population. There are statistically significant differences in favor of propafenone SR 325 mg bid and 425 mg bid compared to placebo

1) When propafenone SR dosage was adjusted for body
2) Time-to patient initiated report of arrhythmia associated symptoms from Day 5, and
3) Time-to-treatment failure.

Dose selection for RAFT study

The dose selection for propafenone SR bid is based upon the efficacy and safety results of 2 Phase III trials (Sections 5.51 and 5.53 of this review), and the PK profile of propafenone SR. The dose selection for this study was based on the area under plasma concentration versus time curves for propafenone (AUC) and the equivalent dosage strengths (IR to SR) which are approximately:

150 mg propafenone IR tid = 325 mg propafenone SR bid.
225 mg propafenone IR tid = 425 mg propafenone SR bid.

A lower dose of 225 mg bid of propafenone SR was also included in the RAFT study to evaluate a lower dose twice daily dosing and to find out if there will be a dose response compared to placebo.

2.6 Efficacy-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 a symptomatic atrial arrhythmia. Patients were censored at the first recurrence of AF symptoms. For efficacy evaluation, a total of 397 patients received propafenone (126 patients received 225 mg bid, 135 received 325 mg bid and 136 received 425 mg bid), and 126 received placebo (Total N=523).

Comparison of treatment groups-RAFT

The treatment groups were well matched with respect to baseline and demographic characteristics. There were no statistically significant differences in any demographic parameter among treatment groups (Table 1). According to the sponsor, the majority of the patients (>80%) had normal physical examination except for examination of the cardiovascular system.

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%). The frequencies of abnormal cardiac examination in each treatment group are 225mg bid (15.1%), 325mg bid (25.9%), and 425 mg bid (27.9%). This imbalance did not significantly influence treatment outcome. A subgroup analysis of efficacy data that includes patients with normal cardiac examination at baseline shows a statistically significant difference between 325 mg bid and 425 mg bid groups compared to placebo ($p=0.00003$ and <0.0001), respectively. In contrast there was no significant difference between the 225 mg bid compared to placebo ($p=0.136$)(Table 31). Compliance was equal among all treatment groups (Appendix 2, page 140).

Table 31: Distribution of tachycardia-free period from Day 1 in patients with normal cardiac exam at baseline by treatment groups – RAFT

		Propafenone			
	Placebo	**225mg bid**	**325mg bid**	**425mg bid**	**Total**
No of pts. with normal cardiac exam at baseline	85 (67.46%)	107 (84.92%)	100 (74.07%)	98 (72.06%)	390 (74.57%)
Pts completing with terminating events	56(65.9%)	57(53.3%)	43(43.0)	29(29.6%)	
p-value (Log Rank Hazard Ratio 95% CI for Hazard ratio	- - -	***0.136** 0.758 (0.52;1.10)	0.0003 0.488 (0.33,0.73)	<0.0001 0.388 (0.25,0.61)	

*** Not significant**

Primary Efficacy conclusion - RAFT

The RAFT study showed a statistically significant increase in the tachycardia-free period from Day 1 of randomization to the first recurrence of symptomatic atrial arrhythmia in all 3 propafenone SR treatment doses compared to placebo.

Secondary Efficacy variable - RAFT

There was also a statistically significant difference in the tachycardia-free period to the first recurrence of symptomatic atrial fibrillation from day 5 of randomization, and for all weight-adjusted dose categories (low, medium, and high) among the FAS population.

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.

Efficacy conclusions for ERAFT study are discussed here in the executive summary only to complement and facilitate comparisons with the RAFT study (Section 5, page 94).

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 87 page 97) 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).
- 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)
- 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)].
- 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. 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.

2.7 Integrated review of efficacy

Although there is compelling evidence from the ERAFT study to support efficacy of propafenone SR in the RAFT study for the indication proposed, this reviewer does not think an integrated review of efficacy is appropriate because there are several differences between the two studies including baseline data and study designs. The

efficacy in the RAFT study is therefore reviewed separately from ERAFT. The efficacy conclusions for RAFT and ERAFT are summarized below only for ease of reference.

2.8 Clinical Review methods and Data integrity

The approach adopted by this reviewer includes the understanding of the clinical trial design (Figures 1 and 13) with particular emphasis on the event driven nature of the trial, the treatment of dropouts, censored patients, the determination of the primary endpoints, the verification of ECG changes in patients classified in the data as having normal sinus rhythm with premature atrial beats. The pivotal trial (RAFT) and the supporting trial (ERAFT) were reviewed separately. The RAFT was reviewed in depth because there was a dose response to the 3 doses whereas the ERAFT used only 2 dose levels and the number of randomized patients was relatively small and the efficacy period was also relatively short. Only one study RAFT has been submitted by the sponsor for evaluation of this NDA application. Symptomatic arrhythmias were documented by telemetry (TTM). Patients were followed up to 39 weeks for RAFT and 95 days for ERAFT unless they completed the study before week 39 or Day 95 because of symptomatic atrial Fibrillation (AF) or AF diagnosed by the investigator. Symptomatic arrhythmias were to be documented by telemetry (TTM).

Data integrity:

To substantiate concerns about data integrity the reviewer has identified a few examples. The following paragraphs exemplified what gave the reviewer some concern about data input:: 1) Center 85009-75 year old Male Caucasian on 225 mg bid body weight 171 pounds, alleged to be on study drug for one day. The records show that the start date was 30th June 98 and the stop date was July 3 98. The unedited AE narrative is as follows: "Description of Adverse Event: Patient 01 was randomized to the study and received propafenone SR 225 mg bid from 30- Jun-1998 to 03- Jul-1998. On 30 - Jun-1998, the patient had pyrexia, which was of mild severity and considered possibly related to study drug by the investigator. The event lasted 4 days. In response to this adverse event, the study medication was permanently discontinued, and the patient recovered without sequelae. On 30- Jun- 98, the patient had palpitations, which were of moderate severity and considered possibly related to study drug by the investigator. The event lasted 4 days. In response to this adverse event, the study medication was permanently discontinued, and the patient recovered without sequelae. On 30- Jun- 98, the patient had paresthesia NEC that was of mild severity and considered possibly related to study drug by the investigator. The event lasted 4 days. In response to this adverse event, the study medication was permanently discontinued, and the patient recovered without sequelae. On 30- Jun- 98, the patient had weakness, which was of moderate severity and considered possibly related to study drug by the investigator. The event lasted 4 days. In response to this adverse event, the study medication was permanently discontinued, and the patient recovered without sequelae. On 02- Jul- 98, the patient had abdominal pain NOS, which was of moderate severity and considered possibly related to study drug by the investigator. The event lasted 2 days. In response to this adverse event the study medication was permanently discontinued, and the patient recovered without sequelae. Medical history: cardiac failure congestive, hypertension, myocardial infarction, sinusitis NOS, facial palsy, dyspepsia, and prostatitis. The question here is whether the patient was on drug for one day or 4 days is not clear from the start and stop dates.

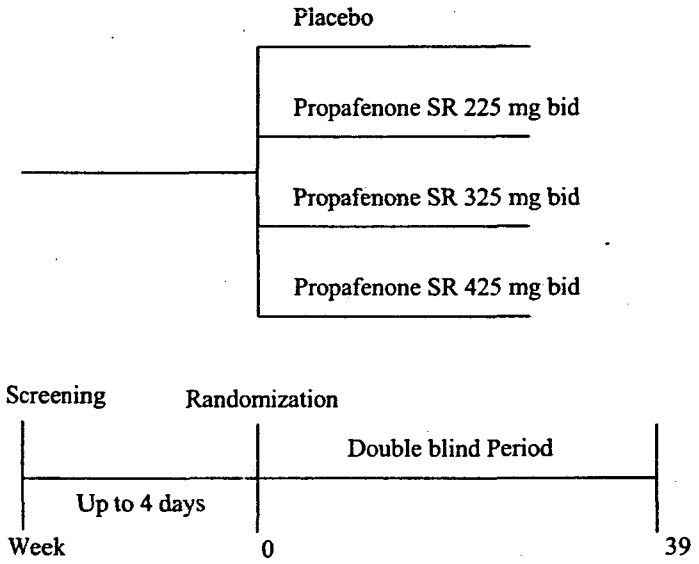
2) Another example is Table 24 submitted by sponsor showing 4 deaths instead of 5. This was correct elsewhere. 3) Another example is a table on electrolytes submitted by

the sponsor where decrease potassium level was separated from hypokalemia in the 425 mg dose group (RAFT study) (Appendix 10 page 156).

3.0 RAFT Study: Protocol P-85-AF/Report Number P-85-AF
Title: A double-blind placebo controlled randomized clinical trial of slow release propafenone (Rhythmol SR) in the prevention of symptomatic recurrences of Atrial fibrillation.

Overall design of RAFT study
This was a double-blind, placebo-controlled, multicenter (in the US), 4-way, parallel group, randomized study to evaluate the efficacy and safety of 3 doses of propafenone SR (225mg bid, 325mg bid, and 425mg bid for up to 39 weeks) in prolonging the time to recurrence of symptomatic atrial fibrillation (Figure 7).

Figure 7: Study Design -RAFT



Pretreatment / screening phase included the procedures and evaluations in Table 33 below. All patients who qualified for the study returned to the study center for randomization within 4 days of completing the screening phase.

Drug supply: The drug supply for RAFT is presented in Table 32.
Table 32: Drug supply - RAFT

Encapsulated microtablets*	Batch Number
Placebo oral b.i.d.	3060 EO 53, 98020IPO,780101PO
Propafenone oral 225 b.i.d.	3060-G-53,780100AO,980310AO,780200AO
Propafenone oral 325mg b.i.d.	3060-F-53,780100AO,980311AO,
Propafenone oral 425mg b.i.d.	3060-E-53,780101AO,980211AO,
Manufacturer	Knoll AG

Protocol-RAFT

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.

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.
- The patient is expected to have reached a steady state plasma propafenone concentration by Day 4/5 (Loading Period) of the first week of blinded 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 in order to begin the efficacy period. The frequency of routine TTM is presented in Table 36. 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 study ineligible for Intent-to-Treat analysis. The originally intended "ITT" population thus becomes a ***"full analysis set"*** or "FAS".
Five hundred and twenty three (523) eligible, (FAS) 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: approximately 110 patients were assigned to each group and monitored for up to 39 weeks (Figure 1). These patients included three hundred and nine males (309) and 214 females. There were 30 (5.74%) blacks and 17 (3.25%) were from other ethnic groups (Table 1). Symptomatic arrhythmias were documented using trans-telephonic ECG monitoring. The tachyarcardia-free period was determined for each treatment group as a measure of primary efficacy. The schedule of procedures is in Table 33.

Table 33: Schedule of procedure - RAFT

Procedure/Evaluation	Screening	Baseline	Week 1 Visit 1	Week 3 Visit 2	Week 6 Visit 3	Week 12 Visit 4	Week 24 Visit 5	Week 39 Visit 6	Pre-discharge study
Medical history	X								
Complete Physical Examination	X								
Internal Physical Examination			X	X	X	X	X	X	X
Informed Consent	X								
Telemetry	X	X							
Scheduled	X		X	X	X	X	X	X	X

Procedure/Evaluation	Screening	Baseline	Week 1 Visit 1	Week 3 Visit 2	Week 6 Visit 3	Week 12 Visit 4	Week 24 Visit 5	Week 39 Visit 6	Pre-discharge study
TTM									
12 lead ECG	X		X	X	X	X	X	X	X
Laboratory Evaluation	X		X	X	X	X	X	X	X
Blood Samples for Digoxin	X		X	X					
Blood Samples for propafenone				X				X	X
Search for Adverse Reaction			X	X	X	X	X	X	X
Study Drug Dispensing		x	X	X	X	X	X		
Compliance Check			X	X	X	X	X	X	X

Patients were instructed to transmit ECG records of symptomatic attacks using a supplied trans-telephonic recorder with additional routine transmissions every 2 weeks. During each scheduled visit, the study coordinator was to reinforce the importance of transmitting an ECG for any shortness of breath, dizziness awareness of heartbeat, chest pain. or anxiety and was instructed not to transmit an ECG on scheduled visits unless the patient was having symptoms.

Inclusion Criteria

Patients who fulfilled the following inclusion criteria were considered 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, β-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.

Population and procedure

The history of atrial fibrillation among the randomized patients ranged from 0 to 576 months, and the median history by treatment group ranged from 12 months

(propafenone SR 225 mg bid and 325 mg bid) to 17 months (placebo). The number of episodes of atrial fibrillation documented prior to study entry ranged from 0 to 480, and the median number was 3 in all treatment groups (Table 34). Approximately 50% of randomized patients had a cardiac history consistent with structural heart disease ranging from 44% for propafenone SR 225 mg bid, 47% for propafenone 325 mg bid to 55.1% for propafenone SR 425 mg bid and placebo 45%.(Table 35). Over 65% of patients during the blinded therapy were on concomitant medication known to decrease heart rate (Table 35).

Table 34: Number and percentage of patients with history of arrhythmia- Full analysis set - RAFT

		Propafenone SR					
Variable	All Patients	450mg/day (225mg bid)	650mg/day (325mg bid)	850mg/day (425mg bid)	All doses of Propafenone SR	Placebo	p-value #
No. of Patients	N=523	N=126	N=135	N=136	N=397	N=126	
Duration of AF DX (in months)							
N	523.0	126.0	135.0	136.0	397.0	126.0	0.5969
MEAN	42.1	38.5	42.0	39.1	39.9	48.8	
SD	67.1	72.3	62.2	61.6	65.2	72.5	
MEDIAN	13.0	12.0	15.0	12.0	12.0	17.0	
MIN							
MAX							
P-value ##							
No. of Paroxysms documented prior to study entry							
N	523.0	126.0	135.0	136.0	397.0	126.0	0.4845
MEAN	14.4	17.1	10.8	16.2	14.7	13.7	
SD	35.7	50.0	21.1	36.5	37.5	29.5	
MEDIAN	3.0	3.0	3.0	3.0	3.0	3.0	
MIN							
MAX							
P-value ##							

AF: Atrial fibrillation
p-value based on analysis of variance for comparison among all treatment groups
p-value based on Dunnett's test procedure for comparison of propafenone SR dose vs placebo (if overall test significant)

There was balance between the treatment groups in RAFT with respect to cardiac history (Table 35) including cardiovascular diagnoses at baseline. When all studies are combined the cardiac history for patients with AF was generally similar across treatment groups. In view of the controversy surrounding the definition and diagnosis of structural heart disease the hemodynamic consequences of SHD was assessed using the NYHA classification (Table 39). Over 90% of the patients in each treatment group had NYHA class I whereas less than 25% had a history of

cardioversion. The frequencies of SHD by NYHA classification is presented by treatment group in Table 39. Less than 10% of the patients in the RAFT trial were classified as NYHA II by the investigator.

Table 35: Cardiac history before randomization - RAFT

		Propafenone		
	Placebo	225mg bid	325mg bid	425mg bid
	N=126(%)	N=126(%)	N=135(%)	N=136(%)
Total no of patients with Cardiovascular diagnosis at baseline 277/523=53%	61(48.4)	71(56.3)	71(52.6)	74(54.4)
History of A Fib (months) Mean±SD Median Range	48.8±72.5 17.0 0.0 - 360.0	38.5 ±72.3 12 1.0-576.0	42.0±62.2 15 0.0-300.0	39.1±61.6 12.0 0.0-384
Number of episodes of AF documented prior to study entry Mean±SD Median Range	13.7±29.5 3.0 0.0-180.0	17.1±50.0 3.0 0.0-480.0	10.8±21.1 3.0 0.0-150.0	16.2±36.5 3.0 0.0-200
SHD	57(45.2)	56(44.4)	63(46.7)	75(55.1)
History of NYHA Uncompromised Slightly compromised Moderately compromised Severely compromised	 122(96.8) 4(3.2) 0(0) 0(0)	 117(92.9) 9(7.1) 0(0) 0(0)	 125(92.6) 10(7.4) 0(0) 0(0)	 126(96.8) 10(7.4) 0(0) 0(0)
History of cardioversion	28(22.2)	22(17.5)	31(23)	31(22.8)
Medications that decrease heart rate	85(67.5)	84(66.7)	95(70.4)	93(68.4)

Table 36 Routine trans-telephonic TTM calls – FAS-RAFT

Table 117 Routine TTM calls (full analysis set)

	Propafenone SR			
	225 mg bid (N=126) n (%)	325 mg bid (N=135) n (%)	425 mg bid (N=136) n (%)	Placebo (N=126) n (%)
Patients with TTM calls (N)	126	135	136	126
Patients with routine TTM calls	118 (93.7)	132 (97.8)	128 (94.1)	114 (90.5)
Total calls (N)	1582	1865	1801	1264
Routine calls	1186 (75.9)	1496 (80.2)	1434 (79.6)	886 (70.1)
TTM calls by diagnosis				
Normal sinus rhythm	897 (57.4)	1188 (63.7)	1142 (63.4)	559 (44.2)
Atrial fibrillation	21 (1.3)	37 (2.0)	31 (1.7)	55 (4.4)
Atrial flutter	6 (0.4)	2 (0.1)	1 (0.1)	0 (0.0)
Other	235 (15.0)	227 (12.2)	235 (13.0)	259 (20.5)
Missing	27 (1.7)	42 (2.3)	25 (1.4)	13 (1.0)

Source: Table 9.3.6.1

The disposition of patients over time showed a reasonable balance between the treatment groups (Table 37). With the exception of abnormal cardiac examination, the baseline covariates that show no significant differences between the groups include demographics (Table 38), structural heart disease and NYHA classification (Table 39), and concomitant medication (Table 40).

Table 37: Disposition of subjects over time – RAFT

		Propafenone SR		
Study in weeks	**Placebo**	**225mg**	**325mg**	**425mg**
	N=126(%)	N=126(%)	N=135(%)	N=136(%)
Baseline	126(100)	126(100)	135(100)	136(100)
4	70(56)	79(63)	96(71)	85(63)
12	43(34)	59(47)	79(59)	67(49)
24	31(25)	47(37)	63(47)	64(47)
36	24(19)	44(35)	57(42)	59(43)
39	15(12)	31(25)	45(33)	42(31)
>39	13(10)	27(21)	43(32)	40(29)

The demographics of the randomized patients show a reasonable balance and no significant differences were observed between the treatment groups (Table 38) except for body weights and abnormal cardiac examination at baseline (Table 44). All patients gave a history of atrial fibrillation documented by 12 lead ECG in hospital telemetry or TTM at screening.

Table 38: Demographics - RAFT

	Propafenone SR				
	Placebo	**225mg**	**325mg**	**425mg**	**p-value**
	N=126(%)	N=126(%)	N=135(%)	N=136(%)	
Male	75(59.5)	76(60.3)	80(59.3)	78(57.4)	0.971
Female	51(40.7)	80(39.7)	55(40.7)	58(42.5)	
Race					
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)	
Age					
Mean	62.5	63.5	63.1	62.8	0.933
Range	28-89	29-87	22-87	31-87	
18-30	2(1.6)	2(1.6)	2(1.5)	0(0.0)	
31-50	20(15.9)	18(14.3)	20(14.8)	28(20.6)	
51-64	37(29.4)	45(35.7)	44(32.6)	33(24.3)	
65-75	49(38.9)	37(29.4)	47(34.8)	53(39.0)	
>75	18(14.3)	24(19.0)	22(16.3)	22(16.2)	
<65	59(46.8)	65(51.6)	66(48.9)	61(44.9)	0.735
>65	67(53.2)	61(48.4)	69(51.1)	75(55.1)	
Weight(kg)					
Mean SD	84.6±17.2	85.5±19.1	85.3±19.1	86.1±19.3	0.933
Range	51.8 –131.2	49.5-148.2	51.3-141.2	45.4-156.2	
SHD*	57(45.2)	56(44.4)	63(46.7)	75(55.1)	

***SHD=Structural Heart Disease (See Table 39 below) > 50% of randomized patients had a history of hypertension.**

Subpopulation with Structural Heart Disease

The distribution of patients with structural heart disease and NYHA classification is presented in Table 39. This shows no significant difference between the treatment groups. Patients with NYHA classification III and IV were virtually excluded from this study.

Over 90% of the patients, in each treatment group had a NYHA classification of Class I, less than 25% of the patients had a history of cardioversion, and over 65% of the patients during the double-blind period were on concomitant medication. Less than 10% of the patients in the trial were classified as NYHA Class II by the investigator. A majority of these patients with a NYHA classification of II had a cardiac history consistent with structural heart disease.

Table 39: Frequency of *structural heart disease by drug group and NYHA classification (See Table 45 for clinical types).

Treatment group	SHD Present(%)	SHD Absent (%)
Placebo (N=126)		
NYHA I	54(42.8)	68(54.0)
NYHA II	3(2.4)	1(0.8)
225mg bid (N=126)		
NYHA I	50(39.7)	67(53.2)
NYHA II	6(4.2)	3(2.4)
325mg bid (N=135)		
NYHA I	56(41.5)	69(51.1)
NYHA II	7(5.2)	3(2.2)
425 mg bid (N=136)		
NYHA I	66(48.5)	60(44.1)
NYHA II	9(6.6)	1(0.7)

***The diagnostic basis for SHD in not clear from data (See table 45).**

3.1 Concomitant Medication

During the pretreatment phase, all antiarrhythmic medications were to be discontinued with the exception of verapamil, diltiazem, β- blockers, and digoxin, for at least 5 half lives before randomization to study drugs. All discontinued medications were recorded in the patient's "Prior Anti-arrhythmics" case report form page. Informed consent was obtained prior to discontinuing medications. Administration of β-blockers, verapamil, diltiazem, and digoxin was maintained at the same dosing level throughout the study and use of all drugs taken by the patient was documented in the patient's case report forms. Since propafenone produces dose related increases in digoxin levels ranging from 35 to 85 %, blood samples for digoxin were taken at baseline, weeks 1 and 3 and shipped for analyses. Patients taking warfarin concomitantly with propafenone had their INR checked periodically. No other antiarrhythmic therapy or agent was allowed to be started during the study.

A total of 509 patients had ongoing medication from baseline (Table 40) into the double-blind period and the percentage of patients was comparable across treatment groups. There was balance between the treatment groups using concomitant medication (Table 40) and the nature of drugs did not seem to affect the study outcomes. A slightly higher percentage of patients in the propafenone SR 425 mg bid treatment group (1 1.8%) took glyceryl nitrate compared to the other propafenone SR treatment groups, 225 mg bid (5.6%) or 325 mg bid (3.7%), and to the placebo group (3.2%). This was expected since an increased number of patients in the propafenone SR 425 mg bid treatment group had a history of coronary artery disease (Table 40).

A total of 330 patients (63.1%) began using a concomitant medication on or after the first dose of study drug. The number and percentage of patients starting a new medication on or after the first dose study drug are summarized in Table 40.

Throughout the study the sponsor claims that anti-arrhythmic medication was stable. The number and percentage of patients on selected concomitant medication is summarized in Table 40.
The list of concomitant medications and dosage used by >10% of patients in this study is presented in Table 40.

Table 40: Concomitant medication at baseline and during study by > 10% of patients in any treatment group - RAFT

	Placebo	Propafenone SR		
Concomitant Medication		**225mg bid**	**325mg bid**	**425mg bid**
Total patients	N=126(%)	N=126(%)	N=135(%)	N=136(%)
Patients on medication	122(96.8)	123(97.6)	131(97.0)	133(97.8)
ASA	39(31)	54(42.9)	49(36.3)	58(42.6)
Estrogen	23(18.3)	16(12.7)	23(17.0)	20(14.7)
Furosemide	8(6.3)	12(9.5)	14(10.4)	14(10.3)
Glyceryl trinitrate	4(3.2)	7(5.6)	5(3.7)	*16(11.8)
Levothyroxine	13(10.3)	16(12.7)	11(8.1)	21(15.4)
Multivitamins	23(18.3)	17(13.5)	10(7.4)	14(10.3)
Tocopherol	19(15.1)	12(9.5)	15(11.1)	15(11.0)
Warfarin sodium	45(35.7)	45(35.7)	56(41.5)	53(39.0)

*Slightly higher frequency than in the other treatment groups.

3.2 Discontinuations and Protocol violations and serious adverse events

The patients who completed the study, or were discontinued or had at least one protocol violation are summarized in Tables 41-43.

Table 41: Patients with at least one protocol violation – RAFT

			Propafenone SR			
Protocol violation	**All patients**	**Placebo**	**225mg bid**	**325 mg bid**	**425mg bid**	**All doses**
No. of patients	N=523	N=126	N=126	N=135	N=136	N=397
No. with violations (%)	39 (7.5)	11 (8.7)	8 (6.3)	11 (8.1)	9 (6.6)	28 (7.1)
Inclusion criteria (%)	16 (3.1)	4 (3.2)	3 (2.4)	7 (5.2)	2 (1.5)	12 (3.0)
Exclusion criteria (%)	23 (4.4)	7 (5.6)	5 (4.0)	4 (3.0)	7 (5.1)	16 (4.0)

A total of 66 patients (12.6%) reported serious adverse events of which 32 were terminated due to the serious adverse events. All patients terminated were not replaced but they returned to complete study termination procedures including laboratory evaluation. The case report forms (CRF) revealed all the reasons for discontinuations and premature termination. There is a significant difference in the frequencies of adverse events between the treated groups compared to placebo (p=0.0029) (Table 42).

Table 42: Patients completed study or discontinued from study - RAFT

Variable	All patients	Placebo	225mg bid	325mg bid	425mg bid	All doses	P-value
N	523(100)	126	126	135	136	397	
Completed study	418 (79.9)	107 (84.9)	102 (81.0)	109 (80.7)	100 (73.5)	311 (78.3)	0.1441
Completed with Terminal event	250 (47.8)	*87 (69.0)	*66 (52.4)	*56 (41.5)	*41 (30.1)	163 (41.1)	0.0000
Completed all visits	174 (33.3)	22 (17.5)	39 (31.0)	54 (40.0)	59 (43.4)	152 (38.3)	-
Discontinued	105 (20.1)	19 (15.1)	24 (19.0)	26 (19.3)	36 (26.5)	86 (21.7)	-
Adverse events	48 (9.2)	8 (6.3)	7 (5.6)	9 (6.7)	24 (17.6)	40 (10.1)	**0.0029**
Lack of efficacy	12 (2.3)	1 (0.8)	5 (4.0)	3 (2.2)	3 (2.2)	11 (2.8)	0.4423
Concomitant Medication	4 (0.8)	2 (1.6)	1 (0.8)	0 (0)	1 (0.7)	2 (0.5)	0.5158
Others	30 (5.7)	5 (4.0)	8 (6.3)	11 (8.1)	6 (4.4)	25 (6.3)	0.4525
Therapy Refusal	7 (1.3)	3 (2.4)	2 (1.6)	1 (0.7)	1 (0.7)	4 (1.0)	0.5804
Administrative	4 (0.8)	0 (0)	1 (0.8)	2 (1.5)	1 (0.7)	4 (1.0)	0.8041

P value based on Fisher's exact test. * = Difference from placebo at 0.05 level.

The trend in the time to dropout is similar between the observed data and the investigator's data. The percent of patients in time to dropout is about the same in all treatment groups except in the 425 mg bid group (26.5%) that is relatively high compared to placebo (15.1%)(Table 43).

Table 43: Time to dropout - Propafenone SR - RAFT

		Propafenone		
	Placebo	**225mg bid**	**325mg bid**	**425mg bid**
No entered	N=126(%)	N=126(%)	N=135(%)	N=136(%)
No and % completed	107 (84.9)	102 (81.0)	109 (80.7)	100 (73.5)
No and % dropping out	19 (15.1)	24 (19)	26 (19.3)	*36 (26.5)
Time to dropout in days Mean±SD	207±11.4	213±10.3	221±8.6	169.9± 9.5
P value				0.457 Log rank
Summary statistics of time to dropout based on observed data-FAS				
No entered	N=126(%)	N=126(%)	N=135(%)	N=136(%)
No of days ± SD	85 ±101	114±117	146±120	139±126

***Relatively high**

There is imbalance between the treatment groups with particular reference to the frequency of abnormal cardiac exams at baseline. There were more patients with abnormal cardiac exams at baseline in the placebo group compared to the treatment groups (Table 44). The relationship of this imbalance is presented in Table 46. However, the impact of this imbalance on the study outcome was not significant.

Table 44: Frequencies of normal & abnormal cardiac exam at baseline - RAFT

		Propafenone			
	Placebo	225mg bid	325mg bid	425mg bid	Total
N patients. with normal cardiac exam at baseline	85 (67.46%)	107 (84.92%)	100 (74.07%)	98 (72.06%)	390 (74.57%)
No of pts. with abnormal cardiac exam at baseline	41 (32.54%)	19 (15.08%)	35 (26.32%)	38 (27.94%)	133 (25.43%)
No of pts. with irregular rhythms at baseline	N=8/19 (42.0%)	N=2/19 (10.5%)	N=5/19 (26.0%)	N=4/19 (21.0%)	19 (100%)
No and % pts. censored	29 (34.12)	50 (46.73)	57 (57.00)	69 (70.41)	205 (52.56%)
No and % pts. failed	56 (65.88)	57 (53.27)	43 (43.0)	29 (29.59)	185 (47.44%)

The different types of cardiac abnormalities recognized in the cardiac history of patients are presented in Table 45 below.

Table 45: Types of Structural heart abnormalities/disease in cardiac history-RAFT

Category	Abnormality /Disease
Coronary Artery Disease	Angina Angioplasty Bypass grafts Coronary artery disease Myocardial Infarction Myocardial ischemia
Myocardial disease/CHF	Cardiomegaly Cardiomyopathy Congestive Heart Failure
Valvular Disease	Aortic sclerosis Aortic valve regurgitation Atrio-ventricular sclerosis Rheumatic heart disease
Congenital	Atrial septal defect ± Repair Cardiac anomalies Ventricular septal defect ± Repair
Conduction abnormality	Pacemaker Sick sinus syndrome W-P-W Syndrome
Cardiac others	Thrombi in atria

Table 46: Relationship between Normal & Abnormal cardiac examination at baseline to Terminating events – First symptomatic AF recurrence event - RAFT

		Propafenone			
	Placebo	225mg bid	325mg bid	425mg bid	Total
No of pts. with normal cardiac exam at baseline	10 (24.39%)	10 (52.63%)	22 (62.86%)	26 (68.42%)	68 (51.13%)
No of pts. with abnormal cardiac exam baseline "T"	31 *(75.61%)	9 (47.37%)	13 (37.14%)	12 (31.58%)	65 (48.87%)
Total	41(30.83%)	19(14.29%)	35(26.32%)	38(28.57%)	133(100%)
At end of study – 39 weeks - censored patients					
No of pts. with normal rhythms at baseline x tmt	29 (34.12%)	50 (46.73%)	57 (57.0%)	69 (70.41%)	205 (52.56%)
No of pts. with abnormal cardiac exam baseline "T"	56 *(65.88%)	57 (53.27%)	43 (43.0%)	29 (29.59%)	185 (47.44%)
Total	85(21.79%)	107(27.44%)	100(25.64%)	98(25.13%)	390(100%)

"T=Terminating event

3.3 Results

Evaluation and Primary efficacy end points - RAFT

- Primary efficacy was the tachycardia-free duration for each dose of propafenone SR (225mg b.i.d, 325mg b.i.d and 425mg b.i.d) compared to placebo.
- For each patient the tachycardia-free period was measured from Day 1 until the first symptomatic recurrence of arrhythmia (Atrial fibrillation, atrial flutter and or PSVT) documented by TTM with the AEC final diagnosis. The only changes in the primary efficacy variable, based on a protocol amendment, were the calculation of the tachycardia-free period that began not from day 5 as in ERAFT but from day 1, and the addition of PSVT as an arrhythmia (Protocol Amendment VII).
- The primary efficacy endpoint was therefore the measurement of the tachycardia free period in days, measured from the beginning of randomization until the first symptomatic recurrence of arrhythmia, documented by TT ECG monitoring with the AEC final diagnosis of atrial fibrillation, atrial flutter or paroxysmal supraventricular tachycardia (PSVT). This was used as the endpoint for the analyses of the data.
- Symptomatic arrhythmias were considered outcome events if the ECG showed any of the following: atrial fibrillation, atrial flutter or PSVT. Symptomatic arrhythmias that occurred during the study drug loading period were documented in the CRFs. AF 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 an outcome event unless an ECG was recorded documenting the episode.
- The AEC reviewed all symptomatic ECGs to make the diagnoses used for efficacy analyses. The diagnoses were made without the knowledge of the identity of the patients randomized to 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 diagnosis were considered final and used as endpoint for statistical analyses (Table 47).

Adverse Event Committee Diagnoses

The distribution of AEC diagnoses for symptomatic terminating events upon which the primary efficacy analysis is based is presented in Table 47. This distribution is similar to the investigators' distribution patterns suggesting the reliability of diagnoses in clinical practice. TTM revealed 10 patients with PSVT and 13 patients with atrial flutter. These patients were terminated (Table 47).

Correlation between Trans-Telephonic Monitoring readings and AEC diagnoses

There was excellent correlation between AEC diagnosis and investigators (r=0.94) suggesting that these results will be in agreement with what obtains in routine medical practice.

Table 47: Distribution of AEC diagnoses for symptomatic terminating events from Day 1 - RAFT

AEC diagnosis		Propafenone SR		
	Placebo	**225mg bid**	**325mg bid**	**425mg bid**
	N=126(%)	**N=126(%)**	**N=135(%)**	**N=136(%)**
AFib	80(91.9)	59(89.3)	50(89.2)	39(95.1)
Atrial flutter	5(5.7)	2(3.0)	4(7.1)	1(2.4)
PSVT	2(2.3)	5(7.5)	2(3.5)	1(2.4)

3.4 Primary Efficacy analysis-RAFT

Primary efficacy was defined as the tachycardia-free duration in days for each dose of propafenone SR (225mg bid, 325mg bid, and 425mg bid) compared to placebo. Tables 47 and 48 show the tachycardia-free period from Days 1 and 5 of randomization in the RAFT study.

The primary efficacy analysis revealed statistically significant increases in the tachycardia–free period from day 1 to the first recurrence of symptomatic atrial arrhythmia in all propafenone SR treatment doses in comparison 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 48). The percentages of patients with terminating events are as follows: - placebo, 69%; 225 mg bid, 52.4%; 325 mg bid, 41.5%; and 425 mg bid 30.1%.

Table 48: Showing tachycardia-free period (days) – Day 1 of randomization -RAFT

Parameter	**Propafenone SR**			
	Placebo	**225mg bid**	**325mg bid**	**425mg 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 Wilcoxon Hazard ratio 95% CI for Hazard Ratio	 - - - -	 0.014 0.064 0.672 (0.488,0.927)	 <0.0001 <0.0001 0.434 (0.309,0.609)	 <0.0001 <0.0001 0.353 (0.243,0.513)

***Patients had a terminating event if they had symptomatic atrial fibrillation. Atrial flutter or PSVT.**

3.5 Dose response-RAFT

Dose response was achieved for the following:

Time to recurrence of symptomatic atrial arrhythmia from

- Day 1 of randomization (Figure 8) Table 48.
- Day 5 of randomization (Table 49).

The study was not powered enough to detect a difference between Propafenone SR treatment groups. However in a post-hoc analysis, the hazard ratio of 0.66 (95% CI 0.461,0.944) for propafenone 325mg bid versus 225mg bid and a hazard ratio of 0.53 (95% CI 0.360,0.785) for propafenone SR 425 mg bid versus 225mg was observed. The hazard ratio was not met for 325mg bid versus 425 mg bid group. Propafenone 225 mg bid was significantly different from placebo (primary analysis), and from 325 mg bid and 425mg bid (post hoc analyses and unadjusted for multiple comparisons).

Secondary efficacy variables included the following:

- Heart rate during the first recurrence of symptomatic arrhythmia in the efficacy period.
- Time from the full loading dose (Day 5) to the first recurrence of symptomatic arrhythmia.
- Time from the beginning of randomization (Day 1) to first patient-initiated report of symptoms (dyspnea, dizziness, palpitations, chest pain, or anxiety).
- Time from the beginning of randomization (Day 1) to treatment failure (defined as first recurrence of symptomatic arrhythmia or withdrawal from the trial for any reason).
- Time from full loading dose (Day 5) to first recurrence of symptomatic arrhythmia by propafenone SR.
- Investigator interpretation of the TTM recording.
- The AEC final diagnosis (TTM recording) compared with the investigator interpretation (same TTM recording).
- Time from the beginning of randomization (Day 1) to the first recurrence of symptomatic arrhythmia by subpopulation: age, gender, history of SHD, use of concomitant medications that lower heart rate, with or without history of cardioversion, NYHA classification, duration of atrial fibrillation, and frequency of atrial fibrillation.
- The average heart rate during the first recurrence of a symptomatic arrhythmia that was the primary endpoint event in the treatment period was treated as a secondary variable.

Figure 8: Survival Analysis of tachycardia free period from Day 1 - FAS–RAFT

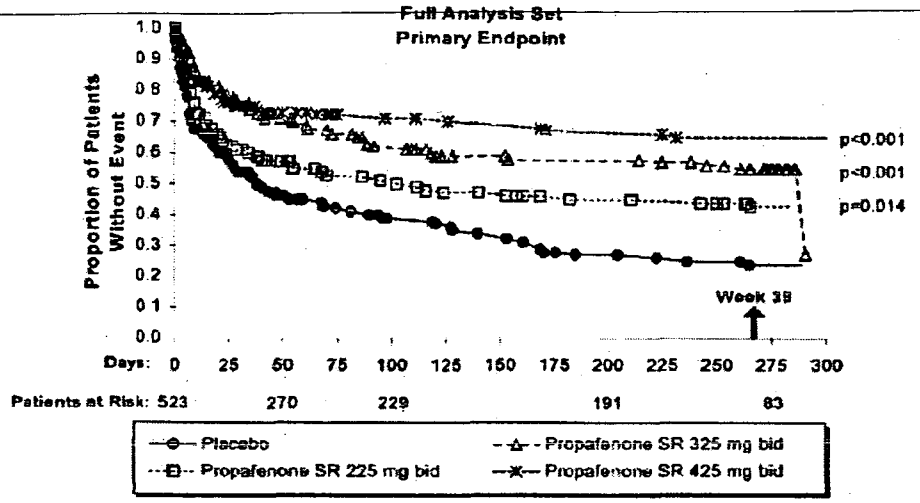


Table 49: Tachycardia-free period (days) - Day 5 of randomization FAS - RAFT

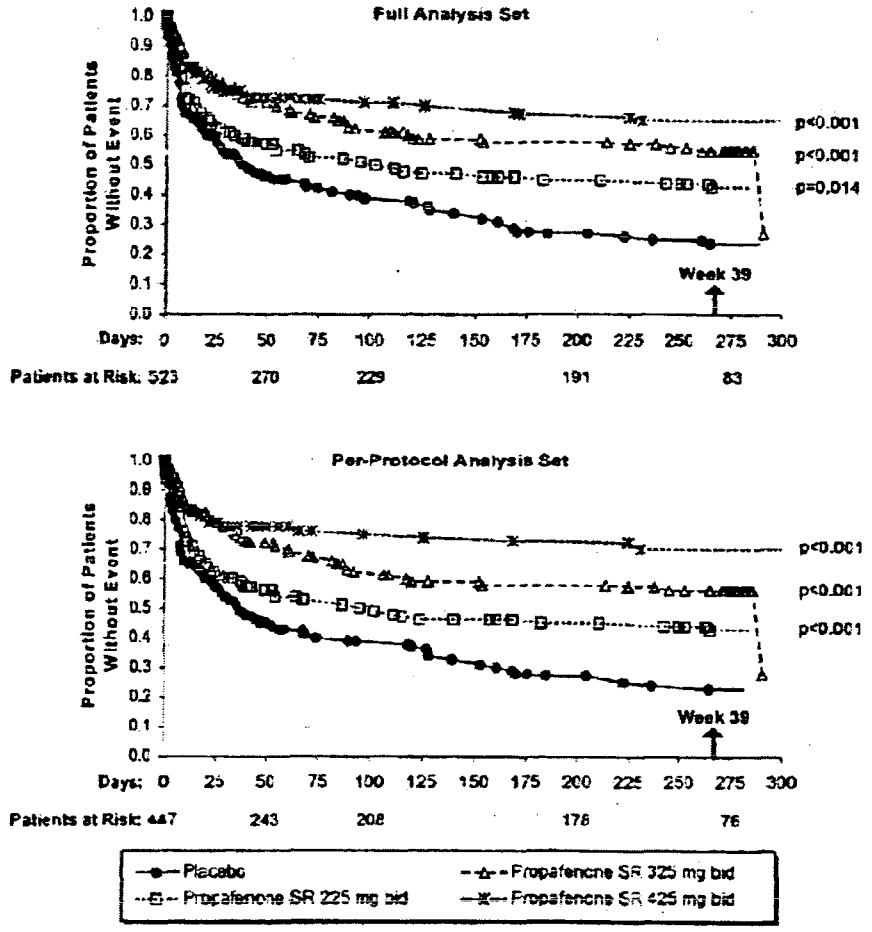
Parameter	Propafenone SR			
	Placebo	225mg bid	325mg bid	425mg bid
	N=124(%)	N=124(%)	N=132(%)	N=131(%)
Patients completing with terminating event*	84 (67.7)	60(48.4)	54(40.9)	36 (27.5)
Comparison of tachycardia- free period Kaplan-Meier Median Range (days)	39.0 0.0-285.0	149.0 0.0-281.0	287.0 0.0-289	- 0.0-296.0
P-value				
Log rank	-	0.002	<0.0001	<0.0001
Wilcoxon	-	0.01	<0.0001	<0.0001
Hazard ratio	-	0.604	0.438	0.319
95% CI for HR	-	0.433.0.842	0.310,0.619	0.216,0.473

***Patients had a terminating event if they had symptomatic atrial fibrillation. Atrial flutter or PSVT.**

The efficacy findings suggest that both primary (Figure 8) and secondary efficacy endpoints (Figure 9, Tables 50-54) were achieved and that there were clinical benefits to patients with atrial fibrillation.

Figure 9 below shows a dose response in RAFT from Day 1 of randomization using Kaplan – Meier survival curves for FAS and PP populations.

Figure 9: Survival curves for Propafenone SR from Day 1-FAS and PP - RAFT



There was also a statistically significant difference in the time (days) from day 1 to patient-initiated report of symptoms of arrhythmia (secondary efficacy variable) only in the 325mg bid. and 425 mg bid dose groups. (p=0.002 and 0.011), respectively, but not in the 225mg bid.(p=0.297), dose group (Table 50). Using the Kaplan-Meier curves and proportional hazard ratio in post-hoc analyses, differences in responses to the doses were confirmed in the RAFT study.

The time to treatment failure is presented in Table 51.

Table 50: Time (days) from day 1 to patient-initiated report of arrhythmia symptoms - RAFT

		Propafenone SR		
Parameter	**Placebo N=126**	**225mg bid N=126**	**325mg bid N=135**	**425mg bid N=136**
Patients completing with symptoms*	101 (80.2)	95 (75.4)	87 (64.4)	87 (64.0)
Comparison of symptom -free period Kaplan-Meier Median Range (days)	12.0 0.0-289.0	20.0 0.0-284.0	29.0 0.0-293.0	18.0 0.0-289.0
P-value	-			
Log rank	-	0.297	0.002	0.011
Wilcoxon	-	0.391	0.006	0.066
Hazard ratio	-	0.864	0.644	0.693
95% CI for HR		0.653,1.144	0.483,0.859	0.520,0.925

Table 51: Time-Treatment (days) failure from Day 1 of randomization - RAFT

		Propafenone SR		
Parameter	**Placebo N=126**	**225mg bid N=126**	**325mg bid N=135**	**425mg bid N=136**
Patients with treatment failure*	106 (84.1)	90(71.4)	82(60.7)	77(56.6)
Comparison of treatment failure periods Kaplan-Meier Median Range (days)	30.0 0.0-285.0	45.5 0.0-293.0	118.0 0.0-293.0	72.5 0.0-300
P-value	-			
Log rank	-	*0.032	*<0.0001	*<0.0001
Wilcoxon	-	0.108	<0.0001	0.002
Hazard ratio	-	0.737	0.512	0.543
95% CI for HR		0.556,0.977	0.383,0.685	0.404,0.730

*** Statistically significant differences compared to placebo.**

3.6 Heart rate during the first recurrence of symptomatic atrial fibrillation

The mean heart rate of patients during the first recurrence of symptomatic arrhythmia for ITT population is shown in Table 52.

Table 52: showing comparison of average heart rate of patients during the first recurrence of symptomatic Atrial Fibrillation-RAFT

Average HR bpm		**Propafenone SR**			
	Placebo	**225mg bid**	**325mg bid**	**425mg bid**	**p-value**
	N=87	**N=66**	**N=56**	**N=41**	
Mean±SD	122.2±29.5	126.4±30.2	109.9±26.1	111.1±38.5	0.0068
Range	64.0-220.0	60.0-240.0	52.0-160.0	41.0-188.0	
p-value	-	0.768	0.054	0.147	-
Patients with average HR	N(%)	N(%)	N(%)	N(%)	
<50bpm	0(0.0)	0(0.0)	0(0.0)	1(2.4)	-
50 - <100	23(26.4)	12(18.2)	20(35.7)	16(39.0)	-
>100 to<110	6(6.9)	8(12.1)	6(10.7)	6(14.6)	-
>110 to130	26(29.9)	23(34.8)	18(32.1)	6(14.6)	-

Table 53: Disposition of patients by body-weight adjusted dose – ITT -- RAFT

Body-weight adjusted	Propafenone SR daily dose			
Dose (mg/kg)		225mg bid	325mg bid	425mg bid
	N (Range)	N=124(%)	N=132(%)	N=135(%)
Low	132 (1.52-3.21)	101 (80.2)	28 (20.7)	3 (2.2)
Medium	132 (3.22-4.47)	24 (19)	72 (53.3)	36 (26.7)
High	132 (4.47-9.35)	1 (0.8)	35 (25.9)	96 (71.1)

Table 54: Tachycardia-free period (days) from Day 5 of randomization by body-weight adjusted dosage – FAS - RAFT

Parameter	Propafenone SR			
	Low N=131	Medium N=129	High N=126	Placebo N=124
Range (mg/kg)	1.52-3.22	3.22 - 4.47	4.47 - 9.35	NA
Patients completing with (a) symptoms (b) All visits	5945.0 4534.4	5542.6 4837.2	3527.8 5946.8	8467.7 2217.7
Comparison of tachycardia -free periods Kaplan-Meier Median Range (days)	262 0.0-281	-- 0-296.0	287 0.0-287.0	39.0 0.0-285.0
P-value Log rank Wilcoxon Hazard ratio 95% CI for Hazard Ratio	<0.0001 0.001 0.543 (0.39,0.76)	<0.0001 <0.0001 0.486 (0.35,0.69)	<0.0001 <0.0001 0.309 (0.21,0.46)	- - - -

3.7 Subpopulation analyses – RAFT study

Subgroup analyses for age, gender, race, NYHA classification, history of cardioversion, medications that lower heart rate, duration and frequency of atrial fibrillation could not be carried out because of small numbers in each treatment group. However, using the proportional hazard method the sponsor reported some differences with respect to age and sex (Tables 55-58 Figures 10 and 12). It is noteworthy that patients with structural heart disease, regardless of associated hemodynamic deficits, showed no significant difference between the treatment groups. This may be due to the exclusion of patients with NYHA III and IV classification among the population studied. This suggests that patients with atrial arrhythmia associated with more severe forms of heart failure (>NYHA II) have not been studied and may not benefit from this drug. This should be reflected in the label.

The study was not powered enough to detect a statistically significant difference between the propafenone treatment groups and placebo for several variables including age, sex, (Tables 55-58), presence of SHD, NYHA classification, history of cardioversion, medications that lower heart rate, duration of atrial fibrillation and frequency of atrial fibrillation. However these analyses were performed using proportional hazards assumptions and are presented graphically in Figures 10 -12 below. For two reasons, this reviewer does not consider the results to be statistically valid and/or interpretable. The first reason is that the patients were not stratified at randomization, and the second reason is that the numbers are too small. However, the hazard ratios, submitted by the sponsor, are in Figures 10 and 12.

Subgroup analyses: Age (See Appendix 15; and Figures 10 and 12)

Table 55: Showing tachycardia-free period (days) – Day 1 of randomization –RAFT by age - < 65years

Parameter	Propafenone SR			
< 65 years	**Placebo**	**225mg bid**	**325mg bid**	**425mg bid**
	N=126(%)	N=126(%)	N=135(%)	N=136(%)
Patients completing with terminating event*		65(51.6	66(48.9)	61(44.9)
Comparison of tachycardia- free period				
Kaplan-Meier Median Range (days)	96 1-281	114 0.0-285.0	148 2-291	135 1-293
p-value Log rank Wilcoxon		0.033	<0.0001	<0.0001
Hazard ratio 95% CI for HR		0.624 (0.40,0.97)	0.360 (0.22,0.59)	0.328 (0.19,0.56)

***Patients had a terminating event if they had symptomatic atrial fibrillation. Atrial flutter or PSVT.**

Table 56: Showing tachycardia-free period (days) – Day 1 of randomization –RAFT by age - > 65years

Parameter	Propafenone SR			
>65 years	**Placebo**	**225mg bid**	**325mg bid**	**425mg bid**
	N=126(%)	N=126(%)	N=135(%)	N=136(%)
Patients completing with terminating event*		61 (48.4)	69(51.1)	75(55.1)
Comparison of tachycardia- free period				
Kaplan-Meier Median Range (days)	72 0-289	114 0.0-281	145 0.0-293.0	144 0.0-300.0
P-value Log rank Wilcoxon	- -	0.149	<0.005	<0.0001
Hazard ratio 95% CI for HR	- -	0.712 (0.45,1.14)	0.509 (0.32,0.82)	0.372 (0.22,0.63)

***Patients had a terminating event if they had symptomatic atrial fibrillation. Atrial flutter or PSVT.**

Gender (See Appendix 15; and Figures 10 and 12)

Table 57: Tachycardia-free period (days) – Day 1 of randomization – RAFT - Males

Parameter	Propafenone SR			
	Placebo	225mg bid	325mg bid	425mg bid
		N=126(%)	N=135(%)	N=136(%)
Patients completing with terminating event*		76(60.3)	80(59.3)	78(57.4)
Comparison of tachycardia- free period				
Kaplan-Meier Mean	85	112	156	152
Range	0-289	0-285	0-293	0-300
P-value				
Log rank		0.154	0.0006	0.0001
Hazard ratio		0.737	0.465	0.396
95% CI for HR		(0.482,1.127)	(0.30,0.73)	(0.24,0.65)

*Patients had a terminating event if they had symptomatic atrial fibrillation. Atrial flutter or PSVT.

Table 58: Tachycardia-free period (days) – Day 1 of randomization –RAFT-Females

Parameter	Propafenone SR			
	Placebo	225mg bid	325mg bid	425mg bid
		N=126(%)	N=135(%)	N=136(%)
Patients completing with terminating event*		50 (39.7)	55 (40.7)	58(42.6)
Comparison of tachycardia- free period				
Kaplan-Meier Mean	84	118	133	122
Range	1-281	0-284	0-291	1-290
P-value				
Log rank		0.036	0.0005	<0.0001
Hazard ratio		0.597	0.407	0.314
95% CI for HR		(0.366,0.975)	(0.241,0.688)	(0.175,0.563)

*Patients had a terminating event if they had symptomatic atrial fibrillation. Atrial flutter or PSVT.

Figure 10: Hazard ratio for tachycardia free period from Day 1 by age- RAFT and ERAFT (See Figure 14 for ERAFT subgroup analysis)

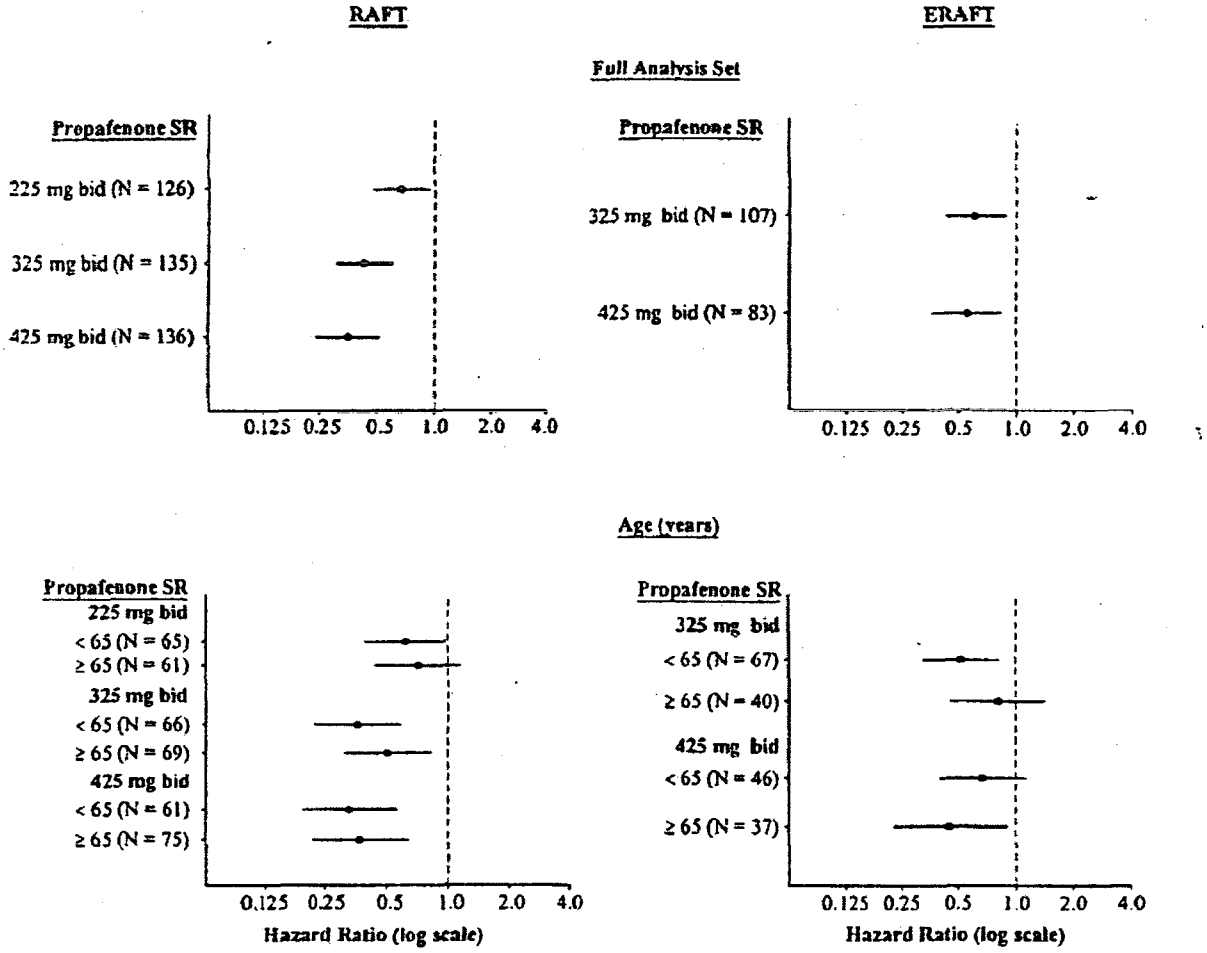


Figure 11: Hazard ratio for tachycardia free period from Day 1 by Structural Heart Disease - RAFT and ERAFT

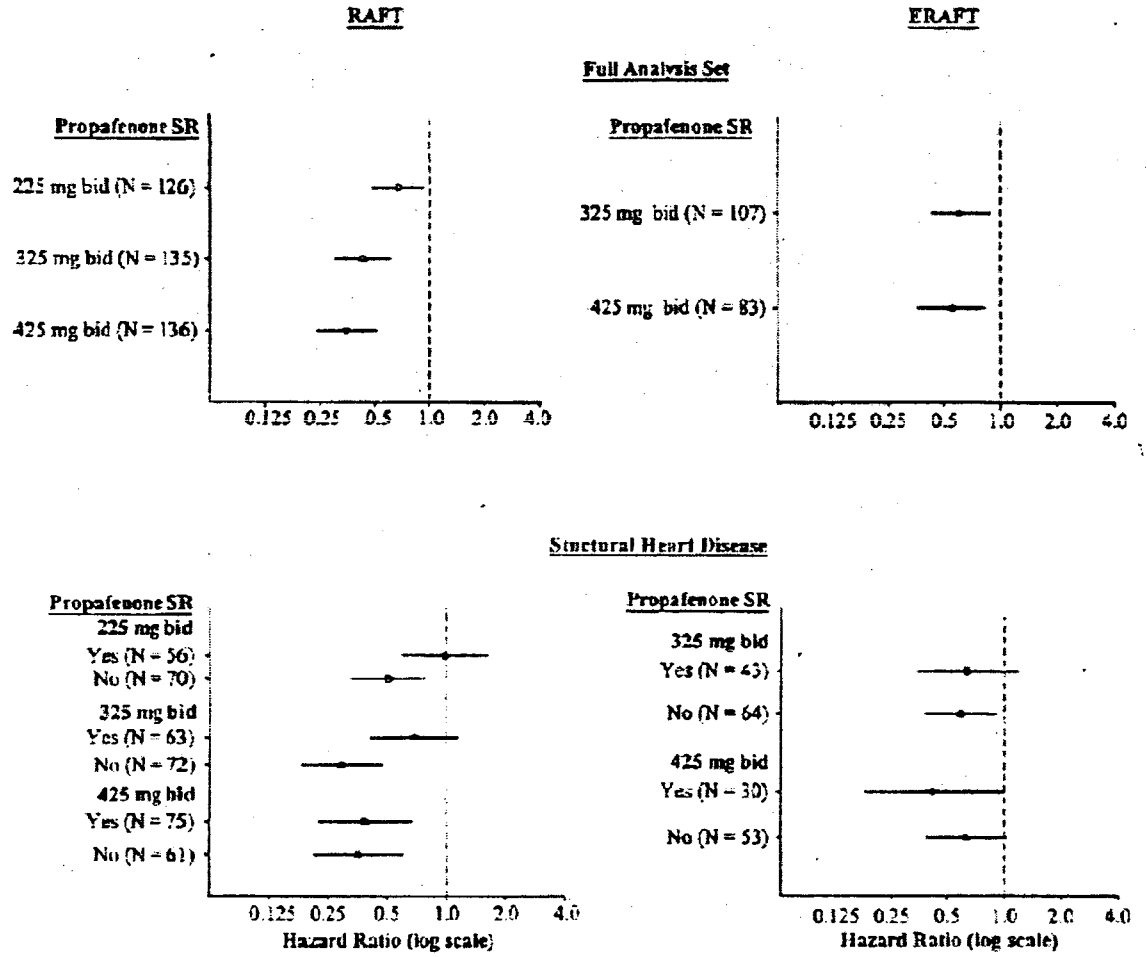
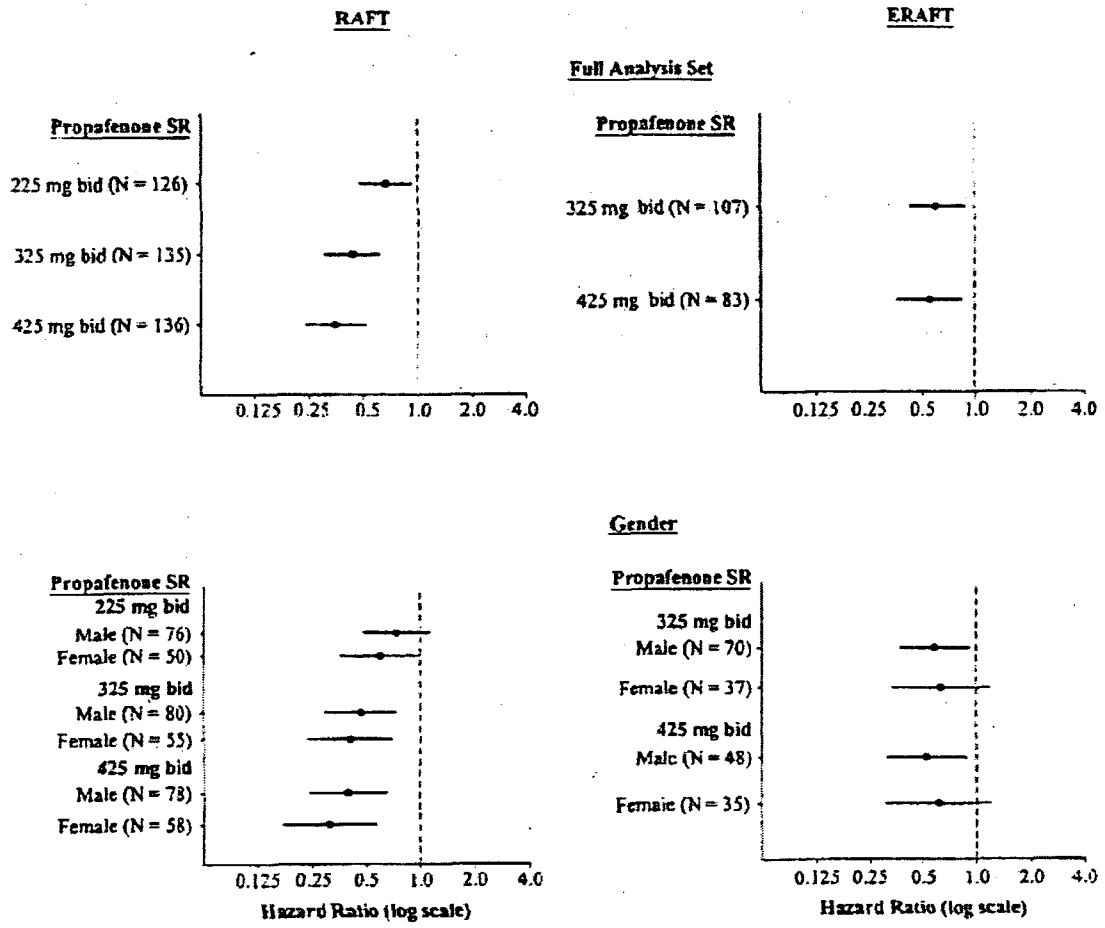


Figure 12: Hazard ratio for tachycardia-free period from Day 1 by Sex – RAFT and ERAFT



Safety findings from clinical studies-RAFT and ERAFT

4.0 Safety

The number of patients and duration of exposure to propafenone in the drug development of propafenone SR is presented in Tables

Table 59: Propafenone SR exposure in Phase II and Phase III studies:

Days of exposure	Placebo	225mg bid	325mg bid	425mg bid
5-10	67	70	63	73
10-14	-	78	76	-
Up to 95	93	-	111	89
Up to 6 months	10	11	13	14
Up to 39 weeks	126	126	135	136

4.1 Duration of exposure

Out of 890 patients, propafenone was administered to a total of 655 patients with AF whereas placebo was administered to 235 patients with AF (Table 60). The integrated

safety review of SR is based on 4 studies combined, namely two phase III studies on AF patients: RAFT (N=523) and ERAFT (N=293); and two phase II studies on 74 AF patients: SR SVA CR D1 and SR SVA CR 11). The duration of exposure to drugs in the RAFT study is presented in Table 61 and in all Phase II and III studies the overall drug exposure of the 890 patients is presented in Tables 59-62

Table 60: 890 AF patients enrolled by study in phases II/III studies combined

Days of exposure	Placebo	225mg bid	325mg bid	425mg bid
	N=235(%)	N=146(%)	N=264(%)	N=245(%)
Propafenone Phase II studies	16(6.8)	20(13.7)	18(6.8)	20(8.2)
Propafenone phase III studies				
RAFT	126(53.56)	126(86.3)	135(51.1)	136(55.5)
ERAFT	93(39.6)	0(0.0)	89(36.3)	89(36.3)

Table 61: Extent of 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)

The duration of drug exposure is presented in Tables 59 and 61. There were no deaths during the treatment phase of the studies. A total of 5 patients had adverse events that led to deaths post-study drug. [(3 and 2 received propafenone [325mg bid and 425mg bid] and placebo, respectively)] (Table 24). The causes of death in these patients included renal failure, malignant renal neoplasm and lung carcinoma and one patient died 30 days post drug following a "fall". (Table 25). The reviewer was unable to obtain details from sponsor about the circumstances surrounding the fatal fall.

A total of 66 patients out of 523 patients (12.6%) reported serious adverse events of which 32 were terminated due to the serious events (Table 62). All patients terminated were not replaced but they returned to complete study termination procedures including laboratory evaluation. The CRFs of the patients revealed the reasons for discontinuations and premature terminations.
The frequency of treatment emergent adverse events is presented in Table 62 below.

Table 62: Overview of Treatment-emergent Adverse events on or after day 1 of randomization - RAFT

		Propafenone SR		
Duration of exposure	**Placebo N=126 N(%)**	**225mg bid N=126 N(%)**	**325mg bid N=135 N(%)**	**425mg bid N=136 N(%)**
At least 1 AE	91(72.2)	97(77.0)	113(83.7)	113(83.1)
AE leading to death	2 (1.6)	0(0.0)	1(0.7)	0(0.0)
At least 1 serious AE**	18(14.3)	13(10.3)	16(11.9)	19(14.0)
At least 1 AE leading to premature withdrawal*	17(13.5)	16(12.7)	19(14.1)	34(25.0)
At least 1 serious AE drug related	2(1.6)	2(1.6)	3(2.2)	4(2.9)
At least 1 serious AE leading to death	2(1.6)	0(0.0)	0(0.0)	0(0.0)

**** Total of 66 SAEs equally observed between the groups. * Total of 86 AEs resulted in withdrawal.**

The majority of adverse events leading to premature termination were considered mild or moderate in severity. Of the 86 patients with adverse events leading to withdrawal, 50 patients withdrew within the first 14 days on study drug. The proportions of patients who withdrew were equally divided between men and women. 'The only adverse events leading to premature termination that were considered definitely related to study drug were dizziness (Patients 85059104. and 85065/02), acute ataxia and peripheral paresthesia (Patient 85014/08), and primary atrio-ventricular block (Patient 85101/01). Except for 2 patients who received placebo and died (Patient 8501 1/05) who had lung cancer and Patient 85077 who had renal failure), all of the patients with serious adverse events recovered without sequelae or the adverse event(s) ongoing after the study drug was discontinued. No adverse events resulted in a dose reduction. Reductions in dose were not permitted by the protocol.

Routine adverse events

Adverse events occurring in greater than 1% or 5% of patients exposed to propafenone SR are presented in Table 63 and 64, respectively. The most commonly reported adverse events in the propafenone SR treatment groups include dizziness, palpitations, dyspnea, nausea, constipation, anxiety, fatigue, upper respiratory tract infection, influenza, vomiting, and taste disturbance. The most commonly reported adverse events in the placebo group include dizziness, palpitations, dyspnea, nausea, anxiety, fatigue, constipation, upper respiratory tract infection and influenza.

Table 63: Overview of Adverse events > 1% in any treatment group – RAFT – (Details in Appendix 14)

		Propafenone SR		
Body System	**Placebo N=126**	**225mg bid N=126**	**325mg bid N=135**	**425mg bid N=136**
Blood and lymphatic system Anemia Lymphadenopathy	**1** **0**	**1** **1**	**2** **2**	**0** **0**
Cardiac disorders Angina pectoris Arrhythmia Atrial fibrillation Atrial flutter	**46**	**51**	**75**	**42**

Body System	Placebo N=126	Propafenone SR 225mg bid N=126	325mg bid N=135	425mg bid N=136
AV block first degree Bradycardia Congestive Cardiac Failure Cardiac murmur Edema Palpitations Sinus bradycardia Tachycardia Ventricular Extrasystoles				
Eye disorders*	1	3	5	9
Ear and labyrinth disorders	0	1	0	2
General disorders Chest pain Fatigue Malaise Pain Pyrexia Rigors Weakness				
G I disorders(Total) Abdominal pain Constipation Diarrhea Diverticulitis Dry mouth Dyspepsia Flatulence GI reflux Melena Nausea Toothache Vomiting	32	41	56	65
Infections and Infestations	23	41	37	28
Musculoskeletal connective tissue and bone	16	14	20	15
Nervous system disorders	36	57	68	87
Respiratory thoracic mediastinal disorders	15	23	31	29
Skin and subcutaneous disorders	10	10	13	19
Renal and urinary disorders	5	9	7	4
Metabolism and nutritional disorders	2	2	4	2
Vascular disorders	5	3	4	6
Psychiatric disorders	15	14	23	16

***Blurred vision**

Adverse events occurring in greater than 5% of patients exposed to propafenone SR are presented below in Table 64.

Table 64: Frequency of Adverse events > 5% in treatment groups - RAFT

Body System	Placebo N=126	Propafenone SR 225mg bid N=126	325mg bid N=135	425mg bid N=136
Cardiac				
Afib	6(4.8)	7(5.6)	6(4.4)	7(5.1)
Edema	8(6.3)	6(4.8)	18(13.3)	10(7.4)
Palpitations	21(16.7)	22(17.5)	30(22.2)	23(16.9)
GI disorders				
Abdominal pain	6(4.8)	7(5.6)	4(3.0)	2(1.5)

		Propafenone SR		
Body System	**Placebo N=126**	**225mg bid N=126**	**325mg bid N=135**	**425mg bid N=136**
Constipation	3(2.4)	10(7.9)	19(14.1)	16(11.8)
Nausea**	11(8.7)	11(8.7)	15(11.1)	23(16.9)
Vomiting	3(2.4)	1(0.8)	-	8(5.9)
General				
Chest pain	16(12.7)	22(17.5)	16(11.9)	19(14.0)
Fatigue	7(5.6)	14(11.1)	17(12.6)	17(12.5)
Infections				
Influenza	6(4.6)	9(7.1)	6(4.4)	6(4.4)
URTI	7(5.6)	11(8.7)	16(11.9)	11(8.1)
Nervous System disorders				
Dizziness	18(14.3)	29(23)	28(20.7)	29(21.3)
Headache	11(8.7)	8(6.3)	12(8.9)	14(10.3)
Taste disturbance**	1(0.8)	7(5.6)	18(13.3)	30(22.1)
Anxiety	13(10.3)	12(9.5)	17(12.6)	16(11.8)
Respiratory				
Dyspnea	9(7.1)	16(12.7)	23(17.0)	17(12.5)

Nausea appears to be dose dependent but drug related causality cannot be established. ** Dose related.

4.2 Integrated review of safety

Although there is compelling evidence of efficacy for the proposed indication, based on RAFT and ERAFT studies, this reviewer is of the opinion that safety analysis should be integrated and evaluated in lieu of a definitive mortality study. This overview will not only evaluate frequencies of adverse events possibly or probably related to propafenone exposure but may contribute to a qualitative assessment of mortality risk that may be associated with long term exposure to the drug. Tables 65 and 66 provide data on demographics and disposition of healthy volunteers, and patients with arrhythmias (atrial and ventricular arrhythmias) exposed to both propafenone IR and SR formulations. This does not include patients from the original NDA on propafenone IR already approved by the agency.

The mean drug exposure to propafenone SR by healthy volunteers was under 10 days, whereas in patients with atrial fibrillation the mean drug exposure was over 100 days and to placebo was significantly less than 65 days (Table 65).

There were two groups of adverse events. Those that were dose related and those that were not dose-related (Table 63-64). Those that were dose related in the RAFT study included:

- Taste disturbance,
- Nausea, and
- Atrio-ventricular block - first degree
- Visual disturbance (blurring of vision)
- ?Bradycardia (Appendix 14 page 159)

The adverse events that were not dose related and were most commonly reported included dizziness, palpitations, chest pain, nausea, dyspnea, and fatigue.

Table 65: Overall drug exposure - Integrated review of safety -US and non-US

	Propafenone SR (mg)						IR (mg)		
Days of exposure	425 od	225 bid	325 bid	400 bid	425 bid	Plcbo	300 od	150 bid	300 bid
Patients with AF									
Total	-	16961	26933	-	24836	15103			
Mean±SD		116.2± 114.9	102.0± 104.4		101.4± 109.3	*64.3± 85.8	- -	- -	- -
Patients with VA									
Total	-	1197	1182	-	287	273	-	-	-
Mean±SD		9.4±3.7	9.8± 3.6		5.4±1.1	5.4±1.4	-	-	-
Healthy volunteers									
Total	46	177	312	90	594	-	23	144	144
Mean±SD	1.9±0.3	6.8±0.7	6.5±0.5	5.0±0.0	8.3±2.7	-	1.0±0.0	6.0±0.0	6.0±0.0

***Significantly less duration of exposure for placebo. The overall duration of exposure was more than 65,000 days. VA=Ventricular arrhythmia.**

Table 66: Disposition of patients with AF - Integrated review of safety**

Days of exposure	Placebo	*225mg bid	325mg bid	425mg bid
(Total N=890)	N=235(%)	N=146(%)	N=264(%)	N=245(%)
Number of patients				
Reaching primary endpoint	152(65)	66(45)	120(45)	81(33)
Completed without reaching endpoint	41(17)	54(37)	95(36)	102(42)
Discontinued	127(54)	89(61)	108(41)	106(43)
Reasons for discontinuation				
Adverse event	22(9)	16(11)	33(13)	51(21)
Lack of efficacy	85(36)	58(40)	51(19)	41(17)
Protocol violation	9(4)	2(1)	5(2)	1(~0)
Therapy refusal	4(2)	2(1)	5(2)	3(1)
Administrative	0(0)	1(1)	2(1)	1(~0)
Others	7(3)	10(7)	12(5)	9(4)

*** This column requires further clarification. The sponsor should clarify these data.**

ECG changes

Based on the pharmacology of propafenone, ECG changes in AF patients are dose related. There is a decrease in heart rate during sinus rhythm, a dose-dependent increase (>10%) in PQ interval across the SR treatment groups, and an increase in QRS duration for the 325mg and 425 mg bid dose levels (Figure 6, Table 69). In addition the QTc increased slightly in the 325 mg bid treatment group only. These changes were not significantly affected by the NYHA classification.

The striking ECG abnormality in the propafenone treated group was the dose-dependent increase in the proportion of patients with AF who developed conduction disturbances and significant frequencies of sinus bradycardia (Tables 70 and 75) compared to placebo.

Similar to the AF patients, there was also a dose-dependent increase (>10%) in PQ and QRS across the SR treatment groups among a total of 281 ventricular arrhythmia patients on propafenone therapy (Tables 67 and 78) compared to placebo. Overall 93% of patients with VA completed the studies in the four treatment groups. The ECG summary data are presented in Table 78.

Overall adverse events (14%) and lack of efficacy (26%) constituted the largest number of causes for discontinuation in the integrated review of safety. Adverse events by race are presented in Table 74.

Table 67: 281 patients with ventricular arrhythmia enrolled by study-phase II

Days of exposure	Placebo	225mg bid	325mg bid	425mg bid
	N=51(%)	N=128(%)	N=121(%)	N=53(%)
Propafenone Phase II studies				
SRVPCCRD1	51(100)	46(35.9)	45(37.2)	45(84.9)
SRVPCCRD2	0(0.0)	4(3.1)	0(0.0)	8(15.1)
*SRVPCCR11	0(0.0)	78(60.9)	76(62.8)	0(0.0)

***Crossover study**

Treatment emergent adverse events are presented in Table 68.

Table 68: Treatment - emergent AEs in patients with AF- Integrated review of safety

	Placebo	225mg bid	325mg bid	425mg bid
	N=235(%)	N=146(%)	N=264(%)	N=245(%)
Patients with at least 1:				
Adverse event	122(52)	109(75)	181(69)	165(67)
Serious Adverse event	19(8)	13(9)	27(10)	29(12)
AE leading to death	2(1)	0(0)	2(1)	1(0)
AE resulting in withdrawal	2(19)	17(12)	33(13)	53(22)
AE with severe intensity	20(9)	19(13)	28(11)	33(13)
AE related to study drug	48(20)	47(32)	96(36)	109(44)

Table 69: Summary statistics of ECG changes baseline to endpoint by patient and treatment group – -RAFT

		Mean±SD		
Parameter/Treatment Group	N	Baseline	Endpoint	Change From Baseline
Ventricular rate (bpm)				
Propafenone SR 225 mg bid	120	67.73±19.94	72.68±22.67	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±11.84
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 70: Selected cardiovascular events and ECG findings by patient and treatment group

	Treatment Group				
	Propafenone SR				
Frequency	225 mg bid	325 mg bid	425 mg bid	Placebo	Total
Normal sinus rhythm	407	491	465	345	1708
Atrial fibrillation/Atrial flutter					
Atrial fibrillation	24	42	22	57	145
Atrial flutter	11	3	6	3	23
Other					
Atrial tachycardia	0	3	0	1	4
Ectopic atrial rhythm	3	3	1	11	18
Sinus tachycardia	0	2	1	0	3
Sinus bradycardia	42	36	34	17	129
Junctional bradycardia	0	0	1	0	1
Ventricular escape rhythm	0	1	0	0	1
Other	3	1	2	1	7
Atrial bigeminy	2	1	0	0	3
Atrial trigeminy	1	0	0	1	2
Premature atrial contractions	4	9	8	9	30
Ventricular premature contractions	8	3	8	22	41

Source: Appendix 2, Listing 2.8.3

Table 71: Central Read Diagnoses for All Symptomatic TTM Calls

	RYTHMOL SR			
Central Read	225 mg BID (N = 126) n (%)[a]	325 mg BID (N = 135) n (%)	425 mg BID (N = 136) n (%)	Placebo (N = 126) n (%)
Sinus tachycardia (rate ≥100 beats/min)	6 (2.5)	6 (2.6)	14 (6.2)	4 (1.6)
Sinus rhythm with premature ventricular beat(s)	16 (6.6)	21 (9.1)	11 (4.9)	22 (8.9)
Sinus rhythm with premature atrial beat(s)	39 (16.0)	24 (10.4)	26 (11.6)	21 (8.5)

[a] Percent of total number of diagnoses (RYTHMOL SR 225 mg, 244; 325 mg, 230; 425 mg, 225; placebo, 248).

Table 72: Asymptomatic atrial fibrillation, atrial flutter, and PSVT for scheduled trans-telephonic monitoring calls – central read diagnosis (full analysis set)

	RYTHMOL SR Dose			
Central Read	225 mg BID (N=126)	325 mg BID (N=135)	425 mg BID (N=136)	Placebo (N=126)
Total recordings	27	39	32	54
Total patients (%)	17(13.5)	20(14.8)	20(14.7)	22(17.5)

Table 73: Frequencies of patient-initiated symptoms and ECG -RAFT

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.

Source: Appendix 2, Listings 2.4.17 and 2.8.4

Table 74: Adverse events >5% in treatment groups by race - RAFT study

Body System/ Symptom N	Placebo N=126 CaucasianN=116 BlackN=6 OrientalN=0 OthersN=4	Propafenone SR 225mg b.i.d N=126 CaucasianN=113 BlackN=8 OrientalN=2 OtherN=3	Propafenone SR 325mg b.i.d N=135 CaucasianN=125 BlackN=5 OrientalN=1 OtherN=4	Propafenone SR 425mg b.i.d N=136 CaucasianN=122 BlackN=11 OrientaN=l0 OtherN=3
No (%) with AEs				
Caucasian	85(73.3)	87(77.0)	106(84.8)	101(82.8)
Black	4(66.7)	6(75.0)	36(0.0)	9(81.8)
Oriental	0(0.0)	1(50.0)	0(0.0)	0(0.0)
Others	2(50.0)	3(100.0)	4(100.0)	3(100.0)
*Taste disturbance T	1(0.8)	7(5.6)	18(13.3)	30(22.1)
Caucasian	1(0.8)	7(6.2)	16(12.8)	28(23.0)
Black	0(0.0)	0(0.0)	1(20.0)	1(9.1)
Oriental	0(0.0)	0(0.0)	1(25.0)	1(33.3)
Others	0(0.0)			
Cardiac disorders AF	6(4.8)	7(5.6)	6(4.4)	7(5.1)
Caucasian	5(4.3)	7(6.2)	6(4.8)	6(4.9)
Black	1(16.7)	0(0.0)	0(0.0)	1(9.1)
Oriental	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Others	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Edema Total	8(6.3)	6(4.8)	18(13.3)	10(7.4)
Caucasian	7(6.0)	5(4.4)	16(12.8)	10(8.2)
Black	1(16.7)	1(12.5)	1(20.0)	0(0.0)

		Propafenone SR		
Body System/ Symptom	**Placebo N=126**	**225mg b.i.d N=126**	**325mg b.i.d N=135**	**425mg b.i.d N=136**
N	**CaucasianN=116 BlackN=6 OrientalN=0 OthersN=4**	**CaucasianN=113 BlackN=8 OrientalN=2 OtherN=3**	**CaucasianN=125 BlackN=5 OrientalN=1 OtherN=4**	**CaucasianN=122 BlackN=11 OrientaN=l0 OtherN=3**
Oriental	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Others	0(0.0)	0(0.0)	1(25.0)	0(0.0)
Palpitations				
Caucasian	18(15.5)	22(17.5)	28(22.4)	23(16.99)
Black	2(33.3)	19(16.8)	0(0.0)	19(15.6)
Oriental	0(0.0)	1(12.5)	0(0.0)	4(36.4)
Others	1(25.0)	0(0.0)	2(50.0)	0(0.0)
GI disorders				
Abdominal Pain	6(4.8)	7(5.6)	4(3.0)	2(1.5)
Caucasian	6(5.2)	5(4.4)	4(3.2)	2(1.6)
Black	0(0.0)	1(12.5)	0(0.0)	0(0.0)
Oriental	0(0.0)	1(33.3)	0(0.0)	0(0.0)
Others	0	0	0	0
*Nausea Total	11(8.7)	11(8.7)	15(11.1)	23(16.9)
Caucasian	11(9.5)	8(7.1)	14(11.2)	23(18.9)
Black	0(0.0)	337.5	0(0.0)	0(0.0)
Oriental	0(0.0)	0(0.0)	125.0	0(0.0)
Others	0(0.0)	0	0	0
General disorders				
Chest Pain	16(12.7)	22(17.5)	1611.9	19(14.0)
Caucasian	13(11.2)	17(15.0)	1512.0	15(12.3)
Black	11(6.7)	0(0.0)	0(0.0)	3(27.3)
Oriental	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Others	250.0	1(25.0)	1(33.3)	1(33.3)
Infections				
Influenza Total	6( )	9(7.1)	6(4.4)	6(4.4)
Caucasian	5( )	7(6.2)	6(4.8)	6(4.9)
Black	1( )	2(25.0)	0(0.0)	0(0.0)
Oriental	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Others	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Upper respiratory tract infections	7(5.6)	11(8.7)	16(11.9)	11(8.1)
Caucasian	7(6.0)	9(8.0)	16(12.8)	9(7.4)
Black	0(0.0)	22(5.0)	0(0.0)	1(9.1)
Oriental	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Others	0(0.0)	0(0.0)	0(0.0)	1(33.3)
Nervous System Disorders Dizziness (excl. Vertigo) Total	18(14.3)	29(23.0)	28(20.7)	29(21.3)
Caucasian	15(12.9)	26(23.0)	25(20.0)	27(22.1)
Black	2(33.3)	1(12.5)	2(40.0)	2(18.2)
Oriental	1(25.0)	2(66.7)	1(25.0)	0(0.0)
Others	0	0	0	0
Headache Total	11(8.7)	8(6.3)	12(8.9)	14(10.3)
Caucasian	10(8.6)	8(7.1)	12(9.6)	13(10.7)
Black	11(6.7)	0(0.0)	0(0.0)	0(0.0)
Oriental	0(0.0)	0(0.0)	0(0.0)	1(33.3)
Others	0(0.0)	0(0.0)	0	0
Psychiatric Anxiety Total	13(10.3)	12(9.5)	17(12.6)	16(11.8)
Caucasian	11(9.5)	11(9.7)	16(12.8)	12(9.8)

		Propafenone SR		
Body System/ Symptom N	**Placebo N=126 CaucasianN=116 BlackN=6 OrientalN=0 OthersN=4**	**225mg b.i.d N=126 CaucasianN=113 BlackN=8 OrientalN=2 OtherN=3**	**325mg b.i.d N=135 CaucasianN=125 BlackN=5 OrientalN=1 OtherN=4**	**425mg b.i.d N=136 CaucasianN=122 BlackN=11 OrientaN=I0 OtherN=3**
Black Oriental Others	11(6.7) 0(0.0) 1(25.0) 0	0(0.0) 1(50.0) 0(0.0) 0	0(0.0) 0(0.0) 1(25.0) 0	3(27.3) 0(0.0) 1(33.3) 0
Respiratory Dyspnea Total Caucasian Black Oriental Others	 9(7.1) 9(7.8) 0(0.0) 0(0.0) 0(0.0)	 16(12.7) 14(12.4) 0(0.0) 1(50.0) 1(33.3)	 23(17.0) 20(16.0) 1(20.0) 0(0.0) 2(50.0)	 17(12.5) 13(10.7) 4(36.4) 0(0.0) 0(0.0)

* Dose related adverse events. The numbers of the non-Caucasian populations are too small for any meaningful conclusions between treatment groups.

ECG- Baseline expectations

Like all other Class 1C anti-arrhythmics, propafenone is a negative inotrope. PQ interval prolongation is more pronounced after SR administration 325mg and 425 mg compared to IR formulation 150mg, 300mg bid, 300mg od.

Based on pharmacology, ECG changes are dose related, decrease in heart rate during sinus rhythm, increased PR/ PQ interval and increase in QRS duration. In addition the QTc may increase in increments equal to increment in QRS duration.

4.3 ECG in AF patients on propafenone- RAFT and ERAFT

Based on the pharmacology of propafenone, ECG changes in AF patients are also dose related (Figure 6). There is 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 the QTc increased slightly in the 325 mg bid treatment group only. These changes are not significantly affected by the NYHA classification (Table 76).

The striking ECG abnormality in the propafenone treated group was the dose dependent increase in the proportion of patients with AF who had conduction disturbances (Tables 74-75).

Table 75: AF patients with treatment-emergent ECG abnormalities-RAFT and ERAFT combined

		Propafenone SR		
Parameter	**Placebo N=215 (%)**	**225mg bid N=124(%)**	**325mg bid N=244(%)**	**425mg bid N=222(%)**
Underlying rhythm	73 (34)	33 (27)	67 (27)	54 (24)
Premature contractions	5 (2)	1 (1)	4 (2)	4 (2)
Conduction disturbances*	9 (4)	14 (11)	39 (16)	46 (21)
Ischemic changes	21 (10)	25 (20)	20 (8)	25 (11)
Others	10 (5)	3 (2)	19 (8)	14 (6)

*** Dose-dependent increases in conduction disturbances**

Table 76: AF patients with structural heart disease with treatment-emergent ECG abnormalities-RAFT and ERAFT combined

		Propafenone SR		
Parameter	**Placebo N=215(%)**	**225mg bid N=124(%)**	**325mg bid N=244(%)**	**425mg bid N=222(%)**
Underlying rhythm	30 (35)	19 (35)	33 (30)	25 (23)
Premature contractions	3 (4)	0 (0)	2 (2)	2 (2)
Conduction disturbances	3 (4)	6 (11)	17 (16)	17 (16)
Ischemic changes	11 (13)	12 (22)	10 (9)	17 (16)
Others	6 (7)	1 (2)	11 (10)	8 (7)

Table 77: AF patients with abnormal ECG related adverse events and prolonged QT- RAFT and ERAFT combined

		Propafenone SR		
Parameter	**Placebo N=235(%)**	**225mg bid N=146(%)**	**325mg bid N=264(%)**	**425mg bid N=245(%)**
QT prolonged	2 (1)	0 (0)	2 (1)	0 (0)
Abnormal ECG	3 (1)	0 (0)	4 (2)	5 (2)

Source: Sponsor's table B2.3.3

ECG in Ventricular arrhythmia patients on propafenone therapy

Similar to the AF patients, there was a dose-dependent increase (>10%) in PQ and QRS across the SR treatment groups.

Table77b: 281 patients with ventricular arrhythmia enrolled by study-phase II

Days of exposure	Placebo	225mg bid	325mg bid	425mg bid
	N=51(%)	N=128(%)	N=121(%)	N=53(%)
Propafenone Phase II studies				
SRVPCCRD1	51(100)	46(35.9)	45(37.2)	45(84.9)
SRVPCCRD2	0(0.0)	4(3.1)	0(0.0)	8(15.1)
*SRVPCCR11	0(0.0)	78(60.9)	76(62.8)	0(0.0)

Table 78: VA patients with dose-dependent increase in ECG at end point - PQ/QRS

		Propafenone SR		
Parameter	**Placebo**	**225mg bid**	**325mg bid**	**425mg bid**
PQ (N)	48(100)	124(100)	115(100)	50(100)
Increase of >10%	12 (25)	47 (38)	50(43)	37 (74)
QRS (N)	49 (100)	126 (100)	121(100)	52 (100)
Increase of >10%	19 (39)	50 (40)	53 (44)	35 (67)

Vital signs

In addition to ECG and heart rate, other cardiovascular safety parameters evaluated included systolic and diastolic blood pressure in patients with atrial fibrillation and healthy volunteers. For diastolic blood pressure, systolic blood pressure endpoint values and changes from baseline were identified using sponsor-defined criteria for clinical importance (Table 79). There were no significant changes in vital signs (SBP, DBP and HR) of clinical importance in healthy volunteers, AF patients with and without SHD, and VA patients exposed to propafenone SR (Tables 80-82). The criteria for the interpretation of the data are strictly those of the sponsor and were not prespecified and agreed upon with the division. The conclusions from these data are therefore not universally acceptable. For example tachycardia is defined as > 120 bpm and bradycardia as < 50 bpm (Table 79).

Table 79: Criteria used for interpretation of vital signs of clinical importance-RAFT

Variable	Criterion value	Change relative to baseline
Systolic Blood Pressure mmHg	>180	Increase of >20
	<90	Decrease of >20
Diastolic Blood Pressure mmHg	>105	Increase of >15
	<50	Decrease of >15
Heart rate bpm	>120	Increase of >15
	<50	Decrease of >15

Table 80: No and % of AF patients with vital sign endpoint results-RAFT

	Propafenone			Placebo
Treatment group	**225mg bid**	**325mg bid**	**425mg bid**	
	N(%)	N(%)	N(%)	N(%)
	18	128	109	106
Systolic BP (mmHg)				
<90mmHg	0	0	0	0
>180mmHg	0	2	0	0
Decrease of >20	1	24	15	19
Increase of > 20	4	14	11	10
<90mmHg and decrease >20	0	0	0	0
>180mmHg and increase of >20	0	2	0	0
Diastolic BP(mmHg)				
<50mmHg	0	0	0	1
>105mmHg	0	1	1	0
Decrease of >15	2	11	4	6
Increase of > 15	2	7	5	5
<50mmHg and decrease >15	0	0	0	1
>105mmHg and increase of >15	0	0	0	0
Pulse Rate N	18	18	20	14
<50	0	0	0	0
>120	1	0	1	1
Decrease of >15	5	3	2	1
Increase of > 15	3	1	2	1
<50mmHg and decrease >15	0	0	0	0
>120 and increase of >20	1	0	1	1
The above data are pooled from several studies including ERAFT. Source Table 82.5.6				

Table 81: Summary statistics vital signs for baseline and endpoint-ERAFT

	Mean ± SD			
Treatment group	**N**	**Baseline**	**Endpoint**	**Change from Baseline**
Systolic BP (mmHg)				
Propafenone 325mg SR	111	134.8±18.9	130.4±15.6	-4.5±18.4
Propafenone 425mg	89	131.6±14.2	131.4±14.5	-0.3±14.0
Placebo	93	133.0±15.0	131.1±13.6	-2.0±14.9
Diastolic BP (mmHg)				
Propafenone 325mg SR	111	81.5±9.1	80.2±9.3	-1.3±9.0
Propafenone 425mg	98	80.9±8.3	81.8±8.2	1.0±8.8
Placebo	93	81.5±7.9	81.9±8.1	0.5±8.6

Source Sponsor's Tables 9.3.5.11 and 9.3.5.1.2

Table 82: Number and percentage of VA patients with vital sign endpoint results of potential clinical importance

	Propafenone			Placebo
Vital sign/ Criteria	**225mg bid n(%)**	**325mg bid n(%)**	**425mg bid n(%)**	**n(%)**
Blood Pressure N	**126**	**121**	**52**	**49**
Systolic Blood Pressure				
<90 mmHg	0	0	0	0
>180 mmHg	0	1	0	1
Decrease of >20	16	14	5	13
Increase of >20	18	18	6	4
<90 and decrease of >20	0	0	0	0
>180 and increase of >20	0	1	0	1
Diastolic Blood Pressure				
<50 mmHg	0	0	0	0
>105 mmHg	1	0	1	0
Decrease of >15	11	14	6	9
Increase of >15	9	9	6	2
<90 and decrease of >15	0	0	0	0
>180 and increase of >15	1	0	1	0
Pulse rate(bpm)				
<50	1	2	0	0
>120	0	0	0	0
Decrease of >15	5	2	0	0
Increase of >15	2	3	0	0
<90 and decrease of >15	0	0	0	0
>180 and increase of >15	0	0	0	0

Pooled data

The clock time of symptomatic TTM calls from Dai in the RAFT study is presented in Table 83. There is no significant difference between the number of events in the three groups receiving propafenone. There were however more events in the placebo group as expected compared to the treated groups.

Table 83: Clock Time of symptomatic TTM from Day 1 -RAFT

Number of events	RYTHMOL SR 225 mg BID (N = 126) n (%)	RYTHMOL SR 325 mg BID (N = 135) n (%)	RYTHMOL SR 425 mg BID (N = 136) n (%)	Placebo (N = 126) n (%)
No and % total of events	66(100)	56(100)	41(100)	87(100)
Number of events in 4 hour clock intervals				
08: to 12:00	14(21.2)	13(23.2)	11(26.8)	19(21.8)
12:01 to 16:00	7(10.6)	9(16.2)	2(4.9)	19(21.8)
16:01 to 20:00	15(22.7)	8(14.3)	8(19.5)	9(10.3)
20:01to 24:00	8(12.1)	5(8.9)	8(19.5)	15(17.2)
00:00 to 04:00	12(18.2)	7(12.5)	6(14.6)	14(16.1)
04:01 to 08:00	10(15.2)	14(25.0)	6(14.6)	11(12.6)
Source: Protocol P- 85 - AF, Table 9.2.15				

4.4 Laboratory safety-RAFT

In addition to hypokalemia being the most frequently reported abnormality, other laboratory abnormalities observed included shifts in sodium levels from normal or high to low at endpoints. None of these abnormalities accounted for discontinuation and none resulted in death.

5.0 Clinical Review of ERAFT

Protocol No - *PROPA SR 008/Report Number MPR/CC 2021 [ERAFT]*

Title: A multinational, multicentre, prospective, randomized, double-blind, placebo-controlled, parallel arm study to assess the efficacy and safety of propafenone slow release 325mg bid and 425 mg bid versus placebo in the prophylaxis of symptomatic paroxysmal atrial fibrillation [ERAFT]

This study was a double-blind, placebo-controlled, multinational, multicenter, parallel group, randomized study to evaluate the 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.

Objective

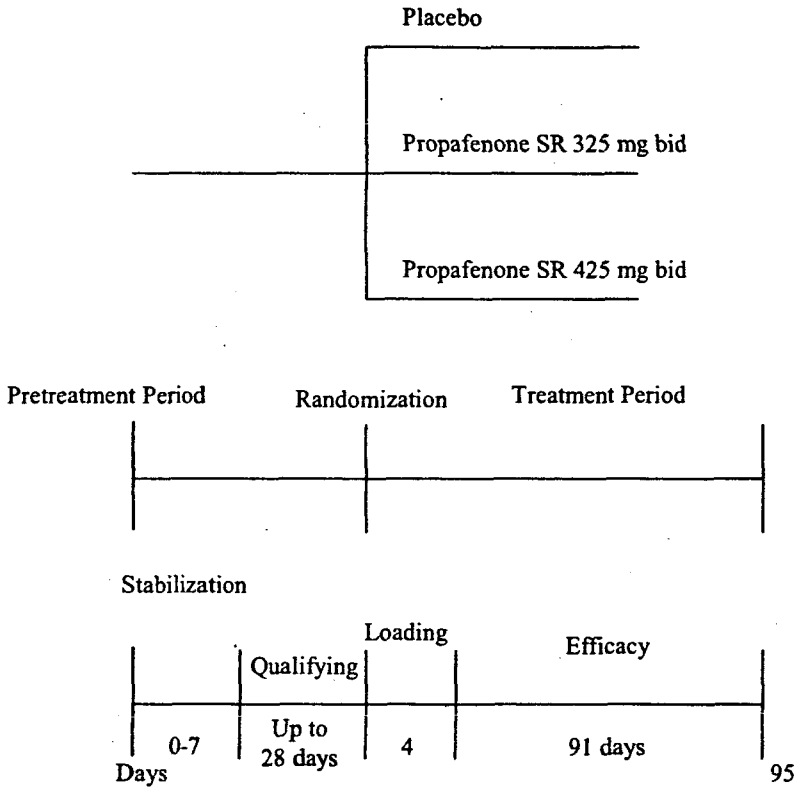
The objective of the ERAFT trial was to show that the prolonged-release formulation of propafenone (325 mg bid and 425 mg bid) administered to eligible patients was superior to placebo in preventing symptomatic paroxysmal atrial fibrillation (PAF). The word "symptomatic" was defined as "subjective awareness 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". Chronic atrial fibrillation, referred to as "permanent atrial fibrillation" (PAF) was not investigated in this study.

Study Centers
Sixty centers participated in the study from the following ten countries: Canada (7); Great Britain (6); Estonia (4); Germany (7); Israel (11); Italy (7); Latvia (3); Lithuania (4); Poland (9); and South Africa (2).

Study dates
28 July 1998 and December 9 1999

Study design ERAFT
See Figure 13 below

Figure 13: Study Design for ERAFT study



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 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.

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.

Removal of patients from therapy or assessment in ERAFT

At any time during the study, patients were free to withdraw without providing a reason or could have been withdrawn at the discretion of the investigator or sponsor.

Additional reasons for withdrawal were as follows:

Adverse events (including intercurrent illnesses), which precluded continuation of the study medication.

Documentation at 1 of the visits of asymptomatic atrial fibrillation of more than 24 hours duration.

The occurrence of documented symptomatic atrial fibrillation, during the qualifying or loading period, which was not terminated (either spontaneously or by DC conversion) within 24 hours of occurring.

The occurrence of a new ventricular or supraventricular arrhythmia (e.g., clinically relevant frequent or complex premature ventricular contractions (PVCs), non- sustained or sustained ventricular tachycardia, ventricular fibrillation, bradycardia of 140 bpm, or

supraventricular or atrioventricular nodal tachycardias) during the treatment period. However, patients with sinus tachycardia, atrial bigemini and single PVCs were not required to withdraw from the study.
Administration of any drug whose use was prohibited by the protocol.
Suspected or confirmed pregnancy.
Unwillingness or inability to use the CardioCall event recorder.
Each patient withdrawn was to undergo a final examination at the time of withdrawal.
The reason for withdrawal was to be documented in the patients' medical records.
Withdrawn patients were not replaced.

Table 84 :Schedule of procedure-ERAFT

	Pretreatment Period				**Treatment Period**			
	Stabilizing Period Up to 7 days		**Qualifying Period Up to 28 days**		**Loading Period 4 days**	**Efficacy Period Up to 91 days**		
	Visit	**0**	**1**	**2 Randomized**	**3**	**4**	**5**	**6 F**
Examination	Day	-35	-28	1	5/6	21	56	96
Complete Physical Examination		X	X					X
Interim Physical Examination			X	X	X	X	X	
Informed Consent		X	X					
Event recording			X	X	X	X	X	X
12 lead ECG		X	X	X	X	X	X	X
Laboratory Evaluation		X	X	X				X
Search for Adverse Reaction			X	X	X	X	X	X
Study Drug Dispensing			X	X	X	X	X	X
Compliance Check				X	X	X	X	X

Secondary efficacy analyses – ERAFT

- 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
- Time (in days) To Treatment Failure from Day 1
- Time to patient-initiated report of symptoms from Day 1
- Hazard Ratios for differences between treatment groups

Eligibility

Inclusion Criteria

- Male or females above 18 years old
- Documented ECG evidence of symptomatic PAF
- Propafenone use was not contraindicated
- Sinus rhythm at the time the patient entered the qualifying period at visit 1

Exclusion criteria

- Patients with contraindications for propafenone use.
- Chronic treatment with propafenone for Afib within the last 5 years.
- Chronic permanent Atrial fibrillation.
- Secondary Atrial fibrillation.
- Class III or IV angina pectoris.
- Acute MI unstable angina and cardiac surgery within the past 12 months.
- W-P-W syndrome.
- Concomitant medication with other anti-arrhythmic drugs including sotalol.
- Amiodarone use.
- Neurologic deficits.
- Chronic renal failure .
- Clinically significant hepatic failure.
- Chronic alcoholic or drug abuse.
- Legal incapacity.

Table 85: Drug Supply - ERAFT

Parameter	Batch Number
Placebo	780102P0;980202P0
325mg	780200A0; 980312A0
425mg	780102A0;980212A0

Dose selection - ERAFT

The doses were selected based upon AUC versus time curves and the equivalent dosage strengths (IR to SR).
150mg propafenone IR t.i.d =325mg propafenone SR b.i.d
225mg propafenone IR t.i.d =425mg propafenone SR b.i.d

Concomitant medication

Concomitant administration with antiarrhythmic drugs including sotalol was not permitted during the study. Before entry to the study all patients who had received such drugs had a washout period of at least 5 times the half-life of the previous treatment (up to a maximum of 5 days). Amiodarone was an exception from the temporal standpoint, when given parenterally for the acute conversion of atrial fibrillation. Drugs that slow AV nodal conduction (β-blockers, digoxin, and calcium antagonists such as diltiazem or verapamil) could be prescribed if considered appropriate by the investigator. The dosage of these drugs remained unchanged throughout the duration of the study if chronically prescribed. All patients with AF were considered to be at risk of thromboembolism for which concomitant warfarin or aspirin was considered appropriate (Table 86). One patient in the RAFT study died of pulmonary embolism but this was after drug had been stopped.

Table 86: Concomitant medication-ERAFT

Concomitant medication	Placebo N=93(%)	Propafenone SR 325mg b.i.d(N=111)	425 mg b.i.d (N=89)
Vitamin K antagonists	3(3.2)	4(3.5)	1(1.1)
Heparin group	1(1.1)	2(1.8)	3(3.4)
Anti-arrhythmics class I and II	5(5.4)	4(3.6)	2(2.2)
Anti-arrhythmics class IA	9(9.7)	7(6.3)	3(3.4)
Organic Nitrates	1(1.1)	4(3.6)	2(2.2)
Dihydropyridine derivatives	1(1.1)	4(3.6)	0(0.0)
Phenylalkyl derivatives	5(5.4)	3(2.7)	1(1.1)

Study schedule for ERAFT is in Table 87.

Table 87: Schedule of procedure - ERAFT

Procedure/Evaluation	<7days	up to 28 days		Loading 4 days	Efficacy period up to 91 days		
Visit	0	1	2R	3	4	5	6F
Day	-35	-28	1	5/6	21	56	96
Complete Physical Examination	X	X					X
Interim Physical Examination		X	X	X	X	X	
Informed Consent	X	X					
Event recording		X	X	X	X	X	X
12 lead ECG	X	X	X	X	X	X	X
Laboratory Evaluation	X	X	X				X
Blood Samples for propafenone			X	X			X
Search for Adverse Reaction		X	X	X	X	X	X
Study Drug Dispensing			X		X		X
Compliance Check		X	X	X	X	X	

Compliance

The investigator assessed the compliance of the patient by counting the number of returned capsules and documented in the CRF. It was found that compliance was satisfactory in accordance with the protocol (>80% and <120%).

There was no difference between the treatment groups for the calculated values of compliance or the investigator assessment of compliance at each visit. There was no difference between treatment groups in the proportions of patients assessed as compliant with use of the event recorder by the investigator.

Statistics
All statistical analyses were performed using the SAS release 6.12 under the Microsoft Windows NT operating system. Data validation was finished before unblinding the randomization code and before the start of the statistical analyses.

Disposition of Patients
A total of 594 patients were screened for the study. A total of 237 (79%) had no qualifying event and were therefore terminated. A total of 301 patients were screened but not randomized for a variety of reasons including protocol violation (8.3%), withdrawal of consent (6.7%) and adverse events (1.3%). A total of 293 patients were randomized in 53 centers.
The numbers of patients completing each assessment is given in Table 88 below.

Table 88: Number of patients completing each assessment - ERAFT

	Placebo N=93	Propafenone SR 325mg bid(N=111) 425 mg bid (N=89)	
Visit	N(%)	N(%)	N(%)
Baseline	93	111	89
End of loading period	92	109	89
Day 21	68	93	69
Day56	22	54	37
Day95	9	34	28

The disposition of the patients is in Tab le 89 below.
Table 89: Summary of patient disposition based on termination case report forms (full analysis dataset) - ERAFT

	Placebo N=93	Propafenone SR 325mg b.i.d(N=111) 425 mg b.i.d (N=89)	
Disposition	N(%)	N(%)	N(%)
No of patients Completed all visits	7(8)	26(23)	24(27)
Investigator assessment: reached endpoint prior to Day 96	73(78)	69(62)	49(55)

5.1 Discontinuations – ERAFT
The discontinuation of patients is presented in Table 90 below.
Table 90: Discontinuations - ERAFT

	Placebo N=93	Propafenone SR 325mg bid (N=111) 425 mg bid (N=89)	
Disposition	N(%)	N(%)	N(%)
No of patients discontinued prematurely			
Adverse events	5(5)	6(5)	13(15)
Protocol violation	7(8)	5(5)	2(2)
Withdrawal of consent	1(1)	4(4)	2(2)
Lost to follow-up	0(0)	1(1)	0(0)

5.2 Demographics – ERAFT
The demographics are presented below. There are no differences between the treatment groups.

Table 91: Demographics - ERAFT

	Placebo	325mgbid	425mgbid	p-value
Number of patients	**93**	**111**	**89**	
Gender				
Male	59(63.4)	71(64.0)	49(55.1)	0.38
Female	34(36.6)	40(36.0)	40(44.9)	
Race				
Caucasian	93(100)	111(100)	89(100)	
Black	0	0	0	
Oriental	0	0	0	
Others	0	0	0	
Age(Mean)	60.9±10.3	60.6±10.5	60.6±10.4	0.96
Range	32-84	20-80	31-78	
18-29	0	1(0.9)	0	
30-49	16(17.2)	11(9.9)	12(13.5)	
50-64	43(46.2)	57(51.4)	37(41.6)	
65-74	26(28.0)	34(30.6)	33(37.1)	
>75	8(8.6)	8(7.2)	7(7.9)	
<65	59(63.4)	69(62.2)	49(55.1)	
>65	34(36.6)	42(37.8)	40(44.9)	
Weight(kg)				
Mean SD	80.5±13.2	80.8±15.0	82.8±15.6	0.26
Range	50.0-119.0	51.0-125.0	51.0-125.5	

Source: Sponsors Table 9.1.1

Phase III study, ERAFT, was also reviewed. The similarities and differences between the RAFT and ERAFT are summarized in Table 100 below.

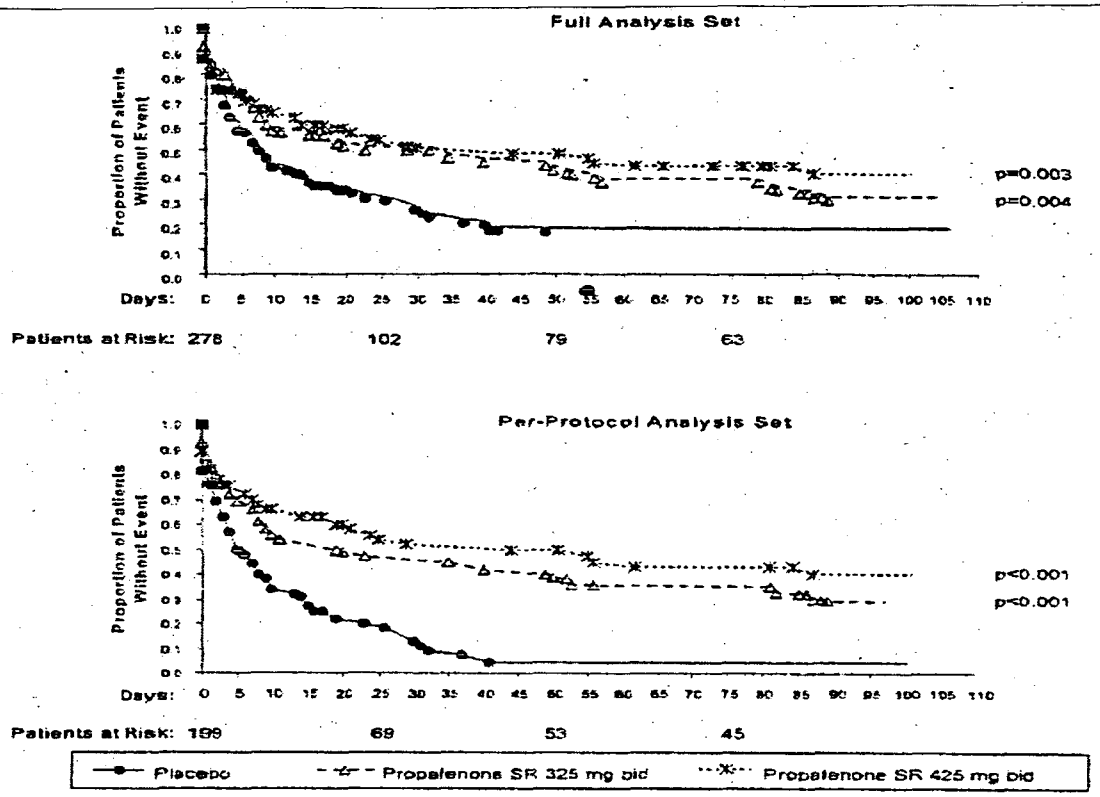
Results

5.3 Primary Efficacy analysis-ERAFT

The primary efficacy analysis 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 values = 0.004 and 0.003 for 325mg b.i.d., and 425mg b.i.d, respectively, using the log rank test; Table 42). There was statistically significant difference when all patients on propafenone was compared to placebo (Hazard ratio 0.58 [95%CI 0.42,0.80;] p=0.001).
A significant increase in survival time was observed for both propafenone treatment groups compared to placebo (Figure 3) or See below on page102 for duplicate figure).

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

The Kaplan- Meier survival curves for the full analysis and per protocol analysis datasets are illustrated in Figure below for ERAFT



5.4 Secondary Efficacy variables -ERAFT

There was also a statistically significant difference in the tachycardia-free period to the first recurrence of symptomatic atrial fibrillation from day 1 of randomization (secondary efficacy variable). Subgroup analyses for age, gender, NYHA classification, history of cardioversion, medications that lower heart rate, duration and frequency of atrial fibrillation could not be carried out because of small numbers.

Using the Kaplan Meier curves and proportional hazard ratio analyses, a dose response to the drug from day 1 was established (Table 93).

Table 92: Tachycardia-free period (days)-Day 5 of randomization - ERAFT

	Placebo	325mg bid	425mg bid
	N=124(%)	N=132(%)	N=131(%)
Patients completing with terminating event*	65(73.9)	66(61.7)	41(49.4)
Comparison of tachycardia- free period Kaplan-Meier Median Range (days)	9.0 0.0 - 106	35.0 0.0 - 105	44.0 0.0 - 101
P-value	-		
Log rank	-	0.004	0.003
Wilcoxon	-	0.007	0.020
Hazard ratio	-	0.60	0.55
95% CI for HR	-	(0.43,0.86)	(0.36,0.82)

***Patients had a terminating event if they had symptomatic atrial fibrillation. Atrial flutter or PSVT.**

Table 93: Showing tachycardia-free period from day 1 -ERAFT

	Placebo	325mg bid	425mg bid
	N=93(%)	N=111(%)	N=89(%)
Patients completing with terminating event*	70(75.3)	71(64.0)	51(57.3)
Comparison of tachycardia- free period Kaplan-Meier Median Range (days)	9.0 0.0-110.0	23.0 0.0-109.0	28.0 0.0-105.0
P-value			
Log rank	-	0.003	0.030
Wilcoxon	-	0.006	0.161
Hazard ratio	-	0.61	0.66
95% CI for HR	-	(0.43,0.85)	(0.45,0.96)

***Patients had a terminating event if they had symptomatic atrial fibrillation. Atrial flutter or PSVT.**

Table 94: Time (days) from day 1 to patient-initiated report of arrhythmia symptoms - ERAFT

Parameter	Placebo N=85	325mg bid N=107	425mg bid N=83
Patients completing with symptoms*	80(90.5)	90(84.1)	66(79.5)
Comparison of symptom -free period Kaplan-Meier Median Range (days)	4.0 0.0-106	5.0 0.0-105.0	5.0 0.0-98.0
P-value	-		
Log rank	-	NA	0.126
Wilcoxon	-	NA	0.535
Hazard ratio	-	0.72	0.77
95% CI for HR		(0.53,0.97)	(0.55,1.08)

Table 95: Treatment (days) failure time from Day 5 of randomization –ERAFT

Parameter	Placebo N=88	325mg b.i.d N=107	425mg b.i.d N=83
Patients with treatment failure*	74(84.1)	77(72.0)	52(62.7)
Comparison of treatment failure periods Kaplan-Meier Median Range (days)	8.0 0.0-1056	19.0 0.0-105	24.0 0.0-101
P-value Log rank Wilcoxon Hazard ratio 95% CI for HR	- - - -	0.002 0.006 0.61 (0.44,0.84)	0.006 0.052 0.60 (0.41,0.86)

Secondary efficacy variable - Heart rate

There is a statistically significant reduction in average heart rate during the first recurrence of symptomatic arrhythmia after Day 5 in the 325mg bid propafenone group compared to placebo whereas there was no reduction in the 425mg bid dose group (Table 96). This could possibly be due to the effect of concomitant medication although this was not established. Similar results were obtained for heart rates after Day 1 (Table 97) and for those receiving medications which slow ventricular response.

Table 96: Comparison of average heart rate of patients during the first recurrence of symptomatic Atrial fibrillation after Day 5 - ERAFT

	Placebo	325mg b.i.d	425mg b.i.d	p-value[a]
Average heart rate	**N=64**	**N=62**	**N=41**	
Mean±SD	114.7±26.1	106.4±25.8	108.4±27.3	0.030
Range	59-182	55-173	70-179	
p-value[c]	-	**0.016**	0.47	-
Least squares mean[b]	115.8±2.7	105.7±2.8	111.2±3.4	
Diff. from placebo		-10.1	-4.6	
95%CI		-18.6,-1.6	-14.2,5.0	

[a]p-value based on ANOVA among the 2 treatment groups. [b]LS means adjusted for qualifying event according to AEC were excluded from this analysis. [c]P value based on Dunnett's test procedure for comparison of propafenone SR versus placebo.

Table 97: Average heart rate of patients during the first recurrence of symptomatic Atrial fibrillation after day 5 whether receiving medications that slow ventricular response – ITT- ERAFT

	Placebo	325mg b.i.d	425mg b.i.d
Avg. heart rate	**N=41**	**N=37**	**N=27**
Yes to medication			
Mean±SEM	113.0±3.4	104.0±4.4	108.4±4.4
No to medication			
	N=23	**N=25**	**N=14**
Mean±SEM	120.6±4.5	108.1±4.4	115.8±5.8

The patients were not evenly distributed across propafenone treatment groups with respect to body weight so there was dose adjusted body weights into low and high (Tables 98,99).

Table 98: Body-weight adjusted dose – ITT - ERAFT

Dose (mg/kg)		325mg bid	425mg bid
	N (Range)	N=110(%)	N=89(%)
Low	100 2.60 –4.58	81 (73.6)	19 (21.3)
High	99 4.62-8.33	29 (26.4)	76 (78.7)

Table 99: Tachycardia-free period (days) from Day 5 of randomization by wt adjusted dose - ERAFT

	Low N=97	High N=92	Placebo N=88
Range (mg/kg)	2.60-4.58	4.62-7.20	NA
Patients completing with terminating events	6573.9	6364.9	4346.7
Comparison of tachycardia -free periods Kaplan-Meier Median Range (days)	 262 0.0-281	 287 0.0-287.0	 39.0 0.0-285.0
P-value Log rank Wilcoxon Hazard ratio 95% CI for HR	 <0.0001 0.001 0.543 0.39,0.76	 <0.0001 <0.0001 0.309 0.21,0.46	 - - - -

Integrated review of efficacy versus review of efficacy in RAFT

Although there is some evidence to support efficacy of this drug for the indication proposed, this reviewer does not think an integrated review of efficacy is appropriate because there are several differences between the RAFT and ERAFT studies including baseline data and study design. Some of these differences are presented in Table 69 below. The RAFT efficacy database is therefore reviewed separately from ERAFT.

Table 100: Demographics and baseline data of RAFT and ERAFT

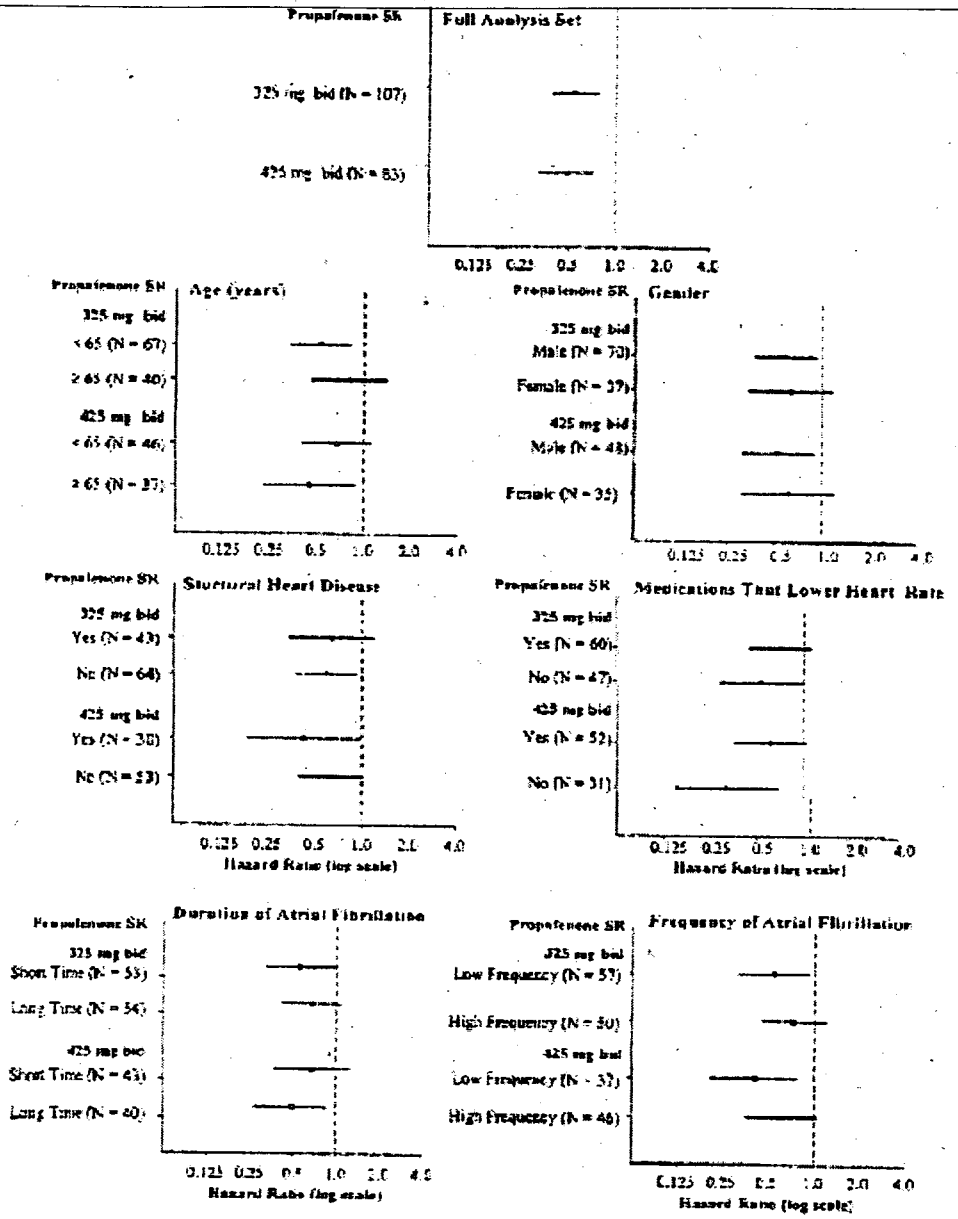
	RAFT				ERAFT		
Patients		Propafenone Total N=523			Propafenone Total N=293		
	Plcbo	225mg	325 mg	425mg	325mg	425mg	Plcbo
N (%)	N=126(%)	N=126(%)	N=135(%)	N=136(%)	111(%)	89(%)	93(%)
Gender							
Male	75(59.5)	76(60.3)	80(59.3)	78(57.4)	71(64.0)	49(55.1)	59(63.4)
Female	51(40.7)	80(39.7)	55(40.7)	58(42.5)	40(36.0)	40(44.9)	34(36.6)

	RAFT				ERAFT		
History of AF median	17months	12 months	15 months	12 months	3.3yrs	3.3yrs	3.7yrs
Frequency of AF							
0	2	1	1	3	-	-	-
1-3	54	51	55	52	21	18	14
4-10	15	25	21	19	38	21	30
11-20	15	6	10	10	23	15	17
>20	14	18	13	15	29	35	32
NYHA class							
I	96.8	92.9	92.6	92.6	-	-	-
II	3.2	7.1	7.4	7.4	-	-	-
SHD	**57(45.2)**	**56(44.4)**	**63(46.7)**	**75(55.1)**	**(42.3)**	**(36.0)**	**(32.3)**
Rate** limiting medication baseline	67.5	66.7	70.4	68.4	55.9	62.9	64.5
History of cardioversion (%)	17.5	23.0	22.8	22.2	-	-	-
*Anti-arrhythmic drugs %	26.2	15.6	22.2	16.9	35.1	32.6	38.7
Race					C	C	C
Caucasian	116(92.1)	113(89.7)	125(92.6	122(89.7)	111(100)	89(100)	93(100)
Black	6(4.8)	8(6.3)	5(3.7)	11(8.1)	0(0.0)	0(0.0)	0(0.0)
Oriental	0(0.0)	2(1.6)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Others	4(3.2)	3(2.4)	4(3.0)	3(2.2)	0(0.0)	0(0.0)	0(0.0)
<65	59(46.8)	65(51.6)	66(48.9)	61(44.9)	69(62.2)	49(55.1)	59(63.4)
>65	67(53.2)	61(48.4)	69(51.1)	75(55.1)	42(37.8)	40(44.9)	34(36.6)
Wt. (kg)							
Mean ± SD	84.6±17.2	85.5±19.1	85.3±19.1	86.1±19.3	80.8±15.0	82.8±15.6	80.5±13.2
Range	51.8 – 131.2	49.5-148.2	51.3-141.2	45.4-156.2	51.0-125.0	51.0-125.5	50.0-119.0

*** Anti-arrhythmics within 6 months before screening; ** rate limiting medication at baseline that was continued during the study. SHD= Structural Heart Disease; SD= Standard Deviation.C=Caucasian.**

Safety review of ERAFT has been integrated with RAFT. Also see Section 5.51 to 5.54 for safety results in Phase II studies.
Efficacy conclusions for ERAFT are in the Executive summary.

Figure 14:Subgroup analysis ERAFT



5.50 Other Clinical Phase II studies

5.51 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)

Objective

To compare the prophylactic anti-arrhythmic efficacy and tolerability of three different dosages (225mg bid, 325mg bid and 425mg bid) of SR in patients with symptomatic PAF versus placebo and versus each other.

Study design

Multicenter, multinational double blind randomized placebo controlled parallel group study with placebo treated for 5 – 10 days. Patients who had received anti-arrhythmics or beta-blockers had a wash out period of 5 times the half-life of the previous treatment (up to a maximum of 5 days). All patients underwent a one-day placebo run-in period before the blinded therapy period. M-Mode echo was performed during wash out/run in period. Vital signs were obtained (BP, HR, ECG, 24 hr Holter monitoring, transesophageal programmed atrial electrostimulation (PAES) and blood sampling for propafenone plasma levels during the one day run in and at the end of treatment period. Blood samples were taken for hematology and blood chemistry. All patients took anticoagulant therapy throughout the study. Compliance was monitored and recorded.

Two hundred patients were planned for the study. Only 122 patients were screened. Of these, 74 were randomized to 225mg bid (20) 325mg bid (18) 425mg bid (20) and placebo (16). Age of the patients was 18-75; males and females who must have had a history of at least 2 episodes of treated or untreated symptomatic PAF during the previous year. The duration of each symptomatic episode of Afib must have been >1 hour. Inducibility of the atrial fibrillation was to be > 1 minute at the baseline PAES.

Efficacy

Efficacy was measured as responder rate if

- Transesophageal PAES only triggered any atrial fibrillation;
- The second transesophageal PAES only triggered atrial fibrillation at a higher (more aggressive stimulation) level than the first transesophageal PAES;
- The second transesophageal PAES triggered atrial fibrillation at the same level as the first transesophageal PAES;
- The duration of the atrial fibrillation was at least 50% shorter than after the first stimulation;
- Change in duration of atrial fibrillation;
- Tolerability of the arrhythmia in patients with inducible atrial fibrillation at the second PAES and sinus rhythm information (sinus cycle length, PQ and P wave width).

Adverse events

- Laboratory investigations
- Blood pressure and pulse rate
- Resting ECG and
- Physical examination

Statistics

Descriptive

Results- Efficacy

The only significant difference between the groups compared to placebo was the change from baseline in the PAES PQ width (See Table below).

Table showing responder rates – Efficacy CD 99018

	Treatment with Propafenone SR			
	225mg bid	**325mg bid**	**425 mg bid**	**Placebo**
Median change from base in duration of Afib (min)	-2.7	-1.1	-26.3	-16.9
Median change from base in duration of sinus cycle (ms)	50.5	0.0	10.5	0.0
Median change from base in duration of PAES PQ width (ms)	25.0	20.0	25	0.0
Number of responders	13/20	9/18	14/19	10/14

Safety

Of the 74 patients randomized 69 (93%) completed the study. Fifteen patients (20%) reported 19 adverse events starting after the first dose. Two were in the placebo group and the remaining 13 in the propafenone group (6,3,4in 225, 325 and 425 mg groups, respectively). No adverse event was reported by more than 2 patients. The possibly related adverse events were a-v block in a patient (325mg bid) and taste disturbance in another patient (425mg bid). There were no deaths or serious adverse events or withdrawals due to adverse events.

Laboratory

There were no laboratory abnormalities of clinical significance.

Vital Signs

The mean change in PQ interval from pre-treatment to endpoint was –5.7ms in placebo compared to 9.4ms, 20.6ms and 22.1 ms in the 225 mg bid 325 mg bid and 425 mg bid respectively. Three patients had prolonged QTc intervals recorded at the end of the treatment period.

Conclusion

This is a small study. It is of short duration. No clinically significant differences were seen for change in duration of inducible atrial fibrillation, sinus cycle length and number of responders. The increased PQ interval in PAES of treated patients confirms the known pharmacologic action of propafenone. The adverse events of Atrio-ventricular block and taste disturbance are consistent with what we have observed in the larger studies.

5.52 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)

Objective

To compare the long-term prophylactic anti-arrhythmic efficacy and tolerability of 3 different dosages 225mg bid, 325mg bid, 425 mg bid SR versus placebo in patients with symptomatic PAF. This was a follow up study of the study above CD 99018 reviewed above (Section 5.51).

Study design

The patients were provided with enough medication and [redacted] Monitor for self-recording of ECGs. In the absence of symptoms the patients were examined after

completing 1,2 4,6 months treatment. At each visit, patients were given study medication. If the patient had symptoms at any other time, they were to document this and return to the investigator. If PAF was detected in any of the recordings the patient was withdrawn from the study and had a final examination. In the absence of any PAF, the study was stopped at 6 months. All patients took anticoagulant therapy. Compliance was monitored.
Forty eight patients entered the long term extension study (11, 13, 14, and 10 patients in the 225mg bid, 325mg bid, 425mg bid and placebo groups respectively.

Efficacy
Efficacy was measured as
Time to recording paroxysmal atrial fibrillation (PAF)

Safety
- Adverse events
- Laboratory investigations
- Vital signs
- Resting ECG and
- Physical examination

Results
There were no differences between the propafenone SR treatment groups and placebo.

Safety results
Sixteen patients (33%) reported 28 adverse events (3,4,6,and 3 in the placebo 225 325 425 mg bid groups respectively. There were no deaths. There was one patient with asthenia in the placebo otherwise there was nothing of significance between the treated groups and placebo.
There were no laboratory abnormalities. The vital signs were normal. There were dose-related increases in the PQ interval from pretreatment values to the end of study. The mean changes in PQ from pretreatment to month 6 are as follows: 0.0 ms for placebo; +2 ms, +17.8 ms and +23.8ms for 225, 325 and 425 mg bid. There was also a mean change of +4ms in QRS complex in the placebo group compared to +6, +5 and +16.3 ms for the 225mg bid, 325mg bid, and 425 mg bid group, respectively. This is consistent with a dose dependent increase in QRS interval. **Ten patients had prolonged QTc during the extension phase of this study.** A total of 24 /48 patients completed the study by not having any PAF for 6 months.

Conclusion
This is a small study that confirms most of the findings already observed in the bigger studies RAFT and ERAFT.

5.53 Phase II - Dose finding study of propafenone SR in symptomatic ventricular arrhythmia (VA) (Protocol SR VPC CR-D1/Report Number MPF/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)