

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S010

STATISTICAL REVIEW(S)

CSO/Oliver

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-287/SE1-010

Date

Drug: Fragmin (Dalteparin Sodium Injection); Drug Class: 10S

Applicant: Pharmacia & Upjohn Company

DEC 14 1998

Indication: Treatment of unstable angina and non-Q-wave myocardial infarction to prevent ischemic complications in patients on concomitant aspirin therapy.

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Statistical Reviewer: A.J. Sankoh, Ph.D.

Medical Reviewer: John Schmeling, M.D.

SUMMARY OF RESULTS

The sponsor submitted two studies (**FRISC** and **FRIC**) in support of the efficacy of Fragmin. These two studies differ in some several major aspects as described below.

Design & Conduct of Studies

While both studies were designed as multi-center, parallel groups, 3-Phase [short-term (Day 1-6), long-term (Day 6-45) and follow-up] trials,

- (i) the primary objective for the **FRISC** study was to demonstrate the short-term benefit of Fragmin compared to placebo, while the primary objective of the **FRIC** study was to demonstrate the long-term benefit of Fragmin compared with placebo; i.e., the two studies have different objectives,
- (ii) the primary endpoint for the **FRISC** study is the composite of *death* and/or *MI*, while the primary endpoint for the **FRIC** study is the composite of *death*, *MI* and/or *recurrent angina* (the primary composite endpoint for the **FRISC** study was identified as a secondary composite endpoint for the **FRIC** study),
- (iii) the control in *Phase I* (short-term) for the **FRISC** study was placebo while the control in *Phase I* (short-term) for the **FRIC** study was heparin; the control in *Phase II* (long-term) for both studies was placebo,
- (iv) randomization for both studies was carried out once in *Phase I* (short-term); while *Phase II* (long-term) **FRISC** patients continued treatment with the same test drugs they were randomized into in *Phase I*, *Phase II*

Key Words/Phrases: Composite endpoint, missing data, treatment allocation.

- (long-term) **FRIC** patients were re-assigned *in a non-random manner* to different test drugs (*NDA documentation did not say how this was done*),
- (v) **FRISC Phase I** was a double-blind while **FRIC Phase I** was an open-label phase

Efficacy & Safety Results

- (i) The efficacy data from the **FRISC** study indicate a short-term (day 1-6) but no long-term (Day 6-45) significant Fragmin advantage over placebo for the treatment of unstable angina and non-Q-wave myocardial infarction to prevent ischemic complications in patients on concomitant aspirin therapy.
- (ii) The efficacy data from the **FRIC** study, on the other hand, indicate no significant short-term (Day 1-6) Fragmin advantage over heparin and no significant long-term (Day 6-45) Fragmin advantage over placebo for the treatment of unstable angina and non-Q-wave myocardial infarction to prevent ischemic complications in patients on concomitant aspirin therapy.
- (iii) Also for the **FRIC** study, *Phase I heparin* (short-term) treated patients who received *Phase II Fragmin* (long-term) treatment fared numerically worse than those (*Phase I heparin* patients) who received *Phase II placebo* (long-term) treatment. On the other hand, *Phase I Fragmin treated* (short-term) patients who received *Phase II Fragmin* (long-term) treatment fared numerically better than those (*Phase I Fragmin* patients) who received *Phase II placebo* treatment.
- (iv) *Thus, it appears that continuous treatment with LMWH (Fragmin) is more beneficial than starting treatment with UFH (heparin) and then switching over to LMWH (Fragmin).*
- (v) Except for minor bleedings for which there were statistically significantly more in the Fragmin than in either heparin or placebo, there were no significant safety event differences between Fragmin and either comparator.

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I. STUDY BACKGROUND

Fragmin is formulated as a sterile solution for intravenous (iv) or subcutaneous (sc) injection. It is currently approved in the U. S. for prophylaxis against deep vein thrombosis (DVT) in patients undergoing abdominal surgery who are at risk for thromboembolic complications (TECs). It is also approved for marketing in more than 40 countries (mostly in Europe). Approved indications in these other countries include treatment of acute DVT, prevention of clotting in the extracorporeal circulation during hemodialysis, acute and prolonged thromboprophylaxis in surgery, and treatment of unstable angina or non-Q-wave myocardial infarction.

Unfractionated heparin (UFH) is an effective anticoagulant. However, it has properties that limit its clinical utility. The binding of heparin to plasma proteins reduces its anticoagulant effect because less heparin is available to interact with antithrombin. The reduced binding of low molecular weight heparins (LMWHs) like Fragmin to plasma proteins and endothelium results in better availability than UFH. The reduced binding of LMWHs to macrophages explains why they are not cleared by hepatic mechanisms to the same extent as UFHs. The increased bioavailability and longer plasma half-life allow LMWHs to provide a predictable anticoagulant response when administered at fixed doses once or twice daily. Fragmin affects platelet function to a lesser extent than heparin, which suggests that it might be preferred in the treatment of unstable coronary artery disease (CAD).

The purpose of this supplemental NDA submission is to demonstrate the efficacy and safety of Fragmin injection as a treatment for unstable angina and non-Q-wave myocardial infarction to prevent ischemic complications in patients on concomitant aspirin therapy. The supplemental NDA submission contains two multicenter, randomized, controlled pivotal studies [FRISC (TRN 91-115) and FRIC (TRN 91-128)] in support of the efficacy and safety of Fragmin for the treatment of patients with acute myocardial infarction. The issues and the extent of the statistical review have been discussed with the clinical review team.

2. FRISC [SWEDISH STUDY #TRN 91-115] (placebo controlled)

2.0 STUDY DESIGN

This trial was conducted in Sweden from April 4, 1992 to March 3, 1995. It was designed as a 3-Phase, randomized, double blind, parallel group, placebo controlled, multicenter (23 centers) study.

2.1 Study Objectives

The primary objective of this study was to compare the efficacy of LMWH Fragmin with placebo regarding the incidence of death or acute myocardial infarction (MI) following the first six days of treatment for unstable coronary artery disease (CAD).

Secondary objectives of the study include:

- 1) Comparing the efficacy of Fragmin with placebo regarding the incidence of death or MI following the first 45 days of treatment.
- 2) Comparing the efficacy of 45 days of treatment with Fragmin to placebo regarding the incidence of death or MI at the 6-month follow-up.
- 3) Comparing the efficacy of Fragmin with placebo regarding the incidence of revascularization after 6 and 45 days of treatment, and at 6-month follow-up.
- 4) Comparing the efficacy of Fragmin with placebo regarding the incidence of indication for coronary angiography after 6, 45 days of treatment, and 6-month follow-up.
- 5) Comparing the efficacy of Fragmin with placebo regarding ischemia during exercise test after six (5-8) and 45 (40-50) days of treatment respectively.
- 6) Comparing the efficacy of Fragmin with placebo by combining death, MI, need for intravenous (iv) heparin, iv nitroglycerine, and revascularization.
- 7) Comparing the efficacy of Fragmin with placebo for the need for iv heparin and iv nitroglycerine.
- 8) Comparing the safety of Fragmin with placebo regarding the incidence of bleeding complications, allergic reactions, and thrombocytopenia following 45 days of treatment.

2.2 Study Plan

Patients who satisfied the inclusion criteria (see below) were randomized into the trial on **Day 1** to receive either Fragmin or placebo. The trial was divided into three phases:

Phase I: This was a weight adjusted treatment phase; randomized patients received Fragmin or matching placebo every 12 hours.

Day 1: patients were randomized and received the first injection.

Day 2: resting ECGs, blood samples were collected for routine lab tests.

Day 3-5: instruction and training were given to perform self-injection for *Phase II*.

Day 6 (5-8): exercise tests, resting ECGs, blood samples were again taken, unused ampoules of study drug documented, and treatment with *Phase II* study drug started.

Phase II: This was a fixed dosing phase; randomized patients from *Phase I* received

a fixed dosing regimen of Fragmin 7500 IU or matching placebo every 24 hours.

Study drug was administered once daily (OD) by the patient or some other suitable person. Exercise tests and resting ECGs were performed; blood samples were taken for routine lab tests; clinical data were documented; patient diaries were checked, and both used and unused syringes were counted, and saved on **Day 45** (40-50).

Phase III: This was a 6-month follow-up period after 45 days of treatment.

Resting ECGs, blood samples were collected for routine lab analysis of hemoglobin and thrombocytes; clinical data were documented.

All patients were to be treated with aspirin (ASA) 100-165 mg daily throughout the study duration, unless they were hypersensitive to ASA.

2.3 Inclusion criteria

Inclusion criteria included a minimum age of 40 years, postmenopausal period of at least 12 months for females, admission to coronary care unit for chest pain with a last chest pain episode within 72 hours before start of treatment, fulfillment of at least one of the following anamnestic conditions:

- newly developed angina pectoris during the last two months,
- increased angina pectoris during the last two months,
- ongoing chest pain, with a suspicion of MI,

and fulfillment of at least one of the following ECG criteria without any other explanation than myocardial ischemia:

- temporary or manifest ST-depression with at least 0, 1 mV ($\geq 1\text{mm}$) in at least two adjacent leads, and
- temporary or manifest T-inversion with at least 0, 1 mV ($\geq 1\text{mm}$) below the baseline in at least two adjacent leads.

3. SPONSOR'S PLANNED ANALYSES & ANALYSIS METHODS

3.0 Primary efficacy Endpoint

The primary efficacy endpoint is a composite endpoint comprising *the first occurrence of death or myocardial infarction (MI)*. Death is defined as all-cause mortality and where possible, the cause was to be established by post-mortem examination. MI was to be confirmed by diagnostic ECG series or by at least two of the following: prolonged angina chest pain, separate diagnostic ECG, and significant rise in relevant enzymes (CK, CK-MB, CK-B or ASAT/ALAT).

A number of secondary endpoints encompassing revascularization, coronary

angiography, need for iv nitroglycerine and/or iv heparin and ischemia during exercise were specified (see secondary objectives above).

3.1 Sample Size Estimation

It was assumed that in order to detect a 50% reduction in the incidence of death or acute MI (from 6% to 3%) during six days of treatment with an 80% powered, .05 two-sided test, about 750 patients per treatment group were required. Due to the dose reduction (from 150 IU/Kg/12 hr to 120 IU/Kg/12 hr), the total sample size was increased from 1500 to 1620 to compensate for the initial 116 patients on 150 IU/Kg/12 hr who the sponsor excluded from the efficacy analyses.

3.2 Randomization & Blinding

Except for 14 randomization patient numbers omitted because of investigator error, and two cases of numbers randomized twice, the randomization plan and its execution appeared satisfactory to this reviewer. Qualifying patients were given consecutive patient numbers on entering the study. Randomization, based on a computer-generated code using a SAS written program, was carried out by the physician in charge, and was done within each center in blocks of size ten (randomization for center # 15 was done in blocks of size 6). The study report indicated that both the Medical Department and the statistician responsible for the analysis of the data were blinded to the randomization codes.

Patient number 25003 (Fragmin) was also randomized as patient number 25004 (Fragmin), and patient number 26058 (Fragmin) was also randomized as patient number 26080 (placebo). According to the study report, it was decided to record these patient numbers as patient numbers 25004 and 26058 (Fragmin) in the database before the blind was broken. Data from patient numbers 25003 and 26080 were not considered in the analyses.

3.3 Statistical Methods

A formal interim analysis was planned following enrollment of 1000 of the originally planned 1500 patients. Study documentation, however, indicated that no interim analysis was conducted; no reason was given for not carrying out this planned interim analysis.

It should be noted, however, that the decision not to proceed with the formally planned interim analysis was made following the implementation of the decision to increase the sample (as per amendment #4 above).

The primary analysis for the composite primary endpoint for the first six days of treatment was done (as per protocol specification) using the Cochran-Mantel-Haenszel (CMH) test; 95% confidence intervals (CIs) were provided. Test of

homogeneity of treatment effect across centers was performed using the Breslow-Day (BD) test.

The primary analysis for the primary endpoint (up to day six) was based on the intent-to-treat (ITT) patient population; that is, all randomized patients who received Fragmin 120 IU/Kg/12 hr or placebo during *Phase I* of the study. Secondary analyses for the secondary endpoint were based on the per-protocol patient population; that is, the subset of all randomized patients who were non-protocol violators. Secondary analyses (through Day 40 and Day 150) were based on the ITT population for the primary and some key secondary endpoints, and on the per-protocol population for some other secondary endpoints.

3.4 Protocol Amendments

The original protocol for this study (dated 01/10/92) was amended five (5) times. The dates of and reasons for the amendments are summarized below.

- 1 03/10/92 (before the trial started) to clarify inclusion/exclusion criteria, statistical analysis and the handling of patients.
- 2 08/21/92 (after the trial started with 116 patients enrolled) to reduce the dose of Fragmin from 150 IU/Kg/12 hrs to 120 IU/Kg/12 hrs (no reason was given for the dose reduction).
- 3 10/09/92 to clarify the exclusion criterion for ulcer disease or known GI bleeding, and defined major bleeding.
- 4 12/03/93 to increase the number of patients from 1500 to approximately 1620 to compensate for the 116 patients treated with Fragmin 150 IU/Kg/12 hrs. (*This amendment also stated that no interim analysis was to be performed even though the original protocol indicated an interim analysis was to be conducted following the enrollment of 67% of the planned patient population*).
- 5 10/03/94 to appoint members of the Endpoint Committee (EC) and Central Evaluation (the EC was to check and evaluate all MIs and deaths independently using the endpoint form); the incidence of coronary angiography was compared instead of the incidence of performed coronary angiography.

Study documentation indicated that amendments two and four above were approved by the Swedish Medical Products Agency, while amendments one, three, and five were submitted for approval; study documentation also indicated that approval was not required.

3.5 Patient Distribution & Baseline Characteristics

Table 1.1 below summarizes the number of patients screened but excluded from the study, the reasons for exclusion, and those enrolled into the study.

Table 1.1/Reasons For Not Enrolling Screened Patients (Data From Sponsor Table 15, Vol. 2)

Total No. of Patients Screened	36480 (100%)
Not eligible	29979 (82.2%)
No diagnosis	1364 (3.7%)
Eligible (inclusion satisfied criteria)	5137 (100%)
# Randomized/Enrolled into Study	1503 (29.3%)
Not Randomized (Studied)	3631 (70.7%)
Reason for exclusion:	1023 (28.2% of 3631)
Risk of bleeding	717 (19.7%)
Q-waves of BBB	156 (4.3%)
Planned revascularization	116 (3.2%)
Other cardiac disease	218 (6.0%)
Other severe disease	120 (3.3%)
Renal or liver insufficiency	7 (0.2%)
Compliance problem	762 (21%)
Unwilling	458 (12.6%)
Not recorded	54 (1.5%)

The disposition of the 1506 randomized patients contained in the sponsor's primary efficacy analyses is given in Table 1.2 below. Note that these 1506 patients do not include the 116 patients who received Fragmin 150 IU/Kg/12 hr in *Phase I* and were subsequently excluded from the efficacy analysis.

Table 1.2/ Disposition of Patients Administered Fragmin 120 IU/Kg/12 hr

Patient Group	Total	Fragmin	Placebo
Randomized & Entered Phase I (1-6 Days)	1506 (100%)	746 (49.5%)	760 (50.5%)
Withdrawn from Treatment in Phase I	273 (18.1%)	127 (17%)	146 (19.2%)
Entered Phase II (6-40 Days)	1233 (100%)	619 (50.2%)	614 (49.8%)
Withdrawn from Treatment in Phase II	269 (21%)	141 (23%)	128 (21%)
Completed Treatment (8 treated for < 40 days)	964 (100%)	478 (49.6%)	486 (50.4%)
Followed For at Least 150 Days	1392 (100%)	686 (49.3%)	706 (50.7%)

Four of the 746 Fragmin and three of the 760 placebo patients who received *Phase I* treatment were excluded from the ITT population for the primary analysis (*through time point Day 6*) of the primary composite endpoint (*incidence of all-cause death and/or MI*). The per-protocol analysis of the primary composite endpoint was based on 682 Fragmin and 795 placebo patients (see Table 1.3 below).

Table 1.3A (attached) presents a comparative summary of patient baseline and demographic characteristics. Sponsor's analyses indicate the two treatment groups are comparable with respect to baseline and demographic characteristics, and selected risk factors. This reviewer's observation suggests no significant differences between the two treatment groups regarding the factors summarized in Table 1.3A (attached).

All patients were on aspirin at admission; comparable numbers of patients were on concomitant medication (coagulation, anti-anginal, and other cardiovascular medication). Although statistically comparable, numerically more Fragmin patients experienced study drug interruptions compared to placebo (7.9% vs. 6.2% in *Phase I*, 1.6% vs. 1.0% in *Phases I & II*, 11.1% vs. 10.1% in *Phase II*, all higher in the

Fragmin treatment group).

Note that the SAS data set submitted by the sponsor indicated a total of 1612 (804 Fragmin and 810 placebo) patients were randomized and received first phase treatment medication. Of these 1612, 114 (61 Fragmin and 53 placebo) received Fragmin 150 IU/kg/ body weight (b. w.)/12 hour regimen and were therefore declared not valid for the primary analysis by the sponsor. This reviewer will comment further on this subset of patients in the reviewer's Comment Section.

4. SUMMARY OF EFFICACY RESULTS & REVIEWER S COMMENTS

Sponsor's primary and secondary efficacy analysis results for the primary composite endpoint (*death and/or MI*) at Day 6 (primary), Day 40 and Day 150 (secondary) are summarized in Table 1.3 below. The results indicate Fragmin has a significant short-term but no long-term advantage over placebo.

Table 1.3/ Sponsor's Primary (Day 6) & Secondary Efficacy Analysis Results: *Incidence of Death/MI*

Population	Treatment Group	n	%	Diff (F-P)*; 95% CICMH P-value		
ITT:	Fragmin (N=741)	13	1.8%	-3.0	(-4.8, -1.2)	0.001
	Placebo (N=757)	36	4.8%			
Day 6	Fragmin (N=738)	59	8.0%	-2.7	(-5.7, 0.2)	0.073
	Placebo (N=755)	81	10.7%			
Day 40	Fragmin (N=726)	102	14.0%	-1.4	(-5.1, 2.2)	0.407
	Placebo (N=749)	116	15.5%			
Day 150	Fragmin (N=682)	11	1.6%	-3.0	(-4.8, -1.2)	0.001
	Placebo (N=695)	32	4.6%			
PP1:	Fragmin (N=657)	50	7.6%	-3.1	(-6.2, 0.0)	0.053
	Placebo (N=674)	72	10.7%			
Day 40	Fragmin (N=647)	89	13.8%	-2.0	(-5.8, 1.9%)	0.282
	Placebo (N=668)	105	15.7%			

1: PP = Per-Protocol data set; *: Diff = (Fragmin - Placebo) incidence rates; CMH = Cochran-Mantel-Haenszel

Other sponsor's analysis results for some secondary endpoints and subgroup analysis results for the primary composite endpoint through Day 6 are summarized in Tables 1.4 and 1.5 below.

Table 1.5A (attached) contains the subgroup analysis results for the primary composite endpoint (*death and/or MI*) through Day 40. These are also consistent with overall efficacy results.

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