CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:	**19151/S002**
Trade Name:	**Rythmol**
Generic Name:	**Propafenone**
Sponsor:	**Knoll Pharmaceuticals**
Approval Date:	**December 23, 1997**
Indication:	**Paroxysmal supraventricular tachycardia (PSVT)**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 19151/S002

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter	X			
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)			X	
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 19151/S002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-151/S-002

SEP 23 1997

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
199 Cherry Hill Road
Parsippany, NJ 07054

Dear Dr. Ashworth:

Please refer to your November 30, 1992 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rythmol (propafenone HCl) 150, 225, and 300 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated September 12 and 26 and November 19, 1997.

The user fee goal date is March 29, 1998.

The supplemental application provides for the new indication of paroxysmal supraventricular tachycardia (PSVT).

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-151/S-002. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

We are also asking at this time that you submit labeling in the form of a supplemental application within 6 months revised as follows:

All statements comparing animal with human doses of propafenone HCl should state the applicable mg/kg dose in the animal, the (total daily) human dose to which it is being compared and the multiple of that human dose calculated on a mg/M^2 basis.

Consideration should be given to deleting the **Animal Toxicology** subsection of the **PRECAUTIONS** section of the labeling. Reassessment of the need for this information regarding liver and kidney pathology in rats should be based on whether there is now sufficient human experience to override concerns based on animal findings at the time of approval of the original Rythmol application.

Should you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
Telephone: (301) 594-5311

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-110
HF-2/MedWatch (with draft/final labeling)
HFD-002/ORM (efficacy supplements only)
HFD-92/DDM-DIAB (with draft/final labeling)
HFD-101 (with draft/final labeling, efficacy supplements only)
HFD-101/L.Carter (efficacy supplements only)
HFD-40/DDMAC (with draft/final labeling)
HFD-613/OGD (with draft/final labeling)
HFD-735/DPE (with draft/final labeling)
HFD-560/OTC (with draft/final labeling- OTC drugs only)
HFD-21/ACS (with draft/final labeling - for supplements discussed at advisory committee)
DISTRICT OFFICE
HFD-810/ONDC Division Director
HFI-20/Press Office (with draft/final labeling)
HFD-110/DWillard/12/23/97
sb/12/23/97

Approval Date: November 27, 1989

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19151/S002

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-151/S-002

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
199 Cherry Hill Road
Parsippany, NJ 07054

SEP 10 1997

Dear Dr. Ashworth:

Please refer to your November 30, 1992 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rythmol (propafenone HCl) 150, 225, and 300 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated August 28, September 19, and October 31, 1995, March 20 and August 16, 1996, and March 18 and July 1, 1997.

The supplemental application provides for the new indication of paroxysmal supraventricular tachycardia (PSVT).

We have completed the review of this supplemental application as submitted with draft labeling and it is approvable. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit sixteen copies of the printed labeling ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

These changes may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
Telephone: (301) 594-5311

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-2/MLumpkin (efficacy supplements only)
HFD-92
HFD-101 (efficacy supplements only)
HFD-110
HFD-40/DDMAC (with labeling)
DISTRICT OFFICE
HFD-110/DWillard/8/4/97
sb/8/5/97

Approval Date: November 27, 1989

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19151/S002

MEDICAL REVIEW(S)

JUN 23 1994

Steven M. Rodin, M.D.
Medical Officer

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Cardio-Renal Drugs
Tel 301-443-0320; FAX-9283

Medical Review of NDA Efficacy Supplement: Addendum #1

1 General information

NDA #:	19-151/ S2
Drug:	propafenone hydrochloride (Rhythmol®, Knoll Pharmaceuticals)
Proposed indication:	prophylaxis of paroxysmal supraventricular tachycardia
Pharmacologic type:	antiarrhythmic (class 1C)
Date of initial review:	30 November 1993
Date of 1st supplemental submission:	31 January 1994
Latest data addendum:	19 May 1994
review last revised:	23 June 1994

2. Table of contents

3. Background

My original review (dated 11/30/93) analyzed studies P-16-OR, P-17-OR, and P-20-OR. This addendum reviews the newly submitted results of study PSD-88-3, as well as addended data from study P-16-OR. My overall conclusions, based on consideration of all four studies, will be presented.

4. Oral propafenone effect on symptomatic PSVT (study PSD-88-3)!

SUMMARY:

This placebo-controlled, double-blind crossover trial was comprised of two consecutive phases conducted in Great Britain. The first (low-dose) phase was a 2 period crossover which randomized 95 subjects[1] (patients with symptomatic paroxysmal supraventricular tachycardia (PSVT), or paroxysmal atrial fibrillation (PAfib)) to receive (in random sequence) placebo. or propafenone (initially a "half dose" for 7 days (300 mg/d) and then a fixed "full dose" (600 mg/d)). The completers of phase I proceeded without further randomization to phase II, a 2 period crossover between a higher dose of propafenone (initially 450 mg/d and then 900 mg/d), and placebo. All crossover periods in each phase of the study continued until there was a recurrent event (either a diary-captured (but otherwise unconfirmed as PSVT/PAfib) symptom event or an EKG-validated PSVT/PAfib recurrence), or until 3 months had elapsed. The pre-specified objective was to compare the time to symptomatic recurrence of events in the two groups during each phase of the study.

PROTOCOL:

- **Enrollment criteria:**

Eligible for enrollment were adults of either sex in whom there was a history of recurrent symptomatic attacks of PSVT, or PAfib. Excluded from enrollment were pregnant women and women of childbearing potential as well as those subjects manifesting:

- a requirement that antiarrhythmic medication not be withdrawn.
- symptoms of hemodynamic collapse during tachycardia.
- left ventricular ejection fraction (LVEF) < 25%, uncontrolled cardiac failure, myocardial infarction or unstable angina within 3 months, sinus node dysfunction, AV block greater than first degree, or hypertension.
- clinically significant hepatic, or renal disease.

[1]five additional randomized subjects had chronic atrial fibrillation and were appropriately excluded from the analyses.

▸ **Qualifying criteria:**

Patients qualified if, after withdrawal of their usual antiarrhythmic medication, they manifested at least two additional EKG-documented recurrences of paroxysmal atrial arrhythmia within three months.

▸ **Treatment regimen:**

Patients were sequence-randomized to placebo, or propafenone (given in equally divided twice-daily doses[2]). In phase I of the study patients were administered a half-dose (as opposed to the final dose ("full dose") for the study phase) of propafenone (300 mg/d) for 7 days, and then force-titrated to a fixed full dose (600 mg/d) for the remainder of the treatment period. No inter-period drug washout was described. The completers of this first phase of the study proceeded without re-randomization[3] to a 2 period crossover between placebo, and a higher dose of propafenone (given in equally divided thrice-daily doses). During phase II patients were administered a half-dose of propafenone (450 mg/d) dose for 7 days and then force-titrated to a fixed full dose (900 mg/d) for the remainder of a treatment period. Each crossover period continued until there was a symptomatic recurrence of atrial tachycardia, or until 3 months had elapsed. Breakthrough arrhythmias were treated either with direct-current cardioversion or standard pharmacological agents (with no protocol specification that these agents be washed out before initiation of the crossover).

▸ **Endpoints:**

Patients kept diary records of symptomatic events possibly attributable to PSVT or PAfib (palpitations, light-headedness, dyspnea, or chest discomfort). They evaluated symptomatic severity by rating events according to duration and severity (using a scale in which zero represented no symptoms and 6 represented the most severe symptoms such as syncope or chest pain). Patients were equipped with portable EKG capturing equipment, and whenever possible symptom events were to be validated with EKG records (which were transtelephonically-transmitted).

For one set of submitted analyses only EKG-assessed symptomatic events were used, specifically the first EKG-validated event of PSVT or PAfib. For another set of submitted analyses the first diary-captured symptom event was used (which was not necessarily confirmed to be PSVT/PAfib).

The protocol specified that the efficacy endpoint would be the duration of the symptomatic recurrence-free interval for recurrences which met the threshold of "sufficient severity to warrant a change in therapy" [this data-filtering criterion, and the sponsor's claimed application of this criterion, are further discussed in the following section entitled "Datasets analyzed"]. The protocol also specified that the frequency of "minor attacks of paroxysmal tachycardia not deemed of sufficient severity to change treatment" would be evaluated. Another protocol-specified efficacy analysis was one in which "... the first 2 weeks under each treatment [within a given phase of the study] are taken into consideration."

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[2]the double-dummy method was used to maintain the blind.

[3]where placebo was administered during the last period of the first phase of the study the patient would receive propafenone during the first period of the subsequent phase, for example.

▸ **Statistical procedures:**

• **Datasets analyzed:**

Fifty two patients with PSVT, and 43 patients with PAfib were randomized. Eight PSVT and 7 PAfib patients were withdrawn prior to the phase I (44 PSVT patients and 36 PAfib patients entered phase II). Five PSVT patients and 3 PAfib patients were withdrawn during the phase II.

The principal analyses were based on a dataset which included non-compliers and other protocol violators. Patients completing 98 days without recurrence of the tachycardia were censored. Only patients who successfully completed both treatment periods of a study phase were included in the efficacy analyses. Five patients were excluded from all analyses because they erroneously entered the study with chronic atrial fibrillation.

Some efficacy analyses were also subjected to the following pre-specified forms of event filtering:

• **Event filtering according to symptom severity criteria:**

The protocol stipulated that patients would record all symptomatic events in a symptom diary, and patients are said by the sponsor to have been instructed to record an EKG during all of these events [as per the submission dated 4/18/94]. The protocol indicated that recurrent arrhythmias would not be counted unless the event met a pre-specified threshold of symptom severity, although the sponsor suggests that this type of event filtering was only applied to the analyses of diary-captured symptom events, as opposed to EKG-confirmed PSVT/PAfib events [submission dated 4/18/94].

Regarding the symptom severity threshold, the protocol specified that the arrhythmic events to be counted were "recurrences of paroxysmal tachycardia of sufficient severity to warrant a change in therapy... " where "sufficient severity" was assessed "...subjectively by the patient and clinical investigators, taking into account the duration of the attack and associated symptoms." Events that were counted after filtering the data according to these criteria will hereafter be referred to as "threshold symptomatic" events.

• **Event filtering according to time-of-event criteria:**

In the *"primary" analysis*, the dataset was subjected to additional pre-specified event filtering. In this analysis the sponsor further excluded:
- arrhythmias which recurred during the 7 days of dosing at half the final dose administered during a study phase, as well as
- arrhythmias which recurred during the first 7 days of dosing at the final dose level of a study phase.

The *"secondary" analysis* did not filter events according to time-of-event criteria, it thus included occurrences at any time during exposure to half-dose (days 0-7) or full-dose (days 7 and thereafter) therapy[4]. The *"tertiary" analysis* included only those events occurring on or after day 4 of full-dose therapy (i.e. day 11 of the study phase).

[4]some of these events would have plausibly occurred prior to the attainment of kinetic steady-state for full-dose therapy.

• **Analyses performed**:

The protocol specified that the efficacy endpoint (symptomatic recurrence-free interval) would be analyzed by a Cox proportional hazards model. The two phases of the trial were analyzed separately using identical statistical procedures. All tests were two sided and carried out at the 0.05 level. Statistically significant results are distinguished by confidence intervals which do not include equality (equality being 1 for relative risk, and 0 for difference in medians).

Retrospectively, the sponsor modified the Cox analysis by applying the method of France et al., (Stat. in Med 1991; 10: 1099-1113). According to this method the patient is said to "prefer" one treatment over the other when there was a longer recurrence time on that treatment, compared to the other. When there was no "preference" for placebo the values for relative risk of recurrence and median recurrence time could not be estimated by this method, but the statistical significance of the treatment effect was calculated using a Binomial or Sign test [although neither of these tests was pre-specified].

The sponsor also calculated the probability that the effect of any treatment-by-period interaction was smaller in magnitude than the treatment effect.

EFFICACY OUTCOMES:

▸ **Demographics**:

Approximately 91% of all enrolled patients did not have histories of cardiovascular disease. Patients had a mean age of 58 years. Fifty-two patients had PSVT, 43 patients had PAfib. The median duration of arrhythmia history for all patients was 5.5 years, and 70% of all patients had received prior antiarrhythmic drugs.

▸ **Period effects**

The statistical reviewer, Dr. Nuri, reports that he has not found evidence of period effects.

▸ **Correlation between symptom events and EKG evidence of arrhythmia**:

Although a number of submitted analyses were based on diary-captured symptomatic events which were not necessarily confirmed to be PSVT/PAfib, the sponsor has neglected to characterize the specificity of symptomatic complaints. It is known from the flecainide NDA experience that the specificity of symptom complaints is poor in patients with PSVT or PAfib. On 5/10/94 I inquired as to the relative proportions of symptomatic events which were associated with EKG evidence of PSVT and/or PAfib vs other arrhythmias vs no EKG evidence of arrhythmia.

▸ **Accuracy of Event Classification as Recurrence vs Adverse event:**

There were relatively small numbers of AE-classified events which may have represented misclassifications of arrhythmia recurrences among propafenone-receiving patients (these are discussed below). However, even assuming each to be a definite misclassification, the directionality of the observed difference in outcomes between propafenone and placebo would not reverse since the arrhythmia-classified events in the placebo groups greatly outnumber those in the propafenone groups. Given this treatment distribution of arrhythmia-classified events it is even implausible that an important degree of bias towards the overestimation of an arrhythmia-delaying effect of propafenone could have been introduced by such relatively small numbers of misclassifications.

The potential misclassifications were as follows: among PSVT patients receiving 600 mg/d propafenone there were 2 events which were classified as AE, but which involved "dizziness" [undefined] or frequent PSVT. However, the arrhythmia-classified events in the placebo group considerably outnumbered those in the propafenone group (32 vs 15, respectively). Similarly, among PSVT patients receiving 900 mg/d propafenone there were 5 events which were classified as AE, but which involved "dizziness" [undefined], lightheadness, or dyspnea (i.e. possible arrhythmia-equivalents). Yet the arrhythmia-classified events were much more numerous in the placebo group (20 vs 3 in the propafenone group).

Among PAF patients receiving 600 mg/d propafenone there were 4 events which were classified as AE, but for which the reported phenomena ("dizziness" [undefined] or Afib) raise the possibility of misclassified recurrences. The arrhythmia-classified events in the placebo vs propafenone groups numbered 21 vs 12, respectively). Among PAF patients receiving 900 mg/d propafenone there were 5 events classified as AE which involved "dizziness" [undefined] or lightheadness, nonetheless the arrhythmia-classified events in the placebo group greatly outnumbered those in the propafenone group (17 vs 1, respectively).

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ON ORIGINAL

▸ **Efficacy outcomes:**

● **Median Recurrence Times-** ***EKG-validated recurrences***:

Propafenone at 600 and 900 mg/d prolonged the time at which 50% of patients manifested a recurrence ("median recurrence time") of EKG-confirmed PSVT/PAfib events (a statistically significant prolongation, at least after 7 days of treatment). The point estimation for median recurrence time among propafenone-treated patients was 6.5 to 8.9 times greater than that for placebo. Although consideration of the protocol leads to the conclusion that this finding refers only to threshold-symptomatic arrhythmias, the sponsor indicates that the finding is irrespective of symptomatic severity. The data are shown below.

Table 1:

Median recurrence time (and 95% confidence interval), in days
[EKG results: study 88-3]

population & dataset	*PHASE I*		*PHASE II*	
	Placebo	*Propaf 600 mg/d*	*Placebo*	*Propaf 900 mg/d*
PSVT "primary" dataset	15 (9-34)	>98* (>98 - >98)	26 (7-97)	>98* (>98- >98)
"secondary" dataset	14 (8-30)	42 (16-96)[5]	14 (8-62)	108* (90-108)
PAF "primary" dataset	11 (9-17)	>98* (90- >98)	no estimate	* no estimate
"secondary" dataset	3 (2-8)	12 (6-70)[6]	4 (2-5)	>98* (28- >98)

[source: modification of tables 14A, 17A, & 17B; vol 60]

*Asterisks denote statistically significant differences from placebo ($p < 0.05$). Patients with AE causing withdrawal were censored. When no patients experienced longer recurrence time on placebo, median recurrence time was not estimable, although significance was calculated using the Sign test. The "**primary**" dataset excluded all arrhythmias which recurred during half-dose therapy (treatment days 0-7 of a study phase) or during the first 7 days of full-dose therapy (treatment days 7-14 of a study phase). The "**secondary**" dataset included arrhythmias occurring during half-dose therapy and at any time during full-dose therapy (treatment day 7 and thereafter of a study phase).*

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[5]the lower bound of the 95% confidence interval for the *difference* in median failure times for PSVT patients was: -14 days.

[6]the lower bound of the 95% confidence interval for the *difference* in median failure times for PAF patients was: -2 days.

● **Relative Risk of Arrhythmia Recurrence-** ***EKG validated recurrences***:

In both PSVT and PAfib patients propafenone (at 600 and 900 mg/d) had a statistically differentiable effect (at least after 7 days of treatment) to reduce the risk of a recurrence of EKG-confirmed PSVT/PAfib. The point-estimate for the risk of recurrence among placebo-treated patients was 1.5 to 16.0 times the risk for propafenone-treated patients (in the "primary" dataset). Once again, although consideration of the protocol leads to the conclusion that this finding refers to threshold-symptomatic arrhythmias, the sponsor indicates that the finding is irrespective of symptomatic severity. The data are shown below.

Table 2:

Relative risk (placebo : propafenone) of arrhythmia recurrence (and 95% confidence interval)
[EKG results: study 88-3]

Population and dataset	PHASE I	PHASE II
	Propaf 600 mg/d	*Propaf 900 mg/d*
PSVT		
"primary" dataset	7.4* (2.3 - 23.3)	15.0* (2.0 - 113)
"secondary" dataset	1.5 (0.8-3.0)	3.0* (1.3-7.2)
"tertiary" dataset	4.1*	16.0*
PAF		
"primary" dataset	5.7* (1.7 - 19)	* no estimate
"secondary" dataset	2.0 (0.9-4.6)	4.9* (1.4-16.7)
"tertiary" dataset	3.8*	4.9*

[source: modification of table 16, vol 60; table on pg 78 of 1/26/94 submission, & table in 3/18/94 submission]

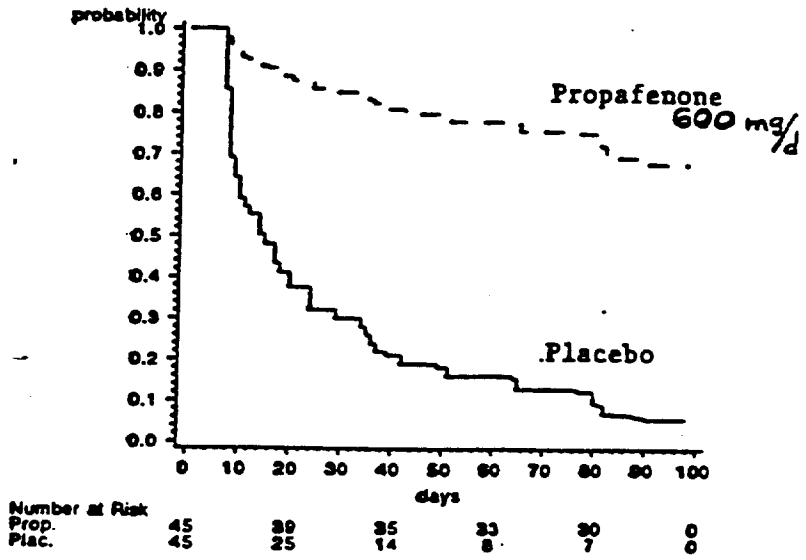
Asterisks denote statistically significant differences from placebo ($p < 0.05$). Patients with AE causing withdrawal were censored. When no patients experienced a longer recurrence time on placebo, relative risk was not estimable, although significance was calculated using the Sign test. The "primary" dataset excluded all arrhythmias which recurred during half-dose therapy (treatment days 0-7 of a study phase) or during the first 7 days of full-dose therapy (treatment days 7-14 of a study phase). The "secondary" dataset included arrhythmias occurring during half-dose therapy and at any time during full-dose therapy (treatment day 7 and thereafter of a study phase). The "tertiary" dataset included arrhythmias occurring on or after day 4 of full-dose therapy (treatment day 11 and thereafter in a study phase).

● **Arrhythmia-free Survival-** ***EKG validated recurrences in PSVT patients*** - 600 mg/d dose:

The results of a life table analysis of EKG-validated recurrences in PSVT patients receiving 600 mg/d propafenone are shown below.

Figure 1:

France-modelled estimates of the cumulative probability of arrhythmia-free survival among propafenone 600 mg/d-treated PSVT patients [EKG results: study 88-3]



[source: figure on pg 84 of submission dated 1/26/94]

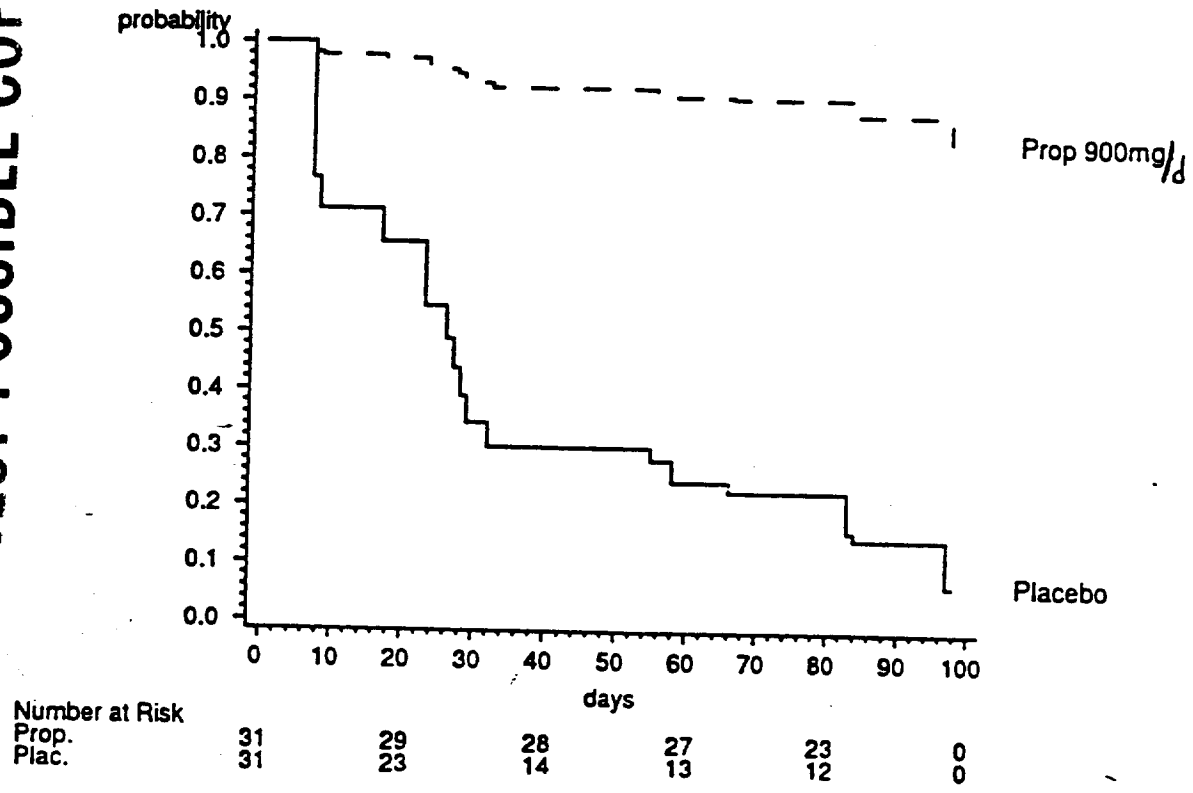
The analysis was based on a "primary" dataset which excluded all arrhythmias which recurred during half-dose therapy (treatment days 0-7 of a study phase), or during the first 7 days of full-dose therapy (treatment days 7-14 of a study phase). Patients with AE causing withdrawal were censored.

● **Arrhythmia-free Survival-** ***EKG-validated recurrences in PSVT patients*** **- 900 mg/d dose:**

The results of a life table analysis of EKG validated recurrences in PSVT patients receiving 900 mg/d propafenone are shown below.

Figure 2:

France-modelled estimates of the cumulative probability of arrhythmia-free survival among propafenone 900 mg/d-treated PSVT patients [EKG results: study 88-3]



[source: figure 9, pg 15866, vol 60; submission dated 1/26/94]

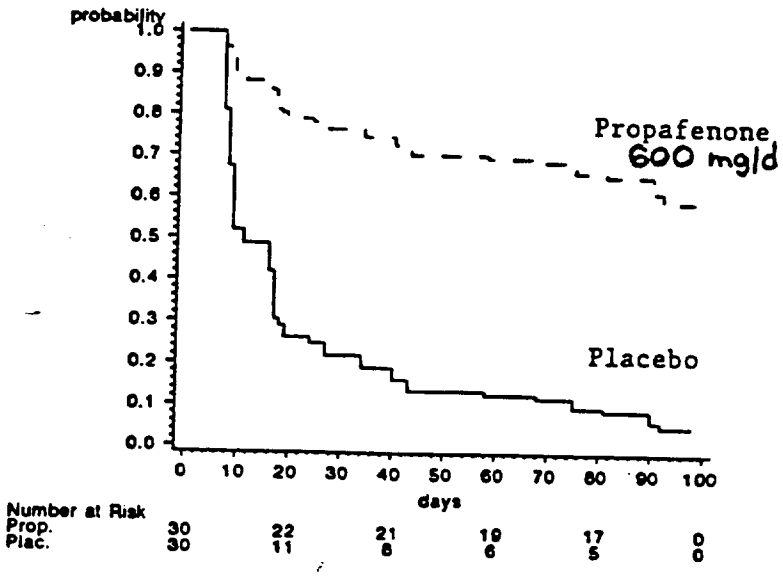
The analysis was based on a "primary" dataset which excluded all arrhythmias which recurred during half-dose therapy (treatment days 0-7 of a study phase), or during the first 7 days of full-dose therapy (treatment days 7-14 of a study phase). Patients with AE causing withdrawal were censored.

● **Arrhythmia-free Survival-** ***EKG-validated recurrences in PAfib patients*** - 600 mg/d dose:

The results of a life table analysis of EKG-validated recurrences in PAfib patients receiving 600 mg/d propafenone are shown below. In PAfib patients the survival curves for propafenone 900 mg/d vs placebo could not be modeled via the method of France since no patients experienced a longer time to recurrence on placebo than on propafenone.

Figure 3:

France-modelled estimates of the cumulative probability of arrhythmia-free survival among propafenone 600 mg/d-treated PAfib patients [EKG results: study 88-3]



[source: figure on pg 85 of submission dated 1/26/94]

The analysis was based on a "primary" dataset which excluded all arrhythmias which recurred during half-dose therapy (treatment days 0-7 of a study phase), or during the first 7 days of full-dose therapy (treatment days 7-14 of a study phase). The analysis was conducted according to the intent-to-treat principle with censoring of patients with AE causing withdrawal.

● **Median Recurrence Times-** ***Diary-captured symptom events***:

The median recurrence times for diary-captured symptom events (time at which 50% of patients had a recurrence of such events) are summarized below. It must be kept in mind that these events were not necessarily confirmed to be PSVT/PAfib recurrences (or any other arrhythmia for that matter). Conclusions are further limited by the presence of a statistically significant (p=0.006) treatment-center interaction. See the table below.

Table 4:

Median recurrence time (and 95% confidence interval), in days
[diary-captured symptom events: study 88-3]

population & dataset	*Placebo*	*Propafenone 600 mg/d*	*Placebo*	*Propafenone 900 mg/d*
PSVT "primary" dataset	12 (9-17)	>98* (41- >98)	15 (8-24)	>98* (>98 - >98)
"secondary" dataset	6 (3-8)	20* (10-58)	12 (6-21)	108* (49-108)
PAF "primary" dataset	8 (7-9)	>98* (43- >98)	no estimate	no estimate, & p value not reported
"secondary" dataset	1 (1-4)	15* (5-50)	4 (2-6)	74* (7- >98)

[source: modification of tables 14A & 17A, vol 60]

These analyses were subject to a significant treatment-center interaction (p= 0.006). Asterisks denote statistically significant differences compared to placebo (p < 0.05). Patients with AE causing withdrawal were censored. These events were not necessarily confirmed to be PSVT/PAfib recurrences. When no patients experienced longer recurrence times on placebo than on propafenone, median recurrence time could not be estimated, although significance was calculated with the Sign test. Both datasets excluded "insufficiently severe" events. The "primary" dataset further excluded all events which ocurred during half-dose therapy (treatment days 0-7 of a study phase) or during the first 7 days of full-dose therapy (days 7-14 of a study phase). The "secondary" dataset included events occurring during half-dose therapy and at any time during full-dose therapy (treatment day 7 and thereafter of a study phase).

● **Relative risk of Recurrence of *Diary-captured symptom events*:**

Propafenone (at 600 and 900 mg/d) had a statistically differentiable effect (at least after 7 days of treatment) to reduce the risk of occurence of diary-captured symptom events of symptomatic severity great enough to meet a pre-specified threshold for the counting of such events (which were not necessarily confirmed to be PSVT/PAfib recurrences). The point estimated placebo risk for these events was 2.1 - 10.5 times the risk of propafenone (as shown in the table below).

Table 5:

Relative risk (placebo : propafenone) of diary-captured symptom event (and 95% confidence interval) [study 88-3]

population & dataset	*Propafenone 600 mg/d*	*Propafenone 900 mg/d*
PSVT		
"primary" dataset	4.0* (1.8 - 8.8)	10.5* (2.5 - 45)
"secondary" dataset	2.1* (1.1 - 4.0)	3.1* (1.4 - 6.9)
PAF		
"primary" dataset	10.0* (2.3 - 42.8)	no estimate; and p value not reported
"secondary" dataset	2.8* (1.1 - 7.5)	3.3* (1.2 - 9.1)

[source: modification of table 16 , & table on pg 78 of submission dated 1/26/94]

*Asterisks denote results which were statistically differentiable from placebo ($p < 0.05$). These events were not necessarily confirmed to be PSVT/PAfib recurrences. When no patients experienced longer recurrence times on placebo than on propafenone, relative risk could not be estimated by the France method, although statistical significance was calculated with the Sign test. Patients with AE causing withdrawal were censored. Both datasets excluded "insufficiently severe" events. The "**primary**" dataset further excluded all events which ocurred during half-dose therapy (treatment days 0-7 of a study phase), or during the first 7 days of full-dose therapy (treatment days 7-14 of a study phase). The "**secondary**" dataset included events occurring during half-dose therapy and at any time during full-dose therapy (treatment day 7 and thereafter of a study phase).*

● **Propafenone effect on ventricular rate during recurrence:**

In PSVT patients the mean heart rate (HR) during arrhythmia recurrences was 37 beats/min (bpm) less during propafenone 600 mg/d treatment than during placebo treatment (p=0.006). A similar, although statistically nonsignificant finding was made in PAfib patients (in whom mean HRs were 23 bpm lesser during recurrences on propafenone than during recurrences on placebo). For the 900 mg/d propafenone dose no statistical comparison of this issue was reported.

● **Propafenone effect on severity of symptomatic recurrences:**

Although the sponsor asserted in their report that they found no effect of propafenone to reduce symptom severity, the analysis they conducted does not validate any such claim. They excluded in their analysis those recurrences of lesser severity than pre-randomization and thereby plausibly biased the assessment towards an underestimation of any propafenone effect to reduce symptom severity.

5. **SAFETY OUTCOMES:**

Deaths: The sponsor reports that no deaths were observed during the study.

Serious adverse events (AE):

Twenty three patients (28.4%) and 13 patients (13%) dropped out after receiving propafenone 900 mg/d vs 600 mg/d, respectively. One PSVT patient developed heart failure during propafenone 900 mg/d treatment.

One patient (1.1%) was reported to develop ventricular tachycardia (VT), which was plausibly a ventricular proarrhythmia. This frequency of 1.1% is comparable to the VT rate reported in the previously submitted study P-20-OR. The patient with VT (patient 27) was a 70 year old female with PAfib who manifested VT after about 3 months of therapy with propafenone 600 mg/d, and was successfully cardioverted.

Frequency of common AE:

The reported rates of common AE among PSVT vs PAfib patients are shown in the following two tables. These AE rates cannot be unambiguously compared to those previously described in study P-20-OR. Whereas the currently reviewed study had placebo controls, and AE analyses according to subgroups, study P-20-OR lacked these features. Comparisons between the two databases are further complicated by the nonidentical means of categorizing AEs.

Table 6:

Reported rates (%) of common AE among PSVT patients (study 88-3)

AE	*Placebo*	*Propafenone 600 mg/d*	*Propafenone 900 mg/d*
asthenia	4.5-7.7	7.7	9.1
AV block (1°)	0-1.9	3.8	2.3
chest pain/tightness	0-4.5	3.8	6.8
constipation	0	3.8	4.5
"dizziness"/ lightheadedness	6.8-7.7	9.6	13.6
headache	4.5-5.8	7.7	4.5
nausea/ vomiting	2.3-3.8	11.5	11.4
taste abnormality	0	3.8	9.1

[source: modification of tables 23, page 110, vol 60]

Frequency of common AE [continued]:

The reported rates of common AE among PAfib patients are shown below.

Table 7:

Reported rates of common AE among PAfib patients (study 88-3)

AE	*Placebo*	*Propafenone 600 mg/d*	*Propafenone 900 mg/d*
abdominal pain/flatulence	0-2.1	8.3	10.8
asthenia	2.7-6.3	6.3	8.1
AV block (1°)	0-2.1	18.7	13.5
constipation	0-2.1	8.3	5.4
diaphoresis/hot flush	0	6.3	13.5
diplopia/blurred vision	0	0	10.8
"dizziness"/faints/ vertigo	2.1-2.7	10.4	27.0
insomnia	0	2.1	5.4
nausea/vomiting	0-4.2	6.3	24.3
paraesthesia	0	4.2	5.4
respiratory infection	0	10.4	10.8
taste abnormality	0	10.4	8.1

[source: modification of table 24, page 113, vol 60]

COMMENTS (study 88-3):

A. The analysis of EKG-validated PSVT/PAfib recurrences in study 88-3 demonstrated that in both PSVT and PAfib patients oral propafenone (at 600 and 900 mg/d) had a statistically differentiable effect (at least after 7 days of treatment) to reduce the risk of developing a PSVT/PAfib recurrence. The point estimate for risk of recurrence in the placebo group ("primary" dataset) ranged from 1.5 to 15 times the risk of the propafenone-treated group.

Similarly, propafenone at 600 and 900 mg/d prolonged the time at which 50% of patients manifested a recurrence of EKG-confirmed PSVT/PAfib ("median recurrence time"). This prolongation was statistically significant, at least after 7 days of treatment. The point estimate for median recurrence time for propafenone-treated patients ranged from 6.5 to 24.5 times greater than that for placebo-treated patients.

B. The analysis of the "tertiary" dataset (which included only those events occurring on or after day 4 of full-dose therapy) supported the conclusion that by the time kinetic steady-state is attained (i.e. by day 4 of full-dose therapy[7]), statistically distinguishable efficacy against PSVT recurrence is manifest.

C. Propafenone at 900 mg/d appeared to be associated with at least tendencies toward greater effect than the 600 mg/d dose. However, it must be considered that recipients of 900 mg/d propafenone were a subset of those initially exposed to the 600 mg/d dose, and that the subset may have been enriched with therapeutic responders and/or subjects with a relative insensitivity to the adverse effects of propafenone.

D. That evidence of efficacy which was provided by study 88-3 was obtained largely in patients without structural heart disease, unlike the previously submitted studies (P-16-OR, and P-17-OR).

E. There are several reasons to not rely on the submitted analyses of diary-captured symptom events. Firstly, these events were not necessarily confirmed to be PSVT/PAfib recurrences (or any other arrhythmias for that matter). The NDA supporting the PSVT indication of flecainide revealed that symptoms attributed by patients to PSVT and/or PAfib are not very specific markers of these events. The sponsor of these propafenone data has, despite my request, neglected to characterize the specificity of symptom complaints in study 88-3.

Secondly, a significant treatment-center interaction was present to complicate one of the analyses of diary-captured symptom events.

Furthermore, the analyses of diary-captured symptom events characterized only threshold-symptomatic events, and the recurrence time for threshold-symptomatic events could plausibly be an overestimate of the recurrence time for *any* symptomatic event. This bias could plausibly have arisen secondary to a propafenone effect to reduce the symptomatic severity of recurrences. One cannot exclude the

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[7]Among the minority of patients (8% of the British population) who slowly metabolize propafenone the mean time to steady state is 3.6 days [Siddoway L.A. et. al. Circulation 75:785-791, 1987].

COMMENTS (study 88-3): [continued]

possibility of such an effect since the sponsor has not submitted an analysis of changes in symptom severity relative to pre-randomization events. Propafenone did substantially reduce ventricular rate during recurrences which, according to the conventional view, would ameliorate symptoms. In the published literature I have found support (and no convincing refutation) for this conventional view. Bhandari, et. al.[8] retrospectively pooled all the EKG-documented PSVT and PAfib events from patients in placebo-controlled flecainide trials and found that mean ventricular rates during PSVT attacks were significantly lower during asymptomatic events (by 25 bpm; $p < 0.05$). The same observation applied to PAfib attacks where, on average, heartrates were 10 bpm less during asymptomatic episodes ($p < 0.001$). Although some have suggested that the data of Page et. al.[9] support the contradictory view that ventricular rate does not influence symptom severity, the data do no support such a suggestion. Page and coworkers reported (in a mere 5 drug-free PAfib patients) that the 95% confidence interval for the difference in ventricular rates between symptomatic and asymptomatic arrhythmias was -13 bpm to 12.2 bpm. This clearly does not allow one to conclude with certainty whether asymptomatic events were associated with more or less tachycardia than symptomatic events. Another often cited flecainide report[10] did not describe drug effect on symptomatic severity per se.

F. Although in the absence of inter-period drug washout in this study there could have plausibly been an overestimation of AE rates among placebo-treated patients (on the basis of drug carryover), and a resultant underestimation of placebo-corrected AE rates among the propafenone-treated, Dr. Nuri (the statistical reviewer) reported that he found no evidence of carryover effects.

5. **Study P-16-OR: sponsor's errata**

The sponsor recently reported [submission dated 5/19/94] that they were in error in previously reporting [as summarized in my review dated 30 November 1993] that arrhythmic events occuring during treatment days 0-3 were excluded from analyses of study P-16-OR.

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[8]American Heart Journal 1992;124:381-386.

[9]Circulation 1994;89:224-227.

[10]Anderson J. et. al. Circulation 1989;80:1557-1570.

6. CONCLUSIONS REGARDING ALL THE SUBMITTED STUDIES:

A. Efficacy

Considering the results of all the studies submitted in this NDA efficacy supplement (P-16-OR, P-17-OR, P-20-OR, and PSD-88-3) the following conclusions are drawn:

i. The relatively large and well-controlled study 88-3 demonstrated that in both PSVT and PAfib patients 600 and 900 mg/d propafenone had a statistically differentiable effect to reduce the relative risk of developing an EKG-documented PSVT/PAfib recurrence, and to prolong the median recurrence time.

ii. In study P-16-OR a statistically significant prolongation of the median time to recurrence of arrhythmias of any symptomatic severity was reported [see my report dated 30 November 1993]. Concerns had been raised by my FDA statistical colleagues about unrecognized type I error (potentially arising from the analysis of a small sample by a method based on large sample theory). However, Dr. Nuri (the current statistical reviewer) indicates that the sponsor's subsequent submission of a simulation of a permutation test is now adequate to obviate concerns about type I error.

iii. Study P-17-OR found that palpitations were recorded during a statistically significantly lesser mean proportion of randomized treatment days in propafenone-treated PSVT patients (15.8%), relative to placebo-treated patients (29.7%; two-sided p= 0.004). This provides additional supportive evidence of the efficacy of propafenone.

iv. I had previously expressed concerns (report dated 11/30/93) that studies P-16-OR, and P-17-OR did not characterize phenomenology in patients without structural heart disease. This is no longer a concern since study 88-3 included substantial numbers of such patients.

B. Safety:

i. What has been estimated, in supraventricular arrhythmia patients, is the relative risk of death *while being administered propafenone*. This estimate was based on an historical comparison of study P-20 data vs the Duke University database. As discussed in my report of 30 November 1993, the age-adjusted hazard ratio for survival during administration of drug (i.e. the ratio of surviving propafenone-treated patients: to those surviving on potentially proarrhythmic treatments other than propafenone) was estimated to be 0.95 (95% CI of 0.4 to 2.2).

There has not been any submitted documentation of patients' survival status during the days immediately after stopping the administration of propafenone (despite the fact that during this time patients were continuing to be systemically exposed to propafenone prior to its complete elimination).

7. RECOMMENDATIONS:

A. Barring any important revelations brought to light by further inspection of the data, propafenone should be approved for the treatment of PSVT/PAfib with labelling which conveys the limitations of the available survival estimate (i.e. with labelling which communicates that the estimate is relative to other potentially lethal antiarrhythmics, and which indicates that there was no accounting for any fatalities which may have occurred during washout of propafenone).

B. In the interest of advancing FDA's understanding of the limits of current research methodology the sponsor should be required to interrogate the study 88-3 database, the largest atrial supraventricular experience ever submitted to the agency, in order to characterize the specificity of symptoms attributed by patients to PSVT and/or PAfib.

Steven M. Rodin MD 6/23/94

Steven M. Rodin, MD Date
Medical Officer

cc: RFenichel/HFD-110; CSO/HFD-110; division file/HFD-110; * **no copy to S.Rodin**

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NOV 30 1993

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Medical Officer

Food and Drug Administration

Division of Cardio-Renal Drugs
Tel 301-443-0320; FAX-9283

Medical Review of NDA Efficacy Supplement

1 General information

NDA #:	19-151/ S2
Drug:	propafenone hydrochloride (Rhythmol®, Knoll Pharmaceuticals)
Proposed indication:	prophylaxis of paroxysmal supraventricular tachycardia (PSVT)
Pharmacologic type:	antiarrhythmic (class 1C)
Dosage:	450-900 mg/d p.o.
NDA classification:	6S
Date of NDA submission:	3 December 1992
Latest data submission:	24 November 1993
Review last revised:	30 November 1993

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3 Chemistry

See the chemist's review for a detailed discussion of chemistry. Briefly, propafenone is a racemic mixture with the formal name, 2'-[2-hydroxy-3-(propylamino)-propoxy]-3-phenylpropiophenone hydrochloride.

4 Preclinical Pharmacology

See the pharmacologist's review for a detailed discussion of pre-clinical pharmacology. Briefly, propafenone is a class Ic antiarrhythmic with local anesthetic effect, membrane stabilizing effect, and low potency beta-adrenergic antagonist action.

5 Clinical Pharmacokinetics and Pharmacology

Propafenone is approved in the United States for the treatment of life-threatening ventricular arrhythmias. See the original NDA for a detailed discussion of clinical pharmacokinetics and pharmacology. Briefly, propafenone is absorbed after oral administration and produces peak plasma concentrations approximately 2-3 hours after administration by this route. Propafenone undergoes extensive hepatic metabolism, including a large first-pass effect (the absolute bioavailability of tablets ranges from 3-10%). The oral kinetics are nonlinear (a more than proportional increase in AUC results from a given increase in either single or steady-state dose). There is large inter-subject variability in kinetics which has been attributed to metabolic polymorphism. There are two genetically-determined patterns of metabolism (extensive vs poor metabolizers). Poor metabolizers have a longer elimination half-life, lower oral clearance, and higher plasma concentrations than do extensive metabolizers. The poor metabolizers achieve steady-state within approximately 72 hours. In poor metabolizers the higher plasma concentrations of parent drug are offset, at least in part, by the reduced formation of an active metabolite.

The two enantiomers of propafenone have different β-adrenergic antagonist activity, but similar sodium channel blocking activity. In humans, propafenone has been shown to slow atrioventricular conduction, to prolong QRS duration, to suppress premature ventricular contractions (PVCs), and to delay the recurrence of ventricular tachycardia. Propafenone doses of 450-900 mg/d produce clinical PVC suppression in both types of metabolizers. The drug also exerts a negative inotropic effect and is pro-arrhythmic (causing new or worsened arrhythmias).

6 Clinical efficacy trials

6.1 Oral propafenone effect on symptomatic PSVT (study P-16-OR)!

SUMMARY:

This placebo-controlled, double-blind, two-period crossover study randomized 25 subjects (patients with symptomatic paroxysmal atrial fibrillation (PAfib), paroxysmal atrial flutter (PAFL), or paroxysmal atrial tachycardia (PAT[1]) who tolerated propafenone during an open-label run-in phase) to receive placebo, or propafenone (600-900 mg/d) in a sequence-randomized crossover. Patients underwent transtelephonic monitoring of symptomatic tachycardia episodes for up to 8 weeks during each period. The objective was to compare the time to first recurrence of tachycardia during each double-blind period.

PROTOCOL:

▸ **Enrollment criteria:**

Enrolled subjects were adults of both sexes in whom there was documentation of either PAT, PAfib, or PAFL within 6 months of the study's initiation. Arrhythmia definitions were as follows:

PAT: a) mean rate ≥ 120 beats/min (bpm); b) QRS morphology during tachycardia that was either normal or functional left bundle branch block (LBBB); c) regular ventricular rate (0.02 sec variation in successive RR intervals); and d) no evidence of AV dissociation.

PAfib: a) mean rate ≥ 120 bpm; b) QRS morphology that was functional LBBB or functional RBBB; c) irregularly irregular ventricular rhythm; and d) absence of a "sawtooth" appearance of the baseline in standard EKG leads.

PAFL: a) mean rate ≥ 120 bpm; b) QRS morphology that was normal or functional LBBB; and c) absence of isoelectric period in the EKG baseline, and a "sawtooth" appearance of the baseline in one or more standard EKG leads.

Excluded from enrollment were pregnant women and women of childbearing potential as well as those subjects manifesting:

- severe valvular disease, uncontrolled cardiac decompensation, acute myocardial infarction, or open heart surgery within the previous 3 months
- second or third degree AV block, complete bundle branch block, intraventricular conduction delay greater than 0.12 seconds, prolonged QT_c interval, or resting ventricular rate less than 55 bpm
- severe obstructive pulmonary disease
- diabetes mellitus not controlled by diet alone
- history of cerebrovascular disease or stroke

[1]PAT denotes paroxysmal supraventricular tachycardia other than PAfib or PAFL.

▸ **Maintenance of blinding:**

Dr. Stan Lin has pointed out that the sponsor, in an internal correspondence dated 3/7/86, had openly identified the randomization schedule. The sponsor reports [in an addendum dated 11/24/93] that the study randomization code was broken on a patient by patient basis beginning on 6/24/86, and that copies of the code were given to various company employees, but not to the analyzing statistician until the study was completed.

▸ **Qualifying criteria:**

After washout of previous antiarrhythmic drugs, patients were enrolled in an open-label run-in (lasting up to 6 months) during which propafenone was started at 600 mg/d (300 mg b.i.d.) with optional downtitration if not tolerated. As tolerated, doses were uptitrated to 900 mg/d (300 mg t.i.d.). Tachycardia recurrences were only if they occurred ≥ 3 days after a dosage uptitration (to allow attainment of steady-state). Patients who tolerated propafenone were to be randomized at the time of first tachycardia recurrence, or after 90 days (in cases without recurrence).

▸ **Randomized treatment regimen:**

Qualified patients were randomized into a placebo-controlled, two-period, double-blind crossover study. During the crossover the propafenone dosage was fixed at the level which was maximally tolerated during the run-in (generally 600-900 mg/d). Each period continued for 60 days or until an episode of symptomatic tachycardia (whichever came first). Between double-blind periods each patient was to receive open-label propafenone for 3-7 days.

▸ **Endpoints:**

Patients underwent symptom-triggered transtelephonic monitoring of EKGs for up to 8 weeks during each treatment period. The prospectively-defined primary efficacy endpoint was the time to first recurrence of tachycardia. A delay of 3 days after the start of each double-blind phase was instituted before counting an observed tachycardia event (to provide for the attainment of a new steady-state). There were no prospectively defined secondary endpoints.

▸ **Statistical procedures:**

• **Dataset analyzed:**

Thirty nine patients entered the open-label run-in, but 15 were excluded from the efficacy analysis. Fourteen of these exclusions were withdrawn prior to randomization (7 were nonresponders, and 7 had adverse events (including pro-arrhythmia, anorexia, diarrhea, and increased pacing threshold)). One patient was censored after withdrawing from the study with motor vehicle trauma. Included in the efficacy analysis were 15 with PAT and 9 with PAfib or PAFL.

▸ **Statistical procedures** [continued]:

• **Pre-specified analyses**:

The protocol pre-specified that the statistical analysis would employ life-table methods for censored survival data, although no discrete testing procedure was prospectively identified. Additionally, no prospective subgroup analyses were performed for PAfib/PAFL vs PAT patients, or for patients with structural heart disease vs. without structural heart disease.

RESULTS:

▸ **Exposure to randomized therapy**:

Among those enrolled in the open-label phase, the maximally tolerated propafenone dose was 300, 600 and 900 mg/d in 1, 11, and 27 patients, respectively.

▸ **Time and Sequence effects**:

No analyses of time or sequence effects were submitted.

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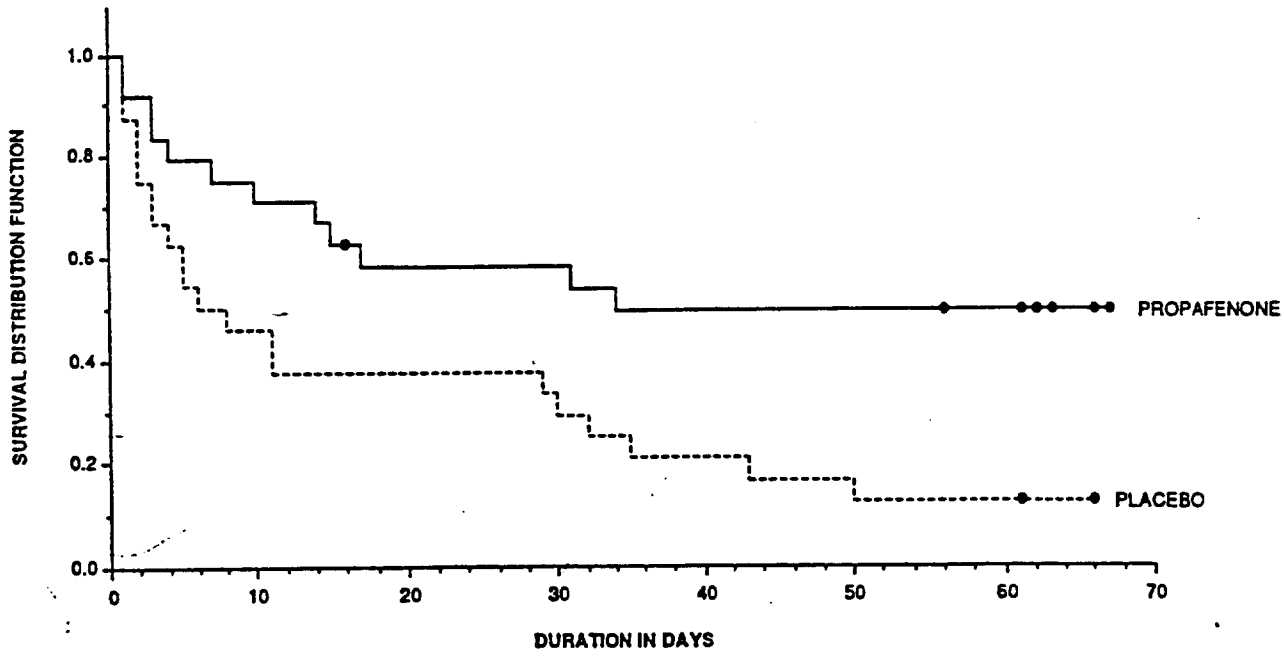
Study P-16-OR

- **Efficacy outcomes:**
  - **Survival curves:**

Figure 1:

Kaplan-Meier survival analysis (study P-16-OR)



Note: • represents censored observations.
* Each treatment group includes the same 24 patients.

- **Results of analyses of tachycardia recurrence:**

Although no discrete test was prospectively identified, the protocol did pre-specify that life-table methods for censored survival data would be employed. The sponsor applied a procedure (the Paired Prentice-Wilcoxon (PPW) test) which was not inappropriate (and which has historical precendent insofar as it was used in the two principal crossover studies contained in the approved flecainide NDA supplement for PSVT). By the PPW test the treatment effect on median recurrence time was statistically significant (two-sided p value = 0.008).

The sponsor also applied the Wilcoxon rank sum test and found (among all analyzed patients) that the median recurrence time was significantly longer in the presence of propafenone (two-sided p value = 0.02), but that the difference was not significant among the subgroups of PAfib/PAFL vs PAT (p = 0.11 to 0.15 in the subgroups)[2].

Although negative findings were reported by the FDA statistical reviewer (2-sample log-rank test: $p \geq 0.21$), upon questioning he (Dr. Stan Lin) stated that his was not a more justified approach, and that the sponsor's test is more appropriate.

Table 1:

Median time (in days) to first tachycardia recurrence (study P-16-OR)

Population	*Treatment group*	*Median recurrence time (days)*	*p value (2-sided PPW test)*
All [n=24]	Placebo	13	0.008
	Propafenone	34	
PAfib/PAFL [n=9]	Placebo	3	not reported
	Propafenone	46	
PAT [n=15]	Placebo	24	not reported
	Propafenone	30	

[source: modification of table on page 1145 of vol 7]

The data were analyzed by a PPW sum test.

[2]the sponsor also described putatively positive results of a Cox proportional hazards analysis, although when questioned they noted that this model is not appropriate for use with a crossover study.

- **Results of analyses of tachycardia recurrence** [continued]:

Table 2:

Difference in median time to first tachycardia recurrence (study P-16-OR)

Analyzed group	*propaf minus placebo*	*p value*
All [n=24]	9.5 days	0.02
PAfib/PAFL [n=9]	38 days	0.11
PAT [n=15]	8 days	0.15

[source: modification of table on page 3 of addendum dated 7/8/93]

The data were analyzed by a Wilcoxon rank sum test.

Tachycardia-free survival rates were also presented by the sponsor. This was a descriptive (and retrospective) analysis, and no statistical comparisons were made.

Table 3:

Estimated tachycardia-free survival rate [and 95% CI] (study P-16-OR)

Analyzed population	*1 month*		*2 months*	
	Propaf	Placebo	Propaf	Placebo
All [n=24]	0.54 [0.32, 0.75]	0.29 [0.10, 0.48]	0.49 [0.28, 0.71]	0.13 [0, 0.26]
PAfib/PAFL [n=9]	0.67 [0.30, 1.00]	0.22 [0, 0.54]	0.67 [0.30, 1.00]	0.22 [0, 0.54]
PAT [n=15]	0.46 [0.18, 0.74]	0.33 [0.07, 0.59]	0.38 [0.10, 0.66]	0.07 [0, 0.21]

[source: modification of table on pg 1143, vol 7 & page 3 of addendum dated 11/12/93]

For PAfib/PAFL patients, those who had a tachycardia had it during the first month with no additional patients having a tachycardia in the second month.

COMMENTS (study P-16-OR):

1. According to life-table analysis (the most appropriate way to analyze these data), in PSVT patients the median time to first tachycardia recurrence was prolonged by propafenone (34 vs 13 days in placebo-treated patients). Although no discrete test was prospectively identified, the protocol did pre-specify that life-table methods for censored survival data would be employed. The sponsor's PPW test was not an inappropriate tool (and it has precendence, having been used in the approved flecainide NDA efficacy supplement for PSVT). By the PPW test the treatment effect on median recurrence time was statistically significant (two-sided p value = 0.008), as it was according to the Wilcoxon rank sum test (two-sided p value = 0.02). A sole negative finding was perhaps overemphasized in the FDA statistical reviewer (2-sample log-rank test: $p \geq 0.21$), since it is not Dr. Stan Lin's view that the log-rank test is a more justified analysis for this study or even as appropriate as the PPW test.

2. Time and sequence effects remain to be adequately analyzed by the sponsor. Nancy Smith, in her flecainide NDA review, asserted that the PPW test for censored paired data (used here in the sponsor's propafenone analysis) does not account for time or sequence effects. Dr. Smith has previously pointed to the applicability of a non-parametric crossover method proposed by Gary Koch.

3. No prospective subgroup analyses were performed to provide evidence for efficacy in the population for which any approved use in PSVT would likely be restricted (i.e. patients without structural heart disease).

4. In this small study, seven patients were withdrawn during the open-label phase with manifestations of nonresponse to therapy. This was in violation of the prospective analysis plan to randomize patients (rather than remove them) at the time of first recurrence. This further enriched an already highly selected population, hence one cannot draw accurate inferences about the incidence of response in an unselected group.

5. Although there was no apparent characterization of specific mechanisms of arrhythmia, PSVT (as defined in this study) is generally secondary to AV reentry, or AV nodal reentry.

6.2 Oral propafenone effect on symptomatic PSVT (study P17-OR)

SUMMARY:

This placebo-controlled, double-blind, 4-period crossover study randomized 22 subjects (patients with histories or previous EKG evidence of PAT[3] and/or PAfib/PAFL who responded to and tolerated propafenone during an open-label run-in phase) to receive placebo, or propafenone (450-900 mg/d) in a sequence-randomized crossover. The objective was to assess drug-associated differences in the patient-reported symptoms during 4 week treatment periods. Symptom-concomitant EKG confirmation of PSVT events was not obtained in the majority of efficacy-analyzed patients.

PROTOCOL:

▸ **Enrollment criteria:**

Enrollment criteria were similar to those described above under study P-16-OR, except for the presence of the following additional exclusion criteria in the present study:

- Afib with Wolf-Parkinson-White syndrome, sick sinus syndrome, unstable angina, or systolic blood pressure below 95 mm Hg
- clinically significant renal or hepatic failure
- clinically significant electrolyte imbalance
- bleeding diathesis

▸ **Qualifying criteria:**

After washout of previous antiarrhythmic drugs, patients were enrolled in an open-label run-in during which propafenone was started at 450 mg/d (150 mg tid) and uptitrated as tolerated to 900 mg/d (300 mg tid).

▸ **Randomized treatment regimen:**

Patients who responded to propafenone and did not manifest a serious adverse event during the open-label phase were randomized into a placebo-controlled, double-blind, 4-period, crossover study. The propafenone dosage was fixed at the level which was maximally tolerated during the run-in (generally 450-900 mg/d). At intervals of 4 weeks patients were switched from propafenone to placebo or from placebo to propafenone. No drug washout periods were interposed between treatment periods.

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[3]the definition of PAT is equivalent to that used in study P-16-OR, although the term was interchanged with the term "PSVT" in the sponsor's report of study P-17-OR.

Study P-17-OR

▸ **Endpoints:**

No efficacy endpoints were explicitly pre-specified in the protocol. The sponsor reported an analysis of the proportion of randomized treatment days in which the patient made a diary recording of at least one of the following symptoms: palpitations, lightheadedness [the sponsor interchanges this term with the term "dizziness"], dyspnea, or chest discomfort [interchanged with the term "angina"]. This endpoint was based on the total days in a crossover period, and the total days with a symptom present, even if the patient was off drug at some time during the period. The association of symptoms with documented PSVT events was largely unconfirmed. Moreover, symptoms reported prior to the presumed attainment of steady-state (i.e. prior to the fourth day of double-blind therapy) were counted as events (unlike in study P-16-OR). Twenty-four hour Holter EKG recordings were also obtained prior to treatment, at the end of the open-label phase, and at the end of each double-blind period.

▸ **Dataset analyzed:**

Thirty three patients entered the open-label phase. Eleven patients withdrew prior to randomization, including six nonresponders[4]. Only those patients who were exposed to placebo and propafenone for a least 3 days each during 2 or more randomized periods were included in the efficacy analysis. Overall, the efficacy-analyzed dataset comprised 18 patients. The underlying disease among the efficacy-analyzed patients was PAT in 8, PAfib or PAFL in 9, and both PAT and PAfib in 1. Seventy-two percent were male. Two randomized patients were excluded from the efficacy analysis with symptoms that are not readily differentiable from those associated with nonresponse. One of these patients (170-52) had recurrent palpitations during double-blind propafenone therapy, and the patient (170-51) discontinued after developing what may have plausibly been an arrhythmia-equivalent (i.e. "dizziness")[5].

Table 4:

Patients in the efficacy-analyzed dataset (study P-17-OR)

Arrhythmia	PT[1]	TP[1]	TOTAL
PAT	170-50, 171-3, 171-6, 171-8	171-4, 171-5, 171-7, 172-8	8
PAF	172-4, 172-6, 172-7, 172-9, 172-12, 172-15, 172-17	172-2, 172-14	9
PAT & PAF		172-5	1
TOTAL	11	7	18

Study Numbers: 170 - Dr. Brodsky, 171 - Dr. Klein, 172 - Dr. Connolly
[1]PT = Placebo followed by propafenone
[1]TP = Propafenone followed by Placebo

[source: modification of photocopy of table on pg 1684 of vol 9]

[4]including patient 172-1.

[5]headache and nausea were also reported in this case.

Study P-17-OR

- **Pre-specified analyses:**

No statistical analyses were pre-specified in the protocol.

- **Analyses performed:**

Retrospectively, the Wilcoxon signed rank test was used to assess treatment group differences in the proportion of days in which at least one symptom was recorded. This analysis was based on the total days in a crossover period and the total days with a symptom present, even if the patient was off drug at some time during the period. With respect to the primary endpoint, no prospective subgroup analyses were performed for PAfib/PAFL vs PAT patients, or for patients with structural heart disease vs. without structural heart disease.

Holter monitoring data was retrospectively evaluated for mean frequency of supraventricular premature beats (SVPBs). A log transformation [LN (SVPBs/hr + 1)] was applied in a model utilizing subject, period and treatment as covariates. Statistical analysis of these Holter data also utilized the Wilcoxon signed rank test.

RESULTS:

- **Exposure to Nonrandomized therapy:**

No potentially confounding additions of concomitant medication were reported.

- **Exposure to randomized therapy:**

Among those enrolled in the open-label phase, the maximally tolerated propafenone dose was ≤300, 600 and ≥900 mg/d in 3, 15, and 14 patients, respectively. The median dose among efficacy-analyzed patients was 600 mg/d.

- **Specificity of symptom "markers" of PSVT:**

In the 6 efficacy-analyzed patients with double-blind, symptom-concomitant EKG data, 14% of the symptoms occurred while the EKG showed no evidence of PSVT.

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▸ **Time and Sequence effects:**

An analysis of sequence and period effects was reported to reveal no significant differences among periods or treatment sequences for any of the 4 symptomatic events analyzed ($p \geq 0.30$, two-sided).

▸ **Percentage of Symptomatic days among All patients:**

Shown below are the mean percentage of symptomatic days during randomized treatment for the overall efficacy-analyzed dataset.

Table 5:

Mean percentage of symptomatic days during randomized treatment
[All efficacy-analyzed patients in study P-17-OR]

symptom	*propaf (%)*	*placebo (%)*	*two-sided p value*
palpitations [n=17]	15.8	29.7	0.004
lightheaded [n=13]	6.3	12.0	0.094
dyspnea [n=10]	15.1	15.8	0.41
chest discomfort [n=10]	11.3	17.7	0.052

[source: modification of table on pg 1685, vol 9]

Shown are the results of the Wilcoxon signed rank test.

▸ **Percentage of Symptomatic days among Subgroups:**

Shown below are the results of the sponsor's retrospective analysis of the mean percentage of symptomatic days during randomized treatment for the subgroups, PAT vs. PAfib/PAFL.

Table 6:

Mean percentage of symptomatic days, for any symptom, among patient Subgroups (P-17-OR)

Subgroup	*propaf (%)*	*placebo (%)*	*two-sided p value*
PAT [n=8]	4.0	15.0	0.02
PAfib/PAFL [n=10]	39.1	51.1	0.15

[source: modification of table 1, addendum dated 10/6/93]

Shown are the results of the signed rank test.

- **Holter monitoring results:**

Table 7:

Frequency of supraventricular premature beats, by Holter monitoring (study P-17-OR)

symptom	*pre-treatment* *[n=9]*	*after propaf* *[n=16]*	*after placebo* *[n=16]*	*two-sided p value*
mean # SVPBs/day	2,762	1,115	1,707	0.17
mean log transform	5.4	2.9	3.7	0.072

[source: modification of table on pg 1686, vol 9; and pg 6 of addendum dated 4/5/93]

Shown are the results of the Wilcoxon signed rank test. The log transformation was [LN (SVPBs/hr + 1)].

- **Efficacy in patients without structural heart disease:**

The sponsor did not conduct an *a priori* analysis to establish efficacy in patients without structural heart disease, that being the subgroup for which any approved use in PSVT would likely be restricted.

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COMMENTS (study P-17-OR):

1. On the mean, palpitations were recorded during a lesser proportion of randomized treatment days in propafenone-treated PSVT patients (15.8%), relative to placebo-treated patients (29.7%). Although the analysis used to ascribe statistical significance to this finding (i.e. a Wilcoxon signed rank test which generated a two-sided p value of 0.004) was not explicitly pre-specified, it remains a convincing finding. It is noteworthy that the value of this metric is limited since it provides no assurance that a drug which decreases the proportion of symptomatic days does not expedite the onset of the first recurrence, or promote more numerous or more severe symptoms on those days in which symptoms are present.

2. There exist two potential sources of bias towards underestimating propafenone effect in this study. Firstly, symptomatic events occurring within the first three days of initiating propafenone were to be counted even though steady-state would not necessarily have been achieved. Secondly, the occurrence of symptoms in the placebo group may have been masked during the first three days after discontinuing propafenone, on the basis of persistent serum drug levels (although the sponsor asserts that an analysis of sequence effects was negative, the power of this analysis could not plausibly have been very great, nor was it reported).

3. The sponsor's analysis excluded two propafenone-randomized patients (who were already screened for their propafenone responsiveness) because of symptoms that are not readily differentiable from those associated with nonresponse. One patient had recurrent palpitations during double-blind propafenone and the other had what was plausibly an arrhythmia-equivalent symptom. This further enriched an already highly selected population, hence one cannot draw accurate inferences about the incidence of response in an unselected group.

4. No prospective subgroup analyses were performed to establish efficacy in the population for which any approved use in PSVT would likely be restricted (i.e. patients without structural heart disease).

5. Symptom-concomitant EKG confirmation of PSVT events was not obtained in the majority of efficacy-analyzed patients. Data external to and within this NDA suggest that patient-reported symptoms are less than highly specific for PSVT. It is plausible that at least one action of propafenone is to reduce symptoms not associated with PSVT (as appeared to be the case in the flecainide NDA database).

7 Safety:

7.1 A nonrandomized, positive-controlled comparison of mortality: (propafenone study P-20-OR vs the Duke University clinic database)!

Background:

In the absence of longterm, placebo-controlled mortality data, the sponsor presented the results of a nonrandomized, positive-controlled comparison of mortality among propafenone-treated PSVT patients (study P-20-OR) vs an historical control group (Duke University database) of PSVT patients treated with a variety of other antiarrhythmic agents.

Summary:

Study P-20-OR was an open-label, uncontrolled trial in which 480 PSVT patients were treated with propafenone (450-900 mg/d) an followed up for a median of 206 days. The historical control (Duke database) included 229 PSVT patients treated with a variety of drugs other than propafenone (including type Ia and Ic antiarrhythmics, calcium antagonists, β-adrenoreceptor antagonists, and digoxin).

Datasets analyzed:

In the P-20-OR dataset 474 patients were included in the survival analysis, whereas 194 patients were included in the survival-analyzed dataset of Duke clinic patients.

Six patients in study P-20-OR were enrolled with ventricular tachycardia, in violation of protocol. These six patients (among whom were 2 deaths) were excluded from the study P-20-OR database. Forty eight patients in the Duke database had been exposed at one time or another to propafenone. Thirty-five of these 48 patients had been exposed to propafenone in clinical investigations, and the data from these were excluded from the Duke database, and included in the P-20-OR database. The other thirteen patients were exposed to propafenone outside of a research study, and for these the data were censored on the first day of propafenone therapy.

Statistical methods:

Kaplan-Meier survival curves were generated, and the Cox proportional hazards model was used to compare mortality between the two populations. Age, race, sex, and the presence of structural heart disease were evaluated as potential effect modifiers and confounders of the relative survival of the two databases. Any covariate that could not be omitted from the Cox model without causing a significant change in the coefficient was included in the final model as a confounder without regard to the statistical significance of its own coefficient.

The homogeneity of survival over two strata (defined by the presence or absence of structural heart disease) was tested with the Log-Rank and the Wilcoxon tests.

No intent-to-treat analyses were submitted.

Patient populations:

On average, the patients in the propafenone-exposed database were older. In the Duke database structural heart disease was more prevalent, and the median duration of followup was much greater. For the 474 patients who remained in the survival-analyzed P-20-OR dataset, the median length of follow up was 206 days. For the 194 patients who remained in the survival-analyzed Duke clinic dataset, the median length of follow up was 1,565 days. See the table below.

Table 8:

Demography in the nonrandomized comparison of mortality

data-base	n	WPW present	PAT as principle arrhythmia	PAfib or PAFL as principle arrhythmia	structural heart disease present	mean age	median follow-up (days)
study P-20-OR	474	10%	58%	42%	55%	57	206
Duke clinic	194	not reported	77%	23%	40%	43	1565

[source: modification of table on pg 2248, vol 11; and addendum dated 4/27/93]

Antiarrhythmic drug exposure:

In the Duke database, patients were treated with a variety of drugs including type Ia and Ic antiarrhythmics, calcium antagonists, β-adrenoreceptor antagonists, and digoxin. The sponsor reports that adequate data are not available for categorizing the distribution of specific antiarrhythmic agents.

[CONTINUED NEXT PAGE]

Antiarrhythmic drug exposure [continued]:

In study P-20-OR the median propafenone dose was 600 mg/d. The distribution of doses is shown in the following table.

Table 9:

Extent of propafenone exposure in study P-20-OR

doseage group (mg/d)	mean days exposed
any	431
≤449	30
450-599	101
600-899	171
≥900	308

[source: modification of table on page 4992, vol 22]

Completeness of patient followup:

There was extensive loss to followup in study P-20-OR. Of the 480 PSVT patients initially treated with propafenone, 290 were lost to followup in the first year, and 444 patients were lost to followup over the entire five year duration of the study.

Table 10:

Loss to followup vs. documented deaths in study P-20-OR

Year	# of surviving patients still followed at end of a given year ["# at risk"]		# of documented deaths during the preceding year		# of patients lost to followup during the preceding yr	
	Propaf	Duke	Propaf	Duke	Propaf	Duke
0	474	194	N/A	N/A	N/A	N/A
1	178	167	6	2	290	25
2	98	152	2	1	78	14
3	58	132	3	5	37	15
4	40	104	3	1	15	27
5	16	69	0	3	24	32

[source: modification of table on page 1 of addendum dated 11/12/93]

RESULTS:

▸ **Effect modifiers and confounders:**

An analysis conducted by the sponsor indicated that patient age as well as the presence of structural heart disease were significant effect modifiers (p=0.01), i.e. they were associated with reduced survival, but neither of these covariates were confirmed as effect modifiers in the analysis conducted by Dr. Wilkinson of Duke University. Age was reported to significantly confound the comparison of survival between the 2 databases, and was thus retained in the final Cox proportional hazards model.

▸ **Survival estimates among entire sample:**

Among the 474 propafenone-treated patients in study P-20-OR, 14 died (3.0%). Among 194 non-propafenone-treated patients (Duke database), 12 died (6.2%). Survival estimates were as follows:

Table 11:

Kaplan-Meier estimated survival probabilities, in percent (study P-20-OR)

	Survival in Propafenone-treated patients		*Survival in the Duke clinic population*	
Years after entry	Point estimate	95% CI	Point estimate	95% CI
1	97.8	95.2-99.0	98.9	95.6-99.7
2	96.4	92.6-98.3	98.3	94.7-99.4
3	92.2	84.7-96.1	94.8	89.9-97.4
4	87.1	77.3-92.9	94.0	88.8-96.9
5	87.1	77.3-92.9	90.6	83.6-94.7

[source: modification of table in addendum dated 10/14/93]

▸ **Survival estimates among Subgroups:**

Among the subset of propafenone-treated patients *without* structural heart disease, one-year survival was estimated to be 0.99. Among the subset of propafenone-treated patients *with* structural heart disease one-year survival was 0.96. All deaths in the non-propafenone-treated group (Duke) occurred in patients with structural heart disease.

▸ **Hazard ratio:**

The unadjusted hazard ratio (propafenone: to non-propafenone) was 1.7 (95% CI= 0.8-3.9) with the p value > 0.15, and the age-adjusted hazard ratio was 0.95 (95% CI= 0.4-2.2) with the p value > 0.90.

▸ **Survival curves:**

Figure 2: Comparative survival curves (not adjusted for age)

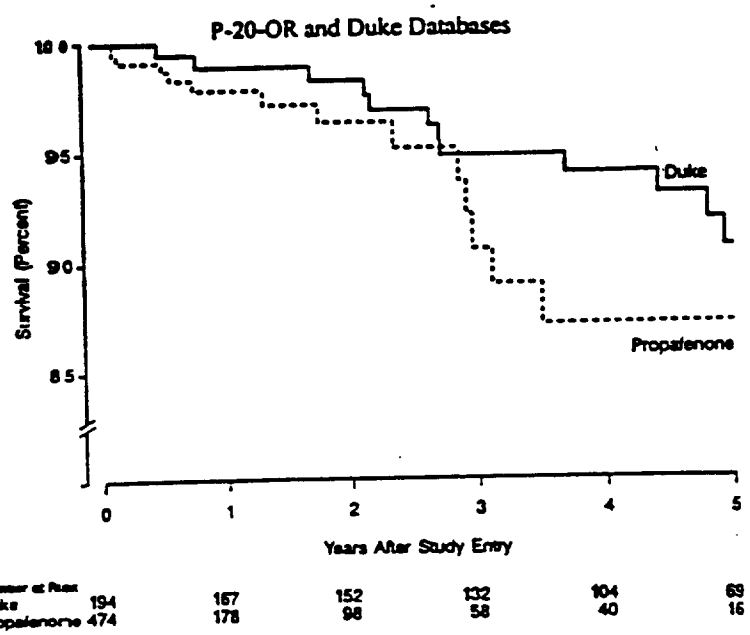
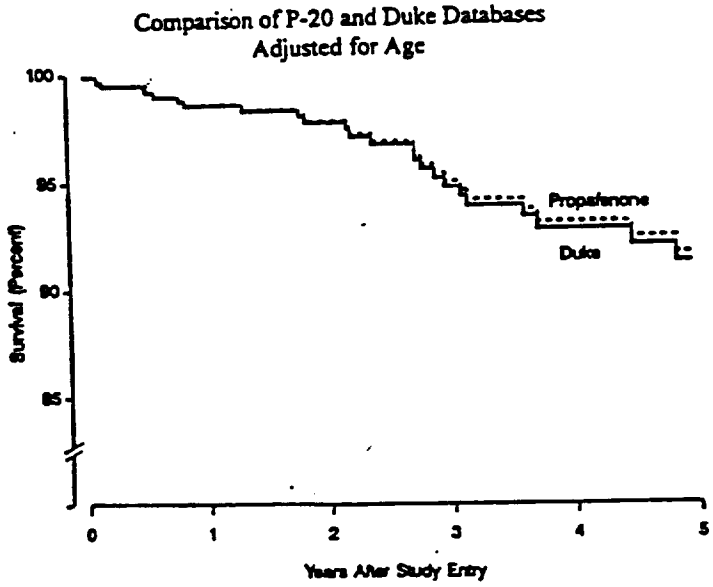


Figure 3: Age-adjusted survival curves



[source: photocopy of figure 3, page 5017, vol 22]

COMMENTS (mortality in study P-20-OR vs the Duke University clinic experience):

1. There was extensive censoring due to loss to followup in study P-20-OR. Of the 480 PSVT patients initially treated with propafenone, 290 were lost to followup in the first year, and 444 patients were lost to followup over the entire five year duration of the study. The potential for substantial bias in the survival estimate must be seriously considered given the dependence of the analysis on the unverified assumption that censoring was independent of outcome and treatment.

2. Issues of bias notwithstanding, the imprecision in the estimate of relative survival does not allow one to exclude a relatively adverse effect of propafenone on the survival of treated PSVT patients. The unadjusted hazard ratio for survival (propafenone: to non-propafenone) was estimated to be 1.7 (95% CI of 0.8 to 3.9), and the age-adjusted hazard ratio was 0.95 (95% CI of 0.4 to 2.2). The estimated one-year survival was 97.8% (95% CI of 95.2 to 99.0) among propafenone-treated patients, and 98.9 (95% CI of 95.6 to 99.7) among patients treated with drugs other than propafenone.

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Safety [continued]

7.2 Overview of Drug exposure in all studies:

In study P-16-OR, twenty patients received 900 mg/d propfenone, four patients received 600 mg/d propafenone, and one patient was administered propafenone at a dose of 300 mg/d. In study P-17-OR, the median propafenone dose was 600 mg/d, as it was in longterm study P-20.

7.3 Overview of Deaths in all studies:

This overview pools the results of studies P-16-OR, P-17-OR, and P-20-OR. The overall proportion of deaths among those atrial arrhythmia patients who were exposed to propafenone (not necessarily randomized patients) was 14/546 (2.6%). Each of the fourteen patients with known fatal outcomes was enrolled in study P-20-OR. The crude proportion of propafenone-associated deaths was higher among males (where the rate was 3.2% vs 1.7% in females), and among patients with PAfib/FL (where the rate was 3.8% vs 1.6% in PSVT patients). The crude proportion of deaths was also greater in the propafenone-treated subgroup with structural heart disease (4.0%), as compared to the subgroup without structural heart disease (0.8%).

The duration of propafenone exposure among the patients who died ranged from 37-1306 days. Of the 14 known propafenone-associated deaths, 4 were cardiac arrests (2 of which were associated with ventricular fibrillation), 4 were secondary to myocardial infarction, 2 were attributed to pulmonary failure, and 1 death each was secondary to stroke, suicide, third-degree heart block, and drowning[6].

Table 12:

Subgroup distribution of propafenone-associated deaths

	SEX		*PROPAFENONE DOSE at time of death*				*INDEX ARRHYTHMIA at the start of the study*		
	male	*female*	*300 mg/d*	*450 mg/d*	*600 mg/d*	*900 mg/d*	*PAfib/ FL*	*PSVT*	*PAfib + PSVT*
# of deaths	10	4	1	6	4	3	9	5	0
sample size	312	234	113	360	393	320	234	306	6

[source: modification of table in addendum dated 10/14/93]

The data are pooled from studies P-16-OR, P-17-OR, and P-20-OR. Most patients received more than one propafenone dose so the number of patients receiving each of the doses is greater than the total number of enrolled patients.

[6] a cardiovascular event was speculated to have possibly preceded the drowning.

7.3 **Overview of Deaths in all studies** [CONTINUED]:

Individual narratives for cases of death are as follows:

Deaths in patients with no structural heart disease:

Death 1: Patient P-20-OR/202/110 was a 51 year old male PSVT patient who died a self-inflicted death while receiving propafenone 900 mg/d.

Death 2: Patient P-20-OR/203/38 was a 70 year old female paroxysmal PAfib patient who died of myocardial infarction while receiving propafenone 450 mg/d.

Deaths in patients with structural heart disease:

Death 3: Patient P-20-OR/202/156 was a 72 year old male PSVT patient who died of stroke while receiving propafenone 600 mg/d.

Death 4: Patient P-20-OR/202/185 was a 73 year old male paroxysmal Afib/AFL patient who died after a ventricular fibrillation arrest while receiving propafenone 450 mg/d.

Death 5: Patient P-20-OR/202/195 was a 88 year old female PSVT patient who died of third-degree heart block while receiving propafenone 450 mg/d.

Death 6: Patient P-20-OR/203/16 was a 71 year old female Afib patient who died of cardiopulmonary arrest while receiving propafenone 450 mg/d.

Death 7: Patient P-20-OR/203/34 was a 62 year old male PAfib patient who died of myocardial infarction while receiving propafenone 600 mg/d.

Death 8: Patient P-20-OR/203/45 was a 71 year old male PAFL patient who died of pulmonary failure (in the setting of lung cancer) and possible arrhythmia while receiving propafenone 900 mg/d.

Death 9: Patient P-20-OR/203/68 was a 54 year old male PAfib patient who died of myocardial infarction while receiving propafenone 600 mg/d.

Death 10: Patient P-20-OR/204/03 was a 79 year old male PSVT patient who died of respiratory arrest while receiving propafenone 450 mg/d.

Death 11: Patient P-20-OR/204/09 was a 60 year old male PSVT patient who died of a ventricular fibrillation arrest while receiving propafenone 900 mg/d.

Death 12: Patient P-20-OR/205/02 was a 78 year old female PAfib patient who died of cardiac arrest while receiving propafenone 450 mg/d.

7.3 **Overview of Deaths in all studies** [continued]:

Deaths in patients with structural heart disease [continued]:

Death 13: Patient P-20-OR/205/17 was a 63 year old male paroxysmal AFL patient who fell backward off of a boat and drowned. Autopsy did not reveal the cause of death, but an arrhythmic precipitating event was speculated. He had been receiving propafenone 600 mg/d.

Death 14: Patient P-20-OR/209/18 was a 74 year old male paroxysmal Afib/AFL patient who died of myocardial infarction while receiving propafenone 300 mg/d.

Fatal outcomes other than propafenone-associated deaths or deaths in PSVT patients:

One additional death by cardiac arrest (in patient P-17-OR/172/3) occurred approximately 24 days after the end of the propafenone trial, and the patient did not require discontinuation from propafenone during the study.

Two additional deaths occurred in patients in whom the underlying arrhythmia was not PSVT, but ventricular tachycardia (VT). The enrollment of these patients was in violation of protocol, and they were appropriately excluded from the analysis of PSVT patienys. One of these (patient P-20-OR/201/01) was a 40 year old male with endstage heart failure who discontinued propafenone for a month and died in the peri-operative period following cardiac transplantation. The other VT patient, P-20-OR/201/02, was a 61 year old male who died of cardiac arrest.

7.4 Proarrhythmic or possibly proarrhythmic events:

There were 25 dropouts associated with arrhythmic events among 521 propafenone-randomized PSVT/PAF patients (4.8%) in studies P-16-OR, P-17-OR, and P-20-OR. Of these, 11 were cases of ventricular arrhythmias, and 14 were supraventricular arrhythmias (for which the differentiation between proarrhythmia and breakthrough of endogenous arrhythmia was not always certain). The distribution of arrhythmias which were associated with dropouts is shown in the following table.

Table 13:

Dropouts associated with proarrhythmic or possibly pro-arrythmic events in pooled studies

Type of event	*Number (%) of events*
ventricular tachycardia (VT)	8 (1.5%)
torsades de pointes	1 (0.2%)
ventricular fibrillation (VF)	2 (0.4%)
PSVT	1 (0.2%)
PAT	1 (0.2%)
PAF	3 (0.6%)
PAFL	2 (0.4%)
junctional rhythm	2 (0.4%)
sinus pause	4 (0.8%)
bradycardia	1 (0.2%)

[source: modification of listing on pages 5005-5009; volume 22]

The results of studies P-16-OR, P-17-OR, and P-20-OR are pooled. Some patients had more than 1 arrhythmia as the basis for dropping out.

7.4 **Proarrhythmic or possibly proarrhythmic events** [continued]:

Narratives for Ventricular arrhythmia-associated dropouts:

Cases with plausibly contributory nondrug factors:

In one case (P16/160-26) the arrhythmia which led to discontinuation of propafenone was later observed in the absence of any antiarrhythmic therapy. This 63 year old male PAF patient experienced (on day 10 of propafenone 600 mg/d) a new, irregular rhythm with wide QRS complexes. It was diagnosed as either VT or Afib with functional bundle branch block, and temporarily discontinued after propafenone was discontinued.

In patient P20/202-124 concomitant acute myocardial infarction (MI) plausibly contributed to a VF event observed while on propafenone therapy.

In two patients exercise-induced myocardial ischemia plausibly contributed to a VT event observed while on propafenone therapy. Patient P20/203-39 was a 66 year old male with a history of atrial arrhythmias (not specified), CAD, and MI who experienced 20 seconds of VT during an exercise test on the sixth day of propafenone (450 mg/d) therapy. Patient P20/203-147 was a 67 year old female with PAfib, and a history of CAD, and sick sinus syndrome. On the twentieth day of propafenone therapy (900 mg/d) she experienced severe, non-sustained VT during an exercise test and was subsequently shown to have multiple coronary occlusions.

In two patients congestive heart failure (CHF) plausibly contributed to a ventricular arrhythmia event during propafenone therapy. Patient P20/203-04 was a 62 year old male PAF patient with a history of CHF, CAD, complete heart block, and prior VT who experienced VF five days after initiating propafenone 450 mg/d. The patient was successfully resuscitated. P20/203-189 was a 63 year old male atrial arrhythmia patient with a history of CHF, nonsustained ventricular ectopy, and valvulopathies who experienced a severe episode of sustained VT after 24 days of propafenone therapy (900 mg/d).

Cases with no clearly identified confounding factors:

Patient P20/209-21 was a 31 year old female PSVT patient with a history of Wolff-Parkinson-White (WPW) syndrome and atrial flutter who arrested with torsades de pointes on the fourth day of propafenone therapy (450 mg/d). The patient recovered.

Patient P20/241-01 was a 29 year old female PSVT patient with a history of WPW syndrome who experienced an episode of VT in the first week of propafenone exposure.

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7.4 **Proarrhythmic or possibly proarrhythmic events** [continued]:

Narratives for Ventricular arrhythmia-associated dropouts [continued]:

Cases with no clearly identified confounding factors [continued]:

Patient P20/203-140 was a 73 year old female PAfib patient with no history of structural heart disease who developed VT on the seventh day of therapy with propafenone 600 mg/d.

Patient P20/202-126 was a 76 year old male PAF patient with pacemaker-dependent tachycardia/bradycardia syndrome who developed PAfib and an unspecified VT event four days after beginning propafenone 1200 mg/d.

Patient P20/202-174 was a 64 year old male PSVT patient with CAD who experienced VT four months after beginning propafenone 1200 mg/d.

Narratives for Supraventricular arrhythmia-associated dropouts:

After survey of the cases of supraventricular arrhythmia-associated dropouts, the following potentially clinically serious arrhythmias were identified:

Patient P20/205-25 was a 78 year old female PAfib patient who experienced sinus node suppression with junctional rhythm after receiving propafenone at an unspecified dose. A physician outside of the study saw the patient during this event, and the clinical details are said by the sponsor to be unavailable.

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7.5 Dropouts associated with non-arrhythmic events:

In placebo-controlled (and short term) PSVT trials one propafenone-treated patient dropped out in association with each of the following AEs: fatigue, malaise, nausea/vomiting, unusual taste, dyspnea, and "dizziness" [undefined]. Among placebo controls the rate of dropout for these AE was similar, with the exception of unusual taste, dyspnea, and "dizziness" (for which there were no discontinuations) [source: table in attachment B (revised), addendum dated 10/6/93].

With uncontrolled (and longterm) propafenone use the most frequently reported dropout-associated AEs were nausea or vomiting (2.9%), ventricular tachycardia (1.9%), "dizziness" [undefined] (1.7%), fatigue (1.5%), unusual taste (1.3%), weakness (1.3%), and dyspnea (1.0%) [source: modification of table in attachment A, addendum dated 5/24/93].

7.6 Common adverse events:

Among patients exposed to propafenone in short-term, placebo-controlled trials the most frequently reported AE during double-blind therapy are shown below.

Table 14:

Common (rate ≥ 5%) AE during short-term controlled studies P-16-OR & P-17-OR

Adverse Event	*propa-fenone [n=47]*	*placebo [n=44]*
unusual taste	17.0%	2.3%
nausea/vomiting	10.6%	2.3%
"dizziness"	10.6%	2.3%
dyspnea	6.4%	4.7%
fatigue	6.4%	9.3%

[source: modification of table on page 4999, vol 22]

Although here counted as an AE by the sponsor, "dizziness" [undefined] was interpretable as evidence of inefficacy in study P-17-OR.

In the long-term uncontrolled PSVT study (P-20-OR) the types, and absolute frequencies of the most common AE were generally similar to those observed in the short-term controlled trials. The principle exception was that the controlled studies, unlike the uncontrolled study, did not commonly report constipation or headache.

7.7 Miscellaneous EKG findings:

The most frequently reported treatment-emergent EKG abnormalities were nonspecific ST-T changes (18%), first degree AV block (14%), sinus bradycardia (9%), intraventricular conduction delay (7%), left axis deviation (5%), and atrial flutter (5%).

7.8 Laboratory findings:

The controlled laboratory data are limited since in the placebo trials few patients had both baseline and followup evaluations. Among the available data there were no clinically significant changes in laboratory values.

7.9 Drug-demographic interactions:

In longterm study P-20-OR, among 314 younger patients (age < 65 years) and 166 older patients (age ≥ 65 years), the rate of treatment-emergent CHF was higher among older patients[7] (4.8%) than among the younger ones (0%). In contrast, the frequency of unusual taste was higher among the younger group (16 vs 9%, respectively).

7.10 Drug-disease interactions:

The following table (divided into parts A and B) compares the AE profile of propafenone in ventricular arrhythmia vs PSVT patients. In the PSVT database the most common AE were generally the same as those previously observed in the ventricular arrhythmia population [as per the current product label], with the principle exception being that dyspnea was not common (< 5% incidence) in the PSVT population.

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[7]this finding is consistent with the propafenone experience in ventricular arrhythmia patients insofar as the prior probability of CAD and CHF is greater among the elderly, and the presence of either of these pre-existing conditions conferred a greater risk of propafenone-associated CHF in previous ventricular arrhythmia studies.

7.10 **Drug-disease interactions** [continued]:

Table 15-A [continued on next page]:

Common (rate ≥ 1%) AE in ventricular arrhythmia patients vs PSVT patients

	Present Labeling for Ventricular Arrhythmias		SVT Submission (From Protocol P-20-OR)	
	Total Incidence (N=2127)	Percentage of Pts. Who Discontinued	Total Incidence (N=480)	Percentage of Pts. Who Discontinued
Dizziness	12.5	2.4	9.4	1.7
Nausea and/or Vomiting	10.7	3.4	10.8	2.9
Unusual Taste	8.8	0.7	13.5	1.3
Constipation	7.2	0.5	8.3	0.2
Fatigue	6.0	1.0	5.8	1.5
Dyspnea	5.3	1.6	2.3	1.0
Proarrhythmia	4.7	4.7	0.0	0.0
Angina	4.6	0.5	1.0	0.0
Headache(s)	4.5	1.0	5.8	0.8
Blurred Vision	3.8	0.8	3.3	0.6
CHF	3.7	1.4	1.9	0.6
Ventricular Tachycardia	3.4	1.2	1.9	1.9
Dyspepsia	3.4	0.9	3.3	0.2
Palpitations	3.4	0.5	1.9	0.2
Rash	2.6	0.8	1.0	0.0
AV Block, First Degree	2.5	0.6	0.6	0.0
Diarrhea	2.4	0.7	1.7	0.4
Weakness	2.4	0.2	2.5	1.3
Dry Mouth	2.2	0.7	2.9	0.0
Syncope/Near Syncope	1.9	0.5	1.3	0.2
QRS Duration Increased	1.8	0.2	0.2	0.0

[source: photocopy of first section of table in attachment A, addendum dated 5/24/93]

One should not be misled by the depiction in this table of a 0% incidence of proarrhythmia among PSVT patients. As shown elsewhere in the table, there were nonzero reported incidences of the proarrhythmic or possibly proarrhythmic events, VT and Afib.

7.10 **Drug-disease interactions** [continued]:

Table 15-B [continued from previous page]:

Common (rate ≥ 1%) AE in ventricular arrhythmia patients vs in PSVT patients

	Present Labeling for Ventricular Arrhythmias		SVT Submission (From Protocol P-20-OR)	
	Total Incidence (N=2127)	Percentage of Pts. Who Discontinued	Total Incidence (N=480)	Percentage of Pts. Who Discontinued
Chest Pain	1.8	0.2	0.8	0.0
Anorexia	1.7	0.4	1.7	0.2
Abdominal Pain/Cramps	1.7	0.4	1.3	0.2
Ataxia	1.6	0.2	1.7	0.0
Insomnia	1.5	0.3	0.2	0.2
PVC's	1.5	0.1	0.0	0.0
Bradycardia	1.5	0.5	1.9	0.2
Anxiety	1.5	0.6	0.4	0.2
Edema	1.4	0.2	0.8	0.0
Tremor(s)	1.4	0.3	1.9	0.4
Diaphoresis	1.4	0.3	1.0	0.4
Bundle Branch Block	1.2	0.5	0.6	0.0
Drowsiness	1.2	0.2	0.8	0.0
Atrial Fibrillation	1.2	0.4	1.3	0.2
Flatulence	1.2	0.1	0.0	0.0
Hypotension	1.1	0.4	0.0	0.0
Intraventricular Conduction Delay	1.1	0.1	0.2	0.0
Pain, Joints	1.0	0.0	0.4	0.4
Increased Liver Enzymes	0.4	0.2	1.0	0.8
Sinus Pause(s)	0.7	0.4	1.5	0.6
Numbness	0.0	0.0	1.0	0.4
Paresthesia	0.0	0.0	1.0	0.2
Vision, Abnormal	0.0	0.0	1.5	0.0

[source: photocopy of second section of table in attachment A, addendum dated 5/24/93]

8 CONCLUSIONS:

A. Efficacy

i. Study P-16-OR:

When placebo-controlled, double-blind, randomized crossover study P-16-OR was evaluated by life-table analysis, in PSVT patients the median time to first tachycardia recurrence was prolonged by propafenone (34 vs 13 days in placebo-treated patients). By the PPW test[8] this treatment effect was statistically significant (two-sided p value = 0.008), as it was also found to be with the Wilcoxon rank sum test (two-sided p value = 0.02). A negative analysis was perhaps overemphasized in the FDA statistical review (2-sample log-rank test: $p \geq 0.21$), since it is Dr. Stan Lin's view that the log-rank test is not a more justified analysis for this study or even as appropriate a tool as the PPW test.

Time and sequence effects were not analyzed. It would be worthwhile for the sponsor to apply the non-parametric crossover method proposed by Gary Koch in order to examine sequence, period, and treatment effects [as per the recommendation of Dr. Nancy Smith in the flecainide NDA].

ii. Study P-17-OR:

In placebo-controlled, double-blind, randomized crossover study P-17-OR, palpitations were recorded during a lesser mean proportion of randomized treatment days in propafenone-treated PSVT patients (15.8%), relative to placebo-treated patients (29.7%). The analysis used to ascribe statistical significance to this finding (i.e. a Wilcoxon signed rank test which generated a two-sided p value of 0.004) was not explicitly pre-specified, but the finding remains convincing. It is noteworthy that the value of this metric is limited since it provides no assurance that a drug which decreases the proportion of symptomatic days does not expedite the onset of the first recurrence, or promote more numerous or more severe symptoms on those days in which symptoms are present.

iii. In neither study was a prospective subgroup analysis performed to characterize efficacy in the population for which any approved use in PSVT would likely be restricted (i.e. patients without structural heart disease).

[8]although not explicitly pre-specified, this was neither an inappropriate test nor one without precedent (having been used in the approved flecainide application for PSVT).

8 CONCLUSIONS [continued]:

B. Safety:

i. Based on a nonrandomized comparison of mortality (study P-20-OR vs the Duke University database), the unadjusted hazard ratio for survival (propafenone: to non-propafenone) was estimated to be 1.7 (95% CI of 0.8 to 3.9), and the age-adjusted hazard ratio was estimated to be 0.95 (95% CI of 0.4 to 2.2). There is potential for substantial bias in this survival estimate given the extensive loss to followup in study P-20-OR, and the absent validation of the assumption that censoring was independent of outcome and treatment. Notwithstanding any bias, the imprecision in the estimate of relative survival does not allow one to exclude a relatively adverse effect of propafenone on the survival of antiarrhythmic-treated PSVT patients.

ii. In the PSVT database the most common AE were generally the same as those previously observed in the ventricular arrhythmia population, with the principle exception being that dyspnea was not common (<5% incidence) in the PSVT population.

iii. the absence of inter-period drug washout in studies P-16-OR and P-17-OR could plausibly result in an overestimation of AE rates among placebo-treated patients (on the basis of drug carryover), and a resultant underestimation of placebo-corrected AE rates among the propafenone-treated.

9 RECOMMENDATIONS:

i. study P-16-OR: the sponsor should be requested to apply the non-parametric crossover method proposed by Gary Koch in order to examine sequence, period, and treatment effects.

ii. nonrandomized comparison of mortality (study P-20-OR vs the Duke database): the FDA statistical reviewer should be requested to verify and comment on the survival analysis.

iii. the sponsor should be requested to present an argument and/or analysis which supports their proposal to market propafenone to a subgroup (i.e. patients without structural heart disease) in whom efficacy has not been formally characterized.

iv. assuming (for the time being) that no unsupportive findings arise from the analyses recommended above, this reviewer would recommend the approval of propafenone for the oral prophylaxis of PSVT, with labelling which conveys the uncertainty and potential bias in the estimate of its relative effect on survival.

Steven M. Rodin, MD 11/30/93

Steven M. Rodin, MD Date
Medical Officer

cc: RFenichel/HFD-110; CSO/HFD-110; division file/HFD-110; * no copy to S.Rodin

WILLARD

AUG 1 1997

MEDICALREVIEWADDENDUM

DRUG NAME:	RYTHMOL
NDA#:	19-151
SPONSOR:	KNOLL
DATE COMPLETED:	8/1/97
STUDY:	PSD-88-3
REVIEWER:	Steven D. Caras, M.D. Ph.D

Brief History

During review of reaudited protocol PSD-88-3, a number of subjects during the 900 mg propafenone period withdrew for adverse events. The subjects were not reported in either the original submission or the reaudited submission.

Review Procedures

Case report forms were submitted for all subjects after a request from Dr. Steve Rodin, medical officer. The subjects who withdrew were reviewed.

In addition, all reaudited endpoints were compared to the submitted case report forms for accuracy.

Review Results

The dropouts during the 900 mg period withdrew because of common side effects associated with propafenone treatment.

The reaudited endpoints are consistent with the submitted case report forms.

Conclusions

Based on the review of the case report forms, the recommendations concerning PSD-88-3 are unchanged.

Respectfully submitted,

Steven D. Caras, MD, PhD
Medical Officer

cc

Document Room
Division Files
Steven Caras
Project Manager

JUN 25 1997

MEDICAL/STATISTICAL REVIEW

DRUG NAME:	RYTHMOL
NDA#:	19-151
SPONSOR:	KNOLL
DATE SUB:	3/18/97
DATE RECEIVED:	3/19/97
DATE COMPLETED:	6/24/97
STUDY:	PSD-88-3
REVIEWERS:	Steven D. Caras, M.D. Ph.D (Medical) Kooros Majoob, Ph.D. (Statistical)

BRIEF HISTORY

Propafenone is a Class IC antiarrhythmic agent with local anesthetic effects and a direct stabilizing action on myocardial membranes. An efficacy supplement was submitted for the use of Rythmol in paroxysmal atrial fibrillation (Afib) and supraventricular tachycardia (PSVT). Two crossover trials were submitted, one utilized transtelephonic monitoring for symptomatic occurrences and the other for symptom reduction only. Since the efficacy database initially submitted had only a small number of subjects, concerns about generalizability were raised. The sponsor then submitted this trial (PSD-88-3). The Advisory Committee recommended approval and an approvable letter was sent. Three sites were inspected and sufficient reason was found that the results could not be relied upon. A non approvable letter was subsequently sent. A new post-hoc analysis by FDA was proposed as a worse case scenario and would be based on verifiable data.

SUBMISSION DETAILS

Brief Review of Study

For full review please refer to Dr. Rodin's review. The study was a double-blind, randomized, placebo-controlled, cross-over study design to

evaluate time to first occurrence of Afib and PSVT. The propafenone doses studied were 600 and 900 mg/day. The first phase was the low dose (600 mg/day) and subjects were randomized to either drug or placebo. The subjects proceeded to the high dose phase (900 mg/day) without further randomization. Each crossover period lasted three months or until an endpoint occurred.

The primary endpoint was the time to the first documented recurrence of Afib or PSVT. This was defined in the protocol as

> "first documented recurrence of paroxysmal tachycardia to warrant a change in therapy. Severity of the attack will be assessed subjectively by the patient and clinical investigators, taking into account the duration of the attack and associated symptoms. Recurrence of paroxysmal tachycardia should be documented by Cardiomemo ECG Recorder if possible, or alternatively by reliable symptoms documented in the diary cards."

Reaudit Procedures

An independent audit was conducted by the firm). Representative of collected transtelephonic ECGs, CRFs and diary card data associated with the transtelephonic ECGs sent. The first ECG documented event occurring greater than or equal to seven days after the start of full dose therapy was recorded. Adverse events were not considered terminating events but censored events. Events for the worst case analysis were determined as follows

ECG sent per diary card	*ECG*	*Terminating Event*
Yes	Present	Yes
Yes	Absent	Prof- yes; Pla- no
No	Present	Yes
Missing	Present	Yes

Terminating events were counted if the

1. ECG was transmitted and showed paroxysmal tachycardia
2. ECG was attempted and subject was on propafenone.
3. Diary card shows an attempt to transmit and the subject was on propafenone.
4. CRF or any supporting records showed evidence of transmission.

Symptomatic diary card entries without evidence of an attempt to transmit were not considered endpoints.

The auditors visited every investigational site to search for any documents in the study records (CRFs, diary cards and patient notes) on site that may effect termination decisions.

According to the sponsor, the audit showed that the arrhythmia free intervals were not affected in 13/17 sites.

REVIEW PROCEDURES

For the primary endpoint, the reaudit submission was compared to the original for consistency. When a discrepancy between the original data generated and the reaudit existed, it was noted. All discrepancies were checked against the results of the reaudit.

The number of voided subjects in both the original and reaudit submission were compared.

REVIEW RESULTS

Discrepancies

There were a few inconsistencies between the original and audited dataset that were not explained in the reaudit. The subjects are noted in the Appendix 1 - Table A1.

Voided Subjects

Subject 9 was voided in the reaudited analysis and not in the original analysis.

Subjects who were voided because of an event within the 7 day censoring window are presented in the Appendix 1 -Table A2.

Dropouts

In the 900 mg dosing period there were a number of subjects who discontinued therapy and were not reported in the original submission. Also, there was no mention of these subjects in the results of the reaudit. Appendix 1 - Table A3 lists these subjects.

Non-Compliance

There were 22 non-compliant subjects in either dose who were excluded in the original submission's primary analysis. Fourteen of these subjects were included in the reaudited analysis. No pattern was evident that would favor propafenone.

CRF Endpoints

Endpoints were checked for those subjects whose CRFs are available (adverse event dropouts) in the original submission. The dates and times observed were consistent with both databases

First Symptoms

Appendix 1 - Table A5 shows the number of subjects who had previous symptoms at least one week prior to attaining an endpoint. In the 600 mg periods, there were just as many subjects with symptoms for both propafenone and placebo. Overall there were fewer subjects with symptoms in the 900 mg periods.

Subjects with symptoms who did not attain an endpoint were counted. Most of the subjects had symptom durations of greater than 10 minutes. There were approximately equal numbers of subjects at each dose for placebo and propafenone.

Reviewers' Worst Case Imputations

In addition to the worst case analysis initially proposed by the agency, a further worst case analysis was done.

Censored Subjects

There were a number of subjects (see Appendix 1 - Table A4) who were censored in any period prior to 3 months without either an endpoint being reached or subject discontinuation. It is assumed that these subjects made their endpoint "subjectively" as stated in the protocol. Worst case values for the primary endpoint were imputed in the following way.

Propafenone	Placebo	Imputation
No event	No event	PRO - yes PLA- no; = 98 days
Event	No Event	PLA = 98 days
No event	Event	PRO=yes

Additional Imputations

For subjects who had an adverse event on propafenone and had no event in the placebo arm at period end, the endpoint was imputed as a tie (Propafenone=Placebo=98 days) .

Subject Initially in Sinus Rhythm

Subjects not in sinus rhythm at the initial visit and continued on with the crossover period were included in this analysis.

STATISTICAL METHODS

Updated datasets from the reaudit were provided by the sponsor. The SAS program written by the sponsor's statistician was checked for accuracy. The sponsor's used the method of France to determine statistical significance. Since the method of France [1] is relatively insensitive to ties between treatments, the reviewers performed further analyses (ANOVA, proportional hazard, Kaplan-Meyer lifetable and MacNemar's test) with the imputed data described above.

Statistical Results

The Kaplan-Meyer curves for both the sponsor's and reviewers' worst case analysis favor propafenone at both doses. In the GRAPHS section are the survival curves for the (1) sponsor's worst case analysis from the reaudit; (2) reviewers' worst case analysis using imputed data. SAS output of the subjects included in the sponsor's and reviewers' analysis is in Appendix II

Table 1 shows the median survival obtained by the sponsor and the reviewing team.

Table 1- Median Survival (S=Sponsor; R=Reviewer)

	S Low Dose		R Low Dose		S Hi Dose		R Hi Dose	
	PRO	PLA	PRO	PLA	PRO	PLA	PRO	PLA
PAF Median Surv	>98	17	>98	32	67	7	>98	29
Difference	81		66		74		69	
PSVT Median Surv.	>98	11	>98	29	97	23	>98	89
Difference	87		69		60		9	

A worst case analysis including censored subjects, subjects who did not have sinus rhythm at the start of a period and imputing ties for adverse events did not change its statistical significance appreciably with either the sponsors chosen method (method of France), ANOVA or proportional hazards models. The median survival difference is not significantly less in our model than the sponsors with the exception of high dose PSVT.

DISCUSSION

Efficacy Results

The efficacy results are robust enough to show statistical significance under the worst case analysis initially proposed by FDA. The reaudited analysis shows that propafenone continues to be statistically significant with median changes of time to event.

In addition further imputations by the reviewing team did not affect the efficacy results. The median survival difference was only a few days less in both PSVT and PAF at the 600mg dose and PAF at the 900 mg dose. Most of the imputed event were ties with placebo rather changes in preference, so there was little or no change in propafenone's median survival. The large increase in the placebo median survival time for PSVT 900 mg and the propafenone median survival time for PAF 900 mg in our analysis is due to the inclusion of ties from censoring and/or adverse events on a smaller subject pool relative to the other periods and is not unexpected.

Events prior to 7 days

There were a number of events prior to 7 days. Most events on placebo were frequent episodes of PSVT or Afib whereas events on

propafenone were adverse event related. Because of a paucity of Afib or PSVT events in the propafenone group during this 7 day period, it is expected that an efficacy analysis including these subjects would not influence the results of trial.

Differences in the Submissions

The discrepancies found would not change the statistical significance of primary efficacy endpoint. However, two discrepancies are worth mentioning. Subject 24 had no evidence of symptomatic events in the original submission for that dose. Subject 113's data were not specifically looked for in the reaudit. These are probably data verification errors in the original submission.

CONCLUSION AND RECOMMENDATIONS

It is apparent from the additional post-hoc analyses that propafenone is efficacious in paroxysmal PSVT and Afib if one believes the reaudited data are reliable. There is no reason to suspect that the reaudited data are not valid at this time.

There were minor problems apparent in data verification and adverse events dropout reporting in the 900 mg dose. Steps should be taken by the sponsor to assure the agency that subsequent submissions should be complete and contain verified data.

It is recommended to consider this trial though not optimal in design and conduct as positive.

The missing CRFs will be requested and reviewed as an addendum review prior to the release of the action letter.

Signed

Steven D. Caras, MD, PhD
Medical Officer

Kooros Majoob, PhD
Statitician

Concur: C Smucco for George Chi
George Chi, PhD 6/25/97

cc Document Room Division Files Steven Caras Project Manager
Kooros Majoob George Chi

REFERENCES

1. France LA, Lewis JA and Kay R. The Analysis of Failure Time Data in Crossover Studies; Statistics in Medicine; 1991:10; 1099-1113.

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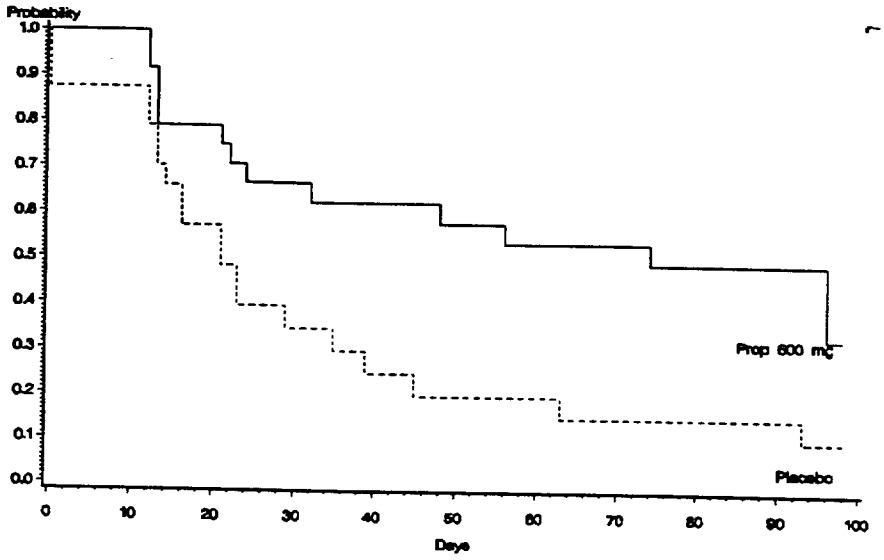
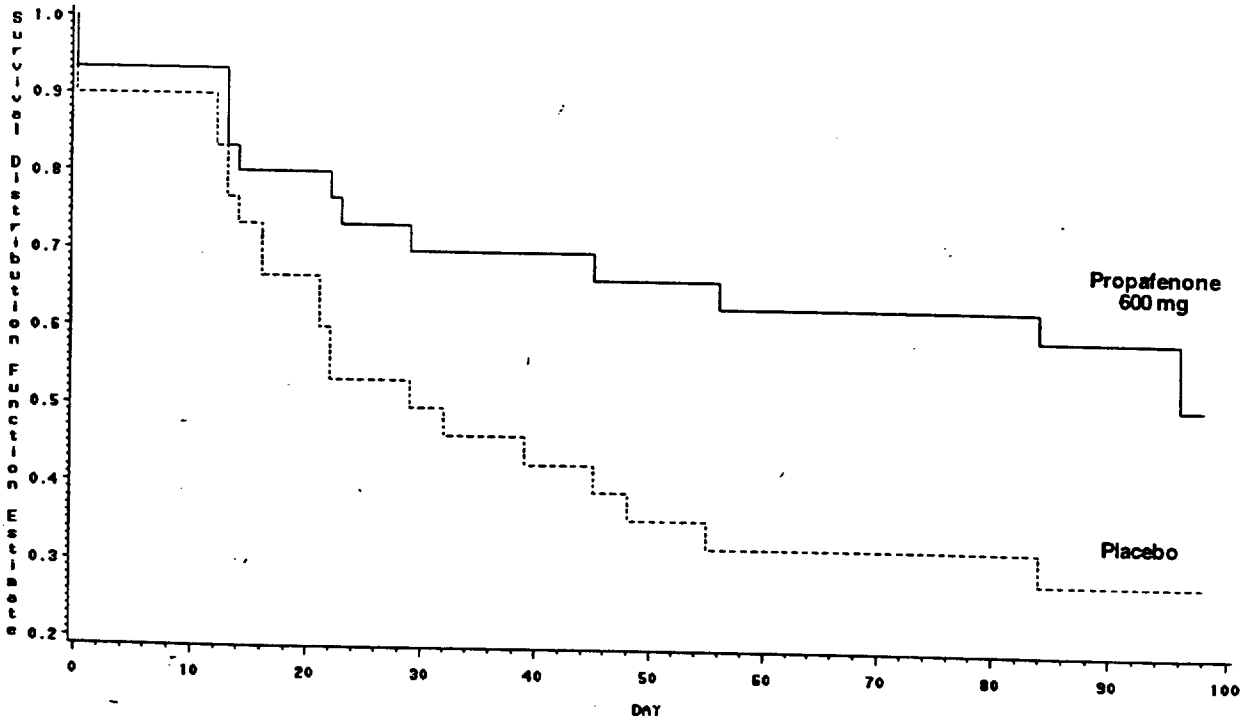
GRAPHS

Sponsor's Worst Case (PAF Low Dose))



Reviewers' Worst Case (PAF Low Dose)



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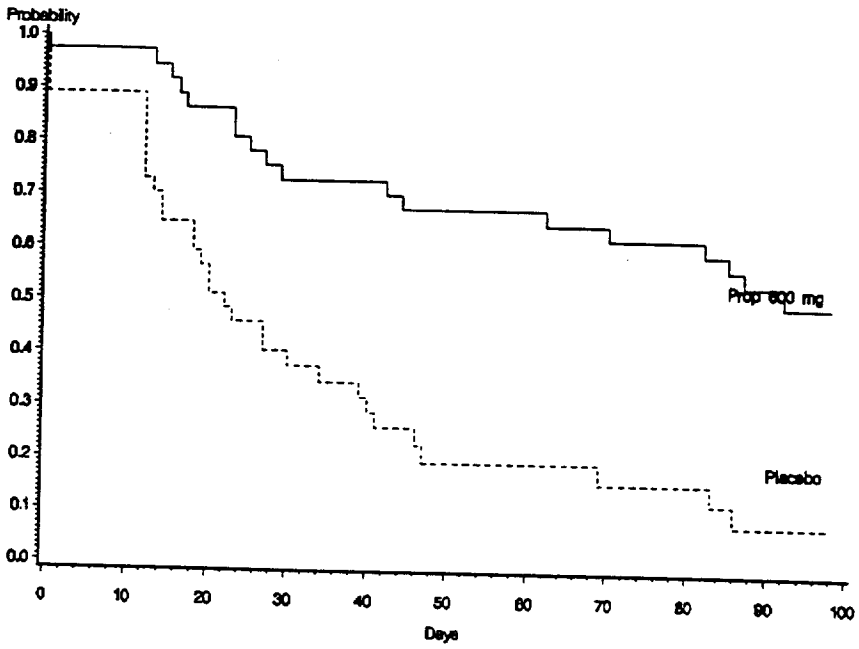
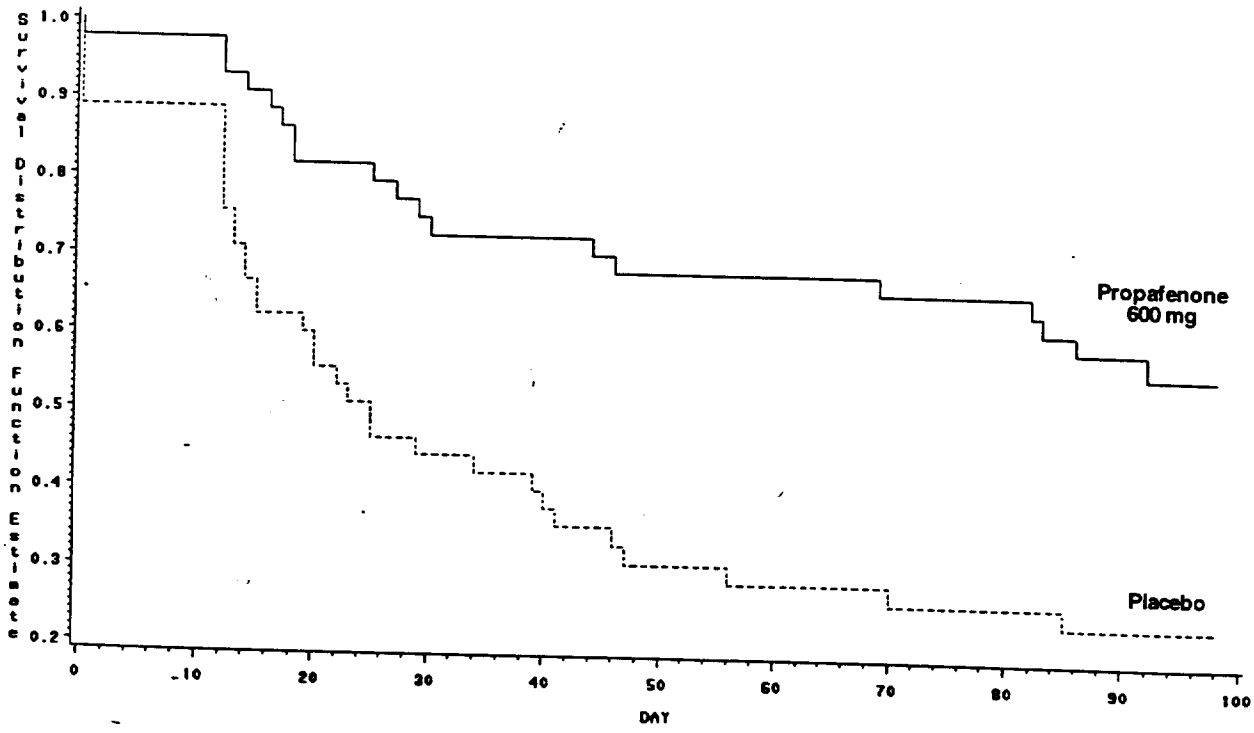
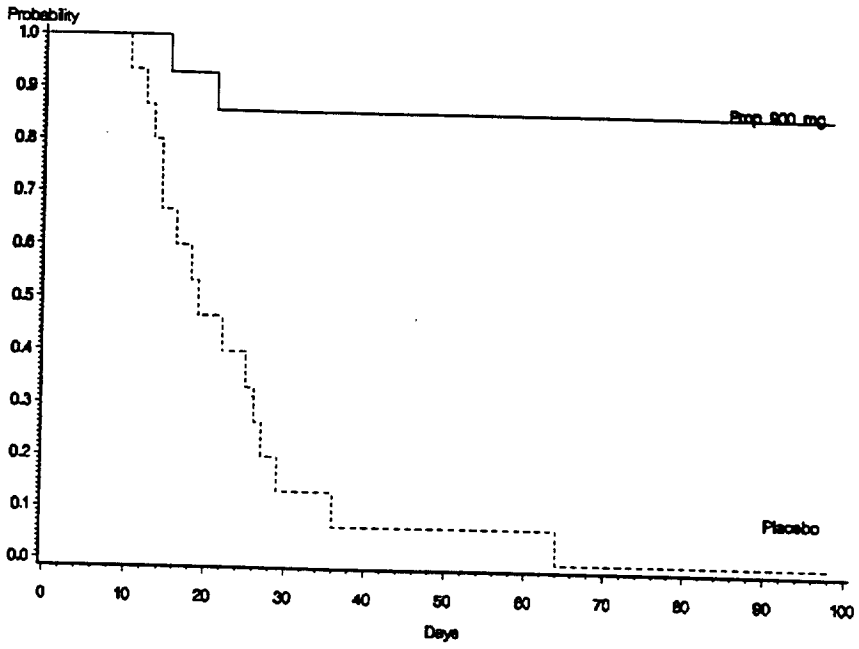
Sponsor's Worst Case (PSVT Low Dose)



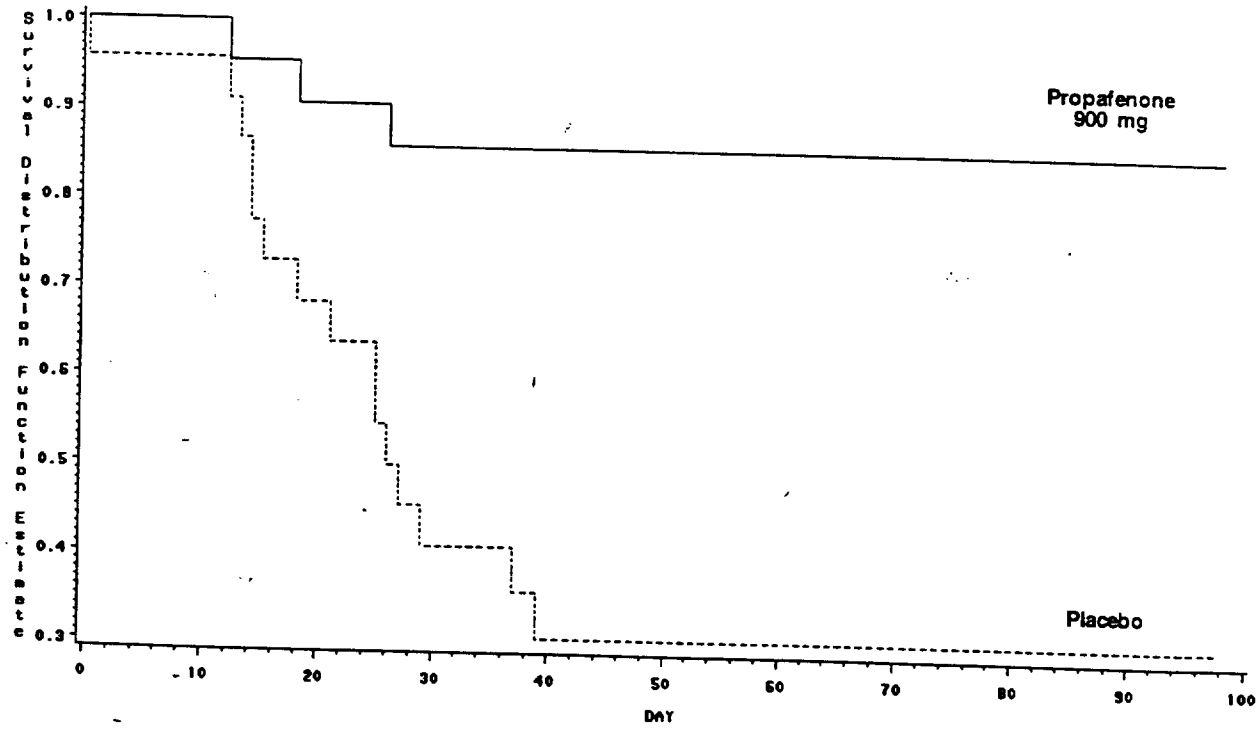
Reviewer's Worst Case (PSVT Low Dose)



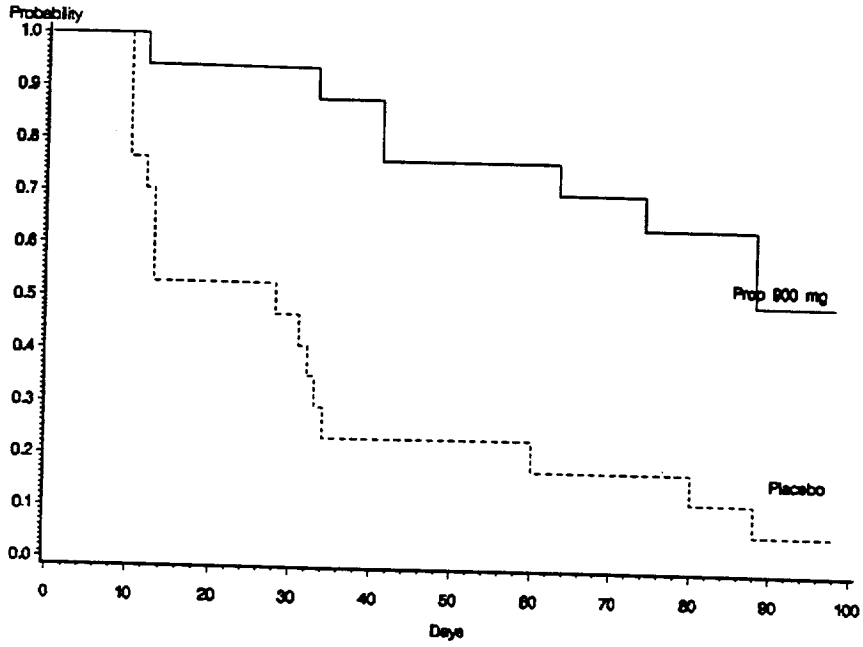
Sponsor's Worst Case (PAF High Dose)



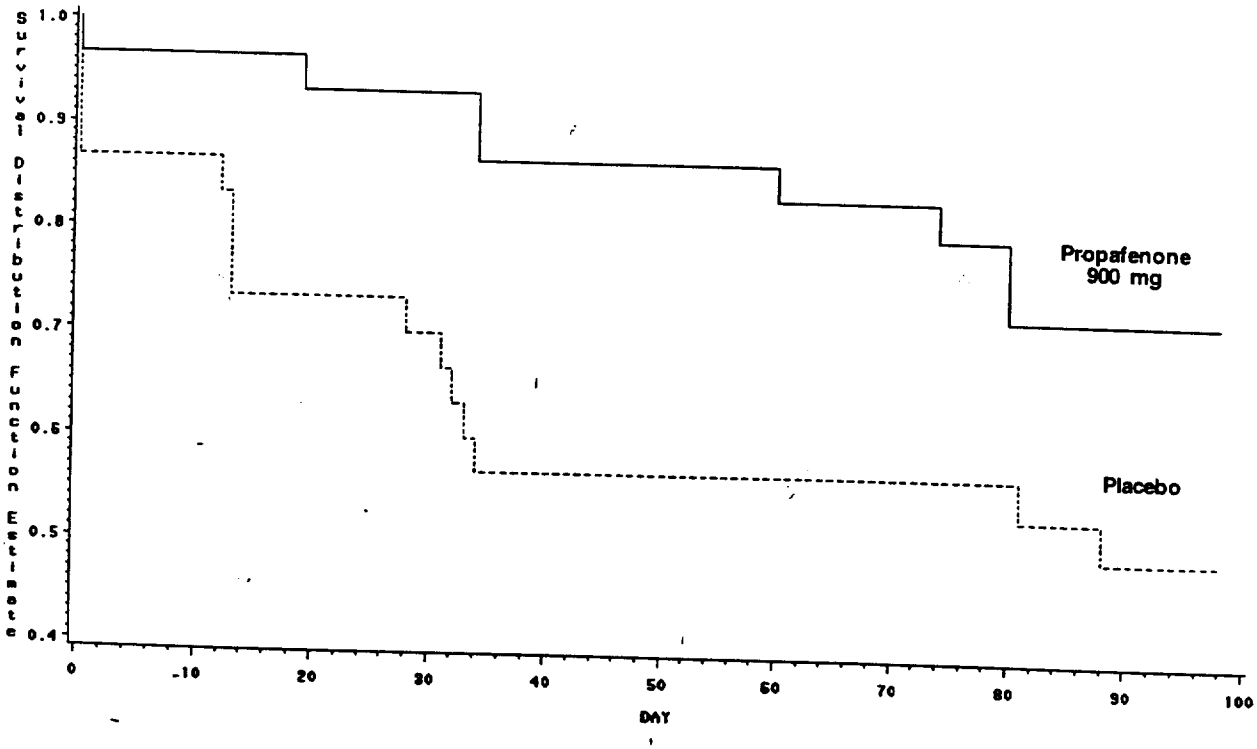
Reviewer's Worst Case (PAF High Dose)



Sponsor's Worst Case (PSVT High Dose)



Reviewer's Worst Case (PSVT High Dose)



APPENDIX I

Table A1 -Discrepancies

PT	Disease	Dose	Discrepancy
7	PAF	PLA LD	No ECG found; Diary (+), should be no event
62	PAF	PRO HD	? Endpoint original on 11/18 (HR=145 bpm); Subject had EGD on that date
24	PSVT	PRO HD	Original submission had no symptomatic or ECG recurrence; but became "worst case" endpoint after audit
40	PSVT	PRO LD	According to reaudit, worst case 8/9/90, within initial 7 day period. Other symptom on 8/16 which is used in time to event calculation.
73	PSVT	PRO HD	Not able to determine date of symptom on diary card reaudit. Original submission shows symptom on 8/20 of severity 3 duration 5 hr; in comparison to 9/17 (endpoint) severity 5 duration 20 min.
96	PSVT	PRO HD	Was event at 90 days in original protocol, but not in reaudited data. ?Review of ECG
113	PSVT	PRO LD	"Found" data in the reaudit. Documents for this subject were not specifically "looked for".

Table A2 - Subjects with an event the first 7 days of therapy

Sub	Disease	Drug/Dose	Reason
3	PAF	PLA600	Afib
4	PAF	BOTH	W/D due to frequent afib
6	PAF	PLA900	Visit 6 omitted due to freq SVT
8	PAF	PLA600	Admin. W/D
12	PAF	PLA900	Visit 7 omitted due to freq
21	PAF	PLA900	Frequent AF
22	PAF	PRO600	Chronic Afib
27	PAF	PRO600	SAE
29	PAF	PL600	unknown
31	PAF	PRO600	Chronic Afib
41	PAF	PRO900	W/D
42	PAF	PRO900	LBBB
46	PAF	PRO900	AE
47	PAF	PRO900	AE
66	PAF	Both	V2 omitted
66	PAF	PLA900	V8 omitted
71	PAF	PRO900	AE
72	PAF	Both	Chronic Afib
81	PAF	PRO600	AE
83	PAF	PLA600	V2 omitted
84	PAF	PLA600	V4 omitted due to afib
108	PAF	PLA600	Palpitations moved to V6
112	PAF	PLA900	Afib at V6
16	PSVT	PLA900	Visit 7 omitted due to freq SVT
32	PSVT	PRO900	V8 Study med withdrawn b/c of lack of efficacy. Placed on sotolol.
43	PSVT	PLA600	AE
59	PSVT	PRO900	AE
60	PSVT	PLA900	Persistant PSVT

Table A3 - Additional Subjects withdrawn during the 900 mg period *

Patient	Disease	Drug	Reason	Stop Rx Noted	Void (Y/N)
4	PAF	Both	Freq. PAF	N	Y
29	PAF	Both	AE	N	N
47	PAF	PRO	AE	Y	Y
48	PAF	PRO	AE	Y	N
71	PAF	PRO	AE	Y	Y
84**	PAF	PLA	Freq. PAF	N	N
95	PAF	PRO	AE	Y	N
99?	PAF	PRO	AE	N	N
15	PSVT	PRO	AE	Y	N
16	PSVT	PRO	AE; Freq PSVT	N	Y
55	PSVT	PRO	AE	Y	N
59	PSVT	PRO	AE	N	Y

* If the subject was not voided the data was included up to event date, then censored. The subject was voided if the event happened within the first 7 days of treatment.
**Died 3 months after dropout.
? In the adverse event section, this subject was moved to the next phase but noted as withdrawn in the CANDA.

Table A4 - Censored Subjects

Patient	Disease	Dose	Result
10	PSVT	LD	PRO E 25; PLA N 57
32	PSVT	LD	PLA E 17; PRO N 77
36	PSVT	LD	PRO E 11; PLA N 39
59	PSVT	LD	PLA N 91; PRO N 7
68	PSVT	LD	PRO E 20; PLA N24
69	PSVT	LD	PRO N 83; PLA N35
89	PSVT	LD	PRO N 88; PLA N 57
10	PSVT	HD	PRO N 91; PLA N 21
37	PSVT	HD	PRO N 81; PLA N 10
39	PSVT	HD	PRO N 77; PLA N 95
89	PSVT	HD	PRO N 91; PLA N 71
93	PSVT	HD	PRO N 91; PLA E 97
113	PSVT	HD	PRO N 95; PLA N 25
117	PSVT	HD	PLA N 41; PRO N 92
12	PAF	LD	PRO N 84; PLA N 90
21	PAF	LD	PRO E 50; PLA N 8
46	PAF	LD	PRO N 98; PLA N7
52	PAF	LD	PRO N 79; PLA N 14
67	PAF	LD	PLA E 10; PRO N 40
94	PAF	LD	PRO N92; PLA N 8

Table A5 - Number of Subjects with Endpoints who had Symptoms at Least 1 week prior.

	LOW	HIGH
Placebo N(%)	9(11)	4 (5)
Propafenone N(%)	8(10)	1(1)

APPENDIX 2 - Patients included in the analysis

Sponsor's

Diagnosis is PAF (low dose)

The PHREG Procedure

Summary of the Number of Event and Censored Values

Stratum	PATIENT	Total	Event	Censored	Percent Censored
1	4	2	2	0	0.00
2	6	2	1	1	50.00
3	7	2	1	1	50.00
4	12	2	1	1	50.00
5	13	2	1	1	50.00
6	18	2	2	0	0.00
7	19	2	1	1	50.00
8	21	2	1	1	50.00
9	30	2	1	1	50.00
10	33	2	2	0	0.00
11	41	2	1	1	50.00
12	44	2	1	1	50.00
13	47	2	1	1	50.00
14	48	2	1	1	50.00
15	49	2	2	0	0.00
16	62	2	1	1	50.00
17	67	2	1	1	50.00
18	70	2	2	0	0.00
19	79	2	1	1	50.00
20	98	2	2	0	0.00
21	99	2	1	1	50.00
22	105	2	2	0	0.00
23	111	2	2	0	0.00
24	112	2	2	0	0.00
Total		48	33	15	31.25

Diagnosis is PSVT (low dose)

Summary of the Number of Event and Censored Values

Stratum	PATIENT	Total	Event	Censored	Percent Censored
1	2	2	2	0	0.00
2	5	2	1	1	50.00
3	9	2	1	1	50.00
4	10	2	1	1	50.00
5	11	2	2	0	0.00
6	15	2	1	1	50.00
7	16	2	1	1	50.00
8	24	2	2	0	0.00

9	26	2	1	1	50.00
10	32	2	1	1	50.00
11	34	2	1	1	50.00
12	35	2	1	1	50.00
13	36	2	1	1	50.00
14	37	2	2	0	0.00
15	38	2	2	0	0.00
16	39	2	1	1	50.00
17	40	2	2	0	0.00
18	42	2	2	0	0.00
19	50	2	1	1	50.00
20	51	2	2	0	0.00
21	54	2	2	0	0.00
22	55	2	1	1	50.00
23	58	2	2	0	0.00
24	60	2	2	0	0.00
25	68	2	1	1	50.00
26	73	2	2	0	0.00
27	80	2	1	1	50.00
28	87	2	1	1	50.00
29	88	2	1	1	50.00
30	96	2	1	1	50.00
31	97	2	1	1	50.00
32	107	2	1	1	50.00

Diagnosis is PAF (high dose)

Summary of the Number of Event and Censored Values

Stratum	PATIENT	Total	Event	Censored	Percent Censored
1	3	2	1	1	50.00
2	13	2	1	1	50.00
3	18	2	1	1	50.00
4	21	2	1	1	50.00
5	33	2	1	1	50.00
6	44	2	1	1	50.00
7	47	2	1	1	50.00
8	52	2	1	1	50.00
9	62	2	1	1	50.00
10	67	2	1	1	50.00
11	83	2	2	0	0.00
12	91	2	1	1	50.00
13	94	2	1	1	50.00
14	105	2	1	1	50.00
15	108	2	1	1	50.00
16	111	2	1	1	50.00
Total		32	17	15	46.88

Diagnosis is PSVT (high dose)

The PHREG Procedure

Summary of the Number of Event and Censored Values

Stratum	PATIENT	Total	Event	Censored	Percent Censored
1	15	2	1	1	50.00
2	24	2	1	1	50.00
3	26	2	1	1	50.00
4	34	2	1	1	50.00
5	36	2	2	0	0.00
6	40	2	1	1	50.00
7	42	2	1	1	50.00
8	50	2	1	1	50.00
9	51	2	2	0	0.00
10	60	2	1	1	50.00
11	68	2	1	1	50.00
12	87	2	2	0	0.00
13	96	2	1	1	50.00
14	107	2	2	0	0.00
15	109	2	1	1	50.00
16	110	2	2	0	0.00
17	114	2	1	1	50.00
18	115	2	2	0	0.00
Total		36	24	12	33.33

Reviewers' Worst Case Analysis

ETIOLOGY=PAF (low dose)

Summary of the Number of Event and Censored Values

Stratum	PATIENT	Total	Event	Censored	Percer Censore
1	4	2	2	0	0.(
2	6	2	1	1	50.(
3	7	2	1	1	50.(
4	12	2	1	1	50.(
5	13	2	1	1	50.(
6	18	2	2	0	0.(
7	19	2	1	1	50.(
8	21	2	1	1	50.(
9	30	2	1	1	50.(
10	33	2	2	0	0.(
11	41	2	1	1	50.(
12	44	2	1	1	50.(
13	46	2	0	2	100.(
14	47	2	1	1	50.(
15	48	2	1	1	50.(
16	49	2	2	0	0.(
17	52	2	0	2	100.(
18	62	2	1	1	50.(
19	67	2	1	1	50.(
20	70	2	2	0	0.(
21	79	2	1	1	50.(
22	91	2	0	2	100.(
23	92	2	0	2	100.(
24	94	2	0	2	100.(
25	95	2	1	1	50.(
26	98	2	2	0	0.(
27	99	2	1	1	50.(
28	105	2	2	0	0.(
29	111	2	2	0	0.(
30	112	2	2	0	0.(
Total		60	34	26	43.3

ETIOLOGY=PSVT (low dose)

Summary of the Number of Event and Censored Values

Stratum	PATIENT	Total	Event	Censored	Percer Censore
1	1	2	0	2	100.(
2	2	2	2	0	0.(
3	5	2	1	1	50.(
4	9	2	1	1	50.(
5	10	2	1	1	50.(
6	11	2	2	0	0.(
7	15	2	1	1	50.(
8	16	2	1	1	50.(
9	24	2	2	0	0.(
10	26	2	1	1	50.(
11	32	2	1	1	50.(
12	34	2	1	1	50.(
13	35	2	1	1	50.(
14	36	2	1	1	50.(
15	37	2	2	0	0.(
16	38	2	2	0	0.(
17	39	2	1	1	50.(
18	40	2	2	0	0.(
19	42	2	2	0	0.(
20	45	2	2	0	0.(
21	50	2	1	1	50.(
22	51	2	2	0	0.(
23	54	2	2	0	0.(
24	55	2	1	1	50.(
25	58	2	2	0	0.(
26	59	2	0	2	100.(
27	60	2	2	0	0.(
28	65	2	0	2	100.(
29	68	2	1	1	50.(
30	69	2	0	2	100.(
31	73	2	2	0	0.(
32	80	2	1	1	50.(

33	87	2			
34	88	2	1	1	50.0
35	89	2	1	1	50.0
36	93	2	0	2	100.0
37	96	2	1	1	50.0
38	97	2	1	1	50.0
39	107	2	1	1	50.0
40	109	2	1	1	50.0
41	110	2	1	1	50.0
42	113	2	1	1	50.0
43	114	2	2	0	0.0
44	115	2	1	1	50.0
45	117	2	1	1	50.0
Total		90	53	37	41.1

ETIOLOGY=PAF (high dose)

Summary of the Number of Event and Censored Values

Stratum	PATIENT	Total	Event	Censored	Percer Censore
1	3	2	1	1	50.0
2	7	2	0	2	100.0
3	13	2	1	1	50.0
4	18	2	1	1	50.0
5	19	2	0	2	100.0
6	33	2	1	1	50.0
7	44	2	1	1	50.0
8	48	2	0	2	100.0
9	52	2	1	1	50.0
10	62	2	1	1	50.0
11	67	2	1	1	50.0
12	70	2	1	1	50.0
13	79	2	0	2	100.0
14	83	2	2	0	0.0
15	91	2	1	1	50.0
16	92	2	0	2	100.0
17	94	2	1	1	50.0
18	95	2	0	2	100.0
19	98	2	2	0	0.0
20	99	2	0	2	100.0
21	105	2	1	1	50.0
22	108	2	1	1	50.0
23	111	2	1	1	50.0
Total		46	18	28	60.8

ETIOLOGY=PSVT (high dose)

Summary of the Number of Event and Censored Values

Stratum	PATIENT	Total	Event	Censored	Percer Censore
1	1	2	0	2	100.0
2	5	2	0	2	100.0
3	10	2	0	2	100.0
4	15	2	1	1	50.0
5	24	2	1	1	50.0
6	26	2	1	1	50.0
7	34	2	1	1	50.0
8	36	2	2	0	0.0
9	37	2	0	2	100.0
10	38	2	0	2	100.0
11	39	2	0	2	100.0
12	40	2	1	1	50.0
13	50	2	1	1	50.0
14	51	2	2	0	0.0
15	58	2	0	2	100.0
16	65	2	0	2	100.0
17	68	2	1	1	50.0
18	69	2	0	2	100.0
19	80	2	1	1	50.0
20	87	2	2	0	0.0
21	88	2	0	2	100.0
22	89	2	0	2	100.0
23	93	2	0	2	100.0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19151/S002

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#: 19-151/S-002
Applicant: Knoll Pharmaceutical Co.
Date: JUN 2 1995
Name of Drug: Rythmol (propafenone HCL)
Indication: Paroxysmal Supraventricular Tachycardia
Document Reviewed: Report on a supplementary data analyses for study PSD-88-3, received 03/22/95.

1. INTRODUCTION

As a result of a statistical "Preliminary Review" of this NDA dated on March 18, 1994, the sponsor was asked to submit two additional analyses on the data of study PSD-88-3: (1) an analysis of the mean number of symptomatic paroxysmal tachycardias per week as documented by patient diary or Cardiomemo (2) an analysis of the first recurrence of a tachyarrhythmia, regardless of the severity or the time to recurrence. On March 22, 1995 the sponsor submitted a report on the results of these analyses, together with the data set (in SAS format), macros and programs which were used for the analyses.

Study PSD-88-3 was a double-blind, placebo-controlled, randomized two periods crossover study to evaluate the efficacy and tolerabilty of the long term oral treatment with propafenone 600 mg and 900 mg for the suppression of symptomatic recurrent paroxysmal supraventricular tachyarrythmias. The study consisted of two phases: "low dose phase" of propafenone 600 mg compared to placebo and a "high dose phase" of propafenone 900 mg compared to placebo. Each phase consists of a 2-period crossover design.

2. REVIEWER'S COMMENTS

On January 6, 1995 this reviewer received a copy of a report issued by the office of scientific investigation about the results of investigating three sites out of a total of 17 sites in the above mentioned study. This report described a number of problems with the data collected from the 38 patients in the three sites, out of a total of 95 patients who entered the study, which include the following.

i. Missing subject diary cards.

ii. Discrepancies between diary cards and case report form(CRF).

iii. Lack of documentation of symptoms and severity of symptoms on diary cards and/or PSVT documentation of severity of symptoms.

iv. Problems with identification of potential endpoints on CRF's.

We really do not know if there are problems with the data collected in the other sites, which were not investigated by the office of scientific investigation.

The contents of the above mentioned report throw a suspicion on the accuracy of all data submitted by the sponsor for this study and in the opinion of this reviewer this data become unreliable.

In the following pages a review of the analyses submitted by the sponsor and a presentation of the results of some analyses, which were conducted by this reviewer, are given. These are based on the the data as originally submitted by the sponsor. Definitive conclusion can not be drawn at this time based on these analyses. As recommended by the scientific investigation's report, the sponsor needs to address the problems identified in the investigation and pending a final resolution of these problems, if possible, a reanalysis by this reviewer would be necessary.

The sponsor has reported the results of two analyses: "Attack Rate" and "Time to First Recurrence of an Attack" as listed below. The results are shown in Tables 1, 2, and 3.

Attack Rate.

To show a significantly lower attack rate, of any severity, for propafenone over that of placebo, the sponsor had conducted an analysis for the "period preference" data (given in contingency tables), which consists of the number of patients who had lower attack rates in one period over the other. The results (shown in Table 2) seem to indicate significant differences between placebo and propafenone for the two diagnostic groups and for the two doses.

However, according to the protocol the weekly attack rate is the second primary endpoint and an analysis of this endpoint had not been provided by the sponsor. This reviewer has conducted this analysis as described later on.

Time to First Recurrence of an Attack.

Table 3 shows the sponsor's results for the first recurrence of a tachyarrhythmia. The results indicate significant differences between placebo and propafenone for the two diagnostic groups and for the two phases.

At first, this reviewer was unable to re-run the above mentioned SAS programs and after searching through the codes of macros and programs it was discovered that the sponsor had not provided some data sets and macros which were necessary to execute these programs. Later on, and after contacting the sponsor about the missing programs, a complete set of the programs which generated the statistical analyses were provided.

By using the data sets provided by the sponsor which contain information about the dates of all symptomatic paroxysmal tachycardias reported by patients, this reviewer had conducted the following two analyses. The first is an analysis of the weekly rate of symptomatic paroxysmal

tachycardias by the diagnostic group and phase of the study using an ANOVA model of a 2x2 crossover design; the results are shown in Table 4. The second is an analysis of the time to first recurrence of a tachyarrhythmia using Cox's proportional hazards linear regression model. The results of this analysis, which are shown in Table 5, confirm the results of the sponsor (see Table 3).

Table 4 shows that for the low dose, and for both the diagnostic groups PAF and PSVT, there is no significant difference in the weekly rate between propafenone and placebo (p-values are 0.4907 and 0.7061, respectively). However, this table shows a significant difference in the weekly rate between propafenone and placebo for the high dose and for both the diagnostic groups PAF and PSVT (the p-values are <0.001).

As an overall assessment of the two primary endpoints, the time to first attack and the weekly rate of attack of symptomatic paroxysmal tachycardias, one needs to examine a summary of results of the corresponding analyses as shown below.

		p-value for the propafeneone versus placebo in	
Diagnostic Group	Phase	Time to first Attack	Weekly Attack Rate
PSVT	Low dose	0.0039	0.7061
	High dose	0.0035	<0.001
PAF	Low dose	0.0521	0.4907
	High dose	0.0088	<0.001

From the above table, and as mentioned earlier, for both the diagnostic groups PAF and PSVT the low dose did not result in a significant difference in the weekly attack rate between propafenone and placebo. Adding to that, if one applies some method (e.g. Benferroni procedure) for adjusting the p-values, because of having two endpoints, one would see that the time to first recurrence of an attack for the low dose of propafenone, in the PAF group, is not significantly different from that of placebo. Thus, these results suggest that only the high dose (900 mg) of propafenone showed a clear evidence of an effect over placebo in the reduction of attacks of symptomatic paroxysmal tachycardias.

Again, it is to be noted that the conclusions of this review are based on the original data as submitted by the sponsor. Pending a resolution of this problem, if possible, a reanalysis by this reviewer would be necessary.

Walid A. Nuri, Ph.D.
Mathematical Statistician

This review consists of 4 pages and five tables.

Concur: Dr. Chi 6/2/95

Dr. Dubey 6/2/95

cc: Orig. NDA 19-151
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Rodin
HFD-110/Ms. Willard
HFD-110/Mrs. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Nuri
Chron:
W A Nuri: 594-5303 SERB: 6-1-95: DISC7/spropf1.

Table 1. ATTACK RATES

The total number of attacks was as shown

				sub-total	sub-total	TOTAL
PSVT						
	low dose	plac	274			
		prop	340			
				614		
	high dose	plac	229			
		prop	71			
				300		
					914	
PAF						
	low dose	plac	269			
		prop	221			
				490		
	high dose	plac	133			
		prop	89			
				222		
					712	
Uncertain Dates						
					2	
TOTAL						1,628

Mean per week attack rates and standard error (se) for each dose regime were as follows.

Dx	Dose	Rx	N	miss*	mean	se	min	max
PSVT	Low dose	Plac	48	3	1.17	1.34	0	6.7
		Prop	49	2	1.00	3.04	0	17.5
	High dose	Plac	41	10	1.17	0.26	0	7.0
		Prop	40	11	0.20	0.08	0	2.7
PAF	Low dose	Plac	42	1	1.98	0.45	0	17.5
		Prop	42	1	1.60	0.69	0	28.0
	High dose	Plac	34	9	1.32	0.22	0	4.7
		Prop	34	9	0.42	0.14	0	3.7

* miss = patient periods for which a weekly rate could not be determined for the particular treatment period, because the patient was withdrawn.

Table 2.

FISHER'S EXACT TEST AND WILCOXON TWO-SAMPLE TEST

(period preference is the period with the lower attack rate)

PSVT

low dose

period preference	plac/ prop	prop/ plac
2	18	7
neither	1	1
1	5	15

N=47 Fisher p=.0003 Wilcoxon p=.0038

high dose

period preference	plac/ prop	prop/ plac
2	16	4
neither	2	2
1	2	12

N=38 Fisher p=.0003 Wilcoxon p=.0001

PAF

low dose

period preference	plac/ prop	prop/ plac
2	16	6
neither	0	1
1	5	13

N=41 Fisher p=.0059 Wilcoxon p=.0314

high dose

period preference	plac/ prop	prop/ plac
2	11	1
neither	2	2
1	4	12

N=32 Fisher p=.0008 Wilcoxon p=.0006

Table 3. TIME TO FIRST FAILURE OF ANY SEVERITY

The numbers of patients analysed were

PSVT	low dose		
not in sinus rhythm	1		
missing data/withdrawn	4		(nos. 25,43,61,86)
no preference	7		
analysable preferences	39		
total		51	
	high dose		
not in sinus rhythm	0		
missing data/withdrawn	9		(nos. 2,25,43,45,61,73, 77,85,86)
no preference	10		
analysable preferences	32		
total		51	
PAF	low dose		
not in sinus rhythm	8		
missing data/withdrawn	5		(nos. 8,27,81,82,106)
no preference	3		
analysable preferences	27		
total		43	
	high dose		
not in sinus rhythm	9		
missing data/withdrawn	6		(nos. 8,27,49,81,82,106)
no preference	9		
analysable preferences	19		
total		43	

The estimated value of the relative risk (RR) of an attack on placebo compared to an attack on propafenone are as follows.

		RR (95% confidence limits)	no preference	N	p
PSVT	low dose	2.88 (1.40 to 5.92)	7	46	.0039
	high dose	3.54 (1.51 to 8.26)	10	42	.0035
PAF	low dose	3.10 (0.99 to 9.72)	3	30	.0521
	high dose	5.66 (1.55 to 20.7)	9	28	.0088

Table 4. The results of ANOVA for a 2x2 Crossover Design for the weekly rate of symptomatic paroxysmal tachycardias (calculated by the reviewer).

PAF Group, Low dose

Source of Var.	DF	SS	MS	F-Value	p-value
Between-subjects					
Carry over	1	22.5094	22.5094	1.0862	0.3037
B-S residual	39	808.1977	20.7230		
Within-subjects					
Treatment	1	4.2157	4.2157	0.4841	0.4907
Period	1	2.4108	2.4108	0.2768	0.6018
W-S residual	39	339.6572	8.7092		
Total	81	1172.0608			

PAF Group, High dose

Source of Var.	DF	SS	MS	F-Value	p-value
Between-subjects					
Carry over	1	0.0056	0.0056	0.0034	0.9538
B-S residual	30	49.5954	1.6532		
Within-subjects					
Treatment	1	48.2991	48.2991	64.0623	<0.001
Period	1	7.3489	7.3489	9.7474	0.0039
W-S residual	30	22.6182	0.7539		
Total	63	85.5947			

Table 4. (Cont'd)

PSV Group, Low dose

Source of Var.	DF	SS	MS	F-Value	p-value
Between-subjects					
Carry over	1	0.2876	0.2876	0.0610	0.8060
B-S residual	45	212.0675	4.7126		
Within-subjects					
Treatment	1	1.0052	1.0052	0.1440	0.7061
Period	1	6.7431	6.7431	0.9659	0.3309
W-S residual	45	314.1588	6.9813		
Total	93	528.4796			

PSV Group, High dose

Source of Var.	DF	SS	MS	F-Value	p-value
Between-subjects					
Carry over	1	2.1681	2.1681	1.8095	0.1869
B-S residual	36	43.1357	1.1982		
Within-subjects					
Treatment	1	51.0343	51.0343	44.2574	<0.001
Period	1	4.2654	4.2654	3.6990	0.0624
W-S residual	36	41.5125	1.1531		
Total	75	101.0690			

Table 5. Results of analysis using Cox's Proportional Hazards linear regression model for data of study PSD-88-3 (calculated by the reviewer).

PSV group, Low dose (Prop 600 mg)

The PHREG Procedure

Data Set: WORK.B1
Dependent Variable: DUR
Censoring Variable: ST
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
97	64	33	34.02

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	523.459	512.114	11.346 with 2 DF (p=0.0034)
Score	.	.	11.672 with 2 DF (p=0.0029)
Wald	.	.	11.071 with 2 DF (p=0.0039)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
TRT	1	-0.856167	0.26044	10.80681	0.0010	0.425
PERIOD	1	-0.119600	0.25103	0.22699	0.6338	0.887

Table 5. (Cont'd)

PAF group, Low dose (Prop 600 mg)

The PHREG Procedure

Data Set: WORK.B1
Dependent Variable: DUR
Censoring Variable: ST
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
77	54	23	29.87

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	419.839	406.157	13.682 with 2 DF (p=0.0011)
Score	.	.	14.032 with 2 DF (p=0.0009)
Wald	.	.	13.160 with 2 DF (p=0.0014)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
TRT	1	-0.965117	0.28709	11.30156	0.0008	0.381
PERIOD	1	-0.355443	0.27661	1.65127	0.1988	0.701

Table 5. (Cont'd)

PSV group, High dose (Prop 900 mg)

The PHREG Procedure

Data Set: WORK.B1
Dependent Variable: DUR
Censoring Variable: ST
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
84	57	27	32.14

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	452.097	441.203	10.894 with 2 DF (p=0.0043)
Score	.	.	11.383 with 2 DF (p=0.0034)
Wald	.	.	10.728 with 2 DF (p=0.0047)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
TRT	1	-0.898107	0.27442	10.71098	0.0011	0.407
PERIOD	1	0.014179	0.26598	0.00284	0.9575	1.014

Table 5. (Cont'd)

PAF group, High dose (Prop 900 mg)

The PHREG Procedure

Data Set: WORK.B1
Dependent Variable: DUR
Censoring Variable: ST
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
71	50	21	29.58

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	379.749	374.056	5.693 with 2 DF (p=0.0580)
Score	.	.	5.895 with 2 DF (p=0.0525)
Wald	.	.	5.743 with 2 DF (p=0.0566)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
TRT	1	-0.594607	0.28817	4.25744	0.0391	0.552
PERIOD	1	-0.306277	0.28571	1.14917	0.2837	0.736

STATISTICAL REVIEW AND EVALUATION
(Preliminary Review)

NDA#: 19-151/S-002 Date: MAR 1 8 1994
Applicant: Knoll Pharmaceutical Co.
Name of Drug: Rythmol (propafenone HCL)
Indication: Paroxysmal Supraventricular Tachycardia
Document Reviewed: Volumes 56, 57, 58, 59, 60, 61
received 1/28/94.

1. INTRODUCTION

The sponsor had submitted earlier the results of two small studies: studies P-16-OR and P-17-OR. Then, on February 1, 1994, the sponsor submitted additional statistical analyses for these studies at FDA's request. On January 29, 1994 this reviewer received the sponsor's submission of the results of a larger study PSD-88-3 from U.K..

2. DESCRIPTION OF STUDY PSD-88-3

This was a double-blind, placebo-controlled, randomized two periods crossover study to evaluate the efficacy and tolerabilty of the long term oral treatment with propafenone 600 mg and 900 mg for the suppression of symptomatic recurrent paroxysmal supraventricular tachyarrythmias. The study consisted of two phases: "low dose phase" of propafenone 600 mg compared to placebo and a "high dose phase" of propafenone 900 mg compared to placebo. Each phase consists of a 2-period crossover design.

According to the protocol the primary endpoint is

"1. The first documented recurrence of paroxysmal tachycardia of a sufficient severity to warrant a change in therapy. Severity of the attack will be assessed subjectively by the patient and clinical investigators, taking into account the duration of the attack and associated symptoms. Recurrence of paroxysmal tachycardia should be documented by Cardiomemo ECG Recorder if poosible, or alternatively by reliable symptoms documented in the diary cards.
Only recurrences occuring from the second week onwards will be taken as endpoints.

2. After three months of therapy without any further recurrences of paroxysmal tachycardia."

Ninety five patients in 19 centers were randomized into this study, of whom 52 patients were with paroxysmal supraventricular tachycardia (PSVT) and 43 patients with paroxysmal atrial fibrillation/flutter(PAF).

Some of the analyses that the sponsor carried out, based on the intent-to-treat principle, were the following. By diagnosis subgroup (PSVT and PAF), by dosage (600 mg/day and 900 mg/day), by whether adverse reactions were considered terminating events, by whether the arrhythmia was documented by patient symptoms or

telemonitored ECG findings.

Cox's Proportional Hazards linear regression model was applied on the patients's preference data in the analysis. The sponsor stated that " *The patient is said to prefer one treatment over the other if there was a greater delay to the recurrence of the arrhythmia on the one treatment compared to the other.*" This analysis on the patients' preference data was not stated in the protocol.

3. REVIEWER'S COMMENTS

1. Studies P-16-OR and P-17-OR were small studies. In study P-16-OR, the number of patients included in the final analysis were 9 patients who had paroxysmal atrial fibrillation (PAF) and 15 patients who had paroxysmal atrial tachycardia (PAT). In study P-17-OR the numbers were: 10 patients had PAF and 8 had PAT.

Some of the sponsor's results of statistical analyses and the sponsor's additional statistical analysis for study P-17-OR showed non-significant treatment effect between propafenone and placebo.

The additional analysis presented by the sponsor for study P-16-OR showed a significant difference in the treatmnet effect between propafenone and placebo. However, it is the understanding of this reviewer that the sponsor had not conducted a randomization test, as was requested by the Division of Biometrics, on the results of this study.

2. Concerning the results of study PSD-88-3, Table 1 shows that for either periods, about 50% of the propafenone 600 mg patients experienced a severe symptom recurrence during the treatment period, and about 20% of the propafenone 900 mg patients experienced a severe symptom recurrence during the treatment period. Whereas about 70%-80% of the placebo patients experienced a severe symptom recurrence during the treatment period.

Table 1 also shows that for patients who did not experience symptom recurrences, the mean duration varies from 45.33 days to 83.17 days. This suggests that the sponsor probably imputed the withdrawal dates as their symptom recurrence dates. The impact of such imputation on the assessment of the effectiveness of propafenone seems minimal in view of the highly significant finding. (In this connection, it should be noted that even though these patients withdrew and did not have severe symptom recurrences prior to their withdrawals, it is not entirely clear whether they had no symptom recurrences at all. They may have symptom recurrences that were not considered to be severe enough prior to withdrawal, but may subsequently develop into more severe symptom recurrences if they managed to be able to stay in

the study. See also discussion in section 2.1 below).

If one adopts this method of imputation and accepts the protocol definition of primary endpoint as clinically meaningful and relevant (see discussion in section 2.1 below), then this reviewer's Cox regression analysis (see results of analysis in Table 4) confirms the sponsor's findings of a significant benifit (p=0.0001) (note that the sponsor's Cox regression analyses on the diagnostic subgroups are not appropriate, since stratified randomization was not used).

2.1. The following comment is more a clinical question than statistical. The question raised here is whether the primary endpoint as defined in the protocol a meaningful one.

In going through some of The Case Report Forms (FDA only has CRF's from patients who withdrew), it becomes apparent that during the first week some patients had recurrences with severity scores of 3 which lasted throughout 24 hours and continued for a number of days until patients were withdrawn or needed a change in therapy. Granted that these patients are only treated conservatively during this first week with half the intended dose, it raises the question as to the appropriate clinical interpretation of the trial results. Does propafenone prevents recurrence of supraventricular tachyarrhythmia? It would be useful to know how frequent patients had recurrences and particularly for patients on 900 mg, whether there are recurrences during the first week of treatment; because during the first week, patients in this arm were given 450 mg (half dose) which is not that different from 600 mg. If patients on 900 mg dose arm also had frequent recurrences in the first week, then it will raise question about the prevention effect of propafenone. It would be interesting to perform the corresponding Cox Regression analysis on the time to recurrence of the really first recurrence of a tachyarrhythmia. This reviewer is not able to perform these analyses, because as of this writing, the data is still pending from the sponsor.

2.2. The sponsor's protocol indicated that "*The main criteria of success for the confirmatory parts of analysis are the following:*

A) Time to an endpoint under the corresponding treatment as defined in the section 'Study Procedure'.

B) Mean number of symptomatic paroxysmal tachycardias per week as documented by patient diary or Cardiomemo; here the first 2 weeks under each treatment are taken into consideration."

Thus, the evidence for efficacy of propafenone are based on the two primary analyses (A) and (B) quoted above which are mutually

complementary. The (B) analysis is related to the question raised in section 2.1 above.

The first primary analysis (A) is the Cox regression analysis on time to recurrence of the primary endpoint as defined in the protocol. The results of this analysis has been discussed briefly above.

The second primary analysis (B) proposed in the protocol is the analysis of frequency of recurrences. This was not done by the sponsor. This reviewer cannot perform this analysis at present pending the sponsor's submission of all recurrence data.

3. Since the primary evidence of efficacy will be based on this large study PSD-88-3, this reviewer cannot draw a definitive conclusion regarding the overall efficacy of propafenone until the above analyses have been performed by this reviewer on the requested data which are pending from the sponsor.

Walid Nuri

Walid A. Nuri, Ph.D.
Mathematical Statistician

This review consists of 4 pages and four tables.

Concur: Dr. Chi 3/18/94

Dr. Dubey 3-18-94

cc: Orig. NDA 19-151
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Rodin
HFD-110/Mrs. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Nuri
Chron:
W A Nuri: x34594 SERB: 3-18-94: DISC6/propfn5.

Table 1. Average time to the first severe symptomatic recurrence of arrhythmia (Study PSD-88-3)

Low Dose

Patients who experienced severe symptom recurrences

PERIOD	TRT	N	DUR(DAYS)
1	PLACEBO	38	17.11
2	PLACEBO	29	17.17
1	PROP600	23	21.78
2	PROP600	21	34.10

Patients who did not experience severe symptom recurrences

PERIOD	TRT	N	DUR(DAYS)
1	PLACEBO	9	45.33
2	PLACEBO	10	56.90
1	PROP600	22	83.14
2	PROP600	23	83.17

High Dose

Patients who experienced severe symptom recurrences

PERIOD	TRT	N	DUR(DAYS)
1	PLACEBO	25	20.36
2	PLACEBO	23	31.22
1	PROP900	8	29.38
2	PROP900	7	28.57

Patients who did not experience severe symptom recurrences

PERIOD	TRT	N	DUR(DAYS)
1	PLACEBO	11	53.64
2	PLACEBO	9	59.67
1	PROP900	30	63.47
2	PROP900	32	66.38

Table 2. Average time to the first severe recurrence of symptomatic arrhythmia (within periods) (Study PSD-88-3)

Low Dose

PERIOD	TRT	N	DUR(DAYS)
1	PLACEBO	47	22.51
2	PLACEBO	39	27.36
1	PROP600	45	51.78
2	PROP600	44	59.75

p-value for Trt*period interaction=0.3327

High Dose

PERIOD	TRT	N	DUR(DAYS)
1	PLACEBO	36	30.53
2	PLACEBO	32	39.22
1	PROP900	38	56.29
2	PROP900	39	59.59

p-value for Trt*period interaction=0.5000

Table 3. Average time to the first severe recurrence of symptomatic arrhythmia (Study PSD-88-3)

Low Dose

TRT	N	DUR(DAYS)
PLACEBO	86	24.71
PROP600	89	55.72

p-value for treatment effect=0.0001

High Dose

TRT	N	DUR(DAYS)
PLACEBO	68	34.62
PROP900	77	57.96

p-value for treatment effect=0.0003

Table 4. The reviewer's analysis using Cox's Proportional Hazard Regression Model on the time to first severe symptomatic recurrence of arrhythmia for all patients. (Study PSD-88-3)

ow Dose

The PHREG Procedure

Data Set: WORK.B1
Dependent Variable: DUR1
Censoring Variable: ST
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
175	111	64	36.57

Testing Global Null Hypothesis: BETA=0

riterion	Without Covariates	With Covariates	Model Chi-Square
2 LOG L	1035.355	1008.383	26.972 with 2 DF (p=0.0001)
Score	.	.	28.018 with 2 DF (p=0.0001)
Wald	.	.	26.060 with 2 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

ariable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
RT	1	-1.001889	0.20043	24.98752	0.0001	0.367
ERIOD	1	-0.166326	0.19140	0.75513	0.3849	0.847

Table 4(Cont'd)

Dose

The PHREG Procedure

Data Set: WORK.B1
Dependent Variable: DUR1
Censoring Variable: ST
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
145	63	82	56.55

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
LOG L	564.607	526.305	38.301 with 2 DF (p=0.0001)
ore	.	.	39.043 with 2 DF (p=0.0001)
ld	.	.	31.577 with 2 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

riable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
r	1	-1.664563	0.29773	31.25663	0.0001	0.189
RIOD	1	-0.172936	0.25353	0.46526	0.4952	0.841

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19151/S002

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 22, 1997

FROM: Director, Office of Drug Evaluation I

SUBJECT: Propafenone SVT supplement, NDA 19-151/S-002

TO: Dr. Lipicky

I have gotten all the changes (yours and a few of mine) onto a single draft. I agree with your evaluation of the Knoll proposed labeling, with the following minor exceptions:

1. The ADR section doesn't quite work as marked up (text refers to ventricular arrhythmia ADR's but puts SVT ADR's first, etc.)

2. We should go to round numbers. It's okay to leave it at 1.5% as the cut off and round to 2%. (I left D/C rates to nearest 0.1%.)

3. On page 13 - the order doesn't matter much. I moved unusual taste but left others alone.

I think we should clean this up and either approve on our draft or show then and get a clean draft from them and go to approval. The work is all done.

Robert Temple, M.D.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 19-151 Trade (generic) names Propafenone

Check any of the following that apply and explain, as necessary, on the next page:

#1 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

P.2

___ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

4/18/95
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 19-151/S-002 Trade (generic) names Rythmol (propafenone HCl)

Check any of the following that apply and explain, as necessary, on the next page:

__✓__ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__✓__ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Ray Lijiehy
Signature of Preparer

7/28/97
Date

cc: Orig NDA
HFD- /Div File
NDA Action Package

EXCLUSIVITY SUMMARY for NDA # 19-151 SUPPL # 002

Trade Name Rythmol Generic Name propafenone

Applicant Name Knoll Pharmaceuticals HFD- 110

Approval Date 12/23/97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /___/ NO /✓/

   b) Is it an effectiveness supplement?

   YES /✓/ NO /___/

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   ---

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-151 Rythmol (propafenone)

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # PSD-88-3

Investigation #2, Study # P-16-OR

Investigation #3, Study # P-20-OR

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # PSO-88-3 (not conducted under IND)

Investigation #2, Study # P-16-OR

Investigation #3, Study # P-20-OR

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #~~1~~ 2 P-16-OR

IND # YES /✓/ NO /___/ Explain: _____

Investigation #~~2~~ 3 P-20-OR

IND # YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 PSO-88-3

YES /___/ Explain _____

NO /✓/ Explain no statement of certification

Investigation #2

YES /___/ Explain _____

NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

Diana M. Willard
Signature
Title: Regulatory Health Project Manager

8/1/97
Date

Ray Lipicky
Signature of Division Director

8/2/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

8/8/95

Rythmol (propafenone HCl) Tablets

NDA 19-151/S-002

Patent Certification Information

Date of Submission of Supplement:	November 30, 1992
Patent:	Rythmol is not currently protected by patent exclusivity in the United States.
Marketing Exclusivity:	A marketing exclusivity period of three years is requested for this supplemental indication based upon the provisions of Section 505 (j)(4)(D)(iii) of the FD&C Act, which requires the conduct of new clinical investigations essential to the approval of the application to be conducted by the applicant.

CERTIFICATION IMPOSED BY GENERIC DRUG ENFORCEMENT ACT
FOR S-002 TO NDA 19-151

Knoll Pharmaceutical Company hereby certifies that in connection with Supplement No. S-002 to NDA 19-151 providing for the indication of PSVT for Rythmol (propafenone) tablets, we did not and will not use in any capacity the services of any person or firm convicted or debarred under Section 306 (a) or (b) of the Act.

No affiliated persons responsible for the development or submission of this application have been convicted as described in Section 306 (a) or (b) within the last five years.

Signature of Responsible Official

Vice President, Regulatory & Technical Affairs
Title

June 1, 1995
Date