

Table 127. Adverse events leading to withdrawal from treatment, Fragmin 120 IU/kg

Patient no.	Adverse event leading to withdrawal	Age (years)	Sex	Day of adverse event	Seriousness
42076	Heart failure	71	M	6	Serious

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3.2.1.12.5 Conclusion

The sponsor showed that Fragmin reduced the primary endpoint (rate of death and/or MI) from 4.8% to 1.8% with a p value of 0.001 during the first 6 days of treatment.

This effect, however, was not still seen at 45 days, or at three months. Although there was a numeric advantage seen in the Fragmin group, it was not statistically significant.

Other, secondary, objectives were also achieved. During the acute phase, the Fragmin-treated patients had a decreased need for heparin and nitroglycerin infusion as compared with placebo.

There was an indication that, at 45 days, the Fragmin group had lower incidence of MI, need for heparin, and need for nitroglycerin infusion and revascularization.

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3.2.2 FRIC**3.2.2.1 Introduction**

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

Phase I (day 1-6) was open label and Phase II (day 6-45) was double-blinded.

Phase I compared Fragmin/ASA to heparin/ASA. Phase II compared Fragmin/ASA to placebo/ASA.

The primary endpoint was the incidence of death, myocardial infarction and/or recurrence of angina during Phase II.

The FRIC study is summarized in the following table (Table 23), followed by further description and discussion of the study.

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3.2.2.2 FRIC study summary

Table 23: Study summary: FRIC trial CTN: 91-128 Low molecular weight heparin, Fragmin, in the treatment of unstable coronary artery disease

Type of study	Prospective, randomized, double blind (in Phase I), placebo controlled (in Phase II), parallel groups, multi-center design. Phase I was open label.
Study period	March 1993-June 1995
Duration of study	Phase I Day 1-6 Phase II Day 6-45
Sites	Austria, Canada, Spain, Scotland, Germany, Netherlands, United States, Norway, Italy
Number of sites	81
Endpoints	

Primary endpoint	To compare the effects of Fragmin and placebo, during treatment between day 6-45 (phase II) in unstable coronary artery disease, on incidence of cardiac events (death, myocardial infarction and/or recurrence of angina) (Appendix 10.10)
Secondary endpoints	<p>Phase I</p> <ol style="list-style-type: none"> 1. Compare Fragmin with heparin concerning the incidence of combinations of death, MI, recurrence of angina and/or revascularization. 2. Compare Fragmin with heparin concerning ischemia during the exercise test on Day 6. 3. Safety of Fragmin concerning bleedings, deaths, allergic reactions, and thrombocytopenia <p>Phase II</p> <ol style="list-style-type: none"> 1. Compare Fragmin with placebo concerning the incidence of combinations of death, MI, recurrence of angina, and/or revascularization. 2. Compare Fragmin with placebo concerning ischemia during the exercise test on Day 45. 3. Compare Fragmin with placebo concerning the incidence of death, MI and/or recurrence of angina in subgroups. 4. Compare Fragmin with placebo, in relation to the treatment in Phase I (Fragmin/heparin), concerning the incidence of death, MI, and/or recurrence of angina. 5. Study safety of Fragmin concerning bleedings, deaths, allergic reactions, and thrombocytopenia. <p>Phase II and until 3-months follow-up</p> <p>Compare Fragmin with placebo concerning the incidence of combinations of death, MI, and/or revascularization (Amendment 3)</p>
Endpoint components	<ol style="list-style-type: none"> 1) Exercise stress test day 6 (5-18) and day 45 (40-50). 2) Indications for revascularization <ul style="list-style-type: none"> • For revascularization to be indicated, the patient had to fulfill the indications for coronary angiography and at least one of the following: <ol style="list-style-type: none"> a) Left main disease b) 3-vessel disease c) Proximal LAD stenosis of at least 75% d) Proximal stenosis in the coronary artery supplying a large part of viable myocardium of at least 75%. e) The presence of disabling angina together with a significant stenosis in any major coronary artery suitable for revascularization
Stratification	
Gender	male/female
Pediatric	
Geriatric	<70, >70
Racial	No
Additional subgroups	<ol style="list-style-type: none"> 1) Sex (male female) 2) Weight (< 70 k.g., >70 k.g.) 3) BMI (≤ 26 k.g./m², > 26 k.g./m²) 4) Current smoker (yes, no). 5) Inclusion diagnosis (unstable angina, non Q-wave MI) 6) Modified Braunwald classification (I, II, III) 7) High risk patient (yes, no) <ul style="list-style-type: none"> • To be classified as a high risk patient, at least one of the following criteria had to be met: <ol style="list-style-type: none"> a) CK or CK-MB twice the normal upper limit. b) Age above 70 years. c) Previous MI. d) Pharmacologically treated diabetes mellitus. e) Pharmacologically treated heart failure f) ASA dose (≤ 125 mg., > 125 m.g.) g) Pre-treated with heparin (yes, no).

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<p>Inclusion criteria</p>	<ol style="list-style-type: none"> 1. Male or female 2. Admitted to Coronary Care Unit or ward because of chest pain or other typical anginal pain with the last episode of pain within 72 hours before start of study drug. Patients were to be included as soon as possible. 3. Fulfilled at least one of the following anamnestic criteria: <ol style="list-style-type: none"> a) Newly developed angina pectoris during the last 2 months. b) Increased angina pectoris during the last 2 months. c) Ongoing chest pain, with a suspicion of myocardial infarction 4. Fulfilled at least one of the following ECG criteria without any other explanation than myocardial ischemia; <ol style="list-style-type: none"> a) Temporary or present (manifest) ST-depression of at least 0.1 mV (≥ 1 mm) in at least 2 adjacent leads (irrespective of T-wave changes). b) Temporary or present manifest T-inversion of at least 0.1 mV (≥ 1 mm) below the base line in at least 2 (except in V₁) adjacent leads (without pathological Q-waves in the same leads. 5. Informed consent
<p>Exclusion criteria</p>	<ol style="list-style-type: none"> 1. Increased bleeding risk, defined as follows: <ol style="list-style-type: none"> a) Cerebral vascular event during the past 3 months. b) Ulcer disease or known gastrointestinal bleeding during the last 3 months (Amendment 2 and 3). c) Undergone surgery during the previous week. d) Undergone eye, ear, or CNS-surgery the previous month. e) Known defect of hemostasis, e.g., thrombocytopenia ($< 100 \times 10^9/L$ or ongoing treatment with oral anticoagulants or heparin. (Heparin allowed under certain conditions, see simultaneous treatments). f) Anemia (males Hg < 125 g/L, females Hg < 110 g/L) 2. Known renal insufficiency (creatinine > 200 μ,mol/l) 3. Known liver insufficiency (Normotest, Simplastin $< 50\%$, or other corresponding tests resulting in INR > 1.5) or prothrombin time above the upper limit of normal. 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 what warranted a strong suspicion of acute posterior myocardial infarction. 5. Newly developed pathological Q-wave. 6. Pathological Q-waves in the same leads as "diagnostic" ST-T changes. 7. Left bundle branch block or pacemaker. 8. Septic endocarditis. 9. Suspected myocarditis or pericarditis. 10. Aortic valvular disease of hemodynamic significance. 11. PTCA/CABG planned or performed the last 3 weeks. 12. Known primary myocardial disease, e.g., hypertrophic or dilative cardiomyopathy. 13. Hypertension with diastolic blood pressure > 120 mmHg during treatment. 14. Hypotension with systolic blood pressure below 90 mmHg. 15. Fever $\geq 39^\circ$ C. 16. Diseases with unfavorable prognosis, e.g., malignancy. 17. Known hypersensitivity to heparin or low molecular weight heparin. 18. Known pregnancy or breast-feeding. 19. Participation in another study or previously included in these study. 20. Residing outside the recruitment area of this trial. 21. Known circumstances which make it difficult for the patient to administer the study drug at home.
<p>Criteria for cessation of treatment</p>	<ol style="list-style-type: none"> 1. Severe or repeated angina unresponsive to nitroglycerine (in hospital) during Phase II. 2. Need for heparin infusion Day 6-45 3. Indications for thrombolytic treatment and/or 4. Q-wave myocardial infarction occurred. 5. Serious adverse event. 6. Performed PTCA/CABG 7. Epidural or spinal anesthesia. 8. Patient request. 9. Serious intercurrent illness which, in the opinion of the Investigator, contraindicated continuation of study drug. 10. Renal or liver insufficiency.
<p>Treatments</p>	

Treatment groups	<p>Phase I. Fragmin 120 IU/kg b.i.d., s.c. Dosed by weight ranges (Appendix 10.7) vs. heparin (5000 U i.v. bolus, 1000U/hr infusion (PTT 1.5-2 x control))</p> <p>at 48 hours, switched to 12,500 IU every 12 hours at discretion of physician for 6 (5-8) days</p> <p>Phase II. Fragmin 7500 IU/o.d. vs. placebo for up to a total of 45 (40-50) days. (Appendix 0)</p>
Treatment start	<ol style="list-style-type: none"> 1. Treatment as soon as possible after enrollment 2. No longer that 72 hours after the last episode of pain.
Other treatments	<ol style="list-style-type: none"> 1. All patients were to be treated with ASA 100-165 mg daily during the entire trial, unless the patient was hypersensitive to ASA. (Amendment 1 and 2). 2. Nitroglycerin infusion was administered according to local routine. 3. β-blockers used according to local routine. 4. Calcium channel blockers were used according to local routine.
Other treatments, not related to the study drug, but related to the protocol, and which could affect endpoints	<ol style="list-style-type: none"> 1. Pretreatment with heparin was accepted provided: <ol style="list-style-type: none"> a) Heparin had been administered for less than 12 hours prior to the start of trial mediation b) The total dose of heparin administered was $\leq 10,000$ IU c) If PTT was > 1.5 times the control value in a patient, randomized to heparin treatment, the initial 5000 IU bolus should not be given.
Reference Drugs	<p>Phase I Heparin either i.v. (5000 or 10,000 IU/ml) and/or s.c. administration (20,000 or 25,000 IU/mL)</p> <p>Phase II placebo was normal saline in matching syringes.</p>
Drug Accountability	Patient diary checked, used and unused syringes were counted and saved.
Follow-up	Follow-up at three months with ECG.
Statistical Methods	
Study configuration	Multi-center
Stratification by enter	Yes
Type of comparison	Phase II component was a trial to show superiority over placebo, null hypothesis was equality of treatment effects and the two-sided alternative hypothesis was that the treatment effects were not equal. It was assumed that there would be a minor difference between Fragmin and heparin treatment during Phase I.
Power	Assumed that the incidence of death, MI, and/or recurrence of angina during the second phase would be 0.10 in the placebo group and 0.05 in the Fragmin group. Power of 80%.
Type of analysis	<ol style="list-style-type: none"> 1. Cochran-Mantel-Haenszel test, stratified by clinic 2. Interaction test for homogeneity of treatment effect among centers. 3. Wilcoxin rank sum test for Phase II. 4. Descriptive statistics for baseline and other patient characteristics.
Interim analysis	No interim analysis.
Blinding	
Type	<p>Phase II was double-blind</p> <p>Phase I was open label</p>

Control groups	
Randomization	<ol style="list-style-type: none"> 1. SAS generated 2. Block size 4,8, 12, 16, or twenty 3. Separate randomization for each center. 4. Patents only randomized once.
Placebo	<p>Phase I: None</p> <p>Phase II: Matching syringe with 0.9% NaCl</p>
Missing values	
Other	At the time when clean file was declared, data on the primary efficacy variable were missing for 90 patients. After examination by the Steering Committee, it was decided that for most of these patients a value could be assessed using other variables in the current database. However, 27 patients required special clarification using a blind editing procedure.
Safety and Tolerability	
Risks anticipated by sponsor	
Clinical monitoring	CG at admission, day 2, day 6 (5-8) day 45 (40-50), and at 3 months.
Laboratory monitoring	<ol style="list-style-type: none"> 1. Liver function and S-creatinine at admission only. 2. Hemoglobin and platelet count at admission and day 2, 6 (5-8), 45 (40-50). 3. PTT day 1, 2, 6 (Heparin group only) 4. Anti-Xa day 2 and 6 (5-8).
Clinical safety assessments.	<ol style="list-style-type: none"> 1. Major bleeding <ol style="list-style-type: none"> a) Fall in hemoglobin of 20 g/L or more in connection with clinical symptoms (Amendment 3). b) Bleeding requiring transfusion of blood. c) Intracranial bleeding d) Bleeding requiring interruption of treatment. e) Bleeding which led to death. 2. Minor bleeding visible but not Major.
Follow-up	3 months
Informed consent required	Yes
IRB approval required	Yes
Safety committee	
AE Reporting procedure	
GCP compliance	Performed according to Pharmacia & Upjohn quality assurance procedures.

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<p>Amendments</p>	<p>10. Amendment 1 dated February 17, 1993 clarified a number of sections including adding an instruction for anti-FXa sampling. The amendment was initiated before the start of the study; no new protocol was printed.</p> <p>11. Amendment 2 dated March 10 1993, provided some minor clarifications and introduced appendix 5 (exercise test instructions).</p> <p>12. Amendment 3 Dated July 16, 1993 introduced several minor clarifications including some parts of "Statistics and Medical Data Management".</p> <p>13. Amendment 4 dated March 7 1994 clarified one of the secondary objectives, the definition of myocardial infarction, instruction for adverse event reporting and a few other minor issues.</p> <p>14. Amendment 5 dated February 7, 1995, extended the trial to also include a one-year follow-up of death, myocardial infarction and revascularization. Code break was decided to take place within the 3 months follow-up was completed. The one-year follow-up is not included in the report. Correct treatment related to ASA, central evaluation of myocardial infarction subgroup analysis and a few other issues were clarified.</p>
<p>Results</p>	
<p>Protocol Deviations</p>	<ol style="list-style-type: none"> 1. Forty-three patient numbers were omitted due to practical mistakes. 2. Sixteen patients were randomized but never received study drug. 3. One patient received only Phase II study drug. 4. Assorted other misrandomizations. 5. Oral, not written, consent obtained at Hospital 10 (Spain). 6. Patients taking ASA does outside the recommended range of 100-165 mg were considered correctly treated. 7. Incorrectly dosed patients. 8. Hospital rather than study heparin used at some centers. 9. Some cases of serious AE reported late. 10. Patient log not evaluated. 11. Patient 11106 diary was missing/
<p>Patient disposition</p>	
<p>Randomized</p>	<p>1499</p>
<p>Started treatment</p>	<p>1482</p>

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	Phase I			Phase II		
	Fragmin	Heparin	Total	Fragmin	Placebo	Total
Randomized	761	738	1499	753	746	1499
ITT	751	731	1482	562	564	1126
Per-protocol	605	451	1056	394	428	812

Treatment arm	Heparin/ Fragmin	Fragmin/ Fragmin	Heparin/ Placebo	Fragmin/ Placebo	Total	See Appendix 10.9 for definition of study arm.
	C	A	D	B		
Randomized	369	384	369	377	1499	
ITT & Safety Phase I	368	378	363	373	1482	
Per-protocol Phase I	224	299	227	306	1062	
ITT Phase II	269	293	272	292	1126	
Safety Phase II	274	293	273	293	1133	
Per-protocol Phase II	184	210	200	218	812	

Demographics

	Phase I		Phase II	
	Fragmin	Heparin	Fragmin	Placebo
Females	281	250	200	205
Males	470	481	362	359
Age				
Mean ± s.d.	64.4±10.0	64.1±10.3	63.7±10.2	64.0±10.2
Range	29-92	25-89	25-89	31-81
Weight (mean ±s.d.)	74.6±11.8	74.9±13.1	74.7±12.5	75.2±12.7
Race				
White	715	708	545	544
Black	8	5	4	4
Asian	11	9	7	6
Other	17	9	6	10
Smoking				
Never	304	292	219	238
Stopped >1 month	259	233	172	189
Smoker	188	206	171	137
Aspirin treatment (ITT)				
	Phase I		Phase II	
	Fragmin (N=738)		Fragmin (N=554)	
	Heparin (N=716)		Placebo (N=553)	
	n	%	n	%
Not taking at start	282	38.2	295	41.2
Already taking	422	57.2	314	56.7
Stopped within 72 hrs	34	4.6	25	3.5
	Fragmin (N=751)		Fragmin (N=562)	
	Heparin (N=731)		Placebo (N=564)	
	n	%	n	%
Use on admission	733	97.6	710	97.1
			542	96.4
			556	98.6

Efficacy					
Primary endpoint: Death, MI and/or recurrent angina during Phase II	Fragmin		Placebo		P value
ITT	69/562	12.3	69/561	12.3	0.956
Per-protocol	50/394	12.7	55/418	13.2	0.953
Secondary endpoints:					
1. Incidence of death, MI, recurrent angina and/or revascularization (Phase II)					
ITT	119/544	21.9	118/547	21.6	0.846
2. Incidence of death an/or MI (Phase II)					
ITT	24/562	4.3	26/558	4.7	0.766
Per-protocol	11/365	3.0	23/392	5.9	0.073
3. Incidence of death (Phase II)					
ITT	11/562	2.0	11/560	2.0	Not calculated by sponsor
Per-protocol	2/538	0.6	8/379	2.1	Not calculated by sponsor
4. Incidence of MI (Phase II)					
ITT	17/556	3.1	20/553	3.6	Not calculated by sponsor
Per-protocol	10/364	2.7	18/387	4.7	Not calculated by sponsor
5. Incidence of recurrent angina (Phase II)					
ITT	60/556	10.8	57/552	10.3	Not calculated by sponsor
Per-protocol	45/390	11.5	44/407	10.8	Not calculated by sponsor
6. Incidence of revascularization (Phase II)					
ITT	76/533	14.3	76/554	14.2	0.962
7. Time to death and/or MI (Phase II)					Log rank test p= 0.0.755
	Fragmin		Heparin		P value
1. Incidence of death, MI, and/or recurrent angina (Phase I)					
ITT	69/743	9.3	55/722	7.6	0.323
2. Incidence of death (Phase I)					
ITT	11/749	1.5	3/729	0.4	Not calculated by sponsor
Per-protocol	7/595	1.2	3/437	0.7	Not calculated by sponsor
3. Incidence of MI (Phase I)					
ITT	19/745	2.6	23/728	3.2	Not calculated by sponsor
Per-protocol	17/599	2.8	18/445	4.0	Not calculated by sponsor
4. Incidence of recurrent angina (Phase I)					
ITT	45/745	6.0	39/726	5.4	Not calculated by sponsor
Per-protocol	41/595	6.9	30/444	6.8	Not calculated by sponsor
5. Incidence of revascularization (Phase I)					
ITT	36/746	4.8	39/729	5.3	0.549
6. Incidence of death and/or MI (Phase I)					
ITT	29/746	3.9	26/727	3.6	0.794
Per-protocol	23/602	3.8	21/446	4.7	0.403
7. Incidence of death, MI, recurrent angina and/or revascularization (Phase I).					

ITT	94/740	12.7	87/721	12.1	0.876	
8. Incidence of death, MI, and/or revascularization (Phase I)						
ITT	59/742	8.0	62/725	8.6	0.578	
9. Incidence of death, MI, and/or recurrent angina, excluding MIs during the first day (Phase I)						
ITT	63/743	8.5	52/722	7.2	0.483	
10. Frequency of ischemia during the first exercise test (Day 5-8) (Phase I)						
ITT	295/511	57.7	272/472	57.6	0.903	
11. Time to death, MI, and/or recurrent angina. (Phase I)						
ITT						
12. Time to death and/or MI (Phase I)						Logrank p=0.246
ITT						logrank p=0.761
SPONSOR'S CONCLUSIONS						
1. In Phase I, the efficacy of Fragmin 120 IU/kg every 12 hrs was comparable to heparin.						
2. Prolonged therapy with Fragmin 7500 IU once daily for approximately 6 weeks did not reduce cardiac events (death, MI, and/or recurrent angina) compared to placebo.						
3. The safety in both Phase I and II was "good"						

3.2.2.3 General study outline

Patients with unstable coronary artery syndromes were treated in two phases. In Phase I (Day 1-6), patients were treated with either heparin/ASA or Fragmin/ASA. In Phase II (Day 6-45), patients were treated with either a lower dose of Fragmin in combination with ASA or placebo/ASA. (See Appendix 10.9)

3.2.2.4 Objectives

The primary objective of the FRIC trial was to determine whether Fragmin treatment, compared to placebo, decreased the incidence of death, MI and/or recurrence of angina in patients during a period 6-45 days after presentation with an unstable coronary artery syndrome. For the first 6 days of the trial, the patients were treated with either Fragmin or heparin

There were several secondary objectives.

During the initial 6 days of treatment, Fragmin and heparin were compared to see if there was an effect on the incidence of death, MI, unstable angina,

and/or revascularization. During the initial 6 days, Fragmin was also compared with heparin concerning safety endpoints (bleeding, death, allergic reaction, and thrombocytopenia) and concerning ischemia during the exercise test on Day 6.

At day 45, patients were evaluated for death, MI, or ischemia in subgroups, ischemia during an exercise test on Day 45, effect of initial treatment during the first 6 days, and safety.

At the 3-month follow-up patients were evaluated for the effect of treatment on the endpoint of death, MI, and/or revascularization.

3.2.2.5 Patient population

1499 patients were randomized, 1482 started treatment.

3.2.2.6 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 (in combination with EKG changes). The appropriateness of this definition is discussed in Section 6.

3.2.2.7 Demographics and baseline characteristics

The patients were predominantly white males. The average age was 64. The youngest enrolled patient was 25.

Gender, age, weight, race, and smoking status, and previous MI were evenly distributed between the Fragmin and control groups, with the exception of previous MI and "current smoker".

The Agency statistician¹² notes that there were -statistically significantly more current smokers in Phase II in the Fragmin group (Fragmin 30.4%/ placebo 24.3%, Fisher's exact = 0.023). There were also more Fragmin patients with a previous MI at study entry (Fragmin 29%/ Placebo 24%, Fisher's exact=0.042) and more Fragmin than heparin patients in Phase one with a previous MI (Fragmin 27% / heparin 22%, Fisher's exact = 0.046).

¹² Statisticians report p.22

3.2.2.8 Aspirin use

It appears that aspirin use on the first day of the study was similar in the Fragmin and heparin groups (Fragmin 97.6%/heparin 97.1%)(Table 24)

It also appears that aspirin use preceding enrolment and after the beginning of the study was similar in the Fragmin and placebo groups.

Table 24: ASA use at admission, ITT group Phase I and Phase II

ASA obligatory	Phase I				Phase II			
	Fragmin (N=751)		Heparin (N=731)		Fragmin (N=562)		Placebo (N=564)	
	n	%	n	%	n	%	n	%
Frequency	733	97.6	710	97.1	542	96.4	556	98.6

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Table 25: Use of ASA, prior to the start of study treatment, ITT group in Phase I and Phase II

ASA, prior to start of study treatment	Phase I				Phase II			
	Fragmin (N=738)		Heparin (N=716)		Fragmin (N=554)		Placebo (N=553)	
	n	%	n	%	n	%	n	%
No	282	38.2	295	41.2	223	40.3	227	41.0
Ongoing at Study Entry	422	57.2	396	55.3	314	56.7	305	55.2
Stopped Within 72 Hrs of Entry	34	4.6	25	3.5	17	3.1	21	3.8

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3.2.2.9 Withdrawals

3.2.2.9.1 Primary reason for withdrawal, Phase I and Phase II

The primary reasons for withdrawal are summarized in Table 26 and Table 27.

In phase I, more patients in the Fragmin group withdrew because of the need for full heparinization. More patients in the heparin group withdrew because of myocardial infarctions or "other" reasons.

Table 26: Primary reason for treatment withdrawal, ITT group Phase I

Reason for withdrawal	Fragmin (N = 751)		Heparin (N = 731)	
	n	%	n	%
Need for heparin infusion	29	3.9	19 ^a	2.6
Myocardial infarction	22	2.9	30	4.1
Thrombolytic treatment	4	0.5	5	0.7
Performed PTCA/CABG	45	6.0	48	6.6
Serious adverse event	11 ^b	1.5	13 ^c	1.8
Epidural or spinal anesthesia	0	0.0	1	0.1
Patient request	28	3.7	29	4.0
Serious intercurrent illness which in the opinion of the investigator, contraindicated continuation of treatment	4 ^d	0.5	4	0.5
Renal, or liver insufficiency	2	0.3	0	0.0
Other reasons	21 ^e	2.8	35	4.8
TOTAL	166	22.1	184	25.2

a) From s.c. injections to i.v. administration.

b) Including two patients with endpoints (Pat.no 3806, 9423), one patient who's AE was reported as non-serious and one patient in whom a breast cancer was diagnosed (Pat.no 9127, event date before Phase I).

c) Including one patient with endpoint (Pat.no 2201).

d) In some cases reported as serious adverse events.

e) Including two patients with unknown reason.

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In phase II, more Fragmin patients withdrew because of myocardial infarctions and patient request.

Table 27: Primary reason for treatment withdrawal, ITT group in Phase II

Reason for withdrawal	Fragmin (N=562)		Placebo (N=564)	
	n	%	n	%
Need for heparin infusion	25	4.4	21	3.7
Myocardial infarction	17(2) ^a	3.0	13	2.3
Thrombolytic treatment	1	0.2	3	0.5
Performed PTCA/CABG	63(3) ^a	11.2	65(1) ^a	11.5
Serious adverse event	6 ^b	1.1	8 ^c	1.4
Epidural or spinal anaesthesia	0	0.0	0	0.0
Patient request	19	3.4	8	1.4
Serious intercurrent illness which in the opinion of the Investigator, contraindicated continuation of treatment	2	0.4	5	0.9
Renal, or liver insufficiency	0	0.0	0	0.0
Other reasons	27	4.8	23	4.1
TOTAL	160	28.5	146	25.9

a) The number of patients within parenthesis are not included into the intention-to-treat analysis due to that the patients incorrectly continued treatment after MI or revascularization in Phase I.
b) Includes one patient with endpoint (Pat.no 3034).
c) Includes five patients with endpoint (Pat.no 2125, 3108, 12101, 12112, 12410), and one patient with an AE reported in Phase I (Pat.no 15001).

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3.2.2.9.2 All reasons for withdrawal, Phase I and Phase II

The sponsor only did an entire study analysis for the primary withdrawal reason. They did not present an analysis of "all reasons".

3.2.2.9.3 Withdrawal due to patient request ITT group, Phase I.

Although there were a total of at least 28 Fragmin and 29 heparin patients who withdrew because of patient request in Phase I, according to the

sponsor's summary in Table 26, only 31 of that total are accounted for in Table 28.

Table 28: Reason for withdrawal due to patients request ITT group in Phase I

TREATMENT ACC TO CDF	L11M-VALUES												L11M-VALUES		
	Developed G-wave		Haematoma		Unwilling to continue inj		Unwilling to participate in study		Unable to perform self inject		Others		Haemat-uria	TOTAL	
	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	
Heparin	1	6.3	2	12.5	4	25.0	5	31.3	3	18.8	.	.	2	6.3	16
Fragmin	5	33.3	8	50.0	.	.	2	13.3	.	.	15
TOTAL	1	3.2	2	6.5	9	29.0	13	41.9	3	9.7	2	6.5	1	3.2	31

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3.2.2.9.4 Withdrawal due to patient request in ITT group, Phase II

According to the sponsor's summary in Table 27, patient request was the primary reason for treatment withdrawal in 19 Fragmin patients and 8 placebo patients. The sponsor only accounts for reasons in 14 of the Fragmin patients and in 5 for the placebo patients.

Table 29: Reason for withdrawal due to patients request in ITT group, in Phase II

TREATMENT DURING 2ND PERIOD	L11M-VALUES										TOTAL		
	Haematoma		Bleeding		Unwilling to continue inj		Unwilling to participate in study		Unable to perform self inject			Others	
	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT		N	
Placebo	1	20.0	2	40.0	1	20.0	2	20.0	5
Fragmin	1	7.1	1	7.1	8	57.1	1	7.1	2	14.3	1	7.1	14
TOTAL	1	5.3	1	5.3	9	47.4	3	15.8	3	15.8	2	10.5	19

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3.2.2.9.5 Withdrawal due to other reasons in Phase I

In their summary in Table 27, the sponsor indicates that 21 Fragmin and 35 heparin patients had a primary reason of other to withdraw from the study.

The sponsor only accounts for 19 of the Fragmin patients and 34 of the heparin patients.

Table 30: Reason for withdrawal due to other reason in ITT group, Phase I

	L118-VALUES												L118-VALUES					TOTAL	
	Incorrectly included		Adverse event		Bleeding		NO-fall		Unable to participate in study		Unable to perform self inject		Others		Others	Planned or failed PTCA	Low cardiac risk by invest		
	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N	PERCENT	N		PERCENT
CONTRACT ACC TO CRF																			
Heparin	9	26.5	2	3.9	2	5.9	1	2.9	1	2.9	.	.	8	23.5	2	5.9	10	29.4	34
Fragmin	4	21.1	2	8.3	1	8.3	2	16.5	9	42.1	2	8.3	7	38.5	19
TOTAL	13	34.5	2	3.9	2	3.8	1	1.9	2	3.8	2	3.8	16	30.2	3	5.7	17	22.8	53

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3.2.2.10 Efficacy results

3.2.2.10.1 Primary endpoint

Fragmin did not show a superior effect over placebo. The incidence of death, MI, and/or recurrent angina at day 45 was the same in the Fragmin and placebo ITT groups (Fragmin 12.3%/ placebo 12.3%, p=0.956). Analysis of the per-protocol group was almost identical.

3.2.2.10.2 Secondary endpoints

3.2.2.10.3 Phase I

None of the endpoints was achieved in either the ITT or per-protocol groups.

The sponsor states that in phase I the efficacy of Fragmin was comparable to heparin.

In fact, for the composite endpoint of death, MI, and/or recurrent angina Fragmin was numerically worse than heparin in the ITT group (Fragmin 9.3%/ heparin 7.6%, p=0.323) and in the per-protocol group (Fragmin 9.8%/ heparin 9.5%, p=0.692).