CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-416

Medical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
HFD 110

Medical Review of NDA

Reviewer:	**A.O.Williams, M.D.**
NDA #:	21-416
Drug:	Rythmol SR
Chemical Name:	Propafenone HCl
Sponsor:	Abbott Laboratories, Abbott Park, Illinois
Proposed indication:	
Pharmacologic type:	Class 1 C anti-arrhythmic agent with local anesthetic effects and a direct stabilizing action on myocardial membranes. It has fast sodium channel blocking activity and consequently lowers conduction. It also has some effect on refractoriness and exerts weak Beta blocking activity and a slight calcium channel blocking effect. It is a negative inotrope.
Date of NDA submission:	March 18, 2002
Medical Review Completed:	December 10, 2002

181pages, 105 tables, 14 Figures, 20 Appendices

Rhythmol
Table of Contents

List of Tables

List of Figures

List of Appendices

Descriptive Outline of Review
by Pages to be Read in Conjunction with Table of Contents

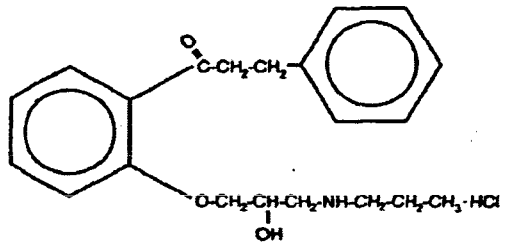
- Pages 1-8 deal with Table of Contents.
- Pages 10 –47 deal with the Executive summary of NDA 21416 with recommendations and conclusions of reviewer.
- Page 48 deals with the Pediatric waiver request, conclusion and recommendation of the reviewer on the sponsor's request for waiver.
- Pages 49-58 deal briefly with the PK and PD of propafenone and a brief overview of the clinical program including Phase II and III studies.
- Pages 59 to 94 deal with the clinical review of RAFT study carried out in the US.
- Pages 95 to 108 deal with the clinical review of ERAFT carried out in Europe.
- Pages 108 to 117 deal with brief reviews of selected Phase II clinical studies.
- Pages 118 to 120 deal with Reviewer's Conclusions and Recommendations.
- Pages 121 to 140 deal with the Label.
- Pages 141 to 179 deal with Appendices.
- Pages 180-181 deal with selected references/publications to the NDA.

1.0 Executive Summary of Primary Clinical Review

Introduction

Propafenone is classified as a class 1C anti-arrhythmic agent with local anesthetic effects and a direct stabilizing action on myocardial membranes. It has fast sodium channel blocking activity and consequently lowers conduction. It also has some effect on refractoriness and exerts weak beta-blocking activity and a slight calcium channel blocking effect.

The structural formula of propafenone HCl is shown below:



$C_{21}H_{27}NO_3 \cdot HCl$ M.W. = 377.92

2'-[2-Hydroxy-3-(propylamino) -propoxy]-3-phenylpropiophenone hydrochloride

- The proposed indication for propafenone sustained release (SR) formulation is to prolong the time to recurrence of symptomatic atrial fibrillation in patients without structural heart disease. The target patients in the study must have a history of symptomatic atrial fibrillation within the last 12 months of randomization and at randomization they should be in normal sinus rhythm.
- Propafenone SR is specifically designed to reduce the dosing frequency of the marketed immediate release formulation (IR) from an 8 hourly to 12 hourly dosing regimen.
- The oral bioavailability of sustained release (SR) formulation, however, is less than that of IR hitherto approved by FDA and marketed in about 60 countries.
- Because of the more gradual release from SR that results in increased overall first pass metabolism to 5-hydroxypropafenone, bioavailability of SR is less than that of IR. Consequently, a higher dose of SR is required to achieve similar plasma concentrations to the IR.
- Propafenone IR was introduced into the global market in 1977 and was approved in December 1989 under NDA 19-151 by the Agency (FDA) for life threatening ventricular arrhythmias.
- There is considerable literature on trials using Propafenone IR and the management of treated patients with supraventricular arrhythmias including atrial fibrillation (Section 10).

The format used for this review is a modification of the proposed FDA clinical review template. The approach adopted by the reviewer includes an understanding of the clinical trial designs of RAFT, the pivotal study, and ERAFT illustrated in Figs.1 and 10. This review notes the event-driven nature of the trial, the treatment of dropouts,

censored patients, the determination of the primary endpoints, and the verification of ECG changes in patients classified in the data.

The sponsor has submitted two Phase III clinical trials referred to as RAFT and ERAFT studies. The pivotal trial is the RAFT study carried out in the US and the supporting trial is the ERAFT study carried out in Europe. The efficacy of the two trials has been reviewed s0eparately because of differences in trial designs. However their safety data have been reviewed separately and also have been integrated. Six additional studies using propafenone IR or SR have been included in the integrated safety review..

The RAFT study is the larger of the two phase III studies with 523 randomized patients who received 3 doses of propafenone SR (225mg bid, 325 mg bid and 425 mg bid) for up to 39 weeks. ERAFT study had 293 randomized patients administered 2 doses of drug (325mg bid and 425 mg bid), and the efficacy period lasted for up to 95 days. The sponsor has submitted the RAFT study only for efficacy evaluation of this application.

The RAFT study [(Protocol P-85-AF (RAFT)] is a double-blind, randomized, placebo-controlled, multi-center, 4-way, parallel group trial. The study evaluated the efficacy and safety of 3 doses of propafenone SR (225 mg bid, 325 mg bid, and 425 mg bid) for up to 39 weeks (Figure 1). The ERAFT study (Protocol PROPASR-008), carried out in Europe, has been submitted to provide supporting data in the evaluation of safety and efficacy of propafenone SR.

RAFT Study Design

There is a pre-treatment phase that includes the following:

- All anti-arrhythmic medications must be discontinued (except verapamil, diltiazem, β-blockers and digoxin) for at least 5 half lives before randomization to study drug.
- All discontinued medications will be documented in the patients' case report forms.
- Informed consent must be obtained prior to discontinuing medications.
- A complete medical history, physical examination, clinical laboratory tests will be performed before blinded therapy started.

The double-blind treatment phase followed the pre-treatment phase.

- Prior to administering the first dose of study drug the patient/study coordinator shall transmit an ECG to the Receiving center.
- The patient must be in sinus rhythm prior to study drug administration.
- The first dose shall be administered in the hospital or clinic and the date and time of the dose recorded in the CRF.
- All study medications will be taken every 12 hours commencing from the time of first dose.
- The patient is expected to have reached a steady state plasma propafenone concentration by Day 4/5 (Loading Period) of the first week of double-blind drug therapy.
- The efficacy period lasted for up to 269 days plus 4 days for loading (39 weeks).

If the patient has atrial fibrillation documented at randomization, the investigator must document a return to sinus rhythm by trans-telephonic monitoring (TTM) in order to begin the efficacy period. If a return to sinus rhythm is documented in such a patient prior to midnight of the fourth day of blinded therapy then the steady state will begin as planned at that time. If the patient fails to have sinus rhythm restored before the 10th day

following randomization, then the patient must be withdrawn from the trial and will not be included in the efficacy analysis. This therefore makes the data ineligible for an Intent to Treat analysis. The patient population thus becomes a ***"full analysis set"*** or "FAS".

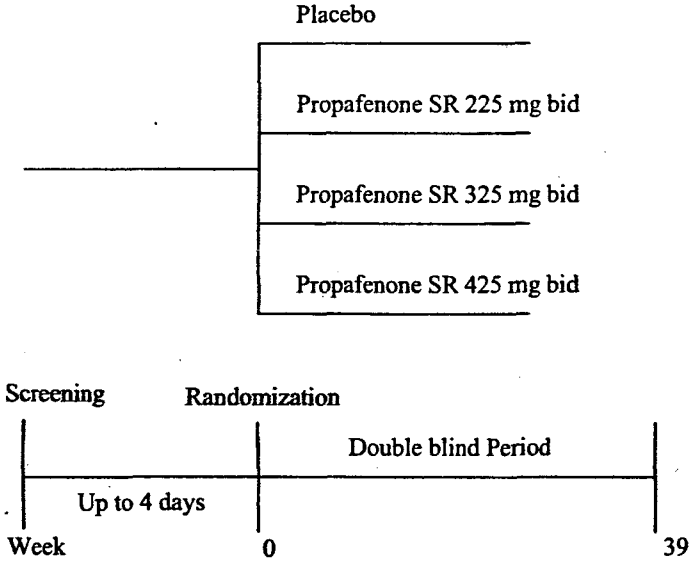
Five hundred and twenty three (523) eligible patients with a history of symptomatic atrial fibrillation, atrial flutter or PSVT were randomized to one of three propafenone SR treatment arms or to placebo in a double blind fashion. A minimum of 110 patients per treatment group was estimated to be adequate for statistical analyses. They were assigned to each group and monitored for up to 39 weeks (Figure 1). The randomized patients included three hundred and nine male's (309) and 214 females. There were 30 (5.74%) blacks and 17 (3.25%) patients were from other ethnic groups (Table 1). Symptomatic arrhythmias were documented using trans-telephonic ECG monitoring. The tachycardia-free period was determined for each treatment group as a measure of primary efficacy.

Table 1: Distribution of randomized "FAS" patients by ethnic origin –RAFT

		Propafenone			
	Placebo	**225mg**	**325mg**	**425mg**	**p-value**
	N=126(%)	**N=126(%)**	**N=135(%)**	**N=136(%)**	
Caucasian	116(92.1)	113(89.7)	125(92.6)	122(89.7)	0.743
Black	6(4.8)	8(6.3)	5(3.7)	11(8.1)	
Oriental	0(0.0)	2(1.6)	1(0.7)	0(0.0)	
Others	4(3.2)	3(2.4)	4(3.0)	3(2.2)	

FAS=Full analysis set.

Figure 1: Study Design for RAFT study



In addition to the full analysis set, the sponsor also prespecified a per protocol population. For the Per protocol (PP) population, a total of 447 patients had at least one dose of propafenone SR, a baseline trans-telephonic monitoring (TTM) recording, completed the study without major violation, and met the study drug compliance criterion of >80% and < 120% for all visits combined. The randomization of patients (FAS) showed no significant difference between the treatment groups (p=0.743 for

Caucasians) (Table 1). The statistical plan and amendments submitted by sponsor are on pages 15-16.

The criteria for eligibility are as follows:
Inclusion Criteria
Patients who fulfilled the following inclusion criteria were considered eligible for inclusion into the study:

- >21 years of age.
- Non-pregnant, non-lactating women.
- Written informed consent.
- Symptomatic atrial fibrillation with ECG documentation within the last 12 months of randomization.
- Irregular ventricular rhythm, and
- Absent p waves or the presence of fibrillatory waves in isoelectric periods of the ECG recording.
- An investigator assessment that anti-arrhythmic therapy for continuing symptomatic Atrial fibrillation was appropriate.
- An assessment by the investigator was required that patient was in sinus rhythm at the time randomized therapy began.
- Patients taking verapamil, diltiazem, ß- blockers or digoxin could be enrolled provided they had symptomatic atrial fibrillation during treatment with those agents.

Exclusion criteria

- Previous exposure to propafenone.
- Patients who were permanently in atrial fibrillation.
- Class III or IV angina pectoris.
- Class III or IV NYHA classification.
- Acute pericarditis within the past 6 months.
- Therapy with other anti-arrhythmic agents within 5 half lives of the date of study entry; use of amiodarone within the past 6 months.
- Cardiothoracic surgery within the past 6 months and others including WPW, stroke, CHF, hepatic failure, digoxin toxicity, implanted defibrillator, clinical hyperthyroidism.

Reviewer's comments on study design - RAFT
The reviewer considered the study design of RAFT as a whole to be appropriate and adequate to test the proposed hypothesis that propafenone SR is an effective anti-arrhythmic agent for the prolongation of time to recurrence of symptomatic atrial fibrillation. The reviewer also considered a period of up to 39 weeks reasonably adequate for evaluation of long-term safety. However, there are a few areas of inadequacies in the study design. These include the following:

- The percentage of patients at least 65 years of age constituted about 52% of total number of patients randomized;
- The percentage of blacks only constituted 5.7% of randomized population. This is considered inadequate. There were no blacks or other ethnic groups in the ERAFT study.
- The sample size in each group is small and not powered enough to show significant differences between each of the treatment groups.

The sample sizes of randomized patients with a history of atrial flutter or PSVT are very small.

The reasons for the inadequacies outlined above are that the total number of randomized patients >65 years is lower than the US demographic profile for symptomatic atrial fibrillation. Similarly the total number of blacks in the study is lower than the US demographics for the black population. The reviewer therefore notes that there are numerical insufficiencies in the enrolled target population. While the sample size is adequate for comparison between each treatment group and placebo as defined in the protocol it was not large enough to compare each treatment group against one another. The majority of randomized patients had only a history of atrial fibrillation (>95%). There was a relative lack of randomized patients with atrial flutter or PSVT thus making a claim for these clinical entities untenable (Tables 34 and 36). Ten patients and 12 patients had PSVT and atrial flutter, respectively, as symptomatic terminating events (Table 47).

Although the randomization was satisfactory, there was significant imbalance between the treatment groups at baseline in respect of abnormal cardiovascular examination. The percentage of patients with abnormal cardiac examination at baseline was higher in the placebo group (32.5%) compared to the combined drug treatment groups (23.2%). (Table 44). This imbalance was thoroughly investigated with the assistance of the statistician, Dr Yang-Cheng Wang. We were able to ascertain that the imbalance had no significant effect on efficacy outcome.

The relationship between normal and abnormal cardiac examinations at baseline to terminating events shows a higher percentage of placebo patients with terminating events (65.9%) compared to 29%, 43%and 57% for the 425mg bid, 325 mg bid and 225 mg bid groups (Table 46). However, the number and percent of patients with history of atrial fibrillation was balanced between the treatment groups (Table 34).

There was balance in the number of patients within each center across treatment groups. The randomization schedule that was prepared by the Statistics Department and the actual randomization at the centers appeared satisfactory and could not account for the observed imbalance between placebo and treated groups.

More than 50% of randomized patients in the RAFT study had hypertension and the remaining had a variety of other illnesses and diseases including a few patients with structural heart disease. For this NDA, NYHA classification was used as a surrogate for structural heart disease since the hemodynamics represented a more reliable parameter than structural cardiac abnormalities (Tables 35, 39, 45). Both the RAFT and ERAFT studies specifically excluded patients with NYHA III and IV classification and III and IV angina (Exclusion criteria). This should be reflected in the label.

The 39-week blinded therapy phase of RAFT is considered by the reviewer to be adequate in duration to evaluate drug efficacy and to provide long term safety data for propafenone SR formulation.

Hypothesis

The RAFT study tested the hypothesis that propafenone SR is an effective anti-arrhythmic agent for the prevention of symptomatic atrial fibrillation and can be administered twice daily orally.

Statistical analysis Plan and amendments
Protocol P-85-AF dated 5 September 1997 included Amendment No. I dated October, 1997, Amendment II dated March, 1998, Amendment III dated 13 October 1998, Amendment IV dated 5 November 1998, Amendment V dated 8 February 1999, Amendment VI dated 16 December 1999, and Amendment VI1 dated 03 January 2001. These collectively form the statistical analysis plan in addition to the original statistical plan submitted.

The tachycardia-free periods were summarized by treatment group using the Kaplan – Meier product-limit method. The efficacy of each of the three doses of propafenone SR in preventing recurrences of symptomatic arrhythmias was tested statistically using the log-rank test. The study was designed to detect with high probability (approximately 90% power), a treatment effect that decreased the recurrence rate of symptomatic arrhythmias by a factor of 2 or more over placebo. An interim (150 patients) analysis will be performed.

Protocol amendments over time that affected the original analysis plan are as follows: Amendment II (March 1998)

1. The primary efficacy analysis will evaluate the efficacy of the 2 higher doses (propafenone SR 425 mg bid and propafenone SR 325 mg bid) of propafenone SR in preventing recurrences of symptomatic arrhythmias. The amendment elaborates that the efficacy of each of the 2 higher doses of propafenone SR in preventing recurrences of symptomatic arrhythmias will be tested statistically using the log- rank test. The analyses will be performed separately for the 2 doses, each at the 2.5% significance level. For each dose, a proportional hazard model with the placebo group represented by an indicator variable will be used to estimate the hazard ratio.

2. The tachycardia-free period for patients who discontinued prematurely will be censored on the day the patient is withdrawn.

3. The secondary efficacy measure of average heart rate was further described to include only those patients included in the primary efficacy analysis.

4. An additional supportive analysis was added to include the lower dose of propafenone SR 225 mg bid.

5. The additional analyses such as analysis of the tachycardia- free period from randomization, treatment- failure time analysis, analysis of time to first patient- initiated report of symptoms, and treatment effect as a function of mg/kg will include all 3 propafenone SR doses.

Amendment IV (November 1998)
History of symptomatic atrial fibrillation including ECG documentation was changed from within 6 months of randomization to within 12 months of randomization.

Amendment VI (December, 1999)
1. The tachycardia-free period changed from Day 5 (steady state because the end of the study drug loading period is Day 4 at midnight) to the beginning of the randomization, period (Day 1) to the first symptomatic arrhythmia recurrence documented by trans-telephonic electrocardiogram monitoring (TTM).

2. The interim (150 patients) analysis will not be performed.

Amendment VI1 (03 January 2001)

The following changes to the efficacy analyses were made.
The primary endpoint was clarified to include symptomatic paroxysmal supraventricular tachycardia (PSVT) in addition to symptomatic atrial arrhythmia (atrial fibrillation, atrial flutter, and or PSVT).

The primary and secondary efficacy analyses were changed to include the propafenone SR 225 mg bid group.

The null hypothesis of no treatment difference in the analysis of the tachycardia-free period will be tested using a closed testing procedure (*Marcus et a1, 1976*) maintaining a Type I probability of at most 0.050 for the following comparisons: propafenone SR 425 mg bid group versus placebo, propafenone SR 325 mg bid group versus placebo, and propafenone SR 225 mg bid group versus placebo. This closed testing procedure first tests the nul1 hypothesis of no difference between propafenone SR 425 mg bid and placebo at the 0.050 level of significance. Only if this test reaches statistical significance will the null hypothesis of no difference between propafenone SR 325 mg bid and placebo be tested again at the 0.050 level. Similarly, if this test reaches statistical significance, the null hypothesis of no difference between propafenone SR 225 mg bid and placebo will be tested again at the 0.050 level. The closed testing procedure will be used for all efficacy variables except for the secondary efficacy variable (average heart rate). All statistical tests will be 2- sided.

To support the primary analysis of the primary variable using the log- rank test, the underlying assumption for the proportional hazard model will be assessed. If the assessments indicate a substantial departure from the model assumption, then the generalized Wilcoxon test will be performed as a secondary method to compare the survival distributions between treatment groups. This rule will also be applied for the analyses of the other survival efficacy variables.

Treatment effect as a function of mg/kg analysis using treatments as covariates in the proportional hazards model was changed to use each patient's body-weight adjusted dose and determine treatment effects as compared to placebo. The statistical methods will be the same as those used in the efficacy analysis from Day 5 of randomization

Investigator read of the TTM ECG recording and agreement between the ECG diagnosis, TTM recording and investigator diagnosis of the same TTM recording were added as other efficacy variables.

The following subpopulation analyses were added for the duration of the tachycardia-free period: NYHA classification and presence or absence of structural heart disease.

Structural Heart Disease

Although the indication for propafenone is for prolongation of time for the recurrence of symptomatic atrial fibrillation in patients **without structural heart disease** (SHD), a history of SHD was obtained at baseline and patients with SHD were enrolled. More than 40% of randomized patients had a history consistent with SHD. The distribution of patients with SHD ranged from about 45% among the placebo group to 55% among those who received propafenone SR 425 mg bid (Tables 33 and 34). The classification

of SHD used for this study was based on 2 published references (*Pritchett et al., 2000 and Conti et al., 2000*) (Section 10.0).

Efficacy endpoint-RAFT

- The primary efficacy endpoint, used for data analyses, was the measurement of tachycardia-free period in days, measured from the beginning of randomization on Day 1 until the first symptomatic recurrence of arrhythmia. This was documented by trans-telephonic (TT) ECG monitoring with final diagnosis from the Adverse Event Committee (AEC) of either atrial fibrillation, atrial flutter or paroxysmal supraventricular tachycardia (PSVT) (Tables 36, and 47).
- Symptomatic arrhythmias were considered as outcome events if ECG recordings showed any of the following 3 features: atrial fibrillation, atrial flutter or PSVT (Table 36) Symptomatic arrhythmias that occurred during the study drug loading period were documented in the CRFs. All patients with symptomatic arrhythmias occurring after the study drug loading period, and or during the randomization period were discontinued provided there was 12 lead ECG or ECG telemetry confirmation of the episode. These were considered as outcome events. Patients who did not record an outcome event were censored in the analysis. Symptoms that suggested an arrhythmia to the patient were not counted as outcome events unless ECGs were recorded to document the episodes (Table 36).
- The AEC reviewed all symptomatic ECGs to make the diagnoses used for the efficacy analyses. The diagnoses were made without the knowledge of the identity of the patients randomized study medication or the investigators' assessment. Each ECG was read independently by 2 readers. If there was no agreement a third independent opinion was sought from a third reader. The central read and the AEC diagnoses were considered final and were used as the endpoint for statistical analyses of data (Tables 47, 71,72).

Human pharmacokinetics and pharmacodynamics

The pharmacokinetics of propafenone is non-linear in extensive metabolizers following administration of propafenone SR capsules. There are disproportionate increases in exposure when 325 mg (2 fold) and 425 mg (3-4 fold) are given compared to 225 mg Propafenone is well absorbed after oral administration. Maximal plasma levels of propafenone are reached between 3-8 hours following oral administration of propafenone SR. Peak plasma concentrations are reached after 2-3 hours (T max). Plasma concentrations and bioavailability increase with repeated administration owing to a saturation of the first pass metabolism in the liver. Absolute bioavailability has not been determined for propafenone SR. Relative bioavailability, however, shows that in extensive metabolizers, 150 mg tid of propafenone IR resulted in about the same exposure at steady state comparable to 325mg bid propafenone SR (e.g. AUC: 4616 for 150 mg tid IR and 4817 for 325 mg bid SR; Cmax: 441 for 150 mg tid IR and 350 for 325 mg bid SR). In the equivalency comparisons exposure to 5-hydroxypropafenone was about 20-25% higher after SR capsule ingestion than after IR tablet administration. Although food increases peak blood level and bioavailability in single dose studies, food effect on bioavailability was not observed with multiple dose administration. The elimination half life of the parent drug is 2-10 hours. In less than 10% of patients, metabolism is slower because the 5-hydroxypropafenone is either not formed or formed minimally. The estimated elimination half life in those patients with slower metabolism ranged from 10-32 hours.

In addition to the two metabolites, nine other metabolites of propafenone have been identified, most of them in trace amounts. Plasma protein binding lies between 85 and

95 % and the volume distribution is between 1.1–3.6l/kg. Only about 1% of unchanged propafenone is excreted through the kidneys.

In vitro studies have shown that 5-hydroxypropafenone and norpropafenone show anti-arrhythmic activity comparable to propafenone but in man, they are usually present in concentrations < 20% of propafenone. The peak to trough fluctuation (PTF) for propafenone and its major metabolites was smaller after SR administration compared to the IR formulation (See Biopharm review). Propafenone is known to pass the placental barrier in humans and it is excreted in breast milk (See Biopharm review).

Drug Class: Propafenone is classified as a class 1C anti-arrhythmic agent but has other pharmacological properties (Page 1). Propafenone is a negative inotrope like most other Class 1C anti-arrhythmics.

Study dates: February 1998 to September 2000

Number of centers in the US for the RAFT study - 111

Established and Proposed Trade Names: RYTHMOL SR
Propafenone hydrochloride Capsules.

The drug supply for the RAFT study is in Table 2.

Table 2: Drug supply for RAFT study

Parameter	Propafenone SR			Placebo
	225 mg bid	325 mg bid	425 mg bid	
Dosage form	encapsulated microtablets	encapsulated microtablets	encapsulated microtablets	encapsulated microtablets
Dose	225 mg	325 mg	425 mg	NAP*
Manufacturer	Kroll AG	Knoll AG	Knoll AG	Knoll AG
Formulation number	3060-G-53	3060-F-53	3060-E-53	3060-EO-53
Batch number	780100AO 980310AO 780200AO	780100AO 980311AO	780101AO 980211AO	980201PO 780101PO

ERAFT
Protocol
Study date: 28 July 1998 to December 9 1999
Objective of ERAFT
The objective of the ERAFT trial was to show that propafenone SR (325 mg bid and 425 mg bid) administered to eligible patients with a past history of atrial fibrillation within 28 days of randomization was superior to placebo in preventing symptomatic, paroxysmal atrial fibrillation (PAF) (Section 5). The word "symptomatic" was defined as "subjective awareness of palpitations, rhythm irregularities, or arrhythmia–related dizziness, chest pain, anxiety, or dyspnea". The word "paroxysmal" was used to describe "recurrent episodes of atrial fibrillation, regardless of whether they terminated spontaneously or required DC cardioversion".
For eligibility, the patient must have had one documented incident of symptomatic paroxysmal atrial fibrillation (PAF) in order to qualify for randomization. The qualifying period was 28 days.

Out of total 594 patients screened, 293 patients (180 males and 113 females) were randomized to 2 treatment arms (325 mg bid and 425 mg bid) and a placebo arm. This is in contrast to the RAFT study with 3 treatment arms (225mg bid, 325mg bid, and 425 mg bid) and a placebo. The use of only two doses made a convincing dose response difficult to evaluate but there is evidence of a dose response on visual observation of the Kaplan Meier survival curves for the full analyses set (Figure 3) (p=0.003 for 425mg bid and p=0.004 for 325mg bid. For per protocol population p= 0.001 for 425mg bid and also for 325 mg bid.

Study design ERAFT

There is a pre-treatment phase that includes the following:

Eligible patients entered a stabilizing period of up to 7 days (Table 76)

- All previous anti-arrhythmic therapies be underwent a wash out period of 5 times the half lives of previous treatment before randomization to study drug.
- Patients requiring rate-limiting drugs i.e. calcium antagonists, β-blockers and digoxin during the study were to start taking them during this period.
- All discontinued medications will be documented in the patients' case report forms.
- Informed consent must be obtained prior to discontinuing medications.
- A complete medical history, 12 lead ECG physical examination, clinical laboratory tests will be performed for safety testing.

The double-blind treatment phase followed the pre-treatment phase.

- Prior to administering the first dose of study drug the patients were provided with a Cardiocall event recorder,
- Patients were instructed to record a Cardiocall each time they had symptoms, such as they experienced in the past.
- In addition to recording the symptomatic event patients were to use the event recorder once a week throughout the study to obtain routine ECGs.
- Patients were provided with diaries.

If the patient had no documented incident of symptomatic PAFs (hard copy ECG via event recorder) by the end of 28 days, then the patient was not randomized to any of the treatment groups. Patients with qualifying events were scheduled for visit 2 when randomization took place. The first dose was administered in the study center or hospital or clinic and the date and time of the dose recorded in the CRF. This marked the start of the efficacy period. The efficacy period began at 00.01 hours of day 5. The patient entered a 4-day double-blind loading period. The patient was expected to have reached a steady state plasma propafenone concentration by Day 5/6 (Loading Period) of the first week of double-blind drug therapy. Documentation of any episode of symptomatic atrial fibrillation or flutter during the loading period was attached to the CRF. These episodes of atrial fibrillation or flutter did not lead to withdrawal provided sinus rhythm was restored within 24 hours either spontaneously or by DC cardioversion. The patient therefore may not be in sinus rhythm prior to study drug administration.

- If any episode of symptomatic atrial fibrillation or flutter persisted beyond the loading period the patient was deemed to have reached the primary endpoint and was withdrawn from the study. On day 5 after randomization, patients entered the efficacy period that lasted for 91 days or until a symptomatic relapse of atrial fibrillation or atrial flutter was documented. Study visits were scheduled at Days 21 and 56. Final evaluation visit was on Day 96 for patients who continued in the study without a relapse, or immediately after a documented symptomatic relapse.

- The relapse was defined as a symptomatic event of atrial fibrillation or flutter with a duration of at least 10 seconds occurring or persisting after the patient had reached the full loading dose and documented by the CardioCall event recorder. Such a relapse was the primary endpoint of the study and led to termination.

Differences between RAFT and ERAFT

Table 100 summarizes the differences in demographics and baseline data between RAFT and ERAFT studies. Although the ERAFT data provide support for efficacy of propafenone SR in the prophylaxis of AF, there were a few significant differences in their study designs. The ERAFT study, being a study carried out in Europe, had no black patient and included only 59% of patients who were at least 65 years old.

Other differences between the RAFT and ERAFT studies include the following:

- The history of atrial fibrillation was much longer in ERAFT (39 months) compared to RAFT (~16 months)
- ERAFT patients were required to experience a documented arrhythmia (AF) within the 28 day qualifying of study whereas patients in the RAFT study were required to have experienced one documented event within 12 months of randomization into the study. RAFT patients were therefore not required to experience a relatively recent AF event during the screening period whereas it was required for the ERAFT study.
- The primary efficacy endpoint for ERAFT was tachycardia-free period from Day 5 of randomization (not consistent with ITT) whereas for the RAFT study it was from Day 1 of randomization consistent with FAS population.
- Other differences between the two studies include higher percentages of patients on anti-arrhythmics on ERAFT compared to RAFT but this was considered not to be significant with respect to providing supportive evidence for efficacy, and did not affect treatment outcomes and inter study comparability (Table 100). However, comparability between the two studies was considered when ERAFT data were used either for comparisons, support efficacy or long term safety data of the RAFT study.
- The duration of drug exposure was longer in the RAFT (39 weeks) compared to ERAFT (14 weeks).

Primary Efficacy endpoint - ERAFT

- The primary efficacy endpoint for ERAFT was the measurement of tachycardia-free period in days, measured from Day 5 until the first symptomatic recurrence of arrhythmia, documented by trans-telephonic (TT) ECG monitoring with the AEC final diagnosis of atrial fibrillation, atrial flutter or paroxysmal supraventricular tachycardia (PSVT). This endpoint was used as the endpoint for data analyses.

Secondary efficacy endpoints-ERAFT

The secondary efficacy variables include the following:

- Time to first relapse after the first dose of study medication.
- Heart Rate during first recurrence of symptomatic atrial fibrillation after reaching the full loading dose
- Resting daytime heart rate during sinus rhythm at each visit after reaching the full loading dose.
- Tachycardia-free period from Day 5-ERAFT
- Time (in days) To Treatment Failure from Day 1 - ERAFT
- Time to patient-initiated report of symptoms from Day 1-ERAFT
- Hazard Ratios for differences between treatment groups-ERAFT

Results

1.1 Efficacy results - RAFT

The review of the efficacy data is based on materials submitted in electronic format (10 CD discs) and hard copies of NDA 21-416, volumes 1-233.

1.2 Primary efficacy analysis - RAFT

The primary efficacy analysis for RAFT is the comparison of propafenone SR 425 mg bid *versus* placebo, propafenone SR 325 mg bid *versus* placebo, propafenone SR 225 mg bid *versus* placebo for the tachycardia-free period from Day 1 of randomization to the first recurrence of symptomatic atrial arrhythmia.

Patients were censored at the first recurrence of atrial fibrillation symptoms and consequently no data were available to evaluate time to subsequent recurrences after the censor.

- The primary efficacy analysis revealed statistically significant increases in the tachycardia-free period from Day 1 to first recurrence of symptomatic atrial arrhythmia in all propafenone SR treatment dose groups compared to placebo (p values = 0.014, <0.0001 and < 0.0001 for 225 mg bid., 325 mg bid., and 425 mg bid., respectively, using the log rank test (Table 3). The data provide evidence of drug effect in prolonging tachycardia-free period at all dose levels compared to placebo (Table 3). The primary efficacy endpoint was therefore achieved. Kaplan-Meier survival curves show a dose response for the primary efficacy end point (Figure 2 page 23).

Primary Efficacy-RAFT

Table 3: Tachycardia-free period (days) From Day 1 / Randomization - RAFT

Parameter	Propafenone SR			
	Placebo	225 mg bid	325 mg bid	425 mg bid
	N=126(%)	N=126(%)	N=135(%)	N=136(%)
Patients completing with terminating event*	87(69.0)	66 (52.4)	56(41.5)	41(30.1)
Comparison of tachycardia- free period				
Kaplan-Meier Median Range (days)	41 0.0-289.0	112 0.0-285.0	291 0.0-293.0	228 0.0-300.0
P-value				
Log rank	-	0.014	<0.0001	<0.0001
Wilcoxon	-	0.064	<0.0001	<0.0001
Hazard ratio	-	0.672	0.434	0.353
95% CI for HR	-	(0.488,0.927)	(0.309,0.609)	(0.243,0.513)

***Patients had a terminating event if they had the first recurrence of symptomatic atrial fibrillation. Atrial flutter or PSVT (Table 36). The time periods to subsequent recurrences of arrhythmia could not be determined because the patients were censored.**

Secondary efficacy analyses –RAFT

The secondary efficacy analyses for RAFT include the comparison of propafenone SR 425 mg bid versus placebo, propafenone SR 325 mg bid versus placebo, propafenone SR 225 mg bid versus placebo for the following parameters:

- Tachycardia-free period from Day 5 of randomization to the first recurrence of symptomatic atrial fibrillation. (*This is the primary efficacy endpoint for ERAFT*).

- Heart rate.
- Time (in days)-to-treatment failure from Day 1.
- Time (in days)-to-patient-initiated report from Day 1.

Results

Results of secondary efficacy analyses – RAFT

Heart Rate during first recurrence of symptomatic atrial fibrillation

- Although there was a significant trend to lower average heart rates in the propafenone treated groups compared to placebo (Table 52 p=0.0068), there were no statistically significant differences in the average heart rates during symptomatic atrial arrhythmia between the propafenone SR 225 mg bid and 425 mg bid dose groups and placebo. In contrast, there was a significant difference in the average heart rate between propafenone SR 325mg bid and placebo during the first recurrence of symptomatic atrial fibrillation (p=0.054) (Table 52).
- The average heart rate was significantly lower in the 325 mg bid group compared to placebo and the average heart rate was also lower, although not statistically significant in the 425 mg bid group compared to placebo (Table 52). This is consistent with the pharmacology of the drug. There was no significant difference in average heart rate between the patients in the 225mg bid group compared to placebo.

Tachycardia-free period from Day 5-RAFT

- There was a statistically significant difference in the tachycardia-free period from Day 5 of randomization to the first recurrence of symptomatic atrial fibrillation (p= 0.002 for the 225 mg bid dose group and p<0.0001 for the 325 mg bid and 425mg bid dose groups) (Table 49), and similarly with weight-adjusted dose categories (low, medium, and high) among the FAS population (Table 54).

Time (in days) To Treatment Failure from Day 1 - RAFT

- The percentages of randomized patients with terminating events were as follows: - placebo = 69%; 225 mg bid = 52.4%; 325mg bid = 41.5%; and 425 mg bid = 30.1%. There were statistically significant differences in time to treatment failure from day 1 of randomization for analyses of terminating events: p values = 0.032, <0.0001 and <0.0001 for 225mg bid., 325mg bid., and 425 mg bid., respectively. These data further provide evidence of treatment effect in prolonging the time to treatment failure at all dose levels compared to placebo (Table 51).

Time to patient-initiated report of symptoms from Day 1-RAFT

- There were statistically significant differences in the time (in days) from day 1 to patient-initiated report of symptoms of arrhythmia in two of the three dose groups, 325 mg bid. and 425 mg bid., p=0.002 and 0.011, respectively, but not in the third and lowest dose group of 225 mg bid., group (Table 50). Using the Kaplan-Meier curves a dose response to propafenone SR was demonstrated for efficacy for all dose groups compared to placebo for this parameter (Figure 2). These data provide evidence of clinical benefit in prolonging the time to patient-initiated periods of symptomatic arrhythmia (Table 50).
- The sponsor did not carry out statistical analyses between each of the drug treatment groups in the RAFT study because of small numbers. Hazard ratios were calculated in post-hoc analyses in order to show any difference between treatment

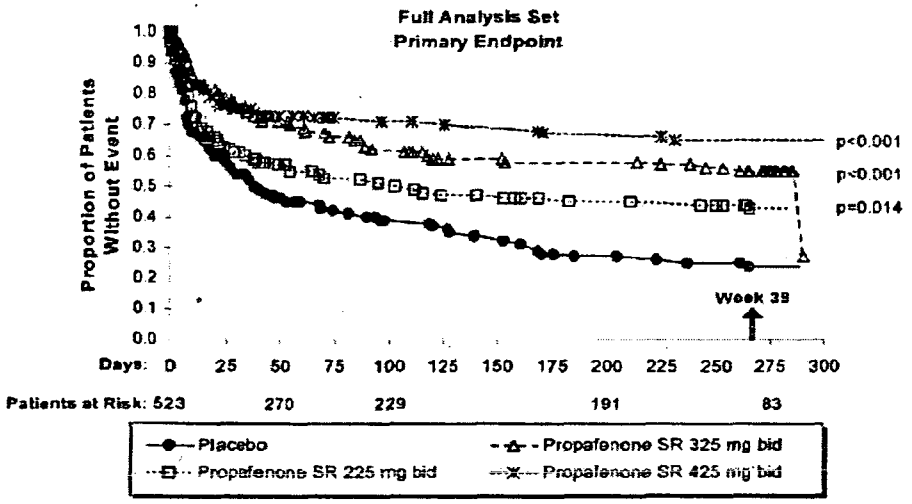
groups (Table 3). The post-hoc analyses however, were not adjusted for multiple comparisons.

Proportional hazards model was applied to assess the effect of any heterogeneity of baseline data between the treatment groups. The hazard ratios with their confidence intervals show differences in dose response between each treatment group. [(0.672(95%CI0.488,0.927) for 225 mg bid; 0.434 (95%CI 0.309,0.609) for 325 mg bid; 0.353 (95%CI 0.243,0.513) for 425 mg bid)] (Table 3 and Figures 10 and 12).

Hazard Ratios for differences between treatment groups-RAFT

- The RAFT study was not powered enough to detect differences between Propafenone SR treatment groups. However, the sponsors carried out post-hoc analyses and found hazard ratios of 0.66 (95%CI: 0.461,0.944) for propafenone SR 325mg bid versus SR 225 mg bid, and 0.53 (95%CI: 0.360,0.785) for propafenone SR 425 mg bid versus 225mg bid. The hazard ratio was not met for 325 mg bid versus 425 mg bid groups. Propafenone SR 225 mg bid was significantly different from placebo as seen in primary analysis, and from 325 mg bid and 425mg bid in the post hoc analyses albeit unadjusted for multiple comparisons (Table 3).

Figure 2: Survival Analysis for tachycardia free period from Day 1-RAFT



Subgroup analyses-RAFT

- Subgroup analyses for age, gender, race, NYHA classification, history of cardioversion, medications that lower heart rate, duration and frequency of atrial fibrillation were not carried out by the sponsors because of small numbers (See statistician's review by Dr Wang). However, using the proportional hazard method the sponsor observed no significant differences with respect to age and sex (Tables 55-58 and Figures 10 and 12).

- It is noteworthy that the patients with structural heart disease, regardless of associated hemodynamic deficits, showed no significant difference between the treatment groups (Figure 11). This may be due to the virtual exclusion of patients with NYHA III and IV classification from the study (Table 39). By excluding patients with atrial arrhythmia associated with more severe forms of heart failure (>NYHA II

classification), this category of patients may not benefit from Propafenone SR (Table 39). This should be reflected in the label.

Compliance

Over 90% of patients in the propafenone SR 225 mg hid, propafenone SR 325 mg bid and placebo treatment groups and over 87% of patients in the propafenone SR 425 mg bid treatment group were compliant according to the protocol *(>80%* and <120%) across all visits. There were no statistically significant differences in overall mean compliance among the 4 treatment groups or between the 3propafenone SR treatment groups compared to placebo ($p > 0.99$ for all comparisons). A total of 42 patients (8.0%) were considered non-compliant (propafenone SR 225 mg bid, 8.7%; propafenone SR 325 mg bid, 5.2%; propafenone SR 425 mg bid, 12.5%; and placebo, 5.6% (Appendix 2).

1.3 Efficacy conclusions - RAFT

- There were statistically significant differences between the propafenone groups compared to placebo for the following reasons:

- The time to first recurrence of symptomatic atrial arrhythmia from Day 1 of randomization shows significant differences between the treated groups compared to placebo [(p=0.014 for 225 mg bid; p<0.0001 for 325 mg bid and p<0.0001 for 425 mg bid using log rank; hazard ratio 0.672 (95%CI 0.488,0.927) for 225 mg bid; 0.434 (95%CI 0.309,0.609) for 325 mg and 0.353 (95%CI 0.243,0.513) for 425 mg bid)].

- The time to first recurrence of symptomatic atrial arrhythmia from Day 5 of randomization shows significant differences between the treated groups compared to placebo [(p=0.002 for 225 mg bid; p<0.0001 for 325 mg bid and p<0.0001 for 425 mg bid using log rank; hazard ratio 0.604 ((95% CI 0.433,0.842)) for 225 mg bid; .0.438 (95% CI 0.310,0.619) for 325 mg bid and 0.319 (95%CI 0.216,0.473) for 425 mg bid)]. Secondary efficacy analysis.

- The time to treatment failure from Day 1 of randomization shows significant differences between the treated groups compared to placebo [(p=0.032 for 225mg bid; p<0.0001 for 325 mg bid and p<0.0001 for 425 mg bid using log rank; hazard ratio 0.737 (95% CI 0.556,0.977) for 225 mg bid; 0.512 (95% CI 0.383,0.685) for 325mg and 0.543 (95%CI 0.404,0.73) for 425 mg bid). Secondary efficacy analysis.

- When the propafenone dose was adjusted for body weight into "low", "medium", and "high", there was a statistically significant difference between the propafenone groups compared to placebo for duration of tachycardia-free time from Day 5 of randomization [(p<0.0001 for either low, medium or high body weight using log rank; hazard ratio 0.543 (95% CI 0.39,0.76) for low body weight, 0.486 (95% CI 0.35,0.69) for medium, and 0.309 (95%CI 0.21,0.46) for high body weight).
- There was a significant increase in the tachycardia-free period in the propafenone groups (FAS and PP populations) with or without body weight adjustment compared to placebo. Secondary efficacy analysis.

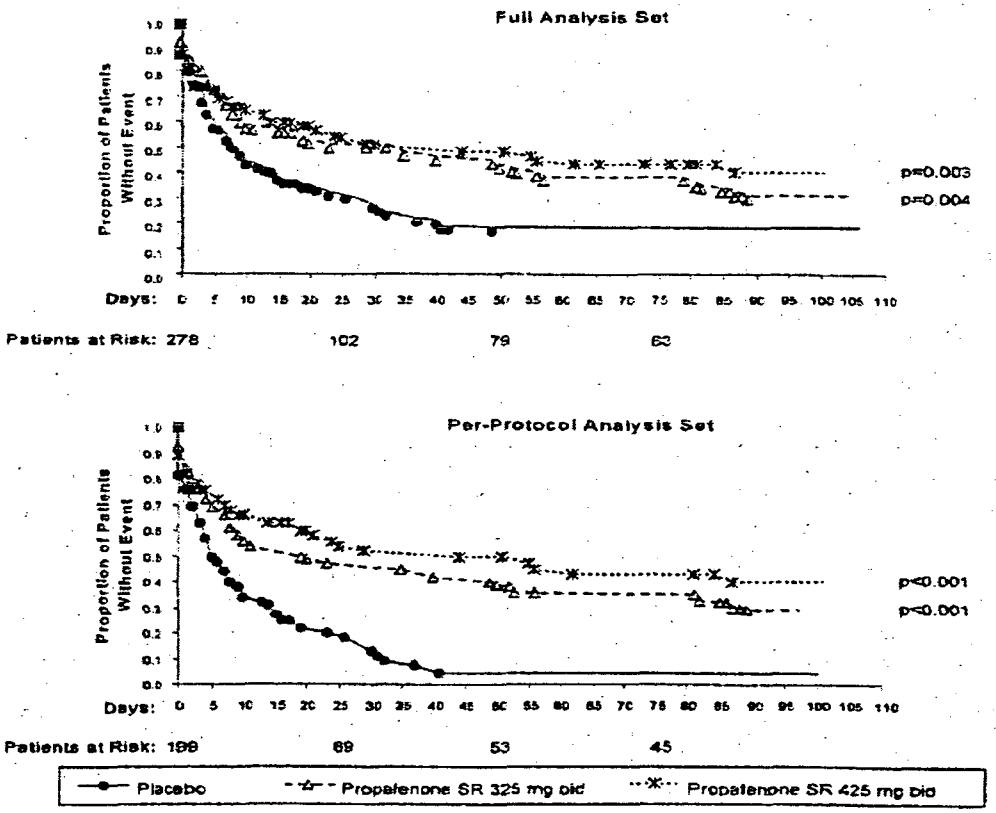
The SR formulation of propafenone shows a dose response at a bid dosing regimen and provides a basis for a bid dosing regimen for the RAFT study using 225mg, 325mg or 425mg SR propafenone.

Efficacy conclusions for ERAFT study is discussed here in the executive summary only to facilitate comparisons with the RAFT study (See section 5 page 95 for review of ERAFT).

1.4 Efficacy conclusions - ERAFT

- There were statistically significant differences between the propafenone groups compared to placebo for the following endpoints:
- The time to first recurrence of symptomatic atrial arrhythmia from Day 5 (Table 92) of randomization shows significant differences between the treated groups compared to placebo (p=0.004 for 325 mg bid and 0.003 for 425 mg bid using log rank; hazard ratio 0.60 (95%CI 0.43,0.86) for 325mg and 0.55 (95%CI 0.36,0.82) for 425 mg bid)]. Primary efficacy analysis (Figure 3 and Table 92).
- The time to first recurrence of symptomatic atrial arrhythmia from Day 1 of randomization shows significant differences between the treated groups compared to placebo (p=0.003 for 325 mg bid and 0.03 for 425 mg bid using log rank; hazard ratio 0.61 (95%CI 0.43,0.85) for 325mg and 0.66 (95%CI 0.45,0.96) for 425 mg bid) (Table 93).
- The time to treatment failure from Day 5 of randomization of randomization shows significant differences between the treated groups compared to placebo (p=0.002 for 325 mg bid and 0.006 for 425 mg bid using log rank; hazard ratio 0.61 (95%CI 0.44,0.84) for 325mg and 0.60 (95%CI 0.41,0.86) for 425 mg bid)] (Table 95).

Figure 3: Survival curves for tachycardia-free periods-ERAFT- FAS and PP



- The time to patient initiated report from Day 1 is presented in Table 94.
- Heart rate at first recurrence of atrial fibrillation from Day 5 is presented in Table 96 and with medication that slows the heart rate in Table 97.
- ///When the propafenone dose was adjusted for body weight into "low" and "high", there was a statistically significant difference between the propafenone groups compared to placebo for duration of tachycardia-free time from Day 5 of randomization [(p=0.005 for low body weight and 0.003 for high body weight using log rank; hazard ratio 0.61 (95%CI 0.43,0.86) for low body weight and 0.55 (95%CI 0.36,0.82) for high body weight). There was a significant increase in the tachycardia-free period in the propafenone groups (FAS and PP populations) with or without body weight adjustment compared to placebo (Tables 98 and 99). Secondary efficacy analysis.

The analysis of the per protocol dataset resulted in greater sensitivity to show treatment differences because lower hazard ratios and greater statistical significance were observed. The hazard ratios obtained were as follows: 0.47 (95% CI 0.31, 0.711), p< 0.001 for propafenone SR 325 mg and hazard ratio of 0.36 (95% CI 0.22, 0.581) p< 0.001 for propafenone SR 425 mg compared to placebo.

1.5 Safety – Clinical - RAFT

The review of safety was based on the following

1) data generated for the RAFT study alone and
2) Integrated review of safety data generated from three clinically distinct target populations exposed to propafenone during development. These included healthy individuals, patients with ventricular arrhythmia (VA), and patients with AF from other clinical studies (Section 5.5).

During drug development, a total of 655 AF patients out of 890 AF patients were exposed to propafenone SR and a total of 235 AF patients received placebo for varying periods of time. This sample size is considered adequate for evaluating safety in this class of drug. Additional information was also available from both short and long term safety data on propafenone IR formulation, albeit for a different indication. For this review, Table 4 below summarizes all AF patients exposed to propafenone SR during drug development.

Table 4: Patients with atrial fibrillation enrolled by study - all studies in drug development (RAFT, ERAFT, and 2 other clinical studies)

		Propafenone SR		
Study Number (Report number)	**Placebo N=235 n(%)**	**225mg bid N=146 n(%)**	**325mg bid N=264 n(%)**	**425mg bid N=245 n(%)**
Propafenone SR SVA CR-D1 (CD99018 / Propafenone SR SVA CR-11 (CD99021)	16(6.8%)	20(13.7%)	18(6.8%)	20(8.2%)
RAFT (P-85-AF)	126(53.3%)	126(86.3%)	135(51.1%)	136(55.5%)
ERAFT(PROPA SR 008	93(39.6%)	0(0.0)	111(42.0%)	89(36.3%)

The database provided by the sponsor and used for overall safety evaluation of this application is based on 4 studies combined, namely:
Two phase III clinical studies on AF patients:

- RAFT (N=523),
- ERAFT (N=293), and
- Two phase II studies (N= 74 AF patients): SR SVA CR D1 (Report Number CD 99018) and SR SVA CR 11 (Report Number CD 99021).

The overall duration of drug exposure for all treatment groups in RAFT and Phase II studies is presented in Table 5. The mean duration of drug exposure to AF patients in all the clinical studies was over 100 days. In contrast, the duration of exposure to placebo was significantly less than 65 days (Table 65). The mean duration of propafenone SR exposure to healthy volunteers was less than 10 days.

Table 5: Drug exposure – FAS - RAFT

		Propafenone SR		
Duration of exposure	**Placebo N=126**	**225mg bid N=126**	**325mg bid N=135**	**425mg bid N=136**
Extent of exposure				
Mean	90.9±102.4	124.4±117.5	148.9±119.1	141.2±125.4
Median	33	61	121	79
Range	2-289	2-285	2-295	3-300
Time on medication	N(%)	N(%)	N(%)	N(%)
<4 weeks	56(44.4)	47(37.3)	39(28.9)	51(37.5)
4 to <12 wks	27(21.4)	20(15.9)	17(12.6)	18(13.2)
12 to <24 wks	12(9.5)	12(9.5)	16(11.9)	3(2.2)
24 to <36 wks	7(5.6)	3(2.4)	6(4.4)	5(3.7)
36 to <39 weeks	9(7.1)	13(10.3)	12(8.9)	17(12.5)
> 39 wks	15(11.9)	31(24.6)	45(33.3)	42(30.9)

In the RAFT safety evaluation, 3 dose-related adverse events occurred. These included:

- **Sinus bradycardia, First degree A-V block and, Disturbance of taste.**

None of these adverse events resulted in death. These dose-related adverse events usually manifested within the first 2 weeks following drug exposure thus permitting early detection. The dose-dependent disturbance of taste was observed almost exclusively among Caucasians regardless of whether they were healthy volunteers or AF patients. This observation may be due to relatively small numbers of non-Caucasians exposed to propafenone in the study. The significance of this observation is not clear. There was no taste disturbance among the placebo group.

Adverse events - RAFT

Across propafenone SR treatment groups, the most common adverse events, possibly, probably or related (incidence at least 5% or greater) with an incidence at least 5% greater than the incidence in the placebo treatment group is summarized in Table 6.

Table 6: Adverse events > 5% - RAFT

Adverse event	Propafenone	Placebo
Dizziness	21.7%	14.3%
Dyspnea	14.1%	7.1%
Taste disturbance	13.9%	0.8%
Fatigue	12.1%	5.6%
Constipation	11.3%	2.4%

The most commonly reported adverse events, possibly, probably or related to the propafenone SR treatment groups included dizziness, palpitations, dyspnea, nausea, constipation, anxiety, fatigue, upper respiratory tract infection, influenza, vomiting, and taste disturbance (Tables 63-64).
The most commonly reported adverse events in the placebo group included dizziness, palpitations, dyspnea, nausea, anxiety, fatigue, constipation, upper respiratory tract, infection and influenza. With the exception of one patient, taste disturbance was not observed among the placebo group.
The relative ratio frequencies of other adverse events and experiences in the RAFT study in at least 1% (Table 63) or 5% (Table 64), and by race are presented in section 4.0 (Table 74). The serious adverse events that led to premature termination are presented in Appendix 5.

Overall in the integrated review of safety, adverse events (14%) and lack of efficacy (26%) constituted the largest number of causes for discontinuation (Table 66).

Vital signs
In addition to abnormalities of ECG and heart rate discussed in the safety review of RAFT in Section 4, other cardiovascular safety parameters evaluated included systolic and diastolic blood pressure in patients with atrial fibrillation and healthy volunteers. These show no significant differences between the treatment groups and placebo (Tables 79-82).

1.6 Clinical Laboratory Safety Evaluations
The abnormal laboratory findings were related to hematology, electrolytes and liver function tests. The number and percentage of all patients with hematology-related abnormalities are presented in Table 7 below. There were no clinically significant differences between the treatment groups and there were no deaths.

Table 7: No and %( ) of patients with hematology-related adverse events-RAFT

	Propafenone			
Term	**225mg bid N=126**	**325mg bid N=135**	**425mg bid N=136**	**Placebo N=126**
Anemia	1(0.8)	2(1.5)	0(0.0)	1(0.8)
Hemoglobin decreased	1(0.8)	0(0.0)	0(0.0)	0(0.0)
White blood cell increased	1(0.8)	0(0.0)	0(0.0)	0(0.0)
Monocyte count increased	0(0.0)	0(0.0)	1(0.7)	0(0.0)
Eosinophil count increased	1(0.8)	0(0.0)	1(0.7)	0(0.0)
Platelet count decreased	0(0.0)	1(0.7)	1(0.7)	1(0.8)

Liver function Tests (LFTs)-RAFT
There were no clinically significant differences between the treatment groups with respect to liver function parameters compared to placebo. There were also no clinically important changes in mean values for any of the liver function parameters at baseline and at endpoints (Tables 8 and 9). However, all abnormalities of LFTs and electrolytes were in the propafenone SR groups (Table 9).

Table 8: Shifts in Liver function parameters from normal (baseline) to high at endpoint - RAFT

Term	Propafenone			
	225mg bid N=110	325mg bid N=124	425mg bid N=124	Placebo N=113
SGOT (U/L)	2(1.8)	5(4.0)	3(2.4)	2(1.8)
SGPT (U/L)	2(1.8)	5(4.0)	2(1.6)	2(0.9)
Total Bilirubin (mg/dL)	0(0.0)	0(0.0)	2(1.6)	0(0.0)
Alkaline Phosphatase (IU/L)	6(5.5)	5(4.0)	7(5.5)	10(8.8)
LDH (IU/L)	5(4.5)	7(5.6)	5(4.0)	3(2.7)

Table 9: Number and percentage of patients with clinically abnormal LFTs-RAFT

Term	Propafenone			
	225mg bid N=122	325mg bid N=134	425mg bid N=136	Placebo N=126
ALT/SGPT (U/L) 3X greater than ULN	1(0.8)	0(0.0)	1 (0.7)	0(0.0)
Total Bilirubin (mg/dL) 2X greater than ULN	0(0.0)	0(0.0)	1(0.7)	0(0.0)
Alkaline Phosphatase (IU/L) 3X greater than ULN	0(0.0)	1(0.7)	1(0.7)	0(0.0)
LDH (IU/L) 3X greater than ULN	0(0.0)	1(0.7)	1(0.7)	0(0.0)

The mean values for 4 electrolytes, sodium, chloride, potassium, and calcium were within normal limits at baseline and at endpoint (Tables 10 and 11). Abnormal laboratory findings were found in respect to potassium, calcium and sodium only in patients administered propafenone SR over time.

There were clinically significant differences between the treatment groups with respect to electrolytes particularly hypokalemia. Hypokalemia was the most frequently reported laboratory adverse event in the propafenone treatment groups {(Propafenone 225 mg bid (1), 325 mg bid (2) and 425 mg bid (2); placebo (0)]. The label only states that propafenone is contraindicated when there is manifest electrolyte imbalance.

Calcium, Sodium and Potassium levels

Other laboratory tests reported show no significant abnormalities (Tables 10 and 11). No laboratory abnormalities accounted for discontinuation or resulted in death.

Table 10 : Summary statistics of Electrolytes at baseline and endpoint - RAFT

Term	Propafenone			
	N	Baseline	Endpoint	Change from baseline
Sodium				
Propafenone SR 225mg bid	122	138.7±2.6	138.8±2.8	0.1±2.8
Propafenone SR 325mg bid	131	138.7±2.1	138.7±3.0	0.1±2.9
Propafenone SR 425mg bid	134	138.5±2.3	138.6±3.0	0.1±3.1
Placebo	120	138.5±2.4	138.6±2.2	0.1±2.6
Potassium				
Propafenone SR 225mg bid	122	4.3±0.4	4.3±0.4	0.1±0.4
Propafenone SR 325mg bid	131	4.2±0.4	4.3±0.4	0.1±0.5
Propafenone SR 425mg bid	134	4.2±0.4	4.3±0.4	0.0±0.4
Placebo	120	4.2±0.4	4.3±0.4	0.0±0.4
Chloride				
Propafenone SR 225mg bid	122	103.3±3.2	103.1±3.3	-0.2±2.8.
Propafenone SR 325mg bid	131	103.6±2.6	103.8±2.9	0.1±2.9
Propafenone SR 425mg bid	134	102.8±3.0	102.8±3.0	-0.0±3.1
Placebo	120	103.3±2.7	103.3±2.7	0.1±2.7

Table 11: Mean values of calcium levels at baseline and endpoint–RAFT

	Propafenone			
	N	Baseline	Endpoint	Change from Baseline
Calciuim				
Propafenone SR 225mg bid	122	9.1±0.4	9.1±0.4	-0.1±0.4
Propafenone SR 325mg bid	131	9.0±0.5	9.0±0.4	-0.1±0.6
Propafenone SR 425mg bid	134	9.1±0.4	9.0±0.4	-0.1±0.4
Placebo	120	91±0.4	9.1±0.4	-0.1±0.4

Electrocardiogram - Baseline expectations in propafenone SR and IR

PQ interval prolongation was more pronounced after SR administration (325 mg bid and 425 mg bid) at 6 hours compared to corresponding doses of IR formulation (150 mg, 300 mg bid, 300 mg od) (Figure 4). Based on the pharmacology of the drug, ECG changes are expected to be dose related, and to result in decrease in heart rate during sinus rhythm, increase PR/PQ interval and also increase QRS duration. In addition, the sponsor claims the QTc interval may increase in increments equal to increment in QRS duration. These pharmacological changes due to propafenone may explain the ECG changes in this study and should be reflected in the label. These changes are illustrated in the 3 graphs generated by the reviewer (Figures 4-6). It is evident that there is minimal effect, if any on QT interval and QTc (Figure 6) regardless of whether it is IR or SR. Based on the pharmacology of propafenone, ECG changes (PQ and QRS intervals) in patients with atrial fibrillation given propafenone SR were dose-related (Figure 6). There was a decrease in heart rate during sinus rhythm, a dose-dependent increase (>10%) in PQ interval across the SR treatment groups, an increase in QRS duration for the 225 mg bid, 325 mg bid and 425 mg bid dose levels. In addition, the QTc increased in the 325 mg bid and 425 mg bid treatment groups (Figure 6). These changes were independent of the presence or absence of structural heart disease. None of these ECG changes were associated or resulted in death (Table 12).

Figure 4: Mean Changes PQ/QRS healthy volunteers on IR Propafenone -

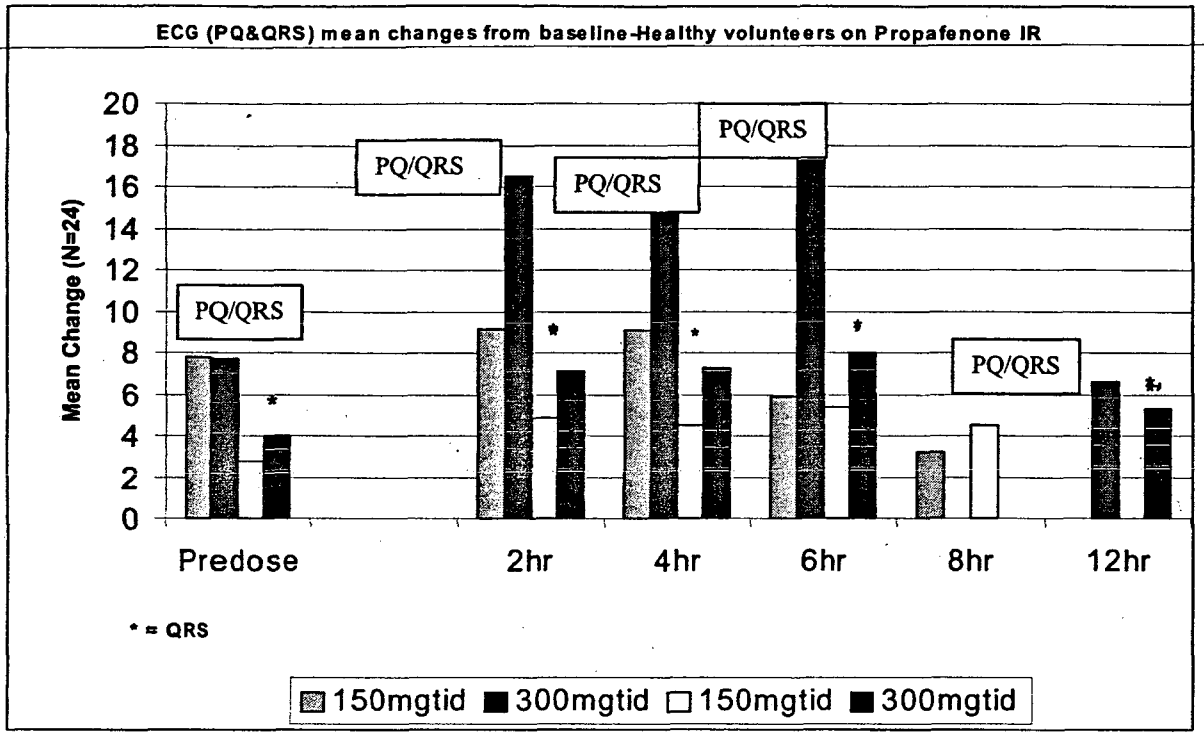
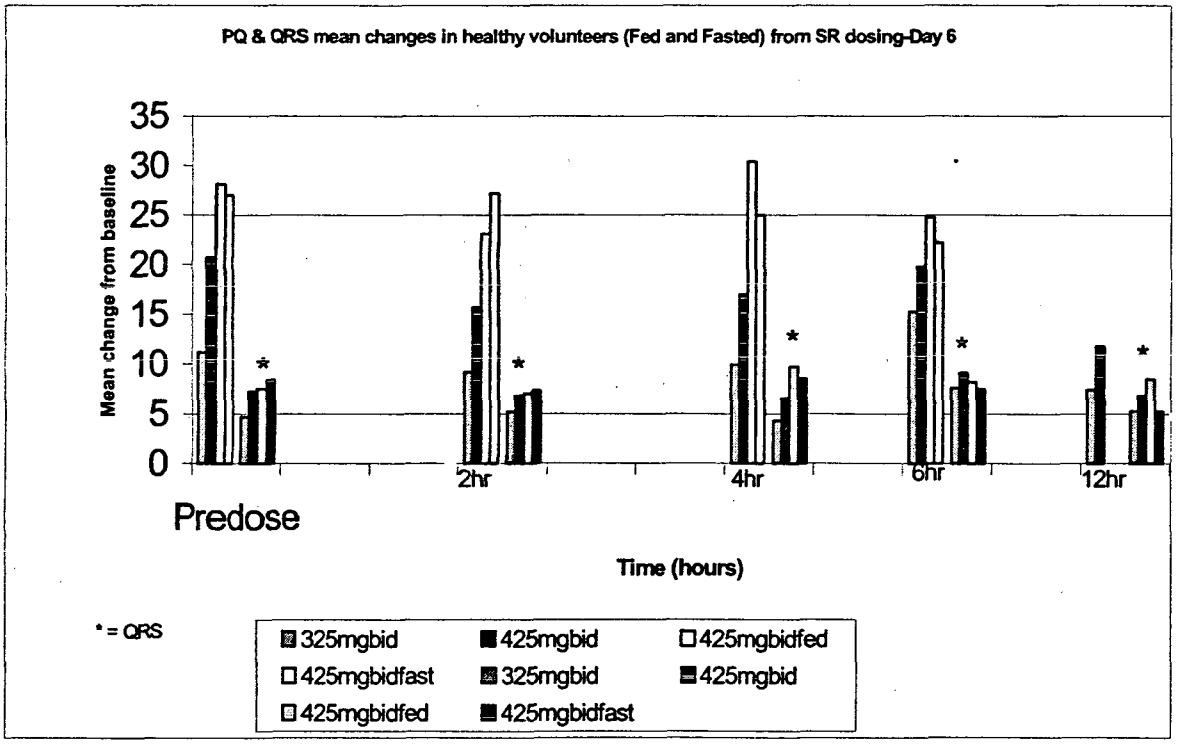
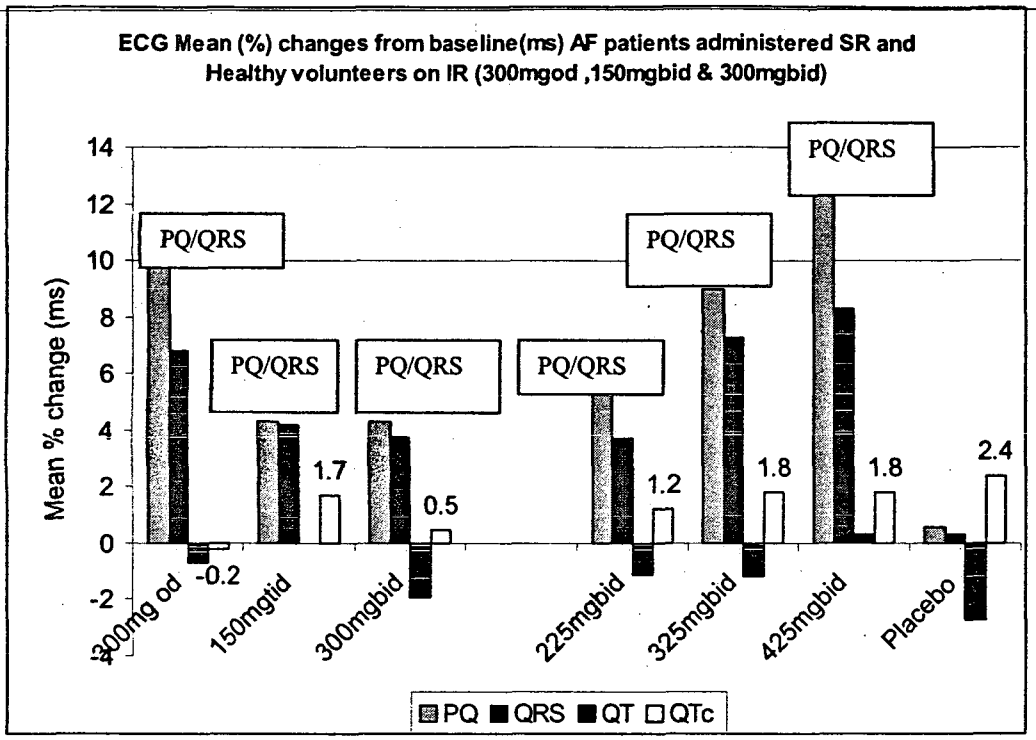


Figure 5: PQ/QRS changes in fed/fasted volunteers on SR -dosing day 6



(Figures 4-6 - Source-Reviewer).

Figure 6: ECG parameters-Mean percent change (ms) in AF patients on SR and Healthy volunteers on IR (Source-Reviewer).



QTc intervals have labeled values. Right of graph: Note dose-related increase of PQ and QRS intervals (Ist and 2nd columns, respectively) with SR and lack of significant effect on QT and QTc intervals compared to placebo. Left of graph: Note dose related decrease of PQ and QRS intervals (1st and second columns,respectively) with IR and lack of significant effect on QT. (Appendix 20 tabulates literature review on ECG changes in patients treated with Rhythmol IR and SR).

The mean increase in ventricular rate was greater in the placebo group compared to the 3 treatment groups (Tables 12 and 14). JTc interval data are still awaited from sponsor.

Table 12: Patients with ECG recordings and changes at endpoint-RAFT

	Propafenone SR			
Parameter	225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Patients with ECGs	123 (97.6)	132 (97.8)	131 (96.3)	120 (95.2)
Heart rate (Ventricular rate: #QRS/minute):				
<50	23 (18.3)	25 (18.5)	24 (17.6)	18 (14.3)
>120	8 (6.3)	8 (5.9)	7 (5.1)	13 (10.3)
Increase ≥15% from baseline	72 (57.1)	74 (54.8)	66 (48.5)	65 (51.6)
Decrease ≥15% from baseline	33 (26.2)	32 (23.7)	35 (25.7)	27 (21.4)

1.7 Electrocardiograms in AF patients on propafenone

There is an increase in QRS duration from baseline to endpoint in all the 3 propafenone groups (Table 13). The changes in mean values from baseline to endpoint in the RAFT

study are presented in Table 14. There is no significant effect on the QT/QTc interval (Tables 14 and 15 and Figures 5 and 6)).

There were about 4 patients with adverse events related QT prolongation in the combined data from RAFT and ERAFT propafenone groups. None of these patients was hospitalized or died (Table 77). There is insufficient temporal (peak or trough) information between the abnormal QT intervals and propafenone concentrations.

Table 13: ECG changes at endpoint in RAFT

Parameter	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 (%)
PR (msec):				
<120	2 (1.6)	1 (0.7)	1 (0.7)	2 (1.6)
>200	37 (29.4)	57 (42.2)	53 (39.0)	17 (13.5)
Increase ≥10% from baseline	57 (45.2)	90 (66.7)	88 (64.7)	28 (22.2)
QRS (msec):				
<70	4 (3.2)	5 (3.7)	2 (1.5)	5 (4.0)
>100	50 (39.7)	61 (45.2)	62 (45.6)	27 (21.4)
Increase of ≥10% from baseline	43 (34.1)	57 (42.2)	57 (41.9)	15 (11.9)
QTc (msec)				
>390 (Males)	41 (33.3)	55 (41.7)	40 (30.5)	45 (37.5)
>440 (Females)	6 (4.9)	9 (6.8)	13 (9.9)	2 (1.7)
Increase of ≥5% from baseline	32 (26.0)	31 (23.5)	34 (26.0)	26 (21.7)

Source: Table 9.3.7.6

Table 14: Mean values change from baseline ECG changes to end-point-RAFT

Parameter/Treatment Group	N	Means:SD Baseline	Endpoint	Change From Baseline
Ventricular rate (bpm)				
Propafenone SR 225 mg bid	120	67.73±19.94	72.68±22.87	4.94±24.24
Propafenone SR 325 mg bid	134	66.01±14.84	72.63±22.22	6.62±22.70
Propafenone SR 425 mg bid	131	67.18±17.38	69.55±19.57	2.37±22.46
Placebo	121	67.23±15.92	75.46±24.87	8.23±27.02
PR (ms)				
Propafenone SR 225 mg bid	103	171.84±34.33	180.91±38.85	9.07±21.53
Propafenone SR 325 mg bid	118	170.38±24.27	182.62±28.87	12.24±23.38
Propafenone SR 425 mg bid	109	169.76±27.61	190.66±33.40	20.90±23.75
Placebo	100	165.23±26.28	166.20±24.85	0.97±15.71
QRS (ms)				
Propafenone SR 225 mg bid	120	89.85±14.18	93.88±17.73	4.03±14.18
Propafenone SR 325 mg bid	134	90.72±15.19	96.99±17.49	6.27±15.18
Propafenone SR 425 mg bid	131	90.58±12.70	96.91±20.54	6.33±15.19
Placebo	121	89.57±14.29	87.98±13.32	-1.60±11.64
QT (ms)				
Propafenone SR 225 mg bid	120	383.07±37.99	373.19±37.51	-9.88±42.81
Propafenone SR 325 mg bid	134	388.13±36.57	378.28±41.85	-9.84±45.73
Propafenone SR 425 mg bid	131	383.53±36.42	383.86±41.39	0.33±41.73
Placebo	121	378.88±41.90	366.80±47.86	-12.08±48.62
QTc (ms)				
Propafenone SR 225 mg bid	120	399.40±29.29	401.78±32.92	2.38±30.35
Propafenone SR 325 mg bid	134	401.84±36.16	406.61±33.09	4.77±36.06

Table 15: Mean changes in ECG recordings – RAFT - Sponsor

	RYTHMOL SR			
	225 mg BID	325 mg BID	425 mg BID	Placebo
	n=126	n=135	n=136	n=126
Ventricular rate (bpm)	4.94±24.24	6.62±22.70	2.37±22.46	8.23±27.02
PR (ms)	9.07±21.53	12.24±23.38	20.90±23.75	0.97±15.71
QRS (ms)	4.03±14.18	6.27±15.18	6.33±15.19	-1.60±11.64
QTc* (ms)	2.38±30.35	4.77±36.06	5.65±36.69	5.20±35.31

*Calculated using Bazett's correction factor

Note prolonged PR interval in treatment groups compared to placebo. Table by sponsor.

Blood level response

A blood level response has not been established for propafenone IR. Although blood samples were collected in both Phase III trials of SR propafenone, the sponsor did not analyze data for a blood level response. Tables 28 and 29 summarize the propafenone plasma concentration levels at weeks 3 and 39. These show no significant changes over the efficacy period.

In general, the frequencies of patient-initiated symptom reports and associated TTM ECG findings did not differ between propafenone SR treatment groups in the integrated review of safety (Table 16). The total percentage of patients within propafenone SR treatment groups reporting shortness of breath, lightheadedness, awareness of heartbeat, chest pain, and anxiety was similar. Table 17 summarizes the frequencies of predefined arrhythmia symptoms (shortness of breath, lightheadedness, awareness of heartbeat, chest pain, and anxiety) without TTM in the RAFT study. There is no difference between the treatment groups and placebo.

The sponsor claims that for each of the patient-initiated symptoms (shortness of breath, lightheadedness, awareness of heartbeat, chest pain, and anxiety) there was a higher percentage of patients in the placebo group compared to patients in each of the 3 propafenone SR treatment groups with atrial fibrillation and a lower percentage of patients had NSR on TTM recording (Tables 16 and 17).

Table 16: Frequencies of patient-initiated symptom reports and ECG reports-Integrated review

Table 118 Frequency of patient initiated symptom reports and ECG diagnosis

Reason/Treatment Group	N	No. (%) of total reports	Number and (%) of reports associated with ECG findings: Normal sinus rhythm	AF	Atrial flutter	Other[a]
Shortness of breath						
Propafenone 225 mg bid	244	73 (29.9)	21 (8.6)	28 (11.5)	2 (0.8)	22 (9.0)
Propafenone 325 mg bid	230	60 (26.1)	27 (11.7)	25 (1.9)	0 (0.0)	8 (3.5)
Propafenone 425 mg bid	225	(64 (29.4)	23 (10.2)	21 (9.3)	1 (0.4)	19 (8.4)
Placebo	248	71 (28.6)	8 (3.2)	40 (16.1)	2 (0.8)	21 (8.5)
Lightheaded						
Propafenone 225 mg bid	244	101 (41.4)	42 (17.2)	29 (11.9)	1 (0.4)	29 (11.9)
Propafenone 325 mg bid	230	71 (30.9)	37 (16.1)	20 (8.7)	0 (0.0)	14 (6.1)
Propafenone 425 mg bid	225	59 (26.2)	29 (12.9)	11 (4.9)	0 (0.0)	19 (8.4)
Placebo	248	75 (30.2)	12 (4.8)	36 (14.5)	2 (0.8)	25 (10.1)
Aware of heart beat						
Propafenone 225 mg bid	244	177 (72.5)	43 (17.6)	67 (27.5)	3 (1.2)	64 (26.2)
Propafenone 325 mg bid	230	174 (75.7)	71 (30.9)	56 (24.3)	1 (0.4)	46 (20.0)
Propafenone 425 mg bid	225	171 (76.0)	78 (34.7)	43 (19.1)	1 (0.4)	19 (21.8)
Placebo	248	193 (77.8)	24 (9.7)	120 (48.4)	6 (2.4)	43 (17.3)
Chest pain						
Propafenone 225 mg bid	244	73 (29.9)	23 (9.4)	24 (9.8)	2 (0.8)	24 (9.8)
Propafenone 325 mg bid	230	47 (20.4)	29 (12.6)	10 (4.3)	0 (0.0)	8 (3.5)
Propafenone 425 mg bid	225	81 (36.0)	43 (19.1)	19 (8.4)	0 (0.0)	19 (8.4)
Placebo	248	73 (29.4)	18 (7.3)	29 (11.7)	1 (0.4)	25 (10.1)
Anxiety						
Propafenone 225 mg bid	244	78 (32.0)	34 (13.9)	18 (7.4)	1 (0.4)	25 (10.2)
Propafenone 325 mg bid	230	60 (26.1)	23 (10.0)	20 (8.7)	1 (0.4)	16 (7.0)
Propafenone 425 mg bid	225	72 (32.0)	37 (16.4)	14 (6.2)	0 (0.0)	21 (9.3)
Placebo	248	76 (30.6)	14 (5.6)	37 (14.9)	3 (1.2)	22 (8.9)

[a] Other = May include ventricular arrhythmia, premature atrial contractions, sinus tachycardia, sinus bradycardia, sinus pause, bradycardia, idioventricular rhythm junctional escape beats, junctional nodal rhythm, wandering atrial pacer, and wide complex tachycardia.

Table 17: Number and percent of patients with predefined symptoms

Table 120 Number and percentage of patients volunteered predefined arrhythmia symptoms

	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 (%)
Patients with reported symptoms				
Short of breath	38 (30.2)	32 (23.7)	40 (29.4)	35 (27.8)
Lightheaded	47 (37.3)	30 (22.2)	33 (24.3)	43 (34.1)
Aware of heart beat	78 (61.9)	67 (49.6)	69 (50.7)	83 (65.9)
Chest pain	36 (28.6)	24 (17.8)	37 (27.2)	38 (30.2)
Anxiety	34 (27.0)	34 (25.2)	44 (32.4)	43 (34.1)

Source: Table 9.3.6.5

A lower percentage of patients in the propafenone SR 325 mg bid and propafenone SR 425 mg bid treatment groups reported lightheadedness and awareness of heartbeat

(propafenone SR 325 mg bid: 22.2% and 49.6%, respectively; propafenone SR 425 mg bid: 24.3% and 50 7%, respectively) compared to the propafenone SR 225 mg bid and placebo treatment groups (propafenone SR 225 mg bid: 37.3% and 61.9%, respectively; placebo: 34.1% and 65.9%, respectively). This suggests that the higher doses of propafenone favorably affected symptoms. However, there was no evidence that propafenone converted patients from symptomatic to asymptomatic atrial fibrillation

In all the propafenone studies, the most striking ECG abnormality in the treated groups was the dose-dependent increase in the proportion of patients with atrial fibrillation who developed treatment emergent conduction disturbances (Table 18).

Table 18: Treatment-emergent cardiovascular AEs >3% in patients with AF - Integrated review of safety

Cardiac disorders	Placebo	225mg bid	325mg bid	425mg bid
	N=235(%)	N=146(%)	N=264(%)	N=245(%)
Atrial Fibrillation	10(4)	7(5)	13(5)	9(4)
A-V Block	3(1)	3(2)	12(5)	18(7)
Bradycardia	2(1)	4(3)	6(2)	7(3)
Edema	8(3)	7(5)	19(7)	11(4)
Palpitations	22(9)	23(16)	35(13)	24(10)
Sinus bradycardia	2(1)	0(0)	12(5)	4(2)

1.8 Electrocardiograms in healthy volunteers on propafenone
Two healthy volunteers administered propafenone SR terminated prematurely due to conduction disorders. One patient received 225 mg bid and another complained of headache and dizziness after receiving 425 mg bid.

Electrocardiograms in ventricular arrhythmia (VA) patients on propafenone
A higher percentage of patients with ventricular arrhythmia (VA) (9%) treated with 425 mg bid group in other clinical studies terminated prematurely due to adverse events compared to those treated with 225mg bid (3%) and 325mg bid, (1%), and placebo (4%).
The frequencies of adverse events in the RAFT study are in Table 19.
Table 19: Adverse events – RAFT

Table 19 continued on next page.

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)

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 (%)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Renal failure NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Respiratory failure (exc neonatal)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Skin & subcutaneous tissue disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Sweating increased	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hydrocele excision	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Umbilical hernia repair	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	3 (2.2)	0 (0.0)	2 (1.6)
Arterial embolism limb	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Carotid artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Carotid artery stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Venous thrombosis deep limb	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)

Source: Table 9.3.2.3

1.9 Deaths

There were no drug-related deaths in both the RAFT and ERAFT studies. There were also no deaths among the healthy volunteers exposed to propafenone SR albeit the relatively small numbers of patients were exposed to drug for relatively short duration.

One patient died about 30 days after stopping propafenone SR. The cause of death was presumably related to a fall. The cause of the fall could not be ascertained from the sponsor. Of the total nine deaths in the propafenone safety database, there were 5 deaths in phase III of the RAFT study but none was related to drug exposure (Table 21,22,25). Three and 2 deaths were among patients who had received propafenone SR and placebo, respectively. The total number of deaths during drug development by study is summarized in Table 22. No deaths were reported among patients with ventricular arrhythmias who also received propafenone SR in separate studies (Table 22).
The temporal relationship between drug exposure and death showed that death of 2/9 patients exposed to the drug for 7 and 11 days occurred 11 and 73 days after drug was stopped (Table 21) The 2D6 status of these 2 patients is not known and there is no evidence that they were on 3A4 inhibitors. Other patients who died were exposed to the drug for periods ranging from 30 to 261 days and time to death after drug was stopped in these patients ranged from 2 to 205 days (Table 21). Since drug-relatedness cannot be established in any of these cases, the question of initiating therapy in hospital cannot be sustained.

Overall there were 9 deaths out of 1400 patients exposed to the drug and placebo in the database (Table 22). Seven of these out of 890 were in the propafenone treated group and 2 out of 360 were in the placebo group (Tables 21 and 22). These numbers are too small for evaluating overall mortality risk of propafenone SR. There were 5 deaths with

the propafenone SR and four deaths were due to causes not related to the drug, e.g. lung neoplasm, brain damage, and renal failure (Table 25). One of the major constraints in mortality analysis of the present NDA and similar studies is the small numbers of deaths. The survival curve constructed for mortality by the sponsor supports this view and the use of proportional hazards ratio that requires a lot of assumptions as exemplified in this study show very wide Confidence Interval limits (Table 26).

1.10 Propafenone overdose

In the safety update report, there have been 4 persons reported with overdose coincident with propafenone therapy between 01 May 2001 and 30th April 2002. Two patients (18 and 22 yr. old) were severely hypotensive (SBP of ~60mmHg), one 12 yr. old patient (176805) developed cardiac arrest and another 48 yr. old patient (176700) developed myoclonic encephalopathy, all of which were considered as serious adverse events. None of these persons died.

1.11 Analysis of mortality data

For overall safety/mortality evaluation, the sponsor created a database on almost all known (8/9) placebo-controlled propafenone studies.

The objectives of the mortality analysis in this NDA are as follows:

- To compare survival between patients on oral propafenone (SR and IR) and placebo in a pooled analysis of randomized clinical trials of patients with supraventricular arrhythmia.
- To compare survival between patients taking oral propafenone from the randomized placebo-controlled clinical trials of patients with supraventricular arrhythmia
- and survival in
  - (a) related patient groups from other drug development programs and
  - (b) related patient groups followed in one arrhythmic clinic.

Statistics in mortality analysis

Eight studies involving 1400 patients were selected and included in the safety database. The studies were double-blind and placebo-controlled initiated after the study presented in the previously published mortality analysis study on atrial fibrillation (*Pritchett et al., 1993).* The reviewer considers this approach inadequate for a mortality study.

The sponsor compiled a summary of all data in the 8 placebo-controlled propafenone studies of supraventricular arrhythmias (atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia with propafenone). This included RAFT and ERAFT studies. The resulting database was used in assessing mortality rates associated with propafenone.

The primary statistical analysis specified and used for the mortality study was the log rank test that compared overall survival between the two treatment groups using the maximum available follow-up time for patients who were alive at the end of each study. The survival distribution was illustrated with Kaplan-Meier curves supplemented with proportional hazards model that was applied to evaluate the effect of any heterogeneity of baseline data. The sponsor proposed an aggregate mortality rate (total number of deaths/total length of follow up) to be reported as a point estimate with 95% CI. These were to be compared with three published mortality rates in related groups, including other antiarrhythmic drugs (dofetilide, encainide, flecainide), and also with groups of patients followed in arrhythmia clinics.

Completeness of Mortality data

- The mortality data submitted are inadequate and furthermore they are heterogenous in origin, design and duration of follow up. The numbers of patients, treated and placebo, in 6 out of 8 studies contributing to the database are too small for meaningful statistical evaluation of mortality risk. (Tables 21-23).

- The demographics of the eight eligible studies selected for inclusion in the database are heterogenous (Table 20). The reason for excluding one study from Italy was inadequate data.

Heterogeneity of data

- There was heterogeneity in the variables from the selected studies. For example, some studies did not collect NYHA classification while the definition of structural heart disease was not uniformly applied to all the studies included.

Verification of treatment groups

- Among the studies included in the database was a placebo group in a cross-over study design. The sponsor claims that the patients had not received propafenone but this could not be verified.

Mortality database

The sponsor pooled a total of 1400 patients from the selected studies for the mortality analysis (Table 20). The pooled size is considered adequate to get a mortality trend. The demographics, duration of exposure, duration of follow up of patients at risk by number of days from first dose of propafenone to time to death in the treatment groups for patients in the safety database are summarized in Tables 21-25. Overall the mean age of all patients was 61 years, 36% were females and 64% males. Less than 10% of the patients were in NYHA class III or IV whereas the rest were NYHA class I or II. The mortality database is therefore composed of majority of patients (>90%) without structural heart disease or heart failure. This should be reflected in the label.

In one of the propafenone studies where placebo patients were discontinued from a crossover study the reasons for discontinuations of the placebo patients were not stated. The use of aggregate mortality rate (defined as total number of deaths / length of follow up) as a surrogate (point estimate) by the sponsor for comparisons of survival is perhaps tenuous since there is temporal variation in follow-up among the 8 studies pooled and analyzed. The significant differences in the patient's baseline characteristics mitigate against a comparison within and between the data in the propafenone groups and with other published studies. The reviewer cannot interpret the data in its present format.

The approach utilized for evaluating mortality risk in this target population is not consistent with previous methodology applied to, for example, DOFETILIDE and DIAMOND study. As a result, it is therefore difficult to interpret the data and to come to meaningful conclusions on mortality risk or rate.

Table 20: Safety /Mortality Demographics – 8 Propafenone studies combined

		Study Medication		
		Placebo N=360	**Propafenone N=1040**	**Total N=1400**
Age(years)	Mean ±	61.7	61.3	61.4
	SD	10.9	12.1	11.8
	Median	62.5	63	63
Sex N(%)	Female	123(34.2)	378(36.3)	501(35.8)
	Male	237(65.8)	662(63.7)	899(64.2)
SHD	N	132(36.7)	325(31.3)	457(32.6)
	Y	87(24.2)	272(26.2)	359(25.6)
	Unknown	141(39.2)	443(42.6)	584(41.7)
NYHA	I	153	440	593
	II	49	140	189
	III	26	54	80
	IV	-	2	2
Time on medication	<14 days	198	390	588
	15-30days	52	115	167
	31-60 days	36	75	111
	61-90 days	10	49	59
	91-120 days	10	70	80
	121-180 days	15	59	74
	181-240days	14	79	93
	241-300days	25	190	215
	301-360days	-	11	11
	>360days	-	2	2
Duration of drug exposure (days)	Mean ±	48.8	96.6	84.3
	SD	77.5	107.1	102.5
	Median	12	36.5	23
	Total	17576	100501	118077
Duration of follow-up (days)	Mean ±	50.5	98.1	85.9
	SD	77.9	107	102.4
	Median	14	38.5	24.5
	Total	18193	102028	120221
No of Deaths	N	2	7	9
Time to death Days	Mean ±	292.5	118.9	157.4
	SD	24.7	93.4	111.7
	Median	292.5	116	118
	Mortality rate*	2/360	7/1040	9/1400

***Crude mortality rate**

According to the reviewer, the inadequacies of the mortality data include the following:

- The heterogeneity of the studies and incompleteness of the data variables are defects that result in its unsuitability for mortality analysis as proposed by the sponsor. For example, about 36% and 41% of patients in the mortality database have no information relating to their NYHA class/structural heart disease status, respectively.

- Furthermore, some propafenone studies used immediate release formulation while others used sustained release formulation and in one study propafenone was given parenterally before it was given orally (Table 27).

Table 21: Duration of Propafenone SR exposure/& time to death for 9 patients*

Study	Patient's ID	Treatment	Duration of exposure	Time to death	Time - death after drug stopped
P17	000203	Propafenone	30	31	2
P76	010043	Propafenone	**7	17	*11
ERAFT	003695	Propafenone	49	118	70
ERAFT	004073	Propafenone	84	116	33
RAFT	001105	Placebo	205	275	71
RAFT	004003	Propafenone	87	292	205
RAFT	006004	Propafenone	**11	83	*73
RAFT	007707	Placebo	261	310	50
RAFT	008701	Propafenone	111	176	66

*** See table 22. Narratives of deaths in Appendix 3. **Pts with relatively short duration of exposure.**

Table 22: Number of patients who died by study and treatment group- 8 studies

Study	Number of deaths /Number of patients included in the analysis		
	Placebo	Propafenone	Overall
PSD88	0/3	0/96	0/99
ORAFIMCR	0/25	0/78	0/103
P17	0/0	1/16	1/16
P76	0/97	1/195	1/292
SVACRD1	0/6	0/20	0/26
SVACR11	0/10	0/38	0/48
ERAFT	0/93	2/200	2/293
RAFT	2/126	3/397	5/523
OVERALL	2/360	7/1040	9/1040

Table 23: Number of patients at risk by number of days from first dose of propafenone

Treatment	0	50	100	150	200	250	300	350	400	450
Placebo	360	85	58	48	30	25	1	0	0	0
Propafenone	1040	494	368	317	243	199	15	2	1	0

No definite conclusion can be drawn by this reviewer from the sponsor's data regarding mortality risk from duration of propafenone exposure (Tables 21-23).
The incidence of adverse events leading to death is presented in Tables 24-25 below.

Table 24: Incidence of adverse events reported as cause of death-RAFT

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 (%)
Cancer	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Adenocarcinoma of lung	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Renal cell carcinoma	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

Table 4 above shows 4 deaths. The fifth patient had a fall and died 30 days after stopping taking propafenone. See Appendix 3 for narratives of 5 deaths. Table 25 below shows temporal relationship of deaths to study drug administration.

Table 25: Serious Adverse events (N=5) leading to death by patient and treatment group RAFT-Narratives *in* Appendix 3.

Treatment Group/ Patient No.	Age/ Gender	Preferred Term	Treatment Days to Onset	Other Adverse Events
Adverse events prior to study drug administration				
Propafenone SR 325 mg bid				
85040/03	49/ Male	Renal cell carcinoma	0[a]	Cough, nausea, thrombosis, chills, fever, atrial fibrillation, urinary tract infection, anxiety, and insomnia
Adverse events during the double-blind period				
Placebo				
85011/05	68/ Male	Adenocarcinoma of the lung[b]	205	Fatigue, Upper respiratory tract infection
85077/07	77/ Male	Renal failure[b]	262	Albumin increased, BUN increased, Edema
Adverse events poststudy drug discontinuation				
Propafenone SR 325 mg bid				
85060/04	77/ Female	Cancer NOS	28 days poststudy drug discontinuation	Embolus, embolism arterial (limb), skin infection, insomnia, and keratitis
Propafenone SR 425 mg bid				
85087/01	84/ Male	Injury NOS	65 days poststudy drug discontinuation	Pneumonia, AV block first degree, diaphoresis, drowsiness, gastroenteritis, nausea, tremor, and vomiting

[a] Present at baseline.

[b] Listed as Serious Adverse Events (SAEs).

1.12 Brief Comparison with Dofetilide, Flecainide and Encainide

Dofetilide is an approved drug for the control of AF in very sick patients with and without extensive structural heart disease. Mortality data from dofetilide studies that have been used for comparative purposes by the sponsor have significantly longer mean follow-up times, and also have a very sick population including NYHA III and IV patients. In the RAFT, ERAFT and other propafenone studies, NYHA class III and IV formed a very small proportion (~6%) of target population, and the mean follow up time was

significantly shorter compared to the Dofetilide studies. The exclusion of class III and IV NYHA patients is due to the fact that propafenone IR is contraindicated in heart failure (See Label for IR and SR; Appendix 20 shows a review of the literature). The reviewer is of the opinion that the target population studied in the propafenone SR studies is not comparable to those in the Dofetilide study or the DIAMOND AF dofetilide study.

The published mortality data in patients treated with flecainide and encainide for supraventricular arrhythmia are also not suitable for comparison with propafenone because the patient populations were different. In the flecainide and encainide studies patients had recent myocardial infarction. In contrast, patients in the RAFT study did not have recent myocardial infarction or acute ischemic heart disease. In fact patients with angina pectoris were excluded. A comparison of mortality rates between SR and IR formulation cannot be effected because of small numbers (Appendix 20).

Table 26: Comparison of Propafenone SR with other anti-arrhythmics

	Flecainide/Encainide	Propafenone IR	Propafenone SR
Hazard Ratio for death	Statistician(Small numbers)	NA	1.5 *(CI 95% 0.4,5.1)
Age-adjusted hazard ratio	NA	NA	0.95 (CI 95% 0.4, 2.2)
Annual Mortality Point estimates: for Flecainide Encainide CAST(Mortality)	1.2% (CI 95% 0.4,1.9) 0.5(CI 0.0-2.7) 1.4(CI 0.6-2.7) 9.1%	2.6% (Open label study P-20-OR)	2.5% *(CI 95% 0.6, 4.4)

*** Wide confidence intervals. NA=Not available.**

Propafenone IR has been approved in about 61 countries and marketed in most of these countries. Patient exposure during the period has been calculated and [redacted] mg of propafenone has been sold during the period up to the submission of the 4-month safety update. In contrast, the total intravenous formulation (IV) sold is [redacted]. The total treatment years with oral propafenone worldwide are [redacted] treatment years. "One hundred and thirty one (131) post-marketed adverse events have been reported world-wide of which 60 were considered to be serious" - Sponsor.

Considering the data submitted, and assuming that a mortality study is either not feasible or cannot be justified, one strong argument in favor of SR safety is the fact that IR formulation that has been approved has so far not been associated with increased mortality rate or risk. It is however important to note that a higher dose of SR will be given to patients compared to IR.

Propafenone SR is a different formulation for a different indication. Ideally a careful and independent evaluation of mortality risk should be carried out in a well designed study. Several thousands of patients will be required for such a study in order to have adequate data for a meaningful mortality analysis. Atrial fibrillation in patients without structural heart disease is a relatively benign condition that has an extremely low risk of mortality if untreated. Therefore this reviewer cannot draw any specific conclusion about the risk/benefit effects of propafenone SR exposure in the target population studied based on the NDA submission.

In summary, abnormal changes in AF patients on propafenone were observed. These changes included a decrease in heart rate during sinus rhythm, a dose-dependent increase (>10%) in PQ interval across the SR treatment groups, and increase in QRS duration for the 325mg and 425 mg bid dose levels. In addition there was prolongation of QTc interval in the 325mg bid and 425mg bid dose levels (Figure 6). There were however no deaths. The sponsor also concluded that the safety/mortality data submitted are only "reassuring" and do not demonstrate reduced mortality risk in the classical form.

Propafenone has been approved in over 60 countries and marketed in most of these countries. Patient exposure during the period has been calculated and is found to be [redacted] mg sold during the period of the update (May 01 2001 to April 30 2002). The total amount of IV propafenone sold is [redacted] mg. and the total treatment years with oral propafenone worldwide are [redacted] One hundred and thirty one (131) postmarketed adverse events have been reported world-wide, of which about 65 were considered to be serious.

1.13 Summary and Recommendations

- Although the RAFT study has shown efficacy in prolonging the time to first recurrence of atrial fibrillation in patients without structural heart disease, there are a number of inadequacies in the RAFT study design. These have been discussed and shown not to have affected the positive efficacy outcome of the RAFT study.

- The reviewer is of the opinion that the RAFT study has demonstrated a dose response between the lowest trial dose of 225 mg bid compared to placebo ($p=0.014$ for FAS population and $p<0.001$ for PP population).

- The study has also demonstrated in the RAFT a dose response between the other 2 doses, 325 mg bid, 425 mg bid compared to placebo ($p<0.001$ and $p<0.001$ for FAS), respectively. The RAFT study has achieved its primary efficacy endpoint.

- The primary efficacy analysis in ERAFT study revealed statistically significant increases in the tachycardia–free period from day 5 to the first recurrence of symptomatic atrial arrhythmia in all propafenone SR treatment doses in comparison to placebo ($p = 0.004$ and 0.003 for 325mg bid., and 425mg bid), respectively, using the log rank test. This provides evidence of efficacy and supports efficacy data in the RAFT study. The duration of the treatment phase of ERAFT study was 91 days whereas it was 39 weeks for RAFT. The 91 day treatment phase for ERAFT is not long enough to provide supportive long-term safety data.

- The reviewer recommends an initial dose of 225 mg bid increasing to 325mg bid propafenone SR if symptoms of atrial fibrillation are uncontrolled and or persists. Every increase in dose should be for a minimum of 5 days in order to reach a steady state. 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 need to be monitored very closely because of dose dependent adverse events (Cardiovascular and gastrointestinal systems in particular) and particularly in the elderly, hepatic impaired and renal impaired patients.

- Although very few patients with a history of atrial flutter or PSVT were randomized in the RAFT study, the reviewer does not think there are enough numbers of patients to

make a specific recommendation for these other "symptomatic" supraventricular arrhythmias within the context of this submission.

- The RAFT study showed statistically significant differences in favor of the 325 mg bid and 425 mg bid compared to placebo for time to patient-initiated report of arrhythmia-associated symptoms from Day 1 of randomization. This is a clinical benefit that supports efficacy.

- The RAFT study showed statistically significant differences in favor of the 225 mg bid, 325 mg bid, and 425mg bid compared to placebo for time-to-treatment failure from Day 1 of randomization. This is also a clinical benefit that supports efficacy.

- The RAFT study showed no significant differences in average heart rates between the treatment groups compared to placebo except in patients given 325 mg bid group where the average heart rate was lower than the placebo group (p=0.054). This can be explained by the pharmacology of the drug and is consistent with the dose related sinus bradycardia observed in the study.

- Hypokalemia was the most frequently reported laboratory abnormality. In addition, dose-dependent increase in calcium levels and a dose-dependent decrease of sodium in patients with AF administered propafenone SR were observed. In contrast none of these changes were seen in placebo group.

- In the integrated safety review, adverse events (14%) and lack of efficacy (26%) in the RAFT study constituted the largest number of causes for drug-related discontinuations.

- There were 66 serious adverse events of which 32 ended in discontinuations. There were prolonged hospitalizations but there were no drug-related deaths.

- The exclusion of patients with angina and NYHA class III and IV from this study and also from the ERAFT study limits the use of the SR formulation to AF patients with NYHA class not > II or AF patients without "structural heart disease".

- The dose-related increase in conduction defects included sinus bradycardia and first degree AV block that are adverse events in a target patient population that has very little or no structural heart disease. These adverse events should be reflected in the label.

- The sponsor has not carried out a mortality study but a meta-analysis has been carried out for IR and SR formulation. The meta-analysis results that were incorporated in the 4-month safety update appear inadequate to evaluate mortality risk of SR.

- Bioavailability of the SR formulation is less than the IR formulation as the more gradual release from SR results in increased overall first pass metabolism to 5-hydroxypropafenone. Consequently, a higher dose of the SR formulation is required to achieve similar plasma concentrations to the IR formulation.

- The sponsor claims that the PQ interval prolongation was more pronounced after SR administration (325 mg bid and 425 mg bid) at 12 hours compared to corresponding doses of IR formulation (150 mg, 300 mg bid, 300 mg od). This reviewer finds that the mean change from baseline for the PQ interval was greater after SR administration from 6 hours compared to the IR formulation (Figures 5 and 6).

- There does not seem to be a significant food effect on propafenone intake but there is prolongation of the QRS interval at 4 hours up to 12 hours in fed state when volunteers had reached steady state compared to the fasted state (Figure 5).

- Taking all the above findings together and the fact that there are other approved products on the market that prolong the time to recurrence of AF in more sick patients, the reviewer can only recommend the SR formulation for approval subject to better data on mortality risk. However, the supportive safety data from ERAFT study, the postmarketing safety data, the safety update report and from the published literature on mortality risk with this class of drugs provide support for approvability of the SR formulation. The postmarketing period of 12 months for adverse events is considered inadequate by this reviewer as a surrogate for a mortality study for the SR formulation. However, there is some information about the relatively low mortality risk for propafenone SR. This is only "reassuring", a word that the sponsor also used in their summary. The lack of a mortality study can be included in the label if this drug is approved without a mortality study.

- It is unlikely the sponsor will agree to undertake a mortality study to show favorable or unfavorable drug effects on mortality rate or risk. This is because the expected mortality risk/ rate in the target population of AF is very low. Even though SR formulation has been approved in Europe, the sponsor should be encouraged to demonstrate favorable or unfavorable effects on mortality through postmarketing safety vigilance.

- The two advantages that the SR formulation has over other comparable products include 1) taking the drug twice a day instead of three times a day for the IR formulation, and 2) cardioversion may not be a prerequisite for its administration and efficacy (Appendix 15, page 164).

- The difficulty that the reviewer has had to contend with was in recommending unqualified approval for SR formulation. This had to do with the issues of inadequate long term safety data on ERAFT and a lack of mortality data in both studies.

- Because there has been no deaths, approvability is recommended but this should be subject to inclusion of a CAST warning in the label and reflection of dose-related adverse events (Table 63).

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. The 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.

1.14 Pediatric Waiver Request

The sponsor has requested for a waiver of pediatric studies. In accordance with the final Pediatric Rule published in the Federal Register and became effective April 1 1999, the sponsor is enjoined to carry out a pediatric assessment. An application can be submitted for a waiver or deferral of studies by sponsors provided there is justification.

The FDA has the authority to grant or reject this application after considering the grounds for the waiver in accordance with the Federal register publication 21 CFR 314.55 (a).

The commonest cause of symptomatic atrial fibrillation in the pediatric age group is structural heart disease. Other non-structural causes of symptomatic atrial fibrillation in the pediatric age group are very rare.

Since propafenone is contraindicated in adults with structural heart disease it is reasonable to assume that it should be contraindicated in the pediatric age group. In a published series, about 50% of children with AF have previously diagnosed congenital heart disease (Gow, 1996), the remainder had severe rheumatic valve disease, cardiomyopathy, infective endocarditis, Marfan syndrome, endocardial fibroelastosis and only about 3% do not have structural heart disease. This is the only ground that the reviewer may support deferral of studies rather than a waiver. The reasons for supporting a deferral rather than a waiver are as follows:

- There is no assurance that the currently available published statistics on pediatric AF frequency is accurate and not an underestimate. The reviewer does not agree with the sponsor that the crude frequency estimate of 38,837 children with supraventricular tachycardia in the US is very small. This is not small. When a global estimate (Europe inclusive) is carried out one may find that the frequency of pediatric AF without structural is relatively high. There may be a justification for carrying out pediatric studies later when there is a better estimate of AF children without structural heart disease.

- The reviewer does not agree with the sponsor that pediatric clinical studies with propafenone are not feasible.

- The reviewer does not agree with the sponsor that propafenone offers no significant improvement compared to a marketed drug labeled for use in the relevant pediatric patient population. The sponsor has no data to support this position.

- Granting a waiver presupposes that a body of knowledge on children with AF and no structural heart disease exists and that propafenone offers no meaningful therapeutic benefit in this target population over an existing treatment.

- The sponsor has neither provided compelling data nor given compelling reasons for justification for this waiver application.

- In conclusion, the reviewer recommends a deferral of studies until more data are available on the size of AF pediatric patients without structural heart disease or hemodynamically classified as NYHA I and II in the US.

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pages of trade secret and/or confidential commercial information

2.0 Brief overview of clinical program

The clinical development program is summarized in Tables27 and 30. It is composed of 5 Phase I studies, 5 Phase II studies, and 2 Phase III studies. Three of the 5 Phase II studies evaluated the potential therapeutic effects of Propafenone SR in patients with ventricular arrhythmia (VA). One of the two phase III trials was in patients with atrial fibrillation, atrial flutter or PSVT (RAFT) and this forms the basis of this NDA application. The second of the two Phase III trials (ERAFT reviewed in Section 5) supports the results of the RAFT study. The protocol and study designs of 3 selected Phase II studies are reviewed in sections 5.51-5.56. The titles of all he phase II studies are as follows:

Phase II - Dose finding study of propafenone SR in symptomatic AF (Protocol SVA CR-D1/Report Number CD 99018)
A double-blind, randomized, placebo-controlled, dose-finding study of propafenone sustained release (SR) in symptomatic paroxysmal atrial fibrillation (Protocol SVA CR-D1/Report Number CD 99018)

Phase II – Follow-up study of propafenone SR in symptomatic AF (Protocol SVA CR-11/Report Number CD 99021).
A double-blind, randomized, placebo-controlled, follow-up study of propafenone sustained release (SR) in symptomatic paroxysmal atrial fibrillation (Protocol SVA CR-11/Report Number CD 99021)

Phase II - Dose finding study of propafenone SR in symptomatic ventricular arrhythmia (VA) (Protocol SR VPC CR-D1/Report Number MPH/H 9406).
A double-blind, randomized, placebo-controlled, dose-finding study of propafenone sustained release (SR) in symptomatic ventricular arrhythmia (Protocol SR VPC CR-D1/Report Number MPF/H 9406)

Phase II – Hemodynamics and PK of propafenone SR in symptomatic VA (Protocol SR VPC CR-D2/Report Number CD00001).
A double-blind, randomized study of two different dosages of propafenone SR on Hemodynamics and pharmacokinetics in patients with symptomatic ventricular arrhythmia (225 mg bid and 425 mg bid) Protocol SR VPC CR-D2/Report Number CD00001).

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 (Protocol VPC CR-11/Report Number CD99022)

2.1 Description of clinical data

The data submitted by sponsor are partly in electronic format, on 10 CDs accessed from the Electronic Document Room (EDR), (Appendix 1) and in 233 volumes of hard copies. In addition to sponsor's tables, the reviewer has generated tables and graphs.

Table 27: Overview of clinical development program of Propafenone

Phase	Population	Protocol Numbers	Report Numbers
~~**Phase I OL**~~	~~**Healthy volunteers**~~	~~**SR-HP-D27/90E**~~	~~**MPF/HP9112E**~~
OL	Healthy volunteers	SR-HP D 28/91 E	MPF/HP9217E
OL	Healthy volunteers	OR-HP N 31/93	MPF/HP9415E
OL	Healthy volunteers	P-86-CP	P-86-CP
OL	Healthy volunteers	PN102	PN102
Phase II	**P. Atrial fibrillation**	**SR SVA CR D1**	**CD99018**
	P. Atrial fibrillation	*SR SVA CR11	CD99021
	Ventricular arrhythmia	*SR VPC CR D1	MPH/H9406
	Ventricular arrhythmia	*SRVPC D2	CD00001
	Ventricular arrhythmia	VPC CR 11	CD99022
Phase IIIRCP	Atrial fibrillation	*P-85-AF	P-85-AF
RPC	P. Atrial fibrillation	*PROPA SR 008	MPR/CC 2021
Overall summary of Populations studied - Propafenone SR*			
	Subject Population	**Propafenone**	**Placebo**
	Healthy volunteers	116	0
	Atrial fibrillation	655	235
	Ventricular arrhythmia*	231	51
***Includes 77 patients in 1 propafenone immediate release (IR) treatment group**			

OL= Open Label study; RPC=Randomized, placebo-controlled study. *See Sections 2.6,5.0 5.51 of this review

2.2 Human PK and PD

The summary of PK findings in this review are based on 116 healthy subjects in 5 phase I studies, and 29 patients from 2 phase II studies. The strengths of the proposed to-be-marketed propafenone SR formulation used for these studies are 225 mg, 325 mg and 425 mg bid.

The pharmacokinetics of propafenone is non-linear in extensive metabolizers following administration of propafenone SR capsules. There are disproportionate increases in exposure when 325 mg (2 fold) and 425 mg (3-4 fold) are given compared to 225 mg (See Biopharm review). Because of the PK findings in patients with different rates of metabolism, there is a large inter-subject variability in blood levels regardless of whether administered as single or multiple doses. This suggests that the drug must be carefully titrated and evidence of toxicity including ECG changes monitored.

Propafenone is well absorbed after oral administration. Maximal plasma levels of propafenone are reached between 3-8 hours following oral administration of propafenone SR. Peak plasma concentrations are reached after 2-3 hours (Tmax). Plasma concentrations and bioavailability increase with repeated administration owing to a saturation of the first pass metabolism in the liver. Absolute bioavailability has not been determined for propafenone SR capsule formulation. Relative bioavailability, however, has been performed for SR formulation. The PK findings of propafenone SR are consistent with those of a drug with a large and saturable first pass effect.

Plasma concentrations of propafenone and its metabolites, 5-hydroxy propafenone and norpropafenone, were measured using sensitive and specific methods. Propafenone IR undergoes extensive and saturable pre-systemic biotransformation (largely through a

2D6 hepatic first pass effect) that results in a dose and dosage form dependent absolute bioavailability. In extensive metabolizers, 150 mg of propafenone IR tid resulted in essentially the same exposure at steady state comparable to 325 mg bid propafenone SR. In the equivalency comparisons exposure to 5-hydroxypropafenone was about 20-25% higher after SR capsule ingestion than after IR tablet administration. Although food increases peak blood level and bioavailability in single dose studies, food effect on bioavailability was not observed with multiple dose administration.
Metabolism of propafenone reveals two genetically determined patterns. In over 90% of patients, the drug is rapidly and extensively metabolized into 2 active metabolites, 5-hydroxypropafenone that is formed by 2D6, and norpropafenone that is formed by 3A4 and 1A2. The elimination half life of propafenone is 2-10 hours. In less than 10% of patients, metabolism is slower because the 5-hydroxypropafenone is either not formed or formed minimally. The estimated elimination half life in those patients with slower metabolism ranges from 10-32 hours. In addition to the two metabolites mentioned above, nine other metabolites of propafenone have been identified, most of them in trace amounts. Plasma protein binding lies between 85 and 95 % and the volume distribution is between 1.1 –3.6 l/kg. Only about 1% of unchanged propafenone is excreted through the kidneys.

In vitro studies have shown that 5-hydroxypropafenone and norpropafenone show anti-arrhythmic activity comparable to propafenone but in man, they are usually present in concentrations < 20% of propafenone. The peak to trough fluctuation (PTF) for propafenone and its major metabolites was smaller after SR administration compared to the IR formulation. Propafenone is known to pass the placental barrier in humans and it is excreted in breast milk (See Biopharm review).

Table 28: Propafenone plasma concentration levels at weeks 3 and 39-RAFT

	Plasma Level (ng/mL) by Time Point				
Timepoint[a]/Treatment Group	N	BQL[b]	Mean±SD	Median	Range
Week 3 Trough					
Propafenone SR 225 mg bid	72	1	242.6±310.7	126.8	
Propafenone SR 325 mg bid	84	2	426.8±453.7	285.6	
Propafenone SR 425 mg bid	77	1	547.1±469.9	424.7	
Any propafenone SR	233	4	409.6±436.5	244.6	
Week 3 Peak					
Propafenone SR 225 mg bid	71	2	255.0±307.7	137.0	
Propafenone SR 325 mg bid	77	0	469.1±453.5	331.8	
Propafenone SR 425 mg bid	70	1	575.2±494.4	400.2	
Any propafenone SR	218	3	433.4±444.6	283.0	
Week 39/Final Trough					
Propafenone SR 225 mg bid	78	10	264.5±355.5	91.4	
Propafenone SR 325 mg bid	89	11	449.6±514.7	232.1	
Propafenone SR 425 mg bid	86	12	630.6±645.7	405.7	
Any propafenone SR	253	33	454.1±541.8	232.0	

[a] The actual times of blood collection did not always follow the time identified in the protocol.

[b] Number of patients beneath quantifiable limit.

Source: Table 9.3.5.1

Blood level response

A blood level response has not been established for propafenone IR. Although blood samples were collected in both Phase III trials, the sponsor did not analyze data for a blood level response. Tables 28 and 29 summarize the propafenone plasma

concentration levels at weeks 3 and 39. These show no significant changes over the efficacy period.

Table 29: 5-hydroxypropafenone plasma concentration levels-weeks 3 & 39-RAFT

	Plasma Level (ng/mL) by Time Point				
Timepoint[a]/Treatment Group	N	BQL[b]	Mean±SD	Median	Range
Week 3 Trough					
Propafenone SR 225 mg bid	68	4	75.5±56.1	70.5	
Propafenone SR 325 mg bid	84	3	103.4±66.7	94.3	
Propafenone SR 425 mg bid	76	2	133.9±81.5	127.5	
Any propafenone SR	228	9	105.3±72.7	93.7	
Week 3 Peak					
Propafenone SR 225 mg bid	68	4	74.3±53.5	71.1	
Propafenone SR 325 mg bid	75	2	103.6±67.2	94.3	
Propafenone SR 425 mg bid	69	1	138.2±79.7	127.2	
Any propafenone SR	212	7	105.4±72.2	97.1	
Week 39/Final Trough					
Propafenone SR 225 mg bid	76	12	64.4±54.2	49.8	
Propafenone SR 325 mg bid	87	11	101.2±74.8	84.8	
Propafenone SR 425 mg bid	85	13	129.7±67.8	120.0	
Any propafenone SR	248	36	99.7±71.4	85.2	

[a] The actual times of blood collection did not always follow the time identified in the protocol.

[b] Number of patients beneath quantifiable limit.

Source: Table 9.3.5.2

2.3 Drug - drug interactions

Metabolism of propafenone reveals two genetically determined patterns. In over 90% of patients, the drug is rapidly and extensively metabolized into 2 active metabolites, 5-hydroxypropafenone that is formed by 2D6, and norpropafenone that is formed by 3A4 and 1A2.

- A possible potentiation of drug efficacy must be taken into consideration when Propafenone is taken in conjunction with local anesthetics (e.g. pacemaker implantation, surgery or dental work), and also with other drugs which have an inhibitory effect on the heart rate and/or myocardial contractility (e.g. beta-blockers, and tricyclic antidepressants).

- Increases in propanolol, metoprolol, despiramine, cyclosporin, and digoxin plasma levels or blood levels have been reported during propafenone therapy. Theophylline plasma concentrations doubled when propafenone was given concomitantly.

- Propafenone may be enhanced if it is given concomitantly with cimetidine or quinidine. This is due to an increase in the propafenone hydrochloride plasma levels.

- Concomitant use of propafenone and phenobarbital and or rifampicin may reduce the anti-arrhythmic efficacy of propafenone HCl. This is due to a reduction in the propafenone plasma levels.

- Monitoring of the clotting status in patients receiving warfarin or other oral anticoagulants is recommended as propafenone may enhance the efficacy of these drugs.

- The Biopharm review will discuss specific interactions of drugs that are metabolized by CYP 3A4 enzymes.

Special populations: No special populations were studied. The proportion of elderly patients >75 years was less than 20% and no children were studied. Hepatic and renally impaired patients were not studied with SR formulation.

Proposed Indication
The indication [redacted]

1

2.4 Overview of clinical trials
Table 30 below summarizes all studies carried out during drug development-Phases I, II, and III for this NDA.

Table 30: Summary of all clinical trials for drug development- NDA 21-416

Phase	Population	Protocol Numbers	Propafenone Treatment/Dose		Duration	R or T N
Phase I	Healthy volunteers	SR-HP-D27/90E	SR	400mg bid	5 days	18
	Healthy volunteers	SR-HP D 28/91 E	SR	425mg bid	6days	24
	Healthy volunteers	OR-HP N 31/93E	IR and SR	150/300 mg IR 325/425mg SR	6 days each	24
	Healthy volunteers	P-86-CP	IR and SR	300 mg IR 325/425mg SR	Single dose	24
	Healthy volunteers	PN102	SR	225/325/425 mg bid	7 days each	26
Phase II	**(S)P. Atrial fibrillation**	**SR SVA CR D1**	**SR**	**225/325/425 mg bid**	**5-10 days**	**16-20**
	(S)P. Atrial fibrillation	SR SVA CR11	SR	225/325/425 mg	6 mths	10-14
	(S)Ventricular arrhythmia	SR VPC CR D1	SR	225/325/425 mg	5-10 days	45-51
	Ventricular arrhythmia	SRVPC D2	SR	225/425mg	3-10 days	**4-8**
	Ventricular arrhythmia	VPC CR 11	IR/SR	150/225/325 mg	10-49 days	83
Phase III	**(S)Atrial fibrillation	P-85-AF	SR	225/325/425 mg	39 wks	523
	(S)P. Atrial fibrillation	PROPA SR 008	SR	325/425mg	96 days	293

R= Randomized; T=Treated. (S)= Symptomatic; ** Pivotal study for NDA. N=Number of patients

2.5 Summary of clinical findings in Phase III studies - RAFT and ERAFT

The RAFT study evaluated efficacy and safety of 3 doses of propafenone SR (225 mg bid, 325 mg bid, and 425 mg bid for up to 39 weeks) in prolonging time to recurrence of symptomatic atrial fibrillation. The screening period up to the time of randomization was used to ascertain that patients met the inclusion criteria, had none of the exclusion criteria, and were in normal sinus rhythm prior to administration of study medication. The 39-week blinded treatment phase was considered appropriate to evaluate the safety and efficacy of propafenone SR and to provide adequate long-term safety data.

However the claim can be sustained for patients with atrial fibrillation. The population also lacked adequate numbers of black patients and the demographics of the patients with atrial fibrillation did not reflect the US demographics for atrial fibrillation.

Because of heterogeneity of body weights across treatment groups at baseline, body weights of patients were adjusted by propafenone dosing into low, medium and high and compared to placebo as a further source of evaluating and confirming efficacy and robustness of the data.

There are statistically significant differences in favor of the 3 doses of propafenone SR compared to placebo for tachycardia free period from Day 1 and from Day 5 of randomization among the full analysis set. There are statistically significant differences in favor of propafenone SR 325 mg bid and 425 mg bid compared to placebo for 1) time-to patient initiated report of arrhythmia associated symptoms from Day 1 and 2) for time-to-treatment failure. In contrast the difference between propafenone SR 225 mg bid and placebo is not significant for time-to-treatment failure and time to patient-initiated report of arrhythmia symptoms. The time-to-treatment failure analyses show significant differences in favor of SR 325 mg bid and SR 425 mg bid compared to placebo regardless of how withdrawals were treated in the analyses. This confirms robustness analyses carried out by Dr Yong-Chen Wang (*"Statistician's review – Table 13 "Robustness analysis for primary endpoint RAFT).*

The dose related adverse events in the RAFT study included bradycardia, first degree atrio-ventricular block and taste disturbance. The serious adverse events that required prolonged hospitalization showed no difference between placebo and the treated groups (Appendices 4 and 5, page 142). The crude incidence rates for deaths for placebo was 3/360 and for propafenone treated groups was 7/1040 (Table 22 page 42). Of the 7 deaths in the propafenone groups, the patients died from unrelated diseases such as lung cancer, renal failure, renal cell carcinoma and an injury. The commonest treatment emergent adverse events across the propafenone SR treatment groups included dizziness, dyspnea, fatigue, constipation and taste disturbance (Table 6).

The European, "ERAFT" study, also evaluated efficacy and safety of 2 doses of propafenone SR (325 mg bid, and 425 mg bid for up to 95 days) in the prophylaxis of symptomatic atrial fibrillation. This study did not have a 225 mg bid dose level.
There are statistically significant differences in favor of the two doses of propafenone SR compared to placebo for tachycardia free period from Day 5 (primary efficacy) and from Day 1(Secondary efficacy) of randomization among the full analysis set and per protocol