CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER

21-416

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

MEDICAL DIVISION: Cardio-Renal Drug Products (HFD-110)

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DRUG NAME: Rythmol SR (propafenone HCl) Capsules

INDICATION:

SPONSOR: Abbott Laboratories

DOCUMENT REVIEWED:

1. Cover letter (CDER REC'D Dates: March 15 and May 8, 2002) including SAS data base
2. Cover letter (CDER REC'D Dates: July 1, 2, & 11 of 2002) including doc file for review's aids, SAS data sets, and SAS codes for the primary and secondary efficacy analyses

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3.1 Conclusion and Recommendations

The clinical study RAFT demonstrates that there are statistically significant differences in favor of all propafenone SR bid treatment groups (225 mg, 325 mg, and 425 mg) compared to placebo for tachycardia-free period (days) from Day 1 of randomization and tachycardia-free period (days) from Day 5 of randomization in Intent-to-Treat (ITT) population. There are statistically significant differences in favor of the propafenone SR 325 mg bid and 425 mg bid treatment groups compared to placebo for time (days) to patient-initiated report of arrhythmia-associated symptoms from Day 1 of randomization in ITT population (but it was not reported in the study ERAFT). When the dose of propafenone SR is adjusted for body weight, there is a statistically significant difference compared to placebo for the time (days) to first recurrence of symptomatic atrial arrhythmia from Day 5 of randomization for all weight-adjusted dose categories (low, medium, and high) in ITT population. The time to treatment failure analysis shows that the significant differences in favor of propafenone SR 325 mg bid and 425 mg bid treatment groups compared to placebo are robust regardless of how withdrawals are treated in analyses.

Though there is a statistically significant difference in favor of the propafenone SR 225 mg bid treatment compared to placebo for the primary endpoint and one of the secondary endpoints (tachycardia-free period from Day 5 of randomization), this demonstration is still questionable. The propafenone SR 225 mg bid treatment was included in only one study RAFT, not in another study ERAFT. The evidence of the demonstration may not be enough. The significance level of the demonstration for the primary endpoint is borderline ($p=0.014$) under the Bonferroni's adjustment ($\alpha=0.017$) and the difference between the propafenone SR 225 mg bid treatment and placebo is not statistically significant for the time to treatment failure analysis or for another secondary endpoint (the time (days) from Day 1 to patient-initiated report of arrhythmia symptoms).

Kaplan-Meier curves and proportional hazard analyses also support those statistical tests. The subgroup analyses results are comparable to the results for the overall primary efficacy analysis. The effects among treatment doses are hardly distinguishable.

3.2 Overview of the Clinical Program and Studies Reviewed

This clinical program is a research and development of new drug Rythmol SR (propafenone HCL) 225 mg, 325 mg, and 425 mg Capsules which is designed by the sponsor, Abbott Laboratories, to provide the treatment for the patients without structural heart disease and with a history of symptomatic atrial fibrillation. The developed drug Rythmol SR is indicated to prolong the time to recurrence of symptomatic atrial arrhythmia which is based on the results of Protocol P-85-AF (RAFT) and Protocol PROPA SR 008 (ERAFT).

Propafenone prolonged-release (SR) is designed to reduce the dosing frequency to twice daily administration. The twice-daily administration is expected to improve patient convenience and reduce the large fluctuation in propafenone plasma levels resulting from the currently marketed

tid dosage regimen. Oral bioavailability of propafenone from the SR formulation is less than that of the immediate-release (IR) formulation as the more gradual release of propafenone from the prolonged-release preparations results in an increase in overall first pass metabolism to 5-hydroxypropafenone. Consequently, higher doses of the SR formulation are needed to achieve plasma concentrations of propafenone relatively similar to those achieved with IR formulation.

This clinical program includes the results of two Phase III studies the US study RAFT and the Europe study ERAFT. The RAFT study serves as the basis for this NDA submission and for FDA approval. The results of the ERAFT study confirm the results of the RAFT study and provide additional supportive evidence of efficacy of propafenone SR (325 mg and 425 mg) administered bid. Both studies are conducted to substantiate the use of Rythmol SR

Of the 890 patients with AF enrolled, most are from the Phase III program, 523 patients from RAFT and 293 patients from ERAFT.

The first major statistical issue in this NDA submission is the statistical analysis method used for the primary efficacy analysis. The sponsor did not perform a robustness analysis. A robustness analysis is a major and important statistical analysis to verify the robustness of statistical results of the primary efficacy analysis to the treatment of the dropout patients. The statistical reviewer conducted a robustness analysis as the major statistical evaluation in efficacy analysis.

The second major statistical issue is the multiple comparison adjustment. There were multiple comparisons in the efficacy analyses where each dose of 225 mg, 325 mg and 425 mg propafenone SR bid would be compared with placebo. The sponsor did not define any adjustment procedure for the multiple comparisons. The sponsor included a statement in the footnotes of the efficacy output tables "statistical significance is based on a closed testing procedure". But the sponsor did not define any closed testing procedure in their protocol. If this closed testing procedure is a post hoc adjustment, the adjustment is problematic. Without any pre-defined multiple comparison adjustment, this statistical reviewer used Bonferroni's procedure for the adjustment.

Another statistical issue is baseline physical examination. Result of the baseline physical examination shows that a higher percentage of patients in the placebo group compared to the propafenone SR treatment groups had an abnormal cardiac heart exam. A subgroup analysis within the normal baseline cardiac heart exam patients is needed.

3.3 Principal Findings

There are statistically significant differences in favor of all propafenone SR bid treatment groups (225 mg, 325 mg, and 425 mg) compared to placebo in ITT population for: (1) time (days) to the first recurrence of symptomatic atrial arrhythmia from Day 1 of randomization (primary efficacy variable); (2) time (days) to the first recurrence of symptomatic atrial arrhythmia from Day 5 of randomization (secondary efficacy variable).

There are statistically significant differences in favor of the propafenone SR 325 mg bid and 425 mg bid treatment groups compared to placebo in ITT population for: (1) time to patient-initiated report of arrhymia-associated symptoms from Day 1 of randomization; (2) time (days) to treatment failure from Day 1 of randomization for analyses of terminating events with any other reason for withdrawal. When the dose of propafenone SR is adjusted for body weight, there is a statistically significant difference compared to placebo for the time (days) to first recurrence of symptomatic atrial arrhythmia from Day 5 of randomization for all weight-adjusted dose categories (low, medium, and high) in ITT population.

Kaplan-Meier curves and proportional hazard analyses also support the above statistical findings for a dose-response to propafenone SR. The results of subgroup analyses for age, gender, race, structural heart disease, NYHA classification, history of cardioversion, medications that lower heart rate, duration of atrial fibrillation, and frequency of atrial fibrillation are comparable to the results for the overall primary efficacy analysis.

4. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

4.1 Introduction and Background

Propafenone is classified as a 1C antiarrhythmic agent with local anesthetic effects and a direct stabilizing action on myocardial membranes. Propafenone has fast sodium channel blocking activity and, consequently, lowers conduction. Unlike other class 1C drugs, propafenone has some effect on refractoriness, and exerts weak β-blocking activity and a slight calcium channel blocking effect. Since its introduction in 1977 as an immediate-release (IR) tablet, propafenone has been marketed in over 80 countries.

The sponsor has conducted 12 clinical studies including 5 Phase I studies, 5 Phase II studies and 2 Phases III studies. This NDA submission includes the results for studies conducted to substantiate the use of Rythmol SR

The sponsor has conducted 2 Phase III studies the US study RAFT and the Europe study ERAFT. RAFT study serves as the basis for this NDA submission and for FDA approval. The results of the ERAFT study confirm the results of the RAFT study and provide additional supportive evidence of efficacy of propafenone SR (325 mg and 425 mg) administered bid.

Most efficacy results reported in this submission have been verified by this reviewer's analyses and are noted in each table. Both the results of the sponsor's and the reviewer's analyses will be presented in the following sections. If the result is the reviewer's analysis only, it will be indicated in the footnote. The sponsor defined the full analysis data set as all randomized patients who are exposed to at least one dose of study medication. It is same as the ITT population in this report and is included in the efficacy analyses.

4.2 Data Analyzed and Sources

The data sets analyzed are submitted by the sponsor on March 15, 2002. The major analyses data sets are submitted by the sponsor on July 2, 2002. All data sets analyzed are electronic documents and are located in the Electronic Document Room (EDR) of CDER of FDA under the Letter Date "15-MAR-2002" and "2-JUL-2002", respectively. The main data set for the efficacy analysis is "DEMO_DER" which defines a dose-response, terminating events and principal withdrawal reasons.

4.3 Statistical Evaluation of Evidence on Efficacy

4.3.1 Sponsor's Results and Conclusions

Table 1 summarizes the results of primary efficacy analysis for the tachycardia-free period (days) from Day 1 of randomization for ITT population. There are statistically significant differences in the tachycardia-free period from Day 1 of randomization to the first recurrence of symptomatic atrial arrhythmia in all 3 propafenone SR treatment groups in comparison to placebo. Kaplan-Meier survival curves for the tachycardia-free period from Day 1 of randomization for ITT population are in Figure 1 which also support the log-rank tests.

Table 1. Primary endpoint: Tachycardia-free period (days) from Day 1 of randomization (ITT population) --- RAFT

	Propafenone SR			
Parameter	225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Patients completing with terminating event[a]	66 (52.4)	56 (41.5)	41 (30.1)	87 (69.0)
Comparison of tachycardia-free periods				
Kaplan-Meier Median	112.0	291.0	228	41.0
Range	0.0 – 285.0	0.0 – 293.0	0.0 – 300.0	0.0 – 289.0
p-value[b]				
Long-rank	0.014	< 0.0001	< 0.0001	NA
Hazard Ratio	0.672	0.434	0.353	NA
95% CI for Hazard Ratio[c]	(0.49, 0.93)	(0.31, 0.61)	(0.24, 0.51)	NA

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Patients had a terminating event if they had symptomatic atrial fibrillation, atrial flutter, or PSVT according to the AEC.

[b] F-value is based on the test of the results for each propafenone SR treatment group versus the results for the placebo group.

[c] Hazard Ratio is based on the proportional-hazards model with the results for the propafenone SR treatment group versus the results for the placebo group as single independent variable.

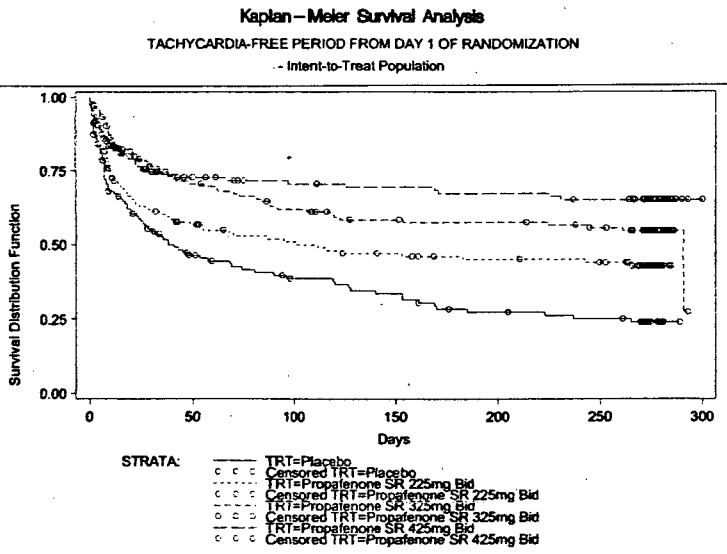

Figure 1. Tachycardia-free period (absence of symptomatic atrial fibrillation, atrial flutter, or PSVT) from Day 1 of randomization (ITT population)

The distribution of AEC diagnoses for symptomatic terminating events for the primary efficacy analysis is presented in Table 2.

Table 2. Distribution of AEC diagnoses for symptomatic terminating events for the primary efficacy analysis (ITT population): RAFT

	Propafenone SR			
AEC Diagnosis	225 mg bid (N = 126) n (%)[a]	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Atrial fibrillation	59 (89.4)	50 (89.3)	39 (95.1)	80 (91.9)
Atrial flutter	2 (3.0)	4 (7.1)	1 (2.4)	5 (5.7)
PSVT	5 (7.5)	2 (3.5)	1 (2.4)	2 (2.3)
Total number of diagnoses	66 (100)	56 (100)	41 (100)	87 (100)

Sponsor's results confirmed by reviewer's analyses.

[a] Percent of total number of diagnoses.

The average heart rate of patients during the first recurrence of symptomatic arrhythmia for ITT population is shown in Table 3. The overall p-value shows that there is a significant difference among the 4 treatment groups. But the significant difference is inconclusive for each treatment group based on the Dunnett's test procedure.

Table 4 summarizes the secondary efficacy analysis results of the tachycardia-free period (days) from Day 5 of randomization for ITT population. There are statistically significant differences in the tachycardia-free period from Day 5 of randomization to the first recurrence of symptomatic atrial arrhythmia in all 3 propafenone SR treatment groups in comparison to placebo.

Kaplan-Meier survival curves for the tachycardia-free period from Day 5 of randomization for ITT population are in Figure 2 which also support the log-rank tests.

Table 3. Secondary endpoint: Comparison heart rate of patients during the first recurrence of symptomatic arrhythmia (ITT population) --- RAFT

	Propafenone SR				
Average heart rate (bpm)	225 mg bid (N = 66)[a]	325 mg bid (N = 56)	425 mg bid (N = 41)	Placebo (N = 87)	p-Value[b]
Mean ± SD	126.4 ± 30.2	109.9 ± 26.1	111.1 ± 38.5	109.9 ± 26.1	0.007
Range	60.0 – 240.0	52.0 – 160.0	41.0 – 188.0	52.0 – 160.0	NA
p-value[c]	0.768	0.054	0.147	0.054	NA
Patients with average heart rate:	n (%)	n (%)	n (%)	n (%)	
< 50 bpm	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	NA
≥50 to < 100 bpm	12 (18.2)	20 (35.7)	16 (39.0)	23 (26.4)	NA
≥ 100 to 110 bpm	8 (12.1)	6 (10.7)	6 (14.6)	6 (6.9)	NA
≥ 110 to 130 bpm	23 (34.8)	18 (32.1)	6 (14.6)	26 (29.9)	NA
≥ 130 to 150 bpm	9 (13.6)	9 (16.1)	7 (17.1)	17 (19.5)	NA
> 150 bpm	14 (21.2)	3 (5.4)	5 (12.2)	15 (17.2)	NA

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Number of patients with AEC diagnosis of symptomatic terminating event (atrial fibrillation, atrial flutter, or PSVT).

[b] Overall p-value is based on an ANOVA among the 4 treatment groups.

[c] P -value is based on the Dunnett's test procedure for comparison of the results for the propafenone SR treatment group versus the results for the placebo group.

Table 4. Secondary endpoint: Tachycardia-free period (days) from Day 5 of randomization (ITT population) --- RAFT

	Propafenone SR			
Parameter	225 mg bid (N = 124) n (%)	325 mg bid (N = 132) n (%)	425 mg bid (N = 131) n (%)	Placebo (N = 124) n (%)
Patients completing with terminating event[a]	60 (48.4)	54 (40.9)	36 (27.5)	84 (67.7)
Comparison of tachycardia-free periods				
Kaplan-Meier Median	149.0	287.0	224	39.0
Range	0.0 – 281.0	0.0 – 289.0	0.0 – 296.0	0.0 – 285.0
p-value[b]				
Long-rank	0.002	< 0.0001	< 0.0001	NA
Hazard Ratio	0.604	0.438	0.319	NA
95% CI for Hazard Ratio[c]	(0.43, 0.84)	(0.31, 0.62)	(0.22, 0.47)	NA

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Patients had a terminating event if they had symptomatic atrial fibrillation, atrial flutter, or PSVT according to the AEC.

[b] P-value is based on the test of the results for each propafenone SR treatment group versus the results for the placebo group.

[c] Hazard Ratio is based on the proportional-hazards model with the results for the propafenone SR treatment group versus the results for the placebo group as single independent variable.

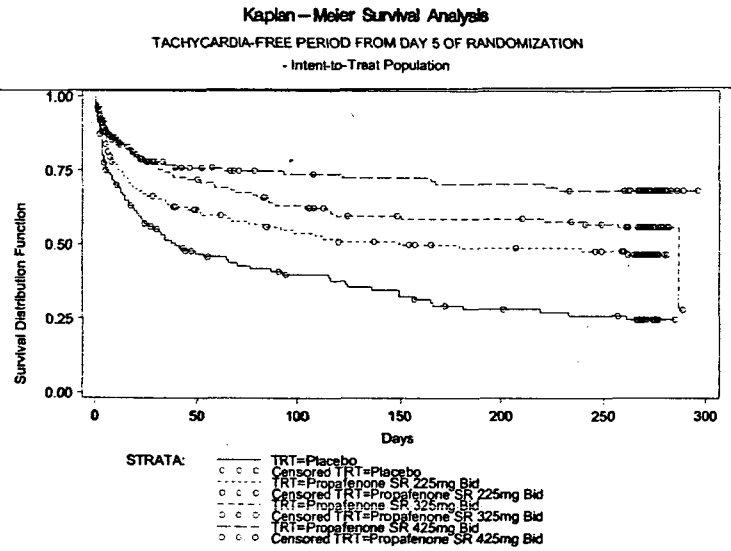

Figure 2. Tachycardia-free period (absence of symptomatic atrial fibrillation, atrial flutter, or PSVT) from Day 5 of randomization (ITT population)

The time (days) from Day 1 of randomization to the patient-initiated report of arrhythmia-associated symptoms (such as dyspnea, dizziness, palpitations, chest pain, or anxiety) with or without a terminating event according to the AEC is presented in Table 5. There are statistically significant differences from placebo in favor of propafenone SR 325 mg bid and 425 mg bid treatment groups and is not statistically significant difference between propafenone SR 225 mg bid and placebo in the time from Day 1 to patient-initiated reports of arrhythmia symptoms.

Table 5. Secondary endpoint: Time (days) from Day 1 to patient-initiated report of arrhythmia symptoms [symptom-free period (ITT population)] --- RAFT

	Propafenone SR			
Parameter	225 mg bid (N = 126) n (%)	325 mg bid (N = 135) n (%)	425 mg bid (N = 136) n (%)	Placebo (N = 126) n (%)
Patients completing with symptoms[a]	95 (75.4)	87 (64.4)	87 (64.0)	101 (80.2)
Comparison of tachycardia-free periods				
Kaplan-Meier Median	20.0	29.0	18.0	12.0
Range	0.0 – 284.0	0.0 – 293.0	0.0 – 300.0	0.0 – 289.0
p-value[b]				
Long-rank	0.297	0.002	0.011	NA
Hazard Ratio	0.864	0.644	0.693	NA
95% CI for Hazard Ratio[c]	(0.65, 1.14)	(0.48, 0.86)	(0.52, 0.93)	NA

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Arrhythmia-associated symptoms include dyspnea, dizziness, palpitations, chest pain, and anxiety.

[b] P-value is based on the test of the results for each propafenone SR treatment group versus the results for the placebo group.

[c] Hazard Ratio is based on the proportional-hazards model with the results for the propafenone SR treatment group versus the results for the placebo group as single independent variable.

The duration of the tachycardia-free period (days) from Day 5 of randomization for ITT population is presented in Table 6. There are statistically significant differences in all 3 body weight-adjusted propafenone SR treatment groups in comparison to placebo.

Table 6. Secondary endpoint: Duration of tachycardia-free period (days) from Day 5 of randomization by body weight-adjusted dose of propafenone SR (ITT population) --- RAFT

	Body Weight-Adjusted Propafenone SR[a]			
Parameter	Low (N = 131) n (%)	Medium (N = 129) n (%)	High (N = 126) n (%)	Placebo (N = 124) n (%)
Range (mg/kg)	1.52 – 3.22	3.21 – 4.47[b]	4.47 – 9.35	NA
Patients completing:				
With terminating event[c]	59 (45.0)	55 (42.6)	35 (27.8)	84 (67.7)
All visits	45 (34.4)	48 (37.2)	59 (46.8)	22 (17.7)
Comparison of tachycardia-free periods				
Kaplan-Meier Median	262.0	---	287.0	39.0
Range	0.0 – 281.0	0.0 – 296.0	0.0 – 287.0	0.0 – 285.0
p-value[d]				
Long-rank	< 0.0001	< 0.0001	< 0.0001	NA
Hazard Ratio	0.543	0.486	0.309	NA
95% CI for Hazard Ratio[e]	(0.39, 0.76)	(0.35, 0.69)	(0.21, 0.46)	NA

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Weight is missing for 1 patient.

[b] Four patients have the same value (4.47 mg/kg). One patient is assigned to the middle group and 3 to the high group.

c Patients had a terminating event if they had symptomatic atrial fibrillation, atrial flutter, or PSVT according to the AEC.

[d] P-value is based on the test of the results for each propafenone SR treatment group versus the results for the placebo group.

[e] Hazard Ratio is based on the proportional-hazards model with the results for the propafenone SR treatment group versus the results for the placebo group as single independent variable.

2.2.1 Statistical Methodologies

The primary efficacy variable is the tachycardia-free period in days measured from the beginning of randomization (Day 1) to the first recurrent symptomatic arrhythmia (atrial fibrillation, atrial flutter, and/or PSVT) documented by TTM with the AEC final diagnosis. The tachycardia-free period is to be censored on the final day of treatment for those patients who discontinued the study prematurely. Patients who completed 39 weeks of the efficacy period without recurrence of an arrhythmia are to also have their tachycardia-free period censored on the final day of treatment. The secondary efficacy variable is the average heart rate during the first recurrence of a symptomatic arrhythmia during the primary endpoint event (TTM ECG). Other efficacy variables are the tachycardia-free period from Day 5 (steady/loading period) of randomization to the recurrence of first symptomatic arrhythmia, time to first patient-initiated report of arrhythmia symptoms from Day 1 of randomization, the treatment failure time – the

time from Day 1 of randomization to the first symptomatic recurrence of arrhythmia or withdrawal from the trial for any reason, treatment effect as a function of mg/kg of propafenone SR expressed in term of dosage (mg) per unit weight (kg), and the AEC final diagnosis (TTM recording) compared with the Investigator's diagnosis (TTM recording).

The analyses by study visit use the following conventions: (1) A baseline value is defined as the last available measurement immediately prior to the first dose of study medication. (2) If the dropout day occurs between any 2 scheduled visits, then any measurement taken on the dropout day will be assigned to the following scheduled visit, provided at least 1 dose of study medication is documented after the previous scheduled visit.

The efficacy analyses include the comparisons of treatment dose to placebo. The log-rank test is used as the primary method to test the null hypothesis of no difference for survival distributions between the treatment and placebo groups for all efficacy variables with the exception of the secondary variable (heart rate). Wilcoxon test is used to support the robustness of the efficacy analysis. Proportional hazard model is used to determine the hazard ratio. The Kaplan-Meier product-limit method is used to estimate and graphically illustrate the proportion of patients in each of the treatment arms remaining free of their arrhythmia on each day of the 39-week follow-up period. ANOVA and Dunnett's test are used for the secondary efficacy variable heart rate with baseline average heart rate.

Fisher's Exact test is used for the patient disposition analysis. For the demographic data, ANOVA and Dunnett's test are used for age, height, weight, and history of arrhythmia and Fisher's Exact test is used for gender, race and stratified age. Subgroup analyses are by age, gender, with and without history of cardioversion, duration of atrial fibrillation, frequency of atrial fibrillation, propafenone SR mg/kg, NYHA classification, history of structural heart disease (yes/no), and concomitant medications that lower heart rate.

2.2.2 Detailed Review of Individual Studies

The study RAFT is a randomized, double-blind, 4-way parallel, placebo-controlled, multi-center clinical trial of slow release propafenone (Rythmol SR) in the prevention of symptomatic recurrences of atrial fibrillation. Symptomatic arrhythmias are documented by telemetry [transtelephonic electrocardiogram monitoring (TTM)]. Patients are followed up to 39 weeks unless they completed the study (before Week 39 and after Day 5) because of symptomatic atrial fibrillation or atrial flutter diagnosed by the investigator. The study is conducted in the US. The planned sample size is 112 patients per treatment group. Protocol Amendment VI added an additional 30 to 50 patients to allow for the higher than anticipated dropout rate. There are 523 patients are finally enrolled for the study.

The Intent-to-Treat population consists of subjects who are exposed to at least 1 dose of study medication. This population is used for all efficacy analyses. The per-protocol population includes all patients who are exposed to at least 1 dose of study drug and who: (1) have a baseline TTM recording that is not reported by the AEC as an atrial arrhythmia (atrial fibrillation, atrial flutter, and/or PSVT); (2) complete the study without major protocol violations/deviations;

(3) meet the criterion for study drug compliance (≥ 80% and < 120%) for all visits combined. Detailed results of the efficacy analyses of the RAFT study are reported in Table 1 – 6.

The study ERAFT is a randomized, double-blind, 3-way parallel, placebo-controlled, multi-center, multi-national, prospective clinical trial of slow release propafenone SR (325 mg bid and 425 mg bid), conducted in Canada, Estonia, Germany, Israel, Italy, Latvia, Lithuania, Poland, South Africa, and Great Britain. The planned sample size is 255 patients (85 patients per treatment group). There are 293 patients are finally enrolled for the study. The results of efficacy analyses of ERAFT are presented in this section.

In efficacy analyses, the tachycardia-free period (days) from Day 1 of randomization for ITT population is shown in Table 7. There are statistically significant differences in the tachycardia-free period (days) from Day 1 of randomization to the first recurrence of symptomatic atrial arrhythmia in both propafenone SR treatment groups in comparison to placebo. Though the propafenone SR 425 mg treatment group has a lower rate of terminating events than the propafenone SR 325 mg treatment group, it has a higher hazard ratio because the sample size is small and there are more terminating events in the last efficacy period.

Table 7. Primary endpoint: Tachycardio-free period (days) from Day 1 of randomization (ITT population) --- ERAFT

	Propafenone SR		
Parameter	325 mg bid (N = 111) n (%)	425 mg bid (N = 89) n (%)	Placebo (N = 93) n (%)
Patients completing with terminating event[a]	71 (64.0)	51 (57.3)	70 (75.3)
Comparison of tachycardia-free periods			
Kaplan-Meier Median	23.0	28.0	9.0
Range	0.0 – 109.0	0.0 – 105.0	0.0 – 110.0
p-value[b]			
Long-rank	0.003	0.030	NA
Hazard Ratio	0.61	0.66	NA
95% CI for Hazard Ratio[c]	(0.43, 0.85)	(0.45, 0.96)	NA

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Patients had a terminating event if they had symptomatic atrial fibrillation or atrial flutter according to the AEC.

[b] P-value is based on the test of the results for each propafenone SR treatment group versus the results for the placebo group.

[c] Hazard Ratio is based on the proportional-hazards model with the results for the propafenone SR treatment group versus the results for the placebo group as single independent variable.

The tachycardia-free period (days) from Day 5 of randomization for ITT population is shown in Table 8. There are statistically significant differences in the tachycardia-free period (days) from Day 5 of randomization to the first recurrence of symptomatic atrial arrhythmia in both propafenone SR treatment groups in comparison to placebo.

Table 8. Secondary endpoint: Tachycardia-free period (days) from Day 5 of randomization (ITT population) --- ERAFT

Parameter	Propafenone SR 325 mg bid (N = 107) n (%)	Propafenone SR 425 mg bid (N = 83) n (%)	Placebo (N = 88) n (%)
Patients completing with terminating event[a]	66 (61.7)	41 (49.4)	65 (73.9)
Comparison of tachycardia-free periods			
Kaplan-Meier Median	35.0	44.0	9.0
Range	0.0 – 105.0	0.0 – 101.0	0.0 – 106.0
p-value[b]			
Long-rank	0.004	0.003	NA
Hazard Ratio	0.60	0.55	NA
95% CI for Hazard Ratio[c]	(0.43, 0.86)	(0.36, 0.82)	NA

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Patients had a terminating event if they had symptomatic atrial fibrillation or atrial flutter according to the AEC.

[b] P-value is based on the test of the results for each propafenone SR treatment group versus the results for the placebo group.

[c] Hazard Ratio is based on the proportional-hazards model with the results for the propafenone SR treatment group versus the results for the placebo group as single independent variable.

The average heart rate of patients during the first recurrence of symptomatic arrhythmia after Day 5 for ITT population is shown in Table 9. There is a statistically significant difference in the lower average heart rate during the first recurrence of symptomatic arrhythmia after Day 5 in propafenone SR 325 mg bid dose group compared with placebo.

Table 9. Secondary endpoint: Comparison of average heart rate of patients during the first recurrence of symptomatic arrhythmia after Day 5 (ITT population) --- ERAFT

Average heart rate (bpm)	Propafenone SR 325 mg bid (N = 62)	Propafenone SR 425 mg bid (N = 41)	Placebo (N = 64)	p-Value[a]
Mean ± SD	106.4 ± 25.8	108.4 ± 27.3	114.7 ± 26.1	0.030
Range	55.0 – 173.0	70.0 – 179.0	59.0 – 182.0	NA
p-value[b]	0.016	0.47	NA	NA

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Overall p-value is based on an ANOVA among the 4 treatment groups.

[b] P-value is based on the Dunnett's test procedure for comparison of the results for the propafenone SR treatment group versus the results for the placebo group.

The treatment failure time (days), which is defined as the time from Day 5 of randomization to the first symptomatic recurrence of atrial fibrillation or atrial flutter or withdrawal from the trial for any reason, is shown for ITT population in Table 10. There are statistically significant differences in the time to treatment failure from Day 5 of randomization to the first recurrence of symptomatic atrial arrhythmia in both propafenone SR treatment groups in comparison to placebo.

The propafenone SR dose is adjusted to the patient's body weight. The weight-adjusted data are arranged in the ascending order and then are divided into 2 equal groups as low and high, and these 2 groups are compared to placebo. The treatment effect as a function of body weight-adjusted propafenone SR mg/kg dose is presented in Table 11. There are statistically significant differences in both body weight-adjusted propafenone SR treatment groups in comparison to placebo.

2.2.3 Statistical Reviewer's Evaluation

This statistical reviewer performed robustness analyses for the primary efficacy variable. This is a major statistical issue for this NDA submission. The robustness analysis is a major and important statistical analysis to verify the robustness of the result of the primary efficacy analysis. Since there is a very high rate (66.7%) of withdrawal patients including the patients who are discontinued with terminating events, the robustness analysis is necessary to test the robustness for different withdrawal groups.

The statistical reviewer used the Bonferroni procedure for the multiple comparisons. Since the overall significance level was 0.05, the adjusted significance level by Bonferroni method was 0.0167 which was used for the comparisons of each of propafenone SR treatment with placebo.

Table 12 shows the principal withdrawal reasons by the treatment groups. The group of lack of efficacy is highly related to the therapy (n = 239). The groups of adverse event and other are also related to therapy (n = 55 and 37, respectively).

Table 12. Principal Withdrawal Reasons (ITT population): RAFT

	Patients without terminating event				Patients with terminating event				Total
	225 mg (N=126) n (%)	325 mg (N=135) n (%)	425 mg (N=136) n (%)	Placebo (N=126) n (%)	225 mg (N=126) n (%)	325 mg (N=135) n (%)	425 mg (N=136) n (%)	Placebo (N=126) n (%)	n
Administrative Problem (ADM)	1 (0.8)	2 (1.5)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4
Concomitant Medication (PV)	1 (0.8)	0 (0.0)	1 (0.7)	2 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	5
Adverse Event (AE)	7 (5.6)	9 (6.7)	24 (17.6)	8 (6.3)	2 (1.6)	0 (0.0)	5 (3.7)	0 (0.0)	55
Lack of Efficacy (LOE)	5 (4.0)	3 (2.2)	3 (2.2)	1 (0.8)	58 (46.0)	53 (39.3)	32 (23.5)	84 (66.7)	239
Therapy Refusal (PAT)	2 (1.6)	1 (0.7)	1 (0.7)	3 (2.3)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	9
Other (OTH)	8 (6.3)	11 (8.1)	6 (4.4)	5 (4.0)	3 (2.3)	0 (0.0)	3 (2.2)	1 (0.8)	37
Total	24 (19.0)	26 (19.3)	36 (26.5)	19 (15.1)	63 (50.0)	55 (40.7)	41 (30.1)	85 (67.5)	349

Reviewer's analyses.

The robustness analyses were performed separately on 4 different types of treatment failures defined as follows: (1) patients with terminating events and withdrawal for the reasons of lack of

efficacy and therapy refusal, (2) patients with terminating events and withdrawal for the reasons of lack of efficacy, therapy refusal and other, (3) patients with terminating events and withdrawal for the reasons of lack of efficacy, therapy refusal, other, and adverse event, and (4) patients with terminating events and withdrawal for any reason. The treatment failure time is defined as the time (days) from randomization to treatment failure. The results of robustness analysis for the primary efficacy variable in ITT population of RAFT study are summarized in Table 13. There are statistically significant differences in the time to treatment failure from Day 1 of randomization to the first recurrence of symptomatic atrial arrhythmia in 325 mg and 425 mg propafenone SR treatment groups in comparison to placebo. Based on Bonferroni's adjustment, statistical significance is inconclusive on the difference in the time to treatment failure from Day 1 of randomization to the first recurrence of symptomatic atrial arrhythmia for 225 mg propafenone SR treatment groups in comparison to placebo.

Table 13. Robustness Analysis for Primary Endpoint (ITT population): RAFT

	Propafenone SR			
	225 mg bid (N = 126)	325 mg bid (N = 135)	425 mg bid (N = 136)	Placebo (N = 126)
Tachycardio-free period (days) from Day 1 of randomization (ITT population): RAFT				
Patients with terminating event [a]	66 (52.4)	56 (41.5)	41 (30.1)	87 (69.0)
p-value [b] (Log-rank)	0.014	< 0.0001	< 0.0001	NA
Hazard Ratio	0.672	0.434	0.353	NA
95% CI for Hazard Ratio [c]	(0.49, 0.93)	(0.31, 0.61)	(0.24, 0.51)	NA
Treatment failure (including LOE, PAT) from Day 1 of randomization (ITT population): RAFT				
Patients with treatment failure [d]	73 (57.9)	60 (44.4)	45 (33.1)	91 (72.2)
p-value (Log-rank)	0.026	< 0.0001	< 0.0001	NA
Hazard Ratio	0.707	0.446	0.371	NA
95% CI for Hazard Ratio	(0.52, 0.96)	(0.32, 0.62)	(0.26, 0.53)	NA
Treatment failure (including LOE, PAT, OTH) from Day 1 of randomization (ITT population): RAFT				
Patients with treatment failure [e]	81 (64.3)	71 (52.6)	51 (37.5)	96 (76.2)
p-value (Log-rank)	0.040	< 0.0001	< 0.0001	NA
Hazard Ratio	0.736	0.492	0.395	NA
95% CI for Hazard Ratio	(0.55, 0.99)	(0.36, 0.67)	(0.28, 0.56)	NA
Terminating events (including LOE, PAT, OTH, AE) from Day 1 of randomization (ITT population): RAFT				
Patients with treatment failure [f]	88 (69.8)	80 (59.3)	75 (55.1)	104 (82.5)
p-value (Log-rank)	0.031	< 0.0001	< 0.0001	NA
Hazard Ratio	0.733	0.510	0.539	NA
95% CI for Hazard Ratio	(0.55, 0.98)	(0.38, 0.69)	(0.40, 0.73)	NA
Terminating events (including any withdrawal) from Day 1 of randomization (ITT population): RAFT				
Patients with treatment failure [g]	90 (71.4)	82 (60.7)	77 (56.6)	106 (84.1)
p-value (Log-rank)	0.030	< 0.0001	< 0.0001	NA
Hazard Ratio	0.735	0.511	0.540	NA
95% CI for Hazard Ratio	(0.56, 0.98)	(0.38, 0.68)	(0.40, 0.73)	NA

Reviewer's results. NA = not applicable.

[a] Patients had a terminating event if they had symptomatic atrial fibrillation, atrial flutter, or PSVT according to the AEC.

[b] P-value is based on the test of the results for each propafenone SR treatment group versus the results for the placebo group.

[c] Hazard Ratio is based on the proportional-hazards model with the results for the propafenone SR treatment group versus the results for the placebo group as single independent variable.

[d] Treatment failure defined as symptomatic atrial fibrillation, atrial flutter or PSVT (AEC) or withdrawal for LOE or PAT.

e Treatment failure defined as symptomatic atrial fibrillation, atrial flutter or PSVT (AEC) or withdrawal for LOE, PAT or OTH.

[f] Treatment failure defined as symptomatic atrial fibrillation, atrial flutter or PSVT (AEC) or LOE, PAT, OTH, or AE reason.

[g] Treatment failure defined as symptomatic atrial fibrillation, atrial flutter or PSVT (AEC) or withdrawal for any reason.

The baseline physical examination shows that a higher percentage of patients in the placebo group (32.5%) had an abnormal cardiac heart exam compared to the propafenone SR treatment 225 mg (15.1%), 325 mg (25.9%) and 425 mg (27.9%). This statistical reviewer conducted a subgroup analysis within the normal baseline cardiac examination patients and summaries the results in Table 14. The propafenone SR 225 mg bid treatment is not significantly different to placebo (p=0.136) but two other propafenone SR doses are significantly different from placebo with p-values 0.0003 and < 0.0001, respectively. There are 13 abnormal baseline cardiac examination patients specified irregular heart rhythm or heart rate. The analysis excluding those patients shows a slight difference from the primary efficacy analysis. It is not reported here.

Table 14. Tachycardia-free period (days) from Day 1 (Patients with normal baseline cardiac heart examination): RAFT

	Propafenone SR			
Parameter	225 mg bid (N = 107) n (%)	325 mg bid (N = 100) n (%)	425 mg bid (N = 98) n (%)	Placebo (N = 85) n (%)
Patients completing with terminating event[a]	57 (53.3)	43 (43.0)	29 (29.6)	56 (65.9)
p-value (Long-rank)[b]	0.136	0.0003	< .0001	NA
Hazard Ratio	0.758	0.488	0.388	NA
95% CI for Hazard Ratio[c]	(0.52, 1.10)	(0.33, 0.73)	(0.25, 0.61)	NA

Reviewer's analyses. NA = not applicable

[a] Patients had a terminating event if they had symptomatic atrial fibrillation, atrial flutter, or PSVT according to the AEC.

[b] P-value is based on the test of the results for each propafenone SR treatment group versus the results for the placebo group.

[c] Hazard Ratio is based on the proportional-hazards model with the results for the propafenone SR treatment group versus the results for the placebo group as single independent variable.

2.3 Findings in Special/Subgroup Population

The sponsor conducted the proportional hazard analysis for subgroup population (age, gender, presence of structural heart disease, NYHA classification, history of cardioversion, and medications that lower heart rate) but did not perform the log-rank test. The reason for this is that it is not powered to detect a statistically significant difference between the propafenone treatment groups and placebo for the subgroup population. The protocol defined the statistical analysis including the subgroup population analyses for the primary efficacy variable. This reviewer performed the log-rank test. The significance tests will show the efficacy of treatments for some subgroup populations.

The results of subgroup population analyses are presented in Table 15. The proportion hazards assumptions are reviewed and are found to be questionable only for the following propafenone SR 225 mg bid treatment group placebo comparisons: age (< 65 or ≥ 65); patients not on heart rate lowering drugs; history of structural heart disease; NYHA Class II (slightly compromised); duration of atrial fibrillation (0 - < months); and for the frequency of atrial fibrillation (< 4). Since most of the patients enrolled in the RAFT study and all of the patients enrolled in the ERAFT study are Caucasian, there is no subgroup population analysis for race.

Table 15. Subgroup Analysis for the Primary Efficacy Endpoint: Tachycardio-free period (days) from Day 1 of randomization (ITT population) --- RAFT

	Propafenone SR		
	225 mg bid (N = 126)	325 mg bid (N = 135)	425 mg bid (N = 136)
Age			
Age < 65 years			
Patients with terminating event[a]	65 (51.6)	66 (48.9)	61 (44.9)
p-value (Log-rank test)[b]	0.033	< 0.0001	< 0.0001
Hazard Ratio (95% CI)[c]	0.624 (0.40, 0.97)	0.360 (0.22, 0.59)	0.328 (0.19, 0.56)
Age ≥ 65 years			
Patients with terminating event	61 (48.4)	69 (51.1)	75 (55.1)
p-value (Log-rank test)	0.149	0.005	0.0001
Hazard Ratio (95% CI)	0.712 (0.45, 1.14)	0.509 (0.32, 0.82)	0.372 (0.22, 0.63)
Gender			
Male			
Patients with terminating event	76 (60.3)	80 (59.3)	78 (57.4)
p-value (Log-rank test)	0.154	0.0006	0.0001
Hazard Ratio (95% CI)	0.737 (0.48, 1.13)	0.465 (0.30, 0.73)	0.396 (0.24, 0.65)
Female			
Patients with terminating event	50 (39.7)	55 (40.7)	58 (42.6)
p-value (Log-rank test)	0.036	0.0005	< 0.0001
Hazard Ratio (95% CI)	0.597 (0.37, 0.98)	0.407 (0.24, 0.69)	0.314 (0.18, 0.56)
Structural Heart Disease			
Yes			
Patients with terminating event	70 (55.6)	72 (53.3)	61 (44.9)
p-value (Log-rank test)	0.001	< 0.0001	< 0.0001
Hazard Ratio (95% CI)	0.508 (0.33, 0.78)	0.294 (0.18, 0.47)	0.357 (0.21, 0.60)
No			
Patients with terminating event	56 (44.4)	63 (46.7)	75 (55.1)
p-value (Log-rank test)	0.933	0.140	0.0004
Hazard Ratio (95% CI)	0.979 (0.60, 1.61)	0.687 (0.42, 1.14)	0.388 (0.22, 0.67)
NYHA Classification			
Class I			
Patients with terminating event	117 (92.9)	125 (92.6)	126 (92.6)
p-value (Log-rank test)	0.0173	< 0.0001	< 0.0001
Hazard Ratio (95% CI)	0.674 (0.48, 0.94)	0.446 (0.31, 0.63)	0.356 (0.24, 0.52)
Class II			
Patients with terminating event	9 (7.1)	10 (7.4)	10 (7.4)
p-value (Log-rank test)	0.671	0.171	0.115
Hazard Ratio (95% CI)	0.740 (0.18, 3.03)	0.389 (0.10, 1.58)	0.314 (0.07, 1.43)
History of Cardioversion			
Yes			
Patients with terminating event	104 (82.5)	104 (77.0)	105 (77.2)
p-value (Log-rank test)	0.001	< 0.0001	< 0.0001
Hazard Ratio (95% CI)	0.543 (0.38, 0.78)	0.405 (0.28, 0.59)	0.300 (0.20, 0.46)
No			
Patients with terminating event	22 (17.5)	31 (23.0)	31 (22.8)
p-value (Log-rank test)	0.171	0.134	0.209
Hazard Ratio (95% CI)	1.634 (0.80, 3.35)	0.565 (0.26, 1.21)	0.612 (0.28, 1.33)
Duration of Atrial Fibrillation			
0 - < 3 Months			
Patients with terminating event	32 (25.4)	28 (20.7)	30 (22.1)
p-value (Log-rank test)	0.683	0.150	0.002

Hazard Ratio (95% CI)	0.869 (0.44, 1.71)	0.580 (0.27, 1.23)	0.249 (0.98, 0.63)
3 – 12 Months			
Patients with terminating event	32 (25.4)	35 (25.9)	46 (33.8)
p-value (Log-rank test)	0.179	0.012	0.005
Hazard Ratio (95% CI)	0.629 (0.32, 1.25)	0.420 (0.21, 0.84)	0.377 (0.18, 0.77)
> 1 Year			
Patients with terminating event	62 (49.2)	72 (53.4)	60 (44.1)
p-value (Log-rank test)	0.030	< 0.0001	0.0002
Hazard Ratio (95% CI)	0.627 (0.41, 0.97)	0.395 (0.25, 0.62)	0.396 (0.24, 0.66)
Frequency of Atrial Fibrillation			
< 4			
Patients with terminating event	65 (51.6)	75 (55.6)	75 (55.1)
p-value (Log-rank test)	0.409	0.019	0.001
Hazard Ratio (95% CI)	0.819 (0.51, 1.32)	0.556 (0.34, 0.92)	0.412 (0.24, 0.72)
4 – 20			
Patients with terminating event		42 (31.1)	40 (29.4)
p-value (Log-rank test)	38 (30.2)	< 0.0001	0.0001
Hazard Ratio (95% CI)	0.008	0.326 (0.19, 0.5792)	0.326 (0.18, 0.60)
> 20	0.486 (0.28, 0.85)		
Patients with terminating event		18 (13.3)	21 (15.4)
p-value (Log-rank test)	23 (18.3)	0.001	0.001
Hazard Ratio (95% CI)	0.052	0.251 (0.10, 0.62)	0.226 (0.09, 0.58)
	0.507 (0.25, 1.03)		

Sponsor's results confirmed by reviewer's analyses. P-value (Long-rank test) is the reviewer's analysis only.

2.4 Statistical and Technical Issues

Interim Analysis

The original protocol did not call for an interim analysis. Protocol Amendment II added an interim analysis when 150 patients had been enrolled. Protocol Amendment VI rescinded the interim analysis. No interim analysis was performed.

Multi-center Study

RAFT was a multi-center study with 111 centers participating. All centers were located in the United States.

Per-Protocol Data Set

The per-protocol data set was also analyzed for the primary efficacy variable. However, the primary analysis of efficacy was based on the full analysis data set (ITT population).

Statistical Robustness Analysis

The major statistical issue in this NDA submission is the statistical analysis method used for the primary efficacy analysis. The sponsor did not perform a robustness analysis in the efficacy analysis. A robustness analysis is a major and important statistical analysis to verify the robustness of the result of the primary efficacy analysis. For a clinical trial, if there is a higher rate of withdrawals, a statistical robustness analysis should be done because the withdrawals may

be highly related to efficacy even if the principal withdrawal reasons for those subjects are not any primary efficacy event. They should be included in the efficacy analyses in some way. Therefore, a statistical robustness analysis is necessary to show the robustness of the results for different withdrawal groups. Actually, those withdrawals are treatment failures. The treatment failure time is defined as the time from randomization to the treatment failure day. A treatment failure analysis is a treatment failure (survival) time analysis.

Adjustment Procedure for Multiple Comparisons

This is a multiple doses study. There are 3 experimental treatment doses. Each experimental treatment dose will be compared with placebo group. It is a typical multiple comparisons trial. The sponsor did not define any adjustment procedure for the multiple comparison tests. The sponsor concluded their results based on the unadjusted efficacy analyses.

Baseline Physical Examination

Result of the baseline physical examination shows that a higher percentage of patients in the placebo group (32.5%) compared to the combined propafenone SR treatment groups (23.2%) had an abnormal cardiac heart exam. The percentage of patients with a baseline abnormal cardiac exam was 15.1% in the propafenone SR 225 mg bid treatment group, 25.9% in the propafenone SR 325 mg bid treatment group, and 27.9% in the propafenone SR 425 mg bid treatment group. A subgroup analysis within the normal baseline cardiac heart exam patients is necessary to support the primary efficacy analysis. A more detailed analysis by treatment group and study centers for the abnormal patients of baseline cardiac heart exam will verify the randomization.

2.5 Statistical Evaluation of Collective Evidence

Tables 1-6 clearly summarized the statistical results of efficacy analyses for primary and secondary efficacy variables and provided the evidence to support the conclusions. The hazard ratio and its 95% confidence interval were used for the survival analysis and Kaplan-Meier survival curves supported the results of survival analyses. The modified Dunnett's test was used by the sponsor to adjust the multiple comparisons between the treatment and placebo groups for demographic and other continuous variables but not for the primary or secondary endpoint of efficacy analyses. Fisher's Exact test was used for discrete variables. The robustness analysis showed the robustness of statistical hypothesis tests.

2.6 Conclusion and Recommendations

The clinical study RAFT demonstrates that there are statistically significant differences in favor of all propafenone SR bid treatment groups (225 mg, 325 mg, and 425 mg) compared to placebo for tachycardia-free period (days) from Day 1 of randomization and tachycardia-free period (days) from Day 5 of randomization in Intent-to-Treat (ITT) population. There are statistically significant differences in favor of the propafenone SR 325 mg bid and 425 mg bid treatment groups compared to placebo for time (days) to patient-initiated report of arrhythmia-associated symptoms from Day 1 of randomization in ITT population (but it was not reported in the study ERAFT). When the dose of propafenone SR is adjusted for body weight, there is a

statistically significant difference compared to placebo for the time (days) to first recurrence of symptomatic atrial arrhythmia from Day 5 of randomization for all weight-adjusted dose categories (low, medium, and high) in ITT population. The time to treatment failure analysis shows that the significant differences in favor of propafenone SR 325 mg bid and 425 mg bid treatment groups compared to placebo are robust regardless of how withdrawals are treated in analyses.

Though there is a statistically significant difference in favor of the propafenone SR 225 mg bid treatment compared to placebo for the primary endpoint and one of the secondary endpoints (tachycardia-free period from Day 5 of randomization), this demonstration is still questionable. The propafenone SR 225 mg bid treatment was included in only one study RAFT, not in another study ERAFT. The evidence of the demonstration may not be enough. The significance level of the demonstration for the primary endpoint is borderline ($p=0.014$) under the Bonferroni's adjustment ($\alpha=0.017$) and the difference between the propafenone SR 225 mg bid treatment and placebo is not statistically significant for the time to treatment failure analysis or for another secondary endpoint (the time (days) from Day 1 to patient-initiated report of arrhythmia symptoms).

Kaplan-Meier curves and proportional hazard analyses also support those statistical tests. The subgroup analyses results are comparable to the results for the overall primary efficacy analysis. The effects among treatment doses are hardly distinguishable.

2.7 Appendix of Individual Studies Reviewed

This NDA submission includes two Phase III studies RAFT and ERAFT. Both are reviewed and presented in this report. There is no another study to be included in this report.

2.8 Appendix of Technical Discussion on Statistical Issues

There is no any detailed technical discussion on statistical issues to be included in this report.

2.9 Appendix of Bibliography and/or References

1. Lee, Elisa T. (1972). Statistical Methods for Survival Data Analysis. New York: John Wiley & Sons.

2. Fleiss, Joseph L. (1986). The Design and Analysis of Clinical Experiments. New York: John Wiley & Sons.

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