Survival With Oral d-Sotalol in Patients With Left Ventricular Dysfunction After Myocardial Infarction: Rationale, Design, and Methods (the SWORD Trial)

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Impaired left ventricular function after acute myocardial infarction (AMI) is associated with an increased risk of death. Despite recent advances in the management of these patients, sudden death accounts for up to 50% of this mortality, and effective treatment strategies have yet to be identified. Preliminary trials with amiodarone have offered promise that drugs that prolong action potential duration by blocking the potassium channel may be useful in reducing this mortality. The *Survival With Oral d-Sotalol* (SWORD) trial is a multicenter, multinational study which tests the hypothesis that the class III agent d-sotalol will reduce all-cause mortality in high-risk survivors of AMI. The trial will enroll 6,400 patients with left ventricular dysfunction (ejection fraction ≤40%) and a recent (6 to 42 days) or a remote (>42 days) AMI with overt heart failure (New York Heart Association class II or III). In approximately 500 centers throughout the world, men and women aged ≥18 years will be enrolled and randomized to placebo or d-sotalol (200 mg/day). The minimal follow-up will be 18 months. The trial has a 90% power to detect a 20% reduction in all-cause mortality. The rationale, design, and trial methods are described.

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d-Sotalol is the dextrorotatory isomer of the racemate d,l-sotalol. Like the racemate, it is a class III antiarrhythmic drug that prolongs the action potential duration and refractoriness of cardiac tissue by blocking the delayed rectifier current of the potassium channel.[1] It is antifibrillatory in some ischemic models,[2] but not in models that are associated with sympathetic hyperactivity.[3] Unlike d,l-sotalol, it has only minimal β-blocking activity in animals,[4] and this activity is not clinically significant in humans.[5] After oral administration, it is nearly 100% absorbed, and is excreted unmetabolized by the kidneys (data on file, Bristol-Myers Squibb, Princeton, New Jersey). In clinical trials, d-sotalol has been well tolerated, with a low incidence of reported adverse events. Torsades de pointes has occurred in approximately 1.2% of those exposed to the drug (data on file, Bristol-Myers Squibb, Princeton, New Jersey).

This report describes the protocol of a study that compares d-sotalol with placebo in the treatment of high-risk survivors of acute myocardial infarction (AMI). The expected treatment differences require a large study population that necessitates a multicenter, multinational design. The trial provides the first opportunity to investigate the benefit of an antiarrhythmic drug that selectively prolongs action potential duration by blockade of the delayed rectifier current of the potassium channel. The results of *S*urvival *W*ith *Or*al *d*-Sotalol (SWORD) will define the role of d-sotalol as a class III agent in this high-risk population and contribute to a more rational management of these patients.

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*See appendix for participating centers.

METHODS

Objectives: The primary objective of SWORD is to determine whether d-sotalol will reduce all-cause mortality compared with placebo in patients with left ventricular dysfunction and coronary artery disease manifested by a prior AMI. It also will compare the safety and tolerance of d-sotalol and placebo when administered long-term to these patients.

Design: SWORD is a multinational, multicenter, randomized, double-blind, placebo-controlled trial in approximately 500 centers worldwide. The study will enroll 6,400 men and women, aged ≥18 years, who have a left ventricular ejection fraction of ≤40% determined by either radionuclide or contrast angiography or echocardiography performed within 6 months of randomization. In addition, these patients must have evidence of a prior AMI. Two such groups will be identified. Group 1 (acute group) will consist of patients with an AMI 6 to 42 days before randomization with or without overt heart failure. Group 2 (remote group) will consist of patients with an AMI occurring >42 days before randomization who also have a history of overt heart failure (New York Heart Association functional class II or III). Criteria for an AMI are the presence of ≥2 of the following: (1) characteristic myocardial ischemic pain in the precordium or associated referral areas lasting ≥20 minutes; (2) elevation of creatine kinase to twice the upper limit of normal for the given hospital in the absence of other explanation, or the presence of creatine kinase-MB >6% of total; (3) development of new (>30 ms) Q waves in ≥2

adjacent electrocardiographic leads, or an R wave (>30 ms) with RS ratio in lead V_1 >1.0 (in the absence of other causes such as right ventricular hypertrophy or right bundle branch block). Eligible women must be either surgically sterile, postmenopausal, or using an acceptable method of contraception. Women of childbearing potential must have a negative pregnancy test before randomization.

Major exclusion criteria include: corrected QT interval >460 ms, recent (within 14 days) coronary angioplasty or bypass graft surgery, unstable angina, history of life-threatening arrhythmia unrelated to an AMI, nonischemic or severe heart failure, sick sinus syndrome or high-grade heart block without a pacemaker, concomitant antiarrhythmic agents or drugs that prolong the QT interval, and specific electrolyte (serum potassium <4.0 mEq/L or serum magnesium <1.5 mEq/L), renal, or liver abnormalities.

The study will consist of a screening and a double-blind phase. During screening, a 3-channel 24-hour ambulatory electrocardiographic recording will identify baseline characteristics, including supraventricular and ventricular rhythm disturbances, heart rate variability, and the presence or absence of signal-averaged electrocardiographic abnormalities. Randomization is not contingent upon the results of the ambulatory ECG.

Eligible patients who consent to participate will enroll in the study. They will be randomly assigned to receive a titrated dose of either d-sotalol or placebo. Doses cannot exceed 200 mg twice daily for the duration of the study. For safety reasons, the dose may be reduced if clinically indicated. During follow-up, concomitant treatment with β blockers (except d,l-sotalol), digoxin, angiotensin-converting enzyme inhibitors, and calcium antagonists, is allowed.

Follow-up: Except for weekly visits for the first 2 weeks, patients will be followed every 3 months for the first year and every 4 months thereafter. Periodic clinical evaluations and laboratory studies will be obtained during the follow-up clinic visits. At month 3, a 3-channel, ambulatory electrocardiographic recording will be repeated. Patients who discontinue the study medication will be followed for the duration of the study. The minimal follow-up period will be for 18 months. A schematic of the study is depicted in Figure 1.

Ethics and informed consent: The protocol must be reviewed and approved by institutional review boards or equivalent committees at each of the participating cen-

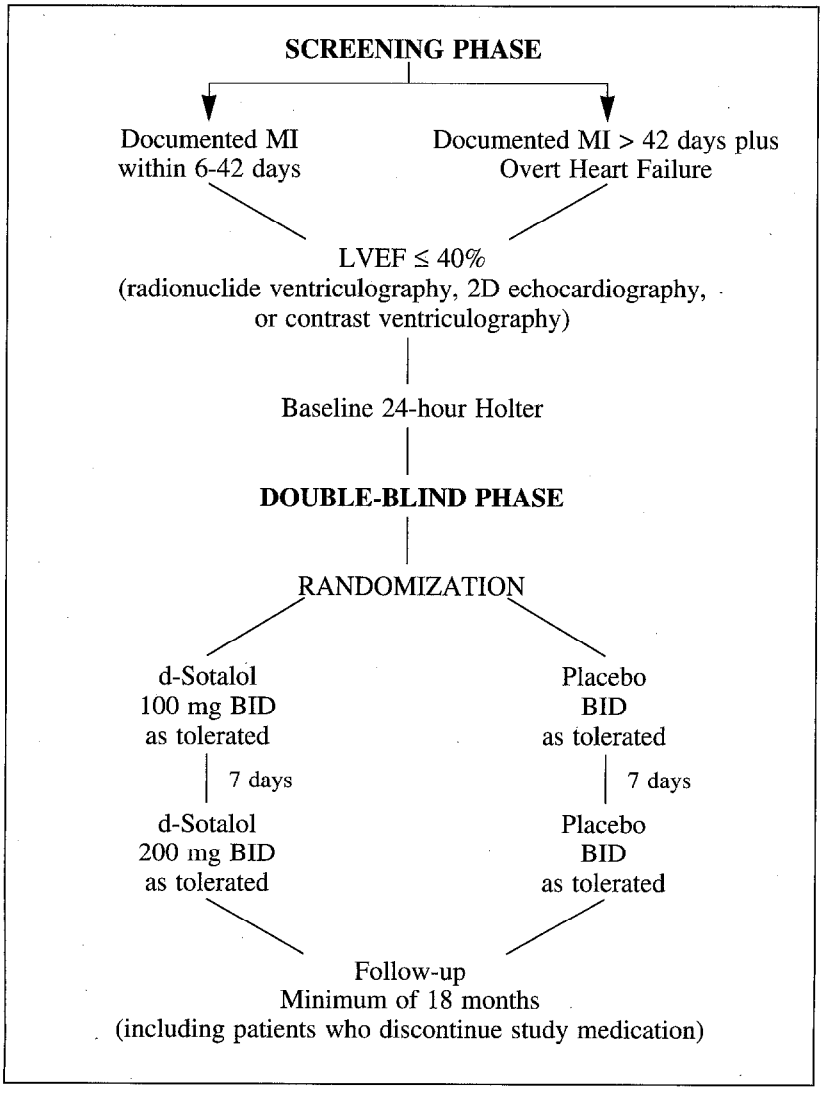

FIGURE 1. Protocol for the Survival With Oral d-Sotalol trial. High-risk survivors of a myocardial infarction are randomized to receive either d-sotalol or placebo and followed for 18 months. BID = twice daily; 2D = 2-dimensional; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

ters. The study objectives, design, risks, benefits, and consequences of trial participation are explained to each study candidate before obtaining consent.

End points: The primary efficacy end point is all-cause mortality. Cardiac mortality is a secondary end point. Tertiary end points are cardiovascular mortality, presumed arrhythmic death, nonfatal severe arrhythmic events, hospitalizations for cardiovascular causes, and composites of these end points. An events committee blinded to treatment assignment will review all deaths, as well as nonfatal severe arrhythmic events, to verify the investigators' interpretation. The final classification of an event is the responsibility of the events committee.

Statistical considerations: RANDOMIZATION: The trial is double-blind. Qualified patients will be randomized centrally using a schedule constructed to ensure that similar numbers of patients are assigned to each of the 2 treatments at all centers. The randomization code is available to an independent statistical center that will perform analyses for the Data and Safety Monitoring Committee. On an emergency basis, each investigator has access to the individual treatment assignment by removing an opaque overlay from a 3-panel, double-blind label provided with the study medication.

SAMPLE SIZE: The goal of the study is to enroll 6,400 patients, all of whom will be in the final analysis. In estimating sample size, the following assumptions were made: (1) a trial duration of 3 years with a minimal patient follow-up of 18 months and an average follow-up of 2¼ years, (2) group 1 (acute group) and group 2 (remote group) patients will enter in a ratio of 2:1, (3) a cumulative average mortality of 17.7% in the placebo-treated patients, (4) a 20% reduction in all-cause mortality associated with d-sotalol, (5) a 2-sided significance level of 0.05, (6) a power of 90%, and (7) 10% dropouts in the d-sotalol group (patients who stop taking study medication) and 5% drop-ins in the placebo group (patients who start taking another antiarrhythmic agent). The sample size estimate is based on the assumption that there will be 1 intent-to-treat analysis at the conclusion of the trial; however, during the study, the Data and Safety Monitoring Committee will make periodic assessments with defined stopping rules which may permit termination of the trial before its completion if appropriate.[6]

For each interim analysis, the assessment of efficacy will be based on a critical boundary value determined by the procedure of Lan and DeMets.[7] Interim assessments of safety will use an advisory statistical boundary as described by DeMets.[8] In addition, the committee will use the stochastic curtailment procedure described by Pawitan and Hallstrom[9] to assess the likelihood that the study will find a favorable result if carried to completion.

Organization: COORDINATING CENTER: The coordinating center is located at Bristol-Myers Squibb Pharmaceutical Research Institute in Princeton, New Jersey. In conjunction with its European office in Brussels, Belgium, it is responsible for worldwide coordination of the trial, allocation of resources, communication, data management, statistical considerations, international regulatory compliance, and quality control. At the conclusion of the trial, the coordinating center will analyze the results. During the study, data files will be prepared and transferred to an independent statistical group which will perform the unblinded analyses for the Data and Safety Monitoring Committee.

COORDINATORS: In geographic regions, countries, or within organized consortia, coordinators will facilitate patient recruitment and communication with investigators. They will work in conjunction with representatives of the coordinating center to identify and resolve trial issues and ensure quality data collection.

DRUG SUPPLY: Both active and placebo study drugs will be manufactured, packaged, and distributed by Bristol-Myers Squibb.

STEERING COMMITTEE: A steering committee is responsible for supervision of all scientific and logistic aspects of the trial. Members were chosen based on skills and disciplines required to manage a large multinational trial.

EVENTS COMMITTEE: The events committee is charged with the blinded review of all reported deaths and nonfatal severe arrhythmic events. They will evaluate these events and verify the investigators' interpretations. In the event of nonconcurrence, they will have the final decision regarding the classification of events. Members of this committee are required to have extensive cardiovascular and clinical trial experience.

DATA AND SAFETY MONITORING COMMITTEE: The committee is an independent body of internationally recognized experts in clinical cardiology and clinical trial methodology. They will periodically monitor the data to evaluate end points and safety. As needed, they will make a recommendation for changes in the study protocol to the steering committee.

EXECUTIVE COMMITTEE: The committee comprises selected representatives from the trial coordinators throughout the world. They are responsible for monitoring and providing strategies for enhancing trial recruitment. They meet with and advise the steering committee on issues relative to worldwide enrollment and study conduct.

DISCUSSION

In the western world, coronary artery disease is the leading cause of death. In up to 50% of cases, the death is sudden and often occurs in patients who have sustained a previous myocardial infarction. Many independent risk factors for sudden cardiac death have been identified. Some of these include, alone or in combination, the presence of premature ventricular complexes, positive signal-averaged electrocardiograms, decreased heart rate variability, abnormalities of baroreflex sensitivity, and left ventricular dysfunction; the last is the most powerful predictor of subsequent mortality.[10–14] Although angiotensin-converting enzyme inhibitors can reduce this mortality, the problem of sudden cardiac death remains.[15–17]

The knowledge that these patients may have baseline ventricular rhythm disturbances or myocardial substrate abnormalities favoring the genesis of arrhythmias has led to a strong interest in the use of antiarrhythmic drugs. Some studies, however, have raised questions about the prudence of these agents in survivors of a myocardial infarction. The Cardiac Arrhythmia Suppression Trial

(CAST) unexpectedly demonstrated that encainide, flecainide, and moricizine were harmful.[18–20] In addition, a recent meta-analysis of mortality data from 138 trials on 98,000 survivors of myocardial infarction also found that class I (sodium channel-blocking) antiarrhythmic drugs were associated with increased mortality.[21] Only class II (β receptor-blocking) and class III (potassium channel-blocking) drugs were associated with a decreased mortality. Unfortunately, in a high percentage of these patients at risk, β blockers are not tolerated or are contraindicated.

The post-myocardial infarction experience with class III agents is quite limited, and is generally with amiodarone. Although this drug possesses multiple antiarrhythmic actions, its ability to prolong the action potential duration and its antifibrillatory properties are considered its important electrophysiologic activities. Several recent trials in post-myocardial infarction patients have provided encouraging results.[22–25] Given these promising data, several large trials are investigating the benefit of amiodarone in reducing mortality in high-risk patients. Amiodarone, however, has important limitations related to its multiple antiarrhythmic activities, complicated kinetics, and potentially very serious adverse events.[26] With the worldwide incidence of coronary artery disease, the continued need to reduce mortality in high-risk patients, the promise of class III antiarrhythmic agents, and the limitations of available drugs, investigation with new class III agents is warranted.

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ADDENDUM

Since the submission of this paper, the SWORD trial was stopped (11/1/94) because the boundary for harm was crossed.

APPENDIX

The following persons participate in the SWORD study. ***Steering Committee:*** A. Waldo (Chairman), A.J. Camm, P. Friedman, D. MacNeil, B. Pitt, C. Pratt, B. Rodda, P.J. Schwartz. ***Coordinating Center:*** Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey: H. deRuyter (Study Director); Clinicians: R. Davies, D. MacNeil, S. Rajfer, M. Teter, E. Veltri; Statistician: J. Pauls; Administration: G. Cucinotta, L. DeCaprio, D. Knaus, C. Luciano, E. Moran, S. Moran, K. Moulton, J. Triscari. *Europe*: Clinicians: F. Claroni, K. Jady, H. Lanz, K. Mellors, J. Petrin, F. Plat, G. Pover, S. Wanless; Statistician: R. Von Frenckell; Administration: C. Anthony, C. Jacobs. *Australia/New Zealand:* S. Humphrey. *Canada:* F. Charette, L. Harvey. *South Africa:* S. Levenstein. ***Coordinators:*** *Argentina:* C. Bertolasi; *Australia:* A. Tonkin; *Czech Republic:* V. Cepelak; *France:* P. Beaufils; *Germany:* M. Bogreffe; *Israel:* D. Tzivoni; *Netherlands:* D. Lok; *New Zealand:* H. White; *Scandinavia:* N. Edvardsson; *South Africa:* P. Commerford; *Spain:* J. Soler Soler; *United States:* R. DiBianco, G. Flaker, R. Henthorn, T. Heywood, J. Kluger, C. Liang, C. Pratt, A. Seals, G. Timmis. ***Events Committee:*** D. Richardson (Chairman), R. Gorlin, M. Green, A. Mitha, A. Moss, D. Myburg, N. Rehnqvist, D. Roden, B. Singh, S. Singh, A. Tonkin, P. Touboul, D. Weaver, H.J.J. Wellens, H. White. ***Data and Safety Monitoring Committee:*** A. Hallstrom (Chairman), G. Breithardt, D. Bristow, S. Goldstein, D. Julian, J. Kostis. ***Central Laboratories: Blood Chemistries:*** SmithKline Beecham, Van Nuys, California; West Middlesex Laboratories, Middlesex, United Kingdom; Claymon Laboratories, Dublin, Ireland; Calab Clinical Trials Center, Stockholm, Sweden. ***Ambulatory Monitoring:*** Research Data Worldwide, Philadelphia, Pennsylvania. ***Signal-Averaged Electrocardiogram/Heart Rate Variability:*** Westfalische Wilhelms-Universitat of Munster, Munster, Germany. ***Drug Supply:*** Bristol-Myers Squibb, New Brunswick, New Jersey; Moreton, United Kingdom.

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