The primary analysis for the primary endpoint was based on the intent-to-treat (ITT) patient population; that is. all randomized patients who received Fragmin 120 IU/Kg/12 hr or matching placebo during *Phase II* of the study. *A primary analysis stratified by treatment received in Phase I was also to be done*. 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.

7.4 *Protocol Amendment*

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

1 02/17/93 (before study initiation) to clarify a number of sections including instructions for anti-FXa sampling;
2 03/10/93 (after study initiation) to provide some clarifications and introduce exercise test instructions;
3 07/16/93 to make several clarifications including some parts of 'Statistics and Medical Data Management (*no specifics were given*).
4 03/07/94 to clarify the secondary objectives, the definition of MI, instructions for adverse event reporting and a few other minor issues.
5 02/07/95 extended trial to also include a one-year follow-up of death, MI and revascularization. Code break was decided to take place when the 3-month follow-up was completed. Correct treatment related to ASA, central evaluation of MI, subgroup analyses and a few other issues (*unnamed*) were defined.

7.5 *Patient Disposition & Baseline Characteristics:*

The disposition of the 1499 randomized (1482 treated) *Phase I* patients is given in Table 2.1 below.

Table 2.1/ Disposition of Randomized & Treated Patients (Data from Sponsor Table 11, Vol. 11)

Patient Group: Phase I	**Total Phase I**	**Fragmin Phase I**	**Heparin Phase I**	
Randomized: Phase I (1-6 Days)	1499 (100%)	761 (50.77%)	738 (49.23%)	
Treated With Phase I Drug (1-6 Days)	1482/(98.87%)	751 (98.69%)	731 (99.05%)	
Withdrawn from Treatment in Phase I	350 (23.62%)	166 (22.10%)[1]	184 (25.17%)[1]	
Phase II (6-40 Days): Treatment Sequence	Hepar – Frag	Frag – Frag	Hepar – Plac	Frag - Place
Entered Phase II (Total =1499)	369 (24.62%)	384 (25.56%)	369 (24.62%)	377 (25.15%)
ITT Safety Phase I (Total=1482)	368 (99.73%)[2]	378 (98.44%)[2]	363 (98.37%)[2]	373 (98.94%)[2]
Per-Protocol Phase I, Efficacy (Tot=1062)	224 (60.70%)[3]	299 (77.86%)[3]	227 (61.52%)[3]	306 (81.12%)[3]
ITT Efficacy Phase II (Total=1126)[4]	269 (72.90%)	293 (76.30%)	272 (73.71%)	292 (77.45%)
ITT Safety Phase II (Total=1133)	274 (74.46%)	293 (77.51%)	273 (75.21%)	293 (78.55%)
Per-Protocol Phase II, Efficacy (Tot=812)	184 (82.14%)	210 (70.23%)	200 (88.11%)	218 (71.24%)

1: % = (withdrawal/Treated) ×100%; 2: % = (ITT Safety/Randomized) ×100%; 3: % = (Per-Protocol/Randomized)×100%;
4: % = (Phase I/Phase II) ×100%.

Overall, about 23.6% *Phase I* and 27.2% *Phase II* patients withdrew from treatment, according to sponsor's descriptive statistic; reasons for withdrawals are summarized in Table 2.2 below. For *Phase I*, the data below indicate that, except for withdrawals

due to a need for heparin infusion, there were significantly more withdrawals in the heparin than in the Fragmin treatment group. For *Phase II*, the data indicate at least numerically more withdrawals due to performed PTCA/CABG and serious adverse events in the placebo than in the Fragmin treatment group. For withdrawals due to need for heparin infusion, MI and patient request, on the other hand, there were at least numerically more in the Fragmin than in the placebo group.

The sponsor indicated that six patients who had MI or revascularization in *Phase I*, and were entered into *Phase II* (5 Fragmin, 1 placebo) were included in the *Phase I* ITT analysis (***even though they should have been excluded***). Four (2 Fragmin, 2 heparin) *Phase I* patients who initially had no information concerning death (*3 were later known to be alive*) were excluded from all analyses involving death. The sponsor indicated that inclusion of these three patients in the analysis did not alter the results.

Table 2.2/ Reasons for Treatment Withdrawals (≥1.0%) [From Sponsor Tables 17 & 18, Vol. 11]

Phase I	Reason	Fragmin (N=751)	Heparin (N=731)	Difference [Fragmin –Heparin]
	Need for Heparin Infusion	29 (3.9%)	19 (2.6%)	1.3% (Fisher's Exact 2p= 0.046)
	MI	22 (2.9%)	30 (4.1%)	-1.2% (0.053)
	Performed PTCA/CABG	45 (6.0%)	48 (6.6%)	-0.6% (0.077)
	Patient Request	28 (3.7%)	29 (4.0%)	-0.3% (0.104)
	Others	42 (5.6%)	58 (7.9%)	-2.3% (0.017)
	Total	**166 (22.1%)**	**184 (25.2%)**	**-3.1% (0.178)**
Phase II	**Reason**	**Fragmin (N=562)**	**Heparin (N=564)**	**Difference [Fragmin –Placebo]**
	Need for Heparin Infusion	25 (4.4%)	21 (3.7%)	0.7% (Fisher's Exact 2p= 0.099)
	MI	17 (3.0%)[2]	13 (2.3%)	0.7% (0.111)
	Performed PTCA/CABG	63 (11.2%)[3]	65 (11.5%)[1]	-0.3% (0.074)
	Patient Request	19 (3.4%)	8 (1.4%)	2.0% (0.016)
	Serious Adverse Event	6 (1.1%)*	8 (1.4%)#	-0.3% (0.184)
	Others	30 (5.3%)	31 (5.5%)	-0.2% (0.104)
	Total	**160 (28.5%)**	**146 (25.9%)**	**+2.6% (0.033)**

1: One of these pts is excluded from sponsor ITT analyses; 2: Two of these pts are excluded from sponsor ITT analyses;
3: Three of these pts are excluded from sponsor ITT analyses; *: Includes **1** pt w/an endpoint; #: Includes **5** pts w/endpoints

Note that this reviewer's analyses (as per SAS data set submitted with the application) indicate significant more withdrawals than summarized in the table above (see attached Table 2.2A).

Attached Table 2.2A presents a comparative summary of patient baseline and demographic characteristics. Sponsor's analyses indicate the two treatment groups were comparable with respect to baseline and demographic characteristics, and selected risk factors.

Except for *previous MI* and current *smokers* in *Phase II*, this reviewer's analysis results for baseline characteristics/risk factors are similar to those by the sponsor. For *Phase II* patients, there were significantly more *current smokers* assigned to the Fragmin than to the placebo treatment group (30.4% Fragmin versus 24.3% placebo, Fisher's exact = 0.023), and more Fragmin than placebo patients with *previous MI* at study entry (29% Fragmin versus 24% placebo, Fisher's exact = 0.042).

Also, there were significantly more Fragmin patients than heparin patients in *Phase I* with *previous MI* at study entry (27% Fragmin versus 22% heparin, Fisher's exact = 0.046); see attached Table 2.2A.

Almost all patients were on aspirin at admission (≥ 97%), and comparable numbers of patients were on concomitant medication (coagulation, anti-anginal, and other cardiovascular medication). Significantly fewer *Phase I* Fragmin patients experienced study drug interruptions compared to heparin (7.9% vs. 19.0, Fisher's exact = <0.0001).

Note that the SAS data set submitted by the sponsor indicated 1495 (757 Fragmin and 738 heparin) Phase I ITT patients, and (752 Fragmin and 743 placebo) Phase II ITT patients.

8. SUMMARY OF EFFICACY RESULTS & REVIEWER S COMMENTS

Sponsor's primary and secondary efficacy analysis results for the primary composite endpoint (death, MI and/or recurrent angina) through Day 6 (*secondary*), Day 6 through 40 (*primary*) are summarized in Table 2.3 below. The results indicate no significant difference among the treatment groups.

Table 2.3/ Sponsor's Primary (Day 6-40) & Secondary (Day 1-6, and Day 80) Efficacy Analysis Results: Primary Composite Endpoint: ***Incidence of Death, MI and /or Recurrent Angina***

Population Treatment Group	n	%	%Diff (F-P)*; 95% CI		CMH P-value
Phase II: Fragmin (N=562)	69	12.3	0.0	(-3.9, 3.8)	0.956
Day 6-40 Placebo (N=561)#	69	12.3	-	-	-
Phase I: Fragmin (N=743)	69	9.3	1.7	(-1.2, 4.5)	0.323
Day 6-40 Heparin (N=722)	55	7.6	-	-	-
PP[1]: Fragmin (N=394)	50	12.7	-0.5	(-5.1, 4.1)	0.953
Day 6-40 Placebo (N=418)	55	13.2	-		
Phase I: Fragmin (N=605)	59	9.8	+0.2	(-3.4, 3.8)	0.692
Day 6-40 Heparin (N=452)	43	9.5	-	-	-

1: PP = Per-Protocol data set; *: Diff = (Fragmin – Placebo) incidence rates; CMH = Cochran-Mantel-Haenszel;
#: 3 placebo patients who left trial with no endpoint prior to Day 40 excluded from ITT analysis

The results for the individual components of the composite endpoints, and some key secondary endpoints: composite endpoint ***death and/or MI*** and revascularization are summarized in Table 2.4 below. *Note that the secondary composite endpoint* ***death and/or MI*** *is the primary endpoint for Study #TRN 91-115 in section I above.* As in Table 2.3 above, no significant differences among the treatment groups are indicated.

Table 2.4/ Other ITT Analysis Results by Sponsor

Endpoint	*Phase I (Day 1-6)* Heparin	Fragmin	*Phase II: Day 6-40* Placebo	Fragmin	*Phase II: Day 6 -80* Placebo	Fragmin
Death/MI	3.6%	3.9%	4.7%	4.6%[1]	5.4%	5.6%
Fragmin – Control*		**+0.3%**		**-0.1%**		**+0.2%**
Death	0.4%	1.5%	2.0%	2.3%[1]	2.2%	2.6%
Fragmin – Control*		**+1.1%[2]**		**+0.3%**		**+0.4%**
MI	3.2%	2.6%	3.6%	3.1%	4.1%	3.8%
Fragmin – Control		**-0.6%**		**-0.5%**		**-0.3%**
Recurrent Angina	5.4%	6.0%	10.3%	{10.8%}	8.8%	{9.2%}
Fragmin – Control*		**+0.6%**		**+0.5%**		**+0.4**
Revascularization	5.3%	4.8%	14.2%	14.3%	20.2%	22.1%
Fragmin – Control*		**-0.5%**		**+0.1%**		**+1.9%**

[1]: As per SAS data set (sponsor's table indicates lower rate); [2]: Significant difference (p=0.036);
*: Denote treatment difference; {}: Denotes observed rate as per SAS data set analysis results.

Analysis results for some subgroups are summarized in Tables 2.4A (attached). The subgroup results are consistent with the overall efficacy results summarized in Tables 2.3 & 2.4 above.

8.0 *Reviewer's Comments*

8.1.0 *Database For Primary Efficacy Analysis & Missing Data*

Except for minor differences, the disposition of patients (as per SAS data set) summarized in Tables 2.5 and 2.6 below is comparable to that of Table 2.1 above.

Table 2.5/Patient Disposition as Per SAS Data Set

	Phase I (Day 1-6)		**Phase II (Day 6-40)**	
	Fragmin	Heparin	Fragmin	Placebo
Randomized/Entered:	740	759	753	746
Received Test Drug	749	733	562	564
Did not Receive Test Drug	10	7	191	182

Table 2.6/Patient Disposition as Per SAS Data Set

Phase ITT	***Phase I* ITT Patients Classified as ITT *Phase II***		
	Phase II Assignment	*Phase II* ITT	Not *Phase II* ITT
Heparin (N=740)	Fragmin (n=372; 50.3%)	273 (36.89%)	99 (13.38%)
	Placebo (n=368; 49.7%)	271 (36.62%)	97 (13.11%)
Fragmin (N=759)	Fragmin (n=381;50.2%)	289 (38.08%)	92 (12.12%)
	Placebo (n=378; 49.8%)	293 (38.60%)	85 (11.20%)

Table 2.5 indicates a total of 373 *Phase I* treated patients did not received *Phase II* test drug; 182 of these were assigned to placebo (*Phase II*) while 191 were assigned to Fragmin (*Phase II*). It is not clear to this reviewer whether all 373 patients did not receive *Phase II* treatment because they had cardiac events in *Phase I*. The protocol did indicate that *Phase I* patients who had cardiac events

were to be discontinued (that is. not continue to *Phase II*). [See Table 2.7 for adjustment of observed results to account for missing evaluations/observations).

The observed incidence rates (as per *Phase II* SAS data set) summarized in Table 2.7 indicate no Fragmin advantage over placebo following six days of treatment with heparin or Fragmin. Specifically, the results indicate the following:

1. For *Phase I* patients treated with heparin, placebo *Phase II* treated patients experienced numerically fewer incidences compared to Fragmin *Phase II* treated patients (10% versus 15%).

2. For *Phase I* patients treated with Fragmin, Fragmin *Phase II* treated patients experienced numerically fewer incidences compared to placebo *Phase II* treated patients (10% versus 14%).

3. Overall, placebo *Phase II* treated patients experienced numerically fewer incidences compared to Fragmin *Phase II* treated patients (12.28% versus 12.58%).

Table 2.7/Efficacy Analysis Results as Per SAS Data Set (Day 6-40)

<table>
<tr><th>Phase I</th><th>Phase II</th><th colspan="4">Phase II Incidence Rate & Treatment effect Size</th></tr>
<tr><th>ITT</th><th>Assignment</th><th>Rate</th><th>Phase Effect Given Phase I</th><th colspan="2">Overall Treatment Effect</th></tr>
<tr><td rowspan="2">Heparin
(N=546)</td><td>Fragmin
(n=372; 50.3%)</td><td>41/277
(14.80%)</td><td rowspan="2">Fragmin – Placebo
14.48-10.41 = 4.07;
P-value = 0.690
(-1.2, 9.9)</td><td>Fragmin</td><td>Placebo</td></tr>
<tr><td>Placebo
(n=368; 49.7%)</td><td>28/269
(10.41%)</td><td>41/277
(14.80%)</td><td>28/269
(10.41%)</td></tr>
<tr><td rowspan="2">Fragmin
(N=582)</td><td>Fragmin
(n=381;50.2%)</td><td>30/289
(10.38%)</td><td rowspan="2">Fragmin – Placebo
10.38-14.00 = -3.62;
P-value = 0.189
(-8.9, 1.7)</td><td>30/289
(10.38%)</td><td>41/293
(14.00%)</td></tr>
<tr><td>Placebo
(n=378; 49.8%)</td><td>41/293
(14.00%)</td><td colspan="2">Fragmin – Placebo
12.54 -12.28 = +0.26;
P-value = 0.892</td></tr>
</table>

8.1.1 *Adjustment of Efficacy Results for Missing Data*

Factoring in the missing event rates among the 373 (191 Fragmin, 182 placebo) missing evaluations/observations, did not change the overall observed efficacy trend. That is, the observed slight placebo numerical edge over Fragmin is maintained (see Table 2.8 below).

Note that to estimate the missing rates (due to missing observations), we assumed the observed rates per treatment group (*12.54% for Fragmin and 12.28% for placebo*) on the missing evaluations. This resulted in 24 (= 191×.1254 = 23.95) addition Fragmin and 22 (= 182×.1228 = 22.35) addition placebo events for placebo. Thus the total *Phase II* events are 71+24 for Fragmin and 69+23 for placebo (see Table 2.9 below).

Table 2.8/Estimated Incidence rates, Factoring in Missing Events (as Per SAS Data Set)

	Fragmin	Placebo	Frag-Plac	P-value
Observed Events (%)	71 (71/566=12.54%)	69 (69/562=12.28%)	+0.26	0.892
Rate Applied to Missing	24 =.1254×191	23 =.1228×1182		
Total Events	95 = 71+24	92 = 69+23		
(%)	(95/757=12.55%)	(92/744=12.37%)	+0.18%	0.914
95% CI on Overall Rate	**(10.3%, 15.1%)**	**(10.1%, 15.0%)**		**(-3.2%, 3.5%)**

Note: +ve difference denotes a placebo numerical edge over Fragmin.

Note that incidence rates are consistent across the 79 centers with *Phase II* patients (results not shown). The Breslow-Day (BD) test for common odds ratios across centers for the primary time point Day 6-40 failed to reject the null hypothesis of uniform treatment effect across centers. The corresponding asymptotic BD p-values for the composite primary endpoint and secondary composite endpoint *death and/or MI* are 0.752 and 0.177 respectively. The p-value for treatment difference regarding the composite primary endpoint is consistent with the result based on the pooled data (2-sided CMH p-value = 0.851).

Similar results (regarding test of homogeneity of odds ratios) are obtained for Day 1-6 (BD p-value for common odds ratios for composite endpoint death and/or MI = 0.164). The corresponding p-value for Day 6-80 is 0.265 (BD).

9. Summary of Safety Events

The protocol specified safety objective of this study was to determine the safety of Fragmin compared with heparin (*Phase I*) and placebo (*Phase II*) regarding the incidence of bleeding complications, death, allergic reactions, and thrombocytopenia following 45 days of treatment. Table 2.9 below contains a comparative summary of some safety events in this study.

Table 2.9/Safety Events Summary (From Sponsor Table 64 Vol. 11)

Safety Variable	*Phase I* (Event Rate)			*Phase II* (Event Rate)		
	Fragmin	Heparin	Fra – Hep	Fragmin	Placebo	Fra - Pla
Major Bleed	9/744(1.2)	7/729(1.0)	+0.2%	3/552 (0.5)	1/544 (0.2)	+0.1%
Minor Bleed	23/744 (3.1)	24/729(3.3)	-0.2%	26/552(4.7)	13/544 (2.4)	+2.3%*
Death	9/749 (1.2)	4/729 (0.5)	+0.7%	4/567 (0.7)	9/566 (1.6)	-0.9%
T Cytopenia[1]	2/738 (0.3)	5/727 (0.7)	-0.4%	0/562 (0.0)	0/610 (0.0)	0.0%
A Reactions	3/747 (0.4)	6/730 (0.8)	-0.4%	4/563 (0.7)	7/562 (1.2)	-0.5%

*: Fisher's exact 2-sided p-value <0.050; Data from sponsor submitted SAS Data set;
[1]: T Cytopenia = Thrombocytopenia and A Reactions = Allergic Reactions.

For Phase I treatment, there was significant difference in any of the safety parameters between Fragmin and heparin. For Phase II treatment, however, there were significantly more minor bleedings in the Fragmin than in the placebo treatment group.

Note that the entry age to this study was 40 years or older. The pediatric implication of this drug is therefore not clear to this reviewer.

10. OVERALL CONCLUSIONS

1. The efficacy data in study 115 (FRISC) suggest a significant short-term (Day 1-6) 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. The efficacy data in this study do not indicate any significant long-term (Day 6-40) 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.

2. The efficacy data in study 128 (FRIC) do not indicate any short-term (Day 1-6) Fragmin advantage over heparin, or long-term (Day 6-40) 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.

3. 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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/S/ [redacted]
Mathematical Statistician

Concur: /S/ [redacted]
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11. ATTACHMENTS

Table 1.3A/ Patient Baseline and Demographic Characteristics *ITT Population*

Group/Risk Factor	Fragmin (n=746)	Placebo (n=760)
Age: Mean ± SD [Range]	67.8 ± 9.2 [40-88]	68.5 ± 9.2 [42-90]
Weight: Mean ± SD [Range]	76.1 ± 12.0 [47-125 Kg]	77.2 ± 12.9 [47-120 Kg]
BMI, Weight/Height [Range]	26.2 ± 3.5 [18-44 Kg/m]	26.3 ± 3.5 [18-38 Kg/m]
Male/Female (%)	63.1/36.9%	64.7/35.3%
Caucasian (%)	99.6%	99.7%
Current or Previous Smokers	**53.6%**	**52%**
History of Angina Pectoris	**91.7%**	**92.0%**
Previous MI	**29.0%**	**29.5%**
# W/Chest Pain On Arrival (%)	**450 (60.3%)**	**428 (56.3%)**
Start of Chest Pain To Study Drug	**25.6 ± 16.2 [0.5-125 Min]**	**26.2 ± 16.1 [1.0-124 Min]**

Data from sponsor Tables 25-34, Vol. 2.

Table 1.5A/ Sponsor's Subgroup ITT Analysis Results Through Day 40: Incidence of Death and/or MI

Subgroup			Fragmin		Placebo		% Difference	CMH
			Rate	%	Rate	%	Frag - Plac	P-val
Sex:		Female	16/271	5.9	27/267	10.1	-4.2	0.084
		Male	43/467	9.2	54/488	11.1	-1.9	0.382
Age (years):		≤70	34/422	8.1	37/398	9.3	-1.2	0.720
		>70	25/316	7.9	44/357	12.5	-4.4	0.060
Weight:(Kg):		≤70	14/249	5.6	26/245	10.6	-5.0	0.044
		>70	45/489	9.2	55/510	10.8	-1.6	0.469
High Risk:		Yes	11/184	6.0	27/197	13.7	-7.7	0.019
		No	48/556	8.6	54/558	9.7	-1.0	0.575
Previous MI:		Yes	18/211	8.5	39/223	13.5	-4.9	0.118
		No	41/527	7.8	51/532	9.6	-1.8	0.278
Smoking:	Smoker/Smoked		36/396	9.1	41/393	10.4	-1.3	0.663
	Never Smoked		23/342	6.7	40/362	11.0	-4.3	0.054
Inclusion Event:	Unstable. Angina		36/451	8.0	39/471	8.3	-0.3	0.951
	Non-Q-Wave MI		23/286	8.0	41/283	14.5	-6.4	0.011
# of Anti-angina Drugs:		0	16/330	4.8	26/328	7.9	-3.1	0.074
		1	21/218	9.6	23/223	10.3	-0.7	0.809
		≥2	22/190	11.6	32/204	15.7	-4.1	0.472

Data extracted from sponsor Table 76 Vol. 2;
CMH = Cochran-Mantel-Haenszel test

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Table 1.11A Incidence Rates by Center for Primary Composite Endpoints

	Clinic	Time Point	Fragmin	Placebo	Differe*
1.	Linkoping	Day 6	2/94 (2.13%)	3/95 (3.16%)	-1.03
2.	Norrköping		1/48 (2.08%)	2/46 (4.34%)	-2.28
3.	Västervik		1/46 (2.17%)	1/46 (2.17%)	+0.0
4.	Oskarshamn		0/26 (0.00%)	2/26 (7.69%)	-7.69
5.	Kalmar		1/47 (2.13%)	2/48 (4.17%)	-2.04
6.	Värnamo		1/33 (3.03%)	1/33 (3.03%)	+0.00
7.	Jönköping		0/64 (0.00%)	4/62 (6.45%)	-6.45
8.	Eksjö		1/46 (2.17%)	1/46 (2.17%)	+0.0
9.	Motala		2/18 (11.11%)	1/16 (6.25%)	+4.86
10.	Uppsala		1/69 (1.45%)	2/68 (2.94%)	-1.49
11.	Västerås		0/28 (0.00%)	1/29 (3.45%)	-3.45
12.	Köping		0/14 (0.00%)	2/15 (13.33%)	-13.33
13.	Ludvika		0/21 (0.00%)	1/24 (4.17%)	-4.17
14.	Mora		3/10 (30.00%)	1/10 (10.00%)	+20.00
15.	Falun		1/64 (1.56%)	6/64 (9.38%)	-7.82
16.	Sandviken		1/17 (5.88%)	2/18 (11.11%)	-5.29
17.	Gävle		0/15 (0.00%)	0/15 (0.00%)	+0.00
18.	Hudiksvall		0/2 (0.00%)	0/3 (0.00%)	+0.00
19.	Bollnäs		0/15 (0.00%)	0/16 (0.00%)	+0.00
20.	Avesta		0/9 (0.00%)	2/10 (20.00%)	+20.00
21.	Karlstad		0/18 (0.00%)	1/19 (5.26%)	+5.26
22.	Danderyd		0/49 (0.00%)	2/49 (4.08%)	+4.08
23.	SöS, Sthlm		1/49 (2.04%)	2/52 (3.85%)	-1.81

Note: 1. Breslow-Day (BD) Test for common odds Ratios across centers: χ^2=14.68, p = 0.743.
2. Cochran-Mantel-Haenszel (CMH) for treatment effect p = 0.002.

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Table 2.2A/Primary Reason for Patient Withdrawal (SAS Data Set)

	Phase I		Phase II	
	Heparin	Fragmin	Placebo	Fragmin
Need for Heparin	41 (6.1%)	53 (7.9%)	43 (6.4%)	51 (7.6%)
MI	43 (6.4%)	43 (6.4%)	38 (5.7%)	48 (7.5%)
Thrombolytic trt.	7 (1.0%)	6 (0.9%)	8 (1.2%)	5 (0.8%)
PTCA/CABG	113 (16.8%)	112 (16.7%)	114 (17.0%)	111 (16.5%)
AE	20 (3.0%)	18 (2.7%)	19 (2.8%)	19 (2.8%)
Patient Request	48 (6.9%)	40 (6.0%)	40 (6.0%)	46 (6.9%)
Intercurrent illness	8 (1.2%)	7 (1.0%)	10 (1.5%)	5 (0.8%)
Others	57 (8.5%0)	56 (8.4%)	52 (7.8%)	66 (9.8%)
Total Withdrawals	336 (50.07%)	335 (49.93%)	323 (48.14%)	348 (61.86%)

Table 2.3A/ Patient Baseline and Demographic Characteristics [Data from Sponsor Tables 19-25 Vol. 11]

Group/Risk Factor	*Phase I*		*Phase II*	
Group/Risk Factor	Fragmin (N=751)	Heparin (N=731)	Fragmin (N=562)	Placebo (N=564)
Age:Mean ± SD [Range]	64.4 ± 10.0 [29-92]	64.1 ± 10.3 [25-89]	63.7 ± 10.2 [25-89]	64.0 ± 10.2 [31-88]
Wt: Mean ± SD [Range]	74.6 ± 11.8 [42-118]	74.9 ± 13.1 [45-153]	74.7 ± 12.5 [44-125]	75.2 ± 12.7 [42-153]
BMI:Mean ± SD [Range]	26.5 ± 3.5 [17-42]	26.4 ± 3.8 [18-46]	26.4 ± 3.6 [19-42]	26.7 ± 3.8 [17-46]
Age ≤/>70 years (%)[1]	563/221 (71%/29%)	528/210 (72%/28%)	536/216 (71%/29%)	528/215 (71/29%)
Gender:Male/Female (%)	470/281 (63%./37%)	481/250 (66%./34%)	362/200 (64%./36%)	359/205 (64%./36%)
Race: Caucasian/Others	715/36 (95.2%/4.8%)	705/23 (96.9%/3.1%)	545/17 (97.0%/3.0%)	544/20 (96.5%/3.5%)
Previous MI	201/749 (26.8%)	163/730 (22.3%)	163/561 (22.3%)	133/563 (24.0%)
# Chest Pain on Arrival	380/751 (50.6%)	372/731 (50.9%)	286/562 (50.9%)	267/564 (47.3%)
Start Chest Pain to Drug	18.4 ± 22.9[-13-456]	17.6 ± 18.4[-94-143]	18.4 ± 25.7[-94-456]	19.2 ± 17.3 [-21-96]
Smoking: Never	304 (40%)	292 (40%)	219 (39%)	238 (42%)
Smoker/Stopped>1 month	188/259 (25%/35%)	206/233 (28%/32%)	171/172 (30%/31%)	137/189 (24%/34%)
UCAD at Entry: All*	622/745 (83.5%)	610/725 (84.1%)	486/560 (86.8%)	462/557 (82.9%)
Class I	164/745 (22.0%)	147/725 (20.3%)	127/560 (22.7%)	110/557 (19.8%)
Class II	174/745 (23.4%)	157/725 (21.7%)	122/560 (21.8%)	118/557 (21.2%)
Class III	284/745 (38.1%)	306/725 (42.2%)	237/560 (42.3%)	234/557 (42.0%)

*: Unstable angina includes modified Brunwald classes I-III; 1: From SAS data sets (unavailable from sponsor's tables)

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Table 2.4A / Sponsor's Subgroup ITT Analysis Results Through Day 6-40: Death, MI, and/or Recurrent Angina

Subgroup		*Phase I*			*Phase II*		
		Heparin	Fragmin	Frag-Hep	Placebo	Fragmin	Frag-Hep
Sex:	Male	42/359 (11.7%)	44/363 (12.1%)	**+0.5%**	41/358 (11.5%)	45/364 (12.4%)	**+0.9%**
	Female	27/187 (14.4%)	27/219 (12.4%)	**-2.0%**	28/204 (13.7%)	26/202 (12.9%)	**-0.8%**
Age (years):	>70	32/149 (21.5%)	18/155 (11.6%)	**-9.9%**	23/151 (15.2%)	27/153 (17.7%)	**+2.5%**
	≤70	37/397 (9.3%)	53/427 (12.4%)	**+3.0%**	46/411 (11.2%)	44/413 (10.7%)	**-0.6**
Weight:(Kg):	>70	39/344 (11.3%)	28/321 (8.7%)	**-2.6%**	29/216 (13.4%)	41/242 (16.9%)	**+3.5%**
	≤70	32/318 (10.1%)	35/347 (10.1%)	**0.0%**	34/224 (15.2%)	36/234 (15.4%)	**+0.2**
High Risk:	Yes	45/319 (14.1%)	42/339 (12.4%)	**-1.7%**	43/337 (12.8%)	44/321 (13.7%)	**+0.9%**
	No	24/226 (10.6%)	29/240 (12.1%)	**+1.5%**	26/224 (11.6%)	27/242 (11.2%)	**-0.4%**
Previous MI:	Yes	13/109 (11.9%)	21/148 (14.2%)	**+2.3%**	19/136 (14.0%)	15/121 (12.4%)	**-1.6%**
	No	56/437 (12.8%)	50/432 (11.6%)	**-1.2%**	50/425 (11.8%)	56/444 (12.6%)	**+0.8%**
Smoking:	Yes	12/158 (7.6%)	17/151 (11.3%)	**+3.7%**	15/136 (11.0%)	14/173 (8.1%)	**-2.9%**
	No	57/388 (14.7%)	54/431 (12.5%)	**-2.2%**	54/426 (12.7%)	57/393 (14.5%)	**+1.8%**