Phase II –III study – Internal Report MPF/H 9406

Title of Study: Double-blind, randomized, placebo-controlled dose finding study of SR propafenone in symptomatic ventricular arrhythmia

Objective
Comparison of the anti-arrhythmic efficacy, tolerability and kinetics of three different dosages of propafenone SR formulation against placebo and against each other in patients with symptomatic ventricular arrhythmias and/or ventricular arrhythmia warranting treatment.

Study design and Methodology
This was a single center, double-blind, parallel group study with a 3 to 5 day placebo run-in period.

The following tests were carried out
- Holter ECG recordings,
- 12 lead resting ECGs,
- Laboratory evaluations,
- Right heart catheterizations,
- Radionuclide ventriculography.

Duration of double-blind treatment period was 5-10 days

Number of patients: For efficacy a total of 144 evaluable patients were randomized to 4 treatment arms of 36 patients each: 225 mg 325mg 425 mg bid and placebo. For safety profile, a total of 187 patients were evaluated. For intent-to-treat population a total of 169 and per protocol population a total of 139 patients were evaluated.

Study dates: spanned over 1.25 years from November 29, 1991 to February 18, 1993

Study Center: 12 centers in Germany

Inclusion criteria
- Male or female in - patients
- Ages between 18 and 70 years
- Patients must have ventricular arrhythmia warranting treatment and a frequency >30 VPCs/hr and optionally complex arrhythmias (Lown IV A/B).

Efficacy
The primary efficacy endpoint was the total hourly number of VPCs and hourly number of single and repetitive VPCs in 24 hour Holter ECG.

Safety
Adverse events, laboratory investigations, vital signs (BP and HR), resting ECG, physical examination, and general tolerability were evaluated.

Statistics
ANCOVA Confirmatory analysis on VPC $_{total}$/hour was carried out using model with factors including dosage, center interaction of dosage and center as well as baseline

VPC $_{total}$/hour covariate. By use of appropriate contrasts each dosage was compared to placebo. In order to keep the global alpha level of 0.05 an alpha adjustment according to Bonferroni-Holm was used for pairwise comparisons.

Efficacy results: See Tables below

Table 101 : :Adjusted mean improvement (%) of VPC total/hour–Propafenone SR MPF/H9406 - Phase II study

	Analyzed population					
	Intent to Treat		Steady State		Per protocol	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Placebo	13.2	-52.9,-50.7	17.3	-57.6,-56.6	19.9	-58.1,-59.4
225mg Propafenone	72.2	51.6,84.0	73.9	53.6,85.4	78.3	58.8,88.6
325mg Propafenone	75.0	52.6,86.8	75.8	54.0,87.3	76.9	55.1,88.2
425mg Propafenone	91.2	85.3,94.8	92.5	87.1,95.7	93.3	88.0,96.3

Table 102: *combined response (%) per treatment group - MPF/H9406-Phase II

	Analyzed population					
	Intent to Treat		Steady State		Per protocol	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Placebo	4.5	0.5,15.5	5.1	0.6,17.3	2.9	0.1,15.3
225mg Propafenone	17.9	7.5,35.5	19.4	8.1,36.0	23.3	10.0,42.3
325mg Propafenone	39.5	24.9,55.6	40.5	25.6,56.7	41.5	26.3,57.9
425mg Propafenone	55.8	39.8,70.9	64.9	47.7,79.8	67.6	49.4,82.6

* Defined as simultaneous reduction of VPC$_{singular}$/hour >75%, couplets/h>90% and salvos =100%

Efficacy Conclusion

The efficacy data above show a dose response at a twice daily dosing regimen. The data from this study, albeit for efficacy in ventricular arrhythmia, form the basis for dose selection used for efficacy in atrial fibrillation RAFT study in the NDA under review.

Safety

Adverse events

In the double-blind treatment period adverse events (AEs) were found in 74 out of 187 patients (40%).

The most commonly reported adverse events were

- Headache (4.3%)
- First degree AV block (18.2%),
- Bundle branch block (3.7%)

There were no deaths.

Six patients were withdrawn from the study due to adverse events (Placebo 2 and Propafenone 4). Two patients experienced pro-arrhythmic effects (Placebo 1, Propafenone 1). A relatively high percentage of ECG changes were disregarded in this study particularly in the 425 mg bid dose group (31.1% versus 23.5% in placebo) (Table 103). The reasons for disregarding these changes are not clear. This raises the issue of long term safety with propafenone SR administration particularly at the high dose.

Table 103: Percent of patients per treatment group with adverse event –VPC- Phase II study

Dosage bid	Placebo	225mg bid	325 mg bid	425 mg bid
All adverse events	29.4	26.1	31.1	57.8
ECG changes disregarded	23.5	13.0	13.3	31.1

Conclusion
The SR formulation of propafenone shows a dose response at a bid dosing regimen and provides a basis for a bid dosing regimen for the RAFT study.

5.54 Phase II – Hemodynamics and PK of propafenone SR in symptomatic — (Protocol SR VPC CR-D2/Report Number CD00001)
A double blind randomized study on Hemodynamics and pharmacokinetics in patients with symptomatic —— arrhythmia (225 and 425 mg bid) Protocol SR VPC CR-D2/Report Number CD00001)
Phase II study - Protocol VPC CR-D2 (including joint evaluation of hemodynamics from Protocol Study Propafenone SR VPC CR-D1).

Title of Study
A double blind, randomized study of two different dosages of propafenone SR on hemodynamics and pharmacokinetics in patients with symptomatic ventricular arrhythmias.

Objective
To investigate and pharmacokinetics and hemodynamics of two doses of propafenone SR 225 mg bid and 425 mg bid in patients with symptomatic ventricular arrhythmias. This study is an extension of study protocol VPC CR D1 that evaluated the PK and hemodynamics of 3 dosages (225, 325, 425 mg bid).

Study design
This was a single center, double-blind, parallel group study with a 3 to 5 day placebo run-in period.

Duration of double-blind treatment period was 5-10 days.

Number of patients: A total of 12 patients were randomized and evaluated.

Study dates: October 11 1993 to March 30 1994

Study Center: Bad Nauheim in Germany

Inclusion criteria
- Male or female in - patients
- Ages between 18 and 70 years
- Patients must have history of treated or untreated ventricular arrhythmias.

Efficacy
The primary efficacy endpoint was the total hourly number of VPCs and hourly number of single and repetitive VPCs in 24 hour Holter ECG.

Safety

Hemodynamic parameters measured by means of right heart catheterization (heart rate, systolic and diastolic blood pressure, mean arterial pressure, systolic and diastolic pulmonary artery pressure, mean pulmonary artery pressure, mean pulmonary capillary pressure, pulmonary artery oxygen saturation, cardiac output, cardiac index, stroke volume, pulmonary arteriolar resistance) and by radionuclide ventriculography (endsystolic volume, endiastolic volume, ejection fraction, peak filling and ejection rate); Adverse events, laboratory investigations, vital signs (BP and HR) , resting ECG, physical examination general tolerability were evaluated.

Statistics

In view of small numbers, single case documentation of efficacy results was reported in descriptive statistics. Joint evaluation of hemodynamic parameters on a total number of patients (32) included data from study propafenone SR VPC CR-D1.

Efficacy results

- Out of the 12 randomized patients only 2 individual Holter ECG recordings from patients given 225 mg were fully evaluable. These data suggest a reduced total hourly frequency of VPCs decreases in incidence of singular and repetitive VPCs and a drop in heart rate.

Efficacy Conclusion

The data is too small to make any meaningful comments.

Safety

The numbers of patients in this protocol are so small that data from another protocol VPC CR-D1 was pooled for hemodynamic assessments as described above. The hemodynamic changes observed were not clinically relevant and too small to constitute a treatment effect. There was no evidence of negative inotropic action in the dose ranges evaluated.

Adverse events

The most commonly reported adverse events were

- Sinus bradycardia and
- First degree AV block,

These adverse events were not dose related but the numbers are too small to come to any meaningful conclusion. There were no deaths.

One patient was withdrawn from the study due to serious adverse event.

There were clinically relevant changes in liver enzymes and creatinine elevations. There were clinically relevant changes in ECG parameters between the treatment groups. These include the following:
Increased PR intervals were evident during the trial. QRS interval was prolonged in 7 patients post treatment.

Conclusions

- This phase II study is relatively small in size to add any significant information to the pivotal study of this NDA. Furthermore, the efficacy endpoint in this phase II study is

not clinically relevant (ventricular arrhythmias) to the endpoint (Supraventricular arrhythmias) of the NDA under review.
- The hemodynamic measurements did not yield a clear indication of treatment effect.
- The safety data have been included in the post hoc meta-analysis for the NDA.
- The safety data confirm the pharmacological action of the drug.

5.55 Phase II – Cross-over study comparing propafenone SR and IR in symptomatic VA (Protocol VPC CR-11/Report Number CD99022)

A double blind randomized placebo controlled cross-over study comparing propafenone SR and IR in patients with symptomatic ventricular arrhythmia requiring treatment Phase II study - Protocol VPC CR-11

Title of Study

A double blind, randomized, placebo-controlled, cross-over study comparing propafenone SR and propafenone IR in patients with symptomatic ventricular arrhythmia requiring treatment. (Protocol VPC CR-11/Report Number CD99022)

Objectives

- To investigate whether propafenone SR 225 mg bid and 325 mg bid were as effective and safe as propafenone IR 150 mg tid and whether one of the two different dosages 225 mg and 325 mg bid of propafenone SR was more effective and or safer than the other.
- A second objective was to analyze the relationship between propafenone plasma levels taken at trough level and efficacy, using different pharmaceutical formulations of propafenone.

Study design

This was a multi-center, double-blind, randomized, crossover study. Patients who had previously been treated with anti-arrhythmic agents or β-blockers were subjected to washout periods equivalent to 5 times the half life of the previous treatment up to a maximum of five days. For screening, determination of propafenone plasma levels were carried out in addition to blood sampling for laboratory tests, documentation of ECG and vital signs (blood pressure and heart rate BP and HR, respectively), and general clinical evaluation. At baseline, determination of propafenone plasma levels were carried out in addition to blood sampling for laboratory tests, documentation of ECG and vital signs, and general clinical evaluation. Patients were then randomized to the assigned treatment sequence before entering a 5-7 day placebo run-in period. There were three treatment periods and at the end of each treatment period the patients underwent a general clinical evaluation, blood sampling for propafenone plasma levels, documentation of ECG and vital signs (BP and HR), and 24-hour Holter monitoring. Each treatment period followed directly on from the previous study. On completion of the third treatment period, blood samples were obtained for laboratory evaluation. Compliance was evaluated throughout the study.

Duration of each double-blind treatment period is 10 to 14 days.

A total of 180 patients should have been enrolled but the study was terminated prematurely because of slow recruitment.

Study dates: October 6 1993 to April 11 1995

Study Centers: Bari in Italy and Firenze in Italy

Inclusion criteria

- ~~Male or female outpatients~~
- Ages between 18 and 80 years
- Patients must have symptomatic stable and frequent ventricular premature contractions (VPCs)
- Patients to have documented variability of less than 35% in the hourly mean VPCs of each of the 2 Holter recordings performed prior to study entry and at least 30 VPCs per hour.

Efficacy

The primary efficacy endpoint is the number of combined responders (patients with 75% reduction of VPC/hr. 90% reduction in couplets if present at baseline) (or patients without couplets at baseline or following treatment) and suppression of non-sustained ventricular tachycardia (NSVT) at baseline or following treatment), and VPCs, supraventricular premature contractions (SVPCs), couplets, runs and mean heart rate per hour.

Safety

Adverse events, laboratory investigations, vital signs and physical examination were documented and analyzed.

Statistics

In view of the small numbers enrolled in the study only descriptive statistics were submitted by the sponsor.

Efficacy results

Out of 83 patients randomized, 71 (86%) completed the study.

Table 104: Number of responders by treatment group – Phase II study

	Propafenone		
	Propafenone IR 150mg tid	**Propafenone SR 225 mg bid**	**Propafenone SR 325 mg bid**
Total N of patients	77	78	76
*Combined responders	27(35%)	20(26%)	36(47%)
VPC/hour	28(36%)	21(27%)	38(50%)
Couplet responders	47(61%)	42(54%)	52(68%)
NSVT responders	76(99%)	71(91%)	72(95%)

- Patients with at least a 75% reduction of VPC/hour compared to baseline, at least 90% reduction of couplets compared to baseline (or absence of couplets at baseline and follow up and a 100% suppression of NSVT compared to baseline (or absence of NSVT at baseline and follow-up.

Efficacy Conclusion

There were more responders in the 325mg bid treatment group compared to the other 2 groups. At a descriptive level, patients in the 325 mg bid treatment group showed significant numerical differences (47%) compared to 150mg tid of IR (35%) formulation and also to 225 mg bid (26%) for combined responder parameter. The sponsor claims that there were no clinically relevant differences between any of the groups but the basis of this claim has not been validated.

Safety

Out of 83 patients randomized, 71 (86%) completed the study.

Table 105: Frequency of adverse events by treatment group- Phase II study

	Propafenone		
Adverse events	**Propafenone IR 150mg tid**	**Propafenone SR 225 mg bid**	**Propafenone SR 325 mg bid**
Total N of patients	83	83	83
At least one adverse event during the study	Total of 30 patients out of 83 (36%) reported 64 adverse event inclusive of placebo run-in period		
At least one adverse event during the placebo run-in period	Total of 9 patients reported 14 Adverse events		
Number of patients (Adverse events by treatment group)	11(reported 18 adverse events)	12(reported 22 adverse events)	7(10 reported adverse events)

Adverse events

The most commonly reported adverse events were

- Sinus bradycardia and
- Abnormal conduction disorders,
- Severe headache and
- Severe insomnia.

These adverse events were not dose related but the numbers are too small to come to any meaningful conclusion. There were no deaths.

Ten patients were withdrawn from the study due to adverse events, 5 received 150 mg tid 4 received 225 mg bid propafenone SR and one patient received propafenone SR 325 mg bid.

There were no clinically relevant changes in laboratory parameters between the treatment groups. There were no clinically relevant changes in vital signs – BP and HR between the treatment groups. There were clinically relevant changes in ECG parameters between the treatment groups. These include the following:
Increased PQ intervals that were evident compared to baseline values. The mean changes in PQ intervals from baseline were +10.3ms for 150 mg tid propafenone IR, + 9.2 ms for 225 mg bid propafenone SR, and +16.4 ms for 325 mg bid propafenone SR. **QTc intervals were also prolonged in 7 patients as new treatment emergent events in propafenone SR treatment groups. The sponsors claim that these QTc prolongations were asymptomatic.**

Conclusions

This phase II study is relatively small in size to add any significant information to the pivotal study of this NDA. Furthermore, the study was terminated prematurely. The efficacy endpoint is not relevant to the endpoint of the NDA under review.
The safety data have been included in the post hoc meta-analysis for the NDA.
The safety data confirms the pharmacological action of the drug in prolonging the PQ, QRS and also QTc intervals of patients exposed even for the relatively short periods of time.

6.0 Summary and Conclusions

~~A summary of clinical findings of RAFT and ERAFT trials is presented on pages 54-55.~~
On the basis of the efficacy data from the RAFT study and the supportive efficacy data from the ERAFT study, the reviewer recommends that the drug be approved for efficacy. The SR formulation of propafenone shows a dose response at a bid dosing regimen and provides a basis for a bid dosing regimen in the RAFT study.

- The reviewer however, is concerned about safety of propafenone SR because of its pharmacologic action on the heart. The differences between the ECG changes following administration of IR and SR are evident in the reviewer's Figures 4, 5 and 6 (pages 31 and 32 of this review). Figure 6 shows dose-dependent increase of PQ and QRS intervals with the SR formulation whereas this is an apparent dose dependent decrease with IR. This is consistent with sustained release of SR formulation compared to immediate release formulation.
- The sponsor has not provided a summary table or sufficient data on QT/QTc intervals to allow a thorough evaluation of the effect of SR on QT interval in patients with AF.
- The sponsor has not carried out a mortality study and acknowledges this fact in the labeling. Evaluation of the mortality risk can be achieved from postmarketing surveillance over time but this reviewer is concerned about the relative inadequacy of submitted data relating to long term safety of the SR formulation. Furthermore, lab. abnormalities and adverse events that can be included in the label include dose dependent increase of conduction disorders, dose dependent increase of blurred vision (Table 63), dose-dependent hypercalcemia, dose-dependent hyponatremia and also hypokalemia only in patients exposed to propafenone.
- There is information on PQ and QRS intervals in these AF patients exposed to SR. Looking at other studies carried out in Phase II there is one study that shows prolongation of QT in patients with ventricular arrhythmia.
- This was a cross-over study that compared propafenone SR and IR in symptomatic VA (Protocol VPC CR-11/Report Number CD99022). It was a double blind, randomized, placebo-controlled cross-over study comparing propafenone SR and IR in patients with symptomatic ventricular arrhythmia requiring treatment (Phase II study - Protocol VPC CR-11). The Title of the Study was "A double blind randomized placebo controlled cross over study comparing propafenone SR and propafenone IR in patients with symptomatic ventricular arrhythmia requiring treatment. (Protocol VPC CR-11/Report Number CD99022)"
- The study also analyzed the relationship between propafenone plasma levels at trough level and efficacy using SR and IR formulations. The relationship between the peak levels and efficacy was not evaluated. The duration of the study was 10 —14 days.
- From the safety review of the above study, ten out of about 180 patients were withdrawn from the study due to adverse events, 5 received 150 mg tid, 4 received 225 mg bid propafenone SR, and one patient received propafenone SR 325 mg bid.

- There were no clinically relevant changes in laboratory parameters between the treatment groups. There were no clinically relevant changes in vital signs – BP and HR between the treatment groups.
- However, there were clinically relevant changes in ECG parameters between the treatment groups that included the following:
- Increased PQ intervals that were evident compared to baseline values.

- The mean changes in PQ intervals from baseline were +10.3ms for 150 mg tid propafenone IR, + 9.2 ms for 225 mg bid propafenone SR, and +16.4 ms for 325 mg bid propafenone SR.
- QTc intervals were also prolonged in 7 patients as new treatment emergent events in propafenone SR treatment groups. The sponsors claim that these QTc prolongations were asymptomatic. This claim by the sponsor has not been verified by the reviewer.

The sponsor has recently provided additional data on JTc and QT intervals (December 30 2002) and these show no significant clinically relevant differences between the groups. The reviewer has prepared graphs of these data (Appendices 17-19 pages 165-167).

The risks of antiarrhythmic therapy have been recognized including therapy with Class 1c agents. The risk of sudden cardiac death is increasingly being recognized when antiarrhythmics are used in patients with coronary artery disease and myocardial ischemia. This was reflected in the overall concept of CAST with an excess of sudden cardiac death mortality. This was recommended for the labeling of propafenone SR in the light of available data from pharmacovigilance of propafenone IR.
Very little is known about the beneficial or hazardous effects of class 1c antiarrhythmics, including propafenone, in patients with atrial fibrillation, atrial flutter, PSVT and myocardial ischemia. Proarrhythmias, fatal and non-fatal, have been reported in patients with structural heart disease or > NYHA class II exposed to propafenone for relatively long periods (>3 months). There is compelling evidence that conduction delay induced by both Class 1c effects and myocardial ischemia invariably resulted in significant proarrhythmia due to loss of antiarrhythmic efficacy and an increase in the heterogeneity of the repolarization process. In patients exposed to propafenone who developed proarrhythmic events, there is insufficient data to identify the predisposing factors or to evaluate mechanistic factors. Electrophysiologically, and clionically to some extent, the QT interval dispersion is one of the most reliable indicators of inhomogeneous ventricular repolarization and susceptibility to ventricular arrhythmias as shown in patients with the congenital long QT syndrome.

In the clinical review of RAFT and ERAFT studies, special attention was paid to abnormalities of the QRS, QT, QTc, JT and JTc intervals in patients treated with propafenone SR since there is very little known about the SR formulation compared to the IR. Two patients with atrial fibrillation developed prolonged QT– related adverse events in both studies (Table 77). The average duration of QTc intervals in 16 propafenone treated patients and 7 placebo patients, discontinued because of serious adverse events and subsequently had prolonged hospitalization, was 417ms and 401ms, respectively (Reviewer's calculation from sponsor's listing). Two of the 16 patients who received propafenone, 325mg bid and 425 mg bid, developed prolonged QTc (466 and 517ms) respectively, in the RAFT study. Serious adverse events led to prolonged hospitalization and discontinuation of these patients. There was no QTc prolongation among the placebo group discontinued and hospitalized for serious adverse events. There was no significant difference between average duration of QTc in these subset of discontinued patients albeit from a limited data. The JTc intervals also showed no difference between the mean changes from baseline among the treatment groups over time (Appendix 17). Although QRS interval was prolonged with propafenone SR the lack of an increase in JTc suggests that the QTc interval is most likely not prolonged by propafenone SR in the RAFT study. This finding is supported by published data in the literature on propafenone IR.

In a randomized, placebo-controlled study, patients pretreated with propafenone before PTCA developed significantly increased QT and QTc intervals during occlusion of the left anterior descending (LAD) coronary artery (9% and 11%, respectively $p<0.05$), whereas occlusion of the circumflex and right coronary artery had no effect on the Qt/QTc intervals. This observation suggested that before and immediately after the end of the balloon inflation in the coronary artery (thus inducing maximal myocardial ischemia), particularly during LAD occlusion, propafenone resulted in a significant increase of QT/QTc intervals. This may explain the relatively few cardiac adverse events in the RAFT study since angina class III and IV as well as NYHA calss Iii and IV were excluded from the study. Only two patients had prolonged QTc interval that led to discontinuation in the RAFT study. The exclusion criteria for both Phase III trials acknowledged that propafenone should not be used in the presence of severe coronary disease and or myocardial ischemia.

The reviewer has searched the literature on safety and efficacy of propafenone SR and propafenone IR from 1978 to 2002 and selecteted 56 published studies carried out in targeted populations of adults and children with arrhythmias treated with propafenone SR and propafenone IR alone or in combination with or compared to other anti-arrhythmics. The synopsis of this literature search is tabulated as an addendum to NDA 21416 in Appendix 20. The purpose of this literature search is to evaluate the safety of propafenone, particularly its effect of the QT interval and possible associated proarrhythmic potential in patients with atrial fibrillation without structural heart disease. The literature review included both ventricular as well as supraventricular arrhythmias that propafenone has been shown to be effective and approved for therapy in several countries including the US. The publications included short and long term studies. In the short term studies patients had drug exposure for less than 7 days. These were very useful from a mechanistic aspect of drug testing but did not provide useful long term safety data that can be related to the review under discussion. However, some of the relatively short-term studies revealed adverse event profiles similar to those seen in long-term (>3 months) drug exposure. These adverse events included first degree a-v block, prolongation of QRS and gastrointestinal disturbances.

The longer term studies (>3 months of exposure) in adult patients with supraventricular arrhythmias, atrial fibrillation (recent or paroxysmal), atrial flutter, PSVT, showed consistent efficacy compared to placebo. In addition, the adverse event profile in the studies were to a large extent consistent and they tended to increase to increase in frequency and severity with increased duration of drug exposure. For example, cardiac adverse events were common observed in follow up of patients > 6 months compared to < 6 months. Of the cardiac adverse events, proarrhythmic events were the most clinically significant followed by congestive heart failure in patients with uncontrolled tachycardia. Bradyarrhythmias were also very common. Conversion of atrial fibrillation to atrial flutter was also observed in a number of studies. Dose dependent proarrhythmias were higher in patients with arrhythmias that were associated with structural heart disease or NYHA class III and IV. Malignant non-fatal proarrhythmic effects were reported with propafenone IR and on a few occasions the proarrhythmia was a cause of sudden death in patients exposed for long periods of time. Torsades has also been reported in patients taking propafenone but none has so far been known to be fatal from this review. Proarrhythmic effects of propafenone were not as a rule associated with documented QT prolongation in most (>90%) of the published studies. This has been confirmed in the clinical review of RAFT and ERAFT studies.

The oxidation phenotype (CYP2D6 metabolism of propafenone IR) of patients with serious adverse events is not known or stated in patients enrolled in almost all the studies. In the study by Jarwinska-Tarnawska and his colleagues ,the antiarrhythmic efficacy of propafenone depended on the oxidation phenotype of the patients. There was 100% efficacy in poor metabolizers, whereas at the dose tested (300-450 mg /day for 3 months) propafenone was ineffective in "very extensive metabolizers". This study recognized 3 categories of metabolizers and correlated propafenone efficacy with the capacity to metabolize the parent drug. The 3 categories of metabolizers were: Poor metabolizers, extensive metabolizers and very extensive metabolizers. It is conceivable that the very extensive metabolizers may have the least frequency of adverse events and the highest percentage of withdrawals due to lack of efficacy as seen in the RAFT study, even at high dose levels (425mg bid).

The plasma concentrations of parent drug in the studies that determined and correlated them with adverse events, varied widely. This may be a reflection of the oxidation phenotype of the patients on inter subject variability. For example, in one study the mean trough plasma level for propafenone IR with an effective response was 756ng/ml and 920ng/ml for intolerable side effects, respectively whereas in another study, plasma concentration of drug when therapy was discontinued was 753+/-428ng/ml.

In patients with ventricular tachycardia administered oral propafenone IR for >6months, there was prolongation of PR and QRS and occasionally prolonged QTc. In the RAFT study, patients with atrial fibrillation on oral propafenone also developed prolonged PR and QRS intervals but there was no prolongation of the QTc interval. In the ERAFT study patients with atrial fibrillation on oral propafenone also developed prolongation of PR and QRS intervals but there was no prolongation of the QTc. The JT and JTc intervals in the RAFT study confirmed that there was no evidence of prolongation of QT/QTc dispersion. Out of 32 patients in the RAFT study with serious adverse events that led to discontinuation and the patients had prolonged hospitalization, there was no prolongation of the QTc except in 2/23 patients (466 and 517ms).

In a large European study of 772 children with arrhythmias, proarrhythmia occurred in 1.9% of children exposed to propafenone. Other adverse events in these children included first degree AV block, sinus node dysfunction, ventricular proarrhythmia in 5 children, and syncope in 1 child. Cardiac arrest or sudden death occurred in 5/772 (0.6%), and SVT due to WPW, within a normal heart, in 2 children. Overall, proarrhythmic effects with propafenone seemed to be less frequent than those reported for encainide or flecainide. However, with propafenone, proarrhythmias occured predominantly in children with structural heart disease (>NYHA II). The sponsor should be requested to carry out a study in children with arrhythmias using propafenone SR. The reviewer recommends that the request for a waiver should not be granted but deferred.

From the review of the literature, there has been a tendency for investigators to enroll a and randomize small numbers of mixed clinical populations with paroxysmal atrial fibrillation (PAF), sustained atrial fibrillation, ventricular fibrillation and PSVT. The treatment objectives in the published studies were invariably different and the duration of treatment varied from one study to another. The RAFT and ERAFT study enrolled only patients with symptomatic PAF/atrial fibrillation of recent onset and also of relatively older vintage (<12 months) all documented by ECG. The ERAFT specifically enrolled patients with PAF that comprised between 25% and 62% of cases of all atrial fibrillation,

with similar underlying causes to those in sustained AF. The main objective of the two studies in this NDA is prevention of paroxysms and long-term maintenance of sinus rhythm through prolongation of time to first recurrence of symptomatic arrhythmias. Class 1c drugs, of which propafenone is an example, are highly effective in PAF although beta-blockers have been shown to be useful alternatives. Depending on the presence or absence of structural heart disease or cardiac decompensation, other antiarrhythmics have been found to be useful either alone or in combination with class 1c antiarrhythmics and other agents.
If patients have severe coronary artery disease or poor ventricular function, amiodarone is probably the drug of choice. The ultimate benefit of therapy is the prevention of thromboembolic episodes, randomized controlled trials of thromboprophylaxis in patients with paroxysmal AF per se are lacking. The management of these patients with paroxysmal AF should be similar to that in patients with sustained AF, with warfarin for 'high risk' patients and aspirin for those at 'low risk'. Other non-pharmacological therapeutic options in the literature include the use of pacemakers, electrophysiological techniques and implantable atrial defibrillator. Although paroxysmal AF is a relatively common condition in adults and in children particularly those with congenital heart disease or WPW, there are relatively few large controlled studies from which compelling evidence of efficacy can be generated. As a result of these numerous small randomized trials, inconsistencies over the definition of the arrhythmia are evident and contradictions in results abound. The inclusion of only symptomatic subjects in some studies in these 2 NDA trials and asymptomatic studies in other studies makes objective comparisons very difficult (Appendix 20).

7.0 Recommendations

- [redacted]

- The primary and secondary efficacy findings suggest propafenone SR to be an effective anti-arrhythmic on a bid dosing for the prolongation of time to recurrence of atrial fibrillation. On this basis alone the drug is approvable.

- However, the reviewer recommends approval of the drug for the proposed indication subject to more satisfactory and convincing data on the mortality risk and effects of propafenone SR on the QT interval in patients with atrial fibrillation. Although the label states that propafenone does not enhance survival this cannot be used as a caveat for increased or reduced mortality risk. The CAST warning in the label may be a mitigating factor for the lack of mortality study but the reviewer is concerned about safety of the SR formulation based on its pharmacologic action compared to the IR formulation.

- The reviewer recommends that PK/PD interaction studies be carried out between propafenone SR and 3A4 inhibitors (for example, ketoconazole) in order to evaluate the safety of co-administration. Alternatively, ketoconazole and other similar compounds can be contraindicated in the label pending further information and or data from the sponosr clarifying the safety issue of propafenone and ketoconazole or other 3A4 inhibitors..

- The reviewer recommends an initial dose of 225 mg bid increasing to 325mg bid propafenone SR if symptoms of atrial fibrillation are uncontrolled and persists. A subsequent increase to 425 mg bid may be indicated if symptoms are uncontrolled by 325 mg bid. Patients on the highest dose of 425mg bid will need to be closely monitored closely because of the relatively high frequencies of dose-dependent adverse events (Cardiovascular and gastrointestinal systems in particular).

7.1 Financial Disclosure

- The sponsor of the submitted studies certified, on form OMB No 0910-0396 of 3/31/2002, that no financial arrangements had been entered into with the clinical investigators who carried out all the clinical studies in this NDA. The certification was made in compliance with 21 CFR part 54 and 21 CFR 54.2 (d).

20 pages redacted from this section of the approval package consisted of draft labeling

9.0 Appendices

Appendix 1: List of Abbreviations

~~FAS~~	~~Full Analysis Set~~
NEC	Not elsewhere classified

Abbreviation	Definition
AEC	Arrhythmia Event Committee
AF	atrial fibrillation
ANOVA	analysis of variance
AV	Atrioventricular
AUC	area under the plasma concentration versus time curves for propafenone
bid	twice a day
bpm	beats per minute
BUN	urea nitrogen
CI	confidence interval
CRF	case report form
ECG	Electrocardiogram
eRT	eResearch Technology
exc	excluding
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IND	Investigational New Drug (application)
IR	immediate release
ISS	Integrated Summary of Safety
IUD	Intrauterine device
LDH	lactic acid dehydrogenase
NDA	new drug application
NEC	not elsewhere classified
NOS	not otherwise specified
NYHA	New York Heart Association
PAF	Paroxysmal atrial fibrillation
PSVT	Paroxysmal supraventricular tachycardia
RAFT	Rythmol-SR Atrial Fibrillation Trial (Protocol P-85-AF)
SD	standard deviation
SR	prolonged-release
$t_{1/2}$	half-life
tid	three times a day
TSH	thyroid stimulating hormone
TTM	Transtelephonic monitoring

Appendix 2: Study drug compliance

Table 28 Study drug compliance

Variable	Propafenone SR 225 mg bid (N = 126) n (%)	Propafenone SR 325 mg bid (N = 135) n (%)	Propafenone SR 425 mg bid (N = 135) n (%)	Placebo (N = 126) n (%)
Pertem compliance				
< 70%	3 (2.4)	1 (0.7)	5 (3.7)	0 (0.0)
70% to < 80%	5 (4.0)	3 (2.2)	8 (5.9)	4 (3.2)
80% to <100%	95 (75.4)	100 (74.1)	93 (68.4)	92 (73.0)
100%	9 (7.1)	11 (8.1)	11 (8.1)	17 (13.5)
>100% to <120%	11 (8.7)	17 (12.6)	15 (11.0)	10 (7.9)
≥120%	3 (2.4)	3 (2.2)	4 (2.9)	3 (2.4)
Mean (%) ± SD	97.3±19.3	98.9±11.0	96.6±23.7	98.9±12.6
Median (%)	97.1	97.6	95.5	98.4
Range (%)	30.0-222.7	30.0-177.3	62.5-316.2	74.1-200.0

Source: Table 9.3.1.2

Appendix 3: Narratives of 5 deaths - RAFT

1) Description of Adverse Event Patient 05 was randomized to the study and received placebo from 13- Apr- 98 to 03- Nov- 98. On 03- Nov- 98, the pdtient had lung cancer, which was considered severe, serious, and unrelated to study drug by the investigator. The event lasted 71 days. In response to this adverse event, study medication was permanently discontinued, and the patient had a diagnostic evaluation. The patient died.

The patient also had the following additional non- serious adverse events: faiigue and upper respiratory tract infection.

Medical history: Aortic valve incompetence, cardiomegaly, hypertension, drug allergy, amnesia NEC, allergic rhinitis, gout, and prostatism.

2) Description of Adverse Event Patient 03 was randomized to the study and received propafenone SR 325 mg bid from 2 Dec- 98 to 16- Mar- 99. On i 7- Feb- 99, the patient had symptomatic atrial fibrillation, which was considered moderate in severity, serious, and possibly related to study drug by the investigator. The event lasted 3 days. In response to this adverse event, the patient was hospitalized and was treated with Lopressor. The patient recovered without sequelae.

On 04- Oct- 99, the patient had renal cancer, which was considered severe, serious, and unrelated to study drug by the investigator. The event lasted 3 days. In response to this adverse event, the patient was hospitalized and received other unspecified therapy. The patient died.

The patient also had the following additional non-serious adverse events: anemia, anxiety NEC, ascites, pulmonary congestion, rigors, cough, pyrexia., insomnia NEC, nausea, thrombosis, and urinary tract infection.
Medical history: Hypertension, gout, renal cancer, and rhinitis NOS.

3) Description of Adverse Event Patient 04 was randomized to the study and received propafenone SR 325 rig bid from 30- Nov- 98 to 10- Dec- 98. On 10- Dec- 98, the patient had an arterial embolism (limb), which was considered severe,serious, and unrelated to study drug by the investigator. The event lasted 2 days. In response to this adverse event, the patient was hospitalized, had a diagnostic evaluation, and received other unspecified therapy. The patient recovered without sequelae.

On 19- Dec- 98, the patient had a skin infection NOS, which was considered severe, serious, and unrelated to study drug by the investigator. The event lasted 19 days. In response to this adverse event, the patient was hospitalized, had a diagnostic evaluation, and received other unspecified therapy. The patient recovered with sequelae.

On 27- Dec- 98, the patient had an embolus, which was considered severe, serious, and unrelated to study drug by the investigator. The event lasted 18 days. In response to this adverse event, the patient was hospitalized and treated with Coumadin. The patient recovered with sequelae.

On 07- Jan- 99, the patient had cancer (not specified) which was considered severe, serious, and unrelated to study drug b j the investigator. The event lasted 45 days. In response to this adverse event, the patient was hospitalized. The patient died.

The patient also had the following additional non-serious adverse events: insomnia NEC and keratitis NOS.

Medical history: Myocardial infarction, palpitations, premature ventricular contractions, supraventricular tachycardia, angioplasty, coronary artery bypass, transient ischemic attacks, coronary artery disease NOS, glaucoma, diverticulosis, drug allergy, bronchitis NOS, herpes zoster, breast biopsy, systemic lupus erythematosus, cararact extraction, hysterectomy, arthritis NOS, food allergy, intervertebral disc disorder (not specified), peripheral vascular disease, and spondylosis.

4) Patient 07 was randomized to the study and received placebo from 08- Oct- 99 to 24- Jun- 00. On 25- Jun- 00, the patient had renal failure NOS, which was considered severe, serious, and unrelated to study drug by the investigator. The event lasted 49 days. In response to this adverse event, study medication was permanently discontinued, and the patient was hospitalized. The patient died.

The patient also had the following additional non- serious adverse events: myocardial infarction, cardiac failure congestive, edema NOS, blood albumin increased, blood urea increased, hyperglycemia NOS, malaise, nausea, pneumonia, pulmonary edema NOS, and respiratory failure.

Medical history: Coronary artery disease NOS, coronary artery bypass, first degree AV block, hypertension, blood alkaline phosphatase NOS, increased creatinine, diabetes mellitus NOS, hypothyroidism, arthritis NOS, and blood lactate. dehydrogenase.

5) Description of Adverse Event Patient 01 was randomized to the study and received propafenone SR 425 rng bid from 20- Aug- 99 to 08- Dec- 99. On 29- Nov- 99, the patient had pneumonia, which was considered severe, serious, and unrelated to study drug by the investigator. The event lasted 17 days. In response to this adverse event, study medication was permanently discontinued, the patient was hospitalized, and he and was treated with Albuterol. The patient recovered without sequelae.
On I 1- Feb- 00, the patient had an injury NOS, which was considered severe, serious, and unrelated to study drug by the investigator. The event lasted 1 day. In response to this adverse event, the patient was hospitalized and died.
The patient aiso had the following additional non-serious adverse events: Atrioventricular block first degree, sweating increased, somnolence, gastroenteritis, nausea, tremor NEC, and vomiting NOS.
Medical history: hypertension, sinus bradycardia, impaired hearing, visual clisturbance, colonic polyp, inguinal hernia, drug allergy, pneumonia, injury NOS, hematuria present, renal cancer, ureter cancer, angioplasty, nephrectomy, prostatic hypertrophy, prostatic operation (not specified), vasectomy (not specified), anxiety NEC, constipation, dizziness (excluding vertigo), insomnia, seborrheic keratosis, and tremor NEC.

Appendix 4 : Incidence of serious cardiovascular adverse events-RAFT

	Propafenone SR			
MedDRA Body System/Preferred Term	225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
No. (%) of pts. with any serious adverse event	13 (10.3)	16 (11.9)	19 (14.0)	18 (14.3)
Cardiac disorders	9 (7.1)	8 (5.9)	14 (10.3)	7 (5.6)
Angina unstable	1 (0.8)	0 (0.0)	1 (0.7)	0 (0.0)
Atrial fibrillation	7 (5.6)	5 (3.7)	7 (5.1)	6 (4.8)
Atrial flutter	3 (2.4)	2 (1.5)	0 (0.0)	1 (0.8)
Bradycardia NOS	0 (0.0)	1 (0.7)	2 (1.5)	0 (0.0)

Appendix 5: Incidence of 32 out of 66 patients with Serious Adverse Events leading to premature termination - RAFT

	Propafenone SR			
MedDRA Body System/Preferred Term	225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
No. (%) of pts. with any serious adverse event	6 (4.8)	6 (4.4)	10 (7.4)	10 (7.9)
Cardiac disorders	6 (4.8)	5 (3.7)	9 (6.6)	6 (4.8)
Angina unstable	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Atrial fibrillation	5 (4.0)	4 (3.0)	4 (2.9)	5 (4.0)
Atrial flutter	2 (1.6)	1 (0.7)	0 (0.0)	1 (0.8)
Bradycardia	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)

MedDRA Body System/Preferred Term	Propafenone SR 225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Cardiac failure congestive	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)
Coronary artery disease NOS	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Sinus arrhythmia	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	2 (1.6)	3 (2.2)	1 (0.7)	1 (0.8)
Abdominal pain NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Appendicitis	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Constipation	1 (0.8)	0 (0.0)	1 (0.7)	0 (0.0)
Diarrhea NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Diverticulitis NOS	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Intestinal obstruction NOS	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Melena	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Nausea	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis NOS	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Vomiting NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
General disorders and administration site conditions	1 (0.8)	2 (1.5)	2 (1.5)	3 (2.4)
Chest pain	1 (0.8)	1 (0.7)	2 (1.5)	3 (2.4)
Weakness	1 (0.8)	1 (0.7)	0 (0.0)	0 (0.0)
Infections and infestations	1 (0.8)	1 (0.7)	2 (1.5)	2 (1.6)
Arthritis infective NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Herpes simplex	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia NOS	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Tooth abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Urinary tract infection NOS	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Injury and poisoning	2 (1.6)	0 (0.0)	0 (0.0)	1 (0.8)
Fracture NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Injury NOS	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Scar	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Prothrombin level decreased	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Neoplasms benign and malignant (including cysts and polyps)	2 (1.6)	0 (0.0)	1 (0.7)	1 (0.8)
Cyst NOS	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Lung cancer stage unspecified	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Ovarian neoplasm NOS	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Skin carcinoma NOS	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	2 (1.6)	1 (0.7)	2 (1.5)	3 (2.4)
Cerebrovascular accident NOS	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness (exc vertigo)	1 (0.8)	1 (0.7)	0 (0.0)	0 (0.0)
Headache NOS	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.8)
Syncope	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.6)
Psychiatric disorders	1 (0.8)	1 (0.7)	0 (0.0)	0 (0.0)
Anxiety NEC	1 (0.8)	1 (0.7)	0 (0.0)	0 (0.0)

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
Propafenone SR 225 mg bid						
85001/06/ 83/ Female	Injury NOS	55	4	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered with sequelae
85003/07 62/ Female	Atrial fibrillation[a]	50	15	Moderate/ Unrelated	Study drug discontinued, other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85006/01 78/ Female	Sinus arrhythmia	120	43	Moderate/ Possible	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85008/03 62/ Female	Constipation	2	8	Moderate/ Possible	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Atrial fibrillation[a]	8	2	Moderate/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Cerebrovascular accident NOS	12	1	Severe/ Unrelated	Further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85018/01/ 61/ Female	Atrial fibrillation	1	2	Moderate/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Atrial flutter	1	2	Moderate/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85023/04 54/ Male	Atrial fibrillation	1	4	Mild/ Unrelated	Study drug interrupted, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85029/16 78/ Male	Cyst NOS	207	4	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered with sequelae

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
85058/23/ 60/ Male	Skin carcinoma NOS	NA[b]	NA	Unknown	Other therapy; premature termination	Unknown
	Scar	NA	NA	Unknown	Other therapy	Unknown
85060/02 81/ Female	Atrial fibrillation[a]	35	3	Severe/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Herpes simplex	35	9	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85071/04 71/ Female	Anxiety NEC	98	1	Moderate/ Unlikely	Required/prolonged hospitalization	Recovered without sequelae
	Chest pain NEC	98	1	Moderate/ Unlikely	Required/prolonged hospitalization	Recovered without sequelae
	Sweating increased	98	1	Moderate/ Unlikely	Required/prolonged hospitalization	Recovered without sequelae
	Dizziness (exc vertigo)	98	1	Moderate/ Unlikely	Required/prolonged hospitalization	Recovered without sequelae
	Nausea	98	1	Moderate/ Unlikely	Required/prolonged hospitalization	Recovered without sequelae
	Weakness	98	1	Moderate/ Unlikely	Required/prolonged hospitalization	Recovered without sequelae
85072/03/ 55/ Male	Atrial fibrillation[a]	9	5	Severe/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85073/02 74/ Male	Angina unstable	56	1	Moderate/ Unrelated	Study drug discontinued, other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without Sequelae
	Atrial flutter[a]	56	1	Moderate/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without Sequelae

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
85109/03/ 62/ Male	Umbilical hernia repair	72	2	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without Sequelae
	Hydrocele excision	212	2	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without Sequelae
	Atrial fibrillation[a]	267	1	Severe/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without Sequelae
	Atrial flutter[a]	267	1	Severe / Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without Sequelae
Propafenone SR 325 mg bid						
85014/05 74/ Female	Anxiety NEC	114	5	Moderate/ Unlikely	Other med/non-drug therapy, required/prolonged hospitalization	Recovered with sequelae
	Weakness	114	5	Moderate/ Unlikely	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered with sequelae
	Dizziness (exc vertigo)	127	6	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85016/11 76/ Female	Chest pain NEC	15	10	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85016/13/ 64/ Male	Bradycardia NOS	36	2	Severe/ Possible	Other med/non-drug therapy	Recovered without sequelae
85029/17/ 73/ Male	Atrial fibrillation[a]	52	1	Moderate/ Possible	Study drug discontinued, other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
85033/03/ 63/ Male	Atrial fibrillation[a]	4	1	Moderate/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85033/07/ 43/ Male	Appendicitis	207	2	Severe/ Unlikely	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Intestinal obstruction NOS[a]	214	29	Severe/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered with sequelae
	Venous thrombosis deep limb[a]	214	29	Severe/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered with sequelae
85040/03/ 49/ Male	Atrial fibrillation	60	3	Moderate/ Possible	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85042/17/ 56/ Male	Atrial fibrillation[a]	7	9	Mild/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85058/15/ 53/ Male	Diverticulitis NOS	68	5	Severe/ Unlikely	Required/prolonged hospitalization	Recovered without sequelae
85060/04/ 77/ Female	Arterial embolism limb	11	2	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85060/08/ 66/ Female	Pneumonia NOS	35	10	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered with sequelae
85061/08/ 75/ Male	Venous thrombosis deep limb	37	11	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered with sequelae

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
85071/03/ 57/ Female	Atrial flutter[a]	121	1	Severe/ Unlikely	Study drug discontinued, other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85072/08/ 75/ Male	Atrial fibrillation[a]	30	2	Severe/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85098/01/ 73/ Male	Pancreatitis	28	4	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85114/05/ 79/ Male	Atrial flutter	65	2	Moderate/ Unrelated	Required/prolonged hospitalization	Recovered without sequelae
Propafenone SR 425 mg BID						
85009/05/ 53/ Male	Angina unstable	90	3	Moderate/ Unlikely	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
	Angina unstable[a]	227	2	Moderate/ Possible	Study drug discontinued, other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85010/02/ 66/ Female	Atrial fibrillation[a]	28	2	Moderate/ Unrelated	Study drug discontinued	Recovered without sequelae
	Chest pain NEC	28	2	Moderate/ Unrelated		Recovered without sequelae
	Constipation	28	2	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85029/14/ 78/ Female	Bradycardia NOS[a]	4	12	Severe/ Possible	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
85033/04/ 48/ Male	Atrial fibrillation	23	3	Moderate/ Unlikely	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85042/06/ 38/ Male	Atrial fibrillation[a]	10	2	Moderate/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85042/14/ 78/ Female	Atrial fibrillation[a]	5	5	Severe/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85044/06/ 37/ Male	Atrial fibrillation	1	2	Severe/ Unlikely	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85056/10/ 69/ Male	Coronary artery disease NOS	57	10	Severe/ Unrelated	Study drug interrupted, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85071/07/ 72/ Female	Atrial fibrillation	12	5	Moderate/ Unrelated	Required/prolonged hospitalization	Recovered without sequelae
85073/07/ 75/ Female	Ovarian neoplasm NOS	64	22	Not assessed/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85077/01/ 76/ Female	Bradycardia NOS[a]	13	1	Severe/ Probable	Study drug discontinued, other med/non-drug therapy	Recovered without sequelae
	Syncope	13	1	Severe/ Probable	Other med/non-drug therapy	Recovered without sequelae
85077/02/ 48/ Female	Headache NOS	236	3	Severe/ Unrelated	Further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85082/05/ 86/ Female	Cardiac failure congestive[a]	14	5	Severe/ Probable	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
85087/01/ 84/ Male	Pneumonia NOS[a]	102	17	Severe/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85100/03/ 56/ Male	Chest pain NEC	4	2	Severe/ Unlikely	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85108/01/ 78/ Female	Prothrombin activity decreased	6	3	Severe/ Unlikely	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Myocardial infarction[b]	9	1	Moderate/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85114/01/ 78/ Female	Cardiac failure congestive	25	6	Moderate/ Unlikely	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85114/03/ 78/ Female	Atrial fibrillation[a]	24	2	Severe/ Unlikely	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85119/03/ 76/ Female	Urinary tract infection NOS	204	43	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
Placebo						
85008/05/ 60/ Female	Atrial fibrillation[a]	171	1	Moderate/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85011/05/ 68/ Male	Lung cancer stage unspecified[a]	205	71	Severe/ Unrelated	Study drug discontinued, further evaluation required	Death

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
85022/02/ 68/ Male	Carotid artery occlusion	9	8	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85028/05/ 47/ Female	Chest pain NEC[a]	84	4	Moderate/ Unrelated	Study drug discontinued, other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85033/02/ 75/ Male	Abdominal pain NOS	1	44	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Diarrhea NOS	1	44	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Melena	1	44	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Vomiting NOS	1	9	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85034/01/ 49/ Female	Pleural effusion	141	2	Moderate/ Unlikely	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Atrial flutter[a]	162	1	Moderate/ Possible	Study drug discontinued, Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85058/21/ 76/ Female	Atrial fibrillation[a]	129	3	Moderate/ Unlikely	Study drug discontinued, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
	Chest pain NEC[a]	129	1	Moderate/ Unrelated	Study drug discontinued, other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
	Respiratory failure (exc neonatal)[a]	129	1	Severe/ Unrelated	Study drug discontinued, other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85060/12/ 69/ Female	Atrial fibrillation[a]	19	3	Severe/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85067/03/ 61/ Male	Atrial fibrillation[a]	13	2	Severe/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85067/06/ 69/ Male	Atrial fibrillation[a]	19	1	Severe/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85067/09/ 59/ Male	Atrial fibrillation	120	2	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
85077/06/ 62/ Male	Chest pain NEC	28	2	Moderate/ Unrelated	Other med/non-drug therapy, further evaluation required, required/prolonged hospitalization	Recovered without sequelae
85077/07/ 77/ Male	Renal failure NOS[a]	262	49	Severe/ Unrelated	Study drug discontinued, required/prolonged hospitalization	Death
85082/03/ 64/ Male	Syncope	5	1	Severe/ Possible	Required/prolonged hospitalization	Recovered without sequelae
85085/01/ 75/ Male	Arthritis infective NOS	84	9	Severe/ Unrelated	Study drug interrupted, other med/non-drug therapy, required/prolonged hospitalization	Recovered with sequelae

Treatment/ Patient/ Age/ Gender	Serious Adverse Event	Study Day at Onset	Duration of Adverse Event	Severity/ Relationship to Study Drug	Action Taken	Outcome
85087/03/ 77/ Female	Fracture NOS	161	5	Severe/ Unrelated	Study drug discontinued, other med/non-drug therapy, required/prolonged hospitalization	Recovered with sequelae
85104/05/ 67/ Female	Carotid artery stenosis	68	19	Severe/ Unrelated	Other med/non-drug therapy, required/prolonged hospitalization	Recovered without sequelae
	Headache NOS	86	20	Severe/ Unrelated	Other med/non-drug therapy, further evaluation required; required/prolonged hospitalization	Recovered without sequelae
85111/07/ 46/ Male	Tooth abscess	140	3	Not assessed/ Unrelated	Study drug interrupted, required/prolonged hospitalization	Recovered without sequelae
	Syncope	280	5	Severe/ Unlikely		Recovered without sequelae

[a] Patient was prematurely terminated due to serious adverse event.

[b] Noted at screening.

Source: Data Listing 2.5.1a and 2.5.1b

Appendix 6: Summary statistics - hematology results - RAFT

Parameter/Treatment Group	N	Mean±SD		
		Baseline	Endpoint	Change From Baseline
Hemoglobin (g/dl)				
Propafenone SR 225 mg bid	119	14.1±1.4	14.0±1.4	-0.1±0.8
Propafenone SR 325 mg bid	133	14.0±1.4	14.0±1.4	-0.0±0.9
Propafenone SR 425 mg bid	131	14.0±1.5	13.9±1.4	-0.1±0.8
Placebo	119	14.1±1.7	14.1±1.4	0.1±1.2
Hematocrit (%)				
Propafenone SR 225 mg bid	119	41.8±4.1	41.7±4.1	-0.2±2.7
Propafenone SR 325 mg bid	133	41.6±3.8	41.5±4.0	-0.0±3.1
Propafenone SR 425 mg bid	131	41.4±4.3	41.0±4.0	-0.4±2.6
Placebo	119	41.8±4.3	42.0±4.1	0.2±3.4
RBC (M/uL)				
Propafenone SR 225 mg bid	119	4.5±0.5	4.5±0.5	-0.0±0.3
Propafenone SR 325 mg bid	133	4.6±0.5	4.5±0.5	-0.0±0.3
Propafenone SR 425 mg bid	131	4.5±0.5	4.5±0.4	-0.1±0.3
Placebo	119	4.5±0.5	4.6±0.5	0.0±0.3
WBC (K/uL)				
Propafenone SR 225 mg bid	119	6.9±1.8	7.0±2.3	0.1±2.2
Propafenone SR 325 mg bid	133	6.9±1.9	6.6±1.9	-0.3±1.5
Propafenone SR 425 mg bid	131	7.0±1.9	6.6±2.0	-0.4±1.6
Placebo	119	6.9±2.2	7.0±2.1	0.1±1.7
Neutrophils (%)				
Propafenone SR 225 mg bid	116	62.3±9.9	63.4±10.1	1.1±9.5
Propafenone SR 325 mg bid	133	61.6±9.7	61.7±9.4	0.1±9.1
Propafenone SR 425 mg bid	131	62.7±8.5	62.0±9.5	-0.6±8.4
Placebo	118	61.7±9.5	62.3±9.3	0.5±8.3
Lymphocytes (%)				
Propafenone SR 225 mg bid	116	27.3±8.8	26.8±9.5	-0.5±7.5
Propafenone SR 325 mg bid	133	28.1±8.8	27.4±9.7	-0.7±6.9
Propafenone SR 425 mg bid	131	27.2±7.6	26.9±7.9	-0.3±6.4
Placebo	118	27.6±8.2	27.2±8.5	-0.3±6.7
Monocytes (%)				
Propafenone SR 225 mg bid	116	7.1±2.3	6.6±2.3	-0.5±2.5
Propafenone SR 325 mg bid	133	7.2±4.2	7.7±2.4	0.4±4.4
Propafenone SR 425 mg bid	131	7.1±1.9	7.6±3.3	0.5±3.3
Placebo	118	7.6±3.3	7.4±2.5	-0.2±3.1
Eosinophils (%)				
Propafenone SR 225 mg bid	116	2.8±2.2	2.8±1.9	-0.1±2.3
Propafenone SR 425 mg bid	131	2.6±1.8	3.0±2.0	0.4±1.8
Placebo	118	2.6±1.6	2.7±1.7	0.1±1.6
Basophils (%)				
Propafenone SR 225 mg bid	116	0.5±0.4	0.5±0.4	-0.0±0.4
Propafenone SR 325 mg bid	133	0.4±0.3	0.5±0.3	0.1±0.4
Propafenone SR 425 mg bid	131	0.5±0.3	0.5±0.4	0.0±0.5
Placebo	118	0.5±0.4	0.5±0.3	-0.0±0.4
Platelets (K/uL)				
Propafenone SR 225 mg bid	119	228.4±56.7	236.4±62.3	8.1±41.7
Propafenone SR 325 mg bid	133	221.5±55.7	229.2±55.0	7.6±37.9
Propafenone SR 425 mg bid	130	224.5±54.6	232.8±65.2	8.4±40.4
Placebo	117	225.5±58.6	230.1±59.8	4.6±37.3

Source: Table 9.3.4.1

Appendix 7 :Summary Statistics Liver Function-Related adverse events

Body System/MedDRA Preferred Term	Propafenone SR 225 mg bid (N = 126) n (%)	Propafenone SR 325 mg bid (N = 135) n (%)	Propafenone SR 425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Gastrointestinal disorders				
Pancreatitis NOS	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hepato-biliary disorders				
Cholelithiasis	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hepatic cyst	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hepatomegaly	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.8)
Investigations				
Blood alkaline phosphatase NOS increased	0 (0.0)	0 (0.0)	4 (2.9)	0 (0.0)
Liver function tests NOS abnormal	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.8)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)
Alanine aminotransferase increased	1 (0.8)	0 (0.0)	2 (1.5)	0 (0.0)

Source: Table 9.3.2.2

Appendix 8 : Summary Statistics Liver function tests

Parameter/Treatment Group	N	Mean±SD Baseline	Endpoint	Change From Baseline
SGOT (IU/L)				
Propafenone SR 225 mg bid	122	21.2±7.0	20.4±6.9	-0.8±6.2
Propafenone SR 325 mg bid	131	22.5±10.3	21.5±9.5	-1.0±11.1
Propafenone SR 425 mg bid	134	20.7±6.5	20.8±8.6	0.0±6.9
Placebo	120	23.2±19.1	21.3±8.6	-1.9±19.7
SGPT (IU/L)				
Propafenone SR 225 mg bid	122	23.1±11.3	21.9±10.7	-1.2±9.6
Propafenone SR 325 mg bid	131	22.8±15.5	23.2±16.5	0.3±18.4
Propafenone SR 425 mg bid	134	20.8±9.1	21.8±11.2	1.1±8.8
Placebo	120	22.5±12.8	21.5±10.5	-1.0±10.2
Total bilirubin (mg/dL)				
Propafenone SR 225 mg bid	122	0.6±0.3	0.6±0.3	-0.0±0.2
Propafenone SR 325 mg bid	131	0.6±0.3	0.5±0.2	-0.1±0.2
Propafenone SR 425 mg bid	134	0.6±0.3	0.6±0.3	-0.1±0.2
Placebo	120	0.6±0.3	0.6±0.3	-0.1±0.2
Alkaline phosphatase (IU/L)				
Propafenone SR 225 mg bid	122	74.1±25.4	75.3±26.4	1.2±14.7
Propafenone SR 325 mg bid	131	74.5±32.4	74.6±28.9	0.1±21.8
Propafenone SR 425 mg bid	134	73.1±20.8	73.3±21.0	0.2±16.0
Placebo	120	71.7±23.2	72.1±22.5	0.4±12.8
LDH (IU/L)				
Propafenone SR 225 mg bid	122	167.7±35.8	170.0±37.9	2.3±28.1
Propafenone SR 325 mg bid	131	180.2±60.3	175.5±56.2	-4.8±40.5
Propafenone SR 425 mg bid	134	173.8±73.7	178.4±76.1	4.6±30.5
Placebo	120	172.7±43.7	172.4±41.3	-0.4±31.5

Source: Table 9.3.4.2

Appendix 9: QT/QTc changes in patients exposed to propafenone SR and IR

Awaiting additional data from sponsor

Appendix 10:Incidence of electrolyte related adverse events - RAFT

	Propafenone SR			
MedDRA Preferred Term	225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Blood chloride decreased	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Blood potassium decreased	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Blood sodium decreased	1 (0.8)	0 (0.0)	2 (1.5)	0 (0.0)
Hypokalemia	1 (0.8)	2 (1.5)	1 (0.7)	0 (0.0)

Source: Table 9.3.2.2

Appendix 11: Summary statistics of renal function test results - RAFT

		Mean±SD		
Parameter/Treatment Group	N	Baseline	Endpoint	Change From Baseline
Creatinine (mg/dL)				
Propafenone SR 225 mg bid	122	0.9±0.2	0.9±0.3	0.0±0.1
Propafenone SR 325 mg bid	131	0.9±0.2	1.0±0.3	0.1±0.2
Propafenone SR 425 mg bid	134	0.9±0.2	1.0±0.3	0.1±0.2
Placebo	120	1.0±0.3	1.0±0.3	0.0±0.1
BUN				
Propafenone SR 225 mg bid	122	15.8±4.8	16.3±6.2	0.6±4.6
Propafenone SR 325 mg bid	131	16.1±4.3	16.7±5.3	0.6±4.2
Propafenone SR 425 mg bid	134	15.9±5.1	16.3±4.9	0.5±3.6
Placebo	120	16.2±5.1	17.1±5.9	0.9±4.8

Source: Table 9.3.4.2

Appendix 12: Summary statistics of other chemistries - RAFT

Parameter/Treatment Group	N	Mean±SD		
		Baseline	Endpoint	Change From Baseline
Glucose (mg/dL)				
Propafenone SR 225 mg bid	122	106.3±41.2	108.7±33.7	2.4±34.8
Propafenone SR 325 mg bid	131	106.7±42.6	100.2±27.9	-6.4±34.9
Propafenone SR 425 mg bid	134	105.9±42.3	109.8±52.1	3.9±46.4
Placebo	120	106.8±39.6	115.7±54.0	8.9±34.2
Uric acid (g/dL)				
Propafenone SR 225 mg bid	122	5.7±1.4	5.9±1.5	0.2±0.9
Propafenone SR 325 mg bid	131	5.8±1.4	5.8±1.6	-0.0±1.0
Propafenone SR 425 mg bid	134	5.8±1.7	5.8±1.5	0.0±0.9
Placebo	120	5.8±1.4	5.7±1.4	-0.0±0.9
Cholesterol (mg/dL)				
Propafenone SR 225 mg bid	122	203.2±36.7	202.2±38.2	-1.0±29.0
Propafenone SR 325 mg bid	131	200.1±38.4	199.1±37.3	-1.0±32.7
Propafenone SR 425 mg bid	134	199.4±35.4	197.5±34.9	-1.9±27.1
Placebo	120	201.2±38.0	199.1±39.8	-2.1±25.3
Calcium (mg/dL)				
Propafenone SR 225 mg bid	122	9.1±0.4	9.1±0.4	-0.1±0.4
Propafenone SR 325 mg bid	131	9.0±0.5	9.0±0.4	-0.1±0.6
Propafenone SR 425 mg bid	134	9.1±0.4	9.0±0.4	-0.1±0.4
Placebo	120	9.1±0.4	9.1±0.4	-0.0±0.4
Total protein (g/dL)				
Propafenone SR 225 mg bid	122	6.9±0.5	6.9±0.5	0.0±0.4
Propafenone SR 325 mg bid	131	6.9±0.5	6.9±0.5	-0.1±0.5
Propafenone SR 425 mg bid	134	7.0±0.5	6.9±0.5	-0.1±0.5
Placebo	120	7.0±0.5	6.9±0.4	-0.1±0.4
Albumin (g/dL)				
Propafenone SR 225 mg bid	122	4.4±0.4	4.3±0.5	-0.0±0.4
Propafenone SR 325 mg bid	131	4.3±0.4	4.3±0.4	-0.1±0.4
Propafenone SR 425 mg bid	134	4.4±0.4	4.3±0.3	-0.1±0.3
Placebo	120	4.4±0.4	4.3±0.4	-0.1±0.3
Phosphorus				
Propafenone SR 225 mg bid	121	3.2±0.5	3.2±0.5	-0.0±0.5
Propafenone SR 325 mg bid	131	3.2±0.5	3.2±0.5	0.0±0.6
Propafenone SR 425 mg bid	134	3.2±0.6	3.3±0.5	0.1±0.6
Placebo	120	3.3±0.5	3.2±0.6	-0.0±0.6

Source: Table 9.3.4.2

Appendix 13 :Patients withdrawing before Day 5 and causes for study withdrawal - ERAFT

Country	Centre number	Patient number	Days in study	Reason for discontinuation	AE which led to: wd?	death?
Treatment group: Propafenone SR 325 mg bid						
Canada	110	3114	2	Protocol violation	No	No
Israel	306	3378	2	Withdrawal of consent	No	No
	308	3409	3	-	No	No
Poland	502	3626	2	Adverse event	Yes	No
Treatment group: Propafenone SR 425 mg bid						
Canada	108	3088	2	Adverse event	Yes	No
Israel	307	3399	4	Adverse event	Yes	No
		3783	3	Adverse event	Yes	No
Poland	506	3914	4	Adverse event	Yes	No
Lithuania	825	4111	4	-	No	No
		4114	4	-	No	No
Treatment group: Placebo						
Germany	202	4184	4	-	No	No
Italy	404	3550	4	Protocol violation	No	No
Poland	506	4178	4	Adverse event	Yes	No
	507	3634	3	Adverse event	Yes	No
Lithuania	823	4017	2	Adverse event	Yes	No

Patients without reason for discontinuation were considered completers in the definition of the protocol by the investigator: either patient recorded symptomatic PAF or patient was not in sinus rhythm at end of loading period

Appendix 14:Incidence of AEs >1% in treatment groups FAS-RAFT

Table 42 Incidence of adverse events >1% in any treatment group (full analysis set)

MedDRA Body System/Preferred Term	Propafenone SR 225 mg bid (N = 126) n (%)	Propafenone SR 325 mg bid (N = 135) n (%)	Propafenone SR 425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Blood and lymphatic system disorders				
Anemia	1 (0.8)	2 (1.5)	0 (0.0)	1 (0.8)
Lymphadenopathy	1 (0.8)	2 (1.5)	0 (0.0)	0 (0.0)
Cardiac disorders				
Angina pectoris	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)
Arrhythmia	0 (0.0)	1 (0.7)	2 (1.5)	0 (0.0)
Atrial fibrillation	7 (5.6)	6 (4.4)	7 (5.1)	6 (4.8)
Atrial flutter	3 (2.4)	2 (1.5)	0 (0.0)	1 (0.8)
AV block first degree	3 (2.4)	3 (2.2)	4 (2.9)	0 (0.0)
Bradycardia	4 (3.2)	4 (3.0)	6 (4.4)	1 (0.8)
Cardiac failure congestive	0 (0.0)	1 (0.7)	3 (2.2)	1 (0.8)
Cardiac murmur	2 (1.6)	3 (2.2)	6 (4.4)	0 (0.0)
Edema	6 (4.8)	18 (13.3)	10 (7.4)	8 (6.3)
Palpitations	22 (17.5)	30 (22.2)	23 (16.9)	21 (16.7)

MedDRA Body System/Preferred Term	Propafenone SR 225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Sinus bradycardia	0 (0.0)	2 (1.5)	0 (0.0)	1 (0.8)
Tachycardia	3 (2.4)	5 (3.7)	2 (1.5)	5 (4.0)
Ventricular extrasystoles	1 (0.8)	0 (0.0)	1 (0.7)	2 (1.6)
Ear and labyrinth disorders				
Tinnitus	1 (0.8)	0 (0.0)	2 (1.5)	0 (0.0)
Eye disorders				
Eye hemorrhage	0 (0.0)	2 (1.5)	2 (1.5)	0 (0.0)
Eye inflammation	0 (0.0)	1 (0.7)	2 (1.5)	1 (0.8)
Vision abnormal	2 (1.6)	1 (0.7)	0 (0.0)	0 (0.0)
Vision blurred	1 (0.8)	1 (0.7)	5 (3.7)	0 (0.0)
Gastrointestinal disorders				
Abdominal pain	7 (5.6)	4 (3.0)	2 (1.5)	6 (4.8)
Constipation	10 (7.9)	19 (14.1)	16 (11.8)	3 (2.4)
Diarrhea	2 (1.6)	3 (2.2)	5 (3.7)	3 (2.4)
Diverticulitis	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)
Dry mouth	1 (0.8)	1 (0.7)	5 (3.7)	1 (0.8)
Dyspepsia	4 (3.2)	6 (4.4)	3 (2.2)	3 (2.4)
Flatulence	3 (2.4)	3 (2.2)	1 (0.7)	0 (0.0)
Gastroesophageal reflux disease	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.6)
Melena	2 (1.6)	0 (0.0)	1 (0.7)	1 (0.8)
Nausea	11 (8.7)	15 (11.1)	23 (16.9)	11 (8.7)
Toothache	0 (0.0)	2 (1.5)	1 (0.7)	0 (0.0)
Vomiting	1 (0.8)	0 (0.0)	8 (5.9)	3 (2.4)
General disorder and administration site				
Chest pain	22 (17.5)	16 (11.9)	19 (14.0)	16 (12.7)
Fatigue	14 (11.1)	17 (12.6)	17 (12.5)	7 (5.6)
Malaise	1 (0.8)	0 (0.0)	2 (1.5)	3 (2.4)
Pain	0 (0.0)	0 (0.0)	2 (1.5)	1 (0.8)
Pyrexia	1 (0.8)	6 (4.4)	3 (2.2)	2 (1.6)
Rigors	2 (1.6)	4 (3.0)	1 (0.7)	0 (0.0)
Weakness	4 (3.2)	6 (4.4)	6 (4.4)	3 (2.4)
Immune system disorders				
Seasonal allergy	2 (1.6)	1 (0.7)	0 (0.0)	0 (0.0)
Infections and infestations				
Arthritis infective	2 (1.6)	0 (0.0)	0 (0.0)	1 (0.8)
Bronchitis	3 (2.4)	3 (2.2)	2 (1.5)	3 (2.4)
Gastroenteritis	0 (0.0)	0 (0.0)	4 (2.9)	0 (0.0)
Gastroenteritis helicobacter	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza	9 (7.1)	6 (4.4)	6 (4.4)	6 (4.8)
Pharyngitis	2 (1.6)	4 (3.0)	1 (0.7)	2 (1.6)
Pneumonia	1 (0.8)	1 (0.7)	2 (1.5)	1 (0.8)
Sinusitis	1 (0.8)	2 (1.5)	2 (1.5)	1 (0.8)
Skin infection	5 (4.0)	2 (1.5)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	11 (8.7)	16 (11.9)	11 (8.1)	7 (5.6)
Urinary tract infection	5 (4.0)	3 (2.2)	2 (1.5)	2 (1.6)
Injury and poisoning				
Burns	0 (0.0)	3 (2.2)	0 (0.0)	1 (0.8)

MedDRA Body System/Preferred Term	Propafenone SR 225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Fracture	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.6)
Injury	3 (2.4)	3 (2.2)	4 (2.9)	4 (3.2)
Investigations				
Alanine aminotransferase increased	1 (0.8)	0 (0.0)	2 (1.5)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)
Bacteriuria present	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Blood alkaline phosphatase increased	0 (0.0)	0 (0.0)	4 (2.9)	0 (0.0)
Blood glucose increased	1 (0.8)	0 (0.0)	1 (0.7)	3 (2.4)
Blood pressure decreased	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)
Blood pressure increased	2 (1.6)	2 (1.5)	2 (1.5)	2 (1.6)
Blood sodium decreased	1 (0.8)	0 (0.0)	2 (1.5)	0 (0.0)
Blood uric acid increased	1 (0.8)	2 (1.5)	2 (1.5)	0 (0.0)
Cardioactive drug level above therapeutic	1 (0.8)	1 (0.7)	3 (2.2)	1 (0.8)
Hematuria present	2 (1.6)	2 (1.5)	4 (2.9)	3 (2.4)
Heart rate irregular	2 (1.6)	2 (1.5)	2 (1.5)	3 (2.4)
Proteinuria present	1 (0.8)	0 (0.0)	1 (0.7)	2 (1.6)
Prothrombin level increased	1 (0.8)	2 (1.5)	1 (0.7)	0 (0.0)
Weight decreased	0 (0.0)	2 (1.5)	1 (0.7)	0 (0.0)
Weight increased	1 (0.8)	0 (0.0)	2 (1.5)	0 (0.0)
Metabolism and nutrition disorder				
Anorexia	0 (0.0)	2 (1.5)	1 (0.7)	0 (0.0)
Gout	1 (0.8)	0 (0.0)	0 (0.0)	2 (1.6)
Hypokalemia	1 (0.8)	2 (1.5)	1 (0.7)	0 (0.0)
Musculoskeletal, connective tissue and bone				
Arthralgia	3 (2.4)	4 (3.0)	4 (2.9)	5 (4.0)
Arthritis	1 (0.8)	2 (1.5)	2 (1.5)	0 (0.0)
Back pain	3 (2.4)	2 (1.5)	3 (2.2)	2 (1.6)
Muscle cramps	1 (0.8)	1 (0.7)	0 (0.0)	2 (1.6)
Muscle spasms	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle weakness	1 (0.8)	5 (3.7)	1 (0.7)	0 (0.0)
Myalgia	1 (0.8)	1 (0.7)	2 (1.5)	2 (1.6)
Neck pain	2 (1.6)	0 (0.0)	2 (1.5)	0 (0.0)
Pain in limb	0 (0.0)	3 (2.2)	1 (0.7)	5 (4.0)
Tendonitis	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)
Neoplasms benign and malignant (including CYS)				
Abdominal neoplasm	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)
Skin carcinoma	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders				
Balance impaired	0 (0.0)	1 (0.7)	2 (1.5)	0 (0.0)
Dizziness (exc vertigo)	29 (23.0)	28 (20.7)	29 (21.3)	18 (14.3)
Gait abnormal	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)
Headache	8 (6.3)	12 (8.9)	14 (10.3)	11 (8.7)
Hypoaesthesia	4 (3.2)	1 (0.7)	0 (0.0)	1 (0.8)
Insomnia	2 (1.6)	1 (0.7)	2 (1.5)	2 (1.6)
Paraesthesia	2 (1.6)	3 (2.2)	1 (0.7)	0 (0.0)
Peripheral neuropathy	2 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)
Somnolence	1 (0.8)	1 (0.7)	4 (2.9)	0 (0.0)
Syncope	0 (0.0)	1 (0.7)	1 (0.7)	2 (1.6)

MedDRA Body System/Preferred Term	Propafenone SR 225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Taste disturbance	7 (5.6)	18 (13.3)	30 (22.1)	1 (0.8)
Tremor	2 (1.6)	0 (0.0)	3 (2.2)	1 (0.8)
Psychiatric disorders				
Anxiety	12 (9.5)	17 (12.6)	16 (11.8)	13 (10.3)
Depression	1 (0.8)	4 (3.0)	0 (0.0)	2 (1.6)
Mental disorder	1 (0.8)	2 (1.5)	0 (0.0)	0 (0.0)
Renal and urinary disorders				
Dysuria	1 (0.8)	3 (2.2)	2 (1.5)	0 (0.0)
Loin pain	2 (1.6)	0 (0.0)	0 (0.0)	3 (2.4)
Pyuria	1 (0.8)	0 (0.0)	1 (0.7)	2 (1.6)
Urinary frequency	2 (1.6)	2 (1.5)	1 (0.7)	0 (0.0)
Urine abnormal	3 (2.4)	2 (1.5)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorder				
Breath sounds decreased	0 (0.0)	1 (0.7)	2 (1.5)	1 (0.8)
Cough	2 (1.6)	4 (3.0)	1 (0.7)	2 (1.6)
Dyspnea	16 (12.7)	23 (17.0)	17 (12.5)	9 (7.1)
Epistaxis	1 (0.8)	2 (1.5)	2 (1.5)	1 (0.8)
Hemoptysis	2 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)
Rales	2 (1.6)	1 (0.7)	3 (2.2)	0 (0.0)
Respiratory failure (exc neonatal)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Wheezing	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)
Skin & subcutaneous tissue disorders				
Dermatitis	2 (1.6)	3 (2.2)	2 (1.5)	3 (2.4)
Dry skin	1 (0.8)	0 (0.0)	0 (0.0)	2 (1.6)
Ecchymosis	2 (1.6)	3 (2.2)	5 (3.7)	0 (0.0)
Erythema	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)
Petechiae	0 (0.0)	0 (0.0)	2 (1.5)	1 (0.8)
Pruritus	1 (0.8)	3 (2.2)	1 (0.7)	1 (0.8)
Sweating increased	4 (3.2)	4 (3.0)	4 (2.9)	3 (2.4)
Urticaria	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)
Vascular disorders				
Hypertension	3 (2.4)	2 (1.5)	6 (4.4)	5 (4.0)
Venous thrombosis deep limb	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)

Source: Table 9.3.2.2

Appendix 15:Hazard ratios for secondary efficacy variables –age, gender, history of cardioversion, structural heart disease, and NYHA - RAFT

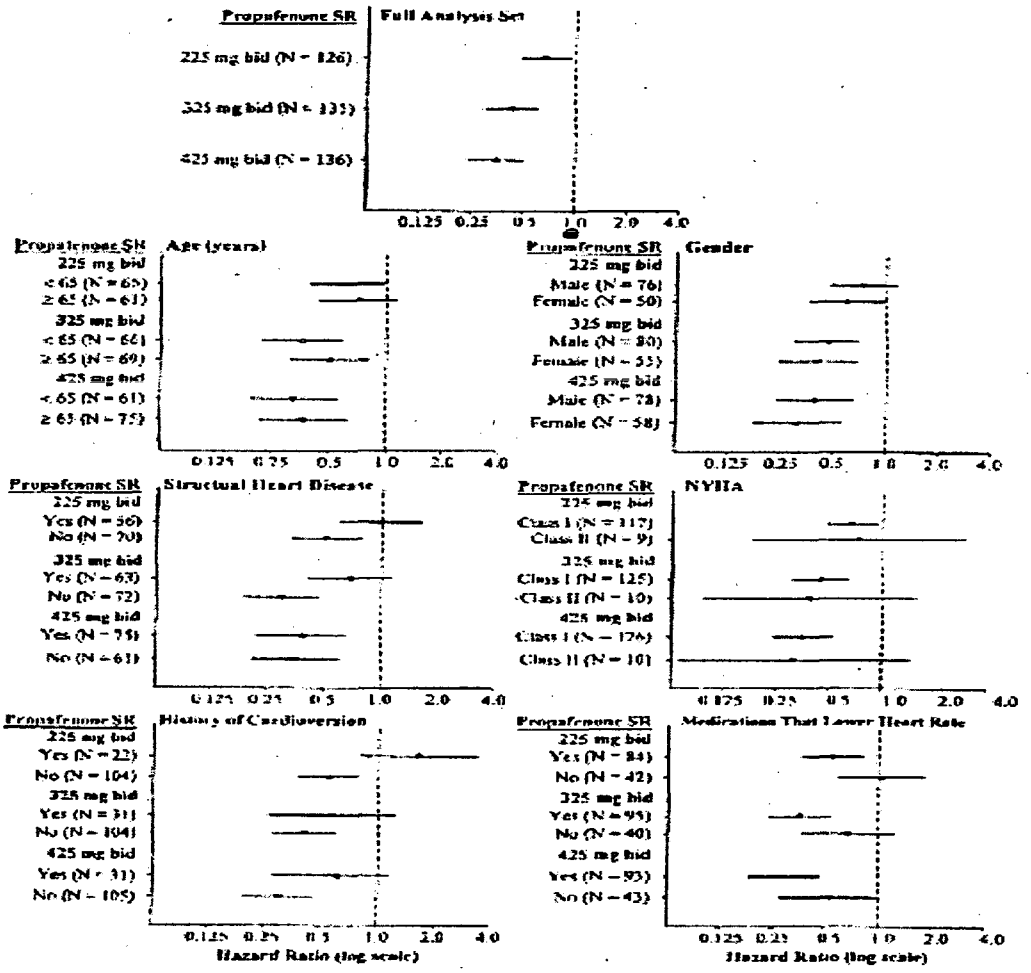
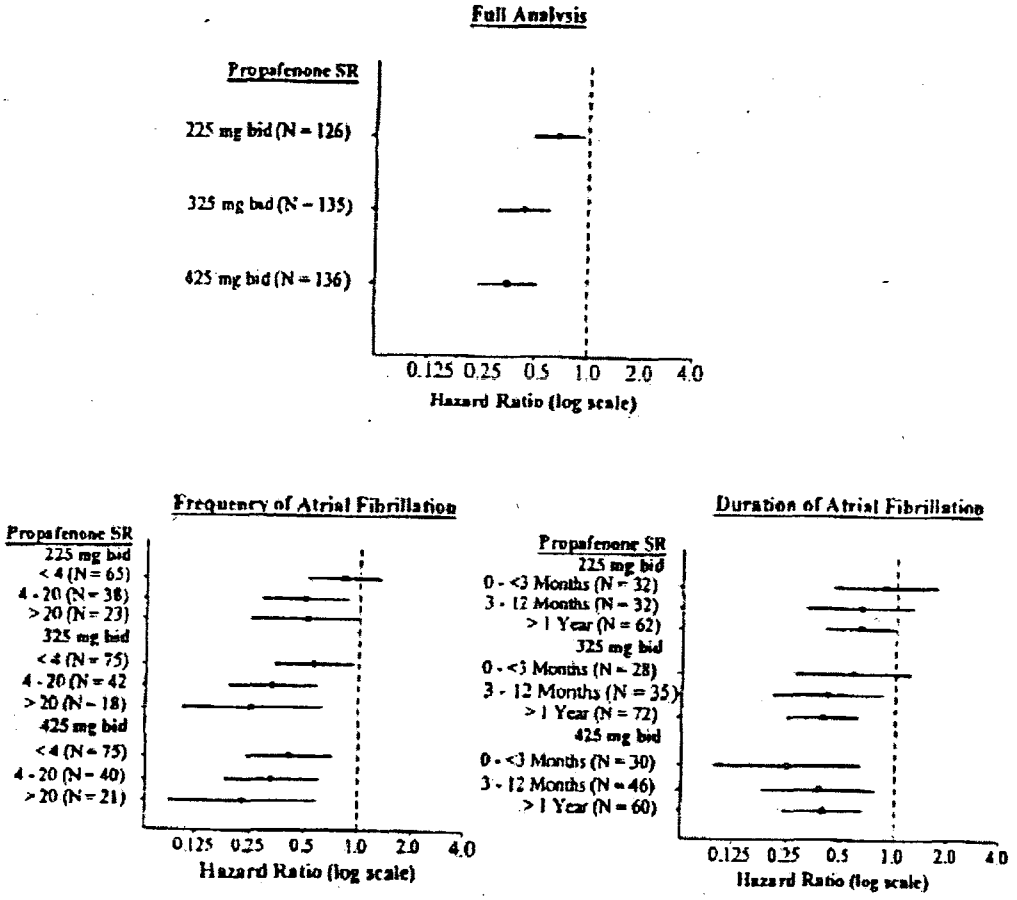


Figure 4 Propafenone SR treatment group versus hazard ratio for the tachycardia-free period from Day 1 of randomization for the full analysis set and for subpopulations (age, gender, history of structural heart disease, NYHA class, history of cardioversion, and concomitant medications that lower heart rate)

See Figures 10-12

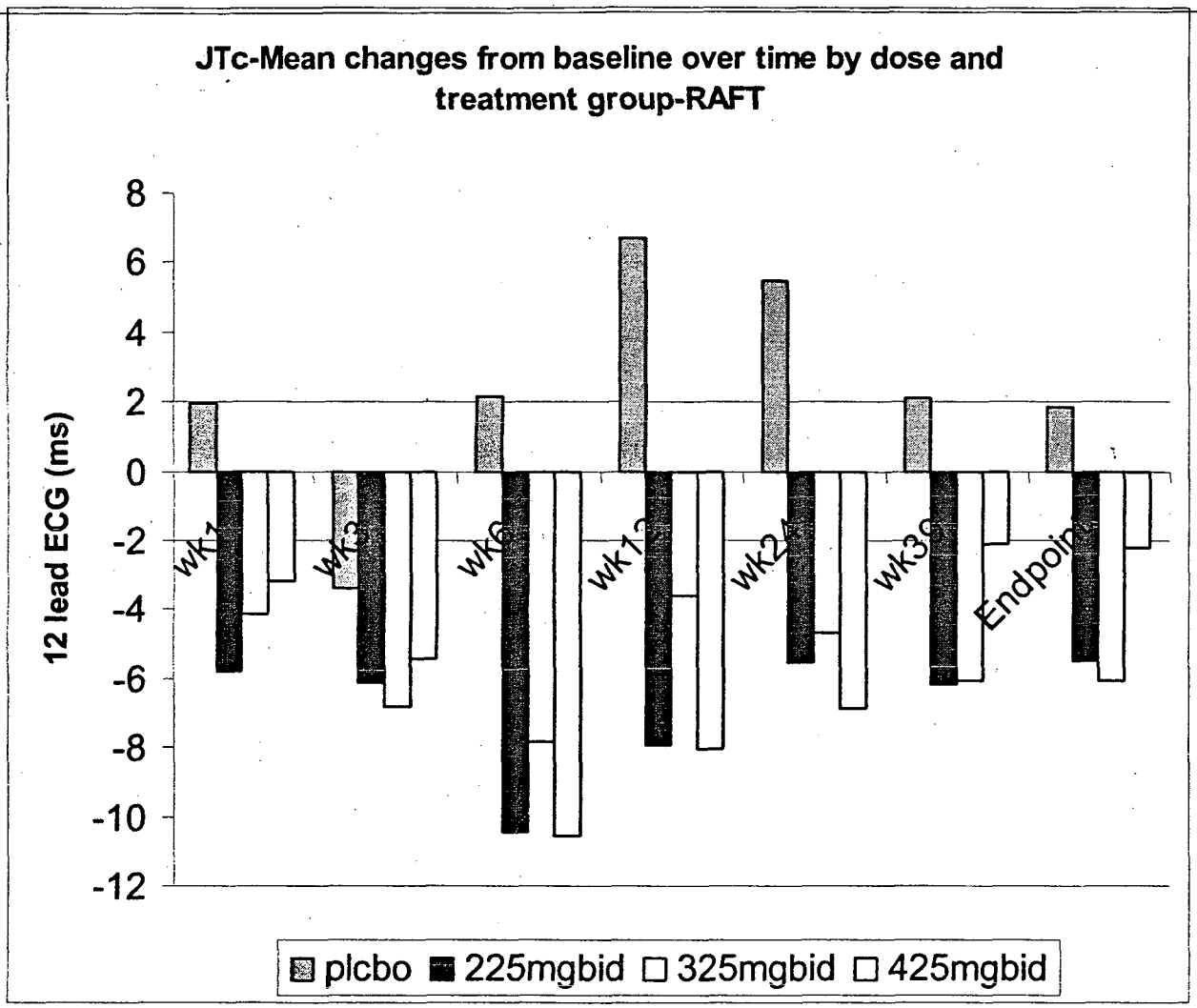
Appendix 16: Hazard ratios for secondary efficacy variables – frequency and duration of atrial fibrillation -RAFT



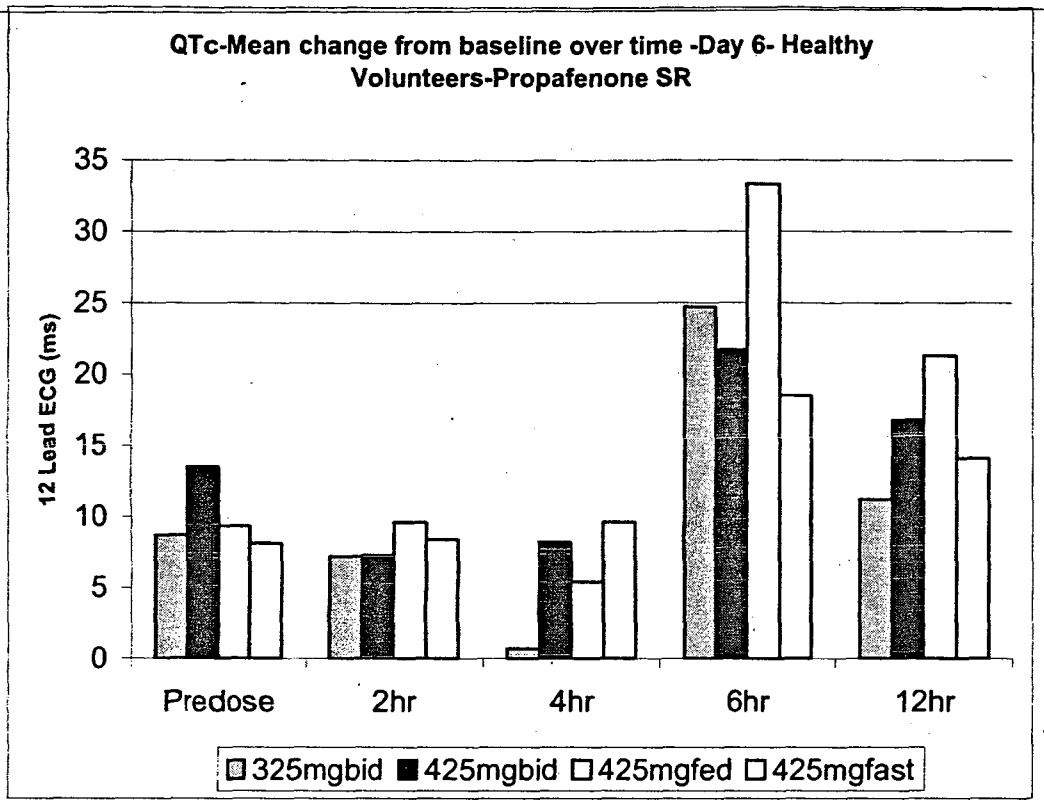
Propafenone SR dose versus hazard ratio for the tachycardia-free period from Day 1 of randomization for the full analysis set and for frequency of atrial fibrillation and duration of atrial fibrillation

See Figures 10-12

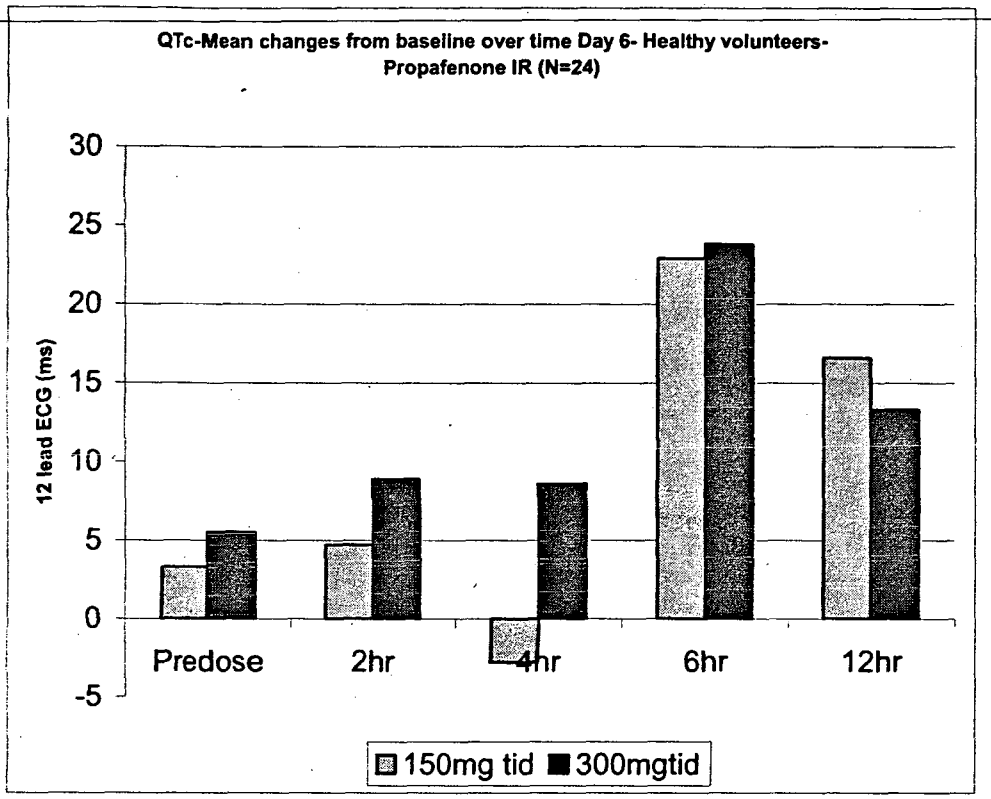
Appendix 17 :JTc interval on ECG - Mean changes from baseline over time by dose and treatment group-RAFT



Appendix 18: QTc-Mean changes from baseline over time in Healthy Volunteers fed and fasted -Propafenone SR (N=24)



Appendix 19: QTc -Mean changes from baseline over time in Healthy volunteers - Day 6 Propafenone IR (N=24)



Appendix 20: Tabulated Literature review-Propafenone IR and SR Based on literature review of 449 publications

Target Population (N)	Study (Yr)	1°Endpoint	Drug±Comparator Duration	ECG changes	Safety
Afib/Aflut	Review Article (1998)	Reduction of SVT, Afib/Aflutter Acute and long term treatment of SVA	Propafenone IR (immediate release)		Dose dependent proarrhythmias - tend to be higher in pts with SHD
>30PVC/hr;<35% variability in 2 24 hr ECG monitoring periods; Symptomatic PVC;(N=80)	(1998) DB,R,PC,Cros-sover; Protocol N=61	Control of PVC and Tolerability	IR 150 mg tid SR325mg bid SR225mg bid 14 days X 3 periods (42 days)	ECGs at baseline and end of each period for VPC. No data for atrial fibrillation or PSVT	
PAF and VPC N=5 each	(1993) Clinical effects of Propafenone on QT, QTc, QRS, PQ and RR intervals		Propafenone IR 450 mg /day for 7 days Disopyramide 300mg /day for 7 days	Propafenone increased QRS but not QTc. Disopyramide prolonged QTc but not QRS.	
Patients hospitalized for Atrial fibrillation N=417	(1997) Retrospective review of hospital charts over 550 hospitalizations	Adverse cardiac events during initiation of therapy in hospital	Propafenone N=110 Procainamide N=189 QuinidineN=179 Sotalol N=72	Most common was bradyarrhythmia (7.9%). QT prolongation in 1.5%,	80 cardiac adverse events in 73/597 trials (13.4%). The risk was greates during the first 24 hours of therapy-no

Target Population (N)	Study (Yr)	1°Endpoint	Drug±Comparator Duration	ECG changes	Safety
			~~Amio N=25~~ Disopyramide20 Flecainide N=2	~~ventricular~~ arrhythmia 1.3%.	~~deaths.~~ Multrivariate analyses showed previous MI and older age associated with increased risk
Atrial fibrillation of recent onset	Review article	Comparative studies for efficacy	IR 600mg	NA	Effective in Afib butincidence of Aflutter during active treatment was similar to placebo
Symptomatic PSVT Afib N=17 PSVT N =16	(1991) 6 month open label followed by R,DB,PC in an outpatient clinic	Time to first recurrence	IR 300mg tid (N=19); 300mg bid (N=3); 150mg bid; (N=1); DB phase 60 days	TTM used - documentingre currence of symptoms	
Chronic Afib N=100	(1996)Cardiovers ion followed by 2 day OL exposure to drug and Plcbo	Evaluate the risk of Prop. before electrical defibrillation	IR 750mg /day		During the 2 day in hospital stay, 6 patients discont - inued because of side effects.
Myocardial Infarction 3 months after infarction N=85	(1997)Determine changes in QTc dispersion and QTc during administration of propafenone and atenolol	QTc changes	IR Propafenone 600mg /day N=39 Atenolol 50mg N=46 Duration 7 days	QTc increased significantly with severity of arrhythmia QTc dispersio n significantly decreases with IR and atenolol QTC decrease s with atenolol and no change with Propaf. IR	
Symptomatic recurrent A Fib N=304 N for IR=102 N sotalol=10 Nplcbo=92	(2001)Random-ized to 3 arms	Proportion of patients in Sinus rhythm in groups. Kaplan Meier curves	One Year Mean daily dose13+/- 1.5mg/kg Propafenone IR; 3+/-0.4mg/kg of Sotalol		Malignant non-fatal pro-arrhythmic effects with sotalol.Recurrences prolonged with sotalol and propafenone
PSVT or PAF N=100 N PSVT=52 NPAF/Aflu=42	(1995) DB,PC, crossover X 2	Efficacy and tolerability	Time to treatment failure-3 mths 300mg bid IR 300mg tid IR	TTM used	One episode of wide complex tachycardia during propafenone
PAF N=293	(2002)DB,PC ERAFT	Time to first recurrence of symptomatic AF	SR 325mg bid SR 425mg bid		%SAE 325mg =10%; 425mg 11.2%
Chronic complex ventricular ectopic activity N=?5	(1985)	Ventricular arrhythmia	IR Digoxin Diuretic	QRS was prolonged Drug related V-tach in 5 patients. 2 died. 3developed ventricular fibrillation. All occurred within the first 3 days of therapy. 2 of these patients had marked impairment of LV function	Proarrhythmic effects of propafenone were not associated with QT prolongation

Target Population (N)	Study (Yr)	1°Endpoint	Drug±Comparator Duration	ECG changes	Safety
Type 1 Atrial flutter N=30 N with drug =15; N without drug =15	(1995)Randomized to 2 treatment arms	Efficacy of combined therapy (TEP and oral propafenone) on termination of atrial flutter	600mg IR Trans –esophageal pacing (TEP) ?1 day		TEP was effective in interrupting flutter cycle in 53 % (8/15) of patients without propafenone whereas 87% 13/15 Aflutter pts benefited from combinatio -n of IR and TEP
Ventricular hyperkinetic arrhythmiaT N=24	(1986) Efficacy	Efficacy	450 mg bolus followed by 600mg /day IR for 7days followed by a wash out	24 hr Holter monitoring	AV block in 4 patients; LBB in 3 patients
Supraventricular Tachycardia N=12	(1996) Efficacy	Distinguishing effects of both propafenone enantiomers and racemic mixture	S- and R-propafenone Intravenous	(S-)significantly increased the atrial effective refractory period and ventricular refractory period compared to (R-) enantiomer	? Similar effects for both enantiomers overall.
Cardiac arrhythmias Atrial and VA N=124	(1978) Efficacy	Efficacy	IR 1-2mg/kg body weight		AV block BB block
Refractory arrhythmias unresponsive to quinidine, amiodarone and beta blockers N=68	(1986)Efficacy and safety		IR 1 day to 33 months Mean 5.6 months		Digestive, Cardiac decompensation asthenia and asthma, conversion of flutter from 2:1 to 1:1
VPCs N=12	(1985) DB, PC, CO X 2	Efficacy during rest and exercise	600-900mg IR daily 3 months	Prolonged PR and QRS in all patients on IR Prop.	LBBB Abnormal taste AV block
Incessant V. Tach.>120bpm	(1990)) Efficacy	Long term follow up	51 months +/-35 months Anti arrhythmics??		6 patients died within 27 months 2 from acute MI and 4 sudden death
Sustained V.tach/V.Fib N=50	(1991) Drug testing	Efficacy	750 – 900mg IR Follow up 20 +/- 15 months		
Accessory AV pathways N=15 PAF N=5 Orthodromic Tach N=10 WPW N=12 Retrograde=3	(1985)) Efficacy OL	Long term efficacy and drug testing in patients with arrhythmia complicating accessory AV conduction pathways	900mg/day 3-6 days Follow up one year + without recurrence		
Cardiac arrhythmias N=70 SVT N= 32 VT N=41	(1984)) Efficacy	Efficacy	900mg /day IR mean duration 6.8 months (max 27 months) Quinidine Beta-blockers Amiodarone	Holter monitoring Prolonged PR, QRS	Compared with quinidine, beta-blockers and amiodarone SA block One case of TdP Gastrointestinal adverse events,

Target Population (N)	Study (Yr)	1°Endpoint	Drug±Comparator Duration	ECG changes	Safety
					~~vertigo. 9 patients~~ with Aflutter did not benefit from propafenone therapy.
PVCs N=16	(1985) DB, PC, R, CO x 2	Efficacy compared to disopyramide	300mg tid IR 200mg Disopyramide tid	Serial 24 hour ambulatory monitoring	
Cardiac arrhythmias (Concurrent SVT and VT) N=33 Afib N=22 PSVTN=11	(1988) Efficacy OL	Efficacy in patients with SVT and VT	Flecainide Encainide	Serial 24 hour ambulatory Holter monitoring	Pts had LVEF 40 +/=15 %. Very sick population with MIs and CHF Proarrhythmias in 27% of patients with uncontrolled SVT.
Refractory V. taccharrhythmias N=60 VT N= 44 Vfib N=16	(1984) Efficacy OL	Efficacy and drug testing	IR 450mg followed by maintenance of 150 –300mg tid for 4 days Follow up post drug 16 months	Serial 24 hour ambulatory monitoring	IR reduces the LVEF further in those with < 50% LVEF. Nausea, CHF, Conduction abnormalities, "Aggravation of arrhythmia" and conduction abnormalities
Stable Ventricular arrhythmias N=30	(1984) DB, PC, CO	Efficacy Total abolition of ventricular tachycardia and paired ventricular ectopy	IR	48 hour ambulatory ECG recording. Prolonged PR and QRS Prolonged QTc in some patients	LBBB
SVT and VT N=71	(1984)	Efficacy	IR 900 mg /day Quinidine Amiodarone Beta-blockers		
Ventricular Tachycardia N=54 40 had coronary artery disease	(1991) Efficacy	Acute and long term efficacy	IR 450-900mg /day for 4-7 days		Eleven out of 16 patients showed a positive response to propafenone IR.
Ventricular arrhythmia N=25	(1985)Efficacy	Efficacy	IR ? dose	Ambulatory 2 - 24 hour Holter monitoring	" Side effects were infrequent, minimal, and of no clinical consequences"
Ventricular . Capture N=18	(1992)	Effects of propafenone on ventricular excitability	900mg /day 9+/-6days on drug	Prolonged QRS in sinus rhythm	Rate dependent failure of ventricular capture associated with prolonged QRS
PSVT N= 28 WPW N=14 AV nodal reentrant T N=10	(1985)	Electrophysiology	i.v.2mg/kg and Oral IR	No difference in the electrophysiological effects between iv and oral IR	No effect on sinus nodal recovery time and SA conduction time Prolonged QRS duration
Refractory Ventricular tachycardia N=16	(1985) Efficacy		IR		Proarrhythmic in patients with ventricular dysfunction
Refractory VPCs in a variety of	(1986) Dose ranging study	Efficacy	IR Follow-up 12.4	PR and QRS were	Intolerable side effects in 7

Target Population (N)	Study (Yr)	1°Endpoint	Drug±Comparator Duration	ECG changes	Safety
cardiac diseases N=45			months	prolonged QTC unchanged	patients. Mean trough plasma level with an effective response was 756ng/ml and 920ng/ml for intolerable side effects
WPW syndrome N=47	(1984) Long term efficacy	Electrophysiological effects	IR Follow up 2-4 years	QRS prolonged	One patient with dilated cardiomyopathy died suddenly.
Patients with impaired LVEF (CHF) and VT N=12	(1985)	Efficacy and safety	Follow up 14 months		Drug discontinued in 3 patients All patients alive at 14 months
VT N=14	(1984)	Electrophysiological effects	i.v. IR	Prolonged PR and QRS	
VT or non-fatal cardiac arrest N=16	(1983) Efficacy	Efficacy	IR 900 mg/day	Prolonged QRS, QT uncorrected	Proarrhythmic in 4 patients. Plasma concentration of drug when therapy was discontinued was 753+/- 428ng/ml "IR has potential for serious adverse events in some patients"
Recent onset of A fib without heart failure N=283	(1996) Conversion of Afib with a single loading dose of IR	Efficacy. Is admission to hospital justified?	IR 450 mg – 600mg oral Digoxin 1 mg Placebo		"Hospitalization not necessary for therapy of Afib with propafenone"
A Fib/Aflutter N=50	(1990) SB, R	Efficacy and safety Conversion to sinus rhythm	IR 2 mg/kg body wt for 10min versus flecainide 2mg/kg for 10 min	Prolonged QRS in flecainide but not in IR	Neither of the drug is effective in atrial flutter N=5 each -after flecainide or IR
Recent onset Afib N=246	(1999) SATE study (Safety antiarrhythmic Therapy Evaluation)	Efficacy	IR 450-600mg alone (N=66); Dig 0.75-1mg i.v. + quinidine 1100mg(N=70) IR+ Dig. 0.75-1mg (N=70), Plcbo (N=40)	24 hour Holter monitoring	No serious adverse events noted in a single oral loading dose of propafenone IR
Elderly >60 and non-elderly <=60 yr old patients with recent (<=7 days) onset of Afib. N=240 hospitalized NYHA class < or =2 without heart failure N >60=64 N<60=55 N Plcbo =62 NPlacebo=59	(1998) Conversion of Afib SB, PC,	Efficacy and age	IR 600 mg single oral loading dose		Adverse events in 14-16 % of treated patients compare to 8% in placebo regardless of age
Children (1 day to 17 years)					
Arrhythmias N=57 SVT N=32 AflutterN=6	1991	Efficacy	IR 13.1mg /kg/day (Range 8-15)		Proarrhythmic at a dose of 13mg/kg/day. This disappeared when

Target Population (N)	Study (Yr)	1°Endpoint	Drug±Comparator or Duration	ECG changes	Safety
VT N=19					drug was discontinued. Less effective in children with heart disease
Arrhythmias Total N=772 N with structural heart disease (SHD) =249 (32.3%)	(1998) European working group on pediatric arrhythmias study	To assess adverse events retrospectively by European Pediatric Cardiologists			Proarrhythmia in 1.9%, AV block, Sinus node dysfunction, ventricular proarrhythmia in 5 syncope in 1 patient. Cardiac arrest or sudden death in 5/772 (0.6%) SVT due to WPW and a normal heart in 2. Proarrhythmic effects seem to be less frequent than those reported for encainide or flecainide and occur predominantly in children with structural heart disease.
Recurrent PSVT N=20 12 females 8 males	(1986) Efficacy	Efficacy	i.v. IR 1.5mg /Kg in 3 minutes	QRS prolonged	
Arrhythmias N=35 Refractory 21/35	(1985) Efficacy	Efficacy	IR oral 300 mg/m^2/day		AV block and drug was discontinued. In 5 patients with PSVT. IR had no effect was observed. Overall no major side effects in children
Biopharm					
*2D6 polymorphism & prophylactic propafenone in PAF patients N=42	(2001) PK/PD	Correlation between efficacy of IR and the oxidation phenotype (CYP2D6)	IR300-450mg /day Duration 3 months of prophylactic IR		Serum samples taken at Day 7, 11 and end of treatment
Active Comparator studies/Combination with propafenone					
SVT without Heart Disease PAF (N=200) PSVT(N+135)	(1995) Efficacy OL, R,PG,	Safety of flecainide versus propafenone for the long term management of symptomatic PSVT (FAPIS group)	Flecainide acetate 100 – 300mg maximum ; IR 450 –900mg Follow-up 12 months or when patients stopped drug		12 patients on flecainide reported 16 cardiac adverse experiences, six discontinued treatment 7 patients on propafenone reported 8 cardiac adverse events, 5 discontinued. Proarrhythmic events: One with propafenone; Two with flecainide. No significant difference between

Target Population (N)	Study (Yr)	1°Endpoint	Drug±Comparator Duration	ECG changes	Safety
					the two drugs.
PAF N=60 Refractory N=19	(2000) OL followed by Randomized DB and then CO for patients with refractory PAF refractory to quinidine	Efficacy	IR 300-450mg /day for 8 weeks IR 450-675mg Or 600mg plus 150mg/day quinidine for 8 weeks then CO	QTc prolonged by 9% due to quinidine. No QTC prolonga -tion with IR+low dose quinidine Holter recording	IR gave 2 GI side effects.1 chf and 1 neurologic AEs resulting in withdrawal with IR =4 patiients (6%). Ventricular proarrhythmia was not seen.
PAF with no history of heart disease N=200	(1996) R, OL, Comparative, parallel study	Safety	Flecainide and IR		7 patients on IR had 8 cardiac adverse events including 1 proarrhythmic event. 10 patients on flecainide had 14 cardiac adverse events with 2 proarrhythmic events
Symptomatic PAF N=200	(1992) Randomized prospective study	Efficacy and safety-long term	IR 300mg bid Or Hydro quinidine Retard 250mg bid Titrated up for efficacy		Propafenone IR had 10% adverse events. Patients with Hydroquinidine treatment had 24% adverse events (p=0.02)
Symptomatic PAF N=41 for IR N=38 for Sotalol	(1997) Efficacy DB, R	Safety and Efficacy	IR 663+/-99mg /day Sotalol200mg +/- 57mg/day	Dose of drugs adjusted if the QT interval= >0.5seconds QRSprolonged significantly No effect of QT/QTc Mean QT =440±47 at baseline and 452±47ms post IR treatment	IR group: 2 patients discontinued for gastrointestinal discomfort and dizziness; Sotalol 4 discontinued 2 for dizziness and 2 for symptomatic bradycardia
Symptomatic Arrhythmia (91%) in sinus rhythm N=65 Afib N=52 AflutterN=13	(1996) R, DB		IR 600mg/day N=31 Cibenzoline 260mg/day N=34 drug exposure 6 months	Holter monitoring Prolonged QRS interval in both but >in Cibenzoline	4 patients in each group discontinued. One proarrhythmic event at 6 months in propafenone IR group
PSVT N=122 symptomatic patients	(2001) R, PC, Parallel group	Efficacy and safety	IR 150mg tid Dofetilide 500mcg bid Placebo 6 months exposure		No proarrhythmia. 3 patients on IR discontinued for SAE. Flecainide had 8.5% AEs ; IR had 16.7% AEs
"Acute Afib" N=117 Randomized N=76 Spontaneous recovery N=41	(1998) R	Efficacy	IR i.v. 2 mg /kg body wt 30 minutes Procainamide bolus of 100 mg i.v. every 5 minutes up to max of 1g.		
Afib and Aflutter N=325	(2000) R, DB, PC (SAFIRE-D) study. Conversion of Afib or Atrial	Efficacy and safety.	Dofetilide 125 250 and 500 micrograms and placebo	Dosages adjusted for QTC and Creatinine clearance	In-hospital initiation of treatment and dose adjustment based on QTc and Cl(Cr) to minimize

Target Population (N)	Study (Yr)	1°Endpoint	Drug±Comparator Duration	ECG changes	Safety
	flutter to sinus rhythm and maintaining SR for 1 year				proarrhythmic risk
Symptomatic PAF N=43	(1999) R, DB, PC, CO	Efficacy	Digoxin Placebo Duration 61 days	Ambulatory ECG recordings	No compelling evidence of anti-arrhythmic effect of digoxin.

R = RANDOMIZED, DB = DOUBLE BLIND, PC = PLACEBO CONTROLLED, CO = CROSSOVER STUDY, OL=OPEN LABEL, SB = SINGLE BLIND.

- *The influence of CYP2D6 polymorphism on the anti-arrhythmic efficacy of propafenone in patients with paroxysmal atrial fibrillation during 3 months propafenone prophylactic treatment. Int J Clin Pharmacol Ther 2001; 39: 288-292*

Conclusion from above PK/PD study
The antiarrhythmic efficacy of propafenone depends on the oxidation phenotype of patients: 100% efficacy was achieved in poor metabolizers, whereas at the dose tested (300-450 mg /day for 3 months) propafenone was ineffective in very extensive metabolizers.

10.0 References
RAFT and ERAFT

Treatment of atrial fibrillation and paroxysmal supraventricular tachycardia with bidisomide. Circulation (1997); 96(8): 2625- 32.

Benditt DG, Williams JH, Jin J, Deering TF, Zucker R, Browne K, Chang- sing P, Singh BN, dl- Sotalol Atrial FibrillationFluXer Study Group. Maintenance of Sinus Rhythrn with Oral d, l- Sotalol Therapy in Patients with Symptomatic Atrial Fibrillation and/ or Atrial Flutter. Am J Cardiol (1999); 84: 270- 277./ Circulation 1993; 87: 1 1 14- 22.

Conti CR. What Is Structural Heart Disease? Clin Cardiol. (2000); 23: 397- 8.

Knoll. Rythmol@ Tablets (prcipafenone hydrochloride) Package Insert. Knoll Pharmaceutical Company. A division of Knoll Pharmaceuiical Company, Mt. Olive, May (1996) (1 999).

Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett ELC. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. Circulation (1994); 891224- 7.

Connolly SJ, Hoffert DL. Usefulness of propafenone for recurrent paroxysmal atrial fibrillation. Am J Cardiol, (1989); 63 :8 17- 8 19.

Freedman LS. Tables of the number of patients required in clinical trials using the log-rank test. Statistics in Medicine, (1982); 1: 121- 129.

Gershlick A. H. Treating the non- electrical risks of atrial fibrillation. Eur Heart J, (1997); 1 S(Supp1ement C): Cl 9- C26.

Hochberg Y, Tamhane AC. Multiple comparison procedures J. Wiley, New York (1987).

Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. J. Wiley, New York (1980).

Pritchett ELC, McCarthy EA, Wilkinson WE. Propafenone treatment of symptomatic paroxysmal supraventricular arrhythmias. A randomized, placebo- controlled, cross- over trial in patients tolerating oral therapy. Ann Int Med, (1991); 114: 539- 544.

Pritchett ELC, Page RL, Connolly SJ, Marcello SR, Schnell DJ, Wilkinson WE and the Azimilide supraventricular arrhythmia program 3 (SVA- 3) investigators. Antiarrhythmic effects of Azimilide in atrial fibrillation. efficacy and dose- response. J Am Coll Cardio, (2000); 36: 794- 802.

The UK Propafenone PSVT Study Group, A randomized, placebo-controlled trial of propafenone in the prophylaxis of paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation. *Circulation* **92** (1995), pp. 2550–2557.

P. Giani, M. Landolina, V. Giudici, Biachini, G. Ferrario, S. Marchi, E. Riva and R. Latini , Pharmacokinetics, and pharmacodynamics of propafenone during acute, and chronic administration. *Eur J Clin Pharmacol* **34** (1988), pp. 187–194

P. Giani, M. Landolina, V. Giudici and R. Latini , Steady-state plasma kinetics of slow-release propafenone, Ist two Isomers, and Ist main metabolites. *Arzneim-Forsch/Drug Res* **45** (1995), pp. 246–249.

E.G. Brown, L. Wood and S. Wood , The medical dictionary for regulatory activities (MedDRA). *Drug Saf* **20** (1999), pp. 107–109.

G.Y.H. Lip and F.L. Li Saw Hee , Paroxysmal atrial fibrillation. *Quart J Med* **94** (2001), pp. 665–678.

E.M. Antman, A.D. Beamer, C. Cantillon, N. McGowan and P.L. Friedman , Therapy of refractory symptomatic atrial fibrillation and atrial flutter: a staged care approach with new antiarrhythmic drugs. *J Am Coll Cardiol* **15** (1990), pp. 698–707.

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The Safety Update review can be found in Dr. Williams' Medical Review.