

Chapter 15. Arrhythmias

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I. INTRODUCTORY REMARKS

Historical Perspective

The development of new antiarrhythmic drugs has become a major challenge since the publication of the Cardiac Arrhythmia Suppression Trial (CAST) results in 1989 (1). This was the first study designed to demonstrate that antiarrhythmic drugs with a potent Class I effect (flecainide and encainide) decrease mortality as compared to placebo in patients with remote myocardial infarction (MI) and frequent ventricular ectopic beats and who are therefore at increased risk for sudden death (SD) due to malignant ventricular arrhythmia. Improved survival was expected as these drugs markedly suppressed premature ventricular contractions in the same study patients. Instead, an increase in mortality was observed on antiarrhythmic drug compared to placebo (2,3).

This result affected antiarrhythmic drug development in two ways. First, the search for more potent drugs with Class I effect, i.e., slowing of conduction velocity by blockade of the sodium channel, was abandoned. In the setting of prior MI or ongoing ischemia, Class I effect was now generally accepted as potentially proarrhythmic. Instead, attention was directed to drugs which prolong action potential duration and refractoriness. In the presence of such a Class III effect, an arrhythmia dependent on a rapidly circulating electrical impulse would be interrupted when the wavefront encountered refractory tissue. The second major result of CAST was the perceived necessity of demonstrating the safety of such drugs in large placebo-controlled trials in patients with underlying cardiac pathology and left ventricular (LV) systolic dysfunction. This also proved to be important for the Class III drugs (3). In susceptible populations or under particular clinical circumstances, these drugs can induce excessive and heterogeneous prolongation of action potential duration with the consequent appearance of triggered automaticity. Such abnormalities can then set the conditions for torsade des pointes, a potentially lethal ventricular arrhythmia (4).

Present Indications for Antiarrhythmic Drug Therapy

Currently, the major indications for antiarrhythmic drug use are atrial fibrillation (AF) and atrial flutter (AFL). AF is a rapid (>400 bpm), disorganized, multi-circuit atrial rhythm whose prevalence increases with age (up to 8% in those over 80 years). It is responsible for approximately one-third of arrhythmia admissions and increases mortality two-fold and the risk of stroke five-fold (5). Acutely, it can manifest with symptoms of palpitations, hypotension, angina or heart failure. Further, if the ventricular response rate remains chronically elevated, it can result in a tachycardia-induced cardiomyopathy (CM). AFL, a single organized circuit usually in the right atrium, is less common but also increases the risk of cardiogenic emboli and provokes similar symptoms. Antiarrhythmic drugs are used acutely as an alternative to electrical cardioversion for both persistent AF and AFL so as to achieve sinus rhythm (SR) and chronically to prevent recurrence. They are also used to diminish the frequency of paroxysmal or spontaneously terminating episodes of AF and AFL. The currently available antiarrhythmics, however, are only moderately effective (30-60%), only a few are safe to administer in the presence of heart failure (dofetilide, amiodarone), and, in the case of the most effective (amiodarone), risk significant organ toxicity (6).

The use of antiarrhythmic drugs for long-term prevention of other supraventricular tachycardias (SVT) such as AV nodal reentry, reentry using an accessory pathway, and, in some centers where the expertise is available, atrial tachycardia and AFL, has taken a distant second place to catheter ablation of the critical component of the arrhythmia circuit. Antiarrhythmic drugs are now mainly used for these arrhythmias only while awaiting definitive curative ablation (7).

Pharmacological prevention of ventricular arrhythmias has also been dramatically challenged. Implantable defibrillators have been demonstrated to be superior to antiarrhythmic drugs in diminishing mortality in survivors of SD secondary to ventricular tachycardia (VT) or fibrillation in the presence of ischemic and non-ischemic CM and impaired systolic LV function (ejection fraction (EF) < 35%) (8,9). In this setting, however, antiarrhythmics can still play an adjunctive role by diminishing the number of episodes of ventricular arrhythmia or by slowing the rate of VT so as to allow painless pacing termination by the

defibrillator. Either effect should ultimately reduce the number of shocks delivered, improve the quality of life (QOL) of the patient and maximize the battery life of the defibrillator. When VT is well tolerated and LV function is relatively well-preserved (EF > 40%), long-term antiarrhythmic therapy with a drug with class III effect (sotalol or amiodarone) instead of defibrillator implantation can still be envisaged (8,9).

Antiarrhythmic drugs have so far not been successful when used as primary prevention of ventricular arrhythmias in patients at risk of SD. In general, drugs with Class I effect should not be given in either ischemic or non-ischemic CM because of increased mortality on drug (10). At best, the drugs studied to date with Class III effects have neutral effects on all-cause mortality in the post-MI patient population with congestive heart failure (CHF) (11). This latter result is in fact hypothesized to be due to a balance between an antiarrhythmic effect and a ventricular proarrhythmic effect (sotalol, dofetilide, azimilide) or the occurrence of serious organ toxicity (amiodarone). In this setting, too, the prophylactic implantation of defibrillators has proven more effective in reducing mortality compared to both placebo and amiodarone when LV systolic function is significantly reduced (EF < 35%) (12). Unfortunately, it is in the setting of CHF that the incidence of AF is highest and contributes significantly to a worse outcome. Therefore, it is necessary to demonstrate at least a neutral effect of drug on mortality in this population in order to allow its administration for atrial arrhythmias in such patients.

Clearly, there is a need for drugs which are more effective and safer in terms of proarrhythmic potential and organ toxicity than those currently available. Phase II studies should therefore compare the efficacy and safety of investigational drug X not only versus placebo but also against reference drug Y currently used in clinical practice. A pharmacokinetic profile allowing once daily dosing as well as minimal interaction with other drugs administered in such clinical settings would also be highly desirable.

II. PHASE II STUDIES TO EVALUATE THE EFFICACY AND SAFETY OF NEW ANTIARRHYTHMIC DRUGS IN ATRIAL FIBRILLATION AND ATRIAL FLUTTER

II.1. Outline of a typical development plan

Phase II studies of antiarrhythmic drugs are primarily directed at demonstrating efficacy and safety in the treatment of the most common atrial arrhythmias, AF and AFL. Various tools are available to document arrhythmia including the 12-lead electrocardiogram (ECG), Holter (24-hour) recording of 2 or 3 leads, and transtelephonic monitoring (TTM) or loop recording. The TTM loop recorder is especially useful in documenting transient episodes of arrhythmia. This can be done either automatically using preestablished criteria (rate and irregularity) for AF or by patient activation during a symptomatic episode. The device then stores in memory the preceding preprogrammed duration of recorded beats as well as an independently preprogrammed duration after activation of the storage function. The stored data can then be transmitted by telephone to a receiving station where symptoms are documented and the rhythm is interpreted.

In addition to arrhythmia documentation, the analysis of drug effect in Phase II studies also involves a detailed observation of effects on various ECG measures reflecting drug action on the sinus node (PP interval), ventricular response rate in AF or AFL, AV node conduction (PR interval) in SR, intraventricular conduction (QRS interval) and ventricular repolarization time in absolute terms (QT interval) as well as when corrected for heart rate (QT_c interval). This latter measure is particularly important as an indicator of appropriate or excessive Class III effect. Other laboratory investigations are directed at modifiers of drug effect (electrolyte levels) or drug pharmacokinetics (eg., renal function tests) or at indicators of potential drug toxicity (eg., liver function tests, hematological values).

II.2. Short-term study

This trial is a multicenter, randomized, double-blind, placebo-controlled, parallel group study of the efficacy and safety of intravenous bolus administration of antiarrhythmic drug X versus reference drug Y in the acute termination of atrial fibrillation and flutter.

This study is often the first type of study done as it involves only single acute intravenous (IV) administration of drug and therefore requires only short-term monitoring of the subject. It incorporates dose ranging to search for effective plasma concentrations and doses and assesses the safety of these doses. Variations of such a study (with or without a reference drug) have been performed in the development of such Class III drugs as dofetilide (13) and ibutilide (14). It should be emphasized that the usual initial clinical approach to a patient presenting with AF/AFL should be followed, i.e., anticoagulation as recommended by current clinical guidelines and control of the ventricular response rate (6) before initiating study drug.

II.2.A. Objectives

Primary Objectives:

- a. To determine the efficacy of bolus I.V. administration of investigational drug X at the highest safe dose compared to placebo and to reference drug Y in achieving conversion of AF or AFL to SR (expressed as percentage conversion within T hours of I.V. dose).
- b. To determine the safety of investigational drug X at the most effective dose compared to placebo in subjects with AF or AFL.

Secondary Objectives:

- a. To determine the efficacy and safety of I.V. investigational drug X at doses A, B, C and D compared to placebo in achieving conversion of AF or AFL to SR.
- b. To assess the effects of doses A, B, C or D of drug X and of reference drug Y on ECG measures (sinus rate, and PR, QRS, QT and QT_c intervals in responders and QRS, QT and QT_c intervals and ventricular response rate in AF or AFL in non-responders).
- c. To determine the pharmacokinetics of investigational drug X administered I.V. in patients with AF or AFL and its modification by concomitant cardiac or minor to moderate hepatic and renal impairment.

II.2.B Primary endpoints

- a. Incidence of conversion to SR within time T of study drug administration.
- b. Incidence of side effects.

II.2.C. Secondary endpoints

- a. Mean time to conversion.
- b. Ventricular rate in non-responders on drug treatment with respect to baseline.

II.2.D. Study Design

Subjects who meet the study inclusion/exclusion criteria will be randomized in double-blind fashion to investigational drug X at dose A, B, C or D, the reference drug Y or placebo with all to be administered as a bolus I.V. In order to assure safety of the study drug at the doses proposed, such a study could be performed in a tiered fashion:

Tier 1: Placebo versus drug X at lowest dose A versus drug X at second lowest dose B versus reference drug Y (80 subjects)

Once safety of doses A and B has been demonstrated, one could proceed to:

Tier 2: Placebo versus drug X at second highest dose C versus drug X at highest dose D versus reference drug Y (80 subjects)

With the safety of drug X at doses C and D demonstrated, the study could continue with randomization of the final 160 subjects among the six groups such that there would be an equal numbers of subjects in each group at the end of the study recruitment phase. If, however, safety is shown to be an issue at the higher doses, the study would continue with only those doses judged to be safe.

II.2.E. Planned Sample

360 subjects for 6 groups with 60 subjects per group to provide 90 % power ($\alpha = 0.05$), to

- a. conclude non-inferiority of the investigational drug when there is no true treatment difference between the investigational drug X and the reference drug Y,
- b. detect a true difference between the reference drug Y or the investigational drug X and placebo under the null hypothesis, and
- c. have sufficient power to examine a dose-response relationship of the investigational drug at different doses.

II.2.F. Study Population

Approximately 400 subjects with AF or AFl of duration longer than 6 hours but less than 60 days will be randomized. A total of 360 would be expected to complete the protocol.

II.2.G. Inclusion Criteria:

- a. Either sex, between 18 and 85 years of age.
- b. AF and/or AFl lasting from 6 hours to 60 days (episodes of AF/AFl of shorter duration are likely to convert to SR on placebo while episodes of very long duration are less likely to respond to drug therapy).
- c. Anticoagulation as recommended by current therapeutic guidelines (all patients are heparinized prior to administration of study drug and anticoagulated for at least one month after conversion to SR; further, if AF/AFl has been present for > 48 hours, adequate anticoagulation (INR 2-3) must have been maintained for at least 3-4 weeks prior to entry into the study or intra-atrial clot must have been excluded by transesophageal echocardiography immediately prior to study drug administration).
- d. Calculated average (beats/12 sec x 5) resting ventricular response rate < 120 bpm achieved by administration of rate-control drugs (β -blockers and/or calcium channel blockers and/or digoxin).

II.2.H. Exclusion Criteria

- a. Females who are currently pregnant or breast feeding.
- b. Hemodynamic instability (CHF, hypotension, angina).
- c. Resting ventricular response rate < 70 bpm in the absence of rate-control drugs or RR interval > 3 sec; if a patient is on rate-control drugs, these must be adjusted so that resting heart rate is not < 70 bpm.
- d. QRS interval > 180 msec or QT_c interval > 440 msec (in the presence of bundle branch block > 500 msec) calculated on the average of 3 QT and RR intervals.
- e. Wolff-Parkinson-White syndrome which has not undergone curative ablation.
- f. History or clinical signs of thyrotoxicosis, confirmed by laboratory studies.
- g. AF or AFl from reversible non-cardiac diseases (eg., pneumonia) or from acute drug effect (eg., excess caffeine, alcohol, bronchodilator therapy).
- h. History of cardiac surgery, MI, or unstable angina within the last 3 months.
- i. History of aborted SD, unexplained syncope, monomorphic or polymorphic VT.
- j. Family history of prolonged QT syndrome.
- k. Known sick sinus syndrome or atrioventricular block greater than first degree.
- l. Presence of cardiac pacemaker or defibrillator.
- m. Diastolic blood pressure (BP) > 105 mm Hg or systolic BP < 90 mm Hg.
- n. Major hematological, pulmonary (necessitating continuous oxygen therapy), hepatic or renal disease (eg. in the case of principal route of elimination via the kidneys of investigational drug X, calculated creatinine clearance (Cl_{Cr}) < 20 ml/min).
- o. Plasma potassium level < 4.0 or > 5.5 mEq, or plasma magnesium level < 0.75 or > 1.25 mEq. Plasma potassium and magnesium may be corrected prior to study entry.
- p. Amiodarone treatment within previous 3 months.
- q. Any Class I or III antiarrhythmic agent, tricyclic or tetracyclic antidepressant, anticonvulsant, or phenothiazine or any other drug known to prolong the QT_c within 5 half-lives before study entry.

- r. Use of an experimental drug within the preceding 4 weeks.
- s. Prior utilization of reference drug Y for I.V. conversion of AF/AFL.
- t. History of substance abuse or dependency or ongoing psychosis.

II.2.I. Tools for assessing endpoints

Assessment Methods

Initial screening consists of a relevant medical history, physical examination, 12-lead ECG and blood sample for routine laboratory tests. An echocardiogram is obtained once the ventricular response rate has been reduced to < 120 bpm prior to study drug administration to assess LV function, valvulopathy, atrial size, and, if indicated, the presence of intra-atrial clot. A Holter recording of 3 ECG leads as well as continuous ECG monitoring (single lead) is started. Study drug is given I.V. following baseline recording for one hour.

Measure of Endpoints

ECG monitoring is continued for a maximum of 24 hours to document conversion to SR. BP and 12-lead ECGs are obtained at the start and end of the baseline period, at the time of drug administration, at 5, 10, 15, 20, 30, 60, 90, 120, 180 min, at 4, 6 and 12 hours, at the predetermined time T following study drug administration, and, finally, at the end of the study period (24 hours). A single-lead ECG may be substituted at the 5-minute intervals if obtaining a 12-lead ECG is technically impossible, but care should be taken to use a lead with an easily measurable QT interval. Preferably, the lead with the longest QT interval as determined from the 12-lead ECG should be chosen. Pharmacokinetic evaluation can be determined from venous blood samples drawn from an indwelling I.V. catheter prior to infusion of study drug (baseline) and at the times specified above.

II.2.J. Specific criteria for early withdrawal or non-utilization of subject data in analysis

- a. Adverse event during drug infusion requiring stopping drug infusion; data from this subject would not be used in efficacy analysis but would still be reported in the tabulation of adverse events.
- b. Protocol violation.
- c. Administrative reasons.

II.2.K. Data Analysis Methods

The proportion of subjects in each treatment group achieving conversion to SR within time T can be compared using a one-way logistic model with treatment as the factor. The survival function for time to conversion can be estimated by Kaplan-Meier analysis. The following pairwise comparisons should be performed:

- a. Investigational vs. reference drug: a non-inferiority test and, if positive, a superiority test of investigational drug doses A, B, C and D vs reference drug Y.
- b. Investigational drug vs. placebo: A. dose-response via a regression analysis, and B. pairwise comparison of investigational drug X at doses A, B, C and D vs. placebo.

The statistical test for each of the pairwise comparisons can be made at a two-sided 0.05 statistical significance level. The predictive value of variables at baseline (e.g., duration of arrhythmia, atrial size, AF vs AFL) on the probability of conversion to SR can be assessed by multiple logistic regression analysis. Mean changes from baseline over time for mean BP, heart rate, and QRS and QT_c intervals can be assessed in non-responders by analysis of covariance.

II.2.L. Comments

If safety and efficacy are demonstrated in such a study, other Phase II studies can be considered. If safety is demonstrated but there is little efficacy of I.V. drug, this does not exclude further clinical studies of drug X. Oral drug which is converted to one or more active metabolites may be effective when single dose I.V. administration is not. Further, an antiarrhythmic drug may not be useful in achieving conversion to SR but may be very effective in preventing recurrence of arrhythmia. However, if safety is clearly an issue,

especially if observed at fairly low doses and plasma levels of drug, there will be little impetus to pursuing further drug testing.

Once I.V. dosing which is both effective and safe has been established for investigational drug X, other questions best answered by physician driven Phase III studies can begin. For example, in patients failing to convert to SR, is electrical cardioversion following I.V. infusion of drug X more effective (higher percentage conversion rate or lower defibrillation threshold) than when performed in the presence of placebo or of reference drug? Further, is I.V. pre-administration of investigational drug X more effective than placebo or reference drug Y in preventing early recurrence of AF or AFL following successful cardioversion?

II.3. Long term studies

II.3.i. Conversion and maintenance sinus rhythm in patients with persistent atrial fibrillation or atrial flutter

This trial is a multicenter, randomized, double-blind, placebo-controlled parallel group study of the efficacy and safety of oral investigational antiarrhythmic drug X versus reference drug Y in converting to and maintaining SR in patients with persistent AF or AFL.

As safety has become such an issue for drugs with Class III effects, long-term Phase II studies should be initiated in a monitored setting in hospital for at least the duration of time necessary to achieve steady-state. Such an approach has been taken with both dofetilide (15) and azimilide (16) in their supraventricular Phase II programs. Also, evaluation of the efficacy of investigational drug X in the context of a long-term oral dosing protocol may now need to be done separately in patients with cardiac pathology and EF < 35 % as compared to those with better preserved EF or with normal hearts. In the former group, defibrillator implantation for SD prevention is now indicated (12,19) especially since the recent presentation of the Sudden Cardiac Death – Heart Failure Trial (12). The dual-chamber pacing capabilities of defibrillators along with various AF prevention pacing algorithms now available may significantly influence drug efficacy and safety. Further, their diagnostic abilities and memory capacity allow documentation of recurrence of atrial arrhythmia as well as of possible ventricular proarrhythmia. The following protocol therefore addresses the evaluation of investigational drug X in converting AF to and maintaining SR only in patients with normal hearts or fairly well-preserved EF (> 35%) despite cardiac pathology.

II.3.i.A. Objectives

Primary Objectives

- a. To determine the efficacy of oral administration of investigational drug X at the highest tolerated dose compared to placebo and to reference drug Y in achieving conversion of persistent AF or AFL to SR within 5 half lives of the start of drug dosing (or within the time to reach maintenance plasma levels if loading doses are used).
- b. To determine the efficacy of chronic oral administration of investigational drug X at the highest tolerated dose compared to placebo and to reference drug Y in maintaining SR following electrical or chemical cardioversion.
- c. To determine the safety of oral administration of the investigational drug X at the most effective dose compared to placebo in subjects with persistent AF or AFL.

Secondary Objectives

- a. To determine the efficacy and safety of oral investigational drug X at doses A, B and C compared to placebo in achieving pharmacological conversion of AF or AFL to SR.
- b. To assess the effect of doses A, B and C of drug X and reference drug Y on ECG measures such as sinus rate, PR, QRS, QT and QT_c intervals in responders or following electrical cardioversion in non-responders as well as on the ventricular response rate in non-responders.

- c. To determine the range of effective plasma levels of investigational drug X in subjects with AF or AFI and its modification by concomitant cardiac or minor to moderate hepatic or renal impairment.

II.3.i.B. Primary endpoints

- a. Incidence of conversion to SR within 5 half-lives of beginning study drug or, if loading doses are used, within the time to reach maintenance plasma levels (see Study Design).
- b. Time to first recurrence of AF or AFI lasting at least 24 hours following electrical or chemical conversion to SR.
- c. Incidence of serious side effects.

II.3.i.C. Secondary endpoints

- a. Mean time to conversion in responders.
- b. Ventricular rate in non-responders with respect to baseline.

II.3.i.D. Study Design

Subjects who meet the study inclusion/exclusion criteria are admitted to telemetry in hospital for the duration of time necessary to reach the plateau effect of investigational drug X or reference drug Y whichever is longer. Randomization is done in a double-blind fashion to oral investigational drug X at doses A, B, or C, the reference drug Y or placebo. Maximum dose of investigational drug X (i.e., dose C) should not exceed that proven safe in Phase III studies of mortality. If investigational drug X is eliminated primarily by the kidneys, dosage adjustment is performed according to calculated Cl_{cr} , as follows:

- a. Cl_{Cr} 40 – 60 ml/min – half of the randomized dose is given,
- b. Cl_{Cr} 20 –40 ml/min –one quarter is given.

A 12-lead ECG is obtained just before the first dose on all days while in hospital. If the QT_c interval is found to increase by > 15 % over baseline, the dose is halved. If QT_c interval exceeds 550 msec or increases by > 25 % over baseline, the subject is withdrawn from the study. It is important to note that in the design of such a study, reference drug Y should use the same predominant route of elimination/metabolism as the investigational drug X, as the dosage adjustments described above may penalize the reference drug Y if it does not depend on renal clearance. On the other hand, when elimination of investigational drug X does not depend on renal clearance and therefore dose adjustments are not necessary, there is a risk of significant toxicity in the case of reference drug Y when its clearance does depend on the kidneys.

In subjects who are exposed to drug for a duration of time to achieve plateau levels and have not converted spontaneously to SR, electrical cardioversion is attempted. Following conversion to SR, subjects are monitored for an additional 24 hours. Those in whom SR cannot be achieved or maintained for 24 hours following electrical or pharmacological conversion are withdrawn from the study. Subjects who are at this point in SR are discharged from hospital on the same dose of study drug as last given in hospital, or on maintenance dosing in those in which the hospitalization period was used for drug loading. Oral anticoagulation is continued for only one month in patients at low risk for cardiac emboli but throughout the course of the study in patients at moderate to high risk (6). Follow-up clinic visits are scheduled at 2, 4, 6, 8, 10, 12 weeks and then every 3 months until one of the study end points is reached: relapse to AF or AFI for at least 24 hours, documented by ECG, or maintenance of SR for one year. Twelve-month survival data (freedom from AF or AFI) is collected for all randomized subjects regardless of treatment duration.

II.3.i.E. Planned Sample

Sample size for a double-blind study can be calculated using the method of Schoenfeld (17) (proportional hazards regression model), assuming a two-sided hypothesis test of the primary endpoint at a significance level of 5 %. Total sample size will then depend on the number of groups (investigational drug X doses studied and on the presence or absence of a reference drug Y group). The distribution of time to first event documented by ECG is assumed to follow an exponential distribution. If the median time to first event is

estimated to be no more than 90 days for placebo, then a sample size of 190 subjects in each treatment group will allow a hazard ratio of 0.67 to be detected with 0.90 probability. With possibly a 10-20% drop out rate, then 210-230 subjects should be enrolled in each treatment group.

II.3.i.F. Study Population

If all the groups mentioned above are used in the study, then a minimum total sample size of 1260 subjects with AF or AFL of duration longer than 2 weeks but less than 26 weeks will be recruited. A total of about 1140 subjects would be expected to complete the protocol. If fewer doses are studied or if no appropriate reference drug Y is available for comparison, then the total population size is correspondingly reduced.

II.3.i.G. Inclusion Criteria

- a. Either sex between 18 and 85 years of age.
- b. AF and/or AFL lasting from 2 to 26 weeks, confirmed by ECG.
- c. Anticoagulation in all patients with a therapeutic INR of 2-3 for at least 3-4 weeks prior to beginning study drug, or, if a patient is not currently anti-coagulated, heparin I.V. is administered and oral anticoagulation is begun. Study drug can be administered early on I.V. heparin if transesophageal echocardiography shows no intra-atrial thrombus.
- d. Average resting ventricular response rate < 120 bpm (see Section II.2.G).

II.3.i.H. Exclusion Criteria

Same as listed in section II.2.H with the addition of the following:

- a. Females who plan to become pregnant during the course of the study or, if sexually active, are not using a hormonal contraceptive as well as a vaginal spermicide.
- b. Presence of severe valvulopathy, such that surgical intervention is considered a possibility within the time course of the study.
- c. Ischemic or non-ischemic CM with EF < 35 %.
- d. Presence of other life-threatening disease with survival expected to be < 2 years.
- e. Use of digoxin, unless plasma levels remain constant.
- f. Absolute contraindications to anticoagulation therapy.
- g. Any unresolved drug-induced organ toxicity.
- h. Concomitant therapy with drugs known to affect the metabolism or elimination of investigational drug X or reference drug Y.
- i. Patients who previously in the opinion of the investigator have failed an antiarrhythmic drug of the class being tested for efficacy reasons.
- j. Patients who have previously participated in a study of investigational drug X or have used reference drug Y for oral conversion to and/or the subsequent maintenance of SR.
- k. If Phase III studies in subjects with underlying ischemic/non-ischemic CM and but less depressed LV function (EF 35-50%) demonstrate significantly higher mortality in the presence of investigational drug X compared to placebo, such patients should also be excluded in chronic studies of efficacy in AF or AFL.

II.3.i.I. Tools for assessing endpoints

Initial screening should include a relevant medical history, complete physical examination, 12-lead ECG, chest X-ray, echocardiogram and blood sample for routine laboratory tests as well as those indicated by the known side effect profile of investigational drug X and reference drug Y. In-hospital, a 12-lead ECG is done each day before the morning dose of study drug. If electrical cardioversion is done or if chemical conversion occurs, an ECG should be obtained immediately to document SR and also 24 hours later. Blood tests before discharge from hospital should include serum chemistry, hematology, and analysis of levels of investigational drug X, reference drug Y and principal active metabolite(s), if applicable.

At follow-up visits, vital signs, cardiopulmonary specific physical examination, event symptom severity checklist (prior to ECG), 12-lead ECG, serum chemistry, hematology, blood samples for analysis of investigational drug X, reference drug Y and active metabolite(s) and assessment of concomitant medications and adverse events are done. Assessment of QOL (SF-36) and the Brignole Atrial Fibrillation Symptom Checklist can be completed on a monthly basis. As well, drug accountability and, in females of childbearing potential, a serum pregnancy test should be performed. At the final visit, either on reaching the primary endpoint or on completion of the total study duration, in addition to the procedures described for the follow-up visits, a complete physical examination, a healthcare resource utilization questionnaire and a chest X-ray are done.

A 12-lead ECG is obtained at each visit, reviewed by the investigator and sent to a central facility which generates a report including an interpretation of the patient's rhythm and interval calculations. If the investigator and central ECG facility interpretations do not agree with respect to possible AF, AFI or SVT, the report should be sent to an Event Committee for a final decision.

Adverse Events (AE) are defined as any undesirable clinical experience during the study, whether or not related to the study drug, including an exacerbation of a preexisting condition. A serious AE is one that results in death or is life threatening, results in hospitalization or prolongation of current hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is judged to be medically significant. All AEs should be judged as to their severity (mild, moderate, severe) and as to their causality (doubtful, possible, probable).

II.3.i.J Specific criteria for early withdrawal of subjects from the study

- a. ECG criteria: ventricular fibrillation, polymorphic VT of any duration, sustained monomorphic VT (> 30 sec) or symptomatic non-sustained VT, incessant VT (recurrent VT < 30 sec interrupted by a few sinus beats), $QT_c > 525$ msec, resting SR remaining < 50 bpm after conversion to SR.
- b. Pregnancy
- c. Noncompliance: missing any 3 scheduled visits or any 2 serum pregnancy tests, stopping contraceptive methods or taking less than 80 % of study drug.
- d. Adverse events or organ toxicity such that withdrawal of the subject is recommended.
- e. Voluntary withdrawal by the subject.
- f. Protocol violation.
- g. Administrative reasons.

II.3.i.K. Data Analysis Methods

Primary endpoints

All intent-to-treat subjects are used in the analysis of the primary efficacy endpoints. The Cochran-Mantel-Haenszel test or the Fisher's exact test can be used to compare the percentage of randomized subjects pharmacologically converting to SR in each investigational drug X group compared to placebo. Similarly, comparison can be made between each investigational drug X group vs. reference drug Y group. Time from the start of the efficacy period to the date of the first documented AF, AFI or SVT of > 24 hours duration is measured and displayed using Kaplan-Meier estimates of the survival curves. Treatment comparisons can be made using log-rank test, differences between the time to event distributions can be quantified by the hazard ratio from proportional hazards regression, Kaplan-Meier estimates of the median time to event, and Kaplan-Meier estimates of the proportion event-free through one year. Pairwise comparisons between investigational drug X at doses A, B or C vs reference drug Y can be performed, as well as pairwise comparisons between investigational drug X at doses A, B or C vs placebo. The predictive value of variables at baseline (e.g., duration of arrhythmia, atrial size, AF vs AFI, LV systolic dysfunction) on the probability of conversion to SR or on time to recurrence of atrial arrhythmias can be assessed by multiple logistic regression analysis.

All subjects randomized to a treatment group are used in safety summaries. Incidence of AEs is compared between all groups and frequencies are tabulated by body system, treatment duration, causality and severity. Mortality rates can be calculated for each group. Treatment comparisons can be made by calculating the mortality relative rate using a Poisson model and the mortality relative risk using the Cochran-Mantel-Haenszel method (18). Efficacy and safety data can be summarized separately for subgroups defined, for example, by sex, age, race/ethnicity, baseline cardiovascular disease state, EF, smoking history, digoxin or β -blocker use and presented as point estimates and estimated standard errors. Descriptive statistics are used to calculate the clinical laboratory data and ECG intervals which can then be presented in shift tables and/or in shift plots.

Secondary endpoints

Time to conversion can be determined by the number of hours from first dose in each group and displayed graphically by means of the Kaplan-Meier (product-limit) method. Ventricular response rates in non-converters at first ECG before study drug administration and prior to electrical cardioversion can be presented in the different groups with descriptive statistics. Change and percentage change can be compared between placebo, investigational drug X groups and reference drug Y group by analysis of variance and Bonferroni t-test. QOL comparisons can be made using analysis of variance or if assumptions of normality and equal variances are not valid, a non-parametric analysis of covariance can be used. Symptom frequency load during the first recurrence can be assessed by constructing contingency tables of number of treatment groups versus number of pre-specified symptoms reported during the first recurrence of atrial arrhythmia and analyzed with the appropriate chi-square test.

II.3.i.L. Comments

Demonstration of efficacy and safety in such a study suggests the possibility of beginning drug on an outpatient basis. However, if the dose must be modified during the first few days either because of excessive effects on the ECG or because of significant proarrhythmic effects, further Phase II studies will require the same initiation protocol, and, once brought to market, initiation in a monitored hospital setting will be mandatory. This would significantly limit this drug's use appropriately to specialists trained in its administration and, perhaps inappropriately, for those for whom financial restrictions and hospital bed availability are not an issue.

Further Phase III studies could determine if defibrillation thresholds for AF are decreased by oral pretreatment with investigational drug X versus placebo or reference drug Y, or in patients with pacemakers or pacemaker/defibrillators with programming capabilities for pacing prevention of AF and AFL, it could be determined if such programs are more effective in preventing recurrence of these arrhythmias in the presence of drug X versus placebo or reference drug Y.

II.3.ii. Prophylactic treatment of paroxysmal atrial fibrillation or atrial flutter

The trial is a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical study to assess the efficacy and safety of the oral investigational antiarrhythmic drug X versus reference drug Y in the prophylactic treatment of paroxysmal atrial fibrillation and atrial flutter.

With the accumulation of data from studies on the acute conversion of AF and AFL with I.V. or oral investigational drug X and the prevention of recurrence of arrhythmia following pharmacological or electrical cardioversion, it is usually possible to identify a dose range which is effective and tolerated. The number of investigational drug groups can now be limited to one or two doses for evaluating efficacy and safety when used for other indications, such as the prevention of paroxysmal AF (PAF). Accumulating data from mortality studies in subjects with moderate systolic LV dysfunction in ischemic or non-ischemic CM will determine whether such a study should be limited to subjects with PAF or PAFI and normal hearts or whether two strata can be studied as described below. If so, as in section II.2, such a chronic study should

exclude patients with ischemic or non-ischemic CM and LVEF < 35% for whom defibrillator implantation is indicated.

II.3.ii.A. Objectives

Primary Objectives

- a. To assess the efficacy of oral investigational drug X at doses A and B compared to placebo and reference drug Y in prolonging the arrhythmia-free period, i.e., time from first dose of study medication to first ECG-documented symptomatic AF, AFI or SVT.
- b. This primary objective can be assessed separately in two strata:
 - subjects with ischemic heart disease (IHD) and/or CHF (EF >35%)
 - subjects with neither of the above

Secondary Objectives

The following secondary objectives can be determined according to stratification between presence or absence of CHF and IHD.

- a. To assess the efficacy of investigational drug X at doses A and B versus placebo and versus reference drug Y in reducing the total number of symptoms reported during the first symptomatic event.
- b. To assess the efficacy of investigational drug X at doses A and B versus placebo and versus reference drug Y in reducing the frequency of symptomatic events.
- c. To assess the efficacy of investigational drug X at doses A and B versus placebo and versus reference drug Y in reducing the total supraventricular arrhythmia burden in patients (i.e., frequency, duration and severity).
- d. To assess the effect of investigational drug X at doses A and B versus placebo and versus reference drug Y on patient QOL.
- e. To assess the number of days in-hospital and number of emergency room visits due to symptomatic PAF, PAFI or PSVT (following initial discharge for subjects hospitalized for drug loading or initiation) between groups receiving investigational drug X at doses A and B versus placebo and versus reference drug Y.
- f. To assess the efficacy of investigational drug X at doses A and B versus placebo versus reference drug Y in reducing the number of asymptomatic events.

And, in both strata combined:

- g. To assess the safety of investigational drug X at doses A and B versus placebo and versus reference drug Y according to incidence and severity of AEs, ECG changes, and new laboratory and chest X-ray abnormalities.

II.3.ii.B. Study Endpoint

Time to a SR containing day after the second confirmed occurrence of symptomatic PAF, PAFI or PSVT.

II.3.ii.C. Study Design

Subjects who meet the study screening inclusion/exclusion criteria are instructed in the use of a TTM. SR at the beginning of the screening period is documented during a training call. Over the following month, subjects transmit a recording obtained whenever they have symptoms suggestive of an arrhythmia. Once symptomatic AF or AFI is documented, subjects transmit again when SR returns. Randomization then occurs between investigational drug X at dose A or B, placebo or reference drug Y. If no spontaneously terminating episode of AF or AFI is documented during a one-month screening phase off antiarrhythmic drugs, the subject is withdrawn from the study. Study drug is initiated only once other Class I or III drugs are stopped for at least 5 half-lives.

Initiation of study drug using in-patient hospitalization, continuous monitoring and a 12-lead ECG prior to each morning dose versus close out-patient monitoring and daily transmission of a rhythm strip prior to morning dose will depend on the incidence of proarrhythmia observed in prior trials with investigational drug X in the absence and the presence of known IHD or CHF as well as on the clinical experience with reference drug Y. In the case of significant renal clearance of drug as well as risk of torsade de pointes, in-hospital initiation of study drug using the dosing design described in section II.2.D should be used. When clearance is primarily by hepatic metabolism and there is little risk of torsade de pointes, out-patient initiation of study drug can be considered, at least in cases of PAF or PAFI in normal hearts.

During the maintenance period of study drug administration, a TTM recording should be transmitted whenever the subject experiences symptoms suggestive of arrhythmia. An Event Symptom Severity Checklist should be obtained by the central TTM facility before transmission. If the subject is in a location where an ECG can be obtained, this checklist should be administered by health care personnel prior to recording the rhythm. All tracings should be sent to the central facility. Documentation of return to SR can be made by TTM, ECG or telemetry. If return to SR does not occur spontaneously, then Class II and/or Class IV drugs and/or digoxin can be administered to slow the ventricular response rate to < 100 bpm, and, if arrhythmia persists, electrical cardioversion can be done. Neither Class I nor Class III drugs should be used. Subjects then continue on the same study drug assigned until documentation of return to SR after the second confirmed symptomatic atrial arrhythmia occurs or until end of study at 12 months.

II.3.ii.D. Planned Sample

Sample size is calculated as in section II.2.E using Schoenfeld's method, assuming two-sided tests, and a time to first event that follows an exponential distribution with a median of 90 days in the placebo group. Since the assigned alpha applies only to the time to first symptomatic event, Hochberg's procedure is applied to the sequence of the 2 tests (17). Allowing for drop-outs, approximately 220 subjects are projected for each group. This would allow an investigational drug to placebo hazard ratio of 0.67 to be detected with 0.90 probability at an alpha of 0.045.

II.3.ii.E. Study Population

If the investigational drug is administered at doses A and B, and both placebo and reference drug Y are used, then a study sample size of 880 subjects with PAF or PAFI are required in each stratum after successful screening. It should be pointed out that the logistics of screening a large patient population to document a symptomatic arrhythmia episode within a one-month period may significantly dampen enthusiasm for a multi-group trial. To be practical and finish the study recruitment in a timely manner, only the most promising dose of investigational drug X may be compared to placebo. Comparison to a drug already on the market may have to wait for positive results of a simpler investigational drug X versus placebo trial.

II.3.ii.F. Inclusion Criteria

Screening Period

- a. Either sex between 18 and 85 years of age.
- b. Symptomatic AF within the previous 6 months, documented by ECG, TTM, or rhythm strip but not by Holter monitor.
- c. Symptoms severe enough to significantly interfere with the subject's usual activities.
- d. SR at the time of starting the screening period.

For Randomization

- a. Within 30 days from starting screening, at least 1 episode of symptomatic AF or AFI documented by TTM or ECG (if no episode occurs on antiarrhythmic drugs, at least 1 episode during a second 30-day screening period after discontinuing these medications).
- b. SR immediately prior to starting study drug.

II.3.ii.G. Exclusion Criteria

Screening Period

- a. Women currently pregnant or breast-feeding, or who plan to become pregnant during the course of the study or are unwilling to use hormone contraceptives with a vaginal spermicide; women postmenopausal for less than one year or not surgically sterile (tubal ligation at least 3 months prior to screening) unless they have been using hormonal contraceptives for at least 3 months prior to entry into the screening phase.
- b. AF or AFl due to acute electrolyte disturbance, hyperthyroidism, pericarditis, or any other acute reversible illness.
- c. Electrical cardioversion within 60 days prior to screening.
- d. Syncope, angina pectoris or pulmonary oedema that is precipitated by attacks of arrhythmia (ventricular or supraventricular).
- e. Polymorphic VT of any duration, sustained (> 30 sec) monomorphic VT, aborted SD or undiagnosed syncope.
- f. Wolff-Parkinson-White syndrome that has not undergone curative ablation.
- g. QRS interval > 180 msec or QT interval > 440 msec (in the presence of bundle branch block > 500 msec) or a family history of prolonged QT syndrome.
- h. Presence of an implanted pacemaker or defibrillator.
- i. History of Class IV New York Heart Association CHF or current acute decompensated CHF. Class I – III patients must have been stable for at least one month.
- j. Ischemic/non-ischemic CM with EF < 35%.
- k. Cardiac surgery, MI, or unstable angina within the last 3 months.
- l. Symptomatic severe valvular disease for which surgery is considered within the duration of the study.
- m. Stroke or a reversible ischemic neurologic deficit within the last 3 months.
- n. Diastolic BP > 105 mm Hg (acceptable value must be present for at least one month on antihypertensive therapy) or systolic BP < 90 mm Hg.
- o. Major hematological, pulmonary (requiring continuous oxygen therapy), hepatic or renal disease (calculated Cl_{Cr} < 20 ml/min).
- p. Unresolved drug-induced organ toxicity.
- q. Substance abuse or dependency or ongoing psychosis.
- r. Previous failure of efficacy of the class of antiarrhythmic drug being tested.
- s. Prior participation in a randomized trial of investigational drug X.
- t. Prior exposure to reference drug Y.
- u. Any investigational drug use in the 30 days before screening.

For Randomization

- a. Electrical cardioversion during the screening period.
- b. Resting SR below 50 bpm.
- c. QT_c interval > 440 msec, calculated as the average of 3 QT and RR intervals recorded during SR.
- d. Class I or Class III drugs within 5 half-lives or amiodarone within one month prior to receiving the first dose of study drug or during the study.
- e. Use of drugs which prolong the QT_c interval when the investigational drug X or reference drug Y is a Class III drug and of any drug that may potentiate a known serious side effect of investigational drug X or reference drug Y for at least 5 half-lives prior to receiving the first dose of study drug or any time during the study.
- f. Potassium < 4 mEq/L or > 5.5 mEq/L or magnesium below the lower limit of normal; both of these electrolyte levels may be corrected prior to beginning study drug.
- g. Hepatic dysfunction (ALT, AST > 2 x normal), severe renal dysfunction (calculated Cl_{Cr} < 20 ml/min).

II.3.ii.H. Tools for assessing endpoints

A baseline visit for randomized subjects is performed within 7 days prior to first dose of study drug. This includes a medical history, complete physical examination, chest X-ray, hematology, blood chemistry (electrolytes including magnesium, renal and hepatic function tests and others as suggested by the side effect profile of both investigational drug X and reference drug Y), blank sample for drug and metabolite plasma levels and serum pregnancy test for women of child-bearing potential. An echocardiogram should have been done to determine eligibility for the study prior to screening. Potassium and magnesium levels must at all times be maintained in the normal range. Immediately prior to the first dose of study drug, vital signs are taken, an event severity checklist is done and then a 12-lead ECG is taken to confirm SR and $QT_c < 440$ msec and serum chemistry is repeated stat if baseline chemistry is not done on day 1 of dosing. Finally, QOL is assessed by SF-36 and Brignole Atrial Fibrillation Symptom Checklist.

Clinic visits and TTM are scheduled often to document asymptomatic/minimally symptomatic recurrence of atrial arrhythmia. TTM transmission can be done weekly if no clinic visit is scheduled for that week with Event Symptom Severity Checklist done before transmission. Clinic visits can be scheduled at the end of week 2, 4, 8, 12, 16, 24, 36, and 52. At each visit the following are recorded: vital signs, Event Symptom Severity Checklist before a 12-lead ECG, blood chemistry, hematology, blood levels of investigational drug X, reference drug Y and possible metabolites, assessment of adverse events and verification of concomitant medications. Also, drug accountability is done at the beginning of the maintenance phase and both drug accountability and QOL assessment are done at weeks 4, 8, 12 and 24 and 52. A pregnancy test is done at monthly intervals in women of child-bearing potential following the baseline test until the end of the patient's participation in the study. At the last visit (week 52 or on early completion or withdrawal) a complete physical examination is performed and a chest X-ray should be obtained.

Post-treatment follow-up is done at day 7 and day 30 following study termination. The same data is collected as above as well as a pregnancy test if indicated at day 30 post-treatment. During this 30-day period subjects continue to transmit recordings during symptoms suggestive of arrhythmia. The TTM is returned only at the end of this 30 day period.

Twelve-lead ECGs obtained at each scheduled or unscheduled visit and any TTM or telemetry recordings are reviewed by the investigator. All the above are sent to a central facility which will generate a report of rhythm diagnosis and interval measurements. If there is disagreement with respect to the rhythm diagnosis, the tracing should be submitted to an Event Committee. QOL questionnaires will be completed at home prior to the appropriate visit. Safety (AEs) will be assessed as described in section II.3.K.

II.3.ii.I. Data Analysis Methods

Primary endpoints

The log-rank test can be used to compare the distribution of the time to first symptomatic event (from day of randomization) between patients in the various groups. Hochberg's procedure can be applied to the sequence of the 2 tests (17). Differences between the time to event distributions can also be quantified by the hazard ratio from a proportional hazards regression, Kaplan-Meier estimates of the median time to event, and Kaplan-Meier estimates of the proportion event-free through 6 months or 12 months. The presence or absence of Class II/III CHF can be used as a stratification variable for the log-rank test and proportional hazards regression in the CHF/IHD stratum.

Secondary endpoints

The number of 6 pre-specified symptoms reported during the first confirmed event (Event Symptom Severity Checklist) are totaled. The total count can be compared between treatment groups, using a chi-square test with rank scores. Also, the percentage of subjects with each specific symptom can be compared using a chi-square test. Symptomatic event rates can be compared between treatment groups and analyzed using a Poisson regression model (18). ECG data can be used to assess subject arrhythmia status over time

and this latter can be combined with symptom count and severity data to classify each subject into an ‘SVA burden state’. The proportion of subjects in each state or combination of states can be compared between treatment groups using a logistic regression or hazard regression model.

The Medical Outcome Study Short Form (SF-36) Health Survey consists of 36 questions which assesses 8 areas one of which is physical functioning. This subscale can be normalized to a 0 – 100 % scale from worst to best functioning. Descriptive statistics (n, mean, median, minimum, maximum and standard errors) can be used to summarize the data and analyses of variance can be used to test for treatment differences in physical functioning. Resource utilization can be assessed by evaluating the number of days in-hospital after in-hospital initiation of study drug or the number of emergency room visits due to atrial arrhythmias normalized by the number of days at risk. This can be modeled using Poisson regression and the relative risk and standard error in investigational drug X group versus placebo or versus reference drug Y can be estimated.

Other analyses can compare the rate of asymptomatic arrhythmias between treatment groups using a Poisson regression model. Other SF-36 QOL measures (eg., general health, vitality, social functioning and mental health) can also be assessed as described above. The Brignole Atrial Fibrillation Symptom Checklist quantifies the presence of 5 symptoms which are disease specific (palpitations, shortness of breath at rest, shortness of breath during physical activity, fatigue during mild physical activity and fatigue at rest) during the past 4 weeks by means of a score scale (0- absent to 10- present). This too can be summarized with descriptive statistics or frequency tables at the scheduled time points. Analysis of variance can be used to test for treatment differences using factors such as baseline value, sex or baseline EF as covariates.

The incidence of AEs can be summarized using tables. Descriptive statistics can be used to summarize laboratory data as well as ECG values (QT, QT_c, PR, QRS and heart rate during sinus rhythm or during atrial arrhythmia) by visit, including absolute values, change and percentage change from baseline. The latter can be presented in shift tables or plots. Reason for drug discontinuation should be presented in frequency tables. Compliance (number of tablets taken divided by number expected to be taken) can be summarized with descriptive statistics.

II.3.ii.J. Specific criteria for early withdrawal or non-utilization of subject data in analysis

- a. ECG criteria: ventricular fibrillation, sustained monomorphic VT (> 30 sec), incessant VT (recurrent VT with episodes lasting < 30 sec and interrupted by a few sinus beats), polymorphic VT or a QT_c > 525 msec on 12-lead ECG or rhythm strip. If a patient is withdrawn from the study for ECG criteria, a blood sample should be obtained for plasma level of investigational drug X and reference drug Y as well as any possible active metabolites and for electrolytes (including Mg⁺⁺).
- b. Pregnancy.
- c. Noncompliance: missing any 3 or 2 consecutive clinic visits, a total of 3 or any 2 consecutive TTM transmissions, or 2 serum pregnancy tests; stopping hormonal contraceptives or vaginal spermicide; use of any excluded concomitant medication.
- d. Adverse events or organ toxicity that require subject withdrawal from the study.
- e. Protocol violation.
- f. Administrative reasons.

II.3.ii.K. Comments

The above Phase II studies represent the core of investigational drug development for the indication of AF or AFL. They provide an excellent evaluation of drug efficacy and safety of both I.V. and oral forms at various doses compared to placebo. Although to date not often done within the same study, incorporating the most effective reference drug Y also provides useful information. It is such a comparison which in

fact determines whether investigational drug X is eventually marketed just as a useful alternative to presently used drugs or whether it can in fact be considered the drug of first choice.

III. PHASE III STUDIES IN PATIENTS AT RISK OF SUDDEN DEATH DUE TO VENTRICULAR ARRHYTHMIAS

The Cardiac Arrhythmia Suppression Trial (1,2), a Phase III study of safety and efficacy of flecainide and encainide in a large patient population at risk of SD in the chronic phase of MI, was carried out well after the introduction of these two drugs to market. Since the finding in this study that mortality was increased on drug, such Phase III testing has been more recently done early and, in fact, prior to obtaining regulatory approval. Indeed, observations made during such a study often can help in designing safer Phase II studies. For example, the most recently published mortality trial compared azimilide to placebo in patients with recent MI (6-42 days) and who were at moderate to high risk for SD as predicted by poor LV systolic function (EF < 35%) with or without low heart rate variability (20). No difference in overall mortality was observed on drug. Although azimilide would therefore not be indicated for prevention of SD, such a study does confirm the safety of its use for atrial arrhythmias in this population and permits inclusion of such patients in clinical trials of drug for supraventricular arrhythmias.

It is unlikely, however, that such placebo-controlled mortality studies in moderate to high risk populations will continue to be performed. The recent publication of MADIT II (19) and the presentation of the SCD-HeFT results (12) have shown the superiority of implantable defibrillators versus placebo in patients with poor LV function and IHD as well as versus placebo and amiodarone in non-ischemic CM (12). The indication now exists, therefore, for implantation of a defibrillator in such patients. As a consequence, long-term mortality trials of oral investigational drug X versus placebo are, in our opinion, no longer ethical in this population. Instead, the focus will likely be shifted to that group of patients with ischemic or non-ischemic CM and with only moderately or minimally depressed LV function (EF 36-50%). These patients, while less at risk for SD from ventricular arrhythmias as a result of the underlying cardiac pathology, may however be at risk for greater mortality on investigational drug X if there is any proarrhythmic potential of the new drug. Such a suggested study is presented.

III.1. Outline of a typical development plan

The study should be a double-blind, placebo-controlled, parallel design to determine the effect of two doses of orally administered investigational drug X versus placebo on survival in ischemic or non-ischemic cardiomyopathy and low to moderate risk of sudden death.

III.2. Long-term studies

III.2.A. Objectives

Primary Objective

To evaluate the effects of investigational drug X at dose A versus placebo or dose B versus placebo on all-cause mortality based on intention-to-treat in subjects at low to moderate risk of SD, i.e., with either ischemic or non-ischemic CM and LV EF 36-50 %.

Secondary Objectives

To evaluate the effects of investigational drug X at doses A and B combined versus placebo on all-cause mortality, based on intention-to-treat analysis.

Tertiary Objectives

These analyses will be based on 'on-treatment' observations, i.e up to 30 days following discontinuation of the study drug.

- a. To evaluate the effects of investigational drug X at dose A versus placebo or dose B versus placebo on all-cause mortality.
- b. To evaluate the effects of investigational drug X at doses A and B combined on arrhythmic, cardiac, and non-cardiac mortality.
- c. To determine the effect of beta blocker and angiotensin converting enzyme inhibitor use on all-cause mortality.

III.2.B. Study Endpoint

The study endpoint is death due to any cause.

III.2.C. Study Design

Patients who meet the study inclusion/exclusion criteria are enrolled in the study and first undergo a 24-hour Holter to determine heart rate variability (HRV) which is analyzed at a central facility. The baseline visit (within 48 prior to initiation of study drug) also includes a complete physical examination, review of concomitant medications, 12-lead ECG, stat potassium and pregnancy test (if applicable) and chemistry and hematology measurements.

The study subjects are then equally randomized among the treatment groups. Short-term hospitalisation during initiation of treatment to achieve plateau drug levels and effect on ECG intervals will depend on the need for continuous monitoring because of risk of early proarrhythmia as suggested by early I.V. or oral single-dose Phase II studies. Dosing for investigational drug X whose elimination is highly dependent on renal function will be adjusted as described in section II.3.D. Further adjustment of drug dose in the case of a Class III drug will also be influenced by the effect on QT_c interval as described in the same section.

Total study duration is two years. Follow-up visits can occur at 2 weeks, and 1, 4, 8, 12, 16, 20 and 24 months and 1 month following the end of the study or 4 weeks following withdrawal from the study. The same evaluations as at baseline, except for the Holter recording, are done at each of these visits. As well, drug compliance evaluation can be performed at months 1, 4, 8, 12, 16, 20 and 24. Serum pregnancy test should be done monthly in patients of childbearing potential. Patients who withdraw early from the study should be followed by telephone contact until a time corresponding to two years since study drug initiation (for assessment of outcome on an intention-to-treat basis).

III.2.D. Planned Sample

If it is assumed that the all-cause mortality in such low to moderate risk patients is 5-8 % over two years, and investigational drug X will reduce this rate by at least 45%, then using the method of Schoenfeld (17), to ensure 90 % power at a significance level of 0.04, at least 4000 subjects must be recruited to show significantly reduced mortality on investigational drug X. If however, the purpose of the study is to only demonstrate safety of drug in this population, then a hypothesis of non-inferiority would require a smaller population sample size.

III.2.E. Study Population

A total of approximately 4000 subjects with ischemic or non-ischemic CM and LV EF of 36 - 50% will be enrolled.

III.2.F. Inclusion Criteria

- a. Ischemic or non-ischemic CM.
- b. LV EF (36-50%).
- c. Male or female between the ages of 18 and 75 years.
- d. If female, post-menopausal for more than one year, surgically sterile (at least 3 months post tubal ligation) or on oral contraceptives for at least 3 months prior to study entry which they will continue to use in addition to a vaginal spermicide during the study.

III.2.G. Exclusion Criteria

- a. If female, currently pregnant or breast feeding, or plan to become pregnant during the course of the study.
- b. History of torsade de pointes or any form of polymorphic VT.
- c. History of sustained (> 30 sec) monomorphic VT.
- d. Syncope or aborted SD.
- e. Resting heart rate below 50 bpm.
- f. Second-degree (Mobitz II) or third degree AV block without a permanent pacemaker.
- g. Implantable cardiac defibrillator.
- h. QT_c interval measuring 450 msec or greater at enrollment or a family history of long QT.
- i. Wolff-Parkinson-White syndrome not having undergone curative ablation.
- j. Decompensated CHF at the time of enrollment.
- k. Unstable angina pectoris.
- l. Angioplasty or coronary artery bypass grafting within one month prior to study entry.
- m. Severe symptomatic valvular disease for which surgery is considered within the time course of the study.
- n. Stroke with significant neurological deficit.
- o. Uncontrolled hypertension (systolic BP > 170 mmHg or diastolic BP > 100 mmHg) at enrollment. BP must be controlled adequately for one month prior to study entry.
- p. Known concurrent illness likely to affect survival within 2 years of study entry.
- q. History of chronic liver disease or significant kidney disease (Cr_{Cl} < 20 ml/min).
- r. History of unresolved organ toxicity secondary to drug use.
- s. Prior to randomization, baseline potassium < 4 mEq/L or > 5.5 mEq/L. Potassium level can be corrected and must be maintained within the acceptable range during the study.
- t. Amiodarone use within one month prior to enrollment; current use of Class I or III antiarrhythmic drugs or within 5 half-lives prior to beginning study drug.
- u. Use of drugs which prolong QT_c interval during or within 5 half-lives prior to study.
- v. Use of any non-approved investigational drug within 30 days prior to enrollment.
- w. Previous participation in a trial of investigational drug X.
- x. Known alcohol abuse or illicit drug use or current, diagnosed psychosis.
- y. Unwillingness or inability to give written informed consent.

III.2.H. Tools for assessing endpoints

Measure of LV EF can be performed by nuclear isotope or invasive contrast ventriculography, or by 2D-echocardiography. Low HRV on 24-hour Holter is assessed by standard methods and defined as less than 20 U. A 12-lead ECG to assess study drug effects on QT_c interval is performed prior to and daily during study drug initiation if indicated with in-hospital monitoring for dose adjustment, and at each follow-up visit.

All-cause mortality is documented, but is further subclassified according to the following definitions:

- a. Cardiac mortality: all deaths except those due to a demonstrated non-cardiac cause.
- b. Non-cardiac mortality: death due to demonstrated non-cardiac cause including vascular mortality (stroke, embolism, ruptured aneurysm).
- c. Arrhythmic mortality: - death within 1 hour on the onset of new symptoms in the absence of severe LV dysfunction or shock; unwitnessed death in an apparently stable patient; unresuscitated ventricular fibrillation; sudden or non-sudden cardiac death with documented or suspected arrhythmia; unwitnessed, sudden, presumed cardiac death.

Adverse events are defined as in section II.3.K.

III.2.I. Data Analysis Methods

The primary efficacy analysis is performed on all-cause mortality in all randomized patients. Kaplan-Meier curves are used to estimate survival for each treatment group. Median time-to-event, with 95% confidence intervals, are determined for each group. More complex statistical analyses can also be performed for each active to placebo comparison. Secondary efficacy analyses based on intention-to-treat observations are performed as for the primary efficacy analysis. The same statistical methods are used for the on-treatment efficacy analyses but data from patients who withdraw early from the study is gathered only until one month following discontinuation of study drug. Interim efficacy analyses can be conducted at pre-determined times during the course of the study and should be based on all-cause mortality. Both, statistically significant decrease or increase in mortality on investigational drug X will be assessed but the study should only be prematurely terminated for a statistically significant increase in all-cause mortality on investigational drug X.

Safety data can be presented using graphs and tables of summary statistics by treatment group. Frequency of AEs, AEs per unit time of study drug exposure are shown. Laboratory data (chemistry, hematology and ECG measurements) are shown as box plots over time. Further, ECG data can be summarized as actual values, change from baseline and percent change from baseline. Efficacy and safety data can be summarized separately for such subgroups as sex, age, ischemic versus non-ischemic CM, Class I versus Class II/III CHF or utilization of β -blockers and/or angiotensin converting enzyme inhibitors.

Interim analyses should be done at predetermined intervals by a statistician not associated with the study and are based on the primary end-point of all-cause mortality. Both, statistically significant improvement or decrease in mortality on investigational drug X should be noted, but recommendation to prematurely terminate the study should only be made if decreased survival is observed on drug X.

III.2.J. Specific criteria for early withdrawal or non-utilization of subject data in analysis

Early withdrawal of subjects from the study is based on the same criteria as in section II.3.J however these data are still used in the intention-to-treat efficacy analyses. Subject data only is not used in the case of protocol violation or for administrative reasons.

III.2.K. Comments

The demonstration of increased mortality in the presence of investigational drug X in patients with underlying cardiac pathology and mild to moderate LV dysfunction would essentially limit the use of the new drug to patients with normal hearts experiencing supraventricular arrhythmias. Even in this setting, long-term use should be frequently reevaluated as the patient ages and develops cardiac disease. If there is a need for in-hospital initiation of drug because of significant incidence of proarrhythmia even in the absence of cardiac pathology, there would be little hope that the new antiarrhythmic drug would be accepted, either by the regulatory boards or by the medical community. In contrast, if decreased or an unaffected mortality rate is demonstrated, this would permit drug use for atrial arrhythmias in patients with moderate LV dysfunction (EF 36-50%).

IV. CONCLUSIONS

Clinical trials of potentially useful antiarrhythmic drugs are at the present time both complex and costly. For the time being, the potential market of patients with AF justifies the effort and expense to complete such studies in order to obtain regulatory board approval. This situation may improve in the future if other classes of drug action are discovered which do not cause proarrhythmia as do the Class I and III compounds. In the meantime, close attention is being paid by the pharmaceutical industry to the ongoing development of and indications for implantable defibrillators in the prevention of SD due to ventricular arrhythmias, and in the case of atrial arrhythmias, to the enormous strides being made in catheter-based ablation techniques.

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