (vs. 0.4% placebo). Injection/infusion site reactions were distributed across the tedisamil doses (i.e., related to the infusion and not to the dose of tedisamil being administered).

Nervous System Disorders

The nervous system disorders of special interest were headache, dizziness, oral paraesthesia, and circumoral paraesthesia. At the recommended doses for males and females, the incidences of headaches and dizziness were either comparable for the two treatment groups or lower in the tedisamil group. While the incidences of oral paraesthesia were low in both treatment groups, but slightly higher in the tedisamil group for males compared to placebo (1.9% vs. 0.4%) and females (0.9% and 0.4%).

Vascular Disorders:

The vascular disorders of interest were hypotension and orthostatic hypotension. A higher incidence of hypotension was reported in the tedisamil-treated males compared to the placebo-treated males (2.3% vs. 0.9%), while the incidence between treatments was similar in the female population (2.7% vs. 3.3%).

Table 6-6 Incidence of TEAEs of Special Interest (non-cardiac disorders) - Integrated Safety Dataset - Males

System Organ Class Preferred Term	**0.16mg/kg (N=66) n (%)**	**0.24 mg/kg (N=6) n (%)**	**0.32 mg/kg (N=172) n (%)**	**0.32-0.48 mg/kg (N=10) n (%)**	**0.48 mg/kg (N=207) n (%)**	**0.48-0.72 mg/kg (N=15) n (%)**	**0.64 mg/kg (N=52) n (%)**	**Combined Tedisamil (N=528) n (%)**	**Placebo (N=231) n (%)**
Gastrointestinal Disorders	**5 (7.6%)**	**1 (16.7%)**	**12 (7.0%)**	**0**	**9 (4.3%)**	**2 (13.3%)**	**5 (9.6%)**	**34 (6.4%)**	**8 (3.5%)**
Hypoaesthesia oral	0	0	0	0	2 (1.0%)	0	1 (1.9%)	3 (0.6%)	0
Diarrhea	0	0	4 (2.3%)	0	1 (0.5%)	0	0	5 (0.9%)	3 (1.3%)
General Disorders & Administration Site Conditions	**7 (10.6%)**	**3 (50.0%)**	**34 (19.8%)**	**0**	**28 (13.5%)**	**2 (13.3%)**	**10 (19.2%)**	**84 (15.9%)**	**18 (7.8%)**
Infusion site burning	2 (3.0%)	3 (50.0%)	3 (1.7%)	0	5 (2.4%)	1 (6.7%)	3 (5.8%)	17 (3.2%)	1 (0.4%)
Infusion site pain	0	0	0	0	1 (0.5%)	1 (6.7%)	0	2 (0.4%)	1 (0.4%)
Infusion site phlebitis	0	0	0	0	0	0	1 (1.9%)	1 (0.2%)	1 (0.4%)
Infusion site pruritis	0	0	0	0	1 (0.5%)	0	0	1 (0.2%)	0
Infusion site reaction	0	0	1 (0.6%)	0	2 (1.0%)	0	0	3 (0.6%)	0
Injection site burning	0	0	1 (0.6%)	0	3 (1.4%)	0	0	4 (0.8%)	0
Injection site inflammation	0	0	0	0	1 (0.5%)	0	0	1 (0.2%)	0
Injection site pain	2 (3.0%)	0	4 (2.3%)	0	5 (2.4%)	0	2 (3.8%)	13 (2.5%)	0
Injection site reaction	1 (1.5%)	0	0	0	0	0	0	1 (0.2%)	0
Venipuncture site pain	0	0	1 (0.6%)	0	0	0	0	1 (0.2%)	0
Nervous System Disorders	**3 (4.5%)**	**2 (33.3%)**	**13 (7.6%)**	**0**	**23 (11.1%)**	**1 (6.7%)**	**8 (15.4%)**	**50 (9.5%)**	**17 (7.4%)**
Dizziness	0	0	5 (2.9%)	0	3 (1.4%)	0	2 (3.8%)	10 (1.9%)	7 (3.0%)
Headache	0	0	3 (1.7%)	0	6 (2.9%)	1 (6.7%)	3 (5.8%)	13 (2.5%)	5 (2.2%)
Paraesthesia circumoral	0	0	0	0	2 (1.0%)	0	0	2 (0.4%)	0
Paraesthesia oral	0	1 (16.7%)	0	0	4 (1.9%)	0	2 (3.8%)	7 (1.3%)	1 (0.4%)
Vascular Disorders	**9 (13.6%)**	**1 (16.7%)**	**15 (8.7%)**	**3 (30.0%)**	**20 (9.7%)**	**3 (20.0%)**	**9 (17.3%)**	**60 (11.4%)**	**24 (10.4%)**
Hypotension	2 (3.0%)	0	4 (2.3%)	0	3 (1.4%)	1 (6.7%)	2 (3.8%)	12 (2.3%)	2 (0.9%)

Table 6-7 Incidence of TEAEs of Special Interest (non-cardiac disorders) - Integrated Safety Dataset - Females

System Organ Class Preferred Term	**0.16mg/kg (N=1) n (%)**	**0.24 mg/kg (N=122) n (%)**	**0.32 mg/kg (N=225) n (%)**	**0.32-0.48 mg/kg (N=7) n (%)**	**0.48 mg/kg (N=34) n (%)**	**0.48-0.72 mg/kg (N=4) n (%)**	**0.64 mg/kg (N=10) n (%)**	**Combined Tedisamil (N=403) n (%)**	**Placebo (N=239) n (%)**
Gastrointestinal Disorders	**0**	**8 (6.6%)**	**13 (5.8%)**	**0**	**4 (11.8%)**	**0**	**2 (20.0%**	**27 (6.7%)**	**23 (9.6%)**
Diarrhea	0	3 (2.5%)	3 (1.3%)	0	1 (2.9%)	0	0	7 (1.7%)	4 (1.7%)
General Disorders & Administration Site Conditions	**0**	**12 (9.8%)**	**26 (11.6%)**	**0**	**9 (26.5%)**	**0**	**3 (30.0%)**	**50 (12.4%)**	**22 (9.2%)**
Infusion related reaction	0	1 (0.8%)	0	0	0	0	0	1 (0.2%)	0
Infusion site burning	0	3 (2.5%)	2 (0.9%)	0	0	0	1 (10.0%)	6 (1.5%)	1 (0.4%)
Infusion site pain	0	1 (0.8%)	3 (1.3%)	0	0	0	0	4 (1.0%)	0
Infusion site reaction	0	0	3 (1.3%)	0	0	0	0	3 (0.7%)	0
Injection site burning	0	0	2 (0.9%)	0	0	0	0	2 (0.5%)	1 (0.4%)
Injection site haemorrhage	0	1 (0.8%)	0	0	0	0	0	1 (0.2%)	0
Injection site pain	0	0	3 (1.3%)	0	1 (2.9%)	0	1 (10.0%)	5 (1.2%)	0
Nervous System Disorders	**0**	**14 (11.5%)**	**22 (9.8%0**	**1 (14.3%)**	**4 (11.8%)**	**0**	**3 (30.0%)**	**44 (10.9%)**	**17 (7.1%)**
Dizziness	0	4 (3.3%)	4 (1.8%)	0	2 (5.9%)	0	0	10 (2.5%)	4 (1.7%)
Headache	0	5 (4.1%)	8 (3.6%)	0	1 (2.9%)	0	1 (10.0%)	15 (3.7%)	8 (3.3%)
Paraesthesia oral	0	1 (0.8%)	2 (0.9%)	0	1 (2.9%)	0	0	4 (1.0%)	1 (0.4%)
Vascular Disorders	**0**	**9 (7.4%)**	**25 (11.1%)**	**4 (57.1%)**	**3 (8.8%)**	**2 (50.0%)**	**3 (30.0%)**	**46 (11.4%)**	**37 (15.5%)**
Hypotension	0	2 (1.6%)	5 (2.2%)	1 (14.3%)	1 (2.9%)	1 (25.0%)	1 (10.0%)	11 (2.7%)	8 (3.3%)
Orthostatic hypotension	0	1 (0.8%)	1 (0.4%)	0	0	0	0	2 (0.5%)	0

Summary of subjects with at least 1 TESAE

TESAEs were reported by similar numbers of subjects in each treatment group in the integrated safety dataset and subject subgroups (Table 6-4 and Table 6-5). Summaries of TESAEs by system organ class are provided for male and female subjects provided in Appendix 3.

In the integrated safety dataset, 8.7% of males and 10.9% of females who received tedisamil experienced a TESAE compared with 8.7% of males and 9.2% of females in the placebo group. No dose related trends were noted within the subject subgroups. The most common types of TESAEs were cardiac disorders, occurring in 5.9% of males and 6.7% of females in the tedisamil group compare with 6.1% and 4.2% in the placebo group. The cardiac disorders are considered of special interest and are discussed in more detail in Section 6.6.

The most common non-cardiac TESAE was lower respiratory tract and lung infections, which occurred at comparable rates in the tedisamil and placebo groups (0.6% vs. 0.9% in males; 0.7% vs. 0.4% in females).

6.5 Deaths

Eleven deaths (4 males and 7 females) occurred in the IV tedisamil antiarrhythmia program: 2 subjects in the Phase II Study S219.2.107, and 9 subjects in the Phase III studies, including 2 subjects who had not received medication (Table 6-8). Therefore, 9 deaths were included in the integrated safety dataset, 6 (0.64%) of the 931 who received tedisamil and 3 (0.64%) of the 470 who received placebo.

Table 6-8 Summary of Deaths in IV Tedisamil AFib/AFl Program by Dose and Gender

Tedisamil Dose Group	Deaths		
	Total	Male	Female
0.24 mg/kg	2	--	2
0.32 mg/kg	3	1	2
0.32-0.48 mg/kg	1		1
Placebo	3	2	1
Total Deaths for Treated Subjects	**9**	**3**	**6**
Randomized in IV study but did not receive study medication	2	1	1
Total Deaths in IV studies	**11**	**4**	**7**

Overall, the majority of deaths were cardiac related (9 of 11), which is expected given the study indication and subject population. The cause of death is described in Table 6-9, followed by brief narratives for each subject who died, including the two subjects who died prior to receiving study drug.

For the 11 deaths, nine deaths were considered by the Investigator to be unrelated to treatment and one death was considered unlikely to be related to study drug. The relationship to study drug of the other death was considered unknown by the investigator, but the primary cause of death was pancreatic cancer and the subject was randomized to placebo. All deaths during the Phase III program were reviewed by the AOC.

Table 6-9 Description of Deaths occurring in the IV Tedisamil Antiarrhythmic Program

Dose Group	Subj # Gender / Age	Preferred Term	Medical History	Days after Dosing	Investigator's Assessment of Relationship
IV Tedisamil					
0.24 mg/kg	61304 Female/75	Pulmonary embolism	Hypertension, obesity, varicose vein, angina pectoris and acute myocardial infarction.	Died on day of infusion	Unrelated
	61508 Female/83	Cerebrovascular accident	Coronary artery disease, diabetes mellitus, cardiac failure, encephalopathy, extrasystoles and hypertension.	16	Unrelated
0.32 mg/kg	44203 Male/72	Acute MI	Hypertension NOS, coronary artery disease NOS, prostatic hypertrophy and urinary tract infection NOS.	7	Unrelated
	67406 Female/80	Acute MI	Coronary artery disease and cardiac failure, myocardial infarction and hypertension.	3	Unrelated
	82506 Female/90	Pneumonia, cardiac failure	Hypertension, diabetes mellitus and ischemic heart disease and heart failure.	7	Unrelated
0.32-0.48 mg/kg	43001 Female/80	Atrial fibrillation, cardiac arrest, electromechanical dissociation, hypotension NOS	Coronary artery disease NOS and age indeterminate myocardial infarction and essential hypertension.	2	Unlikely
Placebo	90242 Male/70	Pancreatic carcinoma	Pancreatitis, coronary artery disease, CABG, diabetes Type II, nephrolithiasis,	18	Unknown
	22101 Male/74	Ventricular fibrillation	Diabetes, infectious hepatitis, gastric ulcer, ischemic heart disease, myocardial infarction, rib and lumber vertebra fractures	17	Unrelated
	82711 Female/85	Cerebrovascular accident	Chronic bronchitis	7	Unrelated
Randomized but not treated	41401 Female/73	Sudden death	Arterial hypertension, coronary artery disease, AFib,	Not applicable. Died prior to receiving infusion	Unrelated
	90188 Male/86	Pulmonary embolism	Myocardial Infarction, rectal carcinoma, ulciosis, cerebral infarction, lung lymphysema, hamvehalt, hypacusis, prostate lymphotropia, cholecystectomia	Not applicable. Died prior to receiving infusion	Unrelated

Abbreviations: CABG = coronary artery bypass graft; MI = myocardial infarction; NOS = not otherwise specified

Deaths that occurred at the **0.24 mg/kg** tedisamil dose group

Subject 61304, (a white female, aged 75, with AFib), in study S219.3.116, died of an AE of pulmonary embolism PT. The event was considered to be a TEAE, unrelated to tedisamil treatment in the investigator's judgment. The subject had a medical history of hypertension, obesity and varicose vein, angina pectoris and acute myocardial infarction. The subject was anticoagulated with heparin 1000 units IV od and heparin 5000 units sc t.i.d. the day prior and day of study drug infusion. The day of infusion, the subject experienced AEs of infusion related reaction (feeling of tweak in the infusion hand), headache and heart rate increased. All events were reported as mild in intensity. Only the event of infusion related reaction was considered by the investigator to be possibly related to study drug. Approximately 10 hours after the initiation of infusion, the subject developed discomfort in her breast, breathlessness, episodes of apnea and developed cyanosis of the upper body. Approximately, 30 minutes later, nodal rhythm and bradycardia were detected during monitoring. The subject died within the following hour. The autopsy revealed a pulmonary trunk thromboembolism. The pulmonary embolism was judged to be severe. The investigator confirmed that the subject did not convert to normal sinus rhythm post infusion. It was considered that the study medication was unrelated to the event by the Investigator.

Subject 61508, (a white female, aged 83, with AFib), in study S219.3.116, died of a TEAE of cerebrovascular accident, considered to be unrelated to study medication in the investigator's judgment. The subject had a medical history of coronary artery disease, diabetes mellitus and cardiac failure, encephalopathy, extrasystoles and hypertension. On the day of infusion, the subject experienced mild extrasystoles and tachycardia. Both events were judged by the investigator to be possibly related to study treatment and were resolved on the day they were reported. Sinus rhythm was not restored during hospitalization. The subject was discharged from 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 hemi paresis. The subject's doctor diagnosed a stroke. Approximately 1 week after this event the subjects' condition worsened and she died at home. The cerebrovascular accident (stroke) was severe in intensity and was the result of a thromboembolism and was unrelated to study medication in the investigator's judgment.

Deaths that occurred at the **0.32 mg/kg** tedisamil dose group

Subject 44203, (a white male, aged 72, with AFib), in study S219.3.114, died of an AE of acute myocardial infarction considered to be unrelated to study treatment according to the investigator. The subject had a medical history of hypertension (not otherwise specified [NOS]), coronary artery disease NOS, prostatic hypertrophy and urinary tract infection NOS. A mild unrelated AE of hypokalaemia was reported the day after infusion. The subject did not convert to NSR. The subject was discharged from hospital on 2 days post infusion. Approximately 1 week later, the subject suffered an SAE of acute myocardial infarction, was hospitalized and did not respond to resuscitation and died.

Subject 67406, (a white female, aged 80, with AFib), in study S219.3.116, died of an AE of acute myocardial infarction that was considered, in the investigator's judgment, to be unrelated to study medication. The subject had a medical history of coronary artery disease and cardiac

failure, myocardial infarction and hypertension. Study drug infusion was prematurely stopped after 7 minutes due to a TEAE of ECG QRS complex prolonged, considered mild in intensity and probably related to study drug by the investigator. The event was noted to resolve on the same day. The day after infusion, DC cardioversion was preformed to restore normal sinus rhythm. The subject was discharged on the same day. On the second day post study drug infusion, the subject developed sudden pain in the retrosternal region and was transferred to hospital. Cardiac arrest occurred. An ECG showed asystole and resuscitation was started. This was unsuccessful and the subject died on the same day. It was considered that the study medication was unrelated to the event by the Investigator.

Subject 82506, in study S219.3.118, (a white female, aged 90, with AFl), died of an AE of pneumonia and cardiac failure, considered unrelated to study medication according to the investigator. The subject had a medical history of hypertension, diabetes mellitus and ischemic heart disease and heart failure. The subject did not convert to NSR. Two days after administration of study treatment the subject experienced fever. Five days after infusion the subjects fever had risen and the subject had purulent sputum with lung crepitation. Leucocytosis and granulocytes were also observed. An SAE of pneumonia was also reported which led to termination. Six days post infusion, the subject was reported with SAE of cardiac failure. Both of these events were severe in intensity and were fatal. It was considered that the study medication was unrelated to the event by the Investigator. The subject had a medical history of hypertension, diabetes mellitus and ischemic heart disease and heart failure.

Deaths that occurred at the **0.32-0.48 mg/kg** tedisamil dose group

Subject 43001, (an Asian female, aged 80, with AFib), in study S219.3.114, died of an AE of AFib, cardiac arrest, electromechanical dissociation and hypotension NOS. According to the investigator's judgment the events were found to be unrelated to the drug treatment. The subject had a history of coronary artery disease NOS and age indeterminate myocardial infarction and essential hypertension. Ten minutes after the initiation of infusion, the subject experienced bradycardia, asystole and low blood pressure and the infusion was stopped. During the infusion a wide QRS complex occurred. The subject underwent cardiopulmonary resuscitation and was intubated. An ECG preformed showed sinus tachycardia with incomplete left bundle branch block, which later reverted to a narrow QRS complex. SAEs of bradycardia NOS, cardiac arrest and hypotension NOS were reported which led to discontinuation of study treatment; all were considered severe and to have a possible relationship with study treatment by the investigator. On the same day as infusion, an SAE of electrocardiogram QRS complex prolonged and AEs of acidosis NOS, pulmonary edema NOS and hypoxic encephalopathy were reported. The SAE was mild in severity. The events of acidosis NOS and hypoxic encephalopathy were mild in severity .The event of pulmonary edema NOS were severe. No judgment from the investigator regarding the relationship of the event to the study treatment was available; however the investigator did judge the event of hypoxic encephalopathy to be unrelated to study treatment. On the day after infusion, the subject was reported with an AE of diabetes mellitus NOS. The event was mild in severity. The investigator was unable to judge the relationship between the event and study treatment. Also the day after the infusion, ventilatory support was changed to CPAP mode, and later to SIMV mode. Cardiovascular pressure was stabilized and ionotropic support was tapered gradually and stopped after the blood pressure was stabilized at 120/80 mmHg. The subject was on antibiotics, ceftriaxone, metrogly, aspirin, nitrates, carvedilol, enalipril diuretics, and IV

ranitidine. The subject was making a satisfactory progress and was extubated 2 days post infusion. Post extubation, the subject again reverted to AFib with slow heart rate and hypotension. She was treated with IV amiodarone 150 mg bolus over 30 mins and another 250 mg over 6 hours, and then was DC cardioverted. The subject did not respond to further treatment and was declared dead. The events of AFib, electromechanical dissociation, hypotension NOS and cardiac arrest on day 2 post infusion were reported as severe SAEs. All events were noted to be fatal, and were judged by the investigator as unlikely to be related to study drug.

Deaths that occurred in the **placebo** group

Subject 90242 (a white male, aged 70, with AFib) entered study S219.2.107 with a known history of coronary artery disease and status post coronary artery bypass graft 6 months previously. The subject was randomized to the placebo group and received study medication per protocol, however was unsuccessful in cardioversion. According to the investigator's judgment the drug was found to be unrelated to these events. The Holter monitor indicated a 3 beat run of monomorphic ventricular tachycardia approximately 4 hours post study drug infusion. He received ibutilide with successful conversion to NSR. He was given sotalol 80 mg p.o. Following discharge, the subject presented to the emergency room with recurrent abdominal pain. He was hospitalized and later diagnosed with pancreatic carcinoma. A renal ultrasound noted small cortical cysts in both kidneys and to a greater extent on the right. During this hospitalization he required several transfusions although the source of bleeding was never determined. His serum glucose levels reached 598 and he was treated by insulin sliding scale. Total parenteral nutrition was discontinued. He was treated with Diflucan for yeast in the sputum. The subject experienced a sudden increase in abdominal pain described as .10 out of 10. Over the course of 30 to 40 minutes he received 14 mg of morphine without any relief of pain. He developed a sudden decrease in consciousness and expired 1 hour and 45 minutes after the onset of pain. In conclusion, this death was considered to be unrelated to study medication and occurred 18 days post-infusion.

Subject 22101 (a white male, aged 74, with AFib) in study S219.3.112 died of pneumonia and progressive heart failure. According to the investigator's judgment these events were found to be unrelated to the drug. The subject was randomized to the placebo group, and was hospitalized for atrial fibrillation with a ventricular frequency of 130-150 bpm. two days after the infusion. The subject also had a history of two episodes of syncope which occurred prior to hospitalization. While hospitalized, the subject experienced sustained ventricular tachycardia 180-190 bpm with syncope which ceased after 150 seconds either spontaneously or due to chest compression. The event of atrial fibrillation was moderate in intensity while the ventricular tachycardia was severe in intensity. Both events were judged to be unrelated to study treatment and the ventricular tachycardia was noted to resolve on the same day it was reported. The event of atrial fibrillation was not noted to resolve and a SAE of ventricular fibrillation was later reported. This event lasted 7 to 7.5 minutes, was severe in intensity and was judged to be unrelated to study treatment. External defibrillation and cardiopulmonary resuscitation were performed and the subject required artificial ventilation. Also, an AE of hypotension NOS was reported. This event was severe in intensity and was judged to be unrelated to study treatment. The event was not noted to resolve. The subject later reported with pyrexia and showed clinical and radiological signs of bronchopneumonia. The AE of pyrexia was moderate in intensity and

was judged to be unrelated to study treatment. The subject experienced oliguria, renal insufficiency, and progressive heart failure without a documented acute myocardial infarction. The event was not noted to resolve. The subject later experienced bradycardia. The subject was resuscitated and had transient cardiac response however this was without hemodynamic effect. There was electromechanical dissociation and the resuscitation was stopped. In conclusion, this death was considered by the investigator to be unrelated to study medication and occurred 17 days post-infusion.

Subject 82711 (a white female, aged 85, with AFib) in study S219.3.118 reported with an AE of acute renal failure and an SAE of myocardial infarction on the day of the infusion. Raised necroenzymes were noted on the same day. Echocardiography revealed non-significant aortic stenosis, normal sized left ventricle and more dilated atriums. The event of acute renal failure was moderate in intensity, and the event of myocardial infarction was severe in intensity. Both events were judged to be unrelated to study treatment. The subject was later reported with an AE of moderate pneumonia, which was judged to be unrelated to study treatment and then an AE of mild hypertension that was judged to be unrelated to study treatment and was noted to resolve. The subject was reported with an SAE of cerebrovascular accident, which was confirmed by computer tomography. During the period of hospitalization, the subject's condition had gradually worsened, the values of kidney function worsened and left-sided weakness of the extremities was observed. A skull CT revealed a stroke with extensive emollition on the right side: sulci were smoothed on the right side of the temporo-occipito-parietal region and the frontal and occipital ventricle corn and lateral ventricle of the right side were compressed and narrower than the left side. The position of the midline remained. An irregular shaped inhomogeneous hypodensity (60 x 94 x 54 mm) was observed on the right temporo-occipito-parietal region, which showed signs of an infarction in the area of the MCA. There were no signs of bleeding and no abnormal density was observed in any other circumscribed areas of the brain. Chest x-ray showed the signs of diffuse congestion on the base of the left side, elevation of the level of the left side of the diaphragm, little fluid and decreased transparency above the bases of both sides, moderate enlargement of the heart, wide pulmonary trunks and branches and aortic sclerosis. The subject's condition worsened, circulation and breathing arrest developed and the subject died due to cardiorespiratory insufficiency. The SAE of cerebrovascular accident was noted to be severe in intensity, led to study termination and fatal. In conclusion, this death was considered by the investigator to be unrelated to study medication and occurred 7 days post-infusion.

Deaths that occurred in subjects randomized but **not treated**

Subject 41401, (a white female, aged 73, with AFib) in study S219.3.114 was randomized to the 0.48-0.72 mg/kg tedisamil group before the protocol was amended to eliminate that dose group, but died prior to receiving treatment. An AE of sudden death was reported; the event was severe and was judged by the investigator to be unrelated to study treatment. In conclusion, this death was considered by the investigator to be unrelated to study medication and occurred prior to infusion.

Subject 90188 (a white male, aged 86, with AFib) in study S219.2.107 was randomized to the placebo group was not given study medication. The subject was admitted to hospital for surgical intervention of a previously diagnosed rectal carcinoma. Post operatively he developed abdominal pain followed by sudden acute dyspnea. An ECG confirmed atrial fibrillation and the subject was randomized in anticipation of entering the trial. An abdominal ultrasound revealed

bilateral renal congestion. Blood gases indicated respiratory failure with PO^2 44.6 mmHg and PCO^2 26.0 mmHg. The subject was treated with high dose heparin (enoxaparin) and further evaluated for respiratory difficulties. His dyspnea worsened and he was transferred to the intensive care unit where heart rate was reported as less than 30. The subject was treated with enoxaparin, promethazine, and furosemide IV. Mechanical ventilation and thoracic compression were unsuccessful. The death summary indicated the subject was suffering from recurrent pulmonary embolism caused by postoperative immobility. An increased propensity thrombophilia was the result of an existing malignant tumor. In conclusion, this death occurred prior to infusion and therefore unrelated to study medication.

6.6 Adverse Events of Special Interest: Cardiac Disorders

Cardiac disorders were the most commonly occurring TEAEs. They occurred in a dose-dependent pattern, and were the most commonly reported type of TEAE leading to premature study termination.

The incidences of selected types of cardiac disorders of interest are presented in Table 6-10 for males and Table 6-11 for females. The incidences of cardiac disorder TEAEs were comparable in the combined tedisamil and placebo groups for males (44.3% vs. 42.0%), while for females, there was a higher incidence of cardiac TEAEs in the tedisamil group than the placebo group (41.2% vs. 28.0%). This same difference was present in the females at the recommended dose of 0.32 mg/kg (40.4% vs. 28.0%).

Ventricular tachycardia (VT) and bradycardia were the most commonly reported cardiac TEAEs in both male and female subjects. (See Section 6.8.2 for adjudicated VTs identified by Holter analysis, but not reported as TEAEs.) In males, there were 61 (11.6%) subjects in tedisamil compared to 16 (6.9%) subjects in placebo who had VT reported as a TEAE; in females, there were 19 (4.7%) subjects in tedisamil compared to 12 (5.0%) subjects in placebo.

Bradycardia was slightly more common in the tedisamil than the placebo group. In males, there were 24 (4.5%) subjects in tedisamil and 13 (5.6%) subjects in placebo who had bradycardia reported as a TEAE; in females, there were 21 (5.2%) in tedisamil and 8 (3.3%) in placebo. Sinus bradycardia was reported by 20 (3.8%) males and 8 (2.0%) females in the tedisamil group compared to 6 (2.6%) males and 5 (2.1%) females in the placebo group.

Two cases of TdP were reported by the investigator as TEAEs. Both cases occurred in females receiving doses of tedisamil of 0.48 mg/kg or 0.64 mg/kg. They were considered severe in intensity and were considered by the investigator to be related to tedisamil. These cases of TdP are reviewed in detail in Section 6.8, with other cases of adjudicated Torsade-like events that were identified during review of Holter data.

The incidence of cardiac TESAEs was comparable between the combined tedisamil and placebo groups in males (5.9% vs. 6.1%) (Table 6-12). There was no apparent dose response pattern in males. In females, the incidence of cardiac TESAEs in the combined tedisamil group was slightly higher than in the placebo group (6.7% vs. 4.2%) (Table 6-13). The most commonly reported cardiac TESAE in females was atrial fibrillation (3.0% vs. 2.1%).

Table 6-10 Incidence of Cardiac Disorder TEAEs of Special interest by Dose – Integrated Safety Dataset - Males

Doses	0.16 mg/kg N=66	0.24 mg/kg N=6	0.32 mg/kg N=172	0.32-0.48 mg/kg N=10	0.48 mg/kg N=207	0.48-0.72 mg/kg N=15	0.64 mg/kg N=52	Combined Tedisamil Group N=528	Placebo N=231
Cardiac Disorders	14 (21.2%)	2 (33.3%)	78 (45.3%)	3 (30.0%)	100 (48.3%)	6 (40.0%)	31 (59.6%)	234 (44.3%)	97 (42.0%)
Atrial tachycardia	0	0	0	0	1 (0.5%)	0	0	1 (0.2%)	0
Bradyarrhythmia	0	0	0	1 (10.0%)	1 (0.5%)	1 (6.7%)	0	3 (0.6%)	0
Bradycardia	1 (1.5%)	0	6 (3.5%)	0	14 (6.8%)	0	3 (5.8%)	24 (4.5%)	13(5.6%)
Sinus bradycardia	0	0	3 (1.7%)	0	12 (5.8%)	1 (6.7%)	4 (7.7%)	20 (3.8%)	6 (2.6%)
Sinus tachycardia	0	0	1 (0.6%)	0	1 (0.5%)	0	1 (1.9%)	3 (0.6%)	0
Superventricular tachycardia	0	0	0	0	1 (0.5%)	1 (6.7%)	2 (3.8%)	4 (0.8%)	2 (0.9%)
Tachyarrhythmia	0	0	1 (0.6%)	0	2 (1.0%)	0	0	3 (0.6%)	1 (0.4%)
Tachycardia	0	0	2 (1.2%)	0	1 (0.5%)	0	0	3 (0.6%)	4 (1.7%)
TdP[a]	0	0	0	0	0	0	0	0	0
Ventricular tachycardia	0	0	17 (9.9%)	2 (20.0%)	26 (12.6%)	3 (20.0%)	13 (25.0%)	61 (11.6%)	16 (6.9%)

[a] No TdPs were reported as TEAEs in males. Adjudicated Torsade-like events identified during Holter analysis or from ECG readings were not reported as adverse events. All Torsade-like events are discussed in Section 6.8.3.

Table 6-11 Incidence of Cardiac Disorder TEAEs of Special Interest by Dose – Integrated Safety Dataset - Females

Doses	0.16 mg/kg N=1	0.24 mg/kg N=122	0.32 mg/kg N=225	0.32-0.48 mg/kg N=7	0.48 mg/kg N=34	0.48-0.72 mg/kg N=4	0.64 mg/kg N=10	Combined Tedisamil Group N=403	Placebo N=239
Cardiac Disorders	0	38 (31.1%)	91 (40.4%)	5 (71.4%)	20 (58.8%)	3 (75.0%)	9 (90.0%)	166 (41.2%)	67 (28.0%)
Atrial tachycardia	0	1 (0.8%)	1 (0.4%)	0	0	0	0	2 (0.5%)	1 (0.4%)
Bradyarrhythmia	0	0	0	0	1 (2.9%)	0	0	1 (0.2%)	0
Bradycardia	0	4 (3.3%)	13 (5.8%)	2 (28.6%)	2 (5.9%)	0	0	21 (5.2%)	8 (3.3%)
Sinus bradycardia	0	2 (1.6%)	4 (1.8%)	0	1 (2.9%)	1 (25.0%)	0	8 (2.0%)	5 (2.1%)
Sinus tachycardia	0	0	0	0	0	0	0	0	1 (0.4%)
Superventricular tachycardia	0	1 (0.8%)	1 (0.4%)	0	0	0	1 (10.0%)	3 (0.7%)	0
Tachyarrhythmia	0	0	0	0	1 (2.9%)	0	0	1 (0.2%)	0
Tachycardia	0	1 (0.8%)	3 (1.3%)	1 (14.3%)	0	0	0	5 (1.2%)	1(0.4%)
TdP [a]	0	0	0	0	1 (2.9%)	0	1 (10.0%)	2 (0.5%)	0
Ventricular tachycardia	0	6 (4.9%)	7 (3.1%)	0	3 (8.8%)	1 (25.0%)	2 (20.0%)	19 (4.7%)	12 (5.0%)

[a] Other adjudicated Torsade-like events identified during Holter analysis or from ECG readings were not reported as TdP adverse events. All Torsade-like events are discussed in Section 6.8.3.

Table 6-12 Incidence of Cardiac TESAEs by Dose – Integrated Safety Dataset - Males

System Organ Class Preferred Term	**0.16 mg/kg** **N= 66** **n (%)**	**0.24 mg/kg** **N= 6** **n (%)**	**0.32 mg/kg** **N= 172** **n (%)**	**0.32-0.48 mg/kg** **N= 10** **n (%)**	**0.48 mg/kg** **N=207**	**0.48-0.72 mg/kg** **N=15** **n (%)**	**0.64 mg/kg** **N=52** **n (%)**	**Combined** **N=528** **n (%)**	**Placebo** **N=231** **n (%)**
Number of male subjects with at least one TESAE [a]	5 (7.6)	1 (16.7)	15 (8.7)	1 (10.0)	19 (9.2)	1 (6.7)	4 (7.7)	46 (8.7)	20 (8.7)
Cardiac disorders	**2 (30)**	**1 (16.7)**	**8 (4.7)**	**1 (10.0)**	**14 (6.8)**	**1 (6.7)**	**4 (7.7)**	**31 (5.9)**	**14 (6.1)**
Coronary artery disease	0	0	1 (0.6)	0	0	0	0	1 (0.2)	0
Cardiac failure	0	0	0	0	0	0	1 (1.9)	1 (0.2)	0
Cardiac failure congestive	0	0	0	0	1 (0.5)	0	0	1 (0.2)	0
Myocardial infarction acute	0	0	1 (0.6)	0	0	0	0	1 (0.2)	0
Myocardial infarction	1 (1.5)	0	0	0	0	0	2 (3.8)	3 (0.6)	1 (0.4)
Bradycardia	1 (1.5)	0	0	0	2 (1.0)	0	0	3 (0.6)	0
Atrial fibrillation	1 (1.5)	0	4 (2.3)	1 (10.0)	9 (4.3)	0	2 (3.8)	17 (3.2)	7 (3.0)
Atrial flutter	0	0	0	0	1 (0.5)	0	1 (1.9)	2 (0.4)	3 (1.3)
Sick sinus syndrome	0	0	0	0	0	0	0	0	1 (0.4)
Supraventricular tachycardia	0	0	0	0	0	1 (6.7)	0	1 (0.2)	0
Cardiac arrest	0	1 (16.7)	0	0	0	0	0	1 (0.2)	1 (0.4)
Ventricular fibrillation	0	0	0	0	1 (0.5)	0	0	1 (0.2)	3 (1.3)
Ventricular tachycardia	0	0	2 (1.2)	0	2 (1.0)	0	1 (1.9)	5 (0.9)	2 (0.9)

Note: Each subject was counted at most once within each system organ class and preferred term. AEs were coded using MedDRA version 5.1.
[a] A subject may have more than one TESAE.

Table 6-13 Incidence of Cardiac TESAEs by Dose – Integrated Safety Dataset - Females

System Organ Class Preferred Term	**0.16 mg/kg** **N=1** **n (%)**	**0.24 mg/kg** **N=122** **n (%)**	**0.32 mg/kg** **N=225** **n (%)**	**0.32-0.48 mg/kg** **N=7** **n (%)**	**0.48 mg/kg** **N=34**	**0.48-0.72 mg/kg** **N=4** **n (%)**	**0.64 mg/kg** **N=10** **n (%)**	**Combined** **N=403** **n (%)**	**Placebo** **N=239** **n (%)**
Number of female subjects with at least one TESAE [a]	0	14 (11.5)	20 (8.9)	3 (42.9)	5 (14.7)	0	2 (20.0)	44 (10.9)	22 (9.2)
Cardiac disorders	**0**	**8 (6.6)**	**12 (5.3)**	**3 (42.9)**	**3 (8.8)**	**0**	**1 (10.0)**	**27 (6.7)**	**10 (4.2)**
Cardiac failure	0	0	3 (1.3)	0	0	0	0	3 (0.7)	0
Cardiac failure congestive	0	0	0	0	1 (2.9)	0	0	1 (0.2)	0
Acute coronary syndrome	0	0	1 (0.4)	0	0	0	0	1 (0.2)	0
Myocardial infarction acute	0	0	2 (0.9)	0	0	0	0	2 (0.5)	0
Myocardial infarction	0	0	1 (0.4)	0	0	0	0	1 (0.2)	1 (0.4)
Bradycardia	0	0	0	1 (14.3)	0	0	0	1 (0.2)	2 (0.8)
Nodal arrhythmia	0	0	1 (0.4)	0	0	0	0	1 (0.2)	0
Atrial fibrillation	0	6 (4.9)	3 (1.3)	2 (28.6)	1 (2.9)	0	0	12 (3.0)	5 (2.1)
Atrial flutter	0	1 (0.8)	1 (0.4)	0	0	0	0	2 (0.5)	0
Cardiac arrest	0	0	0	1 (14.3)	0	0	0	1 (0.2)	1 (0.4)
Electromechanical dissociation	0	0	0	1 (14.3)	0	0	0	1 (0.2)	0
TdP [b]	0	0	0	0	1 (2.9)[b]	0	0	1 (0.2)[b]	0
Ventricular fibrillation	0	0	0	1 (14.3)	0	0	1 (10.0)	2 (0.5)	1 (0.4)
Ventricular tachycardia	0	1 (0.8)	0	0	1 (2.9)	0	0	2 (0.5)	0

Note: Each subject was counted at most once within each system organ class and preferred term. AEs were coded using MedDRA version 5.1.

[a] A subject may have more than one TESAE.

[b] This TdP was originally reported as a TESAE by the investigator. Another case of TdP at 0.64 mg/kg was reported as a TEAE, but was not assessed as serious by the investigator. Other adjudicated Torsade-like events identified by Holter data were not reported as TEAEs; those are discussed in Section 6.8.3.

6.7 TEAEs that Led to Study Termination

A small percentage of subjects discontinued the study due to a TEAE in both treatment groups, but the incidence was higher in the tedisamil group for both the male and female subjects, as shown in Table 6-14 and Table 6-15. As previously stated, cardiac disorders were the most common TEAEs that led to study termination in both male and female subgroups. At the recommended dose in males, ECG prolonged QT (1.4%) and bradycardia (0.5%) were the only TEAEs that led to study termination; no male subjects in placebo discontinued due to those TEAEs. At the recommended dose for females, acute myocardial infarction, bradycardia, extrasystoles, and VT were responsible for the discontinuation of one (0.4%) subject each. No male or female at the recommended doses discontinued the study due to hypotension.

Table 6-14 Incidence of TEAEs Leading to Study Termination by Dose - Integrated Safety Dataset - Males

TEAE Leading to Study Termination	Tedisamil							Combined Tedisamil Group	Placebo
	0.16 mg/kg	0.24 mg/kg	0.32 mg/kg	0.32-0.48 mg/kg	0.48 mg/kg	0.48-0.72 mg/kg	0.64 mg/kg		
Male									
Total # Subj	1 (1.5%)	0	2 (1.2%)	1 (10.0%)	4 (1.9%)	0	3 (5.8%)	11 (2.1%)	2 (0.9%)
Bundle branch block bilateral	0	0	0	1(10.0%)	0	0	0	1 (0.2%)	0
Acute myocardial infarction	0	0	1 (0.6%)	0	0	0	0	1 (0.2%)	0
Bradycardia	0	0	0	0	1 (0.5%)	0	0	1 (0.2%)	0
Ventricular extrasystoles	0	0	0	0	0	0	1(1.9%)	1 (0.2%)	0
Ventricular fibrillation	0	0	0	0	0	0	0	0	1(0.4%)
VT	0	0	1 (0.6%)	0	0	0	1 (1.9%)	2 (0.4%)	0
Injection site pain	1(1.5 %)	0	0	0	0	0	0	1(0.2%)	0
Injection site reaction	1(1.5 %)	0	0	0	0	0	0	1(0.2%)	0
ECG QT prolonged	0	0	0	0	3 (1.4%)	0	2 (3.8%)	5 (0.9%)	0
Pancreatic carcinoma	0	0	0	0	0	0	0	0	1(0.4%)
Hypotension	0	0	0	0	0	0	1 (1.9%)	1 (0.2%)	0

Table 6-15 Incidence of TEAEs Leading to Study Termination by Dose - Integrated Safety Dataset - Females

TEAE Leading to Study Termination	Tedisamil							Combined Tedisamil Group	Placebo
	0.16 mg/kg	0.24 mg/kg	0.32 mg/kg	0.32-0.48 mg/kg	0.48 mg/kg	0.48-0.72 mg/kg	0.64 mg/kg		
Females									
Total # Subj	0	2 (1.6%)	5 (2.2%)	1 (14.3%)	1 (2.9%)	0	1 (10.0%)	10 (2.5%)	3 (1.3%)
Acute myocardial infarction	0	0	1(0.4%)	0	0	0	0	1 (0.2%)	0
Bradycardia	0	0	1(0.4%)	1 (14.3%)	0	0	0	2 (0.5%)	0
Extrasystoles	0	0	1(0.4%)	0	0	0	0	1 (0.2%)	0
Cardiac arrest	0	0	0	1(14.3%)	0	0	0	1 (0.2%)	0
TdP	0	0	0	0	1 (2.9%)	0	0	1 (0.2%)	0
VT	0	0	1 (0.4%)	0	0	0	0	1 (0.2%)	0
Pneumonia	0	0	1 (0.4%)	0	0	0	0	1 (0.2%)	0
Hip fracture	0	0	0	0	0	0	0	0	1(0.4%)
Contusion	0	0	1 (0.4%)	0	0	0	0	1 (0.2%)	0
ECG QRS complex prolonged	0	0	0	1(14.3%)	0	0	0	1 (0.2%)	0
Cerebro-vascular accidents	0	1(0.8)%	0	0	0	0	0	1 (0.2%)	1(0.4%)
Apnoea	0	0	0	0	1(2.9%)	0	0	1 (0.2%)	0
Pulmonary embolism	0	1(0.8)%	0	0	0	0	0	1 (0.2%)	0
Hypotension	0	0	0	1 (14.3%)	1 (2.9%)	0	1 (10.0%)	3 (0.7%)	1 (0.4%)

6.8 Safety Data from ECG Measurements

6.8.1 Coding of Ventricular Events

As part of each study protocol, a 24-hour Holter ECG was started 10 min before start of the study drug infusion. The Holter tapes were centrally analyzed, by a specialized contract research organization, for arrhythmias according to specific Holter analysis definitions. All events of 3 or more abnormal/aberrant ventricular complexes with a rate of >100 bpm were defined as single episodes of VT, coded and adjudicated by the AOC according to the following predefined categories:

Monomorphic VT — Ventricular rhythm faster than 100 bpm with a regular rate and consistent beat to beat morphology (all events of 3 or more abnormal/aberrant ventricular complexes with a rate of >100 bpm were defined as single episodes of VT)

Polymorphic VT	Frequent changes in QRS morphology and/or axis, which – if sustained –must occur at least every 1 or 2 seconds
Sustained VT	Equal to or longer than 30 seconds
Non-sustained VT	Shorter than 30 seconds
Torsade-like VT	Polymorphic VT, associated with a preceding prolonged QT or increased U-wave amplitude, starting with a long-short RR interval sequence and changing amplitude, appearing to twist around an isoelectric line

The events were reviewed by the AOC, which consisted of 3 independent cardiologists and a non-voting Sponsor representative. The initial assessment by a specialized contract research organization was accepted if agreed by at least 2 of the 3 AOC members.

6.8.2 Polymorphic and Monomorphic Ventricular Tachycardia

The incidences of any adjudicated VTs (including Torsade-like events) and the various types of VTs are summarized for males in Table 6-16 and for females in Table 6-17. The incidence of any type of adjudicated VT was slightly higher in the combined tedisamil group than in the placebo group (26.4% and 20.4%, respectively), but there was no dose response apparent in the tedisamil group.

Monomorphic runs were slightly more common than polymorphic runs in both the tedisamil and placebo groups and the vast majority of adjudicated VTs were non-sustained

Polymorphic VTs are of particular interest. At the recommended doses of tedisamil, the incidence of adjudicated non-sustained polymorphic VTs was 16.9% in males and 8.4% in females, compared to 14.7% and 6.4%, respectively for placebo. Adjudicated sustained polymorphic VTs were experienced by 2 (0.4%) tedisamil males and, 2 (0.5%) tedisamil females compared to no (0.0%) placebo male and 1 (0.4%) placebo female.

Torsade-like events, based on Holter analysis and adjudicated by AOC, were reported for 12 subjects, 10 tedisamil subjects and 2 placebo subjects (Table 6-15 and Table 6-16). However, one of the placebo subjects (female) experienced a machine-induced (a non-synchronized DC–induced) adjudicated Torsade-like event and has been excluded from consideration. Another Torsade-like events was identified from an ECG reading in a female (at 0.48 mg/kg tedisamil) and was reported as an adverse event, but was not coded under the term TdP. Therefore, the accurate count of adjudicated Torsade-like events in the arrhythmia studies is 11 (1.2%) tedisamil subjects and 1 (0.2%) placebo subject (Table 6-17).

In the male subgroup, the adjudicated Torsade-like events were reported for 5 (1.0%) tedisamil males versus 1 (0.4%) placebo male. Two of the 5 adjudicated Torsade-like events in males occurred at tedisamil doses ≤0.48 mg/kg for an incidence of 0.4% (2/447) in males at or below the recommended dose. In the female subgroup, adjudicated Torsade-like events were reported (from Holter and ECG data) for 6 (1.5%) tedisamil females versus 1 (0.4%) placebo female, but

that one placebo event was machine-induced, so a more accurate account is 1.5% vs. 0%. Five of the 6 adjudicated Torsade-like events in females occurred at doses higher than the recommended dose (0.32 mg/kg). Therefore, the incidence of adjudicated Torsade-like events in females at tedisamil doses ≤0.32 mg/kg was 0.3% (1/345). The incidence of adjudicated Torsade-like events is discussed further in Section 6.8.3.

Table 6-16 Summary of Ventricular Tachycardia from Holter Analysis - Final Assessment Rating - Integrated Safety Dataset - Males

	0.16 mg/kg (N=58)	0.24 mg/kg (N=0)	0.32 mg/kg (N=172)	0.32-0.48 mg/kg (N=10)	0.48 mg/kg (N=207)	0.48-0.72 mg/kg (N=15)	0.64 mg/kg (N=52)	Combined Tedisamil (N=514)[a]	Placebo (N=225)[a]
Any VT	18 (31.0%)	0	43 (25.0%)	6 (60.0%)	65 (31.4%)	8 (53.3%)	22 (42.3%)	162 (31.5%)	58 (25.8%)
Monomorphic and Non-Sustained	16 (27.6%)	0	33 (19.2%)	2 (20.0%)	44 (21.3%)	6 (40.0%)	17 (32.7%)	118 (23.0%)	42 (18.7%)
Monomorphic and Sustained	0	0	0	0	0	0	0	0	0
Polymorphic and Non-Sustained	12 (20.7%)	0	20 (11.6%)	4 (40.0%)	35 (16.9%)	5 (33.3%)	10 (19.2%)	86 (16.7%)	33 (14.7%)
Polymorphic and Sustained	0	0	0	0	1 (0.5%)	0	1 (1.9%)	2 (0.4%)	0
Torsade-Like	0	0	1 (0.6%)	0	1 (0.5%)	1 (6.7%)	2 (3.8%)	5 (1.0%)	1 (0.4%)

Note: Subjects may be counted in more than one category, e.g., Torsade-like events are also counted under 'polymorphic and sustained' or 'polymorphic and non-sustained'.

[a] Study S219.2.102 did not collect Holter data, so no data were available for 14 tedisamil and 6 placebo male subjects.

Table 6-17 Summary of Ventricular Tachycardia from Holter Analysis - Final Assessment Rating - Integrated Safety Dataset - Females

	0.16 mg/kg (N=0)	0.24 mg/kg (N=120)	0.32 mg/kg (N = 225)	0.32-0.48 mg/kg (N = 7)	0.48 mg/kg (N = 34)	0.48-0.72 mg/kg (N = 4)	0.64 mg/kg (N = 10)	Combined Tedisamil (N = 400)[a]	Placebo (N = 236)[a]
Any VT	0	21 (17.5%)	40 (17.8%)	3 (42.9%)	9 (26.5%)	1 (25.0%)	5 (50.0%)	79 (19.8%)	36 (15.3%)
Monomorphic and Non-Sustained	0	15 (12.5%)	27 (12.0%)	1 (14.3%)	6 (17.6%)	1 (25.0%)	5 (50.0%)	55 (13.8%)	24 (10.2%)
Monomorphic and Sustained	0	0	0	0	1 (2.9%)	0	0	1 (0.3%)	0
Polymorphic and Non-Sustained	0	7 (5.8%)	19 (8.4%)	1 (14.3%)	4 (11.8%)	0	1 (10.0%)	32 (8.0%)	15 (6.4%)
Polymorphic and Sustained	0	0	0	0	1 (2.9%)	0	1 (10.0%)	2 (0.5%)	1 (0.4%)[b]
Torsade-Like	0	0	1 (0.4%)	1 (14.3%)	2 (5.9%)	0	1 (10.0%)	5 (1.3%)	1 (0.4%)[b]

Note: Subjects may be counted in more than one category, e.g., Torsade-like events are also counted under 'polymorphic and sustained' or 'polymorphic and non-sustained'.

[a] Study S219.2.102 did not collect Holter data, so no data were available for 3 tedisamil and 3 placebo female subjects.

[b] One female subject in the placebo group experienced a Torsade-like event (polymorphic and sustained VT) as a result of a non-synchronized DC cardioversion and was excluded from consideration.

6.8.3 Adjudicated Torsade-Like Events

Adjudicated Torsade-like VTs, as assessed by the AOC based on Holter analysis, were reported for 12 subjects (10 tedisamil and 2 placebo). However, one of the placebo subjects (female) experienced a Torsade-like VT as a result of a non-synchronized DC cardioversion and has been excluded from consideration. Another Torsade-like VT was identified from an ECG reading in a female (at 0.48 mg/kg tedisamil) for which no Holter data was available, but which was reported as an adverse event as "drug-induced prolonged QT syndrome with non-sustained polymorphic ventricular tachycardia". Therefore, the accurate count of adjudicated Torsade-like VTs in the arrhythmia studies was 11 (1.2%) tedisamil subjects and 1 (0.2%) placebo subject. Of these 12 adjudicated TdPs, seven were classified as non-sustained and five sustained polymorphic VTs. The latter all received DC cardioversion. Only in two cases was the adjudicated Torsade-like event actually reported as an adverse event of TdP (ie, as a TEAE) by the investigator; one female case in 0.48 mg/kg, and one female case in 0.64 mg/kg dose group.

A dose relationship was observed with more of the adjudicated Torsade-like events occurring at doses >0.48 mg/kg in males and at >0.32 mg/kg in females, as shown in Table 6-18. For the doses at the recommended dose of 0.48 mg/kg tedisamil for males, 1 adjudicated TdP (0.5%) was observed; and for females, at the recommended dose of 0.32 mg/kg tedisamil, 1 adjudicated Torsade-like event (0.4%) occurred. With placebo, one (0.4%) male subject experienced an adjudicated Torsade-like event, and no (0.0%) female subject.

Table 6-18 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

[a] Incidences and CIs are not given for 0.24 mg/kg for males and 0.16 mg/kg for females due to low number; no adjudicated Torsade-like events occurred at these doses.
[b] Clopper-Pearson confidence interval.
[c] Doses included: 0.64 mg/kg and 0.48-0.72 mg/kg.
[d] Including 10 male subjects on 0.32-0.48 mg/kg.
[e] Doses included: 0.32-0.48 mg/kg, 0.48 mg/kg, 0.64 mg/kg and 0.48-0.72 mg/kg.
[f] One of these 3 subjects was diagnosed from an ECG reading, while the others were all identified by Holter analysis.
[g] The one female placebo subject who had a non-synchronized DC-induced Torsade-like event was not included in this summary table.

Table 6-19 provides a brief by subject summary that includes the type of VT that led to the adjudicated Torsade-like events and its timing in relationship to study drug infusion. All adjudicated Torsade-like cases in the tedisamil group occurred within the initial 50 min of infusion, with one exception. A non-sustained polymorphic VT was observed in a male subject, on the extended dose of 0.72 mg/kg tedisamil, 18 hours after the start of infusion. Based on the subject's PK profile showed low plasma concentration (preceding the Torsade-like event, plasma concentration was 54 ng/mL compared to a C_{max} of 1319 ng/mL for the recommended dose of 0.48 mg/kg in males) and the QTcB preceding the Torsade-like event was 437 msec, indicating that this case was unlikely to be related to the drug. In addition, one placebo-treated subject experienced an adjudicated Torsade-like event after 4.5 hours.

Six of 12 subjects were in NSR before the adjudicated Torsade-like events occurred and remained in NSR after the events. DC cardioconversion was applied to subjects who experienced a sustained polymorphic Torsade-like event that ended in NSR. Subjects who had non-sustained polymorphic VTs, including Torsade-like events, did not require DC cardioconversion.

Table 6-19 Subjects Who Experienced Adjudicated Torsade-like Events by Gender

Subject No	Age (yr)	Tedisamil dose (mg/kg)	Rhythm preceding Torsade-like event	Time of Torsade-like event after start of infusion	Type of Torsade-like event	TdP Reported as TEAE	DC Cardio-version	Status Post Torsade-like event Manage-ment
Males								
42301	55	0.48-0.72	AFib	18 h	NS-PVT	No	Not done	AFib
22401	86	0.64	AFl	48 min	NS-PVT	No	Not done	AFl
25825	79	0.64	NSR	15 min	S-PVT	No	Done → NSR	NSR with 1st degree AV block
41420	54	0.48	NSR	40 min	S-PVT	No	Done → NSR	NSR
41021	54	0.32	AFib	11 min	S-PVT	No	Done → NSR	NSR with intermittent episodes of sinus arrhythmia and premature non-conducted P-waves
42503	67	placebo	AFib	4.5 h	NS-PVT	No	Not done	AFib
Females								
25414	64	0.64	NSR	30 min	S-PVT	Yes	Done → NSR	NSR
23405	61	0.48	AFib	20 min	S-PVT	Yes [b]	Done → NSR	NSR
25810	74	0.48	AFib	20 min	NS-PVT	No	Not done	AFib
90644[a]	87	0.48	NSR	45 min	NS-PVT	No[a]	Not done	NSR with ventricular and atrial ectopies
41411	76	0.32-0.48	NSR	45 min	NS-PVT	No	Not done	NSR
80613	69	0.32	NSR	21 min	NS-PVT	No	Not done	NSR with some SVEs and aberrancies

S-PVT = sustained polymorphic ventricular tachycardia; NS-PVT = non-sustained polymorphic ventricular tachycardia; NSR = normal sinus rhythm; AFib = atrial fibrillation; AFl = atrial flutter; AV = atrioventricular; SVE = supraventricular extrasystoles

[a] Subject whose adjudicated Torsade-like events was diagnosed from an ECG reading and was reported as an adverse event as "drug-induced prolonged QT syndrome with non-sustained polymorphic ventricular tachycardia."

[b] This TdP was reported as a serious TEAE.

6.8.4 Other Holter Monitoring Data Parameters

Holter data were also analyzed for any supraventricular tachycardia, bradycardia, or pauses, and these data are summarized in Table 6-20 and Table 6-21 for males and females. The incidences of supraventricular tachycardia identified on Holter tapes were higher in males treated with tedisamil at 0.48 mg/kg than placebo (40.3% vs. 28.4%) and in females treated with 0.32 mg/kg compared to placebo (37.0% vs. 29.9%).

Similarly, bradycardia identified on Holter tapes was experienced by more subjects in the recommended dose for males (32.7% vs. 24.2%) and for females (27.5% vs. 17.9%) compared to placebo.

These findings in the Holter data confirm the safety profile observed with TEAEs.

Table 6-20 Incidence (from Holter Data) of Supraventricular Tachycardia, Bradycardia, and Pauses – Integrated Safety Dataset - Males

	0.16 mg/kg N=58	0.24 mg/kg N=0	0.32 mg/kg N=172	0.32-0.48 mg/kg N=10	0.48 mg/kg N=207	0.48-0.72 mg/kg N=15	0.64 mg/kg N=52	Combined Tedisamil N=514	Placebo N=225
Number of subjects with Holter Data	54	0	156	10	196	15	50	481	211
Any Supraventricular Tachycardia	15 (27.8%)	0	50 (32.1%)	4 (40.0%)	79 (40.3%)	5 (33.3%)	26 (52.0%)	179 (37.2%)	60 (28.4%)
Any Bradycardia	14 (25.9%)	0	30 (19.2%)	2 (20.0%)	64 (32.7%)	1 (6.7%)	15 (30.0%)	126 (26.2%)	51 (24.2%)
Any Pauses	28 (51.9%)	0	61 (39.1%)	4 (40.0%)	72 (36.7%)	3 (20.0%)	15 (30.0%)	183 (38.0%)	98 (46.4%)

Table 6-21 Incidence (from Holter Data) of Supraventricular Tachycardia, Bradycardia, and Pauses – Integrated Safety Dataset - Females

	0.16 mg/kg N=0	0.24 mg/kg N=120	0.32 mg/kg N=225	0.32-0.48 mg/kg N=7	0.48 mg/kg N=34	0.48-0.72 mg/kg N=4	0.64 mg/kg N=10	Combined Tedisamil N=400	Placebo N=236
Number of subjects with Holter Data	0	114	200	7	32	4	9	366	224
Any Supraventricular Tachycardia	0	35 (30.7%)	74 (37.0%)	2 (28.6%)	7 (21.9%)	2 (50.0%)	7 (77.8%)	127 (34.7%)	67 (29.9%)
Any Bradycardia	0	35 (30.7%)	55 (27.5%)	2 (28.6%)	7 (21.9%)	2 (50.0%)	2 (22.2%)	103 (28.1%)	40 (17.9%)
Any Pauses	0	59 (51.8%)	79 (39.5%)	4 (57.1%)	13 (40.6%)	2 (50.0%)	1 (11.1%)	158 (43.2%)	94 (42.0%)

6.8.5 Changes in Resting ECG Parameters

QT intervals were corrected for analyses. It is known that the Fridericia correction (QTcF) does not result in a "complete correction" of QT interval for heart rate i.e.: the relation between QTc and heart rate does not have a slope zero. At slower heart rates, this correction tends to over estimate the QT interval. The opposite is true for QTcB and this over estimates QT interval at faster heart rates. This factor complicates matters when assessing the effect of tedisamil on QT interval in subjects with AFib/AFl, which includes subjects who converted and those who did not. Both QTcB and QTcF measurements were analyzed and provided similar overall conclusions related to the tedisamil effect. The QTcB results are discussed in this section.

Changes in QTc Bazett measurements

The mean changes from baseline in QTcB over time are shown by recommended dose group in Table 6-22 for males and females. In subjects who received tedisamil, the maximum mean increase in QTcB was observed at 30 minutes after the start of infusion and was dose related. The largest drop from the peak at 30 minutes occurred between 1.0 and 1.5 hours after the start of infusion. Values stabilized more quickly in females than males and were below baseline levels by 4 hours, while in males, QTcB values stabilized by 6 hours. In the placebo group of subjects, QTcB decreased from baseline at most timepoints.

Table 6-22 Mean Changes from Baseline QTc Bazett Measurements - Integrated Safety Dataset - Male and Female Subgroups

Timepoint	Statistics	Male		Female	
		Tedisamil 0.48 mg/kg N=207	Placebo N=231	Tedisamil 0.32 mg/kg N=225	Placebo N=239
Baseline	Mean Baseline, msec	427.1 (33.0) n=199	427.4 (49.1) n=225	436.2 (32.0) n=211	434.7 (34.9) n=224
5 min	Mean change (SD)	13.3 (26.3) n=193	-1.0 (22.4) n=210	5.9 (25.2) n=199	-0.4 (23.1) n=212
10 min	Mean change (SD)	28.9 (33.3) n=183	-0.8 (22.8) n=217	16.8 (28.2) n=194	-0.8 (23.1) n=212
30 min	Mean change (SD)	41.0 (38.1) n=169	-1.3 (25.3) n=215	24.7 (38.5) n=191	-0.1 (23.3) n=219
45 min	Mean change (SD)	33.9 (36.8) n=170	1.5 (25.9) n=204	21.9 (33.4) n=198	-1.8 (24.8) n=205
1 hr	Mean change (SD)	29.2 (35.1) n=173	-4.6 (22.6) n=217	17.1 (32.0) n=198	-0.2 (24.7) n=215
1.5 hr	Mean change (SD)	17.6 (33.0) n=178	-2.2 (25.0) n=209	11.5 (34.6) n=196	1.3 (26.6) n=206
2 hr	Mean change (SD)	13.4 (28.6) n=178	-1.1 (26.6) n=217	7.4 (29.7) n=194	1.3 (26.4) n=205
2.5 hr	Mean change (SD)	9.7 (30.9) n=180	-1.9 (25.2) n=210	7.6 (32.2) n=194	1.9 (25.9) n=206
4 hr	Mean change (SD)	5.7 (33.2) n=128	-4.2 (30.8) n=163	-3.0 (37.1) n=115	-5.0 (29.3) n=137
6 hr	Mean change (SD)	2.5 (30.6) n=186	-7.2 (29.0) n=205	-1.5 (31.3) n=199	-2.3 (30.0) n=204
8 hr	Mean change (SD)	2.4 (34.1) n=135	-7.3 (32.6) n=160	-2.2 (34.6) n=122	-4.1 (31.9) n=140
12 hr	Mean change (SD)	3.4 (27.7) n=160	-4.3 (23.0) n=169	-0.5 (24.0) n=177	0.5 (26.3) n=173
24 hr	Mean change (SD)	-6.4 (31.0) n=182	-7.6 (31.3) n=215	-4.8 (27.4) n=199	-4.2 (30.3) n=215

Note: These QTcB values were derived from 12-lead ECG data; data were not available at all timepoints for all subjects.

Assessing QT interval in subjects with AFib/AFl is complicated. The population is comprised of subjects who converted and those who did not. Subjects who had converted to NSR would be expected to have a marked heart rate slowing. In order to more appropriately predict the effect of tedisamil infusion on QTc, data in healthy subjects or subjects without atrial fibrillation should be considered. The QTcB (placebo corrected values) is available from a Phase I study with healthy volunteers (S219.1.116) using the same two-step, 30 minute infusion regimen as that used in the Phase II and III studies. For QTcB, as reported in Section 3.3, the values reached a peak between 25-35 minutes and steadily declined up to 1.5 hours post–infusion. Between 1.5 and 2 hours post-infusion, there was the largest drop in the mean change from baseline from 17.1 msecs to 5.4 msecs. Values had returned to baseline by 4 hours.

Incidence of maximum QTcB measurements ≥550 msec, ≥500 msec

The majority of maximum QT measurements (≥550 and ≥500 msec) occurred during the initial 2.5 hours after start of infusion. As expected with a Class III antiarrhythmic drug, the incidence of QTcB measurements ≥500 msec was higher in the tedisamil groups compared to placebo, and the incidence increased as the tedisamil dose increased. A similar pattern was observed in males with the incidence of QTcB ≥550 msec; for females the incidence of QTcB ≥500 msec was also higher in the tedisamil compared to placebo, but the incidence of QTcB ≥550 msec was the same for tedisamil and placebo at the recommended dose (Table 6-23).

Table 6-23 Summary of Incidence of Maximum QTc Measurements ≥550 msec, ≥500 msec in Males and Females at 2.5 Hrs after Start of Infusion

QTc Bazett	Males		Females	
	0.48 mg/kg N=207	Placebo N=231	0.32 mg/kg N=225	Placebo N=239
Incidence of measurements ≥550 msec	7.5%	0.9%	1.8%	1.8%
Incidence of measurements ≥500 msec	33.0%	6.7%	24.3%	10.7%

QTcB measurements were also analyzed to determine the number of subjects who had QTcB changes from baseline by the following amounts: 30-<60 msec, 60-<90 msec and >90 msec. The results, summarized in Table 6-24 for the 0.32 mg/kg and 0.48 mg/kg doses, displayed a dose-relationship. The incidences in each of the categories were higher in the tedisamil groups than the placebo group at timepoints close to baseline. The highest incidence of QTcB change from baseline ≥60 msec occurred at 30 minutes after the start of the study drug infusion in both the male and female tedisamil subjects. By 2.5 hours, the percentages of subjects with QTcB changes ≥60 msec were similar to placebo in the tedisamil recommended doses (0.32 mg/kg and 0.48 mg/kg).

Table 6-24 Incidence of QTc Bazett Measurements <30 msec, 30-<60 msec, 60-<90 msec, ≥90 msec – Integrated Safety Dataset

QTc Bazett measurements [a]	Statistics	Male Subjects		Female Subjects	
		Tedisamil 0.48 mg/kg	Placebo	Tedisamil 0.32 mg/kg	Placebo
Change from Baseline to 10 min	n	183	217	194	212
<30msec	n (%)	99 (54.1%)	205 (94.5%)	139 (71.6%)	199 (93.9%)
30-<60msec	n (%)	54(29.5%)	11(5.1%)	43 (22.2%)	12 (5.7%)
60-<90msec	n (%)	23 (12.6%)	1(0.5%)	11 (5.7%)	0
≥90msec	n (%)	7 (3.8%)	0	1 (0.5%)	1 (0.5%)
Change from Baseline to 30 min	n	169	215	191	219
<30msec	n (%)	59 (34.9%)	199 (92.6%)	100 (52.4%)	201 (91.8%)
30-<60msec	n (%)	66 (39.1%)	15 (7.0%)	64 (33.5%)	16 (7.3%)
60-<90msec	n (%)	27 (16.0%)	1 (0.5%)	22 (11.5%)	2 (0.9%)
≥90msec	n (%)	17 (10.1%)	0	5 (2.6%)	0
Change from Baseline to 1 hour	n	173	217	198	215
<30msec	n (%)	94 (54.3%)	204 (94.0%)	141 (71.2%)	201 (93.5%)
30-<60msec	n (%)	47 (27.2%)	13 (6.0%)	44 (22.2%)	11 (5.1%)
60-<90msec	n (%)	22 (12.7%)	0	10 (5.1%)	3 (1.4%)
≥90msec	n (%)	10 (5.8%)	0	3 (1.5%)	0
Change from Baseline to 2.5 hours	n	180	210	194	206
<30msec	n (%)	144 (80.0%)	188 (89.5%)	159 (82.0%)	190 (92.2%)
30-<60msec	n (%)	30 (16.7%)	21 (10.0%)	29 (14.9%)	11 (5.3%)
60-<90msec	n (%)	5 (2.8%)	1 (0.5%)	5 (2.6%)	4 (1.9%)
≥90msec	n (%)	1 (0.6%)	0	1 (0.5%)	1(0.5%)
Change from Baseline to 4 hours	n	128	163	115	137
<30msec	n (%)	104 (81.3%)	139 (85.3%)	100 (87.0%)	127 (92.7%)
30-<60msec	n (%)	16 (12.5%)	23 (14.1%)	12 (10.4%)	10 (7.3%)
60-<90msec	n (%)	6 (4.7%)	1 (0.6%)	2 (1.7%)	0
≥90msec	n (%)	2(1.6%)	0	1 (0.9%)	0
Change from Baseline to 8 hours	n	135	160	122	140
<30msec	n (%)	112 (83.0%)	145 (90.6%)	105 (86.1%)	123 (87.9%)
30-<60msec	n (%)	18 (13.3%)	12 (7.5%)	14 (11.5%)	14 (10.0%)
60-<90msec	n (%)	3 (2.2%)	2 (1.3%)	2 (1.6%)	3 (2.1%)
≥90msec	n (%)	2(1.5%)	1 (0.6%)	1 (0.8%)	0
Change from Baseline to 24 hours	n	182	215	199	215
<30msec	n (%)	162(89.0%)	201 (93.5%)	184 (92.5%)	186 (86.5%)
30-<60msec	n (%)	18 (9.9%)	11 (5.1%)	12 (6.0%)	26 (12.1%)
60-<90msec	n (%)	2 (1.1%)	0	3 (1.5%)	1 (0.5%)
≥90msec	n (%)	0	3 (1.4%)	0	2 (0.9%)

[a] These QTcB values were derived from 12-lead ECG data; data were not available at all timepoints for all subjects.

6.9 Safety Associated with Concomitant Antiarrhythmic Medication

The safety of subjects receiving concomitant antiarrhythmic drugs administered 24 hours after the start of tedisamil infusion was assessed. The concomitant medications of interest were sotalol, propafenone, amiodarone, dofetilide, flecainamide, ibutilide and procainamide. This evaluation was based on the number of subjects receiving these medications (24 hours after initiation of infusion), reporting TEAEs in the combined tedisamil group compared to the respective placebo group.

The incidence of TEAEs was lower in the tedisamil group versus the placebo group for subjects who received sotalol (2.8% vs. 4.5%) or propafenone (5.8% vs. 7.9%) 24 hours after initiation of infusion. This appears to indicate that there was no drug-drug interaction of these concomitant treatment regimens administered after 24 hours.

The incidence of subjects in the combined tedisamil compared to the placebo group who experienced TEAEs following concomitant amiodarone treatment was 12.2% and 9.6% subjects. The most common of these were cardiac disorders.

Overall, a low percentage of subjects reported TEAEs following concomitant treatment with dofetilide (0.4% tedisamil vs. 0.4% placebo), flecainamide (0.5% tedisamil vs. 0.6% placebo), ibutilide (0.1% tedisamil vs. 1.5% placebo) and procainamide (0.8% tedisamil vs. 0.4% placebo), indicating no drug-drug interactions with Class I or Class III antiarrhythmic agents administered after 24 hours.

Overall, the range of TEAEs experienced in subjects receiving the antiarrhythmic medication was comparable to those observed for subjects who did not receive this medication. The most common events observed were cardiac disorders and vascular disorders.

6.10 Laboratory Findings

Evaluations of laboratory data are based on individual study reports and no integration was performed. No marked differences of clinical concern were observed between tedisamil and placebo groups in changes in laboratory parameters.

Low hematocrit levels and abnormal gamma glutamyl transferase (gamma-GT) levels were the most common clinically significant abnormalities observed, and were reported at similar incidences in the tedisamil and placebo groups. Other common clinically significant blood chemistry abnormalities observed across both treatment arms were increased uric acid and urea nitrogen levels.

6.11 Safety in Subgroups

The safety of tedisamil in subjects with known risk factors, such as the elderly, those with congestive heart failure (NYHA Class I-III), and those with renal impairment was assessed. In this section, overviews of adverse events (incidences of TEAEs, TESAEs, Deaths, and discontinuations due to TEAEs) are summarized for the recommended doses by these subgroups and the subgroup of subjects who did and did not use beta-blocking agents.

Age

No clinically relevant differences were observed between treatment groups in the incidence of TEAEs, TESAEs, or discontinuations due to TEAEs reported by subjects <65 years of age or by subjects >65 years of age at the doses recommended for males and for females, as shown in Table 6-25. There was no difference between treatment for either gender for deaths in the <65 age subgroups. In the ≥65 age group, the deaths were lower in the tedisamil than the placebo group for males (0 vs. 2 subjects), but were not meaningfully different for females (2 vs. 1 subject).

Table 6-25 Overview of TEAEs by Age for Recommended Doses

Number of Subjects with at least one of the following:	Males		Females	
	0.48 mg/kg n (%)	Placebo n (%)	0.32 mg/kg n (%)	Placebo n (%)
<65 yrs	N=119	N=144	N=69	N=77
Death	0	0	0	0
TESAE	11 (9.2)	12 (8.3)	5 (7.2)	4 (5.2)
Discontinuation due to TEAE	1 (0.8)	0	1 (1.4)	0
TEAE	84 (70.6)	84 (58.3)	45 (65.2)	51 (66.2)
≥65 yrs	N=88	N=87	N=156	N=162
Death	0	2 (2.3)	2 (1.3)	1 (0.6)
TESAE	8 (9.1)	8 (9.2)	15 (9.6)	18 (11.1)
Discontinuation due to TEAE	3 (3.4)	2 (2.3)	4 (2.6)	3 (1.9)
TEAE	56 (63.6)	59 (67.8)	101 (64.7)	99 (61.1)

NYHA Class

No clinically relevant differences were observed between treatment groups in the incidence of TEAEs, deaths, TESAEs, reported by NYHA Class I subjects or by NYHA II/III subjects at the doses recommended for males and for females, as shown in Table 6-26. Discontinuations due to TEAEs in the NYHA Class II/III subjects were slightly higher in the tedisamil group than placebo group for both male and female subjects.

Table 6-26 Overview of TEAEs by NYHA Class (I and II/III) for Recommended Doses

Number of Subjects with at least one of the following:	Males		Females	
	0.48 mg/kg n (%)	Placebo n (%)	0.32 mg/kg n (%)	Placebo n (%)
NYHA Class I	N=123	N=137	N=91	N=95
Death	0	1 (0.7)	1 (1.1)	1 (1.1)
TESAE	11 (8.9)	9 (6.6)	8 (8.8)	12 (12.6)
Discontinuation due to TEAE	1 (0.8)	1 (0.7)	2 (2.2)	2 (2.1)
TEAE	83 (67.5)	85 (62.0)	58 (63.7)	67 (70.5)
NYHA Class II/III	N=74	N=83	N=108	N=121
Death	0	1 (1.2)	1 (0.9)	0
TESAE	7 (9.5)	10 (12.0)	8 (7.4)	7 (5.8)
Discontinuation due to TEAE	3 (4.1)	1 (1.2)	3 (2.8)	1 (0.8)
TEAE	51 (68.9)	54 (65.1)	70 (64.8)	66 (54.5)

Creatinine Clearance

Subjects were grouped according to baseline CrCL <60 mL/min and CrCL ≥60 mL/min. (Severe renal impairment [CrCL <30 mL/min] was an exclusion criteria in the study protocols). Overviews of TEAEs are shown for these subgroups by the recommended doses in Table 6-27. At the recommended doses, male or female subjects with CrCl <60 mL/min in the tedisamil groups had either comparable or lower incidences of TEAEs, TESAEs, and discontinuations due to TEAEs than comparable male or female subjects in the placebo groups. For subjects with CrCL ≥60 mL/min, while low, the incidence of discontinuations due to a TEAE was higher for males in the tedisamil group (1.7%) than the placebo group (0%). For females with CrCL ≥60 mL/min, the incidence of discontinuations due to a TEAE was not notably different (2 vs. 1 subject).

Table 6-27 Overview of TEAEs by Renal Status for Recommended Doses

Number of Subjects with at least one of the following:	Males		Females	
	0.48 mg/kg n (%)	Placebo n (%)	0.32 mg/kg n (%)	Placebo n (%)
CrCL <60 mL/min	N=23	N=26	N=63	N=64
Death	0	1 (3.8)	2 (3.2)	1 (1.6)
TESAE	1 (4.3)	1 (3.8)	10 (15.9)	12 (18.8)
Discontinuation due to TEAE	0	1 (3.8)	3 (4.8)	2 (3.1)
TEAE	12 (52.2)	19 (73.1)	36 (57.1)	42 (65.6)
CrCL ≥60 mL/min	N=177	N=191	N=154	N=168
Death	0	0	0	0
TESAE	18 (10.2)	17 (8.9)	9 (5.8)	9 (5.4)
Discontinuation due to TEAE	3 (1.7)	0	2 (1.3)	1 (0.6)
TEAE	121 (68.4)	116 (60.7)	105 (68.2)	105 (62.5)

Concomitant Medication – Beta-Blocking Agents

The safety of using tedisamil with other medications, particularly concomitantly with beta-blocking agents, was investigated. An overview of TEAEs is shown in Table 6-28 for the recommended doses for subjects who did and those who did not use beta-blocking agents during the study. For subjects who did use beta-blocking agents, there were no differences between treatment groups for either the male or female subjects. For subjects who did not use concomitant beta-blocking agents, there was a higher rate of TESAEs in tedisamil males than placebo males; the incidence of TESAEs was comparable in the treatment groups for females.

Table 6-28 Overview of TEAEs by Use of Beta-Blocking Agents for Recommended Doses

Number of Subjects with at least one of the following:	Males		Females	
	0.48 mg/kg n (%)	Placebo n (%)	0.32 mg/kg n (%)	Placebo n (%)
Beta-Blocking Agents (Yes)	N=137	N=158	N=181	N=187
Death	0	2 (1.3)	1 (0.6)	1 (0.5)
TESAE	13 (9.5)	18 (11.4)	18 (9.9)	19 (10.2)
Discontinuation due to TEAE	2 (1.5)	2 (1.3)	3 (1.7)	3 (1.6)
TEAE	95 (69.3)	104 (65.8)	119 (65.7)	118 (63.1)
Beta-Blocking Agents (No)	N=70	N=73	N=44	N=52
Death	0	0	1 (2.3)	0
TESAE	6 (8.6)	2 (2.7)	2 (4.5)	3 (5.8)
Discontinuation due to TEAE	2 (2.9)	0	2 (4.5)	0
TEAE	45 (64.3)	39 (53.4)	27 (61.4)	32 (61.5)

6.12 Safety Summary for Oral Tedisamil Studies

6.12.1 Safety Summary from Oral Studies in AFib/AFl Subjects

Two studies in AFib/AFl subjects were conducted with oral tedisamil. Study S219.2.101 was a placebo-controlled Phase II study conducted in AFib/AFl subjects who were randomized to receive, by oral administration, tedisamil at doses of 80 mg b.i.d. (n=52 subjects); 120 mg b.i.d. (n=46 subjects); or placebo (n=46). Study S219.2.103 was an extension of that study and enrolled only 9 subjects (4, 3, and 2 in the respective treatment groups).

Studies S219.2.101 and S219.2.103 were prematurely discontinued following the recommendation of the Drug Safety Monitoring Board (DSMB) based on the expectation that Study S219.2.101 could not meet its primary efficacy aim (maintenance of sinus rhythm following cardioversion). Also, the immediate release (IR) form of the oral tedisamil resulted in a high incidence of diarrhea (83% on tedisamil 120 mg b.i.d. vs. 11% on placebo). The most frequently reported TESAE in those oral tedisamil studies was ventricular tachycardia (22% tedisamil 120 mg b.i.d. vs. 7% placebo). Two subjects died in Study S219.2.101 (both in 120 mg group): one subject due to cardiopulmonary arrest following an acute myocardial infarction and one subject with arrhythmia. Subsequently, the development of the oral IR form for AFib/AFl was discontinued based on high incidence of diarrhea with and without plasma electrolyte disturbances.

6.12.2 Safety Summary for the Angina Program

As part of an extensive safety review of tedisamil, the safety data collected during oral tedisamil angina program was reviewed for safety signals that could be relevant to the IV tedisamil antiarrhythmia program. The angina program consisted of multiple-dose, long-term (up to one year) studies.

The angina program conducted in subjects with stable angina pectoris due to coronary artery disease (CAD) used an oral formulation of tedisamil that was administered b.i.d. at doses ranging

from 20 to 160 mg (tedisamil free base) for up to one year. This program included 56 studies with 3246 subjects, 537 were healthy or symptomatic subjects, 2631 were CAD subjects, and 78 were other cardiac subjects. Some studies included comparisons with reference drugs. From the 2631 CAD subjects, 1668 were administered oral tedisamil and 70 intravenously. Of the 1668 subjects with stable angina pectoris due to CAD who were exposed to oral tedisamil, 921 subjects were exposed for up to 28 weeks, 354 subjects for 29 to 52 weeks, and 383 subjects received tedisamil for one year or longer. The number of subjects exposed (years) per dose were 75 (3.0) for 25 mg bid; 798 (30.5) bid for 50 mg bid; 674 (391.2) for 75 mg bid; 589 (96.0) for 100 mg bid, 112 (2.8) for 150 mg bid and 62 (1.6) for 200 mg bid. The total exposure of subjects with stable angina pectoris to oral tedisamil was calculated to be 524.1 patient-years.

The majority of subjects in the angina program were male (88.2%) and Caucasian (99%). The mean age of the subjects who received oral tedisamil was 60.6 years; 72.2% were between 50-69 years and 16.1% were 70 years or older.

Safety Conclusions from the Angina Program:

The subjects who received IV tedisamil doses (0.1 – 0.3 mg/kg) during the angina program were predominately enrolled in Phase I studies and included healthy and symptomatic subjects. Injection site pain was the most common TEAE reported for these subjects, and was reported more frequently in the tedisamil group than the placebo group. Injection site reactions were also commonly reported in the antiarrhythmia program. The other incidences of other types of TEAEs, such as headache, were either the same or lower in the tedisamil group than the placebo group.

Across all studies and subject populations, the most frequent and dose-dependent TEAE with orally administered tedisamil was diarrhea (13.8%).

A difference was observed in the incidence of TEAEs between females and males. There were 566 male and 75 female subjects exposed to tedisamil in reference-controlled CAD studies of which 48.1% of males and 64.0% of females experienced at least one TEAE.

SAEs occurred as frequently with tedisamil as with reference agents. The most frequently reported SAEs were angina pectoris and myocardial infarction, which are typical for the population with CAD. In the angina program across all studies and doses, no (0/70) subjects after IV and 5.2% (86/1668) subjects after oral administration reported an SAE with tedisamil. Mainly cardiovascular adverse events were reported as serious (3.8% for oral), with angina pectoris being the most common event (1.6% for oral).

All cause mortality was below 1% with a fairly equal distribution among groups and doses.

The incidence of arrhythmic events with tedisamil, as recorded in the resting or 24-hour Holter ECG, was not higher than with placebo and equal to reference agents. Individual cases of symptomatic ventricular arrhythmia were observed. One case of TdP in a female subject on 100 mg tedisamil occurred during a right heart catheterization procedure.

Tedisamil induced a modest bradycardic effect in excess of placebo, which showed some degree of dose-dependency. Both the QT and QTc intervals of the surface ECG were prolonged by tedisamil in a dose-dependent manner. Tedisamil had no relevant effect on diastolic or systolic blood pressure and did not alter blood pressure over time.

Both the risk and the seriousness of TEAEs in subjects taking oral tedisamil b.i.d. dosing increased with worsening renal impairment. Subjects with a creatinine clearance of >90 ml/min, 60-90 ml/min, or <60 ml/min had TESAEs at the incidence of 4.4%, 7.9%, and 11.7%. This is in contrast to the results with IV tedisamil, which had similar efficacy and safety profile in subjects with mild or moderate renal impairment.

The integrated safety summary (ISS) for the angina program concluded that the relative risk of experiencing an SAE with tedisamil was enhanced in female subjects, in subjects with a history of MI, and in subjects with a borderline prolongation of the QTc interval prior to treatment.

6.13 Nonclinical Toxicology Studies

A full battery of non-clinical studies has been performed using tedisamil. No indication of carcinogenicity, mutagenicity, or impairment of fertility was seen in animal studies. Oral carcinogenicity studies in rats and mice did not reveal a carcinogenic potential of tedisamil. Tedisamil was not genotoxic in a battery of Ames assays, human peripheral lymphocyte assay, and mouse micronucleus test. Similarly, no drug related effects on fertility or mating were noted in a reproductive study in rats in which tedisamil was administered orally to both sexes up to 60 mg/kg/day. On a C_{max} basis, corrected for protein binding, the highest dose tested was approximately three times the maximum recommended human dose.

6.14 Overall Assessment of Safety of IV Tedisamil for AFib/AFl Subjects

The safety profile of tedisamil, when administered at the gender-specific recommended doses, appears to be comparable to that reported in the literature for other Class III antiarrhythmic medications. [13,15,25-32] Safety data for tedisamil did not reveal any unexpected safety findings compared to other drugs in the class.

A total of 1137 subjects have been exposed to IV tedisamil. The integrated safety dataset consists of data collected from 931 IV tedisamil AFib/AFl subjects enrolled in Phase II or Phase III studies and the 470 placebo AFib/AFl subjects in those studies. In these studies tedisamil doses ranged from 0.16 mg/kg to 0.64 mg/kg and were administered using a two-step infusion regimen.

TEAEs: Treatment-emergent adverse events (TEAEs) were reported for a similar percentage of subjects in the tedisamil and placebo groups (66.9% vs. 61.9% for males; 66.5% vs. 62.8% for females). In most cases TEAEs were transient, and mild or moderate in severity. The most commonly occurring TEAEs were cardiac disorders, which were reported in a dose-dependent pattern. The percentage of subjects reporting cardiac disorders at the recommended dose (0.48 mg/kg) in males was 48.3% with tedisamil and 42.0% with placebo, and at the recommended dose (0.32 mg/kg) in females was 40.4% versus 28.0%.

Ventricular tachycardia (VT) and bradycardia were the most commonly reported cardiac TEAEs in both male and female subjects. The incidence of VTs reported as TEAEs was slightly higher

in the male tedisamil subjects (11.6%) than the male placebo subjects (6.9%), but the incidence was similar in the female treatment groups (4.7% vs. 5.0%). The incidence of VT was 3.1% in females (0.32 mg/kg) and 12.6% in males (0.48 mg/kg) at the recommended doses. Bradycardia reported as a TEAE was not different between the tedisamil and placebo male subjects (4.5% vs. 5.6%), and only slightly higher in the tedisamil female subjects than the placebo female subjects (5.2% vs. 3.3%).

The most commonly occurring non-cardiac TEAEs in males at the recommended dose were headache (reported by 2.9% of tedisamil subjects vs. 2.2% placebo subjects), infusion site burning (2.4% vs. 0.4%), injection site pain (2.4% vs. 0.0%), hypotension (1.4% vs. 0.9%), and oral paraesthesia (1.9% vs. 0.4%). In females at the recommended dose, they were headache (3.6% vs. 3.3%), hypotension (2.2% vs. 3.3%), and dizziness (1.8% vs. 1.7%). Infusion site burning, injection site pain, and oral paraesthesia were reported by 0.9%, 1.3%, and 0.9% of females at the recommended dose (vs. 0.4%, 0.0%, and 0.4%, respectively, with placebo). Except for infusion site reactions and oral paraesthesia, no meaningful difference was observed between tedisamil and placebo.

TESAEs: Treatment-emergent serious adverse events (TESAEs) were reported for 9.7% (90/931) of tedisamil and 8.9% (42/470) of placebo subjects. Cardiac disorders were the most common type of TESAEs. The incidence of cardiac TESAEs was comparable between the combined tedisamil and placebo groups in males at the recommended dose of 0.48 mg/kg (6.8% vs. 6.1%). There was no apparent dose response pattern in males. In females, the incidence of cardiac TESAEs at the recommended dose of 0.32 mg/kg was 5.3% compared to 4.2% with placebo. The most commonly reported cardiac TESAE was atrial fibrillation, which was reported for 4.3% males at the recommended dose of tedisamil compared to 3.0% of placebo males. Atrial fibrillation was reported for 1.3% of females at the recommended dose compared to 2.1% with placebo.

Deaths: Tedisamil did not result in a higher incidence of deaths. Eleven deaths (4 males and 7 females) occurred in the IV tedisamil antiarrhythmia program. Two of the 11 subjects were randomized, but died before receiving treatment. The other nine deaths were included in the safety dataset and occurred at an equal rate in both treatment groups: 0.64% (6/931 tedisamil and 3/470 placebo subjects). The majority of deaths were cardiac related and none were considered related to study drug.

Discontinuations due to TEAEs: The number of subjects who terminated the study due to a TEAE was low and was distributed evenly across all dose groups. Discontinuations due to a TEAE at the recommended doses were: 4 (1.9%) of 207 tedisamil males (vs. 0.9% in placebo) and 5 (2.2%) of 225 tedisamil females (vs. 1.3% in placebo).

ECG Measurements: Mean QTcB values increased in a dose-dependent manner in the tedisamil groups, reaching a maximum at 30 minutes after start of infusion. QTcB measurements had generally stabilized at 2.5 hours after the initiation of infusion. The majority of maximum QTcB measurements occurred during the initial 2.5 hours post-baseline. The incidence of QTcB measurements ≥550 msec was low, with a higher incidence at the higher dose groups.

As with other Class III antiarrhythmics, tedisamil can cause QT prolongation, and TdP is a major safety concern. Adjudicated Torsade-like VTs, as assessed by the AOC based on Holter analysis, were reported for 12 subjects (10 tedisamil and 2 placebo). However, one of the placebo subjects (female) experienced a Torsade-like VT as a result of a non-synchronized DC cardioversion and was excluded from consideration. Another Torsade-like VT was identified from an ECG reading in a female (at 0.48 mg/kg tedisamil) for which no Holter data was available, but which was reported as an adverse event as "drug-induced prolonged QT syndrome with non-sustained polymorphic ventricular tachycardia". Therefore, the accurate count of adjudicated Torsade-like VTs in the arrhythmia studies was 11 (1.2%) tedisamil subjects and 1 (0.2%) placebo subject. Of these 12 adjudicated TdPs, seven were classified as non-sustained and five sustained polymorphic VTs. The latter all received DC cardioversion. Only in two cases was the adjudicated TdP actually reported as an adverse event of TdP (i.e., as a TEAE) by the investigator; one female case in the 0.48 mg/kg dose group, and one female case in the 0.64 mg/kg dose group.

A dose relationship was observed in the incidence of the adjudicated Torsade-like events, with increases occurring at doses >0.48 mg/kg in males and >0.32 mg/kg in females. For the recommended dose of 0.48 mg/kg tedisamil for males, 1 adjudicated Torsade-like event (0.5%) was observed; for females at the recommended dose of 0.32 mg/kg tedisamil, 1 adjudicated Torsade-like event (0.4%) occurred. With placebo, one (0.4%) male subject and no (0.0%) female subjects experienced an adjudicated Torsade-like event. Also worth noting is that most (10/12) adjudicated Torsade-like events occurred within 50 minutes after initiation of infusion; the other two occurred at 4.5 and 18 hours after initiation of infusion. All sustained Torsade-like events occurred within 40 minutes after the start of infusion. DC cardioconversion was applied to the subjects who experienced a sustained, polymorphic, Torsade-like VT and NSR was achieved. Subjects who had non-sustained polymorphic VTs, including Torsade-like events, did not require DC cardioconversion.

Safety in Subgroups: Safety was assessed in subgroup populations including subjects over age 65 years, with congestive heart failure (NYHA Class II/III), using beta-blocking agents; and with renal impairment. Tedisamil was found to have a favorable safety profile as follows:

- No clinically relevant differences between tedisamil and placebo were observed at the recommended doses in the incidence of TEAEs or TESAEs in subjects <65 and ≥65 years of age.

- In subjects with NYHA Class I and in NYHA Class II/III, no meaningful differences were observed between tedisamil and placebo in the incidence of TEAEs at the recommended doses. Therefore, tedisamil is recommended for use in male and female subjects who are categorized up to NYHA Class III. (NYHA Class IV was excluded from the clinical studies and therefore no safety information is available.)

- Tedisamil can be used in patients with mild to moderate renal impairment (<60 mL/min) without dose adjustment. Subjects with severe renal impairment (<30 mL/Min) were excluded from the efficacy studies and use in this population is contraindicated.

- For subjects not taking concomitant beta-blocking agents, a slightly higher rate of TESAEs in tedisamil treated male subjects was observed in comparison to placebo subjects. This phenomenon was not observed in female subjects. Otherwise, the occurrence of adverse events was comparable in the tedisamil and placebo groups at the recommended doses, whether or not the subject was receiving concurrent beta-blocking agents.

7 Benefit/Risk Discussion

Tedisamil is a Class III antiarrhythmic drug that prolongs cardiac action potential duration and refractory period predominantly in the atria as compared to the ventricles. Tedisamil also blocks the specific atrial channels I-K_{UR} as well as I-K_{Ach}.

Benefit Discussion

As noted in Section 2, there is clearly an unmet medical need for treatment alternatives to provide rapid, effective restoration of NSR in patients with AFib/AFl. When used according to the recommended doses, tedisamil's clinical benefits are significant and directly address the areas of unmet medical need. The clinical program has evaluated tedisamil in both male and female populations, and has allowed for an appropriate characterization of the efficacy and safety profile in each, leading to a gender-specific dosing regimen that provides the most favorable benefit/risk balance for this compound:

- AFib/AFl in Males: 0.48 mg/kg
- Afib/Afl in Females: 0.32 mg/kg
- Dosage regimen for both genders is a two-step IV infusion (half of the dose over 10 mins and remainder over 20 mins).

At the recommended doses, the benefits of tedisamil include:

- Conversion to NSR at recommended doses
- Rapid conversion to NSR
- Sustained conversion, i.e., remaining in NSR for 24 hours and at hospital discharge
- The benefits of tedisamil are seen across subgroups. It should be noted that tedisamil has:
    - Efficacy in patients over 65 years of age
    - Efficacy in AFib of longer duration (up to 45 days)
    - Efficacy in congestive heart failure (through NYHA III)
    - Adequate safety data in males and females, including subjects over age 65 years
    - Tolerability, with a low incidence of AEs and discontinuations
    - Safety when used in patients with mild to moderate renal impairment (no dose adjustment needed)
- Hepatic impairment not expected to have a significant effect on tedisamil elimination

- Can be administered concurrently with a broad range of medications, with very limited potential for drug interactions, because tedisamil is not metabolized in humans.

Risk Discussion

The risks associated with tedisamil are similar to those already identified for other Class III antiarrhythmics. Solvay has clearly and completely disclosed these risks in the proposed labeling and in the recommended dosage regimen. Moreover, these risks will be further minimized by gender-specific doses and the implementation of the RiskMAP.

The risks associated with tedisamil are cardiovascular in nature and include:

- TdPs
- Other types of ventricular arrhythmias
- Bradycardia
- Hypotension

The level of risk may be altered if patient selection, dose calculation, or drug administration is inappropriate or incorrect.

Tedisamil must be administered in a hospital setting that allows for continuous ECG monitoring for at least 2 hours (i.e., the 30 minute infusion period and the following 1.5 hours). This is important for the early identification and treatment of potential life-threatening ventricular arrhythmias, particularly polymorphic sustained ventricular tachycardia.

Dose Rationale

Doses between 0.16 and 0.64 mg/kg were included in the clinical program, enabling gender-specific doses to be identified that produce the most favorable tedisamil's benefit/risk relationship, particularly in relation to cardiac events. At the doses recommended in the label, the incidence of adjudicated Torsade-like events was 0.5% for males (at 0.48 mg/kg), and 0.4% for females (at 0.32 mg/kg). These rates are lower than comparable data reported in the literature for other Class III drugs.[15,23-26,33-35]

- In males, tedisamil efficacy was shown to be dose-dependent between 0.32 to 0.64 mg/kg; however, the incremental benefit of the increase from 0.48 to 0.64 mg was determined to be associated with an unacceptable increase in AEs, including Torsade-like events. The dose of 0.48 mg/kg was chosen to have an adequate benefit/risk profile.
- In females, the most favorable dose was determined to be 0.32 mg/kg, as an increase to 0.48 mg/kg would provide minimal additional efficacy while being associated with increased safety risks, including Torsade-like events.
- Dosage regimen for both genders is a two-step infusion (half over 10 minutes and the remainder over 20 minutes).
- Tedisamil dose need not be adjusted for use in special populations (e.g. age, hepatic impairment, or mild to moderate renal impairment).

Tedisamil has a relatively narrow therapeutic window. Precisely determining the correct dose is important for safe and effective use of the drug. The algorithm for dosing is a combined

height/weight calculation, and there is a risk of human error in the calculation. To minimize this risk and to help identify the appropriate volume of tedisamil concentrate for infusion, detailed gender-specific height/weight charts are provided in the prescribing information (see Appendix 4) and via the Risk MAP

Patient Selection and Preparation

Careful patient selection using the information supplied in the label is required to reduce the risks associated with tedisamil use. The proposed labeling provides clear direction on appropriate patient selection based on patient history, presenting condition, potential drug interactions and other factors, which have been summarized in the following list. The risk of AEs and negative outcomes will be increased when these recommendations are not followed.

- Tedisamil should only be used in hemodynamically stable AFib/AFl patients. Use in hemodynamically unstable patients has not been studied.
- In line with normal clinical practice and current anti-coagulation guidelines, subjects with an AFib/AFl episode longer than 48 hours must be anti-coagulated prior to treatment with tedisamil.
- Tedisamil is contraindicated in patients with severe renal impairment and known congenital or acquired long QT syndrome
- Tedisamil should be used cautiously in patients with clinical conditions or symptoms that may contribute to ventricular pro-arrhythmias. It should not be used in patients who have been treated with drugs known to prolong QT intervals.
- Patients who are on non-potassium sparing diuretics or who have other conditions known to affect other electrolytes should have appropriate electrolyte measurements taken and abnormalities corrected prior to tedisamil dosing.
- Tedisamil should not be used in patients with known sick sinus (without a pacemaker), severe bradycardia, or NYHA Class IV CHF.
- Tedisamil should not be used concurrently Class I or III antiarrhythmics (due to lack of experience). Further, these medications should be withheld for at least 24 hours after initiation of treatment with tedisamil.
- Experience in non-white populations is limited.

Administration and Monitoring

The recommended dosage regimen for both genders is a two-step infusion (half of the dose over 10 minutes and remainder over 20 minutes). This is the regimen used most successfully during the clinical trials, and lack of compliance may reduce efficacy and/or increase the risk of adverse events.

Due to the potential for pro-arrhythmic events, tedisamil must be administered in an appropriate treatment environment in a hospital. The labeling requires for 2 hours (from start of infusion) of ECG monitoring by appropriately trained personnel during and following the infusion to enable TdP to be detected early and treated immediately. This two-hour period is supported by the following key observations:

- During the clinical program, most adjudicated Torsade-like events occurred early (within 50 minutes of tedisamil initiation).
- Within two hours, QTcB measurements among those subjects converting had returned to normal.
- Most QTcB ≥ 500 and ≥550 msec occurred within the initial 2.5 hours of treatment.

Summary

With appropriate care in selection, preparation, dosing and monitoring, tedisamil can be used safely in many patients. The drug does not appear to pose any additional risk over and above that seen for intravenous Class III antiarrhythmics in general when used for pharmacological cardioversion, and in fact offers incremental benefits, particularly in the treatment of several subgroups, including angina or congestive heart failure (NYHA II-III), the elderly, and patients with moderate renal dysfunction. Solvay has developed and is committed to implementing a Risk Management Program that will help assure compliance with the label and promote the safe use of tedisamil in the marketplace.

In conclusion, considering the product's efficacy and safety profile in the context of existing treatments for arrhythmia, tedisamil clearly demonstrates a positive risk/benefit relationship and merits approval for the indication of rapid restoration of atrial fibrillation or atrial flutter to normal sinus rhythm.

8 Risk Management Plan

In order to minimize the risks described for tedisamil, the sponsor is committed to executing a comprehensive tedisamil Risk Management Plan designed to produce the most favorable the benefit/risk ratio of tedisamil. The plan includes pharmacovigilance and drug safety elements appropriate to the product. Labeling is the primary risk minimization tool. The effectiveness of labeling in the prevention and minimization of adverse events (AEs) will be monitored through spontaneous reports for potential safety signals and an observational study.

The focus of the remainder of this section will be on the RiskMAP, which has been designed to help assure product use consistent with the label. This program has been developed through an iterative process of risk identification and assessment, analysis, program development, evaluation and refinement. It has been pre-tested and refined based on discussions with physicians and other healthcare professionals in both the United States and Europe.

The tedisamil RiskMAP is designed to help assure that the drug is used according to the label to minimize the occurrence of serious and potentially fatal risks, specifically Torsades de Pointes, ventricular tachycardia and bradycardia.

The RiskMAP provides educational tools to help achieve the following objectives each and every time tedisamil is used:

- Appropriate patient selection
- Correct dose and administration
- Treatment in appropriate setting (in hospital with ECG monitoring)

- Monitoring for 2.0 hours

Several tools have been developed and prototypical versions have been included in Appendix 4:

- Separate, color-coded height- and weight-based dosing charts for males and females will assist the prescribing physician in selecting the proper dose.
- A physician checklist and infusion bag sticker will be packaged with tedisamil vials to ensure that they are available to prescribers and other health care professionals (HCPs) at the time of use. The checklist leads the physician through a flowchart describing safe usage. The sticker ensures that the dose calculation will be checked by another HCP in addition to the prescriber, thus reducing the potential for miscalculation.
- The arrhythmia guide, QTc guide, HCP administration and monitoring and dose guide are shown as loose-leaf pages for insertion into a ring binder. They will also be combined as a single wallchart for display in the patient care area and will be made available in pocket book format.
- All of these tools have been developed with the input of potential users and have been tested in both the US and EU.

The program will be formally evaluated at regular intervals following launch enabling revisions to be made to improve its effectiveness. Surveys and other measures of distribution and usage of the materials themselves will be undertaken.

In addition to standard pharmacovigilance activities, an observational study is planned.
A hospital discharge database (Premier Inc) will be used for an observational study to evaluate safety outcomes for events of special interest. This study will evaluate the safety of iv tedisamil in a real-life setting by comparing serious outcomes from an IV tedisamil group with patients receiving other IV agents for cardioversion (such as amiodarone, sotalol, flecainide or ibutilide). A feasibility study has confirmed that the proposed observational study could be designed to include no fewer than 3000 subjects (1000 subjects per treatment group; 1000 receiving iv tedisamil, 500 receiving each of amiodarone, ibutilide, flecainide, sotalol or alternatives) in a two-year period currently anticipated to run from 2008 to 2010. The protocol will be developed and the study would be run by the Boston Collaborative Drug Surveillance Programme, which has wide experience in successful design and completion of numerous observational studies to meet both FDA and EMEA requirements.

In summary, Solvay considers the RiskMAP to be integral to the safe and successful use of tedisamil, and is committed to its complete and ongoing implementation.

9 Conclusions

Tedisamil is a Class III antiarrhythmic agent indicated for the restoration of NSR in subjects with AFib/AFl. The efficacy and safety of tedisamil has been established during a comprehensive clinical development program that has led to a gender-specific dosage regimen to produce the most favorable risk/benefit relationship for the product.

Tedisamil provided rapid (within 30 minutes) and sustained (through 24 hours) restoration of NSR for a significant proportion of the population. This effect remained consistent across a range of subgroups, including gender, age, concomitant use of beta-blocking agents, NYHA

class, first and recurrent arrhythmia episodes, and in mild to moderate renal impairment. Tedisamil was more effective in AFib subjects and in subjects whose current arrhythmic episode was 48 hours or less in duration. Subjects continued on rate control agents (digoxin, beta-blocking agents) throughout the studies and multiple other drugs were used concomitantly without causing drug interactions.

Safety data for tedisamil did not reveal any unexpected safety findings compared to other drugs in the class. It was well-tolerated by various subgroups including subjects with congestive heart failure (NYHA I-III), and mild or moderate renal insufficiency. The most common TEAEs were cardiac disorders, which were also the most common cause of study withdrawal. As with other Class III antiarrhythmics, tedisamil can cause QT prolongation, and TdP is a concern. In the clinical program, the risk of adjudicated Torsade-like events at the recommended doses was 0.5% or less for both males and females. The proposed labeling calls for two hours of ECG monitoring from the initiation of the infusion to enable early identification and treatment of potential life-threatening ventricular arrhythmias, particularly sustained polymorphic ventricular tachycardia, should it occur.

The tedisamil RiskMAP has been developed to increase the care devoted to patient selection, help make dosing more accurate, and generally improve compliance with the requirements related to administration and monitoring. The end result is expected to be close alignment between product usage and product labeling, effectively minimizing the risk to patients.

In conclusion, considering the efficacy and safety profile, the positioning of tedisamil in the armamentarium of treatments for arrhythmia, and the risk management plan, tedisamil shows a positive risk/benefit balance and merits approval for the proposed indication:

> *The rapid conversion of recent onset (3 hours to 45 days) atrial fibrillation or atrial flutter to normal sinus rhythm.*

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Appendix 1

Charter for the Adjudication and Oversight Committee

CHARTER FOR THE ADJUDICATION AND OVERSIGHT COMMITTEE

Protocols: S219.3.112
S219.3.114
S219.3.116
S219.3.117
S219.3.118

Version Date : 19 JUL 2004

Approved by: _____ / _____
Dr. C. Steinborn Date

_____ / _____
Dr. M. Straub Date

Approved and accepted by:

_____ / _____
Dr. Peter Kowey Date

_____ / _____
Dr. Stefan Hohnloser Date

_____ / _____
Dr. Paul Dorian Date

1 INTRODUCTION

This charter is designed for the Adjudication and Oversight Committee (AOC) for tedisamil studies S219.3.112, S219.3.114, S219.3.116, S219.3.117 and S219.3.118

S219.3.112 was a multi-center, double-blind, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety of intravenous tedisamil sesquifumarate in the rapid conversion to normal sinus rhythm. Originally, the study population consisted of male and female subjects with recent onset atrial fibrillation or flutter, receiving doses of 0.32 mg/kg body weight (bw), 0.48 mg/kg bw and 0.64 mg/kg bw and placebo over 30 minutes. During the course of the study the decision was made to exclude females and to cancel the 0.64 mg/kg dose in males, since female gender and high dose were associated with an increased TdP risk. This study is completed. The safety sample consists of 272 subjects, of which 236 are males and 36 are females.

S219.3.114 is a multi-center, double-blind, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety of intravenous tedisamil sesquifumarate in the rapid conversion to normal sinus rhythm. Originally, the study population consisted of male and female subjects with recent onset atrial fibrillation or flutter, receiving doses of 0.32 mg/kg bw and 0.48 mg/kg bw and placebo over 30 minutes with possible extension of infusion to 50 minutes. During the course of the study the decision was made to exclude females and to cancel the extension part of the infusion for safety reasons (see study S219.3.112). Instead, a dose of 0.16 mg/kg bw was added. Thus, a target number of 212 male atrial fibrillation subjects will be enrolled in this trial.

S219.3.116 is a multi-center, double-blind, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety of intravenous tedisamil sesquifumarate in the rapid conversion to normal sinus rhythm in female subjects with recent onset atrial fibrillation or flutter (Amendment 1), receiving doses of 0.16 mg/kg bw, 0.24 mg/kg bw and 0.32 mg/kg bw and placebo over 30 minutes. A target number of 480 atrial fibrillation subjects will be enrolled in this trial.

S219.3.117 is a multi-center, double-blind, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety of intravenous tedisamil sesquifumarate in the rapid conversion to normal sinus rhythm in male subjects with recent onset atrial fibrillation or flutter, receiving a dose of 0.48 mg/kg bw and placebo over 30 minutes. A target number of 100 atrial fibrillation subjects will be enrolled in this trial.

S219.3.118 is a multi-center, double-blind, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety of intravenous tedisamil sesquifumarate in the rapid conversion to normal sinus rhythm in female subjects with recent onset atrial fibrillation or flutter, receiving a dose of 0.32 mg/kg bw and placebo over 30 minutes. A target number of 140 atrial fibrillation subjects will be enrolled in this trial.

The primary objective of all the above studies is to demonstrate the superiority of any dose 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.

In all studies, safety will be assessed on an ongoing basis by the AOC.

2 GUIDELINES FOR BLINDED SAFETY EVALUATION OF VENTRICULAR TACHYARRHYTHMIAS

Safety reasons of concern are unacceptable high incidences of serious adverse events (SAEs) and/or pro-arrhythmic events as assessed by the AOC. The AOC consists of 3 independent cardiologists and a Sponsor representative (GCD, non-voting member).

For blinded review (i.e. treatment code is not revealed) of safety data any SAE or ventricular tachycardia (VT) is assumed to be related to the study drug rather than placebo. In case the incidence of serious adverse events/pro-arrhythmic events gives a concern to one or more members of the AOC, the AOC shall recommend to the sponsor to take a formal unblinded interim safety look into the given study, unblinding the cases of concern to the AOC members only. If following the unblinding the level of concern is unchanged, the data will be opened and formally discussed within the AOC in presence of the sponsor representative. A joint decision whether or not to stop the study or a dose level will be taken by the sponsor and the AOC.

2.1 Serious Adverse Events (SAEs)

SAEs will be evaluated per study in a blinded fashion by the AOC on an ongoing basis. Conferences will be organized by Quintiles PM on regular intervals as needed to review accumulated SAEs (see tabulation: Appendix 2).

2.2 Pro-arrhythmic events

Proarrhythmic events can have 4 main sources, the 12-lead resting ECG, the 120 seconds rhythm strip, the telemetry and the 24-hour Holter monitoring. In the studies, the safety of tedisamil regarding pro-arrhythmic events will be judged on the basis of data generated by 24-hour Holter monitoring only. According to the protocols, a 24-hour Holter ECG will be started 10 min before start of the study drug infusion. The Holter tapes will be centrally analyzed for arrhythmias according to specific Holter analysis definitions. Ventricular events will be coded according to a predefined coding system.

The events will be analyzed by the Holter analysis company (Spacelabs Medical Data (SMD), see Appendix 1, Holter alert fax) and reviewed by the AOC. The members of the AOC sign and, if appropriate, amend the alert fax form. All events will eventually be adjudicated by the AOC (see tabulation: Appendix 3).

Terminology used in the tabulation:

Category VT:
- 3.1 polymorphic
- 3.2 monomorphic
- 4.1 sustained
- 4.2 non-sustained
- 5 torsade-like

All events of 3 or more abnormal/aberrant ventricular complexes with a rate of > 100 beats per minute will be defined as single episodes of VT; monomorphic relates to the morphology of the wave, and sustained to > 30 seconds.

Torsade-like VTs are considered polymorphic VTs, associated with a preceding prolonged QT or increased U-wave amplitude, starting with a long-short RR interval sequence and with changing amplitude, appearing to twist around the iso-electric line.

In case the number of VT episodes, as observed during the Holter observation period, exceeds five events, the fastest polymorphic ventricular run, the second fastest polymorphic ventricular run, the longest polymorphic ventricular run, the fastest ventricular run and the longest ventricular run will be documented. All events categorized in this charter will be distributed by SMD to the members of the AOC, and, if appropriate (as judged per individual case by the AOC), it will include all relevant information per individual event.

The Holter alert fax will be sent by SMD to members of the AOC and copied to Solvay and Quintiles in a blinded fashion within 24 hours after assessment by SMD. If possible, all three independent cardiologists of the AOC will feed back to the initial SMD assessment within 48 hours, whether or not there is agreement with the assessment of SMD. This feedback will be registered and all assessments will be compared. The initial SMD assessment is accepted, if agreed by two of the three AOC members. In case two or all three AOC members disagree, final agreement will be reached (adjudication) in the scheduled teleconferences. Any torsade or torsade-like VT will also be discussed. The updated assessment tabulation will be sent to SMD and each AOC member prior to each teleconference in case of incompatibility of the VT assessment.

2.3 Scheduled teleconferences

In order to review accumulated SAEs and to resolve disagreement on the SMD judgement of VT events by at least 2 AOC members, telephone conferences will be organized for adjudication. The organization of these teleconference meetings lies within Quintiles and is scheduled quarterly or more frequently if needed. For final adjudication of events at least two members of the AOC need to be present.

The safety of a given Tedisamil dose may be assessed based on the number of polymorphic, sustained or torsade-like VTs. Initially it is assumed that all these events occurred on tedisamil. Because of the blind the exact number of patients who received the tedisamil dose is unknown. It will be approximated as 3/4 times the total number of patients randomized in studies S219.3.112, S219.3.114 and S219.3.116 and as 1/2 times the total number of patients randomized in studies S219.3.117 and S219.3.118. The AOC will provide an expert opinion on the safety of tedisamil on an ongoing basis.

The AOC has the right to recommend to the sponsor to take a formal unblinded interim safety look into the given study, unblinding the cases of concern to the AOC members only. If following the unblinding the level of concern is unchanged, the data will be opened and formally

discussed within the AOC in presence of a sponsor representative. A joint decision whether or not to stop the study or a dose level will be taken by the sponsor and the AOC.

APPENDICES

1. Holter alert fax
2. SAE log
3. Charter for VT evaluation

Appendix 1: Holter Alert Fax

SOLVAY TEDISAMIL S.219.3.11x
SPACELABS MEDICAL DATA
HOLTER ALERT FAX
ADJUDICATION AND OVERSIGHT COMMITTEE EVALUATION FORM

To: AOC Members	Dr. Peter Kowey	Fax: + 1 610 649 6990
	Dr. Stephan Hohnloser	Fax: + 49 69 6301 7017
	Dr. Paul Dorian	Fax: + 1 416 864 5283
To: Solvay	Dr. Hans-Josef Weimann	Fax: + 49 511 857 2916
To: Quintiles	Dr. Pawel Skowronski	Fax: + 39 0 292 606450
To: Investigator	Attn: _____	Fax: _____

Alert Fax Date/Time: _____ (dd/mm/yyyy) _____:_____ (hh : mm)

Patient Number: __ __ __-__ __ (3 characters for site; 2 characters for patient)

Sex: _____ Male _____ Female

Holter Start Date/Time: _____ (dd/mm/yyyy) _____:_____ (hh : mm)

Please be notified that there is evidence of a significant Holter finding in this recording.

	VT number				
Ventricular Tachycardia: ≥ 3 Beats & ≥ 100 BPM	1	2	3	4	5
Time of VT	:	:	:	:	:
Heart rate (bpm)					
Is this VT polymorphic or monomorphic? 1 = polymorphic 2 = monomorphic					
Is this VT sustained or non-sustained? 1 = sustained (≥ 30 sec) 2 = non- sustained (≥ 30 sec)					
Number of beats					
Is this VT Torsade-like? 1 = yes 2 = no 3 = unable to determine (due to length, etc)					

Definitions applying to Holter Alert Fax

Monomorphic VT	ventricular rhythm faster than 100 bpm with a regular rate and consistent beat to beat morphology
Polymorphic VT	frequent changes in QRS morphology and/or axis, which - if sustained - must occur at least every 1 or 2 seconds
Sustained VT	equal to or longer than 30 seconds
Non-sustained VT	shorter than 30 seconds
Torsade-like VT	polymorphic VT, associated with a preceding prolonged QT or increased U-wave amplitude, starting with a long-short RR interval sequence and changing amplitude, appearing to twist around an isoelectric line

Other Significant Findings:

- ☐ Sustained Tachycardia: > 30 seconds @ > 200 BPM
- ☐ Sustained Bradycardia: > 30 seconds @ < 50 BPM
- ☐ 3rd Degree AV Block
- ☐ Sustained 2nd Degree AV Block: > 30 seconds
- ☐ Pauses > 3000 msec.
- ☐ VE's: > 500 per hour

Analyzed by Date Signature	Checked by Date Signature
Adjudication and Oversight Committee Reviewed by (print name) _____ _____ Date (dd/mm/yyyy) Agreed yes ☐ no ☐ Signature:	

Appendix 2: SAE Log Protocol S219.3.11_

Investigator	Site #	Patient #	Date SAE observed	SAE description	Date SAE to QUINTILES	Date SAE to Solvay	Reported by	Follow-up report (FU)	Date FU to Solvay	Reviewed by AOC Y/N	Outcome

Appendix 3: Charter for Blinded Evaluation of VT's Protocol S219.3.11_

Date	Pt no.	VT no	Category of event					AOC members agreement						Adjudication required		Category of event				
			3.1	3.2	4.1	4.2	5	PC		PD		SH				3.1	3.2	4.1	4.2	5
								Y	N	Y	N	Y	N	Y	N					

Appendix 2

Baseline Characteristics for Integrated Safety Dataset

Baseline Characteristics – Integrated Safety Dataset – Males

Baseline Characteristics	Integrated Safety Dataset - Males								
	0.16 mg/kg (N=66)	0.24 mg/kg (N=6)	0.32 mg/kg (N=172)	>0.32 – 0.48 mg/kg (N=10)	0.48 mg/kg (N=207)	>0.48 – 0.72 mg/kg (N=15)	0.64 mg/kg (N = 52)	Combined Tedisamil (N = 528)	Placebo (N = 231)
Age, mean, y	61.3	70.3	59.7	60.5	62.1	55.4	58.9	60.8	60.3
Age range, y	26, 91	60, 85	29, 86	43, 76	30, 85	28, 75	35, 86	26, 91	20, 88
<65 y, %	57.6%	33.3%	61.6%	80.0%	57.5%	73.3%	67.3%	319 (60.4%)	144 (62.3%)
≥65 y, %	42.4%	66.7%	38.4%	20.0%	42.5%	26.7%	32.7%	209 (39.6%)	87 (37.7%)
Race, White, %	98.5%	100%	98.3%	100%	98.1%	86.7%	100%	518 (98.1%)	226 (97.8%)
BMI, mean kg/m^2	28.79	32.55	28.46	28.73	28.32	26.71	28.43	28.44	28.26
SBP, mmHg	130.0	145.0	128.1	142.7	130.0	137.0	132.4	130.2	129.1
DBP, mmHg	80.2	87.8	80.0	85.7	81.1	87.3	81.5	81.0	80.5
Pulse, bpm	96.7	83.0	99.3	108.7	97.6	114.7	95.7	98.4	98.8
NYHA I, %	45.5%	--	65.7%	40.0%	59.4%	20.0%	71.2%	310 (58.7%)	137 (59.3%)
NYHA II, %	34.8%	--	30.2%	60.0%	30.4%	60.0%	25.0%	166 (31.4%)	74 (32.0%)
NYHA III, %	7.6%	--	1.7%	0%	5.3%	13.3%	3.8%	23 (4.4%)	9 (3.9%)
Baseline CrCL									
<30 mL/min, %	0%	0%	0%	0%	0.5%	0%	0%	1 (0.2%)	0
≥30 - <60 mL/min,%	7.6%	0%	7.0%	0%	10.6%	13.3%	3.8%	43 (8.1%)	26 (11.3%)
≥60 - <90 mL/min, %	37.9%	50.0%	32.0%	30.0%	36.7%	33.3%	34.6%	185 (35.0%)	74 (32.0%)
≥90 mL/min, %	51.5%	50.0%	57.6%	70.0%	48.8%	46.7%	55.8%	280 (53.0%)	117 (50.6%)
Duration Afib/Afl, %									
3-48 h	43.9%	0%	57.6%	30.0%	56.5%	66.7%	63.5%	291 (55.1%)	130 (56.3%)
>48 h – 45 d	48.5%	66.7%	42.4%	70.0%	43.0%	33.3%	36.5%	229 (43.4%)	97 (42.0%)
>45 d	7.6%	33.3%	0%	0%	0%	0%	0%	7 (1.3%)	4 (1.7%)
Baseline QTcB, %									
<400 msec	36.4%	66.7%	29.7%	10.0%	20.8%	6.7%	32.7%	141 (26.7%)	49 (21.2%)
≥400-470 msec	56.1%	33.3%	63.4%	80.0%	66.2%	73.3%	55.8%	333 (63.1%)	156 (67.5%)
>479 msec	1.5%	--	5.2%	10.0%	9.3%	0%	5.8%	33 (6.3%)	20 (8.7%)

Baseline Characteristics – Integrated Safety Dataset – Females

Baseline Characteristics	Integrated Safety Dataset - Females								
	0.16 mg/kg (N=1)	0.24 mg/kg (N=122)	0.32 mg/kg (N=225)	>0.32 – 0.48 mg/kg (N=7)	0.48 mg/kg (N=34)	>0.48 – 0.72 mg/kg (N=4)	0.64 mg/kg (N=10)	Combined Tedisamil (N=403)	Placebo (N = 239)
Age, mean, y	71.0	68.8	68.6	69.3	69.7	67.3	66.0	68.7	68.6
Age range, y	--	47, 85	38, 91	46, 80	29, 87	59, 80	57, 73	29, 91	37, 92
<65 y, %	0%	27.0%	30.7%	14.3%	23.5%	50.0%	40.0%	117 (29.0%)	77 (32.2%)
≥65 y, %	100%	73.0%	69.3%	85.7%	76.5%	50.0%	60.0%	286 (71.0%)	162 (67.8%)
Race, White, %	0%[a]	98.4%	97.8%	85.7%	100%	100%	90.0%	393 (97.5%)	236 (98.7%)
BMI, mean kg/m^2	30.50	29.24	28.97	28.73	28.78	25.15	30.06	29.02	30.13
SBP, mmHg	150.0	131.4	132.6	136.4	139.6	136.3	127.8	132.9	131.5
DBP, mmHg	78.0	79.8	80.7	83.0	79.9	81.3	81.3	80.4	80.2
Pulse, bpm	100	98.2	97.1	100.3	100.3	86.3	111.9	98.0	97.4
NYHA I, %	0%	32.8%	40.4%	42.9%	35.3%	75.0%	40.0%	153 (38.0%)	95 (39.7%)
NYHA II, %	0%	49.2%	42.2%	42.9%	64.7%	25.0%	50.0%	186 (46.2%)	99 (41.4%)
NYHA III, %	0%	11.5%	5.8%	14.3%	0%	0%	10.0%	29 (7.2%)	22 (9.2%)
Baseline CrCL									
<30 mL/min, %	0%	1.6%	0%	14.3%	0%	0%	0%	3 (0.7%)	5 (2.1%)
≥30 - <60 mL/min,%	0%	30.3%	28.0%	42.9%	23.5%	50.0%	10.0%	114 (28.3%)	59 (24.7%)
≥60 - <90 mL/min, %	100%	45.1%	41.8%	28.6%	47.1%	50.0%	40.0%	174 (43.2%)	93 (38.9%)
≥90 mL/min, %	0%	21.3%	26.7%	14.3%	20.6%	0%	50.0%	99 (24.6%)	75 (31.4%)
Duration Afib/Afl, %									
3-48 h	0%	30.3%	40.9%	57.1%	85.3%	50.0%	10.0%	165 (40.9%)	91 (38.1%)
>48 h – 45 d	0%	68.9%	58.7%	42.9%	14.7%	50.0%	90.0%	235 (58.3%)	145 (60.7%)
>45 d	100%	0%	0%	0%	0%	0%	0%	1 (0.2%)	3 (1.3%)
Baseline QTcB, %									
<400 msec	100%	18.0%	10.7%	14.3%	11.8%	0%	20.0%	54 (13.4%)	34 (14.2%)
≥400-470 msec	0%	56.6%	68.4%	85.7%	64.7%	100%	70.0%	262 (65.0%)	159 (66.5%)
>479 msec	0%	13.9%	14.7%	0%	20.6%	0%	10.0%	58 (14.4%)	31 (13.0%)

[a] The one female subject in 0.16 mg/kg group was Black.

Appendix 3

Incidence of TESAEs - Integrated Safety Dataset

Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup

Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 66)	0.24 mg/kg Tedi (N = 6)	0.32 mg/kg Tedi (N = 172)	0.32 - 0.48 mg/kg Tedi (N = 10)
Number of Subjects With at Least One TESAE	n (%)	5 (7.6%)	1 (16.7%)	15 (8.7%)	1 (10.0%)
CARDIAC DISORDERS	n (%)	2 (3.0%)	1 (16.7%)	8 (4.7%)	1 (10.0%)
CORONARY ARTERY DISORDERS NEC	n (%)	0	0	1 (0.6%)	0
CORONARY ARTERY DISEASE	n (%)	0	0	1 (0.6%)	0
HEART FAILURES NEC	n (%)	0	0	0	0
CARDIAC FAILURE	n (%)	0	0	0	0
CARDIAC FAILURE CONGESTIVE	n (%)	0	0	0	0
ISCHAEMIC CORONARY ARTERY DISORDERS	n (%)	1 (1.5%)	0	1 (0.6%)	0
ACUTE MYOCARDIAL INFARCTION	n (%)	0	0	1 (0.6%)	0
MYOCARDIAL INFARCTION	n (%)	1 (1.5%)	0	0	0
RATE AND RHYTHM DISORDERS NEC	n (%)	1 (1.5%)	0	0	0
BRADYCARDIA	n (%)	1 (1.5%)	0	0	0
SUPRAVENTRICULAR ARRHYTHMIAS	n (%)	1 (1.5%)	0	4 (2.3%)	1 (10.0%)
ATRIAL FIBRILLATION	n (%)	1 (1.5%)	0	4 (2.3%)	1 (10.0%)
ATRIAL FLUTTER	n (%)	0	0	0	0
SICK SINUS SYNDROME	n (%)	0	0	0	0
SUPRAVENTRICULAR TACHYCARDIA	n (%)	0	0	0	0
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST	n (%)	0	1 (16.7%)	2 (1.2%)	0
CARDIAC ARREST	n (%)	0	1 (16.7%)	0	0
VENTRICULAR FIBRILLATION	n (%)	0	0	0	0
VENTRICULAR TACHYCARDIA	n (%)	0	0	2 (1.2%)	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.48 mg/kg Tedi (N = 207)	0.48 - 0.72 mg/kg Tedi (N = 15)	0.64 mg/kg Tedi (N = 52)
Number of Subjects With at Least One TESAE	n (%)	19 (9.2%)	1 (6.7%)	4 (7.7%)
CARDIAC DISORDERS	n (%)	14 (6.8%)	1 (6.7%)	4 (7.7%)
CORONARY ARTERY DISORDERS NEC	n (%)	0	0	0
CORONARY ARTERY DISEASE	n (%)	0	0	0
HEART FAILURES NEC	n (%)	1 (0.5%)	0	1 (1.9%)
CARDIAC FAILURE	n (%)	0	0	1 (1.9%)
CARDIAC FAILURE CONGESTIVE	n (%)	1 (0.5%)	0	0
ISCHAEMIC CORONARY ARTERY DISORDERS	n (%)	0	0	2 (3.8%)
ACUTE MYOCARDIAL INFARCTION	n (%)	0	0	0
MYOCARDIAL INFARCTION	n (%)	0	0	2 (3.8%)
RATE AND RHYTHM DISORDERS NEC	n (%)	2 (1.0%)	0	0
BRADYCARDIA	n (%)	2 (1.0%)	0	0
SUPRAVENTRICULAR ARRHYTHMIAS	n (%)	9 (4.3%)	1 (6.7%)	3 (5.8%)
ATRIAL FIBRILLATION	n (%)	9 (4.3%)	0	2 (3.8%)
ATRIAL FLUTTER	n (%)	1 (0.5%)	0	1 (1.9%)
SICK SINUS SYNDROME	n (%)	0	0	0
SUPRAVENTRICULAR TACHYCARDIA	n (%)	0	1 (6.7%)	0
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST	n (%)	3 (1.4%)	0	1 (1.9%)
CARDIAC ARREST	n (%)	0	0	0
VENTRICULAR FIBRILLATION	n (%)	1 (0.5%)	0	0
VENTRICULAR TACHYCARDIA	n (%)	2 (1.0%)	0	1 (1.9%)

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	Combined Tedi (N = 528)	Placebo (N = 231)
Number of Subjects With at Least One TESAE	n (%)	46 (8.7%)	20 (8.7%)
CARDIAC DISORDERS	n (%)	31 (5.9%)	14 (6.1%)
CORONARY ARTERY DISORDERS NEC	n (%)	1 (0.2%)	0
CORONARY ARTERY DISEASE	n (%)	1 (0.2%)	0
HEART FAILURES NEC	n (%)	2 (0.4%)	0
CARDIAC FAILURE	n (%)	1 (0.2%)	0
CARDIAC FAILURE CONGESTIVE	n (%)	1 (0.2%)	0
ISCHAEMIC CORONARY ARTERY DISORDERS	n (%)	4 (0.8%)	1 (0.4%)
ACUTE MYOCARDIAL INFARCTION	n (%)	1 (0.2%)	0
MYOCARDIAL INFARCTION	n (%)	3 (0.6%)	1 (0.4%)
RATE AND RHYTHM DISORDERS NEC	n (%)	3 (0.6%)	0
BRADYCARDIA	n (%)	3 (0.6%)	0
SUPRAVENTRICULAR ARRHYTHMIAS	n (%)	19 (3.6%)	11 (4.8%)
ATRIAL FIBRILLATION	n (%)	17 (3.2%)	7 (3.0%)
ATRIAL FLUTTER	n (%)	2 (0.4%)	3 (1.3%)
SICK SINUS SYNDROME	n (%)	0	1 (0.4%)
SUPRAVENTRICULAR TACHYCARDIA	n (%)	1 (0.2%)	0
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST	n (%)	7 (1.3%)	5 (2.2%)
CARDIAC ARREST	n (%)	1 (0.2%)	1 (0.4%)
VENTRICULAR FIBRILLATION	n (%)	1 (0.2%)	3 (1.3%)
VENTRICULAR TACHYCARDIA	n (%)	5 (0.9%)	2 (0.9%)

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 66)	0.24 mg/kg Tedi (N = 6)	0.32 mg/kg Tedi (N = 172)	0.32 - 0.48 mg/kg Tedi (N = 10)
GASTROINTESTINAL DISORDERS	n (%)	0	0	1 (0.6%)	0
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	n (%)	0	0	0	0
ABDOMINAL PAIN LOWER	n (%)	0	0	0	0
GASTROINTESTINAL STENOSIS AND OBSTRUCTION NEC	n (%)	0	0	1 (0.6%)	0
MECHANICAL ILEUS	n (%)	0	0	1 (0.6%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	0	0	1 (0.6%)	0
PAIN AND DISCOMFORT NEC	n (%)	0	0	1 (0.6%)	0
CHEST PAIN	n (%)	0	0	1 (0.6%)	0
INFECTIONS AND INFESTATIONS	n (%)	0	0	1 (0.6%)	0
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	n (%)	0	0	1 (0.6%)	0
BRONCHITIS	n (%)	0	0	1 (0.6%)	0
BRONCHITIS ACUTE	n (%)	0	0	0	0
PNEUMONIA	n (%)	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	n (%)	0	0	1 (0.6%)	0
RESPIRATORY TRACT AND THORACIC CAVITY PROCEDURAL COMPLICATIONS	n (%)	0	0	1 (0.6%)	0
POSTOPERATIVE THORACIC PROCEDURE COMPLICATION	n (%)	0	0	1 (0.6%)	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Statistic	0.48 mg/kg Tedi (N = 207)	0.48 - 0.72 mg/kg Tedi (N = 15)	0.64 mg/kg Tedi (N = 52)
GASTROINTESTINAL DISORDERS	n (%)	0	0	0
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	n (%)	0	0	0
ABDOMINAL PAIN LOWER	n (%)	0	0	0
GASTROINTESTINAL STENOSIS AND OBSTRUCTION NEC	n (%)	0	0	0
MECHANICAL ILEUS	n (%)	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	0	0	0
PAIN AND DISCOMFORT NEC	n (%)	0	0	0
CHEST PAIN	n (%)	0	0	0
INFECTIONS AND INFESTATIONS	n (%)	2 (1.0%)	0	0
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	n (%)	2 (1.0%)	0	0
BRONCHITIS	n (%)	0	0	0
BRONCHITIS ACUTE	n (%)	1 (0.5%)	0	0
PNEUMONIA	n (%)	1 (0.5%)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	n (%)	0	0	0
RESPIRATORY TRACT AND THORACIC CAVITY PROCEDURAL COMPLICATIONS	n (%)	0	0	0
POSTOPERATIVE THORACIC PROCEDURE COMPLICATION	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 528)	Placebo (N = 231)
GASTROINTESTINAL DISORDERS	n (%)	1 (0.2%)	1 (0.4%)
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	n (%)	0	1 (0.4%)
ABDOMINAL PAIN LOWER	n (%)	0	1 (0.4%)
GASTROINTESTINAL STENOSIS AND OBSTRUCTION NEC	n (%)	1 (0.2%)	0
MECHANICAL ILEUS	n (%)	1 (0.2%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	1 (0.2%)	1 (0.4%)
PAIN AND DISCOMFORT NEC	n (%)	1 (0.2%)	1 (0.4%)
CHEST PAIN	n (%)	1 (0.2%)	1 (0.4%)
INFECTIONS AND INFESTATIONS	n (%)	3 (0.6%)	2 (0.9%)
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	n (%)	3 (0.6%)	2 (0.9%)
BRONCHITIS	n (%)	1 (0.2%)	0
BRONCHITIS ACUTE	n (%)	1 (0.2%)	0
PNEUMONIA	n (%)	1 (0.2%)	2 (0.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	n (%)	1 (0.2%)	0
RESPIRATORY TRACT AND THORACIC CAVITY PROCEDURAL COMPLICATIONS	n (%)	1 (0.2%)	0
POSTOPERATIVE THORACIC PROCEDURE COMPLICATION	n (%)	1 (0.2%)	0

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 66)	0.24 mg/kg Tedi (N = 6)	0.32 mg/kg Tedi (N = 172)	0.32 - 0.48 mg/kg Tedi (N = 10)
INVESTIGATIONS	n (%)	0	0	0	0
ECG INVESTIGATIONS	n (%)	0	0	0	0
ELECTROCARDIOGRAM AMBULATORY ABNORMAL	n (%)	0	0	0	0
VASCULAR IMAGING PROCEDURES NEC	n (%)	0	0	0	0
ANGIOGRAM	n (%)	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	n (%)	1 (1.5%)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE SIGNS AND SYMPTOMS NEC	n (%)	1 (1.5%)	0	0	0
PAIN IN EXTREMITY	n (%)	1 (1.5%)	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	n (%)	0	0	0	0
PANCREATIC NEOPLASMS MALIGNANT (EXCL ISLET CELL AND CARCINOID)	n (%)	0	0	0	0
PANCREATIC CARCINOMA	n (%)	0	0	0	0
NERVOUS SYSTEM DISORDERS	n (%)	2 (3.0%)	0	1 (0.6%)	0
CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR ACCIDENTS	n (%)	1 (1.5%)	0	1 (0.6%)	0
CEREBROVASCULAR ACCIDENT	n (%)	1 (1.5%)	0	0	0
ISCHAEMIC STROKE	n (%)	0	0	1 (0.6%)	0
CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS NEC	n (%)	0	0	0	0
CAROTID ARTERY STENOSIS	n (%)	0	0	0	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.48 mg/kg Tedi (N = 207)	0.48 - 0.72 mg/kg Tedi (N = 15)	0.64 mg/kg Tedi (N = 52)
INVESTIGATIONS	n (%)	1 (0.5%)	0	0
ECG INVESTIGATIONS	n (%)	1 (0.5%)	0	0
ELECTROCARDIOGRAM AMBULATORY ABNORMAL	n (%)	1 (0.5%)	0	0
VASCULAR IMAGING PROCEDURES NEC	n (%)	0	0	0
ANGIOGRAM	n (%)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	n (%)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE SIGNS AND SYMPTOMS NEC	n (%)	0	0	0
PAIN IN EXTREMITY	n (%)	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	n (%)	0	0	0
PANCREATIC NEOPLASMS MALIGNANT (EXCL ISLET CELL AND CARCINOID)	n (%)	0	0	0
PANCREATIC CARCINOMA	n (%)	0	0	0
NERVOUS SYSTEM DISORDERS	n (%)	2 (1.0%)	0	0
CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR ACCIDENTS	n (%)	1 (0.5%)	0	0
CEREBROVASCULAR ACCIDENT	n (%)	0	0	0
ISCHAEMIC STROKE	n (%)	1 (0.5%)	0	0
CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS NEC	n (%)	1 (0.5%)	0	0
CAROTID ARTERY STENOSIS	n (%)	1 (0.5%)	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 528)	Placebo (N = 231)
INVESTIGATIONS	n (%)	1 (0.2%)	1 (0.4%)
ECG INVESTIGATIONS	n (%)	1 (0.2%)	0
ELECTROCARDIOGRAM AMBULATORY ABNORMAL	n (%)	1 (0.2%)	0
VASCULAR IMAGING PROCEDURES NEC	n (%)	0	1 (0.4%)
ANGIOGRAM	n (%)	0	1 (0.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	n (%)	1 (0.2%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE SIGNS AND SYMPTOMS NEC	n (%)	1 (0.2%)	0
PAIN IN EXTREMITY	n (%)	1 (0.2%)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	n (%)	0	1 (0.4%)
PANCREATIC NEOPLASMS MALIGNANT (EXCL ISLET CELL AND CARCINOID)	n (%)	0	1 (0.4%)
PANCREATIC CARCINOMA	n (%)	0	1 (0.4%)
NERVOUS SYSTEM DISORDERS	n (%)	5 (0.9%)	0
CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR ACCIDENTS	n (%)	3 (0.6%)	0
CEREBROVASCULAR ACCIDENT	n (%)	1 (0.2%)	0
ISCHAEMIC STROKE	n (%)	2 (0.4%)	0
CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS NEC	n (%)	1 (0.2%)	0
CAROTID ARTERY STENOSIS	n (%)	1 (0.2%)	0

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 66)	0.24 mg/kg Tedi (N = 6)	0.32 mg/kg Tedi (N = 172)	0.32 - 0.48 mg/kg Tedi (N = 10)
NERVOUS SYSTEM DISORDERS (cont'd)					
DISTURBANCES IN CONSCIOUSNESS NEC	n (%)	1 (1.5%)	0	0	0
SYNCOPE	n (%)	1 (1.5%)	0	0	0
RENAL AND URINARY DISORDERS	n (%)	0	0	1 (0.6%)	0
RENAL FAILURE AND IMPAIRMENT	n (%)	0	0	1 (0.6%)	0
RENAL FAILURE ACUTE	n (%)	0	0	1 (0.6%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	0	0	0	0
BREATHING ABNORMALITIES	n (%)	0	0	0	0
DYSPNOEA	n (%)	0	0	0	0
PULMONARY OEDEMAS	n (%)	0	0	0	0
PULMONARY CONGESTION	n (%)	0	0	0	0
PULMONARY OEDEMA	n (%)	0	0	0	0
VASCULAR DISORDERS	n (%)	1 (1.5%)	0	1 (0.6%)	0
AORTIC NECROSIS AND VASCULAR INSUFFICIENCY	n (%)	1 (1.5%)	0	0	0
AORTIC STENOSIS	n (%)	1 (1.5%)	0	0	0
PERIPHERAL EMBOLISM AND THROMBOSIS	n (%)	1 (1.5%)	0	0	0
ARTERIAL THROMBOSIS LIMB	n (%)	0	0	0	0
DEEP VEIN THROMBOSIS	n (%)	1 (1.5%)	0	0	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.48 mg/kg Tedi (N = 207)	0.48 - 0.72 mg/kg Tedi (N = 15)	0.64 mg/kg Tedi (N = 52)
NERVOUS SYSTEM DISORDERS (cont'd)				
DISTURBANCES IN CONSCIOUSNESS NEC	n (%)	0	0	0
SYNCOPE	n (%)	0	0	0
RENAL AND URINARY DISORDERS	n (%)	0	0	0
RENAL FAILURE AND IMPAIRMENT	n (%)	0	0	0
RENAL FAILURE ACUTE	n (%)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	0	0	1 (1.9%)
BREATHING ABNORMALITIES	n (%)	0	0	0
DYSPNOEA	n (%)	0	0	0
PULMONARY OEDEMAS	n (%)	0	0	1 (1.9%)
PULMONARY CONGESTION	n (%)	0	0	0
PULMONARY OEDEMA	n (%)	0	0	1 (1.9%)
VASCULAR DISORDERS	n (%)	1 (0.5%)	0	0
AORTIC NECROSIS AND VASCULAR INSUFFICIENCY	n (%)	0	0	0
AORTIC STENOSIS	n (%)	0	0	0
PERIPHERAL EMBOLISM AND THROMBOSIS	n (%)	1 (0.5%)	0	0
ARTERIAL THROMBOSIS LIMB	n (%)	1 (0.5%)	0	0
DEEP VEIN THROMBOSIS	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 528)	Placebo (N = 231)
NERVOUS SYSTEM DISORDERS (cont'd)			
DISTURBANCES IN CONSCIOUSNESS NEC	n (%)	1 (0.2%)	0
SYNCOPE	n (%)	1 (0.2%)	0
RENAL AND URINARY DISORDERS	n (%)	1 (0.2%)	0
RENAL FAILURE AND IMPAIRMENT	n (%)	1 (0.2%)	0
RENAL FAILURE ACUTE	n (%)	1 (0.2%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	1 (0.2%)	2 (0.9%)
BREATHING ABNORMALITIES	n (%)	0	1 (0.4%)
DYSPNOEA	n (%)	0	1 (0.4%)
PULMONARY OEDEMAS	n (%)	1 (0.2%)	1 (0.4%)
PULMONARY CONGESTION	n (%)	0	1 (0.4%)
PULMONARY OEDEMA	n (%)	1 (0.2%)	0
VASCULAR DISORDERS	n (%)	3 (0.6%)	1 (0.4%)
AORTIC NECROSIS AND VASCULAR INSUFFICIENCY	n (%)	1 (0.2%)	0
AORTIC STENOSIS	n (%)	1 (0.2%)	0
PERIPHERAL EMBOLISM AND THROMBOSIS	n (%)	2 (0.4%)	0
ARTERIAL THROMBOSIS LIMB	n (%)	1 (0.2%)	0
DEEP VEIN THROMBOSIS	n (%)	1 (0.2%)	0

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Statistic	0.16 mg/kg Tedi (N = 66)	0.24 mg/kg Tedi (N = 6)	0.32 mg/kg Tedi (N = 172)	0.32 - 0.48 mg/kg Tedi (N = 10)
VASCULAR DISORDERS (cont'd)					
VASCULAR HYPERTENSIVE DISORDERS NEC	n (%)	0	0	1 (0.6%)	0
HYPERTENSION	n (%)	0	0	1 (0.6%)	0
VASCULAR HYPOTENSIVE DISORDERS	n (%)	0	0	0	0
HYPOTENSION	n (%)	0	0	0	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Statistic	0.48 mg/kg Tedi (N = 207)	0.48 - 0.72 mg/kg Tedi (N = 15)	0.64 mg/kg Tedi (N = 52)
VASCULAR DISORDERS (cont'd)				
VASCULAR HYPERTENSIVE DISORDERS NEC	n (%)	0	0	0
HYPERTENSION	n (%)	0	0	0
VASCULAR HYPOTENSIVE DISORDERS	n (%)	0	0	0
HYPOTENSION	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-51 Incidence of TESAEs, Integrated Safety Sample, Male Subgroup - continued
Gender=Male - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 528)	Placebo (N = 231)
VASCULAR DISORDERS (cont'd)			
VASCULAR HYPERTENSIVE DISORDERS NEC	n (%)	1 (0.2%)	0
HYPERTENSION	n (%)	1 (0.2%)	0
VASCULAR HYPOTENSIVE DISORDERS	n (%)	0	1 (0.4%)
HYPOTENSION	n (%)	0	1 (0.4%)

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup

Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 1)	0.24 mg/kg Tedi (N = 122)	0.32 mg/kg Tedi (N = 225)	0.32 - 0.48 mg/kg Tedi (N = 7)
Number of Subjects With at Least One TESAE	n (%)	0	14 (11.5%)	20 (8.9%)	3 (42.9%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	n (%)	0	0	0	0
MARROW DEPRESSION AND HYPOPLASTIC ANAEMIAS	n (%)	0	0	0	0
PANCYTOPENIA	n (%)	0	0	0	0
CARDIAC DISORDERS	n (%)	0	8 (6.6%)	12 (5.3%)	3 (42.9%)
HEART FAILURES NEC	n (%)	0	0	3 (1.3%)	0
CARDIAC FAILURE	n (%)	0	0	3 (1.3%)	0
CARDIAC FAILURE CONGESTIVE	n (%)	0	0	0	0
ISCHAEMIC CORONARY ARTERY DISORDERS	n (%)	0	0	4 (1.8%)	0
ACUTE CORONARY SYNDROME	n (%)	0	0	1 (0.4%)	0
ACUTE MYOCARDIAL INFARCTION	n (%)	0	0	2 (0.9%)	0
MYOCARDIAL INFARCTION	n (%)	0	0	1 (0.4%)	0
RATE AND RHYTHM DISORDERS NEC	n (%)	0	0	1 (0.4%)	1 (14.3%)
BRADYCARDIA	n (%)	0	0	0	1 (14.3%)
NODAL ARRHYTHMIA	n (%)	0	0	1 (0.4%)	0
SUPRAVENTRICULAR ARRHYTHMIAS	n (%)	0	7 (5.7%)	4 (1.8%)	2 (28.6%)
ATRIAL FIBRILLATION	n (%)	0	6 (4.9%)	3 (1.3%)	2 (28.6%)
ATRIAL FLUTTER	n (%)	0	1 (0.8%)	1 (0.4%)	0
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST	n (%)	0	1 (0.8%)	0	2 (28.6%)
CARDIAC ARREST	n (%)	0	0	0	1 (14.3%)
ELECTROMECHANICAL DISSOCIATION	n (%)	0	0	0	1 (14.3%)

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.48 mg/kg Tedi (N = 34)	0.48 - 0.72 mg/kg Tedi (N = 4)	0.64 mg/kg Tedi (N = 10)
Number of Subjects With at Least One TESAE	n (%)	5 (14.7%)	0	2 (20.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	n (%)	0	0	0
MARROW DEPRESSION AND HYPOPLASTIC ANAEMIAS	n (%)	0	0	0
PANCYTOPENIA	n (%)	0	0	0
CARDIAC DISORDERS	n (%)	3 (8.8%)	0	1 (10.0%)
HEART FAILURES NEC	n (%)	1 (2.9%)	0	0
CARDIAC FAILURE	n (%)	0	0	0
CARDIAC FAILURE CONGESTIVE	n (%)	1 (2.9%)	0	0
ISCHAEMIC CORONARY ARTERY DISORDERS	n (%)	0	0	0
ACUTE CORONARY SYNDROME	n (%)	0	0	0
ACUTE MYOCARDIAL INFARCTION	n (%)	0	0	0
MYOCARDIAL INFARCTION	n (%)	0	0	0
RATE AND RHYTHM DISORDERS NEC	n (%)	0	0	0
BRADYCARDIA	n (%)	0	0	0
NODAL ARRHYTHMIA	n (%)	0	0	0
SUPRAVENTRICULAR ARRHYTHMIAS	n (%)	1 (2.9%)	0	0
ATRIAL FIBRILLATION	n (%)	1 (2.9%)	0	0
ATRIAL FLUTTER	n (%)	0	0	0
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST	n (%)	2 (5.9%)	0	1 (10.0%)
CARDIAC ARREST	n (%)	0	0	0
ELECTROMECHANICAL DISSOCIATION	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 403)	Placebo (N = 239)
Number of Subjects With at Least One TESAE	n (%)	44 (10.9%)	22 (9.2%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	n (%)	0	1 (0.4%)
MARROW DEPRESSION AND HYPOPLASTIC ANAEMIAS	n (%)	0	1 (0.4%)
PANCYTOPENIA	n (%)	0	1 (0.4%)
CARDIAC DISORDERS	n (%)	27 (6.7%)	10 (4.2%)
HEART FAILURES NEC	n (%)	4 (1.0%)	0
CARDIAC FAILURE	n (%)	3 (0.7%)	0
CARDIAC FAILURE CONGESTIVE	n (%)	1 (0.2%)	0
ISCHAEMIC CORONARY ARTERY DISORDERS	n (%)	4 (1.0%)	1 (0.4%)
ACUTE CORONARY SYNDROME	n (%)	1 (0.2%)	0
ACUTE MYOCARDIAL INFARCTION	n (%)	2 (0.5%)	0
MYOCARDIAL INFARCTION	n (%)	1 (0.2%)	1 (0.4%)
RATE AND RHYTHM DISORDERS NEC	n (%)	2 (0.5%)	2 (0.8%)
BRADYCARDIA	n (%)	1 (0.2%)	2 (0.8%)
NODAL ARRHYTHMIA	n (%)	1 (0.2%)	0
SUPRAVENTRICULAR ARRHYTHMIAS	n (%)	14 (3.5%)	5 (2.1%)
ATRIAL FIBRILLATION	n (%)	12 (3.0%)	5 (2.1%)
ATRIAL FLUTTER	n (%)	2 (0.5%)	0
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST	n (%)	6 (1.5%)	2 (0.8%)
CARDIAC ARREST	n (%)	1 (0.2%)	1 (0.4%)
ELECTROMECHANICAL DISSOCIATION	n (%)	1 (0.2%)	0

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 1)	0.24 mg/kg Tedi (N = 122)	0.32 mg/kg Tedi (N = 225)	0.32 - 0.48 mg/kg Tedi (N = 7)
CARDIAC DISORDERS (cont'd)					
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST (cont'd)					
TORSADE DE POINTES	n (%)	0	0	0	0
VENTRICULAR FIBRILLATION	n (%)	0	0	0	1 (14.3%)
VENTRICULAR TACHYCARDIA	n (%)	0	1 (0.8%)	0	0
GASTROINTESTINAL DISORDERS	n (%)	0	1 (0.8%)	1 (0.4%)	0
DIVERTICULA	n (%)	0	1 (0.8%)	0	0
DIVERTICULUM INTESTINAL HAEMORRHAGIC	n (%)	0	1 (0.8%)	0	0
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	n (%)	0	0	1 (0.4%)	0
ABDOMINAL PAIN UPPER	n (%)	0	0	1 (0.4%)	0
GASTROINTESTINAL SIGNS AND SYMPTOMS NEC	n (%)	0	0	0	0
ACUTE ABDOMEN	n (%)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	0	0	1 (0.4%)	0
FEBRILE DISORDERS	n (%)	0	0	1 (0.4%)	0
PYREXIA	n (%)	0	0	1 (0.4%)	0
PAIN AND DISCOMFORT NEC	n (%)	0	0	0	0
CHEST PAIN	n (%)	0	0	0	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	0.48 mg/kg Tedi (N = 34)	0.48 - 0.72 mg/kg Tedi (N = 4)	0.64 mg/kg Tedi (N = 10)
CARDIAC DISORDERS (cont'd)				
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST (cont'd)				
TORSADE DE POINTES	n (%)	1 (2.9%)	0	0
VENTRICULAR FIBRILLATION	n (%)	0	0	1 (10.0%)
VENTRICULAR TACHYCARDIA	n (%)	1 (2.9%)	0	0
GASTROINTESTINAL DISORDERS	n (%)	1 (2.9%)	0	0
DIVERTICULA	n (%)	0	0	0
DIVERTICULUM INTESTINAL HAEMORRHAGIC	n (%)	0	0	0
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	n (%)	0	0	0
ABDOMINAL PAIN UPPER	n (%)	0	0	0
GASTROINTESTINAL SIGNS AND SYMPTOMS NEC	n (%)	1 (2.9%)	0	0
ACUTE ABDOMEN	n (%)	1 (2.9%)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	0	0	0
FEBRILE DISORDERS	n (%)	0	0	0
PYREXIA	n (%)	0	0	0
PAIN AND DISCOMFORT NEC	n (%)	0	0	0
CHEST PAIN	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 403)	Placebo (N = 239)
CARDIAC DISORDERS (cont'd)			
VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST (cont'd)			
TORSADE DE POINTES	n (%)	1 (0.2%)	0
VENTRICULAR FIBRILLATION	n (%)	2 (0.5%)	1 (0.4%)
VENTRICULAR TACHYCARDIA	n (%)	2 (0.5%)	0
GASTROINTESTINAL DISORDERS	n (%)	3 (0.7%)	0
DIVERTICULA	n (%)	1 (0.2%)	0
DIVERTICULUM INTESTINAL HAEMORRHAGIC	n (%)	1 (0.2%)	0
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	n (%)	1 (0.2%)	0
ABDOMINAL PAIN UPPER	n (%)	1 (0.2%)	0
GASTROINTESTINAL SIGNS AND SYMPTOMS NEC	n (%)	1 (0.2%)	0
ACUTE ABDOMEN	n (%)	1 (0.2%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	1 (0.2%)	1 (0.4%)
FEBRILE DISORDERS	n (%)	1 (0.2%)	0
PYREXIA	n (%)	1 (0.2%)	0
PAIN AND DISCOMFORT NEC	n (%)	0	1 (0.4%)
CHEST PAIN	n (%)	0	1 (0.4%)

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 1)	0.24 mg/kg Tedi (N = 122)	0.32 mg/kg Tedi (N = 225)	0.32 - 0.48 mg/kg Tedi (N = 7)
HEPATOBILIARY DISORDERS	n (%)	0	1 (0.8%)	0	0
CHOLECYSTITIS AND CHOLELITHIASIS	n (%)	0	1 (0.8%)	0	0
CHOLELITHIASIS	n (%)	0	1 (0.8%)	0	0
INFECTIONS AND INFESTATIONS	n (%)	0	0	3 (1.3%)	0
INFLUENZA VIRAL INFECTIONS	n (%)	0	0	1 (0.4%)	0
INFLUENZA	n (%)	0	0	1 (0.4%)	0
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	n (%)	0	0	2 (0.9%)	0
BRONCHITIS ACUTE	n (%)	0	0	1 (0.4%)	0
PNEUMONIA	n (%)	0	0	1 (0.4%)	0
UPPER RESPIRATORY TRACT INFECTIONS	n (%)	0	0	0	0
CHRONIC SINUSITIS	n (%)	0	0	0	0
INVESTIGATIONS	n (%)	0	0	1 (0.4%)	1 (14.3%)
COAGULATION AND BLEEDING ANALYSES	n (%)	0	0	0	0
COAGULATION TIME SHORTENED	n (%)	0	0	0	0
ECG INVESTIGATIONS	n (%)	0	0	0	1 (14.3%)
ELECTROCARDIOGRAM QRS COMPLEX PROLONGED	n (%)	0	0	0	1 (14.3%)
LIVER FUNCTION ANALYSES	n (%)	0	0	1 (0.4%)	0
LIVER FUNCTION TEST ABNORMAL	n (%)	0	0	1 (0.4%)	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.48 mg/kg Tedi (N = 34)	0.48 - 0.72 mg/kg Tedi (N = 4)	0.64 mg/kg Tedi (N = 10)
HEPATOBILIARY DISORDERS	n (%)	0	0	0
CHOLECYSTITIS AND CHOLELITHIASIS	n (%)	0	0	0
CHOLELITHIASIS	n (%)	0	0	0
INFECTIONS AND INFESTATIONS	n (%)	1 (2.9%)	0	0
INFLUENZA VIRAL INFECTIONS	n (%)	0	0	0
INFLUENZA	n (%)	0	0	0
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	n (%)	1 (2.9%)	0	0
BRONCHITIS ACUTE	n (%)	0	0	0
PNEUMONIA	n (%)	1 (2.9%)	0	0
UPPER RESPIRATORY TRACT INFECTIONS	n (%)	0	0	0
CHRONIC SINUSITIS	n (%)	0	0	0
INVESTIGATIONS	n (%)	0	0	0
COAGULATION AND BLEEDING ANALYSES	n (%)	0	0	0
COAGULATION TIME SHORTENED	n (%)	0	0	0
ECG INVESTIGATIONS	n (%)	0	0	0
ELECTROCARDIOGRAM QRS COMPLEX PROLONGED	n (%)	0	0	0
LIVER FUNCTION ANALYSES	n (%)	0	0	0
LIVER FUNCTION TEST ABNORMAL	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 403)	Placebo (N = 239)
HEPATOBILIARY DISORDERS	n (%)	1 (0.2%)	0
CHOLECYSTITIS AND CHOLELITHIASIS	n (%)	1 (0.2%)	0
CHOLELITHIASIS	n (%)	1 (0.2%)	0
INFECTIONS AND INFESTATIONS	n (%)	4 (1.0%)	2 (0.8%)
INFLUENZA VIRAL INFECTIONS	n (%)	1 (0.2%)	0
INFLUENZA	n (%)	1 (0.2%)	0
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	n (%)	3 (0.7%)	1 (0.4%)
BRONCHITIS ACUTE	n (%)	1 (0.2%)	1 (0.4%)
PNEUMONIA	n (%)	2 (0.5%)	0
UPPER RESPIRATORY TRACT INFECTIONS	n (%)	0	1 (0.4%)
CHRONIC SINUSITIS	n (%)	0	1 (0.4%)
INVESTIGATIONS	n (%)	2 (0.5%)	1 (0.4%)
COAGULATION AND BLEEDING ANALYSES	n (%)	0	1 (0.4%)
COAGULATION TIME SHORTENED	n (%)	0	1 (0.4%)
ECG INVESTIGATIONS	n (%)	1 (0.2%)	0
ELECTROCARDIOGRAM QRS COMPLEX PROLONGED	n (%)	1 (0.2%)	0
LIVER FUNCTION ANALYSES	n (%)	1 (0.2%)	0
LIVER FUNCTION TEST ABNORMAL	n (%)	1 (0.2%)	0

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08

Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	0.16 mg/kg Tedi (N = 1)	0.24 mg/kg Tedi (N = 122)	0.32 mg/kg Tedi (N = 225)	0.32 - 0.48 mg/kg Tedi (N = 7)
METABOLISM AND NUTRITION DISORDERS	n (%)	0	0	0	0
SODIUM IMBALANCE	n (%)	0	0	0	0
HYPONATRAEMIA	n (%)	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	n (%)	0	1 (0.8%)	1 (0.4%)	0
LEUKAEMIAS NEC	n (%)	0	1 (0.8%)	0	0
LEUKAEMIA	n (%)	0	1 (0.8%)	0	0
URINARY TRACT NEOPLASMS UNSPECIFIED MALIGNANCY NEC	n (%)	0	0	1 (0.4%)	0
RENAL NEOPLASM	n (%)	0	0	1 (0.4%)	0
NERVOUS SYSTEM DISORDERS	n (%)	0	1 (0.8%)	3 (1.3%)	0
CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR ACCIDENTS	n (%)	0	1 (0.8%)	3 (1.3%)	0
CEREBROVASCULAR ACCIDENT	n (%)	0	1 (0.8%)	2 (0.9%)	0
ISCHAEMIC STROKE	n (%)	0	0	1 (0.4%)	0
SEIZURES AND SEIZURE DISORDERS NEC	n (%)	0	0	1 (0.4%)	0
EPILEPSY	n (%)	0	0	1 (0.4%)	0
TRANSIENT CEREBROVASCULAR EVENTS	n (%)	0	0	0	0
TRANSIENT ISCHAEMIC ATTACK	n (%)	0	0	0	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08 Page 10/18
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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	0.48 mg/kg Tedi (N = 34)	0.48 - 0.72 mg/kg Tedi (N = 4)	0.64 mg/kg Tedi (N = 10)
METABOLISM AND NUTRITION DISORDERS	n (%)	0	0	0
SODIUM IMBALANCE	n (%)	0	0	0
HYPONATRAEMIA	n (%)	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	n (%)	0	0	0
LEUKAEMIAS NEC	n (%)	0	0	0
LEUKAEMIA	n (%)	0	0	0
URINARY TRACT NEOPLASMS UNSPECIFIED MALIGNANCY NEC	n (%)	0	0	0
RENAL NEOPLASM	n (%)	0	0	0
NERVOUS SYSTEM DISORDERS	n (%)	0	0	1 (10.0%)
CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR ACCIDENTS	n (%)	0	0	1 (10.0%)
CEREBROVASCULAR ACCIDENT	n (%)	0	0	0
ISCHAEMIC STROKE	n (%)	0	0	1 (10.0%)
SEIZURES AND SEIZURE DISORDERS NEC	n (%)	0	0	0
EPILEPSY	n (%)	0	0	0
TRANSIENT CEREBROVASCULAR EVENTS	n (%)	0	0	0
TRANSIENT ISCHAEMIC ATTACK	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08 Page 11/18
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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 403)	Placebo (N = 239)
METABOLISM AND NUTRITION DISORDERS	n (%)	0	1 (0.4%)
SODIUM IMBALANCE	n (%)	0	1 (0.4%)
HYPONATRAEMIA	n (%)	0	1 (0.4%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	n (%)	2 (0.5%)	0
LEUKAEMIAS NEC	n (%)	1 (0.2%)	0
LEUKAEMIA	n (%)	1 (0.2%)	0
URINARY TRACT NEOPLASMS UNSPECIFIED MALIGNANCY NEC	n (%)	1 (0.2%)	0
RENAL NEOPLASM	n (%)	1 (0.2%)	0
NERVOUS SYSTEM DISORDERS	n (%)	5 (1.2%)	2 (0.8%)
CENTRAL NERVOUS SYSTEM HAEMORRHAGES AND CEREBROVASCULAR ACCIDENTS	n (%)	5 (1.2%)	1 (0.4%)
CEREBROVASCULAR ACCIDENT	n (%)	3 (0.7%)	1 (0.4%)
ISCHAEMIC STROKE	n (%)	2 (0.5%)	0
SEIZURES AND SEIZURE DISORDERS NEC	n (%)	1 (0.2%)	0
EPILEPSY	n (%)	1 (0.2%)	0
TRANSIENT CEREBROVASCULAR EVENTS	n (%)	0	1 (0.4%)
TRANSIENT ISCHAEMIC ATTACK	n (%)	0	1 (0.4%)

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08 Page 12/18

Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 1)	0.24 mg/kg Tedi (N = 122)	0.32 mg/kg Tedi (N = 225)	0.32 - 0.48 mg/kg Tedi (N = 7)
RENAL AND URINARY DISORDERS	n (%)	0	0	0	0
RENAL FAILURE AND IMPAIRMENT	n (%)	0	0	0	0
RENAL FAILURE ACUTE	n (%)	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	n (%)	0	0	1 (0.4%)	0
PELVIS AND BROAD LIGAMENT DISORDERS NEC	n (%)	0	0	1 (0.4%)	0
PELVIC HAEMATOMA	n (%)	0	0	1 (0.4%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	0	2 (1.6%)	1 (0.4%)	0
BREATHING ABNORMALITIES	n (%)	0	0	0	0
APNOEA	n (%)	0	0	0	0
BRONCHOSPASM AND OBSTRUCTION	n (%)	0	0	0	0
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	n (%)	0	0	0	0
NASAL DISORDERS NEC	n (%)	0	1 (0.8%)	0	0
EPISTAXIS	n (%)	0	1 (0.8%)	0	0
PULMONARY OEDEMAS	n (%)	0	0	1 (0.4%)	0
ACUTE PULMONARY OEDEMA	n (%)	0	0	1 (0.4%)	0
PULMONARY THROMBOTIC AND EMBOLIC CONDITIONS	n (%)	0	1 (0.8%)	0	0
PULMONARY EMBOLISM	n (%)	0	1 (0.8%)	0	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08 Page 13/18
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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.48 mg/kg Tedi (N = 34)	0.48 - 0.72 mg/kg Tedi (N = 4)	0.64 mg/kg Tedi (N = 10)
RENAL AND URINARY DISORDERS	n (%)	0	0	0
RENAL FAILURE AND IMPAIRMENT	n (%)	0	0	0
RENAL FAILURE ACUTE	n (%)	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	n (%)	0	0	0
PELVIS AND BROAD LIGAMENT DISORDERS NEC	n (%)	0	0	0
PELVIC HAEMATOMA	n (%)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	2 (5.9%)	0	0
BREATHING ABNORMALITIES	n (%)	1 (2.9%)	0	0
APNOEA	n (%)	1 (2.9%)	0	0
BRONCHOSPASM AND OBSTRUCTION	n (%)	1 (2.9%)	0	0
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	n (%)	1 (2.9%)	0	0
NASAL DISORDERS NEC	n (%)	0	0	0
EPISTAXIS	n (%)	0	0	0
PULMONARY OEDEMAS	n (%)	0	0	0
ACUTE PULMONARY OEDEMA	n (%)	0	0	0
PULMONARY THROMBOTIC AND EMBOLIC CONDITIONS	n (%)	0	0	0
PULMONARY EMBOLISM	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08 Page 14/18
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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta- tistic	Combined Tedi (N = 403)	Placebo (N = 239)
RENAL AND URINARY DISORDERS	n (%)	0	1 (0.4%)
RENAL FAILURE AND IMPAIRMENT	n (%)	0	1 (0.4%)
RENAL FAILURE ACUTE	n (%)	0	1 (0.4%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	n (%)	1 (0.2%)	0
PELVIS AND BROAD LIGAMENT DISORDERS NEC	n (%)	1 (0.2%)	0
PELVIC HAEMATOMA	n (%)	1 (0.2%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	5 (1.2%)	2 (0.8%)
BREATHING ABNORMALITIES	n (%)	1 (0.2%)	0
APNOEA	n (%)	1 (0.2%)	0
BRONCHOSPASM AND OBSTRUCTION	n (%)	1 (0.2%)	0
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	n (%)	1 (0.2%)	0
NASAL DISORDERS NEC	n (%)	1 (0.2%)	0
EPISTAXIS	n (%)	1 (0.2%)	0
PULMONARY OEDEMAS	n (%)	1 (0.2%)	1 (0.4%)
ACUTE PULMONARY OEDEMA	n (%)	1 (0.2%)	1 (0.4%)
PULMONARY THROMBOTIC AND EMBOLIC CONDITIONS	n (%)	1 (0.2%)	1 (0.4%)
PULMONARY EMBOLISM	n (%)	1 (0.2%)	1 (0.4%)

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08

Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.16 mg/kg Tedi (N = 1)	0.24 mg/kg Tedi (N = 122)	0.32 mg/kg Tedi (N = 225)	0.32 - 0.48 mg/kg Tedi (N = 7)
VASCULAR DISORDERS	n (%)	0	1 (0.8%)	1 (0.4%)	1 (14.3%)
NON-SITE SPECIFIC EMBOLISM AND THROMBOSIS	n (%)	0	0	0	0
THROMBOSIS	n (%)	0	0	0	0
PHLEBITIS NEC	n (%)	0	1 (0.8%)	0	0
PHLEBITIS	n (%)	0	1 (0.8%)	0	0
VASCULAR HYPERTENSIVE DISORDERS NEC	n (%)	0	0	0	0
HYPERTENSION	n (%)	0	0	0	0
VASCULAR HYPOTENSIVE DISORDERS	n (%)	0	0	1 (0.4%)	1 (14.3%)
HYPOTENSION	n (%)	0	0	0	1 (14.3%)
ORTHOSTATIC HYPOTENSION	n (%)	0	0	1 (0.4%)	0

Note(s) Percentages are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08

Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Sta-tistic	0.48 mg/kg Tedi (N = 34)	0.48 - 0.72 mg/kg Tedi (N = 4)	0.64 mg/kg Tedi (N = 10)
VASCULAR DISORDERS	n (%)	1 (2.9%)	0	1 (10.0%)
NON-SITE SPECIFIC EMBOLISM AND THROMBOSIS	n (%)	0	0	0
THROMBOSIS	n (%)	0	0	0
PHLEBITIS NEC	n (%)	0	0	0
PHLEBITIS	n (%)	0	0	0
VASCULAR HYPERTENSIVE DISORDERS NEC	n (%)	0	0	0
HYPERTENSION	n (%)	0	0	0
VASCULAR HYPOTENSIVE DISORDERS	n (%)	1 (2.9%)	0	1 (10.0%)
HYPOTENSION	n (%)	1 (2.9%)	0	1 (10.0%)
ORTHOSTATIC HYPOTENSION	n (%)	0	0	0

Note(s) Percentages based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08 Page 17/18
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Table 2.7.4.7-52 Incidence of TESAEs, Integrated Safety Sample, Female Subgroup - continued
Gender=Female - SAFETY SAMPLE

Primary SOC HLT PT	Statistic	Combined Tedi (N = 403)	Placebo (N = 239)
VASCULAR DISORDERS	n (%)	5 (1.2%)	4 (1.7%)
NON-SITE SPECIFIC EMBOLISM AND THROMBOSIS	n (%)	0	1 (0.4%)
THROMBOSIS	n (%)	0	1 (0.4%)
PHLEBITIS NEC	n (%)	1 (0.2%)	0
PHLEBITIS	n (%)	1 (0.2%)	0
VASCULAR HYPERTENSIVE DISORDERS NEC	n (%)	0	1 (0.4%)
HYPERTENSION	n (%)	0	1 (0.4%)
VASCULAR HYPOTENSIVE DISORDERS	n (%)	4 (1.0%)	2 (0.8%)
HYPOTENSION	n (%)	3 (0.7%)	2 (0.8%)
ORTHOSTATIC HYPOTENSION	n (%)	1 (0.2%)	0

Note(s) Percentages of all other AEs are based on the number of subjects in the Safety Sample.
Each subject is counted at most once within each SOC, HLT and PT. AEs were coded using MedDRA version 5.1.

Source: [Q:\Solvay\TedisamilCTD\Integration\Programs\Tables] AET011M.SAS, Quintiles. Run 19APR2006 17:08 Page 18/18

Appendix 4

RiskMAP Tools

Common tachyarrhythmias

Remember: Treat the patient not the ECG! Look for and treat underlying causes.

Supraventricular tachycardia (SVT)/narrow complex tachycardias

(QRS complex <120 msec)

(1 Large square = 0.2 secs for all ECGs)

Atrial fibrillation (AF)

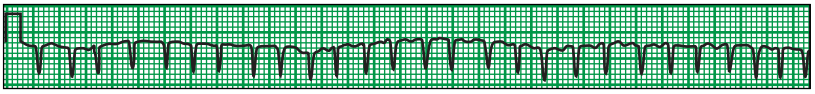
- Rapid, irregular atrial rhythm due to re-entry mechanism.
- Most common sustained arrhythmia.
- Strongly age-dependent; affects >5% of over 75 year-olds.
- Commonly occurs in association with CV disease and mitral valve disease (especially in younger patients), and idiopathic as lone atrial fibrillation in 15% of cases.

Symptoms: Palpitations, fatigue, dyspnea, chest pain, syncope, dizziness.

Signs: Irregular pulse, possibly hypotension and signs of poor perfusion, CHF, embolization.

ECG: Irregular ventricular rate, no true p waves, baseline irregularities.

Example



AF plus Wolff-Parkinson-White (WPW, see next page) is considered a medical emergency.

Atrial flutter

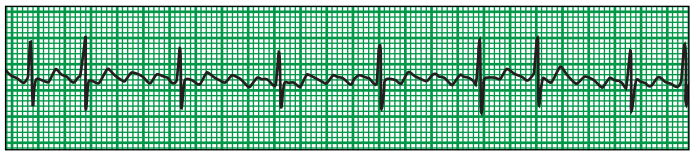
- Rapid, regular atrial rhythm typically due to large re-entrant circuit in the right atrium.
- More common in men, incidence increases with age.
- Can degenerate to AF.

Symptoms: Palpitations, fatigue, dyspnea, chest pain, syncope.

Signs: Cardiac rate often around 150 bpm due to 2:1 AV block, heart beat usually regular, possibly signs of CHF, embolization.

ECG: Flutter waves may produce classic saw tooth baseline, QRS complexes usually normal, atrial rate usually 250-350 bpm, ventricular rate depends on AV nodal conduction - typically 150-220 bpm.

Example



Supraventricular tachycardia (SVT)/narrow complex tachycardias

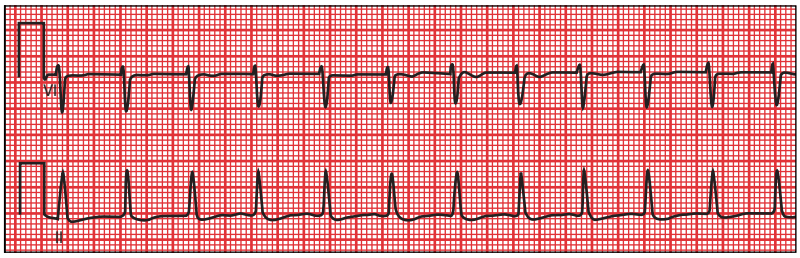
(QRS complex <120 msec) (Continued)

Atrioventricular nodal re-entry tachycardia (AVNRT/AVNT/AVJRT)

- Regular tachycardia due to re-entry through abnormal pathways within/besides the AV node.
- Typically starts in late teens or 20s.
- Usually paroxysmal.

ECG: Narrow QRS, p waves often hidden in QRS, rate typically 160-180 bpm.

Example

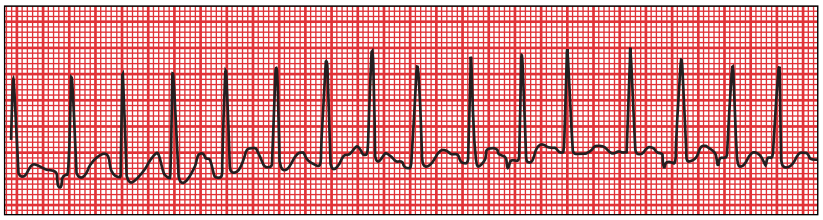


Atrial tachycardias

- Rapid, regular atrial rhythm due to focal autonomic activity (may be multiple) or intra-atrial re-entry.
- Can occur at any age, often associated with atrial disease or chemical toxicity.

ECG: Abnormal p waves, rate 140-240 bpm.

Example

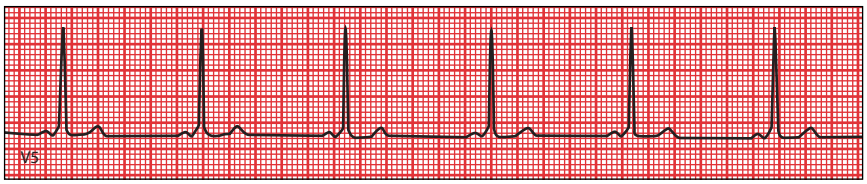


Wolff-Parkinson-White syndrome (WPW)

- Paroxysmal, regular tachycardia due to re-entry AV pathway bypassing the AV node.
- Can occur from infancy onwards, affects 1-3 per 1000 people.
- Due to congenital accessory atrial tissue on the fibrous ring separating the atria and ventricles.

ECG: Resting ECG may show short PR interval, slurred start to QRS (delta wave), narrow QRS; p waves may be hidden in QRS in tachycardia ECG.

Example



AF plus WPW can cause a dangerously fast ventricular rate and is a medical emergency.

Common tachyarrhythmias (Continued)

VT/broad complex tachycardias (QRS >120 msec)

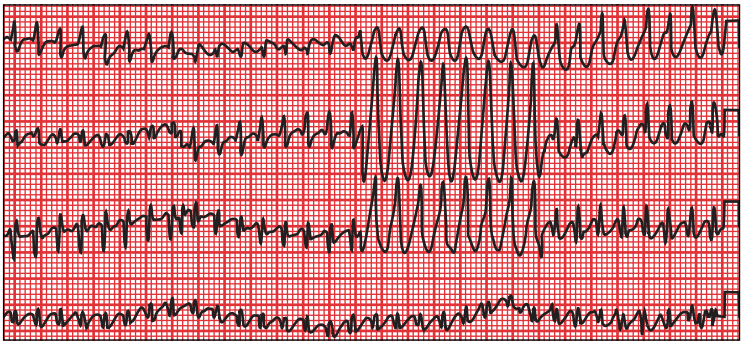
Ventricular tachycardia

- Rapid, regular ventricular rhythm, mainly due to re-entry mechanism.
- Broad complex tachycardia is ventricular tachycardia until proved otherwise.
- Usually associated with established heart disease.

ECG: Rate >120 bpm, broad complex >120 msec, abnormal QRS shape, no p waves, abnormal axis, concordant QRS, possible capture/fusion beats.

Treatment: Follow resuscitation protocol.

Example



Torsades de pointes (TdP)

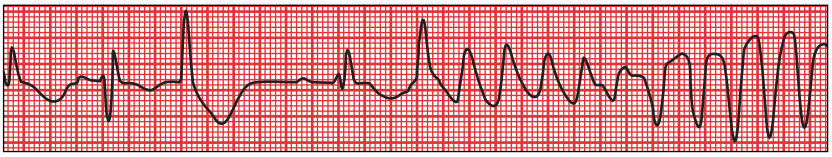
- Can be asymptomatic.
- May develop following administration of I.V. antiarrhythmics.

Symptoms: Recurrent dizziness or syncope.

ECG: Prolonged QT syndrome with broad complex, alternating electrical axis, may start with normal sinus rhythm or with pre-existing ventricular tachycardia.

Treatment: Discontinue predisposing drugs or other agents. Avoid empirical antiarrhythmic drug therapy. Individual paroxysms of TdP are normally self-limiting, but if persistent, cardiac arrest will occur and emergency defibrillation is necessary. Use IV magnesium sulphate (8 mmol over 10-15 min, repeat if necessary) to prevent recurrent paroxysms of tachycardia. If TdP is associated with bradycardia, heart rate should be increased to 90-100 bpm by atrial or ventricular pacing or isoproterenol (isoprenaline) infusion. Hypokalemia should be corrected.

Example



VT/broad complex tachycardias (QRS >120 msec) (Continued)

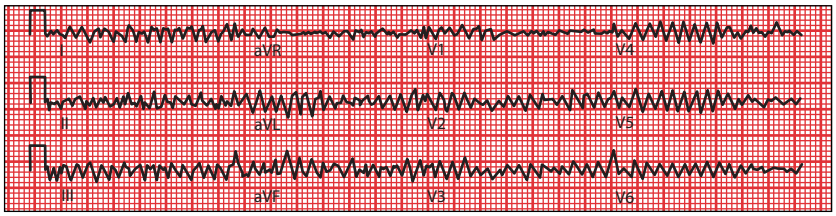
Ventricular fibrillation (VF)

- Rapid, totally unco-ordinated contraction of ventricular myocardial fibres.
- Causes circulatory arrest; unconsciousness develops within 10 to 20 seconds.

ECG: Irregular, chaotic electrical activity.

Treatment: Defibrillation: follow resuscitation protocol.

Example



Prescribing and administration guidelines for Pulzium® (tedisamil sesquifumarate) I.V.

Prescribing information highlights

Therapeutic indication

Pulzium® I.V. solution is indicated for the rapid conversion of atrial fibrillation or atrial flutter of recent onset (3 h to 45 days) to normal sinus rhythm.

Contraindications

Pulzium® is contraindicated in patients with:

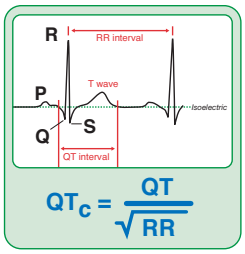
- severe renal impairment (GFR < 30 ml/min)
- known congenital or acquired long QT syndrome.

Appropriate prescribing information will be included for the final distributed version of this tool.

Please see full prescribing information for important safety information.

Visit the Pulzium® website for further information, including an online dose volume calculator (add website address)

Monitoring QT and QTc



Pulzium® can prolong QT and QTc in a dose-dependent manner.

ECG monitoring is therefore advised before, during and for 1.5 hours after treatment.

Caution should be exercised in patients with a pacemaker or bundle branch block.

Class I and Class III antiarrhythmic drugs should not concomitantly be used with Pulzium® due to lack of experience. Before Pulzium® infusion there should be a wash-out period of at least 5 half-lives (3 months for amiodarone) of Class I and other Class III antiarrhythmic agents. Class I and other Class III antiarrhythmics should be withheld for 24 h after start of the Pulzium® infusion.

The potential for pro-arrhythmia may increase with the concomitant administration of Pulzium® with drugs that prolong QT interval, such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, certain antihistamine drugs and systemically administered ketoconazole. Therefore Pulzium® should be used with caution in patients with concomitant medication which prolongs QT interval.

A full list of drugs with a risk of causing torsades de pointes by prolonging QT interval is available at www.torsades.org.

- Use the table below to calculate QTc prior to Pulzium® treatment.
- Acceptable values are in black in the table below.
- Patients with a QTc value **>470 msec** (values in red) are not suitable for Pulzium® treatment.

QT/QTc table for infusion initiation

		QT (ms)											
		360	370	380	390	400	410	420	430	440	450	460	470
HR (bpm)	RR (s)	QTc (ms)											
50	**1.200**	329	338	347	356	365	374	383	393	402	411	420	429
55	**1.091**	345	354	364	373	383	393	402	412	421	431	440	450
60	**1.000**	360	370	380	390	400	410	420	430	440	450	460	470
65	**0.923**	375	385	396	406	416	427	437	448	458	468	479	489
70	**0.857**	389	400	410	421	432	443	454	464	475	486	497	508
75	**0.800**	402	414	425	436	447	458	470	481	492	503	514	525
80	**0.750**	416	427	439	450	462	473	485	497	508	520	531	543
85	**0.706**	428	440	452	464	476	488	500	512	524	536	548	559
90	**0.667**	441	453	465	478	490	502	514	527	539	551	563	576
95	**0.632**	453	466	478	491	503	516	528	541	554	566	579	591
100	**0.600**	465	478	491	503	516	529	542	555	568	581	594	607
105	**0.571**	476	489	503	516	529	542	556	569	582	595	609	622
110	**0.545**	487	501	515	528	542	555	569	582	596	609	623	636
115	**0.522**	498	512	526	540	554	568	581	595	609	623	637	651
120	**0.500**	509	523	537	552	566	580	594	608	622	636	651	665

Values in red: do not prescribe, value above acceptance range.

- Continue to monitor QTc during treatment.
- Discontinue the infusion immediately if the value rises **>550 msec** (values in red).

QT/QTc table for infusion discontinuation

		QT (ms)											
		430	440	450	460	470	480	490	500	510	520	530	540	550
HR (bpm)	RR (s)	QTc (ms)												
50	**1.200**	393	402	411	420	429	438	447	456	466	475	484	493	502
55	**1.091**	412	421	431	440	450	460	469	479	488	498	507	517	527
60	**1.000**	430	440	450	460	470	480	490	500	510	520	530	540	550
65	**0.923**	448	458	468	479	489	500	510	520	531	541	552	562	572
70	**0.857**	464	475	486	497	508	518	529	540	551	562	572	583	594
75	**0.800**	481	492	503	514	525	537	548	559	570	581	593	604	615
80	**0.750**	497	508	520	531	543	554	566	577	589	600	612	624	635
85	**0.706**	512	524	536	548	559	571	583	595	607	619	631	643	655
90	**0.667**	527	539	551	563	576	588	600	612	625	637	649	661	674
95	**0.632**	541	554	566	579	591	604	617	629	642	654	667	679	692
100	**0.600**	555	568	581	594	607	620	633	645	658	671	684	697	710
105	**0.571**	569	582	595	609	622	635	648	661	675	688	701	714	728
110	**0.545**	582	596	609	623	636	650	663	677	691	704	718	731	745
115	**0.522**	595	609	623	637	651	665	678	692	706	720	734	748	761
120	**0.500**	608	622	636	651	665	679	693	707	721	735	750	764	778

Values in red: discontinue infusion immediately.

Prescribing and administration guidelines for Pulzium® (tedisamil sesquifumarate) I.V. (Continued)

Calculating the correct dose volume

- Dose is dependent on **gender**, **height** and **weight**.
- Pulzium® I.V. solution is supplied as a 20 mg/10 ml sterile solution in a 10 ml vial.
- The recommended dose is 0.48 mg/kg in males and 0.32 mg/kg in females.
- The tables below show the Pulzium® **dose volume** (**not** the dose rate) for males and females.
- See the Guide to administration on the next sheet for important information on how to infuse the calculated dose volume.

Dose volume calculator for males

See the table on the reverse side of this sheet.

If the height or weight is in between values shown in the table, take the lower value (e.g. if the height is 165 cm, take 164 cm).

If the height and/or weight are outside the ranges of the table, calculate the dose based on weight and height (see below) and use the lowest dose:

- Weight-based calculation: [(weight in kg) x 0.48 mg/kg] / 2 mg/ml = x ml Pulzium® solution.
- Height-based calculation: [28 x (height in metres)^2 x 0.48 mg/kg] / 2 mg/ml = y ml Pulzium® solution.

Dose volume calculator for females

See the table on the next sheet.

If the height or weight is in between values shown in the table, take the lower value (e.g. if the height is 165 cm, take 164 cm).

If the height and/or weight are outside the ranges of the table, calculate the dose based on weight and height (see below) and use the lowest dose:

- Weight-based calculation: [(weight in kg) x 0.32 mg/kg] / 2 mg/ml = x ml Pulzium® solution.
- Height-based calculation: [28 x (height in metres)^2 x 0.32 mg/kg] / 2 mg/ml = y ml Pulzium® solution.

Pulzium® dose volume calculator - MALES

Pulzium® dose volume of concentrate from ampoule shown in ml.

Height (m or ft'/in")

Weight (kg or lb)

	ft'in":	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"		
lb	kg	m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24	lb	kg
100	45		10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	100	45
105	48		11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	105	48
110	50		12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	110	50
115	52		12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	115	52
120	54		13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	120	54
125	57		13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	125	57
130	59		14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	130	59
135	61		14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	135	61
140	63		15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	140	63
145	66		15.6	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	145	66
150	68		15.6	16.1	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	150	68
155	70		15.6	16.1	16.7	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	155	70
160	73		15.6	16.1	16.7	17.2	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	160	73
165	75		15.6	16.1	16.7	17.2	17.8	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	165	75
170	77		15.6	16.1	16.7	17.2	17.8	18.3	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	170	77
175	79		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	175	79
180	82		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	180	82
185	84		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	185	84
190	86		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	190	86
195	88		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	195	88
200	91		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	200	91
205	93		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	205	93
210	95		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	210	95
215	98		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	215	98
220	100		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	220	100
225	102		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	225	102
230	104		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	230	104
235	107		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	235	107
240	109		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	240	109
245	111		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	245	111
250	113		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.2	27.2	27.2	27.2	27.2	27.2	27.2	27.2	27.2	250	113
255	116		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	27.8	27.8	27.8	27.8	27.8	27.8	27.8	27.8	255	116
260	118		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.3	28.3	28.3	28.3	28.3	28.3	28.3	28.3	260	118
265	120		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	28.8	28.8	28.8	28.8	28.8	28.8	28.8	265	120
270	122		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.4	29.4	29.4	29.4	29.4	29.4	270	122
275	125		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	29.9	29.9	29.9	29.9	29.9	275	125
280	127		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.5	30.5	30.5	30.5	30.5	280	127
285	129		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.6	31.0	31.0	31.0	31.0	285	129
290	132		15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.6	31.3	31.6	31.6	31.6	290	132
	ft'in":	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"		
	m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24		

Pulzium® dose volume calculator - FEMALES

Pulzium® dose volume concentrate from ampoule shown in ml.

Height (m or ft'/in")

Weight (kg or lb)

	ft'in":	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"		
lb	kg	m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24	lb	kg
100	45		7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	100	45
105	48		7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	105	48
110	50		8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	110	50
115	52		8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	115	52
120	54		8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	120	54
125	57		9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	125	57
130	59		9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	130	59
135	61		9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	135	61
140	63		10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	140	63
145	66		10.4	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	145	66
150	68		10.4	10.7	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	150	68
155	70		10.4	10.7	11.1	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	155	70
160	73		10.4	10.7	11.1	11.5	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	160	73
165	75		10.4	10.7	11.1	11.5	11.8	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	165	75
170	77		10.4	10.7	11.1	11.5	11.8	12.2	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	170	77
175	79		10.4	10.7	11.1	11.5	11.8	12.2	12.6	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	175	79
180	82		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	180	82
185	84		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	185	84
190	86		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	190	86
195	88		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	195	88
200	91		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	200	91
205	93		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	205	93
210	95		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	210	95
215	98		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	215	98
220	100		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	220	100
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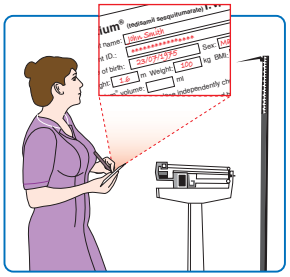
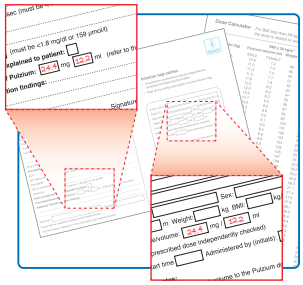
230	104		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	230	104
235	107		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	235	107
240	109		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	240	109
245	111		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	245	111
250	113		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	250	113
255	116		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	255	116
260	118		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	18.9	18.9	18.9	18.9	18.9	18.9	18.9	18.9	260	118
265	120		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.2	19.2	19.2	19.2	19.2	19.2	19.2	265	120
270	122		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.6	19.6	19.6	19.6	19.6	19.6	270	122
275	125		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.0	20.0	20.0	20.0	20.0	275	125
280	127		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.3	20.3	20.3	20.3	20.3	280	127
285	129		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.4	20.7	20.7	20.7	20.7	285	129
290	132		10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.4	20.9	21.0	21.0	21.0	290	132
	ft'in":	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"		
	m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24		

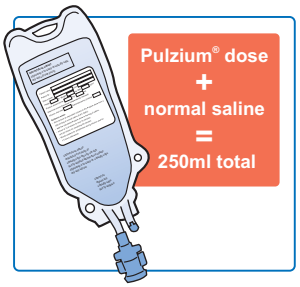
Guide to administration



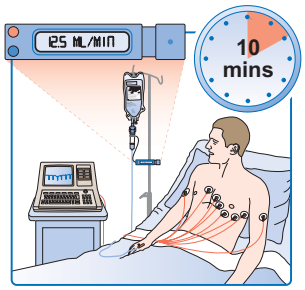
1 Check and record the patient's height, weight and gender on the Pulzium® Infusion Bag Sticker.



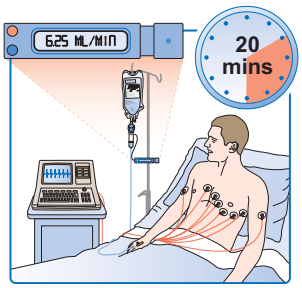
2 Take the appropriate number of Pulzium® vials from the fridge. Use the Dose Calculator opposite to check the drug volume; ensure that this corresponds with the physician prescribed dose, then record on the Sticker.



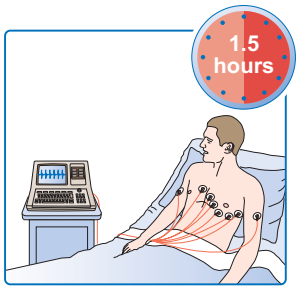
3 Withdraw the volume that you have just calculated from a 250 ml bag of normal saline (0.9% NaCl). Add the drug volume to the saline bag and mix.



4 Infuse at **12.5 ml/min** for the first **10 minutes** (rapid infusion phase). Discontinue if QTc >550 msec.



5 Infuse at **6.25 ml/min** for the following **20 minutes** (slow infusion phase). Discontinue if QTc >550 msec.



6 Monitor the patient for arrhythmias during the infusion and for **1.5 hours** afterwards.

Abbreviations

AF - Atrial fibrillation
AVNT - AV nodal tachycardia
CHF - congestive heart failure
SVT - supraventricular tachycardia
AV - atrioventricular
BPM - beats per minute
ECG - electrocardiogram
VT - ventricular tachycardia
AVJRT - junctional tachycardia
CV - cardiovascular
QTc - corrected QT interval

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Prescribing and administration guidelines for Pulzium®
(tedisamil sesquifumarate) I.V.

Including a guide to common tachyarrhythmias

Contents

Common tachyarrhythmias

Remember: Treat the patient not the ECG!
Look for and treat underlying causes.

Supraventricular tachycardia (SVT)/narrow complex tachycardias (QRS complex <120 msec)

(1 Large square = 0.2 secs for all ECGs)

Atrial fibrillation (AF)

- Rapid, irregular atrial rhythm due to re-entry mechanism.
- Most common sustained arrhythmia.
- Strongly age-dependent; affects >5% of over 75 year-olds.
- Commonly occurs in association with CV disease and mitral valve disease (especially in younger patients), and idiopathic as lone atrial fibrillation in 15% of cases.

Symptoms: Palpitations, fatigue, dyspnea, chest pain, syncope, dizziness.

Signs: Irregular pulse, possibly hypotension and signs of poor perfusion, CHF, embolization.

ECG: Irregular ventricular rate, no true p waves, baseline irregularities.

Example

AF plus Wolff-Parkinson-White (WPW, see following pages) is considered a medical emergency.

Supraventricular tachycardia (SVT)/narrow complex tachycardias (QRS complex <120 msec) (Continued)

Atrial flutter

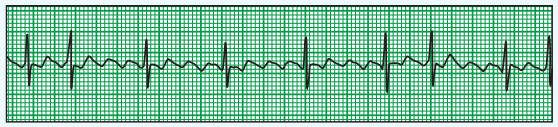
- Rapid, regular atrial rhythm typically due to large re-entrant circuit in the right atrium.
- More common in men, incidence increases with age.
- Can degenerate to AF.

Symptoms: Palpitations, fatigue, dyspnea, chest pain, syncope.

Signs: Cardiac rate often around 150 bpm due to 2:1 AV block, heart beat usually regular, possibly signs of CHF, embolization.

ECG: Flutter waves may produce classic saw tooth baseline, QRS complexes usually normal, atrial rate usually 250-350 bpm, ventricular rate depends on AV nodal conduction - typically 150-220 bpm.

Example



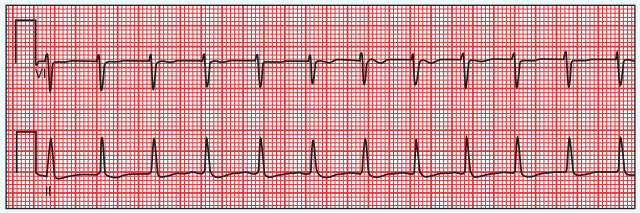
Supraventricular tachycardia (SVT)/narrow complex tachycardias (QRS complex <120 msec) (Continued)

Atrioventricular nodal re-entry tachycardia (AVNRT/AVNT/AVJRT)

- Regular tachycardia due to re-entry through abnormal pathways within/besides the AV node.
- Typically starts in late teens or 20s.
- Usually paroxysmal.

ECG: Narrow QRS, p waves often hidden in QRS, rate typically 160-180 bpm.

Example

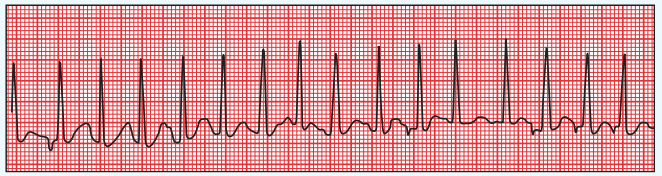


Atrial tachycardias

- Rapid, regular atrial rhythm due to focal autonomic activity (may be multiple) or intra-atrial re-entry.
- Can occur at any age, often associated with atrial disease or chemical toxicity.

ECG: Abnormal p waves, rate 140-240 bpm.

Example



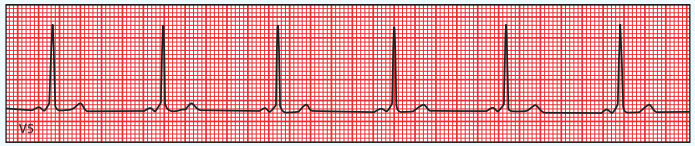
Supraventricular tachycardia (SVT)/narrow complex tachycardias (QRS complex <120 msec) (Continued)

Wolff-Parkinson-White syndrome (WPW)

- Paroxysmal, regular tachycardia due to re-entry AV pathway bypassing the AV node.
- Can occur from infancy onwards, affects 1-3 per 1000 people.
- Due to congenital accessory atrial tissue on the fibrous ring separating the atria and ventricles.

ECG: Resting ECG may show short PR interval, slurred start to QRS (delta wave), narrow QRS; p waves may be hidden in QRS in tachycardia ECG.

Example



AF plus WPW can cause a dangerously fast ventricular rate and is a medical emergency.

VT/broad complex tachycardias (QRS >120 msec)

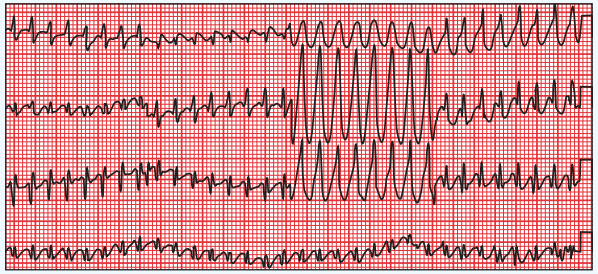
Ventricular tachycardia

- Rapid, regular ventricular rhythm, mainly due to re-entry mechanism.
- Broad complex tachycardia is ventricular tachycardia until proved otherwise.
- Usually associated with established heart disease.

ECG: Rate >120 bpm, broad complex >120 msec, abnormal QRS shape, no p waves, abnormal axis, concordant QRS, possible capture/fusion beats.

Treatment: Follow resuscitation protocol.

Example



VT/broad complex tachycardias (QRS >120 msec) (Continued)

Torsades de pointes (TdP)

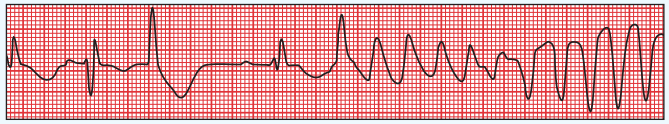
- Can be asymptomatic.
- May develop following administration of I.V. antiarrhythmics.

Symptoms: Recurrent dizziness or syncope.

ECG: Prolonged QT syndrome with broad complex, alternating electrical axis, may start with normal sinus rhythm or with pre-existing ventricular tachycardia.

Treatment: Discontinue predisposing drugs or other agents. Avoid empirical antiarrhythmic drug therapy. Individual paroxysms of TdP are normally self-limiting, but if persistent, cardiac arrest will occur and emergency defibrillation is necessary. Use IV magnesium sulphate (8 mmol over 10-15 min, repeat if necessary) to prevent recurrent paroxysms of tachycardia. If TdP is associated with bradycardia, heart rate should be increased to 90-100 bpm by atrial or ventricular pacing or isoproterenol (isoprenaline) infusion. Hypokalemia should be corrected.

Example



VT/broad complex tachycardias (QRS >120 msec) (Continued)

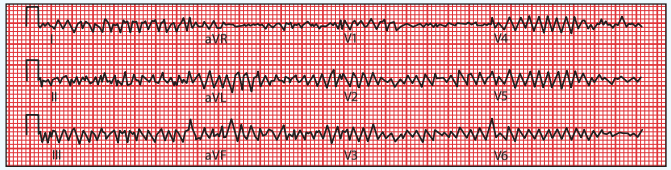
Ventricular fibrillation (VF)

- Rapid, totally unco-ordinated contraction of ventricular myocardial fibres.
- Causes circulatory arrest; unconsciousness develops within 10 to 20 seconds.

ECG: Irregular, chaotic electrical activity.

Treatment: Defibrillation: follow resuscitation protocol.

Example



Prescribing and administration guidelines for Pulzium®

(tedisamil sesquifumarate) I.V.

Prescribing information highlights

Therapeutic indication

Pulzium® is indicated for the rapid conversion of recent onset (3 h to 45 days) atrial fibrillation or atrial flutter to normal sinus rhythm.

Contraindications

Pulzium® is contraindicated in patients with:

- severe renal impairment (GFR < 30 ml/min)
- known congenital or acquired long QT syndrome.

Visit the Pulzium® website for further information, including an online dose volume calculator (add website address)

Appropriate prescribing information will be included for the final distributed version of this tool.

Please see full prescribing information for important safety information.

Monitoring QT and QTc

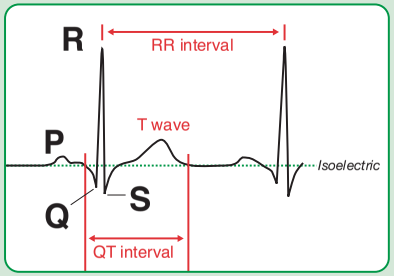
Pulzium® can prolong QT and QTc in a dose-dependent manner.

ECG monitoring is therefore advised before, during and for 1.5 hours after treatment.

Caution should be exercised in patients with a pacemaker or bundle branch block.

Class I and Class III antiarrhythmic drugs should not concomitantly be used with Pulzium® due to lack of experience. Before Pulzium® infusion there should be a wash-out period of at least 5 half-lives (3 months for amiodarone) of Class I and other Class III antiarrhythmic agents. Class I and other Class III antiarrhythmics should be withheld for 24 h after start of the Pulzium® infusion.

The potential for pro-arrhythmia may increase with the concomitant administration of Pulzium® with drugs that prolong QT interval, such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, certain antihistamine drugs and systemically administered ketoconazole. Therefore Pulzium® should be used with caution in patients with concomitant medication which prolongs QT interval.



$$QT_c = \frac{QT}{\sqrt{RR}}$$

A full list of drugs with a risk of causing torsades de pointes by prolonging QT interval is available at www.torsades.org.

Monitoring QT and QTc (Continued)

- Use the table below to calculate QTc prior to Pulzium® treatment.
- Acceptable values are in black in the table below.
- Patients with a QTc value **>470 msec** (values in red) are not suitable for Pulzium® treatment.

QT/QTc table for infusion initiation

		QT (ms)											
		360	370	380	390	400	410	420	430	440	450	460	470
HR (bpm)	RR (s)	QTc (ms)											
50	**1.200**	329	338	347	356	365	374	383	393	402	411	420	429
55	**1.091**	345	354	364	373	383	393	402	412	421	431	440	450
60	**1.000**	360	370	380	390	400	410	420	430	440	450	460	470
65	**0.923**	375	385	396	406	416	427	437	448	458	468	479	489
70	**0.857**	389	400	410	421	432	443	454	464	475	486	497	508
75	**0.800**	402	414	425	436	447	458	470	481	492	503	514	525
80	**0.750**	416	427	439	450	462	473	485	497	508	520	531	543
85	**0.706**	428	440	452	464	476	488	500	512	524	536	548	559
90	**0.667**	441	453	465	478	490	502	514	527	539	551	563	576
95	**0.632**	453	466	478	491	503	516	528	541	554	566	579	591
100	**0.600**	465	478	491	503	516	529	542	555	568	581	594	607
105	**0.571**	476	489	503	516	529	542	556	569	582	595	609	622
110	**0.545**	487	501	515	528	542	555	569	582	596	609	623	636
115	**0.522**	498	512	526	540	554	568	581	595	609	623	637	651
120	**0.500**	509	523	537	552	566	580	594	608	622	636	651	665

Values in red: do not prescribe, value above acceptance range.

Monitoring QT and QTc (Continued)

- Continue to monitor QTc during treatment.
- Discontinue the infusion immediately if the value rises **>550 msec** (values in red).

QT/QTc table for infusion discontinuation

		QT (ms)												
		430	**440**	**450**	**460**	**470**	**480**	**490**	**500**	**510**	**520**	**530**	**540**	**550**
HR (bpm)	**RR (s)**	QTc (ms)												
50	**1.200**	393	402	411	420	429	438	447	456	466	475	484	493	502
55	**1.091**	412	421	431	440	450	460	469	479	488	498	507	517	527
60	**1.000**	430	440	450	460	470	480	490	500	510	520	530	540	550
65	**0.923**	448	458	468	479	489	500	510	520	531	541	552	562	572
70	**0.857**	464	475	486	497	508	518	529	540	551	562	572	583	594
75	**0.800**	481	492	503	514	525	537	548	559	570	581	593	604	615
80	**0.750**	497	508	520	531	543	554	566	577	589	600	612	624	635
85	**0.706**	512	524	536	548	559	571	583	595	607	619	631	643	655
90	**0.667**	527	539	551	563	576	588	600	612	625	637	649	661	674
95	**0.632**	541	554	566	579	591	604	617	629	642	654	667	679	692
100	**0.600**	555	568	581	594	607	620	633	645	658	671	684	697	710
105	**0.571**	569	582	595	609	622	635	648	661	675	688	701	714	728
110	**0.545**	582	596	609	623	636	650	663	677	691	704	718	731	745
115	**0.522**	595	609	623	637	651	665	678	692	706	720	734	748	761
120	**0.500**	608	622	636	651	665	679	693	707	721	735	750	764	778

Values in red: discontinue infusion immediately.

Calculating the correct dose volume

- Dose is dependent on **gender**, **height** and **weight**.
- Pulzium® I.V. solution is supplied as a 20 mg/10 ml sterile solution in a 10 ml vial.
- The recommended dose is 0.48 mg/kg in males and 0.32 mg/kg in females.
- The tables on pages 15 and 16 show the Pulzium® **dose volume** (**not** the dose rate) for males and females.
- See the Guide to administration on page 18 for important information on how to infuse the calculated dose volume.

Dose volume calculator for males

If the height or weight is in between values shown in the table, take the lower value (e.g. if the height is 165 cm, take 164 cm).

If the height and/or weight are outside the ranges of the table, calculate the dose based on weight and height (see fold-out) and use the lowest dose:

- Weight-based calculation:
  [(weight in kg) x 0.48 mg/kg] / 2 mg/ml = x ml Pulzium® solution.
- Height-based calculation:
  [28 x (height in metres)^2 x 0.48 mg/kg] / 2 mg/ml = y ml Pulzium® solution.

MALE

Pulzium® dose volume calculator - MALES

Pulzium® dose volume of concentrate from ampoule shown in ml.

Height (m or ft/in")

Weight (kg or lb)

ft'in":	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"		
lb kg m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24	lb	kg
100 45	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	100	45
105 48	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	105	48
110 50	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	110	50
115 52	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	115	52
120 54	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	120	54
125 57	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	125	57
130 59	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	130	59
135 61	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	135	61
140 63	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	140	63
145 66	15.6	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	145	66
150 68	15.6	16.1	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	150	68
155 70	15.6	16.1	16.7	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	155	70
160 73	15.6	16.1	16.7	17.2	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	160	73
165 75	15.6	16.1	16.7	17.2	17.8	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	165	75
170 77	15.6	16.1	16.7	17.2	17.8	18.3	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	170	77
175 79	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	175	79
180 82	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	180	82
185 84	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	185	84
190 86	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	190	86
195 88	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	195	88
200 91	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	200	91
205 93	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	205	93
210 95	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	210	95
215 98	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	215	98
220 100	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	220	100
225 102	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	225	102
230 104	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	230	104
235 107	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	235	107
240 109	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	240	109
245 111	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	245	111
250 113	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.2	27.2	27.2	27.2	27.2	27.2	27.2	27.2	27.2	250	113
255 116	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	27.8	27.8	27.8	27.8	27.8	27.8	27.8	27.8	255	116
260 118	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.3	28.3	28.3	28.3	28.3	28.3	28.3	28.3	260	118
265 120	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	28.8	28.8	28.8	28.8	28.8	28.8	28.8	265	120
270 122	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.4	29.4	29.4	29.4	29.4	29.4	270	122
275 125	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	29.9	29.9	29.9	29.9	29.9	275	125
280 127	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.5	30.5	30.5	30.5	30.5	280	127
285 129	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.6	31.0	31.0	31.0	31.0	285	129
290 132	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.6	31.3	31.6	31.6	31.6	290	132
ft'in":	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"		
m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24		

Pulzium® dose volume calculator - FEMALES Pulzium® dose volume of concentrate from ampoule shown in ml.

Height (m or ft/in')

Weight (kg or lb)

ft/in':	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"	
lb kg m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24	lb kg
100 45	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	100 45
105 48	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	105 48
110 50	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	110 50
115 52	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	115 52
120 54	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	120 54
125 57	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	125 57
130 59	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	130 59
135 61	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	135 61
140 63	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	140 63
145 66	10.4	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	145 66
150 68	10.4	10.7	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	150 68
155 70	10.4	10.7	11.1	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	155 70
160 73	10.4	10.7	11.1	11.5	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	160 73
165 75	10.4	10.7	11.1	11.5	11.8	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	165 75
170 77	10.4	10.7	11.1	11.5	11.8	12.2	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	170 77
175 79	10.4	10.7	11.1	11.5	11.8	12.2	12.6	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	175 79
180 82	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	180 82
185 84	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	185 84
190 86	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	190 86
195 88	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	195 88
200 91	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	200 91
205 93	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	205 93
210 95	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	210 95
215 98	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	215 98
220 100	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	220 100
225 102	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	225 102
230 104	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	230 104
235 107	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	235 107
240 109	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	240 109
245 111	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	245 111
250 113	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	250 113
255 116	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	255 116
260 118	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	18.9	18.9	18.9	18.9	18.9	18.9	18.9	18.9	260 118
265 120	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.2	19.2	19.2	19.2	19.2	19.2	19.2	265 120
270 122	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.6	19.6	19.6	19.6	19.6	19.6	270 122
275 125	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.0	20.0	20.0	20.0	20.0	275 125
280 127	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.3	20.3	20.3	20.3	20.3	280 127
285 129	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.4	20.7	20.7	20.7	20.7	285 129
290 132	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.4	20.9	21.0	21.0	21.0	290 132
ft/in':	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"	
m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24	

Dose volume calculator for females

If the height or weight is in between values shown in the table, take the lower value (e.g. if the height is 165 cm, take 164 cm).

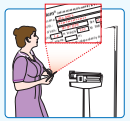
If the height and/or weight are outside the ranges of the table, calculate the dose based on weight and height (see fold-out) and use the lowest dose:

- Weight-based calculation:
  [(weight in kg) x 0.32 mg/kg] / 2 mg/ml = x ml Pulzium® solution
- Height-based calculation:
  [28 x (height in metres)^2 x 0.32 mg/kg] / 2 mg/ml = y ml Pulzium® solution.

FEMALE

Guide to administration

1

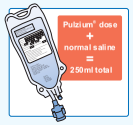


Check and record the patient's height, weight and gender on the Pulzium® Infusion Bag Sticker.

2

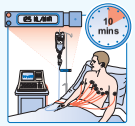
Take the appropriate number of Pulzium® vials from the fridge. Use the Dose Calculator to check the drug volume; ensure that this corresponds with the physician prescribed dose, then record on the Sticker.

3



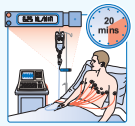
Withdraw the volume that you have just calculated from a 250 ml bag of normal saline (0.9% NaCl). Add the drug volume to the saline bag and mix.

4



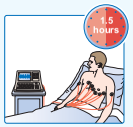
Infuse at **12.5 ml/min** for the first **10 minutes** (rapid infusion phase). Discontinue if QTc >550 msec.

5



Infuse at **6.25 ml/min** for the following **20 minutes** (slow infusion phase). Discontinue if QTc >550 msec.

6



Monitor the patient for arrhythmias during the infusion and for **1.5 hours** afterwards.

Abbreviations

AF - Atrial fibrillation
AV - atrioventricular
AVJRT - junctional tachycardia
AVNT - AV nodal tachycardia
BPM - beats per minute
CV - cardiovascular
CHF - congestive heart failure
ECG - electrocardiogram
QTc - corrected QT interval
SVT - supraventricular tachycardia
VT - ventricular tachycardia

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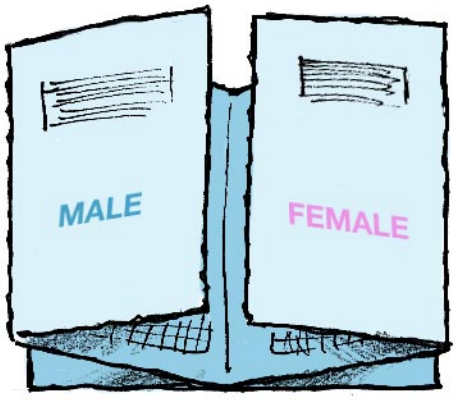
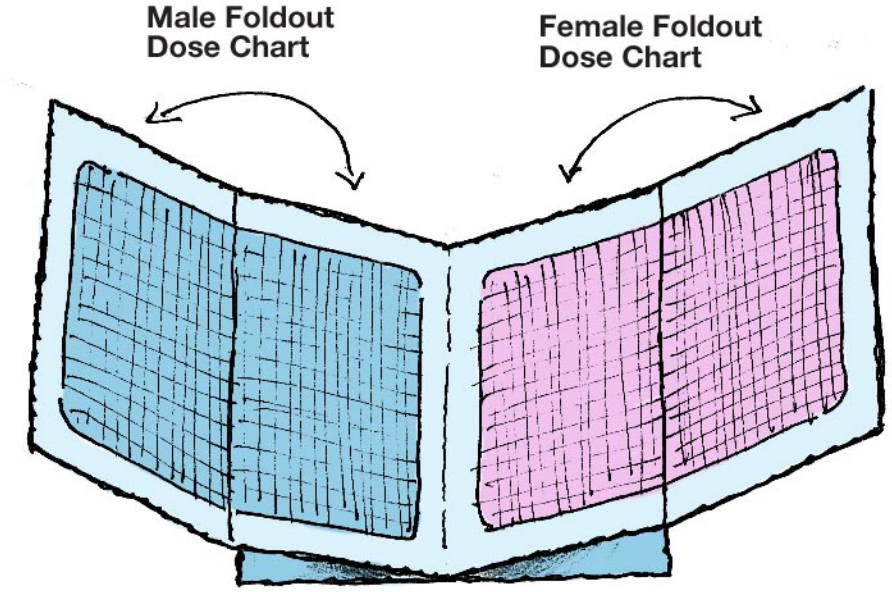
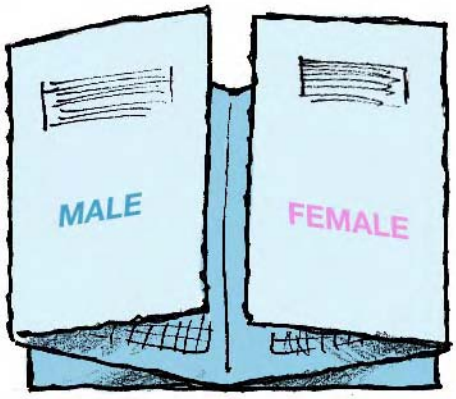
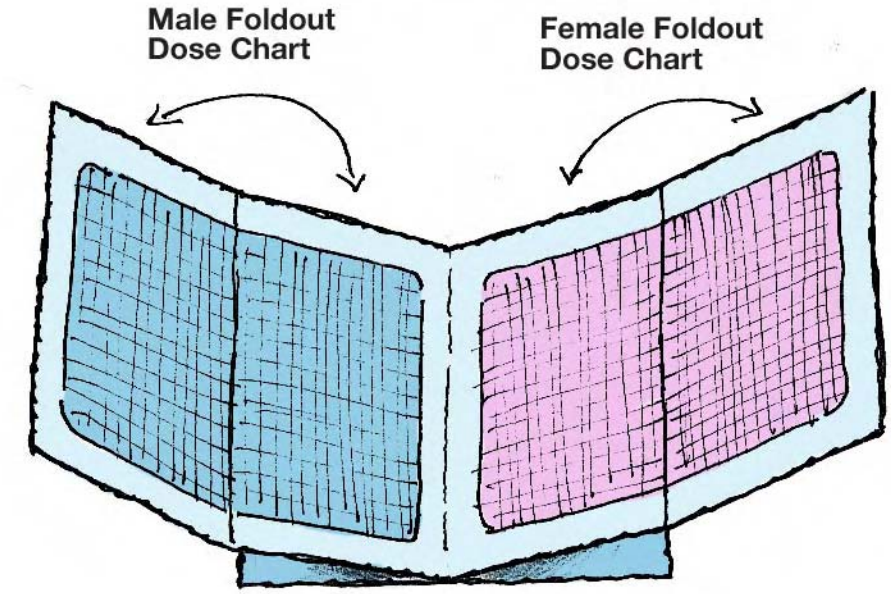
A6 Pocket Book layout for fold-out pages (US)





A6 Pocket Book layout for fold-out pages (US)





Pulzium® (tedisamil sesquifumarate) I.V. prescribing checklist

See the full prescribing information for important safety information.

Patient name: _____

_____

Gender: _____

Height: _____

Weight: _____

Has the patient been diagnosed with **atrial fibrillation** or **atrial flutter** (and not any other form of arrhythmia)?

If yes, PROCEED

Was the onset between **3 hours** and **45 days** ago?

If yes, PROCEED

WARNING: If any of the following apply to your patient, do not prescribe Pulzium®

Known hypersensitivity to tedisamil/product excipients	Known congenital or acquired long QT syndrome	Severe renal impairment (GFR < 30 ml/min*)	Left atrial thrombus	Inadequate anticoagulation (if onset > 2 days ago)
DISCONTINUE	**DISCONTINUE** QTc: _____	**DISCONTINUE** GFR: _____	**DISCONTINUE**	**DISCONTINUE** INR: _____

* Measure GFR from creatinine level using Cockroft-Gault equation or similar

KEY PRECAUTIONARY CONDITIONS: please tick any that apply to your patient and proceed with caution

Conditions/drugs affecting electrolytes (e.g. diarrhea, non-potassium-sparing diuretics)	Drugs causing QT prolongation (e.g. phenothiazines, tricyclic antidepressants); or recent antiarrhythmics	Previous history of long QTc/TdP/bradycardia	Hypertension	Hypotension
Serum potassium: _____ ☐ Serum magnesium: _____ ☐	☐	☐	☐	☐

Physician name: _____

Signature: _____

Date: DD / MM / YYYY _____

CALCULATE volume of Pulzium® required, based on patient's height, weight and gender (see dose volume calculation charts)

Prescribed Pulzium® dose volume: _____ ml

MONITOR the patient before, during and for 1.5 hours after treatment (including QTc value)

Solvay Pharmaceuticals

SOLVAY

Infusion bag sticker

- A healthcare professional should independently complete the following information.
- Peel off the sticker and attach it to the infusion bag.

Pulzium® (tedisamil sesquifumarate) I.V.

Patient name:

Patient ID.:

Height: m / ft', in" (circle the units)

Weight: kg / lbs (circle the units)

Sex:

Pulzium® volume: ml

(Check your calculated dose against the prescriber's calculation)

Infusion start time: HH : MM

Infusion stop time: HH : MM

Guidance notes:

- First remove the calculated equivalent volume (see prescribing information) to the Pulzium® dose from a 250 ml bag of normal saline (0.9% NaCl).
- Add the calculated Pulzium® volume to the saline bag. Initials
- Infuse at 12.5 ml/min for first 10 minutes. Initials
- Infuse at 6.25 ml/min for remaining 20 minutes. Initials
- Monitor patient for arrhythmias during infusion and for 1.5 hours afterwards.

Visit the Pulzium® website for more information, including an online dose calculator

(Add website address)

Common tachyarrhythmias

Supraventricular tachycardia (SVT)/narrow complex tachycardias (QRS complex <120 msec)

(1 Large square = 0.2 secs for all ECGs)

Atrial fibrillation (AF)

- Rapid, irregular atrial rhythm due to re-entry mechanism.
- Most common sustained arrhythmia.
- Strongly age-dependent; affects >5% of over 75 year-olds.
- Commonly occurs in association with CV disease and mitral valve disease (especially in younger patients), and idiopathic as lone atrial fibrillation in 15% of cases.

Symptoms: Palpitations, fatigue, dyspnea, chest pain, syncope, dizziness.
Signs: Irregular pulse, possibly hypotension and signs of poor perfusion, CHF, embolization.

ECG: Irregular ventricular rate, no true p waves, baseline irregularities.

Example

AF plus Wolff-Parkinson-White (WPW, see opposite) is considered a medical emergency.

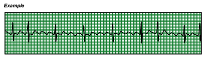
Atrial flutter

- Rapid, regular atrial rhythm typically due to large re-entrant circuit in the right atrium.
- More common in men, incidence increases with age.
- Can degenerate to AF.

Symptoms: Palpitations, fatigue, dyspnea, chest pain, syncope.
Signs: Cardiac rate often around 150 bpm due to 2:1 AV block, heart beat usually regular, possibly signs of CHF, embolization.

ECG: Flutter waves may produce classic saw tooth baseline, QRS complexes usually normal, atrial rate usually 250-350 bpm, ventricular rate depends on AV nodal conduction - typically 150-220 bpm.

Example



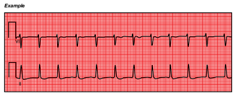
Atrioventricular nodal re-entry tachycardia

(AVNRT/AVNT/AVJRT)

- Regular tachycardia due to re-entry through abnormal pathways within/besides the AV node.
- Typically starts in late teens or 20s.
- Usually paroxysmal.

ECG: Narrow QRS, p waves often hidden in QRS, rate typically 160-180 bpm.

Example

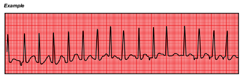


Atrial tachycardias

- Rapid, regular atrial rhythm due to focal autonomic activity (may be multiple) or intra-atrial re-entry.
- Can occur at any age, often associated with atrial disease or chemical toxicity.

ECG: Abnormal p waves, rate 140-240 bpm.

Example

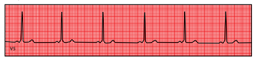


Wolff-Parkinson-White syndrome (WPW)

- Paroxysmal, regular tachycardia due to re-entry AV pathway bypassing the AV node.
- Can occur from infancy onwards, affects 1-3 per 1000 people.
- Due to congenital accessory atrial tissue on the fibrous ring separating the atria and ventricles.

ECG: Resting ECG may show short PR interval, slurred start to QRS (delta wave), narrow QRS; p waves may be hidden in QRS in tachycardia ECG.

Example



AF plus WPW can cause a dangerously fast ventricular rate and is a medical emergency.

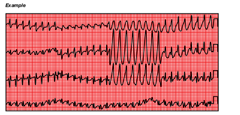
VT/broad complex tachycardias (QRS >120 msec)

Ventricular tachycardia

- Rapid, regular ventricular rhythm, mainly due to re-entry mechanism.
- Broad complex tachycardia is ventricular tachycardia until proved otherwise.
- Usually associated with established heart disease.

ECG: Rate >120 bpm, broad complex >120 msec, abnormal QRS shape, no p waves, abnormal axis, concordant QRS, possible capture/fusion beats.
Treatment: Follow resuscitation protocol.

Example



Torsades de pointes (TdP)

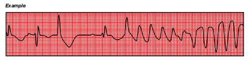
- Can be asymptomatic.
- ~~May develop following administration of I.V. antiarrhythmics.~~

Symptoms: Recurrent dizziness or syncope.

ECG: Prolonged QT syndrome with broad complex, alternating electrical axis, may start with normal sinus rhythm or with pre-existing ventricular tachycardia.

Treatment: Discontinue predisposing drugs or other agents. Avoid empirical antiarrhythmic drug therapy. Individual paroxysms of TdP are normally self-limiting, but if persistent, cardiac arrest will occur and emergency defibrillation is necessary. Use IV magnesium sulphate (8 mmol over 10-15 min, repeat if necessary) to prevent recurrent paroxysms of tachycardia. If TdP is associated with bradycardia, heart rate should be increased to 90-100 bpm by atrial or ventricular pacing or isoproterenol (isoprenaline) infusion. Hypokalemia should be corrected.

Example



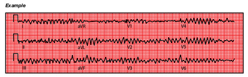
Ventricular fibrillation (VF)

- Rapid, totally unco-ordinated contraction of ventricular myocardial fibres.
- Causes circulatory arrest; unconsciousness develops within 10 to 20 seconds.

ECG: Irregular, chaotic electrical activity.

Treatment: Defibrillation: follow resuscitation protocol.

Example



Remember:
Treat the patient not the ECG!
Look for and treat underlying causes.

Prescribing information highlights

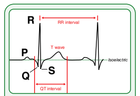
Therapeutic indication
Pulzium is indicated for the rapid conversion of recent onset (3 h to 45 days) atrial fibrillation or atrial flutter to normal sinus rhythm.

Contraindications
Pulzium is contraindicated in patients with:
- severe renal impairment (GFR < 30 ml/min)
- known congenital or acquired long QT syndrome.

Appropriate prescribing information will be included for the final distributed version of this tool.

Prescribing and administration guidelines for Pulzium® (tedisamil sesquifumarate) I.V.

Monitoring QT and QTc



$$QT_c = \frac{QT}{\sqrt{RR}}$$

Pulzium® can prolong QT and QTc in a dose-dependent manner.

ECG monitoring is therefore advised before, during and for 1.5 hours after treatment.

Caution should be exercised in patients with a pacemaker or bundle branch block.

Class I and Class III antiarrhythmic drugs should not concomitantly be used with Pulzium® due to lack of experience. Before Pulzium® infusion there should be a wash-out period of at least 5 half-lives (3 months for amiodarone) of Class I and other Class III antiarrhythmic agents. Class I and other Class III antiarrhythmics should be withheld for 24 h after start of the Pulzium® infusion.

The potential for pro-arrhythmia may increase with the concomitant administration of Pulzium® with drugs that prolong QT interval, such as phenothiazines, tricyclic antidepressants, tetracyclic antidepressants, certain antihistamine drugs and systemically administered ketoconazole. Therefore Pulzium® should be used with caution in patients with concomitant medication which prolongs QT interval.
A full list of drugs with a risk of causing torsades de pointes by prolonging QT interval is available at www.torsades.org.

- The table below shows how to calculate QTc prior to Pulzium® treatment.
- Acceptable values are in black in the table below.
- Patients with a QTc value **>470 msec** (values in red) are not suitable for Pulzium® treatment.

QT/QTc table for infusion initiation

HR (bpm)	RR (s)	QT (ms) 360	370	380	390	400	410	420	430	440	450	460	470
		QTc (ms)											
50	**1.200**	329	338	347	356	365	374	383	393	402	411	420	429
55	**1.091**	345	354	364	373	383	393	402	412	421	431	440	450
60	**1.000**	360	370	380	390	400	410	420	430	440	450	460	470
65	**0.923**	375	385	396	406	416	427	437	448	458	468	479	489
70	**0.857**	389	400	410	421	432	443	454	464	475	486	497	508
75	**0.800**	402	414	425	436	447	458	470	481	492	503	514	525
80	**0.750**	416	427	439	450	462	473	485	497	508	520	531	543
85	**0.706**	428	440	452	464	476	488	500	512	524	536	548	559
90	**0.667**	441	453	465	478	490	502	514	527	539	551	563	576
95	**0.632**	453	466	478	491	503	516	528	541	554	566	579	591
100	**0.600**	465	478	491	503	516	529	542	555	568	581	594	607
105	**0.571**	476	489	503	516	529	542	556	569	582	595	609	622
110	**0.545**	487	501	515	528	542	555	569	582	596	609	623	636
115	**0.522**	498	512	526	540	554	568	581	595	609	623	637	651
120	**0.500**	509	523	537	552	566	580	594	608	622	636	651	665

Values in red: do not prescribe, value above acceptance range.

- Continue to monitor QTc during treatment.
- Discontinue the infusion immediately if the value rises **>550 msec** (values in red).

QT/QTc table for infusion discontinuation

HR (bpm)	RR (s)	QT (ms) 430	440	450	460	470	480	490	500	510	520	530	540	550
		QTc (ms)												
50	**1.200**	393	402	411	420	429	438	447	456	466	475	484	493	502
55	**1.091**	412	421	431	440	450	460	469	479	488	498	507	517	527
60	**1.000**	430	440	450	460	470	480	490	500	510	520	530	540	550
65	**0.923**	448	458	468	479	489	500	510	520	531	541	552	562	572
70	**0.857**	464	475	486	497	508	518	529	540	551	562	572	583	594
75	**0.800**	481	492	503	514	525	537	548	559	570	581	593	604	615
80	**0.750**	497	508	520	531	543	554	566	577	589	600	612	624	635
85	**0.706**	512	524	536	548	559	571	583	595	607	619	631	643	655
90	**0.667**	527	539	551	563	576	588	600	612	625	637	649	661	674
95	**0.632**	541	554	566	579	591	604	617	629	642	654	667	679	692
100	**0.600**	555	568	581	594	607	620	633	645	658	671	684	697	710
105	**0.571**	569	582	595	609	622	635	648	661	675	688	701	714	728
110	**0.545**	582	596	609	623	636	650	663	677	691	704	718	731	745
115	**0.522**	595	609	623	637	651	665	678	692	706	720	734	748	761
120	**0.500**	608	622	636	651	665	679	693	707	721	735	750	764	778

Values in red: discontinue infusion immediately.

Calculating the correct dose volume

- Dose is dependent on **gender**, **height** and **weight**.
- Pulzium® I.V. solution is supplied as a 20 mg/10 ml sterile solution in a 10 ml vial.
- The recommended dose is 0.48 mg/kg in males and 0.32 mg/kg in females.
- The tables below show the Pulzium® **dose volume** (<u>not</u> the dose rate) for males and females.
- See the Guide to administration opposite for important information on how to infuse the calculated dose volume.

Pulzium® dose volume calculator - MALES

Pulzium® dose volume of concentrate from ampoule shown in ml.

Weight (kg or lb) / Height (m or ft'/in")

lb	kg	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"	lb	kg
	m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24		
100	45	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	100	45
105	48	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	105	48
110	50	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	110	50
115	52	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	115	52
120	54	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	120	54
125	57	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	125	57
130	59	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	130	59
135	61	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	14.7	135	61
140	63	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	140	63
145	66	15.6	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	15.8	145	66
150	68	15.6	16.1	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	150	68
155	70	15.6	16.1	16.7	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	16.9	155	70
160	73	15.6	16.1	16.7	17.2	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	160	73
165	75	15.6	16.1	16.7	17.2	17.8	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	165	75
170	77	15.6	16.1	16.7	17.2	17.8	18.3	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	170	77
175	79	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	175	79
180	82	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	19.6	180	82
185	84	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	20.1	185	84
190	86	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	20.7	190	86
195	88	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	21.2	195	88
200	91	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	200	91
205	93	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	22.3	205	93
210	95	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	22.9	210	95
215	98	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4	215	98
220	100	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	23.9	220	100
225	102	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	225	102
230	104	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	230	104
235	107	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6	235	107
240	109	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	26.1	240	109
245	111	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	26.7	245	111
250	113	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.2	27.2	27.2	27.2	27.2	27.2	27.2	27.2	27.2	250	113
255	116	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	27.8	27.8	27.8	27.8	27.8	27.8	27.8	27.8	255	116
260	118	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.3	28.3	28.3	28.3	28.3	28.3	28.3	28.3	260	118
265	120	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	28.8	28.8	28.8	28.8	28.8	28.8	28.8	265	120
270	122	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.4	29.4	29.4	29.4	29.4	29.4	270	122
275	125	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	29.9	29.9	29.9	29.9	29.9	275	125
280	127	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.5	30.5	30.5	30.5	30.5	280	127
285	129	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.6	31.0	31.0	31.0	31.0	285	129
290	132	15.6	16.1	16.7	17.2	17.8	18.3	18.9	19.5	20.0	20.7	21.2	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.4	27.1	27.7	28.4	29.2	29.9	30.6	31.3	31.6	31.6	31.6	290	132
	ft'in":	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"		
	m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24		

- If the height or weight is in between values shown in the table, take the lower value (e.g. if the height is 165 cm, take 164 cm).
- If the height and/or weight are outside the ranges of the table, calculate the dose based on weight and height (see below) and use the lowest dose:
  - Weight-based calculation: [(weight in kg) x 0.48 mg/kg] / 2 mg/ml = x ml Pulzium® solution.
  - Height-based calculation: [28 x (height in metres)^2 x 0.48 mg/kg] / 2 mg/ml = y ml Pulzium® solution.

Pulzium® dose volume calculator - FEMALES

Pulzium® dose volume of concentrate from ampoule shown in ml.

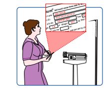
Weight (kg or lb) / Height (m or ft'/in")

lb	kg	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"	lb	kg
	m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24		
100	45	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	100	45
105	48	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	7.6	105	48
110	50	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	110	50
115	52	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	115	52
120	54	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	8.7	120	54
125	57	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	9.1	125	57
130	59	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	9.4	130	59
135	61	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	9.8	135	61
140	63	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2	140	63
145	66	10.4	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	145	66
150	68	10.4	10.7	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9	150	68
155	70	10.4	10.7	11.1	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	155	70
160	73	10.4	10.7	11.1	11.5	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	11.6	160	73
165	75	10.4	10.7	11.1	11.5	11.8	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	165	75
170	77	10.4	10.7	11.1	11.5	11.8	12.2	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	12.3	170	77
175	79	10.4	10.7	11.1	11.5	11.8	12.2	12.6	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	12.7	175	79
180	82	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	13.1	180	82
185	84	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	185	84
190	86	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	13.8	190	86
195	88	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	14.2	195	88
200	91	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	200	91
205	93	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	205	93
210	95	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2	210	95
215	98	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	215	98
220	100	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	220	100
225	102	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	225	102
230	104	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7	230	104
235	107	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	17.1	235	107
240	109	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	17.4	240	109
245	111	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	17.8	245	111
250	113	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	250	113
255	116	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	255	116
260	118	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	18.9	18.9	18.9	18.9	18.9	18.9	18.9	18.9	260	118
265	120	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.2	19.2	19.2	19.2	19.2	19.2	19.2	265	120
270	122	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.6	19.6	19.6	19.6	19.6	19.6	270	122
275	125	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.0	20.0	20.0	20.0	20.0	275	125
280	127	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.3	20.3	20.3	20.3	20.3	280	127
285	129	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.4	20.7	20.7	20.7	20.7	285	129
290	132	10.4	10.7	11.1	11.5	11.8	12.2	12.6	13.0	13.4	13.8	14.2	14.6	15.0	15.4	15.8	16.3	16.7	17.1	17.6	18.0	18.5	19.0	19.4	19.9	20.4	20.9	21.0	21.0	21.0	290	132
	ft'in":	5'	5'1"	5'2"	5'3"	5'4"	5'5"	5'6"	5'7"	5'8"	5'9"	5'10"	5'11"	6'	6'1"	6'2"	6'3"	6'4"	6'5"	6'6"	6'7"	6'8"	6'9"	6'10"	6'11"	7'	7'1"	7'2"	7'3"	7'4"		
	m:	1.52	1.55	1.57	1.60	1.63	1.65	1.68	1.70	1.73	1.75	1.78	1.80	1.83	1.85	1.88	1.91	1.93	1.96	1.98	2.01	2.03	2.06	2.08	2.11	2.13	2.16	2.18	2.21	2.24		

- If the height or weight is in between values shown in the table, take the lower value (e.g. if the height is 165 cm, take 164 cm).
- If the height and/or weight are outside the ranges of the table, calculate the dose based on weight and height (see below) and use the lowest dose:
  - Weight-based calculation: [(weight in kg) x 0.32 mg/kg] / 2 mg/ml = x ml Pulzium® solution.
  - Height-based calculation: [28 x (height in metres)^2 x 0.32 mg/kg] / 2 mg/ml = y ml Pulzium® solution.

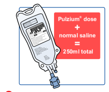
Solvay Pharmaceuticals

Guide to administration

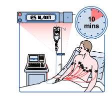


1 Check and record the patient's height, weight and gender on the Pulzium® Infusion Bag Sticker.

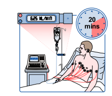
2 Take the appropriate number of Pulzium® vials from the fridge. Use the Dose Calculator opposite to check the drug volume; ensure that this corresponds with the physician prescribed dose, then record on the Sticker.



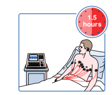
3 Withdraw the volume that you have just calculated from a 250 ml bag of normal saline (0.9% NaCl). Add the drug volume to the saline bag and mix.



4 Infuse at **12.5 ml/min** for the first **10 minutes** (rapid infusion phase). Discontinue if QTc >550 msec.



5 Infuse at **6.25 ml/min** for the following **20 minutes** (slow infusion phase). Discontinue if QTc >550 msec.



6 Monitor the patient for arrhythmias during the infusion and for **1.5 hours** afterwards.

Visit the Pulzium® website for further information, including an online dose volume calculator (add website address)

Please see full prescribing information for important safety information.

Abbreviations

AF - Atrial fibrillation, AV - atrioventricular, AVJRT - junctional tachycardia, AVNT - AV nodal tachycardia, BPM - beats per minute, CV - cardiovascular, CHF - congestive heart failure, ECG - electrocardiogram, QTc - corrected QT interval, SVT - supraventricular tachycardia, VT - ventricular tachycardia