Intent-to-Treat 2	2 (6.3%)	0	2

*Patients may be counted more than once.
Reviewer's table

Belgium – Center 4 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	27	27	54
Prophylaxis period completed	26	25	51
Discontinued prematurely	1	2	3
Other reason	1 (WC)	2 (WC)	3
Efficacy Analysis			
Per-protocol	22 (81.5%)	24 (88.9%)	46 (85.2%)
Intent-to-Treat 1	22 (81.5%)	24 (88.9%)	46 (85.2%)
Intent-to-Treat 2	27 (100%)	27 (100%)	54
Excluded from PP , ITT*	5	3	8
Inadequate central reading	1	0	1
Missing	1 (pt # 5116)	0	1
No phlebography	3	3	6
Efficacy Results			
Per-protocol	3 (13.6%)	0	3
Intent-to-Treat 1	3 (13.6%)	0	3
Intent-to-Treat 2	3 (11.1%)	0	3

*Patients may be counted more than once.
Reviewer's table

Denmark – Center 1 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	20	21	41
Prophylaxis period completed	20	17	37
Discontinued prematurely	0	4	4
Adverse Event	0	1	1
Other reason	0	3 (AP, NC, WC)	3
Treated no operation	0	2	2
Efficacy Analysis			
Per-protocol	19 (95%)	15 (71.4%)	34 (82.9%)
Intent-to-Treat 1	19 (95%)	15 (71.4%)	34 (82.9%)
Intent-to-Treat 2	20	21	41
Excluded from PP and ITT*	1	6	5
Inadequate central reading	1	0	1
Missing	0	2 (pt # 9040, 9098)	2
No operation	0	2	2
No phlebography	0	4	4
Efficacy Results			
Per-protocol	1 (5.3%)	0	1
Intent-to-Treat 1	1 (5.3%)	0	1
Intent-to-Treat 2	1 (5%)	0	1

*Patients may be counted more than once.
Reviewer's table

Denmark – Center 2 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	27	25	52
Prophylaxis period completed	21	21	42
Discontinued prematurely	6	4	10
Adverse Event	1	0	1
Other reason	5 (1 AP, 2 PX, 2 WC)	4 (2 AP, 1 PX, 1 WC)	9
Treated, but no operation	3 (2 PX, 1 WC)	2 (AP)	5
Efficacy Analysis			
Per-protocol	19 (70.4%)	19 (76%)	38 (73.1%)
Intent-to-Treat 1	19 (70.4%)	19 (76%)	38 (73.1%)
Intent-to-Treat 2	27	25	54
Excluded from PP , ITT*	8	6	14
Inadequate central reading	1	2	3
No operation performed	3	2	5
No phlebography	7	4	11

Efficacy Results			
Per-protocol	0	2 (10.5%)	2
Intent-to-Treat 1	0	2 (10.5%)	2
Intent-to-Treat 2	0	2 (8%)	2

Patients may be counted more than once.
Reviewer's table

Denmark – Center 3 Results–

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	14	15	29
Prophylaxis period completed	13	13	26
Discontinued prematurely	1	2	3
Death	0	0	0
Adverse Event	0	0	0
Other reason	1 (WC)	2 (PX, WC)	3
Treated, but no operation	0	0	0
Efficacy Analysis			
Per-protocol	11 (78.6%)	12 (80%)	22 (75.9%)
Intent-to-Treat 1	11 (78.6%)	12 (80%)	23
Intent-to-Treat 2	14	15	29
Excluded from PP , ITT	3	3	6
Inadequate central reading	2	1	3
No phlebography	1	2	3
Efficacy Results			
Per-protocol	0	0	0
Intent-to-Treat 1	0	0	0
Intent-to-Treat 2	0	0	0

Patients may be counted more than once.
Reviewer's table

Denmark – Center 4 Results–

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	29	28	57
Prophylaxis period completed	23	26	49
Discontinued prematurely	6	2	8
Death	0	0	0
Adverse Event	2	1	3
Other reason	4 (2 PX, 2 WC)	1 (WC)	5
Treated, but no operation	3 (AE, 2 PX)	0	3
Efficacy Analysis			
Per-protocol	20 (69%)	22 (78.6%)	42 (89.4%)
Intent-to-Treat 1	20 (69%)	22 (78.6%)	42 (89.4%)
Intent-to-Treat 2	29	28	57
Excluded from PP , ITT*	9	6	15
Missing	1 (pt # 9132)	1 (pt # 9072)	2
No operation	3	0	3
No phlebography	8	5	13
Efficacy Results			
Per-protocol	0	0	0
Intent-to-Treat 1	0	0	0
Intent-to-Treat 2	0	0	0

Patients may be counted more than once.
Reviewer's table

France – Center 1 Results–

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	23	26	49
Prophylaxis period completed	23	26	49
Discontinued prematurely	0	0	0
Efficacy Analysis			
Per-protocol	20 (87%)	21 (80.8%)	41 (83.7%)
Intent-to-Treat 1	20 (87%)	22 (84.7%)	42
Intent-to-Treat 2	23	26	49
Excluded from PP and ITT*	3	4	7
Inadequate central reading	1	0	1

Missing	1 (pt # 7011)	4 (pt # 7008, 7010, 7017, 7114)	5
No phlebography	1	0	1
Excluded from PP	0	1	1
Phlebography performed at wrong time	0	1	1
Efficacy Results			
Per-protocol	2 (10%)	2 (9.5%)	4
Intent-to-Treat 1	2 (10%)	2 (9.1%)	4
Intent-to-Treat 2	2 (8.7%)	2 (7.7%)	4

Patients may be counted more than once.
Reviewer's table

France – Center 2 Results–

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	8	11	19
Prophylaxis period completed	8	11	19
Discontinued prematurely	0	0	0
Efficacy Analysis			
Per-protocol	7 (87.5%)	11	18 (94.7%)
Intent-to-Treat 1	7 (87.5%)	11	18 (94.7%)
Intent-to-Treat 2	8	11	19
Excluded from PP, ITT	1	0	1
Missing	1 (pt # 7026)	0	1
Efficacy Results			
Per-protocol	2 (28.6%)	1 (9.1%)	3
Intent-to-Treat 1	2 (28.6%)	1 (9.1%)	3
Intent-to-Treat 2	2 (25%)	1 (9.1%)	3

Patients may be counted more than once.
Reviewer's table

France – Center 3 Results–

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	15	16	31
Prophylaxis period completed	13	13	26
Discontinued prematurely	2	3	5
Death	0	0	0
Adverse Event	1	1	2
Other reason	1 (PX)	2 (AP, PX)	3
Treated, but no operation	1 (AE)	1 (PX)	2
Efficacy Analysis			
Per-protocol	11 (73.3%)	13 (81.3%)	24 (77.4%)
Intent-to-Treat 1	13 (86.7%)	15 (93.8%)	28 (90.3%)
Intent-to-Treat 2	15	16	
Excluded from PP and ITT*	2	3	5
No operation	1	1	2
No phlebography	2	2	4
Excluded from PP* only	2	0	2
Concomitant medication not allowed	2	0	2
Efficacy Results			
Per-protocol	1 (9.1%)	2 (15.4%)	3
Intent-to-Treat 1	1 (7.7%)	2 (13.3%)	3
Intent-to-Treat 2	1 (6.7%)	2 (12.5%)	3

Patients may be counted more than once.
Reviewer's table

France – Center 4 Results–

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	25	26	51
Prophylaxis period completed	24	25	49
Discontinued prematurely	1	1	2
Death	0	0	0
Adverse Event	0	1 (PE)	1
Other reason	1 (AP)	0	1
Treated, but no operation	0	0	0
Efficacy Analysis			

Per-protocol	7 (28%)	10 (38.5%)	17 (33.3%)
Intent-to-Treat 1	7 (28%)	11 (42.3%)	18 (35.3%)
Intent-to-Treat 2	25	26	51
Excluded from PP , ITT*	18	16	34 (66.7%)
Concomitant medication not allowed	0	1	1
Inadequate central reading	0	3	3
Missing	15 (pt # 7083, 7084, 7086, 7087, 7089, 7094, 7095, 7149, 7150, 7151, 7157, 7163, 7164, 7165, 7168)	11 (pt # 7075, 7079, 7085, 7088, 7090, 7091, 7093, 7145, 7158, 7159, 7160)	26 (51%)
No phlebography	3	2	5
Excluded from PP*	0	1	1
Concomitant medication not allowed	0	1	1
Efficacy Results			
Per-protocol	1 (14.3%)	4 (40%)	5
Intent-to-Treat 1	1 (14.3%)	4 (36.4%)	5
Intent-to-Treat 2	1 (4%)	4 (15.4%)	5

Patients may be counted more than once.
Reviewer's table

Germany – Center 1 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	66	66	132
Prophylaxis period completed	63	65	128
Discontinued prematurely	3	1	4
Adverse Event	3	1	4
Treated, but no operation	0	1 (AE)	1
Efficacy Analysis			
Per-protocol	46 (69.7%)	54 (81.1%)	100 (75.8%)
Intent-to-Treat 1	47 (71.2%)	56 (84.8%)	103 (78%)
Intent-to-Treat 2	66	66	132
Excluded from PP and ITT*	19	10	29 (22%)
Concomitant medication, not allowed	1	2	3
Inadequate central reading	5	1	6
Missing	8 (pt # 6065, 6082, 6111, 6114, 6127, 6150, 9964, 9967)	4 (pt # 6063, 6072, 6151, 9952)	12
No operation	0	1	1
No phlebography	6	4	10
Excluded from PP* only	1	2	3
Concomitant medication, not allowed	1	2	3
Efficacy Results			
Per-protocol	5 (10.9%)	2 (3.7%)	7
Intent-to-Treat 1	5 (10.6%)	2 (3.6%)	7
Intent-to-Treat 2	5 (7.6%)	2 (1.5%)	7

Patients may be counted more than once.
Reviewer's table

Germany – Center 2 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	44	44	88
Prophylaxis period completed	43	43	86
Discontinued prematurely	1	1	2
Other reason	1 (WC)	1 (WC)	2
Efficacy Analysis			
Per-protocol	34 (77.3%)	30 (68.2%)	64 (72.7%)
Intent-to-Treat 1	34 (77.3%)	31 (70.5%)	65 (73.9%)
Intent-to-Treat 2	44	44	88
Excluded from PP and ITT	10	13	23 (26.1%)
Inadequate central reading	6	10	16
No phlebography	4	3	7
Excluded from PP only	0	1	1
Concomitant medication not allowed	0	1	1

Efficacy Results			
Per-protocol	2 (5.9%)	3 (10%)	5
Intent-to-Treat 1	2 (5.9%)	3 (9.7%)	5
Intent-to-Treat 2	2 (4.5%)	3 (6.8%)	5

Patients may be counted more than once.
Reviewer's table

Italy – Center 1 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	31	32	63
Prophylaxis period completed	29	29	58
Discontinued prematurely	2	3	5
Adverse Event	2	2	4
Other reason	0	1 (PX)	1
Efficacy Analysis			
Per-protocol	19 (61.3%)	22 (68.8%)	43 (68.3%)
Intent-to-Treat 1	21 (67.8%)	24 (75%)	45 (71.4%)
Intent-to-Treat 2	31	32	63
Excluded from PP and ITT	10	8	18 (28.6%)
Inadequate central reading	2	2	4
Missing	1 (pt # 7677)	2 (pt # 7502, 7565)	3
No phlebography	7	4	11
Phlebography performed at wrong time	0	1	1
Excluded, from PP	2	2	4
No phlebography	1	0	1
Phlebography performed at the wrong time	1	2	3
Efficacy Results			
Per-protocol	2 (10.5%)	1 (4.5%)	3
Intent-to-Treat 1	2 (9.5%)	1 (4.2%)	3
Intent-to-Treat 2	2 (6.5%)	1 (3.1%)	3

* Patients may be counted more than once.
Reviewer's table

Italy – Center 2 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	34	36	70
Prophylaxis period completed	33	35	68
Discontinued prematurely	1	1	2
Adverse Event	1	1	2
Efficacy Analysis			
Per-protocol	28 (82.4%)	29 (80.6%)	57 (81.4%)
Intent-to-Treat 1	28 (82.4%)	29 (80.6%)	57 (81.4%)
Intent-to-Treat 2	34	36	70
Excluded from PP and ITT	6	7	13
Inadequate central reading	1	0	1
Missing	1 (pt # 7542)	0	1
No phlebography	4	7	11
Efficacy Results			
Per-protocol	2 (7.1%)	1 (3.4%)	3
Intent-to-Treat 1	2 (7.1%)	1 (3.4%)	3
Intent-to-Treat 2	2 (5.9%)	1 (2.8%)	3

* Patients may be counted more than once.
Reviewer's table

Italy – Center 3 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	35	35	70
Prophylaxis period completed	34	34	68
Discontinued prematurely	1	1	1
Adverse Event	1	1	1
Efficacy Analysis			
Per-protocol	30 (85.7%)	25 (71.4%)	55 (78.6%)
Intent-to-Treat 1	30 (85.7%)	25 (71.4%)	55 (78.6%)

Intent-to-Treat 2	35	35	70
Excluded from PP and ITT	5	10	15
Inadequate central reading	2	5	7
Missing	2 (pt # 7256, 7616)	0	2
No phlebography	1	5	6
Efficacy Results			
Per-protocol	4 (13.3%)	2 (8%)	6
Intent-to-Treat 1	4 (13.3%)	2 (8%)	6
Intent-to-Treat 2	4 (11.4%)	2 (5.7%)	6

* Patients may be counted more than once.
Reviewer's table

Netherlands 1 – Center 1 Results – [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	25	25	50
Prophylaxis period completed	24	23	47
Discontinued prematurely	1	2	3
Adverse Event	0	2	2
Other reason	1 (AP)	0	1
Efficacy Analysis			
Per-protocol	16 (64%)	16 (64%)	32 (64%)
Intent-to-Treat 1	17 (68%)	17 (68%)	34 (68%)
Intent-to-Treat 2	25	25	50
Excluded from PP and ITT	8	8	16 (32%)
Inadequate central reading	1	5	6
Missing	1 (pt # 8042)	0	1
No phlebography	6	3	9
Excluded from PP only	1	1	2
Concomitant medication not allowed	1	1	2
Efficacy Results			
Per-protocol	2 (12.5%)	1 (6.3%)	3
Intent-to-Treat 1	2 (11.8%)	1 (5.9%)	3
Intent-to-Treat 2	2 (8%)	1 (4%)	3

* Patients may be counted more than once.
Reviewer's table

Netherlands – Center 2 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	41	42	83
Prophylaxis period completed	40	40	80
Discontinued prematurely	1	2	3
Adverse Event	1	2	3
Efficacy Analysis			
Per-protocol	16 (39%)	16 (38.1%)	32 (38.6%)
Intent-to-Treat 1	17 (41.5%)	17 (40.5%)	34 (41%)
Intent-to-Treat 2	41	42	83
Excluded from PP and ITT*	24	25	49 (59%)
Concomitant medication, not allowed	2	0	2
Inadequate central reading	4	9	13
Missing	1 (pt # 8115)	2 (pt # 8112, 8180)	3
No phlebography	19	13	32
Phlebography performed at the wrong time	0	1	1
Excluded from PP only	1	1	2
Concomitant medication, not allowed	1	0	1
Phlebography performed at the wrong time	0	1	1
Efficacy Results			
Per-protocol	1 (6.3%)	1 (6.3%)	2
Intent-to-Treat 1	1 (5.9%)	1 (5.9%)	2
Intent-to-Treat 2	1 (2.4%)	1 (2.4%)	2

* Patients may be counted more than once.
Reviewer's table

Netherlands – Center 3 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)

Randomized	36	35	71
Prophylaxis period completed	28	31	59
Discontinued prematurely	8	4	12
Adverse Event	2	2	4
Other reason	6 (2 AP, 1 PX, 2 WC, 1 NC)	2 (WC)	8
Efficacy Analysis			
Per-protocol	12 (33.3%)	18 (51.4%)	30 (42.3%)
Intent-to-Treat 1	15 (41.7%)	19 (54.3%)	34 (47.9%)
Intent-to-Treat 2	36	35	71
Excluded from PP , ITT*	21	16	37 (52.1%)
Concomitant medication not allowed	1	0	1
Inadequate central reading	7	7	14
Missing	0	2 (pt # 8144, 8619)	2
No phlebography	14	7	21
Phlebography performed at the wrong time	0	1	1
Excluded, from PP*	3	1	4
Concomitant medication not allowed	0	1	1
Phlebography performed at the wrong time	3	1	4
Efficacy Results			
Per-protocol	1 (8.3%)	0	1
Intent-to-Treat 1	1 (6.7%)	0	1
Intent-to-Treat 2	1 (2.8%)	0	1

* Patients may be counted more than once.
Reviewer's table

Spain – Center 1 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	21	20	41
Prophylaxis period completed	19	17	36
Discontinued prematurely	2	3	5
Death	0	0	0
Adverse Event	1 (DVT)	2	3
Other reason	1 (PX)	1 (AP)	2
Efficacy Analysis			
Per-protocol	12 (57.1%)	11 (55%)	23 (56.1%)
Intent-to-Treat 1	12 (57.1%)	12 (60%)	24 (58.5%)
Intent-to-Treat 2	21	20	41
Excluded from PP , ITT*	9	8	17
Concomitant medication not allowed	0	1	1
Inadequate central reading	5	6	11
No phlebography	4	2	6
Phlebography performed at the wrong time	1	0	1
Excluded, from PP	0	1	1
Phlebography performed at the wrong time	0	1	1
Efficacy Results			
Per-protocol	0	2 (18.2%)	2
Intent-to-Treat 1	0	2 (16.7%)	2
Intent-to-Treat 2	0	2 (10%)	2

*Patients may be counted more than once.
Reviewer's table

Spain – Center 2 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	30	29	59
Prophylaxis period completed	28	24	52
Discontinued prematurely	2	5	7
Death	0	1	1
Adverse Event	2	1	3
Other reason	0	3 (PX)	3
Treated, but no operation	0	4 (3 PX, 1 AE)	4
Efficacy Analysis			
Per-protocol	22 (73.3%)	16 (55.2%)	38
Intent-to-Treat 1	23 (76.7%)	16 (55.2%)	39
Intent-to-Treat 2	30	29	59
Excluded from PP and ITT*	7	13	20

Inadequate central reading	3	2	5
Missing	2 (pt # 6629, 6661)	5 (pt # 6594, 6602, 6612, 6628, 6635)	7
No operation	0	4	4
No phlebography	2	6	8
Excluded from PP* only	1	0	1
Concomitant medication, not allowed	1	0	1
Efficacy Results			
Per-protocol	3 (14.4%)	1 (6.3%)	4
Intent-to-Treat 1	3 (13%)	1 (6.3%)	4
Intent-to-Treat 2	3 (10%)	1 (3.4%)	4

* Patients may be counted more than once.
Reviewer's table

Sweden – Center 1 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	52	53	105
Prophylaxis period completed	49	47	96
Discontinued prematurely	3	6	9
Adverse Event	0	1 (PE)	1
Other reason	3 (2 PX, 1 WC)	5 (2 AP, 2 PX, 1 WC)	8
Treated, but no operation	0	3 (2 AP, 1 AE)	3
Efficacy Analysis			
Per-protocol	45 (86.5%)	42 (79.2%)	87 (82.9%)
Intent-to-Treat 1	45 (86.5%)	42 (79.2%)	87 (82.9%)
Intent-to-Treat 2	52	53	105
Excluded from PP , ITT	7	11	18
Concomitant medication not allowed	1	0	1
Inadequate central reading	2	4	6
No operation	0	3	3
No phlebography	5	7	12
Phlebography performed at the wrong time	0	1	1
Efficacy Results			
Per-protocol	5 (11.1%)	2 (4.8%)	7
Intent-to-Treat 1	5 (11.1%)	2 (4.8%)	7
Intent-to-Treat 2	5 (11.1%)	2 (1.9%)	7

* Patients may be counted more than once.
Reviewer's table

Sweden – Center 2 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	54	53	107
Prophylaxis period completed	54	51	105
Discontinued prematurely	0	2	2
Adverse Event	0	0	0
Other reason	0	2 (PX)	2
Efficacy Analysis			
Per-protocol	42 (77.8%)	44 (83%)	86 (80.4%)
Intent-to-Treat 1	42 (77.8%)	44 (83%)	86 (80.4%)
Intent-to-Treat 2	54	53	107
Excluded from PP , ITT	12	9	21
Concomitant medication not allowed	0	1	1
Inadequate central reading	9	5	14
Missing	0	1 (pt # 9693)	1
No phlebography	3	3	6
Efficacy Results			
Per-protocol	2 (4.8%)	1 (2.3%)	3
Intent-to-Treat 1	2 (4.8%)	1 (2.3%)	3
Intent-to-Treat 2	2 (3.7%)	1 (1.9%)	3

* Patients may be counted more than once.
Reviewer's table

Sweden – Center 3 Results– [redacted]

	Enoxaparin (number	Desirudin (number of	Total (number

	of patients)	patients)	of patients)
Randomized	47	46	93
Prophylaxis period completed	42	43	85
Discontinued prematurely	5	3	8
Death	0	0	0
Adverse Event	0	0	0
Other reason	5 (4 PX, 1 WC)	3 (AP, 2 PX)	8
Treated, but no operation	3 (2 AP, 1 WC)	1 (AP)	4
Efficacy Analysis			
Per-protocol	33 (70.2%)	32 (69.6%)	65 (69.9%)
Intent-to-Treat 1	33 (70.2%)	32 (69.6%)	65 (69.9%)
Intent-to-Treat 2	47	46	93
Excluded from PP , ITT	14	14	28
Inadequate central reading	6	8	14
Missing	0	3 (pt # 9789, 9805, 9807)	3
No operation	3	1	4
No phlebography	7	3	10
Phlebography performed at wrong time	0	1	1
Efficacy Results			
Per-protocol	2 (6.1%)	0	2
Intent-to-Treat 1	2 (6.1%)	0	2
Intent-to-Treat 2	2 (4.3%)	0	2

* Patients may be counted more than once.
Reviewer's table

Sweden – Center 4 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	41	41	82
Prophylaxis period completed	38	36	74
Discontinued prematurely	3	5	8
Adverse Event	1 (DVT)	2	3
Other reason	2 (PX)	3 (PX, 2 WC)	5
Treated, but no operation	1 (PX)	0	1
Efficacy Analysis			
Per-protocol	30 (73.2%)	28 (68.3%)	58 (70.7%)
Intent-to-Treat 1	31 (75.6%)	28 (68.3%)	59 (72%)
Intent-to-Treat 2	41	41	82
Excluded from PP and ITT*	10	13	23
Inadequate central reading	2	4	6
Missing	1 (pt # 9866)	0	1
No operation	1	0	1
No phlebography	7	9	16
Phlebography performed at the wrong time	0	1	1
Excluded, from PP	1	0	1
Phlebography performed at the wrong time	1	0	1
Efficacy Results			
Per-protocol	2 (6.7%)	2 (7.1%)	4
Intent-to-Treat 1	2 (6.7%)	2 (7.1%)	4
Intent-to-Treat 2	2 (4.9%)	2 (7.1%)	4

* Patients may be counted more than once.
Reviewer's table

Switzerland – Center 1 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	27	27	54
Prophylaxis period completed	26	27	53
Discontinued prematurely	1	0	1
Adverse Event	1	0	1
Efficacy Analysis			
Per-protocol	24 (88.9%)	25 (92.6%)	49 (90.7%)
Intent-to-Treat 1	25 (92.6%)	25 (92.6%)	50 (92.6%)

Intent-to-Treat 2	27 (100%)	27 (100%)	54
Excluded from PP , ITT*	2	2	4
Inadequate central reading	2	1	3
Missing	0	1 (pt #5525)	1
Excluded, from PP*	1	0	1
Phlebography performed at the wrong time	1	0	1
Efficacy Results			
Per-protocol	2 (8.3%)	2 (8%)	4
Intent-to-Treat 1	2 (8%)	2 (8%)	4
Intent-to-Treat 2	2 (7.4%)	2 (7.4%)	4

Patients may be counted more than once.
Reviewer's table

Switzerland – Center 2 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	27	27	54
Prophylaxis period completed	26	25	52
Discontinued prematurely	1	2	3
Adverse Event	1	1	2
Other reason	0	1 (WC)	1
Efficacy Analysis			
Per-protocol	20 (74.1%)	21 (77.8%)	41 (75.9%)
Intent-to-Treat 1	21 (77.8%)	21 (77.8%)	42 (77.8%)
Intent-to-Treat 2	27 (100%)	27 (100%)	54
Excluded from PP and ITT*	6	6	12
Inadequate central reading	3	4	7
Missing	1 (pt # 5539)	0	1
No phlebography	2	2	4
Phlebography performed at the wrong time	1	0	1
Excluded from PP* only	1	0	1
Phlebography performed at the wrong time	1	0	1
Efficacy Results			
Per-protocol	1 (5%)	2 (9.5%)	3
Intent-to-Treat 1	1 (4.8%)	2 (9.5%)	3
Intent-to-Treat 2	1 (3.7%)	2 (7.4%)	3

Patients may be counted more than once.
Reviewer's table

Switzerland – Center 3 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	9	8	17
Prophylaxis period completed	7	5	12
Discontinued prematurely	2	3	5
Adverse Event	1	1	2
Other reason	1 (NC)	2 (AP)	3
Treated, but no operation	1 (AP)	0	1
Efficacy Analysis			
Per-protocol	7 (77.8%)	3 (37.5%)	10 (58.8 %)
Intent-to-Treat 1	7 (77.8%)	4 (50%)	11 (64.7%)
Intent-to-Treat 2	9 (100%)	8 (100 %)	17 (100%)
Excluded from PP and ITT*	2	4	6
No operation	0	1	1
No phlebography	2	4	6
Excluded from PP only	0	1	1
Phlebography performed at the wrong time	0	1	1
Efficacy Results			
Per-protocol	1 (14.3%)	0	1
Intent-to-Treat 1	1 (14.3%)	0	1
Intent-to-Treat 2	1 (11.1%)	0	1

* Patients may be counted more than once.
Reviewer's table

Switzerland – Center 4 Results– [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	1	2	3
Prophylaxis period completed	0	1	1
Discontinued prematurely	0	1	1
Other reason	0	1 (AP)	1
Efficacy Analysis			
Per-protocol	0 (0%)	1 (50%)	1 (33.3%)
Intent-to-Treat 1	1 (100%)	1 (50%)	2 (66.7%)
Intent-to-Treat 2	1 (100%)	2 (100%)	3
Excluded from PP and ITT*	0	1	1
Concomitant medication not allowed	0	1	1
No phlebography	0	1	1
Excluded from PP only	1	0	1
Concomitant medication not allowed	1	0	1
Efficacy Results			
Per-protocol	0	0	0
Intent-to-Treat 1	0	0	0
Intent-to-Treat 2	0	0	0

* Patients may be counted more than once.
Reviewer's table

Country and Center Analysis- RH/E28

Denmark – Center 1 Results - Soren Solgaard MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	14	15	29
Prophylaxis period completed	12	15	27
Discontinued prematurely	2	0	2 (6.9%)
Adverse Event	1	0	1
Other reason	1	0	1
Efficacy Analysis			
Per-protocol	12 (85.7%)	14 (93.3%)	26 (89.7%)
Intent-to-Treat 1	12 (85.7%)	15	27
Intent-to-Treat 2	14	15	29
Excluded from PP and ITT	2	0	2
No phlebography	2	0	2
Excluded from PP only	0	1	1
Concomitant medication not allowed	0	1	1
Efficacy Results			
Per-protocol	1 (8.3%)	0	1
Intent-to-Treat 1	1 (8.3%)	0	1
Intent-to-Treat 2	1 (7.1%)	0	1

Reviewer's table

Denmark – Center 2 Results - Carsten Torholm MD PhD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	15	17	32
Prophylaxis period completed	14	15	29
Discontinued prematurely	1	2	3
Death	0	0	0
Adverse Event	0	1	1
Other reason	1 (WC)	1 (PX)	2
Efficacy Analysis			
Per-protocol	12 (80.0%)	11 (64.7%)	23 (71.9%)
Intent-to-Treat 1	13 (86.7%)	11 (64.7%)	24 (75%)
Intent-to-Treat 2	15	17	32
Excluded from PP and ITT	2	5	7
Inadequate central reading	1	4	5
No operation	0	1	1
No phlebography	1	2	3
Excluded from PP only	1	0	1
Concomitant medication not allowed	1	0	1
Efficacy Results			
Per-protocol	3 (25%)	1 (9.1%)	4

Intent-to-Treat 1	3 (23.1%)	1 (9.1%)	4
Intent-to-Treat 2	3 (20%)	1 (5.9%)	4

Reviewer's table

Denmark – Center 3 Results - Per Willie Jorgenson MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	12	12	24 (100%)
Prophylaxis period completed	10	10	20 (83.3%)
Discontinued prematurely	2	2	4 (16.7%)
Death	0	0	0
Adverse Event	0	1	1 (4.2%)
Other reason	2 (PX, WC)	1 (WC)	3 (12.5%)
Efficacy Analysis			
Per-protocol	9 (75%)	8 (66.7%)	17 (70.8%)
Intent-to-Treat 1	9 (75%)	8 (66.7%)	17 (70.8%)
Intent-to-Treat 2	12	12	24
Excluded from PP and ITT	3	4	7
Inadequate central reading	1	2	3
No phlebography	2	2	4
Efficacy Results			
Per-protocol	2 (22.2%)	1 (12.5%)	3
Intent-to-Treat 1	2 (22.2%)	1 (12.5%)	3
Intent-to-Treat 2	2 (16.7%)	1 (8.3%)	3

Reviewer's table

Sweden – Center 1 Results - Bengt Eriksson MD PhD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	21	22	43
Prophylaxis period completed	20 (95.2%)	19 (86.4%)	39 (90.7%)
Discontinued prematurely	1 (4.8%)	3 (13.6%)	4 (9.3%)
Death	0	0	0
Adverse Event	0	0	0
Other reason	1 (PX)	3 (AP, PX, WC)	4 (9.3%)
Efficacy Analysis			
Per-protocol	19 (90.5%)	17 (77.3%)	36 (83.7%)
Intent-to-Treat 1	20 (95.2%)	18 (81.8%)	38 (88.4%)
Intent-to-Treat 2	21	22	43
Excluded from PP and ITT	1	4	5
Inadequate central reading	1	0	1
No phlebography	1	4	5
Excluded from PP only	1	1	2
Concomitant medication not allowed	1	0	1
Phlebography at wrong time	0	1	1
Efficacy Results			
Per-protocol	5 (26.3%)	2 (11.8%)	7
Intent-to-Treat 1	6 (30%)	2 (11.1%)	8
Intent-to-Treat 2	6 (28.6%)	2 (9.1%)	8

Reviewer's table

Sweden– Center 2 Results - Lennart Ahnfelt MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	28	30	58
Prophylaxis period completed	26 (92.9%)	28 (93.3%)	54 (93.1%)
Discontinued prematurely	2 (7.1%)	2 (6.7%)	4 (6.9%)
Death	0	0	0
Adverse Event	1	2	3 (5.2%)
Other reason	1 (PX)	0	1 (1.7%)
Efficacy Analysis			
Per-protocol	22 (78.6%)	24 (80%)	46 (79.3%)
Intent-to-Treat 1	22 (78.6%)	25 (83.3%)	47 (81%)
Intent-to-Treat 2	28	30	58
Excluded from PP and ITT	6	5	11
Inadequate central reading	2	2	4

No phlebography	4	3	7
Excluded from PP only	0	1	1
Phlebography at wrong time	0	1	1
Efficacy Results			
Per-protocol	6 (27.3%)	0	6
Intent-to-Treat 1	6 (27.3%)	0	6
Intent-to-Treat 2	6 (21.4%)	0	6

Reviewer's table

Sweden – Center 3 Results - Claes Rothelius MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	25	24	49
Prophylaxis period completed	21 (84%)	19 (79.2%)	40 (81.6%)
Discontinued prematurely	4 (16%)	5 (20.8%)	9 (18.4%)
Death	0	0	0
Adverse Event	4	1	5 (10.2%)
Other reason	0	4 (3 PX, WC)	4 (8.2%)
Efficacy Analysis			
Per-protocol	18 (72%)	16 (66.7%)	34 (69.2%)
Intent-to-Treat 1	19 (76%)	17 (70.8%)	36 (73.5%)
Intent-to-Treat 2	25	24	49
Excluded from PP and ITT	6	8	14
Concomitant medication not allowed	0	1	1
Inadequate central reading	0	2	2
No phlebography performed	6	5	11
Excluded from PP only	1	1	2
Concomitant medication not allowed	1	1	2
Efficacy Results			
Per-protocol	2 (11.1%)	4 (25%)	6
Intent-to-Treat 1	2 (10.5%)	4 (23.5%)	6
Intent-to-Treat 2	2 (8%)	4 (16.7%)	6

Reviewer's table

Sweden – Center 4 Results - Per-Olof Kroon MD PhD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	21	21	42
Prophylaxis period completed	18 (85.7%)	19 (90.5%)	37 (88.1%)
Discontinued prematurely	3 (14.3%)	2 (9.5%)	5 (11.9%)
Adverse Event	1	1	2 (4.8%)
Other reason	2 (PX, WC)	1 (PX)	3 (7.1%)
Efficacy Analysis			
Per-protocol	15 (71.4%)	17 (81%)	32 (76.2%)
Intent-to-Treat 1	15 (71.4%)	17 (81%)	32 (76.2%)
Intent-to-Treat 2	21	21	42
Excluded from PP and ITT	6	4	10
Inadequate central reading	0	1	1
No phlebography	6	3	9
Efficacy Results			
Per-protocol	8 (53.3%)	2 (11.8%)	10
Intent-to-Treat 1	8 (53.3%)	2 (11.8%)	10
Intent-to-Treat 2	8 (38.1%)	2 (9.5%)	10

Reviewer's table

Sweden – Center 5 Results - Sven Bjorkstrom MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	20	18	38
Prophylaxis period completed	18 (90%)	18	36 (94.7%)
Discontinued prematurely	2 (10%)	0	2 (5.3%)
Adverse Event	1	0	1 (2.6%)
Other reason	1 (PX)	0	1 (2.6%)
Efficacy Analysis			
Per-protocol	18 (90%)	12 (66.7%)	30 (78.9%)
Intent-to-Treat 1	18 (90%)	14 (77.8%)	32 (84.2%)

Intent-to-Treat 2	20	18	38
Excluded from PP and ITT	2	4	6
Inadequate central reading	0	3	3
No phlebography	2	1	3
Excluded from PP only	0	2	2
Concomitant medication not allowed	0	2	2
Efficacy Results			
Per-protocol	5 (27.7%)	0	5
Intent-to-Treat 1	5 (27.7%)	0	5
Intent-to-Treat 2	5 (20%)	0	5

Reviewer's table

Sweden – Center 6 Results - Ralph Berg MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	26	27	53
Prophylaxis period completed	23 (88.5%)	23 (85.2%)	46 (86.4%)
Discontinued prematurely	3 (11.5%)	4 (14.8%)	7 (13.2%)
Adverse Event	1	2	3 (5.7%)
Other reason	2 (AP, PX)	2 (PX)	4 (7.5%)
Efficacy Analysis			
Per-protocol	22 (84.6%)	20 (74.1%)	42 (79.2%)
Intent-to-Treat 1	22 (84.6%)	20 (74.1%)	42 (79.2%)
Intent-to-Treat 2	26	27	53
Excluded from PP and ITT	4	7	11
Inadequate central reading	1	3	4
No phlebography	3	4	7
Efficacy Results			
Per-protocol	1 (4.5%)	2 (10%)	3
Intent-to-Treat 1	1 (3.8%)	2 (10%)	3
Intent-to-Treat 2	1 (3.8%)	2 (7.4%)	3

Reviewer's table

Sweden – Center 7 Results - Julius Soreff MD PhD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	25	27	52
Prophylaxis period completed	20 (80%)	24 (88.9%)	44 (84.6%)
Discontinued prematurely	5 (20%)	3 (11.1%)	8 (15.4%)
Death	0	0	0
Adverse Event	2	1	3 (5.8%)
Other reason	3 (2 PX, WC)	2 (PX)	5 (9.6%)
Efficacy Analysis			
Per-protocol	20 (80%)	23 (85.2%)	43 (82.7%)
Intent-to-Treat 1	20 (80%)	23 (85.2%)	43 (82.7%)
Intent-to-Treat 2	25	27	52
Excluded from PP and ITT	5	4	9
Inadequate central reading	1	0	1
No operation	0	1	1
No phlebography	4	4	8
Phlebography at wrong time	1	0	1
Efficacy Results			
Per-protocol	6 (30%)	0	6
Intent-to-Treat 1	6 (30%)	0	6
Intent-to-Treat 2	6 (24%)	0	6

Reviewer's table

Sweden – Center 8 Results - Bengt Ellene MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	13	12	25
Prophylaxis period completed	11 (84.6%)	12	23 (92%)
Discontinued prematurely	2 (15.4%)	0	2 (8%)
Adverse Event	2	0	2 (8%)
Other reason	0	0	0
Efficacy Analysis			

Per-protocol	10 (76.9%)	12 (100%)	22 (88%)
Intent-to-Treat 1	10 (76.9%)	12 (100%)	22 (88%)
Intent-to-Treat 2	13	12	25
Excluded from PP and ITT	3	0	3
Inadequate central reading	1	0	1
No phlebography	2	0	2
Efficacy Results			
Per-protocol	2 (20%)	1 (8.3%)	3
Intent-to-Treat 1	2 (20%)	1 (8.3%)	3
Intent-to-Treat 2	2 (20%)	1 (8.3%)	3

Reviewer's table

Appendix 3

Safety Data for Study RH/E 23

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

BODY SYSTEM CLASSIFICATION / ADVERSE EXPERIENCE (IMM PREFERRED TERM)	Unfractionated Heparin Dose 5000 IU N = 277		CGP 39 393 Dose 10 mg N = 283		CGP 39 393 Dose 15 mg N = 277		CGP 39 393 Dose 20 mg N = 282		TOTAL N = 1119	
	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %
APPLICATION SITE DISORDERS TOTAL		32 11.6	2 0.7	25 8.8		27 9.7	1 0.4	24 8.5	3 0.3	108 9.7
INJECTION SITE MASS		30 10.8	1 0.4	25 8.8		27 9.7		24 8.5	1 0.1	106 9.5
INJECTION SITE REACTION		2 0.7					1 0.4	2 0.7	1 0.1	4 0.4
INJECTION SITE INFLAMMATION		3 1.1								3 0.3
INJECTION SITE PAIN					1 0.4			2 0.7	1 0.1	2 0.2
APPLICATION SITE REACTION			1 0.4						1 0.1	
AUTONOMIC NERVOUS SYSTEM DISORDERS TOTAL							1 0.4		1 0.1	
SWEATING INCREASED							1 0.4		1 0.1	
BODY AS A WHOLE - GENERAL DISORDERS TOTAL	41 14.8	26 9.4	43 15.2	26 9.2	46 16.6	36 13.0	39 13.8	35 12.4	169 15.1	123 11.0
FEVER	18 6.5	7 2.5	19 6.7	5 1.8	23 8.3	12 4.3	19 6.7	8 2.8	79 7.1	32 2.9
WOUND SECRETION	4 1.4	18 6.5	4 1.4	21 7.4	6 2.2	24 8.7	4 1.4	24 8.5	18 1.6	87 7.8
HYPERPYREXIA	15 5.4		17 6.0		16 5.8		15 5.3		63 5.6	
EDEMA LEGS	4 1.4	2 0.7	1 0.4	3 1.1	3 1.8	3 1.1	4 1.4	4 1.4	14 1.3	12 1.1
PAIN CHEST	3 1.1	2 0.7	4 1.4	3 1.1	1 0.4	1 0.4	1 0.4	1 0.4	9 0.8	7 0.6
ALLERGIC REACTION	1 0.4				3 1.1	1 0.4	1 0.4	1 0.4	5 0.4	2 0.2
EDEMA PERIPHERAL	3 1.1				3 1.1				6 0.5	
EDEMA		1 0.4	2 0.7				1 0.4		3 0.3	1 0.1
PAIN POSTOPERATIVE			1 0.4		1 0.4		1 0.4		3 0.3	

The given figures are: -'Total': the number of patients with any adverse experience in this category, most closely related to treatment
-the number of patients reporting at least once the adverse experience,
in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

BODY SYSTEM CLASSIFICATION / ADVERSE EXPEPERIENCE (IMM PREFERRED TERM)	Unfractionated Heparin Dose 5000 IU N = 277		CGP 39 393 Dose 10 mg N = 283		CGP 39 393 Dose 15 mg N = 277		CGP 39 393 Dose 20 mg N = 282		TOTAL N = 1119	
	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %
BODY AS A WHOLE - GENERAL DISORDERS										
WOUND PHENOMENA			1 0.4		1 0.4		1 0.4		3 0.3	
COMPLICATION OF PROCEDURE								2 0.7		2 0.2
FATIGUE	1 0.4	1 0.4							1 0.1	1 0.1
PAIN					1 0.4		1 0.4		2 0.2	
PAIN CHEST SUBSTERNAL			2 0.7						2 0.2	
PHLYCTENOSIS					1 0.4		1 0.4		2 0.2	
TRAUMA	1 0.4						1 0.4		2 0.2	
CYANOSIS	1 0.4								1 0.1	
EDEMA DEPENDENT	1 0.4								1 0.1	
FALLING DOWN NOS					1 0.4				1 0.1	
INJURY							1 0.4		1 0.1	
INTOXICATION/POISONING					1 0.4				1 0.1	
MALAISE			1 0.4						1 0.1	

The given figures are: -'Total': the number of patients with any adverse experience in this category, most closely related to treatment
-the number of patients reporting at least once the adverse experience,
in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

BODY SYSTEM CLASSIFICATION / ADVERSE EXPEPERIENCE (IMM PREFERRED TERM)	Unfractionated Heparin Dose 5000 IU N = 277		CGP 39 393 Dose 10 mg N = 283		CGP 39 393 Dose 15 mg N = 277		CGP 39 393 Dose 20 mg N = 282		TOTAL N = 1119	
	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %
CARDIOVASCULAR DISORDERS, GENERAL TOTAL	14 5.1	4 1.4	12 4.2	5 1.8	16 5.8	8 2.9	16 5.7	4 1.4	58 5.2	21 1.9
HYPOTENSION	8 2.9	4 1.4	5 1.8	3 1.1	8 2.9	6 2.2	4 1.4	2 0.7	25 2.2	15 1.3
HYPERTENSION	3 1.1		4 1.4		3 1.0	1 0.4	11 3.9		23 2.1	1 0.1
SYNCOPE	1 0.4		2 0.7	2 0.7	2 0.7		1 0.4	2 0.7	6 0.5	4 0.4
HYPOTENSION POSTURAL	1 0.4				2 0.7	1 0.4	1 0.4		4 0.4	1 0.1
CARDIAC FAILURE	1 0.4		1 0.4				1 0.4		3 0.3	

The given figures are: -'Total': the number of patients with any adverse experience in this category, most closely related to treatment
-the number of patients reporting at least once the adverse experience,
in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

BODY SYSTEM CLASSIFICATION / ADVERSE EXPEPERIENCE (IMM PREFERRED TERM)	Unfractionated Heparin Dose 5000 IU N = 277		CGP 39 393 Dose 10 mg N = 283		CGP 39 393 Dose 15 mg N = 277		CGP 39 393 Dose 20 mg N = 282		TOTAL N = 1119	
	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %
CENTRAL AND PERIPHERAL NERVOUS SYSTE TOTAL	5 1.8	3 1.1	12 4.2	1 0.4	7 2.5	4 1.4	14 5.0	4 1.4	38 3.4	12 1.1
DIZZINESS	1 0.4	2 0.7	4 1.4	1 0.4	3 1.1	4 1.4	2 0.7	3 1.1	10 0.9	10 0.9
HEADACHE	1 0.4		4 1.4		3 1.1	1 0.4	6 2.1		14 1.3	1 0.1
PARALYSIS			1 0.4		1 0.4		2 0.7		4 0.4	
PARESTHESIA	2 0.7		1 0.4						3 0.3	
DYSPHONIA	1 0.4						1 0.4		2 0.2	
HYPOESTHESIA							2 0.7		2 0.2	
MUSCLE CONTRACTIONS INVOLUNTARY					1 0.4		1 0.4		2 0.2	
NEUROPATHY			1 0.4		1 0.4				2 0.2	
PARESIS		1 0.4					1 0.4		1 0.1	1 0.1
CRANIAL INJURY NOS							1 0.4		1 0.1	
HYPOTONIA			1 0.4						1 0.1	
MIGRAINE	1 0.4								1 0.1	
NEURALGIA			1 0.4						1 0.1	
SENSORY DISTURBANCE								1 0.4		1 0.1
GASTROINTESTINAL SYSTEM DISORDERS TOTAL	44 15.9	9 3.2	46 16.3	7 2.5	45 16.2	8 2.9	43 15.2	4 1.4	178 15.9	28 2.5
NAUSEA	26 9.4	5 1.1	22 7.8	4 1.8	23 8.3	5 1.8	23 8.2	2 0.7	94 8.4	15 1.3
VOMITING	11 4.0	1 0.4	11 3.9	3 1.1	12 4.3	1 0.4	10 3.5		44 3.9	5 0.4

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(DATASET: RANDOMISED PATIENTS)

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	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %
GASTROINTESTINAL SYSTEM DISORDERS										
CONSTIPATION	8 2.9		9 3.2		8 2.9		6 2.1		31 2.8	
DYSPEPSIA	5 1.8		6 2.1		1 0.4		3 1.1		15 1.3	
PAIN ABDOMINAL	4 1.4		2 0.7		4 1.4		3 1.8		15 1.3	
DIARRHEA	3 1.1	2 0.7	4 1.4		4 1.4		1 0.4		12 1.1	2 0.2
GASTRITIS	3 1.1		3 1.1			1 0.4		1 0.4	6 0.5	2 0.2
HEMATEMESIS		1 0.4		1 0.4		2 0.7	1 0.4	1 0.4	1 0.1	5 0.4
MOUTH DRY	3 1.1				1 0.4				4 0.4	
ANOREXIA	2 0.7								2 0.2	
ESOPHAGITIS			1 0.4			1 0.4			1 0.1	1 0.1
FLATULENCE	1 0.4	1 0.4							1 0.1	1 0.1
HEMORRHOIDS					2 0.7				2 0.2	
ABDOMEN ENLARGED					1 0.4				1 0.1	
GASTROINTESTINAL DISORDER NOS			1 0.4						1 0.1	
GI HEMORRHAGE	1 0.4								1 0.1	
HEMORRHAGE RECTUM		1 0.4								1 0.1
HEMORRHOIDS THROMBOSED		1 0.4								1 0.1
HERNIA HIATAL	1 0.4								1 0.1	

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GASTROINTESTINAL SYSTEM DISORDERS										
HICCUP			1 0.4						1 0.1	
ILEUS PARALYTIC							1 0.4		1 0.1	
PEPTIC ULCER	1 0.4								1 0.1	
PRURITUS ANI							1 0.4		1 0.1	
STOMATITIS						1 0.4				1 0.1
STOMATITIS ULCERATIVE			1 0.4						1 0.1	
HEART RATE AND RHYTHM DISORDERS TOTAL	7 2.5		5 1.8	1 0.4	5 1.3	1 0.4	4 1.4	1 0.4	21 1.9	3 0.3
TACHYCARDIA	2 0.7		1 0.4	1 0.4	1 0.4		2 0.7		4 0.5	1 0.1
FIBRILLATION ATRIAL	2 0.7		1 0.4			1 0.4	2 0.7		5 0.4	1 0.1
BRADYCARDIA	2 0.7		2 0.7				1 0.4		5 0.4	
ARRHYTHMIA	1 0.4				3 1.1				4 0.4	
EXTRASYSTOLE VENTRICULAR			1 0.4						1 0.1	
EXTRASYSTOLES					1 0.4				1 0.1	
FIBRILLATION VENTRICULAR								1 0.4		1 0.1
HEMIC AND RETICULOENDOTHELIAL(RES)SY TOTAL					1 0.4				1 0.1	
HEMATOLOGICAL DISORDER					1 0.4				1 0.1	

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LABORATORY ABNORMALITY TOTAL	21 7.6	1 0.4	21 7.4		22 7.9	2 0.7	26 9.2		90 8.0	3 0.3
HYPOKALEMIA	19 6.9	1 0.4	19 6.7		22 7.9		24 8.5		84 7.5	1 0.1
GLYCOSURIA	1 0.4		1 0.4						2 0.2	
HYPERGLYCEMIA	1 0.4		1 0.4						2 0.2	
HYPERKALEMIA							1 0.4		1 0.1	
HYPOCALCEMIA						1 0.4				1 0.1
HYPOMAGNESEMIA			1 0.4						1 0.1	
LAB ABN - CLINICAL CHEMISTRY							1 0.4		1 0.1	
LIVER ENZYMES ELEVATED						1 0.4				1 0.1
METABOLIC AND NUTRITIONAL DISORDERS TOTAL	1 0.4		1 0.4		2 0.7		5 1.1	2 0.7	7 0.6	2 0.2
HYPOVOLEMIA			1 0.4					2 0.7	1 0.1	2 0.2
GOUT					1 0.4		1 0.4		2 0.2	
HYPONATREMIA					1 0.4		1 0.4		2 0.2	
GLUCOSE TOLERANCE ABNORMAL	1 0.4								1 0.1	
HYPERURICEMIA							1 0.4		1 0.1	

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MUSCULOSKELETAL SYSTEM DISORDERS TOTAL	16 5.8		15 5.3	4 1.4	21 7.6	5 1.8	11 3.9	4 1.4	63 5.6	13 1.2
PAIN MUSCULO-SKELETAL	7 2.5		8 2.8	3 1.1	8 2.9	2 0.7	3 1.1	3 1.1	26 2.3	8 0.7
JOINT DISLOCATION	2 0.7		1 0.4		6 2.2		4 1.4		13 1.2	
ARTHRALGIA	5 1.8		3 1.1		1 0.4		2 0.7		11 1.0	
ARTHROSIS			1 0.4	1 0.4	2 0.7	1 0.4			3 0.3	2 0.2
PAIN BACK					1 0.4	1 0.4	2 0.7	1 0.4	3 0.3	2 0.2
CRAMPS LEG	2 0.7				1 0.4	1 0.4			3 0.3	1 0.1
FRACTURE	1 0.4		1 0.4		1 0.4				3 0.3	
MYALGIA			1 0.4				1 0.4		2 0.2	
ARTHRITIS					1 0.4				1 0.1	
BONE DISORDER					1 0.4				1 0.1	
CRAMPS MUSCLE					1 0.4				1 0.1	
MYO ENDO PERICARDIAL & VALVE DISORDE TOTAL			6 2.1	1 0.4			1 0.4	2 0.7	7 0.6	3 0.3
ANGINA PECTORIS			4 1.4	1 0.4			1 0.4		5 0.4	1 0.1
MYOCARDIAL INFARCTION			2 0.7					1 0.4	2 0.2	1 0.1
MYOCARDIAL ISCHEMIA								1 0.4		1 0.1

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		unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %
PLATELET, BLEEDING & CLOTTING DISORD	TOTAL	22	7.9	46	16.6	24	8.5	47	16.6	21	7.6	65	23.5	21	7.4	63	22.3	88	7.9	221	19.7
HEMORRHAGE NOS		22	7.9	37	13.4	26	9.2	41	14.5	22	7.9	56	20.2	23	8.2	51	18.1	93	8.3	185	16.5
HEMATOMA		2	0.7	15	5.4	4	1.4	6	2.1	2	0.7	17	6.1	2	0.7	18	6.4	10	0.9	56	5.0
COAGULATION DISORDER								1	0.4											1	0.1
PSYCHIATRIC DISORDERS	TOTAL	24	8.7			22	7.8	4	1.4	20	7.2	3	1.1	19	6.7	2	0.7	85	7.6	9	0.8
INSOMNIA		22	7.9			17	6.0	3	1.1	15	5.4	1	0.4	15	5.3	2	0.7	69	6.2	6	0.5
CONFUSION		1	0.4			1	0.4	1	0.4	3	1.1	1	0.4	2	0.7			7	0.6	2	0.2
ANXIETY						2	0.7					1	0.4	1	0.4			3	0.3	1	0.1
HALLUCINATION						3	1.1											3	0.3		
AGITATION		1	0.4					1	0.4									1	0.1	1	0.1
DEPRESSION												1	0.4	1	0.4			1	0.1	1	0.1
NERVOUSNESS						1	0.4											1	0.1		
NEUROSIS										1	0.4							1	0.1		
PERSONALITY DISORDER										1	0.4							1	0.1		
RED BLOOD CELL DISORDERS	TOTAL	24	8.7	9	3.2	17	6.0	14	4.9	13	4.7	13	4.7	11	3.9	11	3.9	65	5.8	47	4.2
ANEMIA		24	8.7	9	3.2	17	6.0	14	4.9	13	4.7	13	4.7	11	3.9	11	3.9	65	5.8	47	4.2

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		unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %
REPRODUCTIVE DISORDERS, FEMALE	TOTAL					1	0.4	1	0.4									1	0.1	1	0.1
EDEMA GENITAL FEMALE						1	0.4											1	0.1		
VAGINAL HEMORRHAGE								1	0.4											1	0.1
RESISTANCE MECHANISM DISORDERS	TOTAL	1	0.4	2	0.7	3	1.1	6	2.1	4	1.4	5	1.8	2	0.7	11	3.9	10	0.9	24	2.1
HEALING IMPAIRED				2	0.7			5	1.8	1	0.4	5	1.8	1	0.4	11	3.9	2	0.2	23	2.1
INFECTION								1	0.4	1	0.4			1	0.4			2	0.2	1	0.1
INFLUENZA-LIKE SYMPTOMS		1	0.4							1	0.4							2	0.2		
MONILIASIS						1	0.4			1	0.4							2	0.2		
ABSCESS						1	0.4											1	0.1		
INFECTION VIRAL						1	0.4											1	0.1		
RESPIRATORY SYSTEM DISORDERS	TOTAL	10	3.6			15	5.3	3	1.1	10	3.6	4	1.4	13	4.6	1	0.4	48	4.3	8	0.7
DYSPNEA		4	1.4			3	1.1	3	1.1	4	1.4			2	0.7			13	1.2	3	0.3
COUGHING		3	1.1			4	1.4			3	1.1			5	1.8			15	1.3		
BRONCHITIS						2	0.7			2	0.7			1	0.4			5	0.4		
EPISTAXIS												4	1.4			1	0.4			5	0.4
PLEURAL EFFUSION						2	0.7			1	0.4			1	0.4			4	0.4		
BRONCHOSPASM		1	0.4			2	0.7											3	0.3		
PHARYNGITIS						1	0.4			1	0.4			1	0.4			3	0.3		

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RESPIRATORY SYSTEM DISORDERS										
ASTHMA			1 0.4				1 0.4		2 0.2	
BRADYPNEA					1 0.4		1 0.4		2 0.2	
PULMONARY INFILTRATION	1 0.4		1 0.4						2 0.2	
APNEA							1 0.4		1 0.1	
ASPIRATION			1 0.4						1 0.1	
INFECTION CHEST			1 0.4						1 0.1	
PLEURISY							1 0.4		1 0.1	
PNEUMONIA					1 0.4				1 0.1	
PNEUMONIA LOBAR							1 0.4		1 0.1	
PNEUMONITIS	1 0.4								1 0.1	
PULMONARY EDEMA							1 0.4		1 0.1	
RESPIRATORY DEPRESSION			1 0.4						1 0.1	
RESPIRATORY DISORDER					1 0.4				1 0.1	
RESPIRATORY INSUFFICIENCY							1 0.4		1 0.1	
RHINITIS	1 0.4								1 0.1	

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SKIN AND APPENDAGES DISORDERS TOTAL	11 4.0	8 2.9	6 2.1	11 3.9	8 2.9	7 2.5	3 1.1	15 5.3	28 2.5	41 3.7
PUPPURA		7 2.5		10 3.5	2 0.7	3 1.1		12 4.3	2 0.2	32 2.9
BULLOUS ERUPTION	5 1.8		2 0.7		2 0.7		5 1.8		14 1.3	
RASH	2 0.7		1 0.4		2 0.7	3 1.1	1 0.4		6 0.5	3 0.3
FLUSHING	2 0.7	1 0.4					1 0.4		3 0.3	1 0.1
RASH ERYTHEMATOUS	2 0.7		1 0.4				1 0.4		4 0.4	
PRURITUS				1 0.4	1 0.4	1 0.4			1 0.1	2 0.2
URTICARIA			1 0.4		1 0.4				2 0.2	
DERMATITIS								1 0.4		1 0.1
DERMATITIS CONTACT			1 0.4						1 0.1	
ECZEMA			1 0.4						1 0.1	
HOT FLUSHES								1 0.4		1 0.1
LIP DISORDER					1 0.4				1 0.1	
RASH MACULOPAPULAR								1 0.4		1 0.1
RASH PUSTULAR	1 0.4								1 0.1	
SKIN DISORDER					1 0.4				1 0.1	
SKIN DRY			1 0.4						1 0.1	
SKIN ULCERATION			1 0.4						1 0.1	

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SPECIAL SENSES OTHER, DISORDERS	TOTAL															1	0.4			1	0.1
TASTE PERVERSION																1	0.4			1	0.1
URINARY SYSTEM DISORDERS	TOTAL	42	15.2	2	0.7	33	11.7			30	10.7	3	1.1	26	9.2	4	1.4	139	12.4	9	0.8
URINARY RETENTION		33	11.9			24	8.5			24	8.7	1	0.4	21	7.4	1	0.4	102	9.1	2	0.2
URINARY TRACT INFECTION		6	2.2	1	0.4	5	1.8			3	1.1			1	0.4			15	1.3	1	0.1
HEMATURIA		1	0.4	1	0.4					2	0.7	3	1.1	1	0.4	4	1.4	4	0.4	8	0.7
CYSTITIS		2	0.7			2	0.7			1	0.4			3	1.1			8	0.7		
DYSURIA		2	0.7							2	0.7			1	0.4			5	0.4		
OLIGURIA						2	0.7			3	1.1							5	0.4		
MICTURITION DISORDER		1	0.4			1	0.4							1	0.4			3	0.3		
ANURIA										1	0.4			1	0.4			2	0.2		
PROCEDURE GENITO-URINARY										1	0.4			1	0.4			2	0.2		
BLADDER DISORDER														1	0.4			1	0.1		
RENAL FUNCTION ABNORMAL										1	0.4							1	0.1		
STRANGURY										1	0.4							1	0.1		
URETHRAL DISORDER										1	0.4							1	0.1		

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SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: *RANDOMISED PATIENTS*)

CENTER:ALL

BODY SYSTEM CLASSIFICATION / ADVERSE EXPEPERIENCE (IMM PREFERRED TERM)		Unfractionated Heparin Dose 5000 IU N = 277				CCP 39 393 Dose 10 mg N = 283				Dose 15 mg N = 277				Dose 20 mg N = 282				TOTAL N = 1119			
		unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %
VASCULAR (EXTRACARDIAC) DISORDERS	TOTAL	14	5.1	35	12.6	10	3.5	16	5.7	12	4.3	12	4.3	4	1.4	14	5.0	40	3.6	77	6.9
THROMBOPHLEBITIS DEEP		12	4.3	29	10.5	9	3.2	12	4.2	11	4.0	8	2.9	3	1.1	10	3.5	35	3.1	59	5.3
THROMBOPHLEBITIS				2	0.7			2	0.7			1	0.4			2	0.7			7	0.6
EMBOLISM PULMONARY		1	0.4	3	1.1	1	0.4							1	0.4			3	0.3	3	0.3
THROMBOPHLEBITIS SUPERFICIAL								1	0.4			2	0.7			1	0.4			4	0.4
THROMBOSIS				1	0.4			1	0.4							1	0.4			3	0.3
CEREBROVASCULAR DISORDER										1	0.4	1	0.4					1	0.1	1	0.1
PAIN VEIN		1	0.4													1	0.4	1	0.1	1	0.1
VISION DISORDERS	TOTAL									1	0.4	1	0.4	1	0.4			2	0.2	1	0.1
CONJUNCTIVITIS										1	0.4							1	0.1		
DIPLOPIA														1	0.4			1	0.1		
VISION ABNORMAL												1	0.4							1	0.1
WHITE CELL SYSTEM DISORDERS	TOTAL									1	0.4							1	0.1		
LEUKOCYTOSIS										1	0.4							1	0.1		

The given figures are: -'Total': the number of patients with any adverse experience in this category, most closly related to treatment
-the number of patients reporting at least once the adverse experience,
in percent of the total number of patients analysed for safety

Sponsor's tables volume 1.70 p.8-23-291-304

Safety Data for Study RH/E 25

CIBA: PROTOCOL RH/E25 — C O N F I D E N T I A L — CGP 39 595 (dmairudin)

TABLE 9.1.2:

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)		unrelated n	%	related n	%	unrelated n	%	related n	%	unrelated n	%	related n	%
APPLICATION SITE DISORDERS	TOTAL	2	0.19	7	0.68	4	0.38	25	2.40	6	0.29	32	1.54
INJECTION SITE MASS				7	0.68	3	0.29	25	2.40	3	0.14	32	1.54
INJECTION SITE PAIN		1	0.10			1	0.10			2	0.10		
INJECTION SITE REACTION		1	0.10							1	0.05		
BODY AS A WHOLE - GENERAL DISORDERS	TOTAL	179	17.28	49	4.73	202	19.37	47	4.51	381	18.33	96	4.62
WOUND SECRETION		48	4.63	32	3.09	62	5.94	28	2.68	110	5.29	60	2.89
FEVER		54	5.21			64	6.14	5	0.48	118	5.68	5	0.24
EDEMA LEGS		27	2.61	9	0.87	29	2.78	13	1.25	56	2.69	22	1.06
HYPERPYREXIA		31	2.99			34	3.26			65	3.13		
PAIN		25	2.41	3	0.29	19	1.82	2	0.19	44	2.12	5	0.24
PAIN CHEST		4	0.39	2	0.19	12	1.15			16	0.77	2	0.10
WOUND PHENOMENA		5	0.48	1	0.10	5	0.48	1	0.10	10	0.48	2	0.10
EDEMA PERIPHERAL		6	0.58	1	0.10	3	0.29			9	0.43	1	0.05
WOUND DEHISCENCE		4	0.39	1	0.10	4	0.38	1	0.10	8	0.38	2	0.10
ALLERGY		5	0.48			4	0.38			9	0.43		
COMPLICATION OF PROCEDURE		5	0.48			2	0.19			7	0.34		
MALAISE		2	0.19					1	0.10	2	0.10	1	0.05

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

	enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS	N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)	unrelated n	%	related n	%	unrelated n	%	related n	%	unrelated n	%	related n	%
BODY AS A WHOLE - GENERAL DISORDERS ALLERGIC REACTION			1	0.10	1	0.10			1	0.05	1	0.05
PALLOR	2	0.19							2	0.10		
PROSTHESIS DISLOCATION	1	0.10			1	0.10			2	0.10		
ASTHENIA							1	0.10			1	0.05
CYANOSIS	1	0.10							1	0.05		
EDEMA					1	0.10			1	0.05		
EDEMA GENERALIZED	1	0.10							1	0.05		
EYELID EDEMA	1	0.10							1	0.05		
INFLUENZA LIKE SYMPTOMS	1	0.10							1	0.05		
INJURY					1	0.10			1	0.05		
MALFUNCTION OF PROSTHESES AND HOMOGRAFTS	1	0.10							1	0.05		
PAIN CHEST PRECORDIAL	1	0.10							1	0.05		
PAIN CHEST SUBSTERNAL	1	0.10							1	0.05		
PERI-PROCEDURAL MEDICATION					1	0.10			1	0.05		
PHLYCTENOSIS					1	0.10			1	0.05		
RIGORS	1	0.10							1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience,

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				TOTAL			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
CARDIOVASCULAR DISORDERS, GENERAL	TOTAL	108	10.42	4	0.39	120	11.51	10	0.96	228	10.97	14	0.67
HYPOTENSION		62	5.98	3	0.29	77	7.38	9	0.86	139	6.69	12	0.58
HYPERTENSION		34	5.28	1	0.10	31	2.97	1	0.10	65	3.13	2	0.10
SYNCOPE		7	0.68			9	0.86			16	0.77		
CIRCULATORY FAILURE		6	0.58			1	0.10			7	0.34		
CARDIAC FAILURE		1	0.10			4	0.38			5	0.24		
HYPOTENSION POSTURAL		2	0.19			2	0.19			4	0.19		
PULMONARY CONGESTION		2	0.19			1	0.10			3	0.14		
BLOOD PRESSURE FLUCTUATION		1	0.10							1	0.05		
HYPERTENSION AGGRAVATED		1	0.10							1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				TOTAL			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
CENTRAL, AUTONOMIC AND PERIPHERAL NERVOUS SYSTEM DISORDERS	TOTAL	52	5.02	4	0.39	49	4.70	6	0.58	101	4.86	10	0.48
HEADACHE		32	3.09			21	2.01	2	0.19	53	2.55	2	0.10
DIZZINESS		4	0.39	3	0.29	8	0.77	2	0.19	12	0.58	5	0.24
HYPOTONIA		4	0.39			7	0.67			11	0.53		
PARESIS		3	0.29			4	0.38			7	0.34		
PARESTHESIA		2	0.19			1	0.10	2	0.19	3	0.14	2	0.10
CONVULSIONS		2	0.19			1	0.10			3	0.14		
NEUROLOGIC DISORDER NOS		1	0.10			2	0.19			3	0.14		
HYPERKINESIA		1	0.10			1	0.10			2	0.10		
HYPOESTHESIA				1	0.10			1	0.10			2	0.10
NEURALGIA		1	0.10			1	0.10			2	0.10		
NEUROPATHY		1	0.10			1	0.10			2	0.10		
TREMOR						2	0.19			2	0.10		
CEREBROSPINAL FLUID ABNORMAL		1	0.10							1	0.05		
DYSPHONIA		1	0.10							1	0.05		
MIGRAINE		1	0.10							1	0.05		
GASTROINTESTINAL SYSTEM DISORDERS	TOTAL	235	22.68	17	1.64	245	23.49	18	1.73	480	23.09	35	1.68

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

	enoxaparin Dose 40 mg				CDP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS	N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
GASTROINTESTINAL SYSTEM DISORDERS NAUSEA	118	10.62	10	0.97	129	12.37	12	1.15	239	11.50	22	1.06
VOMITING	71	6.85	5	0.48	70	6.71	3	0.29	141	6.78	8	0.38
CONSTIPATION	64	6.18			66	6.33	1	0.10	130	6.25	1	0.05
DIARRHEA	23	2.22			24	2.30	2	0.19	47	2.26	2	0.10
PAIN ABDOMINAL	9	0.87			10	0.96			19	0.91		
DYSPEPSIA	8	0.77	1	0.10	6	0.58	1	0.10	14	0.67	2	0.10
HEMATEMESIS	1	0.10	2	0.19			2	0.19	1	0.05	4	0.19
GASTRITIS	3	0.29			1	0.10			4	0.19		
FLATULENCE	1	0.10			2	0.19			3	0.14		
ANOREXIA					2	0.19			2	0.10		
GASTROINTESTINAL DISORDER NOS	1	0.10			1	0.10			2	0.10		
ABDOMEN ENLARGED					1	0.10			1	0.05		
ANUS DISORDER					1	0.10			1	0.05		
DUODENAL ULCER							1	0.10			1	0.05
EDEMA ORAL					1	0.10			1	0.05		
ENTERITIS	1	0.10							1	0.05		
ENTEROCOLITIS	1	0.10							1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

	enoxaparin Dose 40 mg				CDP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS	N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
GASTROINTESTINAL SYSTEM DISORDERS ESOPHAGITIS	1	0.10							1	0.05		
FECAL INCONTINENCE					1	0.10			1	0.05		
GASTRIC ULCER	1	0.10							1	0.05		
GASTRIC ULCER PERFORATED					1	0.10			1	0.05		
GINGIVAL BLEEDING			1	0.10							1	0.05
GLOSSITIS	1	0.10							1	0.05		
HEMORRHOIDS					1	0.10			1	0.05		
ILEUS PARALYTIC	1	0.10							1	0.05		
INTESTINAL OBSTRUCTION					1	0.10			1	0.05		
MELENA					1	0.10			1	0.05		
ORAL PAIN	1	0.10							1	0.05		
PEPTIC ULCER HEMORRHAGIC					1	0.10			1	0.05		
REFLUX DUODENO-GASTRIC	1	0.10							1	0.05		
STOMATITIS					1	0.10			1	0.05		
TONGUE DISCOLORATION					1	0.10			1	0.05		
TONGUE DYSESTHESIA	1	0.10							1	0.05		
TOOTH ACHE					1	0.10			1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IMM PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
HEARING AND VESTIBULAR DISORDERS	TOTAL	4	0.39			5	0.48			9	0.43		
VERTIGO		3	0.29			5	0.48			8	0.38		
EAR ACHE		1	0.10							1	0.05		
HEART RATE AND RHYTHM DISORDERS	TOTAL	38	3.67	1	0.10	35	3.36	1	0.10	73	3.51	2	0.10
BRADYCARDIA		16	1.54			17	1.63			33	1.59		
FIBRILLATION ATRIAL		6	0.58	1	0.10	8	0.77	1	0.10	14	0.67	2	0.10
TACHYCARDIA		8	0.77			5	0.48			13	0.63		
ARRHYTHMIA		3	0.29			5	0.48			8	0.38		
EXTRASYSTOLE VENTRICULAR		1	0.10			1	0.10			2	0.10		
PALPITATION		2	0.19							2	0.10		
ARRHYTHMIA ATRIAL		1	0.10							1	0.05		
AV BLOCK		1	0.10							1	0.05		
BUNDLE BRANCH BLOCK						1	0.10			1	0.05		
CARDIAC ARREST						1	0.10			1	0.05		
FIBRILLATION CARDIAC		1	0.10							1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IMM PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
INFECTIONS AND INFESTATIONS	TOTAL	10	0.97			14	1.34	1	0.10	24	1.15	1	0.05
INFECTION		5	0.48			11	1.05	1	0.10	16	0.77	1	0.05
INFECTION VIRAL		3	0.29			2	0.19			5	0.24		
HERPES SIMPLEX						1	0.10			1	0.05		
MONILIASIS		1	0.10							1	0.05		
VAGINAL INFECTION NOS		1	0.10							1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IMM PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
LABORATORY ABNORMALITY	TOTAL	61	5.89	5	0.48	44	4.22	7	0.67	105	5.05	12	0.58
HYPOKALEMIA		48	4.63	1	0.10	33	3.16	1	0.10	81	3.90	2	0.10
LAB ABN - CLINICAL CHEMISTRY		5	0.48			2	0.19	2	0.19	7	0.34	2	0.10
LIVER ENZYMES ELEVATED		3	0.29	3	0.29	1	0.10	1	0.10	4	0.19	4	0.19
HYPOPROTEINEMIA		4	0.39			3	0.29			7	0.34		
GAMMA-GT INCREASED		2	0.19			2	0.19			4	0.19		
LAB ABN - HEMATOLOGY				1	0.10			2	0.19			3	0.14
PHOSPHATASE ALKALINE INCREASED		3	0.29							3	0.14		
CALCIUM DEFICIENCY						1	0.10			1	0.05		
ESR INCREASED						1	0.10			1	0.05		
HYPERGLYCEMIA						1	0.10			1	0.05		
HYPERKALEMIA						1	0.10			1	0.05		
HYPOCALCEMIA		1	0.10							1	0.05		
HYPOGLYCEMIA		1	0.10							1	0.05		
HYPOMAGNESEMIA						1	0.10			1	0.05		
PROTEINURIA								1	0.10			1	0.05

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IPM PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
LIVER AND BILIARY SYSTEM DISORDERS	TOTAL	2	0.19	2	0.19	3	0.29	1	0.10	5	0.24	3	0.14
JAUNDICE		1	0.10			3	0.29			4	0.19		
HEPATIC FUNCTION ABNORMAL				2	0.19			1	0.10			3	0.14
CHOLELITHIASIS		1	0.10							1	0.05		
METABOLIC AND NUTRITIONAL DISORDERS	TOTAL	54	5.21	1	0.10	61	5.85			115	5.53	1	0.05
HYPOVOLEMIA		47	4.54	1	0.10	54	5.18			101	4.86	1	0.05
HYPERURICEMIA		4	0.39			4	0.38			8	0.38		
GOUT		3	0.29			3	0.29			6	0.29		
HYPONATREMIA						2	0.19			2	0.10		
DEHYDRATION		1	0.10							1	0.05		
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	TOTAL	184	17.76	8	0.77	176	16.87	7	0.67	360	17.32	15	0.72
ARTHRALGIA		143	13.80	3	0.29	145	13.90	2	0.19	288	13.85	5	0.24
PAIN LEG		13	1.25	5	0.48	10	0.96	4	0.38	23	1.11	9	0.43
JOINT DISLOCATION		12	1.16			5	0.48			17	0.82		
PAIN BACK		6	0.58			10	0.96			16	0.77		
CRAMPS LEG		4	0.39			5	0.48			9	0.43		
ARTHROSIS		4	0.39			3	0.29			7	0.34		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closly related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

	enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS	N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IPM PREFERRED TERM)	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS CRAMPS MUSCLE	6	0.58			1	0.10			7	0.34		
MYALGIA	2	0.19			2	0.19			4	0.19		
BONE DISORDER	2	0.19							2	0.10		
HYPERTONIA	2	0.19							2	0.10		
FRACTURE	1	0.10							1	0.05		
HEMARTHROSIS							1	0.10			1	0.05
INTERVERTEBRAL DISC DISORDER					1	0.10			1	0.05		
MUSCLE SPASMS					1	0.10			1	0.05		
MYOGELOSIS	1	0.10							1	0.05		
OSTEONECROSIS	1	0.10							1	0.05		
PAIN ARM	1	0.10							1	0.05		
PAIN SKELETAL	1	0.10							1	0.05		
TENDINITIS					1	0.10			1	0.05		
TORTICOLLIS					1	0.10			1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closly related to trial treatm.)
- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CSP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
MYO ENDO PERICARDIAL & VALVE DISORDERS	TOTAL	8	0.77	1	0.10	11	1.05			19	0.91	1	0.05
ANGINA PECTORIS		6	0.58	1	0.10	9	0.86			15	0.72	1	0.05
MYOCARDIAL INFARCTION		2	0.19			1	0.10			3	0.14		
CORONARY ARTERY DISEASE NOS						1	0.10			1	0.05		
PLATELET, BLEEDING & CLOTTING DISORDER	TOTAL	150	14.48	175	16.89	147	14.09	172	16.49	297	14.29	347	16.69
HEMORRHAGE NOS		144	13.90	124	11.97	145	13.90	124	11.89	289	13.90	248	11.93
HEMATOMA		25	2.41	61	5.89	31	2.97	60	5.75	56	2.69	121	5.82
COAGULATION DISORDER								2	0.19			2	0.10
THROMBOCYTHEMIA		2	0.19							2	0.10		
PROTHROMBIN DECREASED								1	0.10			1	0.05

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- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CSP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
PSYCHIATRIC DISORDERS	TOTAL	165	15.93	3	0.29	154	14.77			319	15.34	3	0.14
INSOMNIA		134	12.93			120	11.51			254	12.22		
AGITATION		10	0.97			14	1.34			24	1.15		
SLEEP DISORDER		11	1.06			13	1.25			24	1.15		
CONFUSION		9	0.87	2	0.19	9	0.86			18	0.87	2	0.10
ANXIETY		3	0.29	1	0.10	7	0.67			10	0.48	1	0.05
DEPRESSION		4	0.39			1	0.10			5	0.24		
NERVOUSNESS		1	0.10			3	0.29			4	0.19		
DRUG ABUSE						1	0.10			1	0.05		
HALLUCINATION		1	0.10							1	0.05		
PANIC DISORDER		1	0.10							1	0.05		
PARANOIRIA						1	0.10			1	0.05		
PSYCHIC DISORDER						1	0.10			1	0.05		
THINKING ABNORMAL						1	0.10			1	0.05		
RED BLOOD CELL DISORDERS	TOTAL	81	7.82	45	4.34	72	6.90	43	4.12	153	7.36	88	4.23
ANEMIA		78	7.53	35	3.38	72	6.90	32	3.07	150	7.22	67	3.22
HEMOGLOBIN DECREASED		3	0.29	10	0.97			11	1.05	3	0.14	21	1.01

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SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)		unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
REPRODUCTIVE DISORDERS, FEMALE	TOTAL			1	0.10							1	0.05
VAGINAL HEMORRHAGE				1	0.10							1	0.05
REPRODUCTIVE DISORDERS, MALE	TOTAL	1	0.10							1	0.05		
PHIMOSIS		1	0.10							1	0.05		
RESISTANCE MECHANISM DISORDERS	TOTAL	1	0.10			3	0.29			4	0.19		
INFECTION FUNGAL		1	0.10			3	0.29			4	0.19		
RESPIRATORY SYSTEM DISORDERS	TOTAL	53	5.12	5	0.48	46	4.41	6	0.58	99	4.76	11	0.53
COUGHING		15	1.45	1	0.10	13	1.25			28	1.35	1	0.05
DYSPNEA		15	1.45	1	0.10	11	1.05	2	0.19	26	1.25	3	0.14
PHARYNGITIS		5	0.48			5	0.48			10	0.48		
HYPOXIA		6	0.58			3	0.29			9	0.43		
RESPIRATORY DISORDER		1	0.10	1	0.10	3	0.29	2	0.19	4	0.19	3	0.14
EPISTAXIS				2	0.19	2	0.19	2	0.19	2	0.10	4	0.19
PNEUMONIA		3	0.29			2	0.19			5	0.24		
BRONCHOSPASM		1	0.10			3	0.29			4	0.19		
PULMONARY EDEMA		2	0.19					1	0.10	2	0.10	1	0.05
RESPIRATORY DEPRESSION		2	0.19			1	0.10			3	0.14		

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- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

	enoxaparin Dose 40 mg				CGP 39393 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS	N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %	unrelated n	unrelated %	related n	related %
RESPIRATORY SYSTEM DISORDERS												
BRONCHITIS	1	0.10			1	0.10			2	0.10		
EDEMA LARYNX	1	0.10			1	0.10			2	0.10		
RHINITIS	2	0.19							2	0.10		
APNEA	1	0.10							1	0.05		
BRADYPNEA					1	0.10			1	0.05		
HYPOVENTILATION	1	0.10							1	0.05		
INFECTION CHEST	1	0.10							1	0.05		
OBSTRUCTIVE AIRWAY DISEASE					1	0.10			1	0.05		
RESPIRATORY INSUFFICIENCY	1	0.10							1	0.05		
SPUTUM INCREASED					1	0.10			1	0.05		
TONSILLITIS	1	0.10							1	0.05		

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- the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg		CGP 39393 Dose 15 mg		TOTAL	
RANDOMISED PATIENTS		N = 1036		N = 1043		N = 2079	
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IDM PREFERRED TERM)		unrelated n X	related n X	unrelated n X	related n X	unrelated n X	related n X
SKIN AND APPENDAGES DISORDERS	TOTAL	56 5.47	3 0.29	43 4.12	5 0.48	79 3.89	8 0.38
BULLOUS ERUPTION		9 0.87		5 0.48	1 0.10	14 0.67	1 0.05
PRURITUS		7 0.68		5 0.48	2 0.19	12 0.58	2 0.10
DERMATITIS CONTACT		5 0.48		8 0.77		13 0.63	
PRESSURE SORE		6 0.58		7 0.67		13 0.63	
RASH		2 0.19	2 0.19	3 0.29		5 0.24	2 0.10
DERMATITIS			1 0.10	3 0.29	2 0.19	3 0.14	3 0.14
SKIN DISORDER				5 0.48		5 0.24	
ECZEMA		2 0.19		2 0.19		4 0.19	
SWEATING INCREASED		3 0.29		1 0.10		4 0.19	
FLUSHING		2 0.19		1 0.10		3 0.14	
RASH ERYTHEMATOUS		1 0.10		2 0.19		3 0.14	
URTICARIA		1 0.10			1 0.10	1 0.05	1 0.05
BRUISING		1 0.10				1 0.05	
EDEMA LIPS		1 0.10				1 0.05	
PSORIASIS				1 0.10		1 0.05	
SKIN ULCERATION		1 0.10				1 0.05	

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SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg		CGP 39393 Dose 15 mg		TOTAL	
RANDOMISED PATIENTS		N = 1036		N = 1043		N = 2079	
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IDM PREFERRED TERM)		unrelated n X	related n X	unrelated n X	related n X	unrelated n X	related n X
SURGICAL AND MEDICAL PROCEDURES	TOTAL	1 0.10				1 0.05	
PROCEDURE BLOOD AND LYMPHATIC		1 0.10				1 0.05	
URINARY SYSTEM DISORDERS	TOTAL	85 8.20	3 0.29	93 8.92	4 0.38	178 8.56	7 0.34
URINARY RETENTION		45 4.34		44 4.22		89 4.28	
URINARY TRACT INFECTION		17 1.64		13 1.25		30 1.44	
OLIGURIA		8 0.77		10 0.96		18 0.87	
CYSTITIS		5 0.48		10 0.96		15 0.72	
HEMATURIA		3 0.29	3 0.29	2 0.19	3 0.29	5 0.24	6 0.29
BLADDER DISORDER		1 0.10		5 0.48		6 0.29	
MICTURITION DISORDER		3 0.29		2 0.19		5 0.24	
ANURIA		1 0.10		1 0.10	1 0.10	2 0.10	1 0.05
OBSTRUCTIVE UROPATHY				2 0.19		2 0.10	
RENAL FUNCTION ABNORMAL				2 0.19		2 0.10	
URINARY INCONTINENCE		1 0.10		1 0.10		2 0.10	
BACTERIURIA NOS		1 0.10				1 0.05	
DYSURIA				1 0.10		1 0.05	
HEMATURIA TRAUMATIC		1 0.10				1 0.05	

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SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CSP 39593 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IMM PREFERRED TERM)		unrelated n	%	related n	%	unrelated n	%	related n	%	unrelated n	%	related n	%
URINARY SYSTEM DISORDERS MICTURITION FREQUENCY		1	0.10							1	0.05		
MICTURITION URGENCY						1	0.10			1	0.05		
PAIN URINARY TRACT		1	0.10							1	0.05		
PYURIA						1	0.10			1	0.05		
STRANGURY						1	0.10			1	0.05		
URINARY TRACT DISORDER		1	0.10							1	0.05		
VASCULAR (EXTRACARDIAC) DISORDERS	TOTAL	31	2.99	41	3.96	28	2.68	35	3.36	59	2.84	76	3.66
THROMBOPHLEBITIS DEEP		20	1.93	20	1.93	20	1.92	12	1.15	40	1.92	32	1.54
THROMBOSIS		2	0.19	16	1.54	1	0.10	18	1.73	3	0.14	34	1.64
THROMBOPHLEBITIS		6	0.58	3	0.29	3	0.29	1	0.10	9	0.43	4	0.19
CEREBROVASCULAR DISORDER				1	0.10	1	0.10	3	0.29	1	0.05	4	0.19
THROMBOPHLEBITIS SUPERFICIAL		2	0.19	1	0.10	1	0.10			3	0.14	1	0.05
EMBOLISM PULMONARY				1	0.10	1	0.10	1	0.10	1	0.05	2	0.10
PHLEBITIS		1	0.10							1	0.05		
THROMBOEMBOLISM						1	0.10			1	0.05		
THROMBOPHLEBITIS ARM						1	0.10			1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
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SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTER:ALL

		enoxaparin Dose 40 mg				CSP 39593 Dose 15 mg				T O T A L			
RANDOMISED PATIENTS		N = 1036				N = 1043				N = 2079			
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IMM PREFERRED TERM)		unrelated n	%	related n	%	unrelated n	%	related n	%	unrelated n	%	related n	%
VISION DISORDERS	TOTAL	3	0.29			4	0.38	1	0.10	7	0.34	1	0.05
CONJUNCTIVITIS		2	0.19			1	0.10			3	0.14		
CONJUNCTIVAL HEMORRHAGE		1	0.10					1	0.10	1	0.05	1	0.05
EYE COMPLAINTS						1	0.10			1	0.05		
EYE DISORDER NOS						1	0.10			1	0.05		
KERATITIS						1	0.10			1	0.05		
WHITE CELL SYSTEM DISORDERS	TOTAL	2	0.19			2	0.19			4	0.19		
LEUKOCYTOSIS		2	0.19			1	0.10			3	0.14		
LEUKOPENIA						1	0.10			1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial treatm.)
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Sponsor's tables volume 1.74 pp. 8-27-151-169

Safety Data for Study RH/E 28

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTRE: ALL CENTRES

BODY SYSTEM CLASSIFICATION / ADVERSE EXPERIENCE (IMM PREFERRED TERM)		Unfractionated Heparin Dose 5000 IU N = 220				CGP 39393 Dose 15 mg N = 225				TOTAL N = 445			
		unrelat. n	%	relat. n	%	unrelat. n	%	relat. n	%	unrelat. n	%	relat. n	%
APPLICATION SITE DISORDERS	TOTAL	1	0.5	2	0.9			5	2.2	1	0.2	7	1.6
INJECTION SITE MASS		1	0.5	2	0.9			4	1.8	1	0.2	6	1.3
APPLICATION SITE REACTION								1	0.4			1	0.2
BODY AS A WHOLE - GENERAL DISORDERS	TOTAL	19	8.6	9	4.1	21	9.3	10	4.4	40	9.0	19	4.3
WOUND SECRETION		2	0.9	5	2.3	13	5.8	6	2.7	15	3.4	11	2.5
FEVER		9	4.1	3	1.4	5	2.2	3	1.3	14	3.1	6	1.3
EDEMA LEGS		3	1.4	1	0.5	3	1.3	1	0.4	6	1.3	2	0.4
PAIN CHEST		5	2.3					2	0.9	5	1.1	2	0.4
RIGORS		1	0.5			1	0.4			2	0.4		
ANAPHYLACTIC SHOCK		1	0.5							1	0.2		
CARDIOVASCULAR DISORDERS, GENERAL	TOTAL	4	1.8	1	0.5	11	4.9	3	1.3	15	3.4	4	0.9
HYPOTENSION		4	1.8			10	4.4	3	1.3	14	3.1	3	0.7
HYPERTENSION				1	0.5							1	0.2
SYNCOPE						1	0.4			1	0.2		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial
- the number of patients reporting at least once the adverse experience,
in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTRE: ALL CENTRES

BODY SYSTEM CLASSIFICATION / ADVERSE EXPERIENCE (IMM PREFERRED TERM)		Unfractionated Heparin Dose 5000 IU N = 220				CGP 39393 Dose 15 mg N = 225				TOTAL N = 445			
		unrelat. n	%	relat. n	%	unrelat. n	%	relat. n	%	unrelat. n	%	relat. n	%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	5	2.3			4	1.8			9	2.0		
DIZZINESS		1	0.5			2	0.9			3	0.7		
NEUROPATHY		1	0.5			1	0.4			2	0.4		
PARESIS		1	0.5			1	0.4			2	0.4		
HEADACHE		1	0.5							1	0.2		
HYPOESTHESIA		1	0.5							1	0.2		
NEURALGIA		1	0.5							1	0.2		
GASTROINTESTINAL SYSTEM DISORDERS	TOTAL	22	10.0	5	2.3	21	9.3	7	3.1	43	9.7	12	2.7
NAUSEA		16	7.3	2	0.9	15	6.7	7	3.1	31	7.0	9	2.0
VOMITING		4	1.8			3	1.3	1	0.4	7	1.6	1	0.2
HEMATEMESIS		1	0.5	1	0.5	2	0.9			3	0.7	1	0.2
DIARRHEA		2	0.9	1	0.5					2	0.4	1	0.2
GASTROENTERITIS		2	0.9			1	0.4			3	0.7		
CONSTIPATION		1	0.5			1	0.4			2	0.4		
PAIN ABDOMINAL		1	0.5			1	0.4			2	0.4		
GASTRIC ULCER PERFORATED				1	0.5							1	0.2
GASTRITIS						1	0.4			1	0.2		
HICCUP						1	0.4			1	0.2		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial
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in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT
(UNRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE,PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)
(DATASET: RANDOMISED PATIENTS)

CENTRE: ALL CENTRES

BODY SYSTEM CLASSIFICATION / ADVERSE EXPERIENCE (INN PREFERRED TERM)		Unfractionated Heparin Dose 5000 IU N = 220		CGP 39393 Dose 15 mg N = 225		TOTAL N = 445	
		unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %
HEART RATE AND RHYTHM DISORDERS	TOTAL	3 1.4		4 1.8		7 1.6	
BRADYCARDIA		2 0.9		2 0.9		4 0.9	
FIBRILLATION ATRIAL		1 0.5		2 0.9		3 0.7	
TACHYCARDIA SUPRAVENTRICULAR				1 0.4		1 0.2	
LABORATORY ABNORMALITY	TOTAL	1 0.5	3 1.4	2 0.9	1 0.4	3 0.7	4 0.9
LIVER ENZYMES ELEVATED			2 0.9		1 0.4		3 0.7
HYPOKALEMIA				2 0.9		2 0.4	
HYPOCALCEMIA		1 0.5				1 0.2	
PHOSPHATASE ALKALINE INCREASED			1 0.5				1 0.2
LIVER AND BILIARY SYSTEM DISORDERS	TOTAL		1 0.5				1 0.2
HEPATOCELLULAR DAMAGE			1 0.5				1 0.2
METABOLIC AND NUTRITIONAL DISORDERS	TOTAL	1 0.5		2 0.9		3 0.7	
HYPOVOLEMIA		1 0.5		1 0.4		2 0.4	
KETOSIS				1 0.4		1 0.2	

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		unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %
MUSCULOSKELETAL SYSTEM DISORDERS	TOTAL	10 4.5		2 0.9	1 0.4	12 2.7	1 0.2
JOINT DISLOCATION		4 1.8		2 0.9		6 1.3	
CRAMPS LEG		2 0.9			1 0.4	2 0.4	1 0.2
PAIN BACK		2 0.9				2 0.4	
ADHESIVE CAPSULITIS		1 0.5				1 0.2	
ARTHRALGIA				1 0.4		1 0.2	
PAIN LEG		1 0.5				1 0.2	
MYO ENDO PERICARDIAL & VALVE DISORDERS	TOTAL	1 0.5	2 0.9	1 0.4		2 0.4	2 0.4
ANGINA PECTORIS		1 0.5	2 0.9			1 0.2	2 0.4
MYOCARDIAL INFARCTION				1 0.4		1 0.2	
PLATELET, BLEEDING & CLOTTING DISORDER	TOTAL	8 3.6	17 7.7	8 3.6	18 8.0	16 3.6	35 7.9
HEMORRHAGE NOS		7 3.2	12 5.5	5 2.2	12 5.3	12 2.7	24 5.4
HEMATOMA		1 0.5	9 4.1	4 1.8	10 4.4	5 1.1	19 4.3
THROMBOCYTOPENIA			1 0.5				1 0.2

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		unrelat. n %	relat. n %	unrelat. n %	relat. n %	unrelat. n %	relat. n %
PSYCHIATRIC DISORDERS	TOTAL	3 1.4	2 0.9	5 2.2	1 0.4	8 1.8	3 0.7
ANXIETY		1 0.5		3 1.3		4 0.9	
CONFUSION		2 0.9	1 0.5	1 0.4		3 0.7	1 0.2
INSOMNIA					1 0.4		1 0.2
NERVOUSNESS				1 0.4		1 0.2	
PSYCHOSIS			1 0.5				1 0.2
RED BLOOD CELL DISORDERS	TOTAL		2 0.9		3 1.3		5 1.1
ANEMIA			2 0.9		3 1.3		5 1.1
REPRODUCTIVE DISORDERS, FEMALE	TOTAL		1 0.5				1 0.2
UTERINE HEMORRHAGE			1 0.5				1 0.2
REPRODUCTIVE DISORDERS, SEX UNSPECIFIE	TOTAL	1 0.5				1 0.2	
MONILIASIS GENITAL		1 0.5				1 0.2	
RESISTANCE MECHANISM DISORDERS	TOTAL	6 2.7		3 1.3		9 2.0	
INFECTION		3 1.4		2 0.9		5 1.1	
MONILIASIS		3 1.4				3 0.7	
HERPES SIMPLEX				1 0.4		1 0.2	

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		unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %
RESPIRATORY SYSTEM DISORDERS	TOTAL	7	3.2	1	0.5	6	2.7	1	0.4	13	2.9	2	0.4
PNEUMONIA		1	0.5	1	0.5	2	0.9			3	0.7	1	0.2
DYSPNEA		1	0.5			2	0.9			3	0.7		
RESPIRATORY DEPRESSION		1	0.5			1	0.4			2	0.4		
ASTHMA						1	0.4			1	0.2		
BRONCHITIS		1	0.5							1	0.2		
BRONCHOSPASM		1	0.5							1	0.2		
COUGHING		1	0.5							1	0.2		
EPISTAXIS								1	0.4			1	0.2
PULMONARY EDEMA						1	0.4			1	0.2		
RHINITIS		1	0.5							1	0.2		

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		unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %
SKIN AND APPENDAGES DISORDERS	TOTAL	4	1.8			11	4.9			15	3.4		
URTICARIA		1	0.5			4	1.8			5	1.1		
BULLOUS ERUPTION						2	0.9			2	0.4		
PRURITUS						2	0.9			2	0.4		
ACNE						1	0.4			1	0.2		
DERMATITIS		1	0.5							1	0.2		
DERMATITIS CONTACT		1	0.5							1	0.2		
INFECTION SKIN						1	0.4			1	0.2		
SEBORRHEA						1	0.4			1	0.2		
SKIN ULCERATION		1	0.5							1	0.2		
URINARY SYSTEM DISORDERS	TOTAL	10	4.5			21	9.3	3	1.3	31	7.0	3	0.7
CYSTITIS		5	2.3			8	3.6			13	2.9		
URINARY TRACT INFECTION		3	1.4			7	3.1	1	0.4	10	2.2	1	0.2
URINARY RETENTION		3	1.4			3	1.3			6	1.3		
HEMATURIA		1	0.5			2	0.9	2	0.9	3	0.7	2	0.4
OLIGURIA						3	1.3			3	0.7		

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		unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %	unrelat. n	unrelat. %	relat. n	relat. %
VASCULAR (EXTRACARDIAC) DISORDERS	TOTAL	28	12.7	10	4.5	8	3.6	4	1.8	36	8.1	14	3.1
THROMBOPHLEBITIS DEEP		27	12.3	10	4.5	8	3.6	4	1.8	35	7.9	14	3.1
THROMBOPHLEBITIS		1	0.5							1	0.2		
VISION DISORDERS	TOTAL	1	0.5							1	0.2		
INFECTION OCULAR		1	0.5							1	0.2		

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Sponsor's tables volume 1.79 p.8-32-157-164

Appendix 4

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Appendix 5- Materials Reviewed:

Materials – reviewed

Volume	Content
1.1	Overview of Application
1.48-1.69	Clinical Pharmacology Studies
1.70-91	Major Clinical Trials, including cardiology
1.92-124, SAS data sets	Case Report Tabulations
1.25-1.37	Case Report Forms

Reviewer's Table

Appendix 6- label

(C)

Number of Pages Redacted 17

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Draft Labeling
(not releasable,

Please see Dr. He's March 7, 2003 MOR for the Safety Update.

/S/ 3-7-02

Alice Kacuba

See the Medical Officer's Review Dated May 11, 2001

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS MEDICAL OFFICER'S REVIEW

NDA:	NDA 21-271/N-000-C
Sponsor:	AVENTIS PHARMACEUTICAL PRODUCTS, INC 200 Crossing Boulevard Bridgewater, NJ 08807-0890 USA
Drug name:	**Iprivask (desirudin)**
Subject:	An amendment to NDA 21-271 with a complete response to the Approvable Letter dated May 14, 2001 and CMC Discipline Review Letter dated April 16, 2001.
Date submitted:	October 3, 2002
Date received:	October 4, 2002
Review completed:	March 4, 2003
Reviewer:	Ruyi He, M.D.

1. EXECUTIVE SUMMARY

This submission is an amendment to NDA 21-271 with a complete response to the Approvable Letter dated May 14, 2001. The sponsor's responses are acceptable. The revised package insert should be further modified as recommended in section 9 (package insert review) below. Also, I recommend that the sponsor be requested to agree to a post-marketing commitment for further study in hepatically impaired patients to provide safety information and appropriate dosing regimen for those patients.

Overall, the safety information presented in the Safety Update Reports for the period between September 2000 and May 2002 is consistent with the known safety profile of desirudin. However, anaphylactic reaction was identified as a potential safety signal because of two case reports in cumulative experience. "Allergic reactions" is listed in the desirudin labeling under the section of **PRECAUTIONS**. "Anaphylactic/anaphylactoid reactions" is added in the section of **ADVERSE REACTIONS**, under the subsection of **Post Marketing.**

2. BACKGROUND:

NDA 21-271 was originally submitted on June 28, 2000 for desirudin. Desirudin (Iprivask, recombinant desulfatohirudin) is a selective thrombin inhibitor. Iprivask is proposed for the indication of the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery. For additional background information, see Medical Officer's Review dated May 11, 2001. The approvable letter for NDA 21-271 was issued on May 14, 2001 in which further CMC, pharmacology and clinical information were requested. Major clinical issues were as following:

- Address safety concerns regarding the proposed 2-count carton.
- Submit revised draft labeling
- Submit an alternate proposed proprietary name.
- Submit safety update

Although not required for approval, the sponsor also was requested to provide following information:

- Safety information from the first market date to the start of the Safety Update.
- Clinical information to support the labeling recommendations for switching from desirudin to other anticoagulants and from other anticoagulants to desirudin.

The letter also mentions that information provided in the NDA did not address use of desirudin in races other than Caucasian or provide safety information and optimal dosing regimen in hepatically impaired patients.

In this submission, the sponsor provides a complete response to the approvable letter and a proposed draft labeling.

3. SAFETY CONCERNS REGARDING THE PROPOSED 2-COUNT CARTON

The 2-count carton was labeled as [redacted] and the Division of Medication Errors considers that it may be mistaken that the total content of the 2-count carton is [redacted] of the active drug.

The sponsor proposed that the number [redacted] be changed to a bolded Two (2) so the content statement reads as follows:

"**Two (2) x** [redacted]

Reviewer's comments: The sponsor's proposal is acceptable from a clinical standpoint. A consultation request was sent to the Divisicn of Medication Errors regarding this issue and the review is pending.

4. ALTERNATE PROPOSED PROPRIETARY NAME

The sponsor submits the proposed proprietary name, IPRIVASK. The Division of Medication Errors has reviewed the proposed proprietary name and found proposed proprietary name, IPRIVASK is acceptable (see the consultation response from the Division of Medication Errors for NDA 21-271 dated December 5, 2002).

5. SAFETY UPDATE

5.1 Safety Update from September 2000 to November 2001

Desirudin is approved in 28 countries for the indication of prophylaxis of DVT in patients undergoing orthopedic surgery. So far, desirudin has not been withdrawn from the market anywhere, nor has its use been suspended anywhere.

Patient exposure

Cumulative worldwide patient exposure from the first quarter of 1999 to November 2001 shows an estimated [redacted] absolute counting units of desirudin with 12,043 patients exposures. For the period of September 2000 to November 2001, there were approximately 6,448 patients exposures for [redacted] absolute counting units.

Individual Case Histories

A total of 10 spontaneous reports were received between September 2000 and November 2001. Six of ten adverse events reported were serious and 3 of 10 (1 serious and 2 non-serious) adverse events were not listed before.

One serious and unexpected adverse event is violent abdominal pain requiring morphine sulfate. This was a 70-year-old female patient with no relevant history. She underwent knee surgery and received her first dose of desirudin SC pre-operatively. Post-operatively, she received a second desirudin injection, and 5 hours later, experienced violent abdominal pain requiring morphine sulfate. In the morning, she was found comatose and had developed hemorrhagic shock after 1300 cc blood loss from the surgical site. The patient recovered without sequelae.

Five serious listed adverse events are summarized below.

Case #	Event	Causality	Outcome
200021292FR	Cutaneous erthematous and pruritus	Possible	Recovered
200021306FR	Hematuria, fever. Urinary cultures negative	Possible, ?	Recovered
200021491DE	73 yo F with plasmacytoma infiltrated to lung, bone marrow and kidney, increase in SGOT to 69, SGPT to 61, bilirubin normal	Possible	Ongoing
200110351FR	80 yo m with staphylococcal osteoarthritis developed pruriginous vesiculo-papular eruption	Possible	Recovered
200111089FR	Pulmonary embolism	Lack of effect	Recovered

Two adverse events which were listed as non-serious and unexpected were burning micturation, severe upper abdominal complaints and intestinal cramps.

Two other non-serious and expected adverse events were urticaria, generalized drug induced exanthema and difficulty in swallowing in the course of allergy.

5.2 Safety Update from November 2001 to May 2002

During the period November 2001 to May 2002, the worldwide sales of desirudin are estimated to be [redacted] counting units. There were approximately 2,551 patients exposed.

During this period, only one spontaneous case (200213786DE) was reported. This case was a 62-year-old woman who experienced erythema, dyspnea and shock five minutes after her first subcutaneous dose of desirudin for thromboembolism prophylaxis. The reporting physician described the event as an anaphylactoid reaction and life-threatening. Her medical history was significant for heparin-induced thrombocytopenia and treatment with lepirudin in 1999.

A search of Aventis's Pharmacovigilance data base revealed one more report (DE01-05640) of allergic reaction. This was a 68 year-old man who experienced tachycardia, hypotension, chill and shock two to three minutes after his first dose of desirudin (15 mg) for thromboembolism prophylaxis.

In both cases, the temporal relationship between event onset and desirudin administration indicates desirudin might have caused the events.

No other adverse event was reported during this period.

5.3 Safety Update from May 2002 to September 2002

Two initial spontaneous reports of thrombocytopenia were reported in this period. In both cases, the patients had previous heparin-induced thrombocytopenia and were being treated concomitantly with heparin initially.

No other adverse event was reported during this period.

5.4 Conclusions of Safety Update

Overall, the safety information presented in these Safety Update Reports for the period between September 2000 and May 2002 is consistent with the known safety profile of desirudin. However, anaphylactic reaction was identified as a potential safety signal because of two cases reports in cumulative experience. Allergic reactions are listed in the desirudin labeling under the section of **PRECAUTIONS**. Anaphylactic/anaphylactoid reactions are added in the section of **ADVERSE REACTIONS**, under the subsection of **Post Marketing.**

According to the sponsor, [redacted]

6. SAFETY INFORMATION FROM THE FIRST MARKET DATE (MALAYSIA-NOV 95) TO THE START OF THE SAFETY UPDATE (MAY 1, 99)

According to the sponsor, desirudin was [redacted] Germany was the first country where it was marketed on September 26, 1998. There had been 5 adverse events reported in 3 patients, as of April 30, 1999. One patient experienced coagulation abnormalities, a second patient developed epistaxis and a third patient developed hemorrhagic shock secondary to an abdominal wall hematoma.

7. CLINICAL INFORMATION REGARDING SWITCHING BETWEEN DESIRUDIN AND OTHER ANTICOAGULANTS

In the approvable letter dated May 14, 2001, the sponsor was requested to provide clinical information to support the labeling recommendations on switching from oral anticoagulants to Iprivask or from Iprivask to oral anticoagulants, under PRECAUTIONS section, Drug interaction subsection. The sponsor was also requested to revise this paragraph to provide what is known and additional guidance how patients should be switched. In this submission, the sponsor has revised this subsection to read as follows:

> *Use in patients switching from oral anticoagulants to* Iprivask *or from* Iprivask *to oral anticoagulants.* [1]
>
> [redacted]

[redacted]

The sponsor referred to a study (RH/E35) report in the original NDA 21-271 submission (6/28/00) to support above labeling recommendations for switching from desirudin to other anticoagulants and from other anticoagulants to desirudin. Study RH/E35 was an open label and single center trial to investigate the possible interaction between CGP 39 393 (rec-hirudin) and warfarin in 12 healthy male volunteers.

This study was a PK/PD study. According to the report, the co-administration of CGP 39 393 and warfarin was well tolerated by healthy volunteers. Bleeding times were comparable pre-dose, warfarin alone, CGP 39 393 alone and warfarin + CGP 39 393. APTT was prolonged for warfarin + CGP 39 393 compared to warfarin alone and PT was slightly prolonged for warfarin + CGP 39 393 compared to CGP 39 393 alone.

Based on the results of this PK/PD study, from a clinical standpoint, the above labeling recommendations are generally acceptable. However, because the oral anticoagulant used in the study was warfarin and oral anticoagulant activity was measured by INR, for greater clarity, I recommend the following modifications:

[redacted] concomitant administration of warfarin did not significantly affect the pharmacokinetic effects of desirudin. When [redacted] warfarin and desirudin were co-administrated [redacted] greater inhibition of hemostasis measured by activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR) was observed. If a patient is switched from [redacted]

[redacted]

8. OTHERS

In the Approvable Letter, the Division informed the sponsor that information provided in the NDA did not address the use in races other than Caucasian or provide safety information and optimal dosing regimen in hepatically impaired patients.

Regarding the use in races other than Caucasian, although in the clinical studies all of the patients were Caucasian, so far no reports or publications suggest that thrombin inhibitor may function differently between the races. Therefore, I consider that further study in different races is not necessary. However, the information about races of study subjects should be included in the CLINICAL TRIAL section of labeling (see section 9 below for detail).

Regarding the use in hepatically impaired patients, although Iprivask is not metabolized and eliminated in liver primarily, thrombin and many other coagulation factors are synthesized by liver. Safety information and information to direct dosing regimen in hepatically impaired patients are needed. Therefore, the sponsor should be requested to agree to a post-marketing commitment for further study (i.e., PK/PD study) in hepatically impaired patients to provide safety information and appropriate dosing regimen for those patients.

9. PACKAGE INSERT REVIEW

I have following recommendations for modifications of the package insert. The rationales will be provided with each recommendation. Otherwise, the revised package insert is acceptable from a clinical stand-point.

- Second paragraph in the section of **CLINICAL TRIALS** is proposed by the sponsor as following:

[ ]

Reviewer's comments: The information about race, the numbers of patients enrolled, treated, and excluded from per-protocol population should be included in this paragraph. It is unnecessary to provide age and sex by treatment groups, because they were very similar in both groups. The sponsor declined to use "all

treatment population" for efficacy analysis as recommended by FDA, because the sponsor considered that it is not known whether non-evaluable patients had clinically occult VTE, the "all treatment analysis" may provide false low incidences of VTE. I recommend that this paragraph be modified as following. Additions are shown by the underline and deletions are shown by double-strikeout.

. A total of 445 patients were randomized in the study, 436 patients were treated, and 85 patients were excluded from efficacy analysis, mainly because of no phlebography or inadequate reading of phlebography.

Patients ranged in age from 34 to 89 years (mean age 68.4 years) with 41.8% men and 58.2% women. All enrolled patients were Caucasian.

- Third paragraph in the section of **CLINICAL TRIALS** is proposed by the sponsor as following:

[ ]

Reviewer's comments: The information about race, the numbers of patients enrolled, treated, and excluded from per-protocol population should be included in this paragraph. It is unnecessary to provide age and sex by treatment groups, because they were very similar in both groups. The sponsor declined to use "all treatment population" for efficacy analysis as recommended by FDA, because the sponsor considered that it is not known whether non-evaluable patients had clinically occult VTE, the "all treatment analysis" may provide false low incidences of VTE. I recommend that this paragraph be modified as following. Additions are shown by the underline and deletions are shown by double-strikeout.

. A total of 2079 patients

were randomized in the study, 2049 patients were treated, and 508 patients were excluded from efficacy analysis mainly because of no phlebography or inadequate reading of phlebography.

Patients ranged in age from 18 to 90 years (mean age 68.5 years) with 41.7% men and 58.5% women. All enrolled patients were Caucasian.

- Under the section of **PRECAUTIONS,** subsection of **Antibodies/Re-exposure**, the sponsor proposed the following:

  Antibodies/Re-exposure: Antibodies have been reported in patients treated with hirudins.

  Allergic events were reported in <2% of patients who were administered desirudin in Phase III clinical trials.

Reviewer's comments: The second sentence should be deleted as shown below, because it does not provide valuable information.

Antibodies/Re-exposure: Antibodies have been reported in patients treated with hirudins.

Allergic events were reported in <2% of patients who were administered desirudin in Phase III clinical trials.

- Under the subsection of **Drug Interactions** in the section of **PRECAUTIONS,** the sponsor proposed the following:

  Use in patients switching from oral anticoagulants to Iprivask *or from* Iprivask *to oral anticoagulants.*

Reviewer's comments: The proposed labeling above is based on a PK/PD study in 12 healthy male volunteers. From a clinical stand-point, it is generally acceptable. However, because the oral anticoagulant used in the study was warfarin and oral anticoagulant activity was measured by INR, for greater clarity, I recommend the following modifications:

The concomitant administration of warfarin did not significantly affect the pharmacokinetic effects of desirudin. When warfarin and desirudin were co-administrated greater inhibition of hemostasis measured by activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR) was observed. If a patient is switched from to Iprivask therapy,

10. REGULATORY RECOMMENDATIONS

From a clinical standpoint, the sponsor's responses to the Division's approvable letter dated May 14, 2001 are acceptable. The revised package insert should be modified as recommended in section 9 (package insert review) of this review. Also, I recommend that the sponsor be requested to agree to a post-marketing commitment for further study (such as PK/PD study) in hepatically impaired patients to provide safety information and appropriate dosing regimen for those patients.

Ruyi He, M.D.

CC:
NDA 21-271/N-000-C
HFD-180/Div. Files
HFD-180/R. Justice
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HFD-181/A. Kacuba
f/t 03/07/03 rh
NDA 21-271/N-000-C. RH

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/s/

Ruyi He
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Kathy Robie-Suh
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MEDICAL OFFICER
Concur.

APPEARS THIS WAY
ON ORIGINAL