

### 3.2 Pivotal studies

The sponsor includes two pivotal studies, FRISC and FRIC, in the current submission.

Each study will be summarized in table format, followed by further description and discussion of the study.

#### 3.2.1 FRISC

##### 3.2.1.1 Introduction

FRISC, the first of two pivotal studies in this submission, was a prospective, randomized, double blind, placebo-controlled, parallel group, multi-center study in patients with unstable coronary artery syndromes (unstable angina or non-Q-wave MI).

Phase I (day 1-6) and Phase II (day 6-45) both compared Fragmin/ASA treatment versus placebo/ASA.

The primary endpoint of the study was death and/or myocardial infarction during the first 6 days of treatment.

APPEARS THIS WAY ON ORIGINAL

Table 2: Summary of studies included in application

Protocol No. [reference] Investigators Study Dates	Study Design	Dose & Regimen	Patients		Location in NDA (Volume / page)
			Enrolled/ Completed	Age (y) Range [Mean]	
<b>Controlled Clinical Trials - Completed</b>					
TFN 91-115 (FRISC) [15] Report 96 10 047 See references below* Prof. L. Wallentin + investigators at 21 additional centers 4/92 - 3/95	Prospective, randomized, double-blind, placebo-controlled, parallel group, multicenter study to compare Fragmin + ASA against placebo + ASA	Fragmin (SC): 150 or 120 IU/kg every 12 h days 1-6; 7500 IU/day days 6-45 Placebo (SC): to match Fragmin Aspirin (PO): 75 mg/day	15061/ 1233 (acute); 964 (chronic)	Fragmin: 40 - 88 [68] Placebo: 42 - 90 [69]	S: 8/1/55 R: 8/1/38 Tab: 11/1/1 CRF: 12/3/320 (d) 12/13/363 (w)
CTN 91-128 (FRIC) [16] Report 97 10 813 Circulation 1997;96:81-8 Am J Cardiol 1997;80(5A): 30E-34E Prof. W. Klein + investigators at 80 additional centers 3/93 - 6/95 †	Prospective, randomized, controlled, parallel group, multicenter study; days 1-6 open-label Fragmin + ASA vs. heparin + ASA; days 6-45 double-blind Fragmin + ASA vs. placebo + ASA	Fragmin (SC): 120 IU/kg every 12 h days 1-6; 7500 IU/day days 6-45 Heparin: 5000 IU IV bolus followed in <2 h by 1000 IU/h continuous IV infusion for ≥48 h, infusion stopped when determined by physician, SC 12500 IU/12 h afterward; days 1-6 Placebo (SC): to match Fragmin days 6-45 Aspirin (PO): 100-165 mg/day	1482/ 1132 (acute); 820 (chronic)	Days 1 to 6 Fragmin: 29 - 92 [64] Heparin: 25 - 89 [64] Days 6 to 45 Fragmin: 25 - 89 [64] Placebo: 31 - 88 [64]	S: 8/10/21 R: 8/10/1 Tab: 11/1/1/1 CRF: 12/18/155 (d) 12/22/101 (w)
<b>Controlled Clinical Trial - Ongoing</b>					
CTN 95-FRAG-025 (FRISC II) No Internal report Prof. L. Wallentin + investigators at 57 additional centers. 6/96 - ongoing §	Prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to compare Fragmin with placebo (5 to 7 days open-label treatment with Fragmin followed by chronic treatment with Fragmin or placebo)	Fragmin (SC): 120 IU/kg every 12 h first 5 to 7 days (all patients); then 5000 IU every 12 h or 7500 IU every 12 h through 90 days Placebo (SC): to match Fragmin 5000 IU every 12 h or 7500 IU every 12 h through 90 days	704/ 583 (acute)	Not specified	S: 8/27/330 R: N/A Tab: N/A CRF: N/A

Table 1 (page 1 of 3)

APPEARS THIS WAY ON ORIGINAL

Protocol No. [reference] Investigators Study Dates	Study Design	Dose & Regimen	Patients		Location in NDA (Volume / page)
			Enrolled/ Completed	Age (y) Range (Mean)	
<b>Other Studies and Information - Completed</b>					
CTN 90-044 (FRAMI) [10] Report 99 10 109 Circulation 1985;91(8): 2111-2 Prof. J. Dale, Dr. F. Kontny, + 13 other investigators 1990 - 1994	Prospective, placebo-controlled, randomized, double-blind, parallel group study	Fragmin (SC): 150 IU/kg every 12 h for 10 days, begun 8 h after end of streptokinase infusion All received aspirin (PO) 150 to 300 mg/day; 90% received streptokinase	794 776	64 ± 12 (mean ± SD)	S: 8/28/9 R: 8/28/13 Tab: 11/20/4 CRF: 12/28/1 (d) 12/27/270 (w)
TRN 91-111 [11] Report 93 98 402 Thromb Haemost 1997; 77(1):57-61 Thromb Haemost 1993; 69(6):648 Thromb Haemost 1993; 69(6):651 Dr. D. Nilsen 3/92 - 11/92	Prospective, open, randomized pilot study with parallel groups	Fragmin (SC): 150 IU/kg every 12 h for 7 days, reduced after 29 pts to 100 IU/kg, begun concomitantly with streptokinase infusion Heparin (SC): 125000 IU every 12 h for 7 days, begun within 4 h of streptokinase All received aspirin (PO) 300 mg initially, then 160 mg/day; streptokinase 1.5 million IU	100/ 96	64 ± 11 (mean ± SD)	S: 8/29/1 R: 8/29/5 Tab: 11/20/74 CRF: 12/28/247 (d) 12/29/141 (w)
CTN 88-009 [9] Report 95 10 319 Thromb Res 1991;64:579-87 U. Abildgaard, J. Dale, A. Nesvold 2/88 - 2/90	Uncontrolled dose-finding study	Fragmin (SC): 240-360 IU/kg every 24 h in 2 to 3 divided doses for 6 to 10 days Concomitant aspirin (300 mg) and Streptokinase (1.5 million IU) if clinically indicated	74/ 72	38 - 75 [66]	S: 8/28/145 R: 8/29/148 Tab: N/A CRF: 12/30/30 (d) 12/30/73 (w)
TRN 88-084 No internal report Haemostasis 1998; 26:247-57 L.-E. Strandberg, T. Kahan, P. Lundin 12/08 - 3/00	Open trial comparing Fragmin + streptokinase to streptokinase alone	Fragmin (SC): 50, 75, or 100 IU/kg every 12 h for 6 days, begun 4 h after start of streptokinase infusion Streptokinase (IV): 1.5 million IU over 1 h	20/ 20	41 - 75 [64]	S: 8/29/281 R: N/A Tab: N/A CRF: N/A

Protocol No. [reference] Investigators Study Dates	Study Design	Dose & Regimen	Enrolled/ Completed	Patients Age (Y) Range [Mean]	M/F W/B/O	Location in NDA (Volume / page)
Other Studies and Information - Not Yet Complete CTN 92-FRAG-012 (BIOMACS II) Final report pending Dr. L. Wallentin + 2 other investigators 5/93 - 6/95	Randomized, double-blind, placebo-controlled, parallel-group, multicenter, pilot trial	Fragmin (SC): 100 IU/kg before thrombolytic therapy and 120 IU/kg 12 hours later All received aspirin (PO) 300 mg initially, then 75 mg/day; streptokinase (IV) 1.6 million IU over 1 h; nitroglycerin (IV) during or early after streptokinase infusion for at least 24 h unless contraindicated	101/ 86	Not specified	Not specified	S: 8/28/143 R: N/A TAB: N/A CRF: N/A

\* Lancet 1996;347:561-6; Am J Cardiol 1997;80(5A):40E-44E; Eur Heart J 1997;18:762-70; Circulation 1996;93(9):1651-7; J Am Coll Cardiol 1987;29(1):49-8; J Am Coll Cardiol 1997;29(2):287; Thromb Haemost 1987 (Suppl):287; Am J Cardiol 1997;80(5A):25E-29E; Circulation 1996;94(8):1742; Thromb Haemost 1997 (Suppl):P-1183; Eur Heart J 1996;(17)32;(Abstr; Suppl.); Thromb Haemost 1997 (Suppl):287

† This number does not include 116 patients who received either placebo or Fragmin 150 IU/kg every 12 h days 1-6. Safety data for these patients are included in an appendix to the Integrated Summary of Safety.

‡ One-year follow-up of the FRIC trial remains ongoing.

§ Safety data provided through August 31, 1997.

Abbreviations: ASA = aspirin; CRF = case report forms; h = hour(s); IU = international units; IV = intravenous; kg = kilogram; mg = milligram; M/F = male/female; PO = oral; pts = patients; R = study report; S = synopsis; SC = subcutaneous; SD = standard deviation; Tab = CRF tabulations; W/B/O = white/black/other; y = years; d = death; w = withdrawal

Table 1 (page 3 of 3)

Sponsor's Table, Page 8/1/28-8/1/80

APPEARS THIS WAY ON ORIGINAL



	h) High risk patient <sup>4</sup> (yes, no)
Endpoint components	1. Exercise stress test day 6 (5-18) and day 45 (40-50).
Patient Population	
Stratification	
Gender	male/female
Pediatric	No
Geriatric	<70, >70
Racial	No
Additional subgroups	<ol style="list-style-type: none"> <li>1. Smoker (Smoker/smoked/never smoked)</li> <li>2. Previous MI (yes/no)</li> <li>3. Inclusion event (unstable angina, non-Q-wave MI)</li> <li>4. Concomitant treatment (0,1, ≥2) (Number of antianginal drugs, β-blocker, Ca-antagonist)</li> <li>5. Modified Braunwald classification               <ol style="list-style-type: none"> <li>I. First appearance of rest angina more than 2 months or no rest angina</li> <li>II. Angina at rest within past two months but not within 48 hrs.</li> <li>III. Angina at rest within 48 hrs</li> </ol> </li> <li>6. High risk patient (yes/no)               <ul style="list-style-type: none"> <li>• Presence of at least two of:                   <ul style="list-style-type: none"> <li>ge above 70 years, previous MI, pharmacological treatment of heart failure (by at least two of the following three treatment principles: diuretic, digitalis, ACE-inhibitor) or diabetes mellitus.</li> </ul> </li> </ul> </li> </ol>
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Males over 40 years of age or females postmenopausal for at least 12 months.</li> <li>2. Admitted to the Coronary Care Unit because of chest pain with the last episode of pain within 72 hrs before treatment start (inclusion). Inclusion was to be done as soon as possible.</li> <li>3. Fulfill at least one of the following history criteria:               <ol style="list-style-type: none"> <li>a) Newly developed angina pectoris during the previous two months.</li> <li>b) Increased angina pectoris during the previous two months.</li> <li>c) Ongoing chest pain, with a suspicion of myocardial infarction.</li> </ol> </li> <li>4. fulfill at least one of the following ECG criteria without any explanation other than myocardial ischemia:               <ol style="list-style-type: none"> <li>a) Temporary or manifest ST-depression with at least 0.1 mV (≥ 1 mm) in at least 2 adjacent leads (irrespective of T-wave changes).</li> <li>b) Temporary or manifest T-inversion with at least 0.1 mV (≥ 1 mm) below the baseline in at least 2 adjacent leads (without pathological Q-waves in the same leads).</li> </ol> </li> </ol>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Increased bleeding risk is defined as follows:               <ol style="list-style-type: none"> <li>a) Cerebral bleeding during the previous three months.</li> <li>b) Ulcer disease or known gastrointestinal bleeding during the previous 5 years .</li> <li>c) Undergone surgery during the previous week.</li> <li>d) Undergone eye, ear, or CNS-surgery during the previous month.</li> <li>e) Known defect in hemostasis, e.g., thrombocytopenia (&lt;100 x 10<sup>6</sup> /l) or ongoing treatment with oral anticoagulants or heparin</li> <li>f) Anemia (male Hb &lt;,125 g/l, female Hb&lt;11)</li> </ol> </li> <li>2. Known renal insufficiency (S-creatinine &gt;200 μmol/l)</li> <li>3. Known liver insufficiency (thrombin time &lt; 50%).</li> <li>4. Indication for thrombolytic treatment, e.g., ongoing chest pain combined with ST-elevation or bundle branch block or pronounced ST-depression in anterior chest leads that warrants a</li> </ol>

<sup>2</sup> Number antianginal drugs, β-blocker, Ca-antagonist or nitrate.

<sup>3</sup> I. First appearance of rest angina more than 2 months ago or no rest angina.  
 II. Angina at rest within past two months but not within 48 hrs.  
 III. Angina at rest within 48 hours.

<sup>4</sup> Presence of at least two of the following criteria: age above 70 years, previous MI, pharmacological treatment of heart failure (by at least two of the following three treatment principles: diuretic, digitalis, ace-inhibitor) or diabetes

	<p>strong suspicion of acute posterior myocardial infarction.</p> <ol style="list-style-type: none"> <li>5. Newly-developed pathological Q-wave.</li> <li>6. Pathological Q-waves in the same leads as "diagnostic" ST-T wave changes.</li> <li>7. Left bundle branch block or pacemaker.</li> <li>8. Septic endocarditis.</li> <li>9. Suspect myocarditis or pericarditis.</li> <li>10. Aortic valvular disease with hemodynamic significance.</li> <li>11. PTCA/CABG planned within three months or performed during the last 3 months</li> <li>12. Known primary myocardial disease, e.g., hypertrophic or dilated cardiomyopathy.</li> <li>13. Hypertension with diastolic pressure &gt; 120 mm Hg during treatment.</li> <li>14. Hypotension with systolic blood pressure below 90 mmHg.</li> <li>15. Fever <math>\geq 39^\circ</math>.</li> <li>16. Diseases with unfavorable prognosis, e.g., malignancy.</li> <li>17. Known hypersensitivity to heparin or low molecular weight heparin/</li> <li>18. Participation in another study or previously included in this study.</li> <li>19. Residing outside of the catch area of this trial.</li> <li>20. Known circumstances which make it difficult for the patient to fulfill the study treatment. In case of doubt, the patient can be included and a renewed decision (continuation or withdrawal) can be made before discharge from hospital on Day 6 (5-8).</li> <li>21. Unwilling to participate             <ul style="list-style-type: none"> <li>• Physical handicap or other conditions that prevented or contraindicated the exercise test were not a reason for excluding the patient from the trial.</li> </ul> </li> </ol>
Criteria for cessation of treatment	<ol style="list-style-type: none"> <li>1. Severe or repeated angina unresponsive to i.v. nitroglycerin for over 24 hours. (in this case study drug is stopped and i.v. heparin started and angiography done)</li> <li>2. Need for heparin infusion.</li> <li>3. Q-wave myocardial infarction</li> <li>4. Thrombolytic treatment.</li> <li>5. PTCA/CABG</li> <li>6. Serious adverse event.</li> <li>7. Epidural or spinal anesthesia.</li> <li>8. Patient request.</li> <li>9. Serious intercurrent illness which, in the opinion of the investigator, contraindicated continuation of the treatment.</li> <li>10. Renal or liver insufficiency.</li> </ol>
<b>Treatments</b>	
Treatment groups	<p>Phase I. Fragmin® 120 IU/kg/ s.c. bid Dosed by weight ranges (Appendix 10.7) vs. placebo (See Amendment 2) for 6 (5-8) days</p> <p>Phase II. Fragmin® 7500 IU s.c. q.d. vs. placebo for up to a total of 45 (40-50) days</p>
Treatment start	<ol style="list-style-type: none"> <li>1. Treatment as soon as possible after enrollment</li> <li>2. No longer than 72 hours after the last episode of pain.</li> </ol>
Other treatments	<ol style="list-style-type: none"> <li>1. ASA was started as soon as possible after admission in all patients unless they had aspirin sensitivity. If they were already taking aspirin, they were continued on 75 mg/day for the duration of the study. If they were not on aspirin, they were given an initial dose of 300 mg, followed by 75 mg/day.</li> <li>2. All patients not receiving <math>\beta</math>-blocker at inclusion, and without contraindications, were started on metoprolol 50-100 m.g. /24 hrs p.o., and i.v. if appropriate.</li> <li>3. Sublingual or oral nitrates</li> <li>4. Calcium channel blockers (diltiazem).</li> </ol>
Drug Accountability	Patient diary checked, used and unused syringes were counted and saved.
Follow-up	Follow-up at 6 months. ECG, hemoglobin, and platelet count.
<b>Statistical Methods</b>	
Study configuration	Multi-center

Stratification by center	Yes
Type of comparison	Trial to show superiority over placebo, null hypothesis is that there is equal treatment effect.
Power	Assumed that Fragmin® reduces the incidence of death and/or MI from 6% to 3% during the first six days of treatment. Power of 80%, $\alpha=0.05$ .
Type of analysis	<ol style="list-style-type: none"> <li>1. Between groups Cochran-Mantel-Haenszel with significance of 5%.</li> <li>2. Interaction test for homogeneity between centers (Breslow-Day).</li> <li>3. Descriptive statistics with confidence intervals.</li> <li>4. Combined ranked variables were analyzed with the Wilcoxin rank sum test.</li> <li>5. Time until an event was evaluated with a logrank test.</li> </ol>
Interim analysis	No interim analysis
Blinding	
Type	Double blinded
Control groups	Placebo
Randomization	<ol style="list-style-type: none"> <li>1. SAS generated</li> <li>2. Blocks of 10 with one extra block at Kalmar with block size 6</li> <li>3. Performed once at beginning of study.</li> <li>4. Not repeated at the end of the acute phase.</li> <li>5.</li> </ol>
Placebo	Phase I: Matching ampoule (1 ml) with 0.9% NaCl Phase II: Matching syringes (0.3 ml) with 0.9% NaCl
Missing values	No values were imputed for missing observations
Other	No adjustment for multiple comparisons was done. Interpretation of results from the secondary analyses must be done with caution.
Risks anticipated by sponsor	
Clinical monitoring	<ol style="list-style-type: none"> <li>1. ECG at admission, day 2, day 6 (5-8), day 45 (40-50), and 6 months.</li> </ol>
Laboratory monitoring	<ol style="list-style-type: none"> <li>1. S-creatinine at admission only[JWS1]</li> <li>2. Liver function tests at admission only</li> <li>3. Admission Haemoglobin and platelet count at, day 2, day 6 (5-8), day 45 (40-50), and 6 months.</li> </ol>
Clinical safety assessments.	<ol style="list-style-type: none"> <li>1. Major bleeding <ol style="list-style-type: none"> <li>a) Fall in hemoglobin of 20 g/L or more in connection with clinical symptoms (Amendment 3).</li> <li>b) Bleeding requiring transfusion of blood.</li> <li>c) Intracranial bleeding</li> <li>d) Bleeding requiring interruption of treatment.</li> <li>e) Bleeding which led to death.</li> </ol> </li> <li>2. Minor bleeding visible but not Major</li> </ol>
Follow-up	6 months
Informed consent required	Yes
IRB approval required	Yes
GCP compliance	Performed according to Pharmacia & Upjohn quality assurance procedures.
Amendments	<ol style="list-style-type: none"> <li>1. Amendment 1 ated march 10, 1992, clarified inclusion/exclusion criteria, statistical analysis and the handling of patients. The amendment was initiated before the trial started, and all necessary changes were made to the staff instructions.</li> <li>2. Amendment 2 Dated August 21, 1992. The dose of Fragmin was reduced from 150 IU/kg/12 hrs to 120 IU/kg/12 hrs after 116 patients had been enrolled. A new protocol was printed, dated August 20, 1992. Drug-boxes for Phase I were given new dose instructions, relabeled and all staff instructions were reprinted.</li> <li>3. Amendment 3 Dated October 9, 1992 clarified the exclusion criteria and defined major bleeding. The exclusion criteria for ulcer disease or known gastrointestinal bleeding and planned PTCA/CABG was amended as follows: <ul style="list-style-type: none"> <li>• Ulcer disease or known gastrointestinal bleeding during the previous 5 years.</li> </ul> </li> </ol>

	<ul style="list-style-type: none"> <li>• PTCA/CABG planned within three months or performed during the last 3 months.</li> <li>• The definition of major bleeding was revised to be a fall in hemoglobin of at least 20 g/L in connection with clinical symptoms.</li> </ul> <p>4. <b>Amendment 4</b>  Dated December 3, 1993. The number of patients was increased by 120 to approximately 1620 to compensate for the 116 patients treated with 150 IU/kg/12 hrs, see Amendment 2. In addition, Amendment 4 stated that no interim analysis would be performed, and added the following to the definition of correct treatment:</p> <ul style="list-style-type: none"> <li>• If the last injection before the exercise test was not given, or if the exercise test was not performed, the patient was still considered as correctly treated in all aspects except the evaluation of the exercise test.</li> </ul> <p>5. <b>Amendment 5</b>  Dated October 3, 1994.</p> <ul style="list-style-type: none"> <li>• Endpoint Committee and central evaluation: The members of the Endpoint Committee were appointed. The endpoint form was appended. It was stated that the Endpoint Committee independent of each other would check and evaluate all MIs and deaths reported by the investigators. If they disagreed, they had to compromise. They also should decide the date of the endpoint (MI).</li> <li>• Secondary objectives: The incidence of indication for coronary angiography was compared instead of the incidence of performed coronary angiography. Nitroglycerine infusion started before or within 12 hrs from the first study drug injection was excluded from analysis.</li> <li>• Safety analyses: Only events occurring, at the latest, on the day after the last study drug injection were to be included.</li> <li>• Intention-to-treat analyses: Patients could be included in the intention-to-treat analyses regardless of laboratory results from samples drawn before randomization.</li> </ul> <p>Combined statistical analysis: The worst endpoint would be counted according to the following rank; death, MI, need for i.v. heparin, need for i.v. nitroglycerine and revascularization.</p>
--	---

**Results**

<b>Protocol Deviations</b>	<ol style="list-style-type: none"> <li>1. Fourteen patients misrandomized.</li> <li>2. Karlstad center not mentioned in initial application.</li> <li>3. Informed consent missing in 95 patients (Fragmin/placebo 43/52).</li> <li>4. Five centers did not reach 30 patients (one had only five).</li> <li>5. Fourteen patients omitted due to investigator error.</li> <li>6. Incorrectly dosed patients. Fragmin 10/746, Placebo 9/760.</li> <li>7. Study drug interruption Fragmin 138/746, Placebo 115/760.</li> </ol>						
<b>Patient disposition</b>							
Screened	36,480						
Eligible	5137 (most were ineligible because of risk for bleeding)						
Enrollment	1622 1506 (120 IU/kg vs. placebo), 116 (150 IU/kg vs. placebo) <sup>5</sup>						
Randomized	1506						
Started treatment	1506						
	Fragmin (120 IU/kg)	Placebo	Total	Fragmin (150 IU/kg)	Placebo	Total	Grand total
Randomized	746	760	1506	63	53	116	1622
Intention to treat <sup>6</sup>	741	757	1498 <sup>7</sup>				
Per-protocol <sup>8</sup>	651	669	1320				

APPEARS THIS WAY ON ORIGINAL

Completed Phase I	619	614	1233				
Entered Phase II	619	614	1233	50	46	96	1329
Completed Phase II	478	486	964				
<b>Safety Analysis<sup>9</sup></b>							
Phase I	746	760	1506	63	53	116	1622
Phase II	618	614	1232	50	46	96	1328
<b>Demographics</b>							
	<b>Fragmin (120 U/kg)</b>		<b>Placebo</b>				
Females	275		268				
Males	471		492				
Age							
Mean $\pm$ s.d.	67.8 $\pm$ 9.2		68.5 $\pm$ 9.2				
Range	40-88		42-92				
Weight (mean $\pm$ s.d.)	76.1 $\pm$ 12 k.g.		77.2 $\pm$ 12.9 k.g.				
Race							
White	743		758				
Black	1		0				
Asian	0		1				
Other	2		1				
Smoking							
Never	346		365				
Stopped >1 month	254		341				
Smoker	146		154				
Aspirin treatment		%		%			
Already taking	264	35.4	281	37.0			
Started within 72 hrs	458	61.4	444	58.4			
None on day 1	24	3.2	35	4.6			
Hypersensitivity	13	1.7	28	3.7			
<b>Efficacy</b>							
	<b>Fragmin</b>		<b>Placebo</b>		<b>P value<sup>10</sup></b>		
Primary endpoint of Death and/or MI through day 6							
ITT	13/741	1.8%	36/757	4.8%	0.001		
Per-protocol	11/682	1/6%	32/695	4.6%	0.001		
Secondary endpoints							

<sup>5</sup> The study dose was decreased to 120 IU after significant bleeding was seen in the patients treated with 150 IU.

<sup>6</sup> Sponsor-defined ITT

<sup>7</sup> ITT for the primary endpoint only. Secondary endpoint "ITT" vary somewhat

<sup>8</sup> For the primary endpoint only.

<sup>9</sup> Not all patients were included in all safety analysis.

<sup>10</sup> Cochran-Mantel-Haenszel test

1. Death and/or MI during through:					
45 days.					
ITT	59/738	8.0	81/755	10.7	0.073
Per-protocol	50/657	7.6	72/674	10.7	0.053
6 months					
ITT	102/726	14	116/749	15.5	0.407
Per-protocol	89/13.8	13.8	105/668	15.7	0.282
2. Cumulative probability of death and/or MI through Day 6	Logrank test, p=0.001)				
3. Incidence of revascularization through:					
6 days					
ITT	3/733	0.4	9/749	1.2	0.07
45 days					
ITT	87/719	12.1	114/735	15.5	0.039
6 months					
ITT	229/696	32.9	254/716	35.5	0.221
4. Indication for coronary angiography.	Analysis not done because the date of indication for coronary angiography was not collected in the CRF.				
5. Ischaemia during exercise test (Appendix 10.4) through:					
6 (5-8) days					
ITT	263/578	45.5	284/562	50.5	0.097
Per-protocol	222/484	45.9	250/488	51.2	0.118
45 (40-50) days.					
ITT	182/452	40.3	192/451	42.6	0.421
Per-protocol	132/331	39.9	139/328	42.4	0.543
6. Incidence of need for i.v. nitroglycerine and/or the need for i.v. heparin	Analysis appears to not have been done as a composite, although this is how the endpoint was defined in the protocol.				
7. Incidence of need for i.v. heparin through <sup>11</sup> :					
6 (5-8) days					
ITT	28/736	3.8	58/753	7.7	0.001
Per-protocol	25/678	3.7	54/692	7.8	0.001
45 (40-50) days					
ITT	61/725	8.4	101/743	13.6	0.001
Per-protocol	54/648	8.3	96/665	14.4	0.001
150 days					
ITT	83/696	11.9	121/724	16.7	0.008
Per-protocol	73/623	11.7	115/648	17.7	0.002
8. Incidence of need for i.v. nitroglycerine through:					
6 (5-8) days					
ITT	36/736	4.9	70/753	9.3	0.001
Per-protocol	33/678	4.9	67/695	9.6	0.001
45 (40-50) days					

<sup>11</sup> Secondary endpoint was originally defined as need for heparin and/or nitroglycerin

ITT	92/726	12.7	127/742	17.1	0.015
Per protocol	84/651	12.9	120/669	17.9	0.009
150 days					
ITT	124/701	17.7	163/729	22.4	0.023
Per-protocol	113/628	17.8	150/656	22.9	0.017
9. Death/MI/heparin/nitroglycerin/revascularizati on through: (See Appendix 10.6)					
6 days					
ITT	59/739	8	106/756	14	0.001
Per-protocol	Analysis appears to not have been done.				
45 days					
ITT	179/739	24.2	222/755	29.4	0.018
Per-protocol	Analysis appears to not have been done.				
6 months.					
ITT	337/732	46.0	364/749	48.6	0.227
Per-protocol	Analysis appears to not have been done.				
<b>SPONSOR'S CONCLUSIONS</b>					
1. Fragmin 120 IU/kg every 12 hours for 6 days during Phase I produced a 63% reduction in death and/or MI and a 50% reduction in the need of heparin or nitroglycerin infusion when compared to placebo					
2. Prolonged treatment (Phase II) with Fragmin once daily for an additional 5 weeks maintains a reduction in MIs, the need of heparin, and the need of nitroglycerin infusion and revascularization.					
3. All subgroup analyses Day 6 favored Fragmin, At day 40 the protective effect of Fragmin was most pronounced in high-risk patients with non Q-wave MI					

Table Constructed by Medical Officer

APPEARS THIS WAY ON ORIGINAL

### 3.2.1.3 General study outline

Patients with unstable coronary artery syndromes were treated during two phases. During Phase I (Day 1-6) they were treated with Fragmin or placebo. During Phase II (Day 6-45), they were treated with a lower dose of Fragmin or placebo.

### 3.2.1.4 Objective

The primary objective of FRISC was to determine whether Fragmin treatment decreased the incidence of death and/or myocardial infarction in

patients with unstable coronary artery syndromes after 6 days of treatment with Fragmin or placebo.

The secondary objectives were to determine whether the incidence of death and/or myocardial infarction, along with several other parameters, were different in the Fragmin and placebo group after six and 45 days of treatment, and at 6 month follow-up.

### **3.2.1.5 Patient population**

1622 patients were randomized.

The study initially used a dose of 150 IU/kg/12hr of Fragmin.

After several patients suffered bleeding problems, the study dose was changed to 120 IU/kg.

Ultimately, 116 patients received the 150 IU/kg dose and an additional 1506 received the 120 IU/kg dose.

### **3.2.1.6 Inclusion criteria**

The main inclusion criterion was the presence of an unstable coronary artery syndrome. Unstable coronary artery disease was defined as either non-Q-wave MI or unstable angina (with EKG changes). The appropriateness of this definition of unstable angina is discussed in Section 6.

### **3.2.1.7 Demographics and other baseline characteristics**

#### **3.2.1.7.1 Demographics**

The patient population was composed predominately of white males, with an average age of 68 years. Patients under the age of forty were not enrolled.

Gender, age, weight, race, and smoking status were, for the most part, evenly distributed between the Fragmin and placebo groups.

#### **3.2.1.8 Aspirin use**

Eleven more patients in the placebo group had no ASA on day 1 than in the Fragmin group (Fragmin 3.6%/placebo 4.2%) (See Table 4).

Table 4: Aspirin use

**Table 4.1. Use of ASA at admission**

Use of ASA	Fragmin (N=746)		Placebo (N=760)	
	n	%	n	%
Continued ASA	264	35.4	281	37.0
Started ASA within 72 hrs	458	61.4	444	58.4
No ASA Day 1	24	3.2	35	4.6
Hypersensitivity to ASA <sup>a</sup>	13	1.7	28	3.7

a) 2 patients in the Fragmin group and 4 patients in the placebo group received ASA although hypersensitive to ASA.

Sponsor's Table, Page 8/1/127

APPEARS THIS WAY ON ORIGINAL

There is no suggestion that there was an imbalance in the way aspirin was given that would affect outcome. There were more patients in the placebo group who did not get aspirin until two days after the study drug was stated, but none of the patients who received aspirin "late", in either the placebo group or the Fragmin contributed to the occurrence of the primary endpoint because all of the patients who did not receive aspirin until day two had not died or had an M.I. at day 6.

APPEARS THIS WAY ON ORIGINAL

### 3.2.1.9 Study treatments

Patients received Fragmin at 120 IU/kg/12 hours for the first six (5-7) days followed by 7500 IU/24 hours for a total of 45 (40-50) days. Both phases were placebo-controlled.

An initial group of patients received a 150 IU/kg/12 hrs dose. See section 3.2.1.5.

### 3.2.1.10 Withdrawals

Withdrawals are summarized in Table 5 and Table 6. Table 5 shows the reasons for withdrawal and the number of patients whose withdrawal was contributed to by that reason, while Table 6 shows the reason for withdrawal and the number of patients who withdrawn primarily because of that reason.

Overall, withdrawals were balanced between the placebo and Fragmin groups in both phases of the study.

However, there were more withdrawals in the placebo group because of thrombolytic treatment, and need for heparin. and there were more withdrawals in the Fragmin group because of patient request and "other."

A higher incidence of patient withdrawal in the placebo group secondary to requirement for thrombolytic treatment or need for heparin could be consistent with a beneficial effect of Fragmin.

APPEARS THIS WAY ON ORIGINAL

Table 5: All reasons for treatment withdrawal for 120 IU/kg/12h

Withdrawal reason	Treatment			
	Fragmin		Placebo	
	Freq	%	Freq	%
Need for heparin infusion	47	6.3	89	11.7
Myocardial infarction	17	2.3	15	2.0
Thrombolytic treatment	12	1.6	32	4.2
Performed PTCA/CABG	58	7.8	63	8.3
Serious Adverse Event	20	2.7	20	2.6
Patient request	87	11.7	65	8.6
Intercurrent illness	6	0.8	5	0.7
Renal or liver insufficiency	1	0.1	2	0.3
Others	47	6.3	31	4.1
Not withdrawn	478	64.1	486	63.9

Sponsor's Table, Page 8/4/160

Table 6: Primary reason for treatment withdrawal per phase for 120 IU/kg/12h

Primary reason for withdrawal	Study Phase							
	Phase I				Phase II			
	Treatment				Treatment			
	Fragmin		Placebo		Fragmin		Placebo	
Freq	%	Freq	%	Freq	%	Freq	%	
Need for heparin infusion	23	3.1	50	6.6	21	3.4	31	5.0
Myocardial infarction	8	1.1	7	0.9	8	1.3	1	0.2
Thrombolytic treatment	3	0.4	20	2.6	4	0.6	8	1.3
Performed PTCA/CABG	3	0.4	2	0.3	50	8.1	49	8.0
Serious Adverse Event	8	1.1	6	0.8	9	1.5	8	1.3
Patient request	52	7.0	45	5.9	32	5.2	18	2.9
Intercurrent illness	4	0.5	2	0.3	2	0.2	2	0.3
Renal or liver insufficiency	0	0	0	0	0	0	1	0.2
Others	26	3.5	14	1.8	16	2.6	10	1.6
Not withdrawn	619	83.0	614	80.8	478	77.2	486	79.2
Total	746	100.0	760	100.0	619	100.0	614	100.0

Sponsor's Table, Page 8/4/159