

Table 6 shows that disproportionately more patients were withdrawn because of "patient request" during Phase II. However, analysis of patients who were withdrawn by their own request does not show any clear pattern (Table 7). Furthermore, a significant number of patients had no comment coded.

Table 8 shows the comments that were coded for patients who were withdrawn for the reason "other" as the primary reason for withdrawal. Table 8 shows a greater number of withdrawals because of the reason "other" in the Fragmin group, compared to placebo, was caused by a combination of six categories; adverse events, development of Q-wave MI, hematoma, bleeding, Hg fall, and unwilling to continue injections (Table 8). Adverse event made up the largest group with 13 (31%) of the Fragmin patients and (2) 8.3% of the placebo patients out of all patients who were withdrawn from treatment because of "other reasons" as the primary reason for withdrawal.

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Table 7: Comment's (coded) given for withdrawal from treatment due to patient's request as primary reason. For patient group 120/IU/kg/12h

Coded withdrawal comment	Treatment			
	Fragmin		Placebo	
	Freq	%	Freq	%
Incorrectly included	1	1.2	0	0
AE	1	1.2	3	4.8
Haematoma	4	4.8	0	0
Bleeding	1	1.2	0	0
HB-fall (without other clinical symptoms)	1	1.2	0	0
Unwilling to continue injections	7	8.3	4	6.3
Unwilling to participate in study (Drop out)	2	2.4	6	9.5
Unable to performe selfinjections	6	7.1	5	7.9
Fam. member refusal	1	1.2	0	0
Other	2	2.4	1	1.6
Haematuria	1	1.2	0	0
No comment (code) given	57	67.9	44	69.8
Total	84	100.0	63	100.0

Sponsor's Table, Page 8/4/217

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Table 8: Comment's (coded) given for withdrawal from treatment due to other reasons as primary reason. (120 IU/kg/12h)

Coded withdrawal comment	Treatment			
	Fragmin		Placebo	
	Freq	%	Freq	%
Incorrectly included	8	19.0	8	33.3
Developed Q-wave	2	4.8	0	0
AE	13	31.0	2	8.3
Haematoma	3	7.1	0	0
Bleeding	4	9.5	2	8.3
HB-fall (without other clinical symptoms)	4	9.5	2	8.3
Unwilling to continue injections	1	2.4	0	0
Unwilling to participate in study (Drop out)	0	0	1	4.2
Unable to perform selfinjections	1	2.4	1	4.2
Other	3	7.1	4	16.7
Planned or failed PTCA	2	4.8	2	8.3
S.c. Heparin	0	0	2	8.3
No comment (code) given	1	2.4	0	0
Total	42	100.0	24	100.0

Sponsor's Table, Page 8/4/218

APPEARS THIS WAY ON ORIGINAL

3.2.1.11 Efficacy results

3.2.1.11.1 Primary endpoint

The sponsor's analysis showed that in the ITT group, Fragmin reduced the incidence of death and/or MI by 63% compared with placebo at day 6 with $p \leq 0.001$ using the Cochran-Mantel-Haentzel test to adjust for inter-center variability. (Fragmin 13/741 and placebo 36/757).

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Table 9: Death and/or MI by day 6 by treatment (sponsors analysis of 120 IU/kg vs. placebo)

Count Col %	FRAGMIN	PLACEBO	
ALIVE, NO MI	728	721	1449
	98.25	95.24	
DEAD/MI	13	36	49
	1.75	4.76	
	741	757	1498
Cochran-Mantel-Haenszel p=0.0013			

Table Constructed by Medical Officer

The sponsor's ITT was a twice-modified ITT. Of the 1622 patients randomized, 116 initial patients who received 150 IU/kg or placebo were dropped because of excessive bleeding.

Secondly, of the 1506 patients who were randomized to receive Fragmin 120 IU/kg or placebo (746 Fragmin/760 Placebo), only 1499 (742 Fragmin/757 Placebo) were included in the sponsors ITT. Furthermore, the sponsor's data set did not include a primary endpoint for one additional placebo patient. In other words, the sponsor's data set did not include an endpoint result for five of the patients in the Fragmin group and three in the placebo group.

Of the 1622 patients randomized for the entire study, 7 Fragmin patients, and three placebo patients do not have a primary endpoint recorded.

3.2.1.11.1.1 Analysis of ITT group with all data points available

If all available data points for the primary endpoint are analyzed, the effect of Fragmin is still statistically significant.

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Table 10: Death and/or MI by day 6 by treatment (using all available data points) for the primary endpoint

Count Col %	FRAGMIN	PLACEBO	
ALIVE, NO MI	786	771	1557
	98.00	95.19	
DEAD OR MI	16	39	55
	2.00	4.81	
	802	810	1612
P=0.0017 CMH two-tailed			

Table Constructed by Medical Officer

3.2.1.11.1.2 Worst case scenario

If the missing data points in the Fragmin group are considered to be deaths/MI, and the missing points in the placebo group are considered to be alive/no MI, then a "worst case" scenario can be calculated (Table 11).

Table 11: Death and/or MI through day six: worst case scenario for the 120 IU Fragmin group

Count Col %	FRAGM IN	PLACE BO	
Alive, no MI	728	724	14 52
	97.59	95.26	
Dead or MI	18	36	54
	2.41	4.74	
	746	760	15 06
P=0.0181 CMH two-tailed			

Table Constructed by Medical Officer

Fragmin continues to show superiority over placebo, at day 6, but the level of significance is decreased from $p=0.001$ to $p=0.0181$ using a two-tailed CMH test with clinic site as the third variable.

If all patients, both the 120 IU and 150 IU/kg groups are considered together, there are 7 Fragmin and 4 Placebo endpoints missing. If all patients are included in the worst case scenario, analysis the level of significance of the difference between Fragmin and placebo drops to $p=0.039$ using a two-tailed CMH test and to $p=0.051$ using a two-tailed Fisher's exact test (Table 12).

If the frequency of death/MI in the Fragmin and placebo groups

Table 12: Death and/or MI through day six: worst case scenario for the 120 IU and 150 IU Fragmin groups combined

Count %	Fr ag mi n	Place bo	
Alive, no MI	78 6	774	15 60
	97. 16	95.20	
Dead or MI	23	39	62
	2.8 4	4.80	
	80 9	813	16 22
P=0.0181 CMH two-tailed			

Table Constructed by Medical Officer

3.2.1.11.2 Primary endpoint components

The sponsor notes that the "63% risk reduction in the Fragmin group was mainly gained by reduction in nonfatal myocardial infarction. Fifteen (15) deaths occurred (Fragmin, 7; placebo, 8)." (Page 8/1/133)

Table 13: Primary endpoint broken down by components

	Fragmin	Placebo
Death	7/741 (0.94%)	8/754 (1.06%)
MI	10/738 (1.36%)	33/754 (4.38%)

Table Constructed by Medical Officer

3.2.1.11.3 Secondary endpoints

There was not a statistically significant reduction of death and/or MI in the Fragmin group at day 45 (40-50). Fragmin had a numeric edge in the ITT group (Fragmin 10.7%/Placebo 8.0%, $p \geq 0.073$) and in the per-protocol group (Fragmin 10.7%/Placebo 7.6%, $p \geq 0.053$).

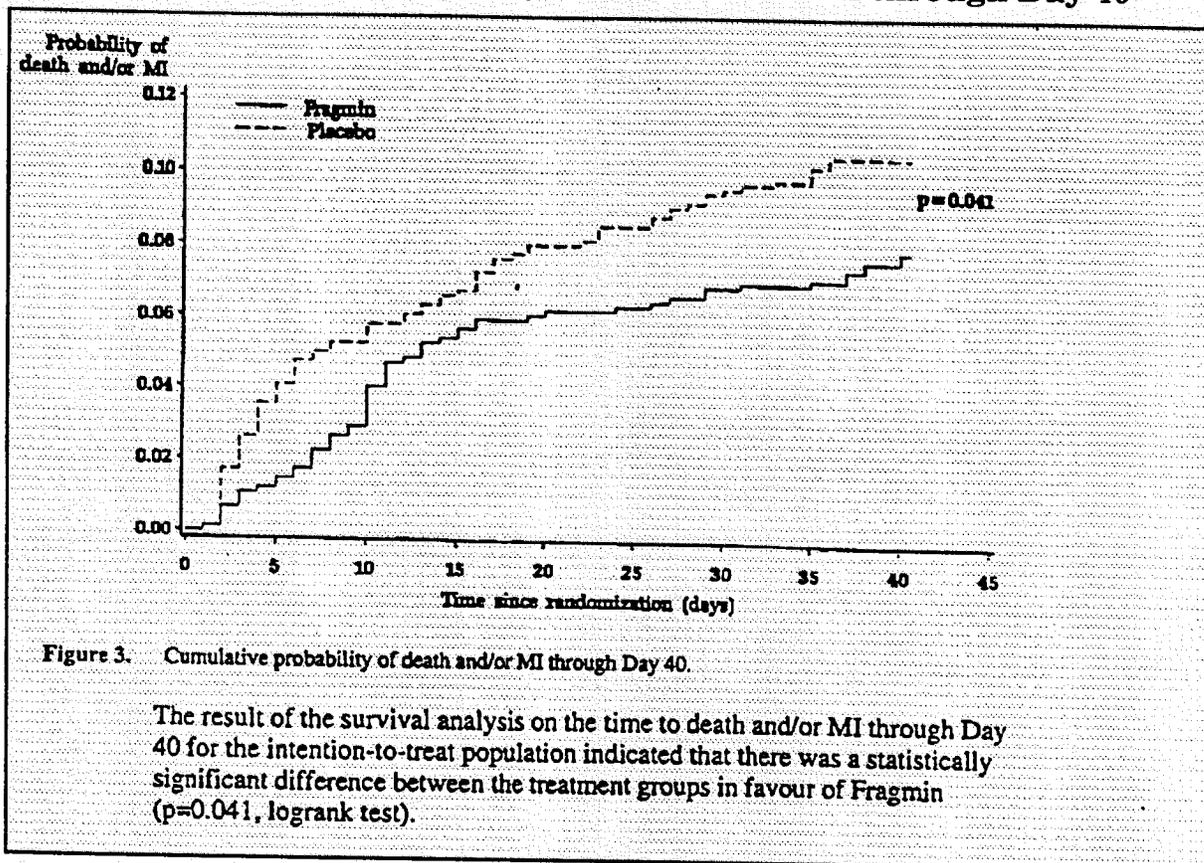
There was also not a statistically significant reduction in the incidence of death and/or MI at day 150. There was a small numeric edge in the ITT group (Fragmin 14.0%/Placebo 15.5%, $p \geq 0.407$) and in the per-protocol group (Fragmin 13.8%/Placebo 15.7%, $p \geq 0.282$).

The sponsor notes that at day 6 there was a reduction in the need of heparin or nitroglycerine in the Fragmin group as compared to placebo and that at day 45 (40-50) there was a reduction in the need for heparin, nitroglycerine, and revascularization.

The sponsor also performed a logrank analysis of the cumulative probability of death and/or M.I. through day 40 (Figure 2). This analysis does not include four silent M.I.'s that were included in the Cochran-Mantel-Haenszel analysis. The logrank analysis shows a statistical difference in death and/or M.I. through day 40, but the sponsor notes that four silent M.I.'s are not included in this analysis because the date of their M.I. was not known. It is also noted that this "contributed" to the difference in the p values between the logrank and Cochran-Mantel-Haenszel analysis.

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Figure 2: Cumulative probability of death and/or MI through Day 40



Sponsor's material, page 8/1/140.

3.2.1.11.4 Variability among centers

No center seemed to contribute disproportionately to the results of the primary endpoint. (See Appendix 10.8).

3.2.1.11.5 Aspirin

It would be a significant confounding factor if there were imbalances between the Fragmin® and placebo groups in the way aspirin was used by patients prior to the start of the study or in the way aspirin was given during the study.

As mentioned in section 3.2.1.11.5, it does not appear that there was a significant imbalance in the way aspirin was handled.

3.2.1.12 Safety summary**3.2.1.12.1 Sponsor-specified safety endpoints**

The protocol-specified safety endpoints of major bleeding, minor bleeding, thrombocytopenia and allergic reactions are summarized in Table 14 and Table 15.

There was more major bleeding in the 150 IU/kg/12h Fragmin group than in the placebo, but it does not appear to be statistically significant.

Minor bleeding was higher in both the 150 and 120 IU/kg/12h Fragmin groups as compared with placebo.

Thrombocytopenia occurred in 3 patients treated with placebo and with none of the Fragmin patients.

Allergic reactions occurred in 8 patients treated with Fragmin and 6 patients treated with placebo.

Table 14: Safety results: Phase I and II, Fragmin 150 IU/kg or placebo

Safety variable	Phase I						Phase II					
	Fragmin			Placebo			Fragmin			Placebo		
	N	n	%	N	n	%	N	n	%	N	n	%
Major bleeding	63	4	6.3	53	0	0.0	49	1	2.0	46	0	0.0
Minor bleeding	63	9	14.3	53	0	0.0	49	4	8.2	46	2	4.3
Thrombocytopenia	63	0	0.0	53	0	0.0	50	1	2.0	46	0	0.0
Allergic reaction	63	0	0.0	53	0	0.0	50	0	0.0	46	1	2.2

Sponsor's Table, Page 8/1/160

APPEARS THIS WAY ON ORIGINAL

Table 15: Safety results: Phase I and II, Fragmin 120 IU/kg

Safety variable	Phase I						Phase II					
	Fragmin			Placebo			Fragmin			Placebo		
	N	n	%	N	n	%	N	n	%	N	n	%
Major bleeding	746	6	0.8	760	4	0.5	616	2	0.3	613	1	0.2
Minor bleeding	746	60	8.0	760	2	0.3	616	39 ^a	6.3	613	17	2.8
Thrombocytopenia	743	0	0.0	755	2	0.3	613	0	0.0	610	0	0.0
Allergic reaction	746	2	0.3	760	0	0.0	617	6	1.0	614	6	1.0

a) Patient 30001 (Fragmin) had both major and minor bleeding in phase II, the minor bleeding is not included.

Sponsor's Table, Page 8/1/161

3.2.1.12.2 Deaths

The cause of death, as judged by the Endpoint Committee, is summarized in Table 16.

The Fragmin group had one fewer death than the placebo group in those patients treated with 120 IU/kg, but the Fragmin group had 8 more deaths than the placebo group in those patients treated with 150 IU/kg (p=0.02 Fisher's exact test).

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Table 16: Death, reason by endpoint committee

Table 121. Death, reason by Endpoint Committee

Cause of death	Fragmin 120 IU/kg (N=746)		Placebo for Fragmin 120 IU/kg (N=760)		Fragmin 150 IU/kg (N=63)		Placebo for Fragmin 150 IU/kg (N=53)	
	n	%	n	%	n	%	n	%
MI	21	2.8	21	2.8	6	9.5	0	0
Sudden death	10	1.3	7	0.9	1	1.6	0	0
Other heart disease	7	0.9	3	0.4	0	0	0	0
Cerebral bleeding	0	0	1	0.1	0	0	0	0
Cerebral emboli/infarction	0	0	1	0.1	0	0	0	0
Pulmonary emboli	0	0	1	0.1	1	1.6	1	1.9
Postoperative	5	0.7	9	1.2	0	0	0	0
Accident	1	0.1	0	0	1	1.6	0	0
TOTAL	44	5.9	43	5.7	9	14.3	1	1.9

Sponsor's Table, Page 8/189

When deaths are analyzed within the 150 IU/kg group (Table 17) there was a statistically significant increase in deaths in the Fragmin group (Fisher's exact test, p=0.021).

Table 17: Death by study phase: Fragmin 150 IU/kg or Placebo

EFFECT BY DRUG

Crosstabs

		DRUG		
		FRAGMIN	PLACEBO	
EFFECT	ALIVE	54 85.71	52 98.11	106
	DEAD	9 14.29	1 1.89	10
		63	53	116

Table Constructed by Medical Officer

Although the initial use of the 150 U /kg dose was stopped because of excess bleeding, the excess number of deaths does not appear to be directly related to problems associated with bleeding. In fact, the excess deaths are predominantly composed of patients who died of a myocardial infarction. (Table 18).

Table 18: Death, reason by endpoint committee

Cause of death	Fragmin 120 IU/kg (N=746)		Placebo for Fragmin 120 IU/kg (N=760)		Fragmin 150 IU/kg (N=63)		Placebo for Fragmin 150 IU/kg (N=53)	
	n	%	n	%	n	%	n	%
MI	21	2.8	21	2.8	6	9.5	0	0
Sudden death	10	1.3	7	0.9	1	1.6	0	0
Other heart disease	7	0.9	3	0.4	0	0	0	0
Cerebral bleeding	0	0	1	0.1	0	0	0	0
Cerebral emboli/infarction	0	0	1	0.1	0	0	0	0
Pulmonary emboli	0	0	1	0.1	1	1.6	1	1.9
Postoperative	5	0.7	9	1.2	0	0	0	0
Accident	1	0.1	0	0	1	1.6	0	0
TOTAL	44	5.9	43	5.7	9	14.3	1	1.9

Sponsor's Table, Page 8/1/189

It is noteworthy that the deaths occurred throughout both the study and follow-up periods (Table 19 and Table 20). The greatest number occurred in the Follow-up II period which looked at patients who had entered Phase II. Follow-up I consisted of patients who did not enter Phase II.

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Table 19: Death by study phase, Fragmin 150 IU/kg or placebo

Table 122. Death by study phase, Fragmin 150 IU/kg or Placebo

Study phase	Fragmin			Placebo		
	N	n	%	N	n	%
Phase I	63	1	1.6	53	0	0.0
Phase II	50	2	4.0	46	0	0.0
Follow-up I	10 ^a	2	20.0	7 ^a	0	0.0
Follow-up II	48 ^a	4	8.3	46 ^a	1	2.2

a) Includes all patients followed post study drug. See Section 9.2.1.2.

Sponsor's Table, Page 8/1/190

Table 20: Death by study phase, Fragmin 120 IU/kg or placebo

Table 123. Death by study phase, Fragmin 120 IU/kg or Placebo

Study phase	Fragmin			Placebo		
	N	n	%	N	n	%
Phase I	746	6	0.8	760	4	0.5
Phase II	618	3	0.5	614	4	0.7
Follow-up I	118 ^a	8	6.8	138 ^a	17	12.3
Follow-up II	609 ^a	27	4.4	609 ^a	18	3.0

a) Includes all patients followed post study drug. See Section 9.2.1.2.

Sponsor's material, page 8/1/90

3.2.1.12.3 Serious adverse events

Certain adverse events, including myocardial infarction, bleeding, and chest pain are not tabulated here because they are included in the clinical or safety endpoints.

3.2.1.12.3.1 Serious adverse events in Fragmin 120 IU/kg vs. placebo group

The serious adverse event that occurred with the highest frequency in Phase I and I was cerebrovascular disorder (Fragmin 3, placebo 5) (See Table 21).

Table 21: Incidence of serious adverse events by phase and preferred terms: Fragmin 120 IU/kg or placebo

Preferred term	Phase I				Phase II			
	Fragmin (N=746)		Placebo (N=760)		Fragmin (N=618)		Placebo (N=614)	
	n	%	n	%	n	%	n	%
Cardiac failure	2	0.3	0	0.0	1	0.2	0	0.0
Asthma	1	0.1	0	0.0	0	0.0	0	0.0
Cerebrovascular disorder	1	0.1	1	0.1	2	0.3	4	0.7
Diverticulitis	1	0.1	0	0.0	0	0.0	0	0.0
Hyperglycaemia	1	0.1	0	0.0	1	0.2	0	0.0
Neoplasm NOS	1	0.1	0	0.0	0	0.0	0	0.0
Pneumonia	1	0.1	1	0.1	1	0.2	0	0.0
Abdominal pain	0	0.0	0	0.0	1	0.2	0	0.0
Accident	0	0.0	0	0.0	1	0.2	0	0.0
Anemia	0	0.0	0	0.0	1	0.2	0	0.0
Aneurysm	0	0.0	0	0.0	0	0.0	2	0.3
Asthenia	0	0.0	0	0.0	1	0.2	0	0.0
Back pain	0	0.0	0	0.0	1	0.2	0	0.0
Cholangitis	0	0.0	1	0.1	0	0.0	0	0.0
Diabetes mellitus	0	0.0	0	0.0	1	0.2	0	0.0
Embolism pulmonary	0	0.0	0	0.0	2	0.3	0	0.0
Endocarditis	0	0.0	0	0.0	1	0.2	0	0.0
Fever	0	0.0	0	0.0	1	0.2	0	0.0

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Preferred term	Phase I				Phase II			
	Fragmin (N=746)		Placebo (N=760)		Fragmin (N=618)		Placebo (N=614)	
	n	%	n	%	n	%	n	%
Fibrillation atrial	0	0.0	0	0.0	2	0.3	1	0.2
Gastritis	0	0.0	0	0.0	2	0.3	0	0.0
Gout	0	0.0	0	0.0	0	0.0	1	0.2
Hypoglycaemia	0	0.0	0	0.0	0	0.0	1	0.2
Hypotension postural	0	0.0	0	0.0	1	0.2	0	0.0
Pulmonary oedema	0	0.0	0	0.0	0	0.0	1	0.2
Syncope	0	0.0	1	0.1	0	0.0	0	0.0
Uraemia	0	0.0	1	0.1	0	0.0	0	0.0

Sponsor's Table, Page 8/1/187-188

The serious adverse event that occurred with the highest frequency in the follow-up period was also cerebrovascular events. (Fragmin 11, placebo 11).

3.2.1.12.4 Adverse events leading to withdrawal from treatment in the Fragmin 120 IU/kg and placebo groups.

There were 54 patients who received Fragmin 120 IU/kg who were withdrawn from the study because of adverse reactions, 17 of which were considered serious. Four of those 17 were withdrawn because of major bleeding.

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Table 22

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
11033 ^a	Cerebral embolus	71	M	2	Serious
11044	Haematuria	76	M	10	Non-serious
11078	Deep venous thrombosis	72	F	5	Non-serious
11088	Haematoma of arm, face, legs	71	M	6	Non-serious
11111	Allergic reaction	67	M	9	Non-serious
11135 ^b	Pulmonary oedema	82	M	5	Serious
11142	Positive stool blood	50	F	13	Non-serious
11147	Fall in Haemoglobin	68	M	5	Non-serious
11157	Fall in Haemoglobin	73	M	7	Non-serious
11167 ^a	Pulmonary embolism	77	F	13	Serious
12025	Haematoma, abdominal	84	F	8	Non-serious
12065 ^c	Suspicion of pulmonary embolism	61	F	42	Serious
12085	Metastases on pulmonary X-ray	60	M	5	Serious
13073 ^a	Bleeding, gastrointestinal	73	F	2	Serious
14030	Elevated ALAT/ASAT	63	F	7	Non-serious
15021	Bleeding, intradermal	68	M	3	Non-serious
15026	Epistaxis and haematoma, abdominal	59	M	1	Non-serious
16009 ^a	Suspected endocarditis	76	M	34	Serious
16012	Haematoma, abdominal	62	F	28	Non-serious
16016	Confusion	85	M	6	Not available
16034	Haematoma and tenderness, abdominal	75	F	7	Non-serious
17052 ^a	Anemia	81	M	34	Serious
17065	Fall in haemoglobin	53	M	2	Non-serious
17083	Epistaxis	81	F	3	Non-serious
17103 ^{a,b}	Pulmonary oedema	69	M	10	Serious
19004	Haematoma, abdominal	55	F	5	Non-serious

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
19006	Diarrhea, fever	77	M	34	Non-serious
19016	Haematoma, abdominal	79	F	7	Non-serious
19030	Haematoma, abdominal	75	M	6	Non-serious
21009	Fall in haemoglobin	79	F	5	Non-serious
21013	Haematoma at injection site	79	F	18	Non-serious
21033	Cerebral infarction	72	F	12	Serious
21043	Fall in haemoglobin	87	M	4	Non-serious
21068	Allergic reaction	57	M	2	Non-serious
21075	Epistaxis	73	F	8	Non-serious
21102	Pain at injection site	71	M	16	Non-serious
21116	Fall in haemoglobin	56	F	6	Non-serious
22023	Confusion	78	M	4	Not available
22042	Rash on stomach	78	F	18	Non-serious
23014	Haematoma of legs	81	M	11	Non-serious
25021 ^a	Bleeding, gastrointestinal	80	F	3	Serious
26091	Fall in haemoglobin	68	F	3	Non-serious
26129	Haematoma at injection site	54	M	2	Non-serious
27006 ^a	Bleeding, gastrointestinal	64	F	2	Serious
27014	Free intraabdominal gas	65	M	2	Serious
27022	Fall in haemoglobin	78	F	3	Non-serious
28019 ^a	Cardiogenic shock after coronary angiography	69	M	13	Serious
31004	Bleeding, rectal	77	F	15	Non-serious
31008 ^a	Stroke	75	M	27	Serious
33001 ^a	Bleeding in rectus abdominis muscle	79	F	3	Serious
33006	Haematoma at injection site	76	F	3	Non-serious
33012 ^a	Bleeding from injection site	53	M	1	Non-serious
33019	Metallic taste in mouth	59	M	13	Not available