Post-operation days 1-10: (Injections should be given at least 10 hours apart)

CGP 39 393 group:	Morning	CGP 39 393
	Evening	CGP 39 393
		Placebo (LMWH)
LMWH group:	Morning	Placebo (CGP 39 393)
	Evening	Placebo (CGP 39 393)
		LMWH

The subcutaneous injections should be rotated between at least four different injection sites in the abdomen.

Sponsor's text 1.76 pp.8-29-13, 14

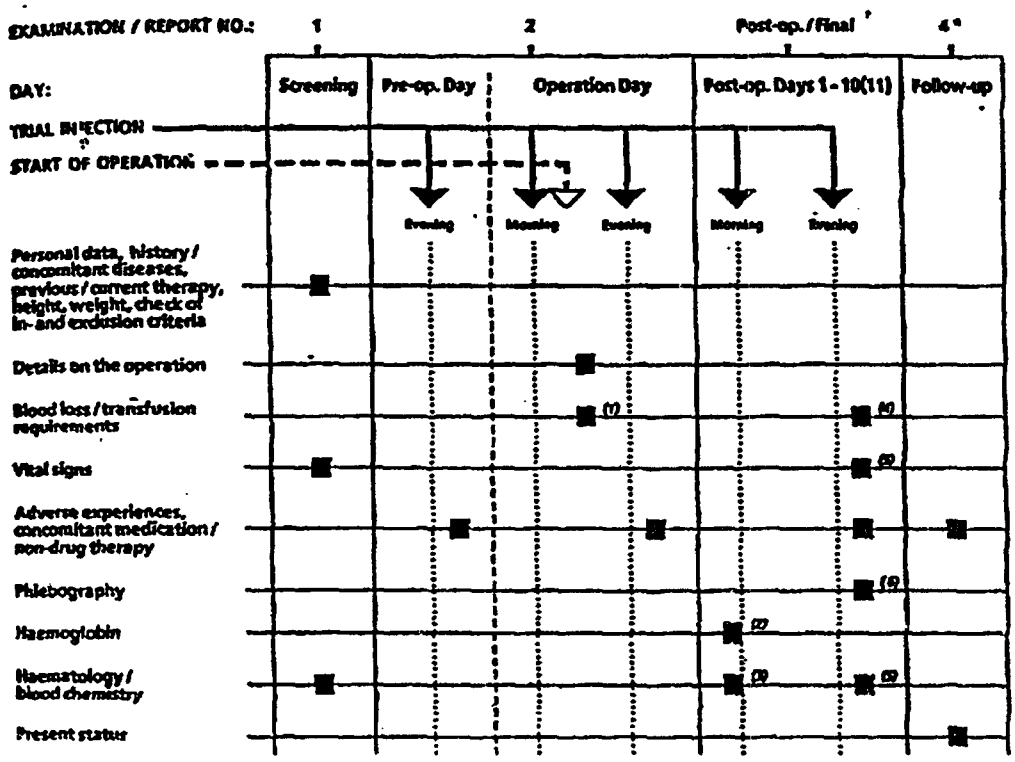
Randomization
Fixed Block randomization was used. Complete randomization blocks were given to different centers. Investigators were instructed to use the lowest allocation number first in order to maintain randomization.

Concomitant Medication
See above section.

Flow of trial
The diagram below outlines the sponsor's flow chart for RH/E 25. Physicians were instructed to operate on patients in the morning and preferentially first if possible. If hemorrhagic or other technical difficulties arose during the administration of regional anesthesia, the patient was to be prematurely discontinued from the trial.

CGP 39 393 (REC-HIRUDIN)

Flow Chart for Clinical Trial Protocol RH/E 25



(1) Cumulative, i.e. from start of surgery up to 12 hours

(2) Morning of post-op. Day 1 only

(3) Morning of post-op. Day 6 only

(4) Cumulative, i.e. from 12 hours after start of surgery to Day 6 inclusive

(5) To be performed on the day of the phlebography or in the event of premature discontinuation of the Prophylaxis Period

(6) To be performed between post-op. Days 8 - 10(11) or earlier if necessary

* To be completed 6 weeks after surgery

Sponsor's chart volume 1.76 p.8-29-77

Premature Discontinuation from the Trial

Patients could be prematurely discontinued from a trial for an endpoint, an adverse event, phlebography prior to day 8, lack of tolerable response, major violation of the protocol, and withdrawal of consent.

Efficacy Measurements

Bilateral Ascending Venography

The protocol required the procedure to be performed on post-operative day 8-12 in all patients who did not manifest clinical evidence of a deep venous thrombosis or pulmonary embolism earlier in the trial. An adequate venogram was defined as a venogram where all veins (muscular, anterior tibial, posterior tibial, fibular, popliteal, superficial femoral, common femoral, deep femoral, and iliac are seen. A local radiologist initially read the films and then the venograms were sent in blinded fashion to be read by the central radiologists.
The venogram was read centrally by two radiologists as either

1) normal (i.e., negative for DVT)
2) presence of an intraluminal defect (i.e., positive for DVT)
3) inadequate

Pulmonary embolism

Ventilation/perfusion scans

Ventilation/perfusion scans were performed if the patient exhibited clinical signs suggestive of a pulmonary embolism.

Ventilation/perfusion scans had three possible readings/scenarios:
1) high probability – ventilation/perfusion scan with either a segmental or greater mismatched defects or large subsegmental defects with ventilation mismatch
2) normal lung scan (i.e. low probability lung scan) - characterized by an absence of perfusion defects in all fields
3) any reading which does not fit into the above categories should be confirmed by a pulmonary angiogram

Patients could also be diagnosed as having a pulmonary embolism if they had a positive angiogram or underwent a pulmonary embolectomy.

Efficacy

Patients are counted only once.
Primary efficacy was defined by the composite endpoint:
1) a positive bilateral ascending phlebography performed at the end of the prophylaxis period and assessed centrally and/or
2) high probability ventilation/perfusion scan and/or
3) positive pulmonary angiogram and/or
4) an autopsy with documented thrombosis and/or
5) unexplained death during the prophylaxis period

The statistical analysis plan was to perform linear logistic regression with treatment and center as fixed factors and a two-sided test for significance at 5%. A 95% confidence interval was to be given for the estimated log odds ratio.

Secondary efficacy was defined by the presence of a composite endpoint:
1) a positive bilateral ascending phlebography performed at the end of the prophylaxis period and assessed centrally and/or
2) high probability ventilation/perfusion scan and/or
3) positive pulmonary angiogram and/or
4) an autopsy with documented thrombosis and/or
5) unexplained death during the prophylaxis period

The overall event rate was to be analyzed using the same method as for the primary outcome.

Severity of thromboembolic events was graded as follows:
Death > pulmonary embolism > DVT (proximal) or DVT (distal).

Patients were excluded from the primary analysis of efficacy based on the following (considered non-evaluable):
1) phlebography is performed before day 8 of prophylaxis and is negative according to central assessment
2) phlebography has not been done within one day after the end of prophylaxis

3) phlebography has been done but not assessed centrally
4) inadequate phlebogram
5) major protocol violation occurs
a) use of oral anticoagulants, thrombolytics, or dextrans
b) less than 80% compliance

Safety assessment

Bleeding complications included two categories:
1) peri-operative (i.e., 12 hour period from the time the operation started)
2) post-operative (i.e., 12 hours to 6 days)

Major bleeding was defined as:
1) fall in hemoglobin of at least 2 gms/dl which is overt or
2) transfusion of $\geq$ 2 units packed red cells in the post-operative period which is overt or
3) retroperitoneal or
4) intracranial or intraocular
5) into a prosthetic joint

Serious bleeding was defined:
1) peri-operative transfusion requirements exceed 5 units of whole blood or packed red blood cells or
2) total transfusion requirements up to post-op day 6 exceeding 7 units
3) total blood loss up to post-op day 6 exceeding 3500 ml

Results of Pivotal Efficacy RH/E 25 Trial

The trial was conducted in 31 centers from 10 countries (2 centers in Austria, 3 centers in Belgium, 4 centers in Denmark, 4 centers in France, 2 centers in Germany, 3 centers in Italy, 3 centers in The Netherlands, 2 centers in Spain, 4 centers in Sweden, and 4 centers in Switzerland). One center in Belgium was never approved by the ERB due to mandatory phlebography. The center accrual ranged from 3 patients in center 4 in Switzerland to 168 patients in each of the two centers in Austria. Austria contributed 336 (16.1%) enrolled patients total out of 2086 enrolled. The total number of patients randomized was 2079.

Premature Discontinuations

Reviewer's Comment: The most frequent reason for premature discontinuation was due to an adverse experience. The most frequent reason for an adverse experience was clinical suspicion of a thrombosis not objectively confirmed.

Number of Patients Discontinued Prematurely in RH/E 25

	Enoxaparin	Desirudin (15 mg)	Total
Enrolled	N/G	N/G	2086
Randomized	1036	1043	2079
Completed			
Discontinued Prematurely (Did not complete)	61 (5.9%)	70 (6.7%)	131
Abnormal laboratory value	1	1	2
Abnormal test procedure	1	4	5
Administrative problems	8	12	20
Adverse Experience	23	30	53
Death[2]	1	1	2
Patient non-compliant	2	1	3
Protocol criteria not met	13	7	20
Trial treatment not required	1	0	1
Withdrawal of consent	11	14	25

[1] One patient randomized twice. One desirudin patient enrolled but removed from trial due to high APTT after test injection.
[2] Only death for desirudin patient counted in primary and secondary efficacy analyses.
[3] Adverse Events not included in PP and ITT analyses and safety assessment. PP/ITT enoxaparin –1 death, desirudin – 1 suspicious for PE –V/Q scan; SAE Bleeding enoxaparin –2, desirudin –5, allergic reaction desirudin –1
Reviewer's Table

Excluded Patients from RH/E 25

The table below shows the patients who were excluded from the evaluable population and modified ITT populations.

Reviewer's Comment: The original sample size calculation based on RH/E 23 anticipated that 500 patients or 25% would be excluded from the efficacy analyses. This reviewer's analysis differs from the sponsor's because it was based on the SAS datasets. The "Missing" category included those patients for whom no reason for exclusion was given by the investigator in the text. The majority of these patients (51%) came from one center in France. There is no significant difference between treatment groups for the number of patients missing.

Patients Excluded from Efficacy Analyses – RH/E 25

	Enoxaparin	Desirudin	Total
Excluded from PP and ITT*	251	257	508 (100%)
Concomitant medication not allowed	5	6	11 (2.2%)
Inadequate central reading	78	94	172 (33.9%)
Missing	41	44	85 (16.7%)
No operation	13	15	28 (5.5%)
No phlebography	131	116	247 (48.6%)
Phlebography performed at wrong time	2	7	9 (1.8%)
Excluded from PP only*	17	15	32 (6.3%)
Concomitant medication not allowed	7	6	13 (2.6%)
Inadequate central reading	0	1	1 (0.2%)
No phlebography	1	0	1 (0.2%)
Phlebography performed at wrong time	9	9	18 (3.5%)
Randomized twice	0	1	1 (0.2%)

* More than one reason per patient.
Reviewer's table

Treatment Allocation

Twelve patients were assigned treatment numbers but never treated due to withdrawal from the study prior to the first injection. These patients were from centers in Belgium, France, The Netherlands, Spain, and Switzerland.

Trial medication packs were mixed up for eleven patients. The sponsor did not exclude these patients from the efficacy analysis. Seven patients received both enoxaparin and desirudin

injections. None of these seven patients experienced a thrombosis. These patients are listed in the sponsor's table below.

Patients where the medication were mixed up

Country	Centno	Select/label No	Injection No. affected	Injection used from label No	Comments
DK	4	9168/1864 CGP 39 393	2,3,5,6	1865 CGP 39 393	Rest of medication of 1865 was not used
E	1	6505/354 enoxaparin	2	356 enoxaparin	Reserve injection No. 81 was used in patient 356 instead
E	2	6624/1753 enoxaparin	3,4	1754 CGP 39 393	
E	2	6623/1754 CGP 39 393	3,4,16	1753 enoxaparin	Reserve injection No. 83 was used in patient 1753 instead of injection No 16
F	1	7115/1965 CGP 39 393	1,2,3,4,5	1966 enoxaparin	Only vial and the pre-filled syringe used from 1966. Rest of medication of 1966 was not used
F	4	7165/1984 enoxaparin	19	1983 enoxaparin	Reserve injection No. 83 was used in patient 1983 instead
F	4	7093/963 CGP 39 393	1 to 29	966 CGP 39 393	Rest of 966 not used
S	1	9539/1097 CGP 39 393	8	1096 enoxaparin	
S	1	9531/1098 enoxaparin	8	1097 CGP 39 393	
S	4	9838/1081 CGP 39 393	23	1082 enoxaparin	Reserve injection No. 81 was used in patient 1082 instead
NL	1	8001/553 enoxaparin	11	554 CGP 39 393	Reserve injection No. 81 was used in patient 554 instead

Sponsor's table volume 1.74 p. 8-29-37

Code Broken

Three patients had their codes broken prior to the unblinding of the trial. Patient number 4618 (enoxaparin) died as a result of the ventricular fibrillation in the setting of a myocardial infarction. Patient number 6131 (enoxaparin) developed painless jaundice and was withdrawn from the study. This patient later died after undergoing an endosccpic papillotomy for obstruction. The Per-protocol analysis included patient number 7148 (desirudin) who had a pulmonary embolism.

Reviewer's Comment: The efficacy results were not significantly impacted by these patients.

Patients with code broken

Country	Select. / Label No.	Reason
A	4618 / 1466	Ventricular fibrillation due to fresh diaphragmal infarction. Code broken by order of the investigator for medical reason.
D	6131 / 1569	Code was broken since hospital head insisted for administrative reason.
F	7148 / 578	Requested by cardiologist in order to adapt the treatment.

Sponsor's table volume 1.74 pp.8-29-38

Exposure
There were no differences between treatment groups for the average total period (10.4 days) and average active treatment period (9.5 days) for the randomized patient population in the trial. Similar results were observed for the evaluable population.

Demographics
There were no significant differences between treatment groups for the randomized or evaluable population for age, sex, smoking history, height, weight, past medical history, and risk factors for thromboembolic disease.

Vital Signs
There were no significant differences between treatment groups for vital signs (pulse, and blood pressure).

Concomitant medications/Operation characteristics
There were no significant differences between treatment groups for concomitant medication or operation characteristics (average duration of operation, type of prosthesis, timing of pre-operative study injection, or timing of anesthesia).

Efficacy Results

Primary Outcome
The sponsor's study report defined the following new populations for analysis. Intent-to-Treat-1 population included all patients with an adequate centrally or locally (if central not available) assessed phlebogram or confirmed major thromboembolic event. The phlebogram could have been performed within 5 days of the end of the prophylactic period. Intent-to-Treat-2 population included all patients who had been randomized and treated. The sponsor's table below demonstrates the efficacy results for the primary outcome using the evaluable population.

Reviewer's Comment: These results suggest a statistically significant difference in favor of desirudin for the primary outcome (centrally confirmed proximal DVT, PE or death due to thromboembolic event or unexplained death). The primary efficacy results are statistically significant for the evaluable population at p < 0.02 level. Similar results were seen for the intent-to-treat populations.

TABLE 8.1.1:

SUMMARY OF PRIMARY EFFICACY OUTCOME DEFINED AS:
OCCURENCE OF THROMBOEMBOLIC EVENTS (PROXIMAL DVT, PULMONARY EMBOLISM, DEATH) DURING THE TRIAL TREATMENT PERIOD
(DATASET: EVALUABLE PATIENTS - PRIMARY OUTCOME)

CENTRE: ALL CENTRES

	enoxaparin Dose 40 mg	CGP 39393 Dose 15 mg	T O T A L
EVALUABLE PATIENTS-PRIMARY OUTCOME	N = 785	N = 802	N = 1587
Proximal DVT	59 (7.5 %)	36 (4.5 %)	95 (6.0 %)
Pulmonary Embolism	2 (0.3 %)	2 (0.2 %)	4 (0.3 %)
Death	0 (0.0 %)	1 (0.1 %)	1 (0.1 %)
Total Number of Events	61 (7.8 %)	39 (4.9 %)	100 (6.3 %)
Total Number of Patients with at least one event	60 (7.6 %)	39 (4.9 %)	99 (6.2 %)
95% Confidence Interval	5.9 % - 9.7 %	3.5 % - 6.6 %	5.1 % - 7.5 %
Comparing CGP 39393 15 mg versus enoxaparin 40 mg:			
relative risk reduction		36.4 %	
absolute risk reduction		2.8 %	

Proximal deep venous thrombosis: confirmed by centrally assessed phlebogram
Pulmonary embolism: confirmed by perfusion/ventilation lung scan, pulmonary angiography or pulmonary embolectomy
Death: related to thromboembolic event or unexplained

Sponsor's table volume 1.74 p.8-27-122

The table below shows the intent-to-treat analysis.

TABLE 8.1.6:

SUMMARY OF PRIMARY EFFICACY OUTCOME DEFINED AS:
OCCURENCE OF THROMBOEMBOLIC EVENTS (PROXIMAL DVT, PULMONARY EMBOLISM, DEATH) DURING THE TRIAL TREATMENT PERIOD
(DATASET: INTENT-TO-TREAT PRIMARY OUTCOME)

CENTRE: ALL CENTRES

	enoxaparin Dose 40 mg	CGP 39393 Dose 15 mg	T O T A L
INTENT-TO-TREAT PRIMARY OUTCOME	N = 803	N = 817	N = 1620
Proximal DVT	59 (7.3 %)	36 (4.4 %)	95 (5.9 %)
Pulmonary Embolism	2 (0.2 %)	2 (0.2 %)	4 (0.2 %)
Death	0 (0.0 %)	1 (0.1 %)	1 (0.1 %)
Total Number of Events	61 (7.6 %)	39 (4.8 %)	100 (6.2 %)
Total Number of Patients with at least one event	60 (7.5 %)	39 (4.8 %)	99 (6.1 %)
95% Confidence Interval	5.8 % - 9.5 %	3.4 % - 6.5 %	5.0 % - 7.4 %
Comparing CGP 39393 15 mg versus enoxaparin 40 mg:			
relative risk reduction		36.1 %	
absolute risk reduction		2.7 %	

Proximal deep venous thrombosis: confirmed by centrally assessed phlebogram
Pulmonary embolism: confirmed by perfusion/ventilation lung scan, pulmonary angiography or pulmonary embolectomy
Death: related to thromboembolic event or unexplained

Sponsor's table volume 1.74 p.8-27-127

Country and Center Effect

Seven of ten countries demonstrated a numerical treatment effect in favor of desirudin. The sponsor performed a treatment by country interaction assessment, however no statistically significant country effect was observed. Twenty centers (64.5%) demonstrated a treatment effect in favor of desirudin, four studies (12.9%) demonstrated no difference in efficacy, and seven centers (22.6%) demonstrated a treatment effect in favor of enoxaparin. For details see Country and Center Analysis – RH/E 25 in Appendix 2.

Reviewer's Comment: The sponsor did not perform a treatment by center assessment. Although center results are not uniform, the majority of centers demonstrated a numerical treatment effect in favor of desirudin. Some of the centers that did not demonstrate a treatment effect in favor of desirudin enrolled few patients and had few qualifying events.

Local versus Central Radiology Readings

There was discrepancy between the central readers and local readers. Local readers more frequently read films as negative for DVT than did central readers. Central readers read more films as inadequate for DVT than did local readers.

PHLEBOGRAPHY: LOCAL VERSUS CENTRAL ASSESSMENT COMPARING PROXIMAL DEEP VENOUS THROMBOSIS
(DATASET: RANDOMISED PATIENTS)

CENTRE: ALL CENTRES

Central Assessment	Local Assessment				
	Proximal DVT	No proximal DVT	Inadequate	Not performed	All
Proximal DVT	43	47	3		93
No proximal DVT	28	1462	31		1521
Inadequate	7	83	121		211
Not performed		1		251	252
All	78	1595	155	251	2079

NOTE: DVT = Deep venous thrombosis
Inadequate refers to a non assessable phlebogram in the popliteal veins or above including unilateral phlebograms without confirmed proximal DVT

Sponsor's table volume 1.74 p. 8-27-126

Secondary Outcome

The numerical difference between primary and secondary outcomes for the evaluable population resulted from the addition of distal DVT to the secondary outcome. The sponsor's table below demonstrates the efficacy results for the secondary outcome using the evaluable population.

Reviewer's Comment: The discrepancy in the number of patients in the evaluable population arises from the fact that the evaluable population for the secondary outcome had to have a venogram that visualized all veins (proximal and distal). Thus, fewer venograms would have met those criteria for adequacy of visualization of the distal venous system.
The secondary results suggest a statistically significant difference in favor of desirudin for the secondary outcome (centrally confirmed DVT (proximal and distal), PE or death due to thromboembolic event or unexplained death). The secondary efficacy results are statistically significant for the evaluable population at $p < 0.01$ level. The sponsor did not provide the ITT analysis.

SUMMARY OF SECONDARY EFFICACY OUTCOME DEFINED AS:
OCCURRENCE OF THROMBOEMBOLIC EVENTS (DVT, PULMONARY EMBOLISM, DEATH) DURING THE TRIAL TREATMENT PERIOD
(DATASET: EVALUABLE PATIENTS - SECONDARY OUTCOME)

CENTRE: ALL CENTRES

	enoxaparin Dose 40 mg	CGP 39393 Dose 15 mg	T O T A L
EVALUABLE PATIENTS-SECONDARY OUTCOME	N = 768	N = 773	N = 1541
DVT	196 (25.5 %)	142 (18.4 %)	338 (21.9 %)
Pulmonary Embolism	2 (0.3 %)	2 (0.3 %)	4 (0.3 %)
Death	0 (0.0 %)	1 (0.1 %)	1 (0.1 %)
Total Number of Events	198 (25.8 %)	145 (18.8 %)	343 (22.3 %)
Total Number of Patients with at least one event	197 (25.7 %)	145 (18.8 %)	342 (22.2 %)
95% Confidence Interval	22.6 % - 28.9 %	16.1 % - 21.7 %	20.1 % - 24.4 %
Comparing CGP 39393 15 mg versus enoxaparin 40 mg:			
relative risk reduction		26.9 %	
absolute risk reduction		6.9 %	

Deep venous thrombosis (DVT): confirmed by centrally assessed phlebogram
Pulmonary embolism: confirmed by perfusion/ventilation lung scan, pulmonary angiography or pulmonary embolectomy
Death: related to thromboembolic event or unexplained

Sponsor's table volume 1.74 p. 8-27-130

Thromboembolic Events by Severity

The sponsor's table below shows the results of a comparison of severity of thromboembolic events. The secondary composite outcome (distal and proximal DVT, PE, and death) demonstrated a lower incidence for desirudin treated patients compared with the enoxaparin patients. Desirudin treated patients had a lower incidence of deep vein thrombosis compared with enoxaparin. There was no difference between treatment groups for pulmonary embolism and death. Review of the overall DVT rate by country demonstrated that 8 countries out of 10 showed a reduced incidence for desirudin treated patients compared with enoxaparin treated patients.

SUMMARY OF THROMBOEMBOLIC EVENTS AT THE END OF THE TRIAL TREATMENT PERIOD ACCORDING TO THE SEVERITY OF THE EVENT (MOST SEVERE EVENT IS COUNTED)
(DATASET: EVALUABLE PATIENTS - SECONDARY OUTCOME)

CENTRE: ALL CENTRES

	enoxaparin Dose 40 mg	CGP 39393 Dose 15 mg	T O T A L
EVALUABLE PATIENTS FOR SECONDARY OUTCOME	N = 768	N = 773	N = 1541
DEATH	0 (0.0 %)	1 (0.1 %)	1 (0.1%)
PULMONARY EMBOLISM	2 (0.3 %)	2 (0.3 %)	4 (0.3%)
DEEP VENOUS THROMBOSIS			
Proximal DVT	58 (7.6 %)	36 (4.7 %)	94 (6.1%)
Distal DVT (Muscular DVT included)	137 (17.8 %)	106 (13.7 %)	243 (15.8%)
Only Muscular DVT	67 (8.7 %)	50 (6.5 %)	117 (7.6%)

Deep venous thrombosis: confirmed by centrally assessed phlebogram
Pulmonary embolism: confirmed by perfusion/ventilation lung scan, pulmonary angiography or pulmonary embolectomy
Death: related to thromboembolic event or unexplained

Sponsor's table volume 1.74 p. 8-29-133

Clinical Signs and Symptoms of a Thromboembolic Event

The following table provides data on those patients who presented with clinical signs and symptoms of a thromboembolic event during Treatment and Follow-up.

Reviewer's Comment: The majority of the DVTs in the table below are distal. There was one proximal DVT in the enoxaparin group during treatment and one proximal DVT in the desirudin group during follow up. The pulmonary embolism data during the follow up period was difficult to assess because some patients only had a perfusion scan but no ventilation scan or other test (e.g., pulmonary angiogram).

Clinical Signs and Symptoms of a Thromboembolic Event in Study RH/E 25

	Desirudin	Enoxaparin	Total
Treatment Period			
Clinical Signs/Symptoms- DVT	12	11	23
Confirmed by centrally assessed phlebography	2	4	6
Phlebography not done	0	1	1
Clinical Signs/Symptoms- PE	8	4	12
Confirmed by V/Q scan	2	2	4
Follow up Period			
Clinical Signs/Symptoms- DVT	12	9	21
Confirmed by locally assessed phlebography	4	1	5
Confirmed by locally Doppler Ultrasound	2	2	4
Clinical Signs/Symptoms- PE	4	7	11
Confirmed by V/Q scan	1	4	5

Reviewer's Table

Deaths During the Treatment and Follow up Period not counted in the Primary outcome

There were two deaths during the treatment period that were not counted in the Primary outcome. During the treatment period, one desirudin patient (#6654) had a ventricular fibrillation arrest during the hip replacement operation and was not successfully resuscitated. An enoxaparin patient (# 4618) experienced chest pain and was found on autopsy to have a fresh diaphragmatic infarction with no evidence of thrombosis or embolism.

There were four deaths during the follow up period. One enoxaparin patient (# 6131) died the day after trial participation ended due to cardiovascular disease. Three desirudin patients died after the conclusion of the trial. One desirudin patient (# 8705) died of a pulmonary embolism approximately one month after trial conclusion. One desirudin patient (# 8679) died of a cerebral hematoma approximately 18 days after receiving the last desirudin injection. This particular patient received other anticoagulants (dalteparin and acenocoumarol) after ending her participation in the trial. One desirudin patient (# 7078) died of "cardiovascular collapse" per the investigator two days after trial ended. The family refused an autopsy.

Reviewer's Comment: This reviewer reviewed these cases and did not always agree with how cause of death was adjudicated. However, these cases were clearly after the medication was stopped and in accordance with the protocol would not have been met the criteria for an endpoint. Even if these cases were included along with the deaths during the trial, the efficacy results would still favor desirudin.

Evaluation of Confounding Factors

The sponsor's tables below show the primary and secondary outcome results for subgroups of treated patients. Subgroup factors such as age, sex, prosthesis type, type of anesthesia, and obesity were evaluated. In all subgroup analyses patients treated with desirudin had a lower event rates.

NUMBER OF DEEP VENOUS THROMBOSIS BY TREATMENT AND SUBPOPULATIONS
(DATASET: EVALUABLE PATIENTS - PRIMARY OUTCOME)

Treatment	enoxaparin Dose 40 mg		CGP 39393 Dose 15 mg		TOTAL	
EVALUABLE PATIENTS - PRIMARY OUTCOME	N = 785		N = 802		N = 1587	
AGE						
< 65 yrs	15 / 333	4.5%	16 / 368	4.3%	31 / 701	4.4%
>=65 yrs	44 / 452	9.7%	20 / 434	4.6%	64 / 886	7.2%
SEX						
male	26 / 323	8.0%	19 / 355	5.4%	45 / 678	6.6%
female	33 / 462	7.1%	17 / 447	3.8%	50 / 909	5.5%
PROSTHESIS						
Cemented	38 / 464	8.2%	21 / 493	4.3%	59 / 957	6.2%
Non-cemented	21 / 321	6.5%	15 / 309	4.9%	36 / 630	5.7%
ANAESTHESIA						
Regional block anaesthesia	22 / 458	5.0%	20 / 441	4.5%	42 / 899	4.8%
General alone	36 / 343	10.5%	16 / 357	4.5%	52 / 700	7.4%
OBESITY						
no	36 / 467	7.7%	21 / 481	4.4%	57 / 948	6.0%
yes	23 / 316	7.3%	14 / 320	4.4%	37 / 636	5.8%

Regional block anaesthesia is defined as either epidural or spinal anaesthesia or a combination of epidural with spinal anaesthesia

Sponsor's table volume 1.74 p.8-27-146

NUMBER OF DEEP VENOUS THROMBOSIS BY TREATMENT AND SUBPOPULATIONS
(DATASET: EVALUABLE PATIENTS - SECONDARY OUTCOME)

Treatment	enoxaparin Dose 40 mg		CGP 39393 Dose 15 mg		T O T A L	
EVALUABLE PATIENTS - SECONDARY OUTCOME	N = 768		N = 773		N = 1541	
AGE						
< 65 yrs	66 / 326	20.2%	49 / 354	13.8%	115 / 680	16.9%
>=65 yrs	130 / 442	29.4%	93 / 419	22.2%	223 / 861	25.9%
SEX						
male	69 / 311	22.2%	56 / 338	16.6%	125 / 649	19.3%
female	127 / 457	27.8%	86 / 435	19.8%	213 / 892	23.9%
PROSTHESIS						
Cemented	118 / 448	26.6%	79 / 462	17.1%	197 / 910	20.8%
Non-cemented	86 / 320	26.9%	63 / 311	20.3%	149 / 631	23.6%
ANAESTHESIA						
Regional block anaesthesia	85 / 430	19.8%	59 / 423	13.9%	144 / 853	16.9%
General alone	119 / 334	32.9%	81 / 346	23.4%	191 / 680	28.1%
OBESITY						
no	108 / 451	23.9%	73 / 461	15.8%	181 / 912	19.8%
yes	88 / 315	27.9%	68 / 311	21.9%	156 / 626	24.9%

Regional block anaesthesia is defined as either epidural or spinal anaesthesia or a combination of epidural with spinal anaesthesia

Sponsor's table volume 1.74 p. 8-27-148

Safety

Overall 71% of patients reported adverse experiences regardless of treatment group. The most frequent adverse event was hemorrhage NOS which occurred in 26% of patients. The incidence of a mild, moderate or severe adverse reaction is listed in the table below. Severe adverse reactions were more frequent for the desirudin treatment group.

Reviewer's Comment: These differences were numerical and not statistically significant.

Severity of Adverse Reactions for Study RH/E 25

	Desirudin (N=1043)	Enoxaparin (N=1036)
Mild	368 (35.3%)	389 (37.5%)
Moderate	316 (30.3%)	310 (29.9%)
Severe	53 (5.1%)	33 (3.2%)

Reviewer's table

The sponsor's tables for all adverse events occurring during this trial are listed in Appendix 3.

The table below shows the statistically significant difference for adverse events between desirudin patients than enoxaparin patients.

Statistically Significant Difference in Adverse Events Seen in RH/E 25

Event	Number/ Percent of Desirudin Patient Reports	Number/ Percent of Enoxaparin Patient Reports	P-value
Injection Site Mass	28 (2.7%)	6 (0.6%)	0.0103

Reviewer's Table

Bleeding Complications Overall

The sponsor's table below shows the frequency of overall bleeding complications. Desirudin is associated with increased major bleeding, increased injection site hematoma/infection, and increased surgical site bleeding.

OCCURRENCE OF INJECTION SITE HAEMATOMA, WOUND HAEMATOMA/INFECTION AND MAJOR OR SERIOUS BLEEDING (DATASET: OPERATED PATIENTS)

ALL CENTRES

	enoxaparin Dose 40 mg		CGP 39393 Dose 15 mg		T O T A L	
Operated patients	N = 1023		N = 1028		N = 2051	
	n	%	n	%	n	%
INJECTION SITE HAEMATOMA	6	0.6	29	2.8	35	1.7
WOUND HAEMATOMA/INFECTION	88	8.6	98	9.5	186	9.1
MAJOR BLEEDING	2	0.2	8	0.8	10	0.5
SERIOUS BLEEDING	20	2.0	20	1.9	40	2.0

Sponsor's table volume 1.74 p.8-27-195

Serious Adverse Events

The sponsor's table below shows the incidence of serious adverse events reported. There is no significant difference between the two treatment groups.

Serious Adverse Events for RH/E 25

	enoxaparin (N=1036)	CGP 39393 (N=1043)	Total (N=2079)
CVA (Cerebro Vascular Accident)	1	2	3
CNS (Central Nervous System)	1	4	5
CVS (Cardio Vascular System)	7	7	14
DEATH	2	4	6
THROMBOEMBOLISM - Pulmonary Embolism *	1	1	2
NOS (Not otherwise specified)	45	41	86
BLEEDING - Surgical bleeding - Spontaneous bleeding - Gastrointestinal bleeding - Wound leakage - Haematoma	 19 0 0 0 6	 24 0 2 0 5	 43 0 2 0 11
IMMUNO ALLERGY	1	1	2
PROCEDURE COMPLICATING	1	0	1
TOTAL	**84**	**91**	**175**
Patients with at least one event	**75 (7.2%)**	**78 (7.5%)**	**153 (7.4%)**

* according to the Trial Protocol, the clinical endpoints, DVT and non-fatal PE, had not to be reported as an SAE.

Sponsor's table volume 1.74 p.8-27-48

Peri-operative, Post-operative Blood and Transfusions

There was no difference between treatment groups for average peri-operative (950 ml) and post-operative blood loss (250 ml). Twelve patients in each treatment group lost more than 3500 ml up to post-op day 6.

Peri-operative transfusion requirement exceeding 5 units of whole blood or concentrated red blood cells occurred in 9 patients in the enoxaparin group and 4 patients in the desirudin

group. Post-operative transfusion requirement up to day 6 exceeding 7 units of whole blood or concentrated red blood cells occurred in 11 patients in the enoxaparin group and 9 patients in the desirudin group. No significant difference was observed in the use of plasma expanders between the treatment groups.

Laboratory abnormalities

There were no significant differences for laboratory abnormalities (hgb, hct, plt, sgot, sgpt, creatinine, and total bilirubin) between the treatment groups. More desirudin patients (24) with a normal baseline creatinine had an elevated creatinine at the end of treatment compared with enoxaparin (12). More desirudin patients (59) with a normal baseline total bilirubin had an elevated total bilirubin at the end of treatment compared with enoxaparin (49). More desirudin patients (43) with normal baseline potassium had elevated potassium at the end of treatment compared with enoxaparin (29).

Trial: RH/E 28

Reviewer's Conclusion regarding RH/E 28
The sponsor conducted a multicenter, randomized, double-blind, parallel-design, active-controlled trial comparing pre-operative desirudin 15 mg with heparin. Overall, the heparin treatment group had a higher primary event rate (DVT, PE, and Death) compared with the desirudin treatment groups ($p < 0.001$) for the evaluable population. Similar results were seen for the intent-to-treat populations. Similar results were also observed for the secondary event rate (severity of thromboembolic event proximal and distal DVT, PE, and Death) ($p< 0.001$). The Agency's Statistical Review and Evaluation concurs with the sponsor's analyses for the primary and secondary event rates. These results were observed in subgroup analyses. The study results were driven by differences in DVT rates. There was no significant difference in safety between the desirudin and enoxaparin treatment groups.

Design:
The trial was a multicenter, randomized, double-blind, parallel-design, heparin-controlled involving 11 centers evaluating the efficacy of one dose of CGP39393 in patients undergoing a primary elective total hip replacement.

Trial was conducted from November 28, 1993 to August 23, 1994.

One amendment was made to the protocol on October 23, 1993 to change the dose of desirudin from 20 mg to 15 mg. This amendment was made one month prior to enrollment of the first patient.

Inclusion and Exclusion Criteria
The sponsor's inclusion and exclusion criteria are printed below.

INCLUSION CRITERIA

In-patients planned to undergo a primary elective total hip replacement are eligible provided the following conditions are fulfilled:

- age $\geq$ 18 years
- weight $\geq$ 50 kg
- an unilateral operation

EXCLUSION CRITERIA

The in-patients must be excluded from the trial if one or more of the following criteria are fulfilled

General

- Amputees of one leg
- Previous hip surgery or fracture within last 3 months
- Known or suspected allergy to natural or recombinant hirudins (i.e. isoforms) or to heparins
- Previous inclusion in this trial
- Women of childbearing potential or nursing mothers (women are considered to be of childbearing potential unless they are post-hysterectomy, one or more years post-menopausal or one or more years post-tubal ligation).

Cardiovascular and Haematologic

- Known haemostatic disorders (congenital or acquired, e.g. liver disease) including thrombocytopenia (< 100×10^9 platelets/L, i.e. < 100'000/mm^3)
- Major surgery, biopsy or puncture of a non-compressible vessel (within the past month)
- History of gastrointestinal or pulmonary bleeding (within the past 3 months)
- History of haemorrhagic stroke, intracranial or intraocular bleeding (including diabetic [haemorrhagic] retinopathy)
- Active bleeding
- Hypertension (i.e. diastolic blood pressure > 110 mm Hg)
- Cerebral ischaemic attacks (within the last 6 months).

Previous Treatments / Concomitant Medications and Therapies

- The use of
  - Heparins (except that used in the present trial, or in connection with the intraoperative salvage of red blood cells)
  - Oral anticoagulants
  - Thrombolytic agents
  - Dextrans
  - Long-acting nonsteroidal anti-inflammatory drugs (defined as those requiring a greater than seven day washout period)
  - Acetylsalicylic acid
  - Dipyridamole
  - Sulphinpyrazone
  - Ticlopidine

  are prohibited within 7 days prior to the start of surgery and during the trial drug prophylaxis period.
- Anticoagulants should not be used during the follow-up period of the trial, unless the need arises (e.g. treatment of DVT or PE).
- Cytolytic treatment within the past 6 months is also prohibited.
- The use of any investigational drug within 30 days prior to the start of the trial is prohibited.
- The use of non graded stockings is prohibited.

Others

- Nephrectomized or kidney transplanted patients
- Renal impairment (defined as a serum creatinine above the upper limit of the clinic)
- Known inflammatory bowel disease
- Contraindication to contrast media e.g. documented history of allergy
- Any other condition which, in the investigator's opinion, might increase the risk to the patient or decrease the chance of obtaining reliable data for the objectives of the trial.

Sponsor's text volume 1.80 p.8-33-14-16

Treatment Administration:
CGP 39393
Dose – 15 mg sc bid

Heparin
Dose – 5000 units sc tid

The sponsor's text below refers to the timing of the injections.

The dosing regimen will be as follows:

Operation day: (afternoon and evening injection should be given at least 6 hours apart)

CGP 39 393 Group:	2 hrs preop.	Placebo
	within 30 min preop. *	CGP 39 393
	Afternoon	Placebo
	Evening	CGP 39 393
UH Group:	2 hrs preop.	UH
	within 30 min preop. *	Placebo
	Afternoon	UH
	Evening	UH

Post-operation days: (Injections should be given at least 6 hours apart)

CGP 39 393 Group:	Morning	CGP 39 393
	Afternoon	Placebo
	Evening	CGP 39 393
UH group:	Morning	UH
	Afternoon	UH
	Evening	UH

* but after regional block anaesthesia if used.

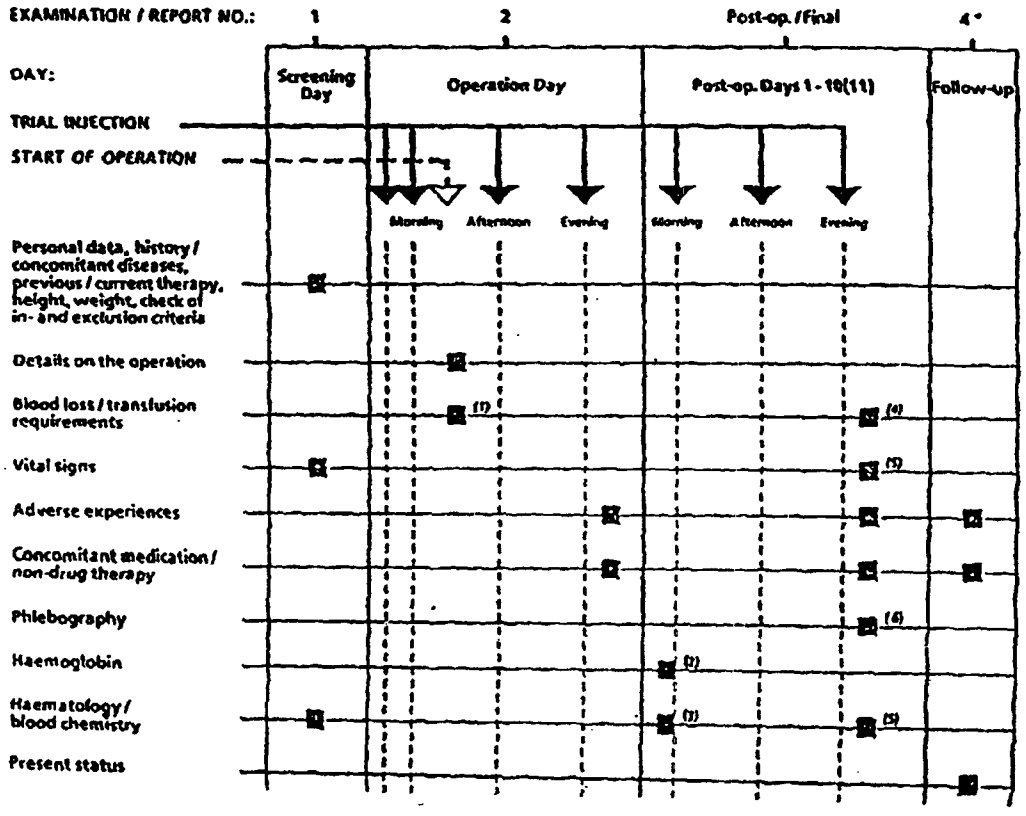
Sponsor's text volume 1.80 p.8-33-11

Randomization
Fixed Block randomization was used. Complete randomization blocks were given to different centers. Investigators were instructed to use the lowest allocation number first in order to maintain randomization.

Concomitant Medication
See above inclusion/exclusion information.

Flow of trial
The diagram below outlines the sponsor's flow chart for RH/E 28. Physicians were instructed to operate on patients in the morning. If hemorrhagic or other technical difficulties arose during the administration of regional anesthesia, the patient was to be prematurely discontinued from the trial.

FLOW CHART



(1) Cumulative start of surgery up to 12 hours post-op.

(2) Morning of post-op. Day 1

(3) Post-op. Day 6 only

(4) Cumulative post-op. 12 hours to Day 6 inclusive

(5) To be performed on the day of the phlebography or in the event of premature discontinuation of the Prophylaxis Period

(6) To be performed between post-op. Days 8 - 10(11) or earlier if necessary

* To be completed 6 weeks after surgery

Sponsor's diagram volume 1.80 p.8-33-52

Premature Discontinuation from the Trial
Patients could be prematurely discontinued from a trial for an endpoint, an adverse event, phlebography prior to day 8, lack of tolerable response, major violation of the protocol, and withdrawal of consent.

Efficacy Measurements

Bilateral Ascending Venography
The protocol required the procedure to be performed on post-operative day 8-12 in all patients who did not manifest clinical evidence of a deep venous thrombosis or pulmonary embolism earlier in the trial. An adequate venogram was defined as a venogram where all veins (muscular, anterior tibial, posterior tibial, fibular, popliteal, superficial femoral, common

femoral, deep femoral, and iliac are seen. A local radiologist initially read the films and then the venograms were sent in blinded fashion to be read by the central radiologists.
The venogram was read centrally by two radiologists as either

1) normal (i.e. negative for DVT)
2) presence of an intraluminal defect (i.e. positive for DVT)
3) inadequate

Pulmonary embolism

Ventilation/perfusion scans

Ventilation/perfusion scans were performed if the patient exhibited clinical signs suggestive of a pulmonary embolism.

Ventilation/perfusion scans had three possible readings/scenarios:

1) high probability – ventilation/perfusion scan with either a segmental or greater mismatched defects or large subsegmental defects with ventilation mismatch
2) normal lung scan (i.e. low probability lung scan) - characterized by an absence of perfusion defects in all fields
3) any reading which does not fit into the above categories should be confirmed by a pulmonary angiogram

Patients could also be diagnosed as having a pulmonary embolism if they had a positive angiogram.

Efficacy

Patients are counted only once.
Primary efficacy was defined by the composite endpoint:

1) a positive bilateral ascending phlebography performed at the end of the prophylaxis period and assessed centrally and/or
2) high probability ventilation/perfusion scan and/or
3) positive pulmonary angiogram and/or
4) an autopsy with documented thrombosis and/or
5) unexplained death during the prophylaxis period

The statistical analysis plan was to perform linear logistic regression with treatment and center as fixed factors and a two-sided test for significance at 5%. A 95% confidence interval was to be given for the estimated log odds ratio. Treatment by center interaction evaluation was to be performed.

Secondary Outcome

Severity of thromboembolic events were graded as follows:
Death > pulmonary embolism > DVT (proximal) or DVT (distal).

Patients were excluded from the primary analysis of efficacy based on the following (considered non-evaluable):

1) phlebography is performed before day 8 of prophylaxis and is negative according to central assessment
2) phlebography has not been done within one day after the end of prophylaxis
3) phlebography has been done but not assessed centrally
4) inadequate phlebogram
5) major protocol violation occurs
   c) use of oral anticoagulants, thrombolytics, or dextrans
   d) less than 80% compliance

Safety assessment
Bleeding complications included:

1) peri-operative (i.e. 12 hour period from the time the operation started)
2) post-operative (i.e. 12 hours to 6 days)

Major bleeding was defined as a:

1) fall in hemoglobin of at least 2 gms/dl which is overt or
2) transfusion of ≥ 2 units packed red cells in the post-operative period which is overt or
3) retroperitoneal or
4) intracranial or intraocular
5) into a prosthetic joint

Serious bleeding was defined:

1) peri-operative transfusion requirements exceed 5 units of whole blood or packed red blood cells or
2) total transfusion requirements up to post-op day 6 exceeding 7 units
3) total blood loss up to post-op day 6 exceeding 3500 ml

Results of Pivotal Efficacy Trial RH/E 28

The trial was conducted in 11 centers from 2 countries (3 centers in Denmark and 8 centers in Sweden). Sweden contributed 360 (79.6%) randomized patients total out of 445 randomized. The total number of patients enrolled was 452.

Reviewer's Comment: The protocol planned for an enrollment of 420 patients.

Premature Discontinuations

The sponsor's table below shows the number of patients who prematurely discontinued. The greatest number of patients discontinued due to an adverse event. None of those discontinuing due to an adverse event experienced a thrombotic endpoint. There was no difference in discontinuation between treatment groups.

Number of Patients Discontinued Prematurely in RH/E 28

	Heparin	Desirudin (15 mg)	Total
Enrolled	N/G	N/G	452
Randomized	220	225	445
Completed	193	202	395
Discontinued Prematurely (Did not complete)	27	23	50 (11.2%)
Administrative problems	1	1	2
Adverse Experience	13	9	22
Protocol criteria not met	8	10	18
Withdrawal of consent	5	3	8

Reviewer's Table

The table below shows the number of patients excluded from the efficacy analyses. The protocol anticipated that 20% of patients would be excluded from the efficacy analyses. Actually 18.8% were excluded. The majority of patients were excluded because they did not have a phlebography.

Reviewer's Comment: The sample size calculation in the original protocol planned for 336 total or 168 evaluable patients in each treatment group.

Patients Excluded from Efficacy Analyses – RH/E 28

	Heparin	Desirudin	Total
Excluded from PP and ITT*	40	45	85 (100%)
Concomitant medication not allowed	0	1	1 (1.2%)
Inadequate central reading	8	15	23 (27.1%)
No operation	0	2	2 (2.4%)
No phlebography	33	28	61 (71.8%)
Phlebography performed at wrong time	1	0	1 (1.2%)

Excluded from PP only	3	6	9 (10.6%)
Concomitant medication not allowed	3	4	7 (8.2%)
Phlebography performed at wrong time	0	2	2 (2.4%)

* More than one reason per patient.
Reviewer's table

Treatment Administration

Medication errors were noted in the desirudin treatment group only. All ten patients received an additional desirudin injection instead of receiving placebo. None of these patients were excluded from the per-protocol analysis.

Center Withdrawal
One center in Sweden discontinued after two patients developed thrombocytopenia.

Code Broken

The table below shows the list of patients who had their code broken during the conduct of the trial. All three patients had their code broken because of a serious adverse event. The sponsor continued these patients in the trial because the endpoint assessment was blinded and was performed.

LIST OF PATIENTS WITH CODE BROKEN

		Code broken		
Country	Patno	by Invest.	by Ciba	Reason
S	131	YES		Suspected thrombocytopenia
	328	YES		Suspected thrombocytopenia
DK	152	YES		Compartment syndrome, haematoma, reoperation Wish of anaesthesiologist

Sponsor's table volume 1.79 p. 8-32-36

Exposure
There were no differences between treatment groups for the average duration of treatment (8.8 days) and average active treatment period (7.8 days) for the ITT population in the trial. Similar results were observed for the evaluable population.

Demographics
There were no significant differences between treatment groups for the randomized or evaluable population for age, sex, smoking history, height, weight, past medical history, and risk factors for thromboembolic disease. In both the randomized and per-protocol patients there were more patients in the desirudin treatment group with obesity (≥ 20% overweight) or history of varicose veins. In both the randomized and per-protocol patients there were more patients in the heparin treatment group with a history of myocardial disorder, respiratory, or musculoskeletal disorder.

Vital Signs

There were no significant differences between treatment groups in vital signs (pulse and blood pressure).

Concomitant medications/Operation characteristics
There were no significant differences between treatment groups in concomitant medication or operation characteristics (average duration of operation, type of prosthesis, timing of pre-operative study injection, or timing of anesthesia).

Efficacy Results

Primary Outcome

The sponsor's study report defined the following new populations for analysis. Intent-to-Treat-1 population included all patients with an adequate centrally assessed phlebogram. The phlebogram could have been performed within 5 days of the end of the prophylactic period. Intent-to-Treat-2 population included all patients who had been randomized and treated.

No patient died or experienced a pulmonary embolism for either treatment group during the trial. Two deaths occurred in the enoxaparin treatment group during the follow up period.

The sponsor's table below shows the efficacy results for the primary outcome using the evaluable population.

Reviewer's Comment: These results demonstrate a statistically significant difference in favor of desirudin for the primary outcome (proximal and distal DVT, PE, and death). The primary efficacy results are statistically significant at p < 0.001 level. Similar results were seen for the other populations (intent-to-treat-1, intent-to-treat-2).

SUMMARY OF THROMBOEMBOLIC EVENTS OCCURING DURING THE TREATMENT PERIOD
(DATASET: PER-PROTOCOL POPULATION)

CENTRE: ALL CENTRES

Thromboembolic Event	Unfractionated Heparin Dose 5000 IU N = 177	CGP 39393 Dose 15 mg N = 174	T O T A L N = 351
DEEP VENOUS THROMBOSIS (based on central reading)	41 (23.2 %)	13 (7.5 %)	54 (15.4 %)
PULMONARY EMBOLISM (confirmed #)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Death ##	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Total Number of Events	41 (23.2 %)	13 (7.5 %)	54 (15.4 %)
Total Number of Patients with at least one event	41 (23.2 %)	13 (7.5 %)	54 (15.4 %)
95% Confidence Interval	17.2 % - 30.1 %	4.0 % - 12.4 %	11.8 % - 19.6 %
Comparing CGP 39393 versus unfractionated heparin:			
relative risk reduction		67.7 %	
absolute risk reduction		15.7 %	

Confirmed by perfusion/ventilation lung scan or pulmonary angiography
Death related to thromboembolic event or unexplained

Sponsor's table volume 1.79 p.8-32-174

Country Effect

The sponsor performed a treatment by country interaction assessment. No interaction was observed.

Reviewer's Comment: The sponsor did not perform a treatment by center interaction assessment. Nine out of eleven centers (81.8%) demonstrated a treatment effect in favor of desirudin.

Local versus Central Radiology Readings

There was discrepancy in readings between the central and local readers. Local readers incorrectly identified 18 films as negative for DVT, which were read by the central readers as positive for DVT.

PHLEBOGRAPHY: LOCAL VERSUS CENTRAL ASSESSMENT
(DATASET: RANDOMISED PATIENTS)

CENTRE: ALL CENTRES

Central Assessment	Local Assessment				
	DVT	No DVT	Inadequate	Missing	All
DVT	36	18	1		55
No DVT	15	270	20		305
Inadequate	1	12	12		25
Missing				67	67
All	52	300	33	67	452

NOTE: DVT = DEEP VENOUS THROMBOSIS

Sponsor's table volume 1.79 p.8-32-140

Secondary Outcome

The sponsor's table below shows the results of the analysis of secondary outcome. For the evaluable population, the proximal and distal DVT rates were lower with desirudin.

SUMMARY OF THROMBOEMBOLIC EVENTS OCCURING DURING THE TREATMENT PERIOD
ACCORDING TO THE SEVERITY OF THE EVENT (MOST SEVERE EVENT IS COUNTED)
(DATASET: PER-PROTOCOL)

CENTRE: ALL CENTRES

	Unfractionated Heparin Dose 5000 IU N = 177	CGP 39393 Dose 15 mg N = 174	TOTAL N = 351
Death *)	0 (0.0 %)	0 (0.0 %)	0 (0.0%)
PULMONARY EMBOLISM (confirmed **)	0 (0.0 %)	0 (0.0 %)	0 (0.0%)
DEEP VENOUS THROMBOSIS (based on central reading)			
Proximal DVT	29 (16.4 %)	6 (3.4 %)	35 (10.0%)
Distal DVT (Muscular DVT included)	12 (6.8 %)	7 (4.0 %)	19 (5.4%)
Only Muscular DVT	8 (4.5 %)	1 (0.6 %)	9 (2.6%)

* Death related to thromboembolic event or unexplained
** Confirmed by perfusion/ventilation lung scan or pulmonary angiography

Sponsor's table p.8-32-147

Clinical Signs and Symptoms of a Thromboembolic Event

The following table provides data on those patients who presented with clinical signs and symptoms of a thromboembolic event during Treatment and Follow-up.

Reviewer' Comment: The table below shows that there were more events during the follow-up period for the heparin treatment group.

Clinical Signs and Symptoms of a Thromboembolic Event in Study RH/E 28

	Desirudin	Heparin	Total
Treatment Period			
Clinical Signs/Symptoms- DVT	4	6	10
Confirmed by centrally assessed phlebography	2	2	4
Clinical Signs/Symptoms- PE	1	2	3
Confirmed by V/Q scan or angiogram	0	0	0
Follow up Period			
Clinical Signs/Symptoms- DVT	4	5	9
Confirmed by locally assessed phlebography	2	2	4
Confirmed by locally Doppler Ultrasound	0	1	3
Clinical Signs/Symptoms- PE	2[1]	5	7
Confirmed by V/Q scan	0	4	4

[1] One patient had no testing performed and the other had a negative angiogram.
Reviewer's Table

Deaths During the Follow up Period

There were two deaths in the follow up period. Both patients received heparin. One patient died two weeks after the end of trial treatment due to a complicated medical course, which included myocardial and cerebral infarction. That patient received additional anticoagulants during the admission for myocardial infarction. The other patient died 1 month after the end of trial treatment after a prolonged course which included the developed of severe thrombocytopenia, retroperitoneal bleeding, and finally sepsis.

Evaluation of Confounding Factors

The sponsor's tables below show the primary and secondary outcome results for subgroups of treated patients. Subgroup factors such as age, sex, and obesity were evaluated. In all subgroup analyses patients treated with desirudin had a lower event rates.

RESULTS OF MODEL FITTING (TREATMENT, COUNTRY, AGE, SEX AND NUMBER OF RISKFACTORS)
OUTCOME VARIABLE - THROMBOEMBOLIC EVENT
(DATASET: PER-PROTOCOL)

Model	Chi-Square Test-Statistic (-2 LOG L)	d.f.		Change in Deviance	d.f.	Significance (p-value)
TREATMENT,Country, AGE, SEX, OBESITY, NUMBER OF RISK FACTORS	19.136	5	(p=0.0018)			
Test on:						
AGE	18.196	4	(p=0.0011)	0.94	1	0.33228
SEX	18.935	4	(p=0.0008)	0.20	1	0.65391
NUMBER OF RISK FACTORS	19.110	4	(p=0.0007)	0.03	1	0.87190

Sponsor's table volume 1.79 p.8-32-155

Safety

Overall 52% of patients reported adverse experiences. Fifty-four percent of patients treated with heparin compared with forty-nine percent with desirudin. The most frequent adverse event (excluding DVT) was hemorrhage NOS which occurred in 5.4% of patients. The incidence of a mild, moderate or severe adverse reaction is listed in the table below. Severe adverse reactions were more frequent for the heparin treatment group.

Severity of Adverse Reactions for Study RH/E 28

	Desirudin (N=225)	Enoxaparin (N=220)	P-value
Mild	62 (27.6%)	67 (30.5%)	0.531
Moderate	43 (19.1%)	31 (14.1%)*	0.0183
Severe	6 (2.7%)	20 (9.1%)	0.042

Reviewer's table

The sponsor's tables for all adverse events occurring during this trial are listed in Appendix 3.

There were no statistically significant differences for adverse events between treatment groups other than those listed above.

Bleeding Complications Overall

The sponsor's table below shows the frequency of overall bleeding complications. Desirudin is associated with wound hematoma/infection.

OCCURRENCE OF INJECTION SITE HAEMATOMA AND WOUND HAEMATOMA/INFECTION
(DATASET: RANDOMISED PATIENTS)

ALL CENTRES

	Unfractionated Heparin Dose 5000 IU N = 220		CGP 39393 Dose 15 mg N = 225		TOTAL N = 445	
	n	%	n	%	n	%
INJECTION SITE HAEMATOMA	4	1.8	4	1.8	8	1.8
WOUND HAEMATOMA/INFECTION	11	5.0	14	6.2	25	5.6

Sponsor's table volume 1.79 p.8-32-175

Serious Adverse Events

The sponsor's table below shows the incidence of serious adverse events reported. An increased number of serious adverse events occurred in the heparin treated patients.

RH/E 28 (n = 445)	15 mg	Heparin	Total
CVA (Cerebral Vascular Accident)	0	2	2
CNS (Central Nervous System)	1	3	4
CVS (Cardio Vascular Sytem)	4	6	10
DEATH	0	2	2
THROMBOEMBOLISM			
- Deep Vein Thrombosis	1	3	4
- Pulmonary Embolism	0	5	5
NOS (Not otherwise specified)	14	17	31
BLEEDING			
- Surgical Bleeding	7	11	18
- Spontaneous Bleeding	0	2	2
- Gastrointestinal Bleeding	0	2	2
- Wound leakage	2	0	2
- Haematoma	0	2	2
THROMBOCYTOPENIA	0	1	1
IMMUNOALLERGY	0	1	1
TOTAL	29	57	86
86 events in 60 patients			

Sponsor's table volume 1.79 p.8-32-47

Peri-operative, Post-operative Blood and Transfusions
There was no significant difference between treatment groups for average peri-operative (1015 ml for heparin and 1050 ml for desirudin) and post-operative blood loss (225 ml for heparin and 210 ml for desirudin). Five heparin patients and one desirudin patient lost more than 3500 ml up to post-op day 6.

Peri-operative transfusions of concentrated red cells were performed in 96 heparin patients (43.6%) compared with 103 desirudin patients (46.2%). Post-operative transfusions of concentrated red cells were performed in 35 heparin patients (16.2%) compared with 48 desirudin patients (22.1%). No significant difference was observed between the use of plasma expanders for both treatment groups.

Laboratory abnormalities
There were no significant differences for laboratory abnormalities (hgb, plt, sgot, and sgpt) between the treatment groups. More heparin patients had an elevation of either sgot or sgpt during the trial. More desirudin patients (9) with a normal baseline total bilirubin had an elevated total bilirubin at the end of treatment compared with enoxaparin (2).

Cardiology Studies

The sponsor provided only synopses and protocols for the Cardiology studies. The information on study design, entrance criteria, treatment doses, and demographics are listed in the appendix. The table below shows the results obtained from those studies.

Reviewer's Comment: The table below represents a synopsis of the sponsor's assessment of the trials. Data and study reports were not provided.

Overview of Sponsor's Assessment of Desirudin Cardiology Trials

Trial	Efficacy Results	Safety Results	FDA reviewer's comment
US01	APTT - best coagulation test for desirudin (dose response), PT insensitive, TT too sensitive	Hematoma for one pt. noted, no SAEs or deaths	Phase I trial to determine dose response relationship of desirudin
RH/PT 2	4/39 heparin treated patients experienced a cardiac event compared with 1/74 desirudin patients	More hemorrhagic complications were noted in the desirudin patients (8 pts) compared with heparin patients (2 pts)	Trial not sized for efficacy; more hemorrhagic complications noted with desirudin
US04	Comparison of improvement in angiographic flow with varying doses of heparin and desirudin	Hemorrhagic complications noted in all groups, however hemorrhagic complications at the highest desirudin dose caused termination of this dose level	Trial not sized for efficacy; hemorrhagic complications noted in all groups
US05	51% of heparin patients failed to achieve TIMI flow grade 3 compared with 35-48% of desirudin patients	Major hemorrhagic complications were 23% of heparin patients compared with 9-29% of desirudin patients	Trial not sized for efficacy; hemorrhagic complications noted in all groups
US07	Event outcome (death, recurrent MI, new or severe CHF, reduced LV function)- 32% heparin treated group compared with 32- 37% desirudin treated groups	Death prior to hospital discharge 2 heparin patients and 4 desirudin treated groups; Spontaneous major hemorrhage not attributable to surgery, invasive procedures, or trauma occurred only in desirudin treatment groups	Trial not sized for efficacy; spontaneous major hemorrhage a concern seen only in desirudin groups
*US09A (TIMI 9A)	Efficacy results not provided because the trial terminated for safety reasons	Higher rates of overall hemorrhage, intracranial hemorrhage, and stroke seen in the desirudin group compared with heparin	Trial terminated because of safety concerns
*US09B (TIMI 9B)	Event outcome (death, recurrent MI, new or severe CHF, shock) - higher in desirudin treated group	Hemorrhage rates similar; stroke rate double for desirudin group; allergic reactions seen with desirudin	Event rate higher for desirudin; stroke rate a concern
*US10A (GUSTO IIA)	Efficacy results not provided because the trial terminated for safety reasons	All adverse events were serious; higher event rates for desirudin particularly mortality, hemorrhagic stroke	Trial terminated because of safety concerns
*US10B (GUSTO IIB)	Primary efficacy results (mortality and re-infarction) not statistically significant	Higher rates of overall hemorrhage and stroke seen in the desirudin group compared with heparin	Efficacy rates similar; safety a concern; not all safety rates (e.g. major hemorrhage) reported in synopsis
RH/E 52	Event outcome (death, nonfatal MI, CABG, repeat angioplasty or stent placement) - 33% heparin treated group compared with 31- 36% desirudin treated groups	More hemorrhagic events in the desirudin groups, allergic reactions seen in desirudin treatment groups only	Trial not sized for efficacy; safety findings a concern

* Phase III trial
Reviewer's table

Reviewer's Comment: Scant information in synopses does not permit further assessment. The safety information is concerning for major hemorrhage.

Integrated Summary of Efficacy

The sponsor's table below shows the efficacy results for the three main trials. Primary efficacy results from the trials could not be combined because there were differences in trial design and endpoints. The table below suggests that desirudin was more efficacious than the active comparator in each trial.

Reviewer's Comment: Although the trials could not be combined in the efficacy table below because the primary endpoints (distal DVT not part of the primary efficacy outcome for RH/E 25) differed, the trials were appropriately designed, conducted, and internally consistent to support the desired indication for desirudin.

Table 6.1-1: Efficacy Results for Individual Studies RH/E23, RH/E28, and RH/E25 in the Per-Protocol Population

	Desirudin 10 mg bid n (%)	Desirudin 15 mg bid n (%)	Desirudin 20 mg bid n (%)	Unfractionated Heparin 5000 IU tid n (%)	Enoxaparin 40 mg qd n (%)
Study RH/E23					
Number Of Patients	213	196	209	219	n/a
Venous Thromboembolic Events*	51 (23.9)	37 (18.9)	38 (18.2)	75 (34.2)	n/a
Deep Vein Thrombosis	51 (23.9)	36 (18.4)	37 (17.7)	75 (34.2)	n/a
Proximal Deep Vein Thrombosis	18 (8.5)	6 (3.1)	5 (2.4)	43 (19.6)	n/a
Pulmonary Embolism	0	1 (0.5)	0	0	n/a
Fatal Pulmonary Embolism	0	0	1 (0.5)	0	n/a
Unexplained Death	0	0	0	0	n/a
Study RH/E28					
Number Of Patients	n/a	174	n/a	177	n/a
Venous Thromboembolic Events	n/a	13 (7.5)	n/a	41 (23.2)	n/a
Deep Vein Thrombosis	n/a	13 (7.5)	n/a	41 (23.2)	n/a
Proximal Deep Vein Thrombosis	n/a	6 (3.4)	n/a	29 (16.4)	n/a
Pulmonary Embolism	n/a	0	n/a	0	n/a
Fatal Pulmonary Embolism	n/a	0	n/a	0	n/a
Unexplained Death	n/a	0	n/a	0	n/a
Study RH/E25					
Number Of Patients	n/a	773	n/a	n/a	768
Venous Thromboembolic Events	n/a	145 (18.8)	n/a	n/a	197 (25.7)
Deep Vein Thrombosis	n/a	142 (18.4)	n/a	n/a	196 (25.5)
Proximal Deep Vein Thrombosis	n/a	36 (4.7)	n/a	n/a	59 (7.7)
Pulmonary Embolism	n/a	2 (0.3)	n/a	n/a	2 (0.3)
Fatal Pulmonary Embolism	n/a	0	n/a	n/a	0
Unexplained Death	n/a	1 (0.1)	n/a	n/a	0

* All five subcategories are not mutually exclusive; therefore they may not sum to the number or percentage of patients with venous thromboembolic events.

The abbreviation *n/a* refers to treatment groups that do not apply to a particular study

Sponsor's table volume 1.83 p.8-36-56

Desirudin efficacy was not affected by the presence of obesity (Body Mass Index $\geq$ 27), smoking, varicose veins, malignancy, cardiovascular disease, previous thromboembolic disease, use of cemented prosthesis, type of anesthesia, and use of concomitant medications.

VII. Integrated Review of Safety

The sponsor's safety review includes the following controlled clinical trials: RH/E 23, RH/E 25 and RH/E 28 and one uncontrolled clinical trial: RH/PT 3.

Discrepancy between Integrated Summary of Safety (ISS) and individual study reports

From the clinical study report for RH/E23, the sponsor excluded desirudin patients who did not receive a full course of the drug. The following patients and events listed in the table below do not appear in the ISS.

Patients excluded from ISS clinical database from Study RH/E23

Patient number	Treatment	Serious or non-serious event	Event Type
945	Heparin	Serious	Major bleeding
318	Desirudin 20 mg bid	Serious	Allergic reaction
667	Desirudin 20 mg bid	Serious	Hypertensive crisis
41	Desirudin 15 mg bid	Serious	Allergic reaction[1]
497	Desirudin 15 mg bid	Serious	Deep vein thrombosis
501	Heparin	Serious	Deep vein thrombosis
562	Desirudin 20 mg bid	Serious	Would hematoma
488	Desirudin 20 mg bid	Serious	Pain
239	Heparin	Serious	Transaminase elevation
392	Desirudin 20 mg bid	Serious	Purpura of right hand[2]

[1] This patient also had hematuria and urinary retention, which were, reported as serious adverse events however only allergic reaction was listed in the clinical database.
[2] This patient was not reported in the pharmacovigilance database nor in the clinical database.
Reviewer's table

There were no discrepancies between the clinical trial report and the pharmacovigilance database for RH/E 25 and RH/E 28 and RH/PT 3 studies.

Total patient drug exposure is listed in the table below.

Numbers of Patients Exposed to Study Medication for Clinical Trials

Study Medication	Number of Patients
Desirudin 10 mg	295
Desirudin 15 mg	1556
Desirudin 20 mg	303
Desirudin 40 mg	3
Unfractionated Heparin	498
Enoxaparin	1036

Reviewer's table

Regardless of treatment group, the average duration of treatment exposure for all patients in clinical trials was 9 to 12 days. The duration of treatment did not differ between treatment groups. Mean age of patients participating in the trials was 66.

The sponsor's table below shows the event rates, which occurred with greater than a 2% frequency.

Reviewer's Comment: The following adverse reactions were seen with greater frequency for the desirudin treatment group compared with the active comparators: edema of legs, increased wound secretion, hypotension, and nausea. Statistically significant differences were observed with increased wound secretion and hypotension. A statistically significant difference was observed for increased wound secretion, hypotension, hemorrhage not otherwise specified, and hypovolemia for desirudin compared with unfractionated heparin. A

statistically significant difference was observed for injection site mass for desirudin compared with enoxaparin.

Table 6.3-1: The Most Frequent (≥2%) Adverse Events Reported during the Treatment Period for Patients in Treatment Grouping 1

Body System Preferred Term	Desirudin 15 mg bid N=1561 n (%)	Unfractionated Heparin 5000 IU tid N=501 n (%)	Enoxaparin 40 mg qd N=1036 n (%)
Patients with at Least One Event	932 (60)	283 (56)	654 (63)
Body as a Whole	367 (24)	102 (20)	204 (20)
Edema Legs	57 (4)	10 (2)	36 (3)
Fever	113 (7)	37 (7)	55 (5)
Hyperpyrexia	50 (3)	15 (3)	31 (3)
Injection Site Mass	59 (4)	33 (7)	7 (<1)
Pain	28 (2)	3 (<1)	28 (3)
Wound Secretion	139 (9)	29 (6)	82 (8)
Cardiovascular System	204 (13)	97 (19)	133 (13)
Hypertension	38 (2)	4 (<1)	35 (3)
Hypotension	114 (7)	17 (3)	65 (6)
Thrombophlebitis Deep	63 (4)	80 (16)	41 (4)
Digestive System	323 (21)	65 (13)	234 (23)
Constipation	81 (5)	11 (2)	66 (6)
Diarrhea	30 (2)	8 (2)	23 (2)
Nausea	193 (12)	47 (9)	121 (12)
Vomiting	90 (6)	16 (3)	76 (7)
Hemic and Lymphatic System	482 (31)	124 (25)	363 (35)
Anemia	138 (9)	37 (7)	117 (11)
Hematoma	127 (8)	30 (6)	87 (8)
Hemorrhage NOS	365 (23)	79 (16)	268 (26)
Laboratory Abnormality	58 (4)	20 (4)	49 (5)
Hypokalemia	58 (4)	20 (4)	49 (5)
Metabolic and Nutritional Disorder	55 (4)	1 (<1)	48 (5)
Hypovolemia	55 (4)	1 (<1)	48 (5)
Musculoskeletal System	151 (10)	6 (1)	146 (14)
Arthralgia	151 (10)	6 (1)	146 (14)

Table 6.3-1: The Most Frequent (≥2%) Adverse Events Reported during the Treatment Period for Patients in Treatment Grouping 1 (continued)

Body System Preferred Term	Desirudin 15 mg bid N=1561 n (%)	Unfractionated Heparin 5000 IU tid N=501 n (%)	Enoxaparin 40 mg qd N=1036 n (%)
Nervous System	158 (10)	24 (5)	157 (15)
Headache	27 (2)	2 (<1)	33 (3)
Insomnia	137 (9)	22 (4)	134 (13)
Urogenital System	72 (5)	36 (7)	45 (4)
Urinary Retention	72 (5)	36 (7)	45 (4)

Sponsor's tables volume 1.85 pp.8-38-353-8-38-354

The sponsor reviewed the adverse events where a statistically significant difference was noted in the table above. The sponsor evaluated the effect of the following cofactors: age,

sex, obesity, cardiovascular disease, diabetes mellitus, malignancy, and concomitant medications. No statistically significant interaction between the above cofactors and adverse events was seen for patients treated with desirudin.

Serious Adverse Events
For overall serious adverse events, heparin had the highest incidence for all patients. The table below illustrates the overall serious adverse event rates for various subpopulations.

Overall Serious Adverse Events

Patient subgroup	Desirudin	Heparin	Enoxaparin
Less than 65 years	31/646 (5%)	20/186 (11%)	14/442 (3%)
65 years and older	66/915 (7%)	54/315 (17%)	33/594 (6%)
75 years and older	35/328 (11%)	25/131 (19%)	13/195 (7%)
Females	56/898 (6%)	48/308 (16%)	25/622 (4%)
Males	41/663 (6%)	26/193 (13%)	22/414 (5%)
Obese	34/626 (5%)	27/170 (16%)	21/431 (5%)
Non-obese	62/929 (7%)	46/326 (14%)	26/602 (4%)
Cardiovascular Disease – yes	14/201 (7%)	14/70 (20%)	6/116 (5%)
Cardiovascular Disease – no	83/1360 (6%)	60/431 (14%)	41/920 (4%)
Diabetes-yes	6/82 (7%)	4/24 (17%)	2/56 (4%)
Diabetes-no	91/1479 (6%)	70/477 (15%)	45/980 (5%)
Malignancy – yes	5/59 (8%)	2/16 (13%)	1/37 (3%)
Malignancy – no	92/1502 (9%)	72/485 (15%)	46/999 (5%)

Reviewer's Table

Allergic Reactions
Two percent of desirudin (15 mg) treatment groups had an allergic reaction compared with one percent for the unfracticnated heparin and enoxaparin treatment groups.

Hemorrhage
The sponsor's table below shows hemorrhage rates. There was a statistically significant difference in any hemorrhage for the desirudin group compared with unfractionated heparin. There was no statistically significant difference in major hemorrhage between desirudin 15 mg and unfractionated heparin or enoxaparin.

Table 6.2-1: Summary of Hemorrhage for Patients in Treatment Groupings 1 and 2

	Desirudin 10 mg bid N=295 n (%)	Desirudin 15 mg bid N=1561 n (%)	Desirudin 20 mg bid N=303 n (%)	All Desirudin N=2159 n (%)	Unfractionated Heparin 5000 IU tid N=501 n (%)	Enoxaparin 40 mg qd N=1036 n (%)
Number of Patients with any Hemorrhage	73 (24.7)	464 (29.7)	98 (32.3)	635 (29.4)	111 (22.2)	341 (32.9)
Number of Patients with Major Hemorrhage	1 (0.3)	13 (0.8)	1 (0.3)	15 (0.7)	0	2 (0.2)
Number of Patients with Serious Hemorrhage	8 (2.7)	41 (2.6)	13 (4.3)	62 (2.9)	15 (3.0)	21 (2.0)

Cross Reference: Appendix 1: Tables 7.1.1 and 7.2.

Sponsor's table volume 1.85 p. 8-38-342

The sponsor's table shows that use of concomitant medication (antiplatelet medication), spinal or epidural anesthesia, diabetes mellitus, cardiovascular disease, and obesity were associated with increased risk of hemorrhage.

Table 6.1-1: Summary of Hemostasis Variables for Each Subgroup

	Age	Sex	Obesity	Cardiovascular Disease	Diabetes Mellitus	Malignancy	Concomitant Medications	Spinal or Epidural Anesthesia
Any Hemorrhage	D: none UH: none E: none	D: none UH:↑ in men E: ↑ in men	D: ↑ UH: none E: ↑	D: ↑ UH: ↑ E: none	D: ↑ UH: none E: none	D: none UH: ↓ E: none	D: ↑ UH: ↑ E: ↑	D: ↑ UH: ↑ E: ↑
Total Blood Loss	D: ↓ UH: ↓ E: ↓	D:↑ in men UH:↑ in men E: ↑ in men	D: ↑ UH: ↑ E: ↑	D: ↓ UH: ↑ E: ↑	D: ↓ UH: ↑ E: ↓	D: ↑ UH: ↓ E: ↑	D: ↑ UH: ↑ E: ↑	D: ↑ UH: ↑ E: ↑
Total Transfusion Requirements (in mL)	Not Assessed						D: ↑ UH: ↑ E: ↑	D: ↑ UH: ↑ E: ↑

Key: D = 15-mg desirudin bid; UH = unfractionated heparin; E = enoxaparin.

↑ = incidence of event, volume of total blood loss, or transfusion requirements are higher in the at-risk group. Therefore, the values would be higher in patients at least 65 years of age, in obese patients, in patients with a history of cardiovascular disease, in patients with diabetes mellitus, in patients with malignancy, in patients taking Class 3 concomitant medications, or in patients receiving any spinal or epidural anesthesia.

None = no difference between the subgroups

↓ = incidence of event, volume of total blood loss, or transfusion requirements are lower in the at-risk group. Therefore, incidence would be lower in patients at least 65 years of age, in obese patients, in patients with a history of cardiovascular disease, in patients with diabetes mellitus, in patients with malignancy, in patients taking Class 3 concomitant medications, or in patients receiving any spinal or epidural anesthesia.

Sponsor's table volume 1.85 p.8-38-337

Blood Loss

Peri-operative, post-operative, and total blood loss were reviewed. Only mean post-operative blood loss was statistically significantly different for desirudin compared with enoxaparin (291.6 ml and 249.2 ml, respectively; $p<0.0001$). Total blood loss was higher for the desirudin (15 mg) compared with enoxaparin however this was not statistically significantly different (1373.4 ml and 1324.4 ml, respectively).

Transfusion Requirements

There were no statistically significant differences between treatment groups for transfusion requirements.

Clinical Laboratory Variables

APTT values differed during the course of the trial for the desirudin 15 mg treatment group compared with the other treatment groups (unfractionated heparin and enoxaparin). The significance of this change was discussed earlier.

The mean alkaline phosphatase, mean aspartate aminotransferase, mean alanine aminotransferase, and mean gamma-glutamyl transferase increased in all treatment groups from baseline to end of study, however the lowest incremental change was for desirudin.

The mean total bilirubin increased in all treatment groups from baseline to end of study, however the highest mean change was for desirudin (1.01micromol/L).

Mean creatinine values decreased during the studies for all treatment groups.

Mean hemoglobin and hematocrit decreased for all treatment groups during the studies. The hematocrit differences between baseline and end of study did not differ by more than 1% between treatment groups.

No clinically meaningful or significant differences for platelet counts (baseline, end of study) were noted within or between treatment groups.

No clinically meaningful or significant differences for potassium or sodium (baseline, end of study) were noted within or between treatment groups.

Drug-Drug Interactions

Drug-Drug interactions were examined in the following phase I studies. The table below discusses the major side effects seen.

Drug-Drug Interactions in Phase I studies
The table below lists only those side effects seen in subjects who received both drugs being studied.

Drug-Desirudin Interactions

Study number	Drugs	Number of patients	Side effects	Severe side effect
RH/E 14	Desirudin DDAVP	12	Headache (3), flushing/facial flushing (9), light headed (2), palpitations (2), all others occurred in 1 patient (pulsating neck veins, paraesthesia, nausea, aching testicles, prolonged bleeding from cannula site)	nausea
RH/E 34	Desirudin, Piroxicam or placebo	12	Swelling of the right mammary gland (1), chest pain (1), nausea (1)	
RH/ET 4	Desirudin, Aspirin 300 mg or placebo	12	Headache (3), heaviness in chest (1), anxious (1), light-headed (1)	
RH/E 35	Desirudin Warfarin	13	Purpura (8), Abdominal pain (4), Headache (4), Back Pain (2), Nausea (2), Pharyngitis (2), dizziness (1), dry mouth (1), eye pain (1), fatigue (1), gastric dilatation (1), Injection site pain (1), myalgia (1), skin discoloration (1)	

Post-marketing

Safety Update

Reviewer's Conclusion regarding the Safety Update

No new safety concerns were identified in the Safety Update. The Safety Update does provide additional concerns regarding the risk of hemorrhage with desirudin particularly in patients who have previously been on another anticoagulant recently. These cases reported above highlight the need for careful labeling.

No new indications, approval, or clinical trials have been conducted with desirudin. The Safety Update submitted contained two sections. The first section described adverse reports submitted to the sponsor and new summary of product characteristics (SPC) labeling proposed by the sponsor to the EMEA. The second described a literature review conducted by the sponsor.

Adverse events

The sponsor sent a submission to the CPMP (EMEA) in August 2000 to update the SPC strengthening the risk of hemorrhage in patients with anticoagulants prior to desirudin treatment and/or in patients having some degree of renal impairment. The sponsor proposes that recent treatment with another anticoagulant may increase risk of hemorrhage although the anticoagulant may have been discontinued 24 hours or more prior to desirudin administration.
The sponsor estimates that approximately 6000 patients have been treated with desirudin. The sponsor has received thirty-two adverse event reports. These adverse event reports came from two sources: spontaneous reports and cases reported to the German Intensified

Monitoring Program. The sponsor has received twenty-four serious adverse event reports. Six patients have died. All adverse event reports are listed below. The sponsor noted that the adverse events listed below are not different from events seen during the clinical trials. The sponsor has not revised the label.

Reviewer's Comment: Listed below are the adverse event cases. Two cases (# FR02-10986, FR02-11040) with severe hemorrhage are in the setting of recent use of another anticoagulant. These cases suggest that additional pre or post-marketing study may be necessary to ensure safety especially for those patients who have had prior anticoagulation.

Reviewer's Assessment of Safety Update for Desirudin

Report Number	Adverse Event	Serious	Pertinent information	Outcome	FDA reviewer's assessment
DE01-05570	Severe Post-op hemorrhage	Yes	Received 7 units of packed red blood cells (on NSAID med)	Recovered	Likely
DE01-05640	Allergic Reaction	Yes	Pt went into anaphylactic shock 2-3 minutes after receiving desirudin for the first time.	Recovered	Likely
DE01-05663	Severe Intramuscular subfascial hematoma	Yes	Pt. experienced compression of ischial nerve. Required a re-operation (on NSAID med)	Not stated on form	Likely
DE01-05737	Post-op hematoma	Yes	Required re-op to remove hematoma (also pt had CLL)	Recovered	Likely
DE01-05738	Post-op hematoma	Yes	Prolonged hospitalization (also on NSAID med)	Recovered	Likely
DE01-05797	Death	Yes	Pt with history of cardiac failure died of cardiac failure	No	Unlikely
DE01-05808	Post-op infected hematoma	Yes	Pt had two additional operations- one for a uncomplicated hematoma and the other for an infection of the same site	Recovered	Likely
DE01-05809	Post-op infected hematoma	Yes	Pt underwent three wound revisions after initial surgery	Recovered	Likely
DE01-05810	Death	Yes	Pt died one day after discontinuing desirudin (treated for 12 days) received after hip replacement	No	Uncertain, no autopsy scant information on form
DE01-05830	Death	Yes	Pt with history of cardiac failure died of cardiac failure	No	Unlikely
DE01-05963	Severe Post-op hematoma	Yes	Prolonged hospitalization (also on NSAID med)	Recovered	Likely
DE01-05964	Severe Post-op hematoma	Yes	Received 3 units packed red blood cells	Not stated	Likely
DE01-06146	Pulmonary Embolism	Yes	Pt. had a PE on desirudin therapy	Not stated	Possibly
DE01-06160	Severe Anemia Bleeding from unligated artery	Yes	Pt. experienced hypotension, tachycardia	Not stated	Unlikely
DE01-06121	Severe Hemorrhage Renal insufficiency	Yes	Serum Creatinine increased to 3.5, experienced severe hemorrhage	Not stated	Possibly scant information on form
DE01-01672	Severe Headache	Unknown	Not enough information to judge	Not stated	Possibly scant information on form
FR02-10457	Severe Hemorrhage, Anemia, thrombocytopenia	Yes	Pt experienced a severe hematoma during and the day after surgery requiring a re-op, in total he received 13 units packed red cells	Recovered	Probably
FR02-10526	Anemia, post-op bleeding	Yes	Pt's hgb dropped to [redacted] also on NSAID med)	Recovered	Likely
FR02-10642	Fatal retroperitoneal	Yes	Complicated case with several episodes of hematoma evacuations,	No	Likely

	hemorrhage, circulatory collapse, anuria		markedly elevated and prolonged APTT		
FR02-10647	Intraop vs. Post-op hemorrhage	Yes	Received 5 units packed red blood cells and 4 units of plasma	Recovered	Likely
FR02-10986	Death, Psoas Muscle Hemorrhage, Renal insufficiency, anemia, shock	Yes	Pt. with antiphospholipid syndrome on long term medication (unknown med), switched to nadroparin pre-op, desirudin post-op, suffered hypovolemic shock, renal insufficiency	No	Likely
FR02-11040	Life threatening hemorrhage	Yes	Pt with history of PE following hip replacement followed by sepsis on enoxaparin sc 2months; enoxaparin stopped the day before the operation with normal PT and APTT, no anti-Xa activity drawn, desirudin given post-op; followed by massive hemorrhage and need for re-op; transfused 29 units packed red blood cells, 19 units plasma, 14 units platelets, and fibrinogen	Recovered	Likely with possible other contributing factors
FR02-11118	Superficial thrombophlebitis	No	Had ultrasound showing thrombophlebitis in several veins the day after stopping desirudin, treated with heparin/anticoagulant	Recovered	Likely
FR02-11180	Pulmonary embolism	Yes	Had pulmonary embolism on desirudin	Recovered	Likely
FR02-11201	Popliteal DVT	Yes	Developed Popliteal DVT on desirudin switched to enoxaparin	Recovered	Likely
FR02-11202	Superficial thrombophlebitis	No	Developed thrombophlebitis on desirudin switched to enoxaparin/anticoagulant	Recovered	Likely
FR02-11204	Thrombosis seen on venogram	No	Developed thrombosis on desirudin switched to enoxaparin	Recovered	Likely
FR02-11396	Fatal gastrointestinal bleeding, shock	Yes	Developed massive GI bleed 4 days after an operation, had been receiving of desirudin for an unknown number of days (also received an NSAID for one day)	No	Probably a significant factor
FR02-11777	Confusion, agitation, abnormal dreams	No	Positive rechallenge; Pt. experienced these symptoms 1 hour after first injection and then had same symptoms occurring within 1 hour after injections 2 and 3	Recovered	Likely
FR02-11819	Purpura	No	Pt. developed purpura at an infusion site	Recovered	Possibly, information scant
FR02-12053	Post-op hemorrhage	Yes	Pt. received 3 units for post-op hemorrhage at the surgical site	Recovered	Likely
GB-01-5541	Intra-op hemorrhage	Too little information to judge	Pt. have received desirudin pre-op however after intra-op bleeding surgery decided to discontinue	Not known	Likely

Reviewer's table

Literature Review

The sponsor performed and submitted a literature survey of published articles. The articles are listed in Appendix 4. The majority of the articles provide information already contained in the NDA submission and are review articles (Andrejak, Hass et. al., Meanear, Nemergut et. al., and Oger et. al.). Several articles (Barbaud, Martin et. al., and Schiffner et. al.) discuss the potential for drug-induced contact dermatitis under various conditions. These articles do not contain new information.
Several articles involve other recombinant hirudins (other than desirudin) or low molecular weight heparins (Harenberg et. al., Komatsu et.al., Martineau et. al., and Tardy-Poncet et. al.).
Klienman et. al. article discusses a GUSTO IIb trial subgroup analysis. The GUSTO IIb trial report was submitted and discussed in the cardiology section previously. The GUSTO IIb trial did not demonstrate statistical significance for the primary outcome (all cause-mortality and myocardial re-infarction at 30 days). The Kleinman article analyses a new outcome (i.e. death and nonfatal reinfarction within the first 24 hours). The article states that the 24-hour death and nonfatal reinfarction event rate was lower for the desirudin group compared with the heparin group (1.3% vs. 2.1%).

Reviewer Comment: The Kleinman article should not be reviewed further without primary data. The Gutso IIb primary data has not been submitted for review only the synopsis and clinical trial report.

VIII. Assessment of Dosing/Regimen/Administration Issues

The sponsor proposes the following regimen and indication: desirudin 15 mg subcutaneously every 12 hours for the prevention of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing hip replacement surgery. The sponsor has performed one uncontrolled dose ranging trial, one controlled dose ranging trial and two active comparator trials in patients with normal renal function (defined as below the laboratory upper limits of normal for serum creatinine). The uncontrolled dose ranging trial (RHI/PT 3) suggested that desirudin 40 mg sc every 12 hours resulted in unacceptable toxicity (major hemorrhage – 3/3). The controlled dose ranging trial reviewed previously suggested a dose response with 10 mg dose regimen as inadequate in terms of efficacy. The controlled trial suggested that there was a slightly higher increase of adverse events with the 20 mg desirudin dose regimen compared with the 15 mg dose regimen with the same efficacy.
Prolongation of the APTT level began at 10 mg desirudin in clinical trials with further prolongation with higher doses.

The sponsor proposes [redacted]

Reviewer's Comment: This reviewer does not agree with the sponsor's proposal. This issue is discussed further in the next section.

The sponsor has not completed required pre-clinical and clinical studies for this drug product.

Reviewer's Comment: The sponsor has not performed a required chronic toxicology study in monkeys as requested in Agency correspondence to the sponsor dated September 1, 2000 and December 15, 2000.

The sponsor needs to complete the required pre-clinical studies and perform a study in hepatically impaired patients. This reviewer is concerned about repeat administration of this drug.

IX. Use in Special Populations
Gender Analysis and Age Analysis

The sponsor's table below illustrates the efficacy results for the gender and age analyses. The active comparator for the desirudin group 1 is the unfractionated heparin group. The active comparator for the desirudin group 2 is the enoxaparin group. For male and female patients, the desirudin treatment was more efficacious than the active comparators. For those patients under 65 years and those 65 and older, the desirudin treatment was more efficacious than the active comparators.

Table 6.8-1: Incidence of Venous Thromboembolic Events for Subgroups in the Per-Protocol Population

	Desirudin 10 mg bid N=213 n (%)	Desirudin Group 1+ 15 mg bid N=370 n (%)	Desirudin Group 2* 15 mg bid N=773 n (%)	Desirudin 20 mg bid N=209 n (%)	Unfractionated Heparin 5000 IU tid N=396 n (%)	Enoxaparin 40 mg qd N=768 n (%)
Age						
< 65	19 / 91 (20.9)	15 / 121 (12.4)	49 / 354 (13.8)	9 / 85 (10.6)	32 / 148 (21.6)	67 / 326 (20.6)
≥ 65	32 / 122 (26.2)	35 / 249 (14.1)	96 / 419 (22.9)	29 / 124 (23.4)	84 / 248 (33.9)	130 / 442 (29.4)
Sex						
Male	14 / 81 (17.3)	14 / 154 (9.1)	57 / 338 (16.9)	10 / 74 (13.5)	40 / 154 (26.0)	70 / 311 (22.5)
Female	37 / 132 (28.0)	36 / 216 (16.7)	88 / 435 (20.2)	28 / 135 (20.7)	76 / 242 (31.4)	127 / 457 (27.8)

+ Desirudin 1 group includes patients from Studies RH/E23 and RH/E28.
* Desirudin 2 group includes patients from Study RH/E 25.
Sponsor's table volume 1.83 p.8-36-86

Race Analysis

The sponsor was requested to provide a race analysis. The following is the sponsor's response.

The three pivotal studies in DVT prevention, RH/E23, RH/E28 and RH/E25, as well as study RH/PT3, were all conducted in Europe and entirely or mostly in Scandinavian countries. Only Caucasian patients were recruited in these studies so analysis of efficacy and safety by race is not possible. Study RH/E24 was conducted in Canada, but was stopped for administrative reasons after only 8 patients were randomized.

Sponsor's text volume from amendment dated 10/11/00 p.6

Reviewer's Comment: The inability to provide information about efficacy and safety of races other than Caucasian is a deficiency. Although an analysis by race may not have been possible given the countries where the studies were conducted, this information is important for both the efficacy and safety of the drug in this country where an ethnically more diverse population exists. The sponsor did not suggest a method of obtaining this information. This lack of information needs to be addressed.

Renal Impairment Studies

Two studies were conducted in subjects or patients. US08A involved studying a single 30 minute intravenous infusion of desirudin given to patients with normal and varying degrees of renal function. Thirteen males enrolled in the trial and were placed into one of the four groups based on inulin clearance at screening:

1) Group A: > 90 ml/min/1.73 m^2 (6 patients)
2) Group B: 61 to 90 ml/min/1.73 m^2 (5 patients)
3) Group C: 31 to 60 ml/min/1.73 m^2 (1 patient)
4) Group D: < 31 ml/min/1.73 m^2 (1 patient)

Pharmacodynamic measurements were performed for the next 36 hours for Groups A and B and 60 hours for Groups C and D. This study was terminated secondary to lack of enrollment One patient had a serum creatinine value 2.4 and another had a serum creatinine value 5.7. All other patients had serum creatinine values less than 1.5. Group A patients had prolongation of their APTT, PT, and TT values which resolved within 6-8 hours, 5-6 hours, and 12-24 hours respectively. Group B patients had prolongation of their APTT, PT, and TT values, which resolved within 8-12 hours, 6 hours, and 24-36 hours respectively. For both groups, not all patients had every time point or documentation of the resolution of all abnormal parameters. The Group C patient achieved a normal APTT at 36 hours, a normal PT at 24 hours, and never had a documented normal TT. The Group D patient achieved a normal APTT at 48 hours, a normal PT at 36 hours, and never had a documented normal TT.

US08B involved studying a single 30 minute intravenous infusion of 0.5 mg/kg desirudin given to patients with normal and varying degrees of renal function. Dose reductions were performed for those in Group C (0.25mg/kg) and D (0.125 mg/kg) listed. One patient in Group C received the same dose as patients in Groups A and B. Twenty-three males enrolled in the trial and were placed into one of the four groups based on inulin clearance at screening:

1) Group A: > 90 ml/min/1.73 m^2 (8 patients)
2) Group B: 61 to 90 ml/min/1.73 m^2 (4 patients)
3) Group C: 31 to 60 ml/min/1.73 m^2 (5 patients)
4) Group D: < 31 ml/min/1.73 m^2 (6 patients)

Pharmacodynamic measurements were performed for the next 36 hours for Group A and B and 60 hours for Groups C and D.
Group A patients had prolongation of their APTT values which resolved on within 5-36 hours. Group B patients had prolongation of their APTT values, which resolved on within 5-12 hours. The Group C patients achieved a normal APTT at 8-36 hours. The Group D patients achieved a normal APTT at 12-48 hours.

Reviewer's Comment: Dose reduction was used appropriately for the majority of patients in Groups C and D seems appropriate. Thus the recommendations in the dosing section should reflect the lower dose used for patients with creatinine clearance less than 61 ml/min.

Hepatic Impairment Studies
No studies have been conducted in patients with hepatic impairment.

Reviewer's Comment: This drug regimen should be studied in hepatically impaired patients.

Patients Over 65 years of age
The following section outline issues of desirudin use in the elderly.

Pharmacokinetic and Pharmacodynamic Studies in Elderly Volunteers
RH/E 15 was a study with 12 healthy elderly volunteers who received a single bolus dose of desirudin and had laboratory parameters checked. The results in the elderly volunteers were compared with eight young healthy volunteers. The comparison of results suggested slight prolongation of the T_{max} in elderly volunteers compared with younger volunteers (median 2.5 hours and 1.75 hours respectively). The comparison of results suggested slight increase in C_{max} for elderly volunteers compared with younger volunteers (59.6 $\pm$ 10. 9 and 54.6 $\pm$ 9.3 nM respectively). An increased AUC for elderly volunteers compared with younger volunteers was observed (446 $\pm$ 70 nmol*hr/l and 344 $\pm$ 50 nmol*hr/l respectively). The half-life was slightly prolonged in elderly volunteers compared with younger volunteers (3.01 $\pm$ 0.48 and 2.41 $\pm$ 0.36 hours, respectively. Total plasma clearance was reduced in the elderly volunteers compared with younger volunteers (110 $\pm$ 19 ml/min and 153 $\pm$ 25 ml/min).

Reviewer's Comment: With age, the creatinine clearance is reduced, this may account for the differences seen. The small differences in the pharmacokinetic parameters between those less than 65 years of age compared with those greater than 65 years of age do not warrant reduced dosing for the elderly beyond the adjustment for renal impairment.

Clinical trials involving the Elderly

The data presented below demonstrate the efficacy and safety results for desirudin based on age category in the pivotal trials. Since trials differed by efficacy endpoint, they are separated. Patients over 75 years had a slightly higher incidence of adverse events and their data are presented separately.

Reviewer's Comment: The differences in event rate between the clinical trials are accounted for the difference in endpoints. RH/E 25 did not include distal DVT in the primary efficacy endpoint. Although the table below demonstrates that the rate of events for patients 65 years and older in RH/E 25 (secondary outcome) was 62% higher than the efficacy rates for patients less than 65 years, the majority of these thromboembolic events were distal DVT which are not clinically meaningful.

Event Rates for Desirudin (15 mg) Observed in the Elderly in Clinical Trials)

	Patients less than 65	Patients 65 years and older
Thromboembolic events – RH/E 23 and RH/E 28 – per-protocol	12.4%	14.1%
Thromboembolic events – RH/E 25-per-protocol	4.3%	4.6%
Thromboembolic events –RH/E 25 per-protocol including distal DVT	13.8%	22.9%

Reviewer's Table

Safety Event Rates

The table below shows the major safety event rates for the age categories.

Reviewer's Comment: The event rates are similar across age groups except for serious adverse event. The serious adverse event rates are higher than those seen with enoxaparin for the same age category but lower than those seen for unfractionated heparin.

Safety Event Rates in Clinical Trials by Age Category

	Patients less than 65	Patients 65 years and older	Patients 75 years and older
Hemorrhage	31%	29%	26%
Major	<1%	<1%	<1%
Adverse Event	72%	67%	67%
Serious	5%	7%	11%

Reviewer's Table

Drug-Drug Interaction Studies

Reviewer's Conclusion: The conclusions drawn from data collected in the drug-drug interaction trials are only applicable to the trial design (i.e. timing, duration, etc.). The study designs do not mimic all potential combinations of timing and duration seen in the clinical practice of medicine. The drug-drug study designs, though limited, should be reflected in the label.

Concomitant Warfarin Use Study

Study RH/E 35 was a study in two parts with 12 healthy male volunteers. In part A, the volunteers received warfarin 10 mg orally for 3 days and had their laboratory parameters checked for two days. The volunteers then underwent a fifteen day washout period prior to

proceeding with part B. In part B, the volunteers were administered a single dose of subcutaneous desirudin (0.3 mg/kg) on day 1 followed by three days of twice daily administration of desirudin and three days of daily administration of 10 mg warfarin. Following last dose of warfarin, laboratory parameters were obtained for the next two days. The study demonstrated an additive effect with coadministration of desirudin with warfarin.

Reviewer's Comment: This study demonstrated an additive effect of desirudin when coadministered with warfarin. However given the design of the study no further comments can be made.

Concomitant Heparin Use Study
Study US03 was a study with 19 healthy male volunteers. Volunteers received a single intravenous bolus dose of desirudin (0.01- 0.1 mg/kg) and then 24 hours later received an intravenous bolus dose of heparin (5000 units) followed by an intravenous infusion. On Day 3 volunteers received another bolus dose of desirudin. Daily the volunteers had their laboratory parameters checked. The study demonstrated an additive effect with coadministration of desirudin with heparin.

Reviewer's Comment: This study demonstrated an additive effect with coadministration of heparin. The study was not of sufficient design to make other evaluations.

Concomitant Desirudin and Non-Steroidal Anti-inflammatory Drug use
Two trials were conducted with a short intravenous infusion of desirudin. RH/ET 4 was a trial in healthy volunteers. Aspirin (300mg) was given on day 1 and day 2. Desirudin infusion (0.3 mg/kg/hr) was given on day 2. The combination did not result in prolongation of the APTT. RH/E 34 was a trial in healthy volunteers where a six hour infusion of desirudin (1.0 mg/kg/hr) was given after an 11 day treatment with piroxicam. Neither bleeding time nor APTT were prolonged by treatment with piroxicam.

Use in Pregnancy

The sponsor did not provide any information regarding use in pregnancy.

Reviewer's Comment: Some Reproduction Toxicity studies performed in support of this NDA suggested skeletal malformations have occurred in rabbits. For further details see section II and the FDA Pharmacology/Toxicology review.

Pediatric Use

The sponsor requested a waiver of pediatric studies for the indication being sought.

Reviewer's Comment: Elective hip replacement surgery in pediatrics is rare. Therefore the indication being sought is not clinically relevant to the pediatric population. The requested waiver for pediatrics should be granted.

X. Conclusions and Recommendations

The current application for Desirudin has certain deficiencies thus cannot be approved at this time. The following issues would need to be resolved prior to Desirudin being approved for marketing:

1) The sponsor must revise the labeling to provide a black box warning for spinal/epidural hematomas.
2) The sponsor has not conducted a chronic toxicity study in monkeys as suggested by the Agency. This reviewer recommends that the sponsor conduct the chronic toxicity study in monkeys as previously suggested in Agency correspondence dated September 1, 2000 and December 15, 2000.

3) The sponsor should revise the label, particularly the section on renal impairment, in order to provide more detailed information on the use of desirudin in patients with renal impairment.
4) The sponsor should provide information the use of desirudin in hepatically impaired patients.
5) The sponsor has not provided any information on the efficacy and safety of this drug product in races other than Caucasian. There are no data to suggest that non-Caucasian races would experience different efficacy and safety issues, however, there has been minimal experience with desirudin use in non-Caucasian patients. The sponsor should provide additional information on the safety and efficacy in other races. This could be accomplished by conducting a pharmacokinetic study in a more ethnically diverse population, or conducting a post-marketing survey of efficacy results in an ethnically diverse patient population. This information could be provided as a phase IV commitment.
6) The sponsor should provide safety information from the time of initial marketing (Malaysia – November 1995) to start of Safety Update (May 1, 1999).
7) Because of safety concerns noted in the Safety Update from Europe, the sponsor should provide additional guidance on how patients should be switched from an oral or other anticoagulant to desirudin.

XI. Appendix 1

Table 1-1: Summary of Studies in Clinical Development of Desirudin

Clinical Pharmacology Studies

Protocol #; Investigators, Publications	Completion Status; Study Time Period	Location Product Code #	Full Report Data Listings	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age Mean Range Gender Ethnic Origin	Duration of Treatment
HIR-001: Not provided. Kinoshita, et al Clinical Medicine. 1995;11(6).	Completed: May 1991 to October 1991	TBD	TBD	TBD	Single- and multiple-dose study	Healthy male volunteers selected from a pretreatment screening exam.	Desirudin/ Intravenous 0.02, 0.04, or 0.10 mg/kg bolus OR 0.05 or 0.1 mg/kg/h infusion	Single Dose: Bolus Injection 0.02 mg/kg: 5 0.04 mg/kg: 5 0.10 mg/kg: 5 Infusion 0.05 mg/kg/h: 5 0.10 mg/kg/h: 5 Multiple Dose: Bolus Injection 0.05 mg/kg: 5 Infusion 0.10 mg/kg/h: 5	32.9 years 24 to 43 years 35 male 0 female Japanese	Single bolus dose once or intravenous infusions over 3 hours for 1 day OR Single dose once daily for 3 consecutive days or intravenous infusion over 3 hours for 3 consecutive days
NL/RH01 J.W. ten Cate, Nurmohamed MT, et al. Thrombosis and Haemostasis 1994;72:685-692	Completed; 12 September 1990 to 01 October 1990	TBD	TBD	TBD	Open-label, comparative, single-dose study	Healthy nonatopic male or female volunteers (ages 21 to 50 years) with no previous exposure to natural or recombinant hirudin.	Desirudin/ Subcutaneous 0.75 mg/kg; Heparin/ Intravenous 2500 IU	6	31 years 26 to 35 years 6 male 0 female ethnic origin not recorded	Desirudin: single dose Heparin single dose

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Clinical Pharmacology Studies

Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report: Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age: Mean; Range; Gender; Ethnic Origin	Duration of Treatment
RH/A02; M. Verstraete J. Kienast J. H. ten Cate; Close P, et al. Coronary Artery Disease. 1994;5:943-949.	Completed; 16 February 1989 to 22 September 1989 (Netherlands) 10 April 1989 to 06 July 1989 (Belgium) 12 April 1989 to 19 July 1989 (Germany)	TBD	TBD	TBD	Open-label study	Volunteers (21 to 50 years) with no previous exposure to natural or recombinant hirudin and negative reactions to intradermal and skin prick tests performed with three concentrations of desirudin.	Desirudin/ Subcutaneous 0.1 mg/kg	184	25.8 years; 19 to 46 years; 140 male, 44 female; ethnic origin not recorded	2 single doses one month apart
RH/E10; T.G. Mant P. Morrison; Not applicable	Completed; 24 April 1989 to 02 May 1989	TBD	TBD	TBD	Single-dose, open-label, balanced, crossover study	Healthy male volunteers between the ages of 18 and 29, who weighed 62 to 81 kg.	Desirudin/ Intravenous and subcutaneous 0.3 and 0.5 mg/kg	IV/SC: 0.3/0.3 mg/kg: 4 0.5/0.5 mg/kg: 4 SC/IV: 0.3/0.3 mg/kg: 4 0.5/0.5 mg/kg: 4	23 years; 18 to 29 years, 16 male, 0 female; ethnic origin not recorded	Single dose
RH/E14; T G. Mant J. Rose; Amin DM, et al. Thrombosis and Haemostasis. 1997;77:127-132	Completed; 02 July 1990 to 31 August 1990	TBD	TBD	TBD	Open-label, placebo-controlled study	Male volunteers (ages 19 to 31 years, who weighed 60.5 to 85.3 kg) who were non-smokers and were shown to be fit on the basis of a prestudy physical examination, laboratory screen, and urinalysis.	Desirudin/ Intravenous 0.2 or 0.3 mg/kg/h; DDAVP/ Intravenous 0.3 mcg/kg	Desirudin: 0.2 mg/kg/h: 6 0.3 mg/kg/h: 6	22.3 years; 19 to 31 years; 12 male, 0 female; ethnic origin not recorded	Desirudin: 1-minute loading dose followed by a continuous infusion for 4 hours; DDAVP: 15-minute infusion

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Clinical Pharmacology Studies

Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report: Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age: Mean; Range; Gender; Ethnic Origin	Duration of Treatment
RH/E15; A.C. Houston; Not applicable	Completed; 17 August 1990 to 12 September 1990	TBD	TBD	TBD	Open-label study	Healthy elderly volunteers.	Desirudin/ Subcutaneous 0.3 mg/kg	12	70 years; 65 to 78 years; 5 male, 7 female; ethnic origin not recorded	Single dose
RH/E21; W. Schramm G. A. Marbet; Not applicable	Completed; 04 February 1991 to 25 October 1991	TBD	TBD	TBD	Double-blind, randomized, placebo-controlled study	Patients aged 21 to 65 years with no previous exposure to natural or recombinant hirudin who were scheduled to undergo a maximum of two dental extractions.	Desirudin/ Subcutaneous 10, 20 or 40 mg; Placebo/ Subcutaneous	Desirudin: 10 mg: 4 20 mg: 6 40 mg: 5 Placebo 5	26.3 years; 21 to 51 years; 20 male, 0 female; ethnic origin not recorded	Desirudin single dose; Placebo single dose
RH/E34; N. Rietbrock S. Harder P. Thurmann; Thürmann P. et al. European Journal of Clinical Pharmacology. 1995;48:241-246.	Completed; 27 January 1993 to 01 April 1993	TBD	TBD	TBD	Double-blind, randomized, placebo-controlled, crossover study	Healthy male volunteers between the ages of 18 to 40 years.	Desirudin/ Intravenous 0.1 mg/kg/h; Piroxicam/ Oral 10 mg; Placebo/ Oral	Desirudin: 12 Piroxicam: 12 Placebo: 12	28.0 years; 22 to 34 years, 12 male, 0 female; ethnic origin not recorded	Desirudin 6-hour infusion; Piroxicam/ Placebo once daily for 11 days

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Clinical Pharmacology Studies										
Protocol #; Investigators, Publications	Completion Status; Study Time Period	Location Product Code #	Full Report: Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age: Mean; Range, Gender; Ethnic Origin	Duration of Treatment
RH/E35; [redacted]	Completed; 06 November 1993 to 23 December 1993	TBD	TBD	TBD	Open-label, non-randomized, two-treatment-period study	Male volunteers (ages 18 to 45 years) who were shown to be fit on the basis of a pretreatment physical examination, laboratory screen, and urinalysis.	Desirudin/ Subcutaneous 0.3 mg/kg; Warfarin/ Oral 10 mg	Desirudin: 13 Warfarin: 17	26.1 years; 21 to 34 years; 17 male, 0 female; ethnic origin not recorded	Desirudin, single dose at Visit 7, then twice a day for 3 days; Warfarin: once a day for 3 days
RH/E36; [redacted]	Completed; 05 September 1994 to 20 October 1994	TBD	TBD	TBD	Single-dose, open-label, two-period, randomized, crossover study	Healthy male volunteers between the ages of 20 to 60 years.	Desirudin/ Subcutaneous 15 mg	12	30.8 years; 21 to 47 years; 12 male, 0 female; ethnic origin not recorded	Single dose
RH/ET1; J. van de Loo J. Kienast; Marbet GA, et al. Journal of Cardiovascular Pharmacology. 1993;22:364-372.	Completed; 14 August 1989 to 22 December 1989	TBD	TBD	TBD	Open-label, single-dose study	Volunteers (ages 21 to 50 years) with no previous exposure to natural or recombinant hirudin and who experienced negative reactions to prick and intradermal skin tests performed with 3 concentrations of desirudin.	Desirudin/ Intravenous Level I: 0.1 mg/kg; Level II: 0.3 mg/kg; Level III: 0.5 mg/kg; Level IV: 1.0 mg/kg	0.1/0.3 mg/kg: 4 0.1/0.5 mg/kg: 4 0.5/1.0 mg/kg: 4 0.3/1.0 mg/kg: 4	27.4 years; 23 to 43 years, 14 male, 2 female; ethnic origin not recorded	1-minute infusion

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Clinical Pharmacology Studies										
Protocol #; Investigators, Publications	Completion Status; Study Time Period	Location Product Code #	Full Report: Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age, Mean; Range; Gender; Ethnic Origin	Duration of Treatment
RH/ET2; G.A. Marbet; Tsarkis DA, et al. Schweiz. med. Wschr. 1991;121:338-340. Marbet GA, et al. Journal of Cardiovascular Pharmacology 1993;22 364-372.	Completed; 29 March 1989 to 20 June 1989	TBD	TBD	TBD	Open-label, comparative, single-dose study	Volunteers (ages 21 to 50 years) who encountered no previous exposure to natural or recombinant hirudin and who experienced negative reactions to prick and intradermal skin tests performed with 3 concentrations of desirudin.	Desirudin/ Intravenous Level I: 0.1 mg/kg/h; Level II: 0.2 mg/kg/h; Level III: 0.3 mg/kg/h	0.1/0.3 mg/kg/h: 4 0.1/0.2 mg/kg/h: 4 0.3/0.2 mg/kg/h: 4	24.3 years; 20 to 35 years, 12 male, 0 female; ethnic origin not recorded	5 hour infusion
RH/ET3; W. Schramm; Versiraete M, et al. Journal of the American College of Cardiology. 1993;22:1080-1088.	Completed; 19 January 1989 to 16 October 1989	TBD	TBD	TBD	Open-label, comparative, single-dose study	Volunteers (ages 21 to 50 years) with no previous exposure to natural or recombinant hirudin and who experienced negative reactions to prick and intradermal skin tests performed with 3 concentrations of desirudin.	Desirudin/ Subcutaneous Level I: 0.1 mg/kg; Level II: 0.2 mg/kg; Level II : 0.3 mg/kg; Level IV: 0.4 mg/kg	0.1/0.3 mg/kg: 8 0.2/0.4 mg/kg: 8	28.3 years; 24 to 35 years, 8 male, 8 female, ethnic origin not recorded	Single dose
RH/ET4, [redacted] Not applicable	Completed; 08 February 1990 to 20 March 1990	TBD	TBD	TBD	Open-label, comparative, single-dose study	Healthy volunteers as determined by prestudy physical exam, lab screen, and urinalysis.	Desirudin/ Intravenous 0.3 mg/kg/h; ASA/ Oral 300 mg; Lactose (placebo)/ Oral 300 mg	12	24.3 years; 20 to 32 years, 12 male, 0 female; ethnic origin not recorded	Desirudin: 5-hour infusion, ASA/Placebo: 3 days

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Clinical Pharmacology Studies										
Protocol #, Investigators, Publications	Completion Status, Study Time Period	Location Product Code #	Full Report Data Listings	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age: Mean, Range; Gender, Ethnic Origin	Duration of Treatment
RH/ET5: G.A. Marbet; Marbet GA, et al. Journal of Cardiovascular Pharmacology. 1993;22:364-372.	Completed; 08 June 1989 to 19 September 1989	TBD	TBD	TBD	Open-label, comparative, multiple-dose study	Volunteers (21 to 50 years) not previously exposed to natural or recombinant hirudin and who had negative reactions to intradermal and skin prick tests performed with 3 concentrations of desirudin.	Desirudin/ Intravenous 0.2 or 0.3 mg/kg/h	0.2 mg/kg/h: 6 0.3 mg/kg/h: 6	25.8 years; 21 to 35 years; 12 male, 0 female; ethnic origin not recorded	72-hour infusion
RH/ET6; W. Schramm; Verstraete M, et al. Journal of the American College of Cardiology. 1993;22:1080-1088.	Completed; 10 August 1989 to 12 January 1990	TBD	TBD	TBD	Open-label, comparative, multiple-dose study	Volunteers (21 to 50 years) who had negative intradermal and skin prick tests to 3 doses of desirudin.	Desirudin/ Subcutaneous 0.3 and 0.5 mg/kg	0.3 mg/kg: 8 0.5 mg/kg: 8	(Age data for treated patients only) 28.3 years; 25 to 35 years; 9 male, 7 female; ethnic origin not recorded	Three times daily for 3 days
RH/ET7: M. Verstraete B. Hoet; Marbet GA, et al. Journal of Cardiovascular Pharmacology. 1993;22:364-372. Hoet B, et al. Drug Invest. 1994;7:127-133.	Completed; 15 April 1989 to 28 June 1989	TBD	TBD	TBD	Open-label, comparative, single-dose study	Volunteers (21 to 50 years) who had negative intradermal and skin prick tests and those who had no previous exposure to natural or recombinant hirudin.	Desirudin/ Intravenous 0.1, 0.3, 0.5, and 1.0 mg/kg	0.1/0.3 mg/kg: 4 0.5/1.0 mg/kg: 4 1.0 mg/kg once: 6	(Age data for treated patients only) 27.1 years; 21 to 34 years; 14 male, 0 female; ethnic origin not recorded	1-minute infusion

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Clinical Pharmacology Studies										
Protocol #: Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report: Data Listings	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age Mean; Range; Gender; Ethnic Origin	Duration of Treatment
RH/ET8: J. W. ten Cate J. A. Hoek M. T. Nurmohamed H. R. Buetler; Verstraete M, et al. Journal of the American College of Cardiology. 1993;22:1080-1088.	Completed; 25 May 1989 to 27 July 1989	TBD	TBD	TBD	Open-label, comparative, single-dose study	Volunteers (21 to 50 years) who had negative intradermal and skin prick test and those who had no previous exposure to natural or recombinant hirudin	Desirudin/ Subcutaneous 0.1, 0.3, 0.5, and 0.75 mg/kg	0.1/0.5 mg/kg: 4 0.3/0.75 mg/kg: 4	34.1 years; 26 to 43 years, 6 male, 2 female; ethnic origin not recorded	Single dose
RH/ET9: J. W. ten Cate H. R. Buetler; Verstraete M, et al. Journal of the American College of Cardiology. 1993;22:1080-1088.	Completed; 06 November 1989 to 22 December 1989	TBD	TBD	TBD	Open-label, comparative, multiple-dose study	Volunteers (21 to 50 years) who had previous exposure to Desirudin during Protocols RH/ET8 or RH/A02 after negative skin tests (intradermal and prick).	Desirudin/ Subcutaneous 0.3 or 0.5 mg/kg	0.3 mg/kg: 4 0.5 mg/kg: 4	30.8 years; 25 to 45 years, 3 male, 5 female; ethnic origin not recorded	Twice daily for 5 consecutive days
US01: J. H. Chesebro; Zoldhelyi P, et al. Circulation. 1993;88:2015-2022. Zoldhelyi P, et al. Circulation. 1994;90:2671-2678.	Completed; 20 February 1990 to 03 July 1991	TBD	TBD	TBD	Single-blind, placebo-controlled, ascending-dose study	Male and female outpatients between the ages of 21 and 75 years with a primary diagnosis of stable coronary artery disease.	Desirudin/ Intravenous 0.02, 0.05, 0.10, 0.20 and 0.30 mg/kg/h; Placebo/ Intravenous	Desirudin: 0.02 mg/kg/h: 6 0.05 mg/kg/h: 7 0.10 mg/kg/h: 6 0.20 mg/kg/h: 6 0.30 mg/kg/h: 7 Placebo: 9	(Treated patients only) 60.5 years, 42 to 71 years, 38 male, 1 female, ethnic origin not recorded	Desirudin, 5-hour infusion; Placebo 5-hour infusion

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Clinical Pharmacology Studies										
Protocol # Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age; Mean; Range; Gender; Ethnic Origin	Duration of Treatment
US03; [redacted]	Completed; 30 October 1990 to 14 December 1990	TBD	TBD	TBD	Open-label, ascending-dose study	Healthy male volunteers between the ages of 18 and 50.	Desirudin/ Intravenous 0.01, 0.03, 0.05 or 0.1 mg/kg; Heparin/ Intravenous Titrated to maintain patient's aPTT at 1.5 to 2.0 times subject's baseline aPTT value.	0.01 mg/kg: 4 0.03 mg/kg: 4 0.05 mg/kg: 6 0.1 mg/kg: 5	29.7 years; 23 to 43 years; 19 male, 0 female; ethnic origin not recorded	Desirudin: single dose followed by a single dose based on lab results; Heparin: single dose, followed by continuous infusion
US08A: [redacted] Not applicable	Completed; 22 January 1992 to 26 June 1993	TBD	TBD	TBD	Open-label, parallel-group study	Male or female subjects between the ages of 18 and 75 years were selected for screening from a list of subjects with known measured creatinine clearances.	Desirudin/ Intravenous 1.0 mg/kg	13	44.3 years; 20 to 72 years, 13 males, 0 females; ethnic origin not recorded	30-minute infusion
US08B; John M. Morgan Paul E. Rotan; Lefevre F, et al. Clinical Pharmacology and Therapeutics. 1997;62:50-59.	Completed; 14 March 1994 to 30 April 1995 (USA) 10 January 1995 to 30 April 1995 (UK)	TBD	TBD	TBD	Open-label, parallel-group study	Male or female subjects between the ages of 18 and 75 years were selected for screening from a list of subjects with known measured creatinine clearances.	Desirudin/ Intravenous 0.5, 0.25 or 0.125 mg/kg	0.5 mg/kg: 12 0.25 mg/kg: 5 0.125 mg/kg: 6	(Age data for treated patients only) 42.9 years; 19 to 69 years; 14 male, 9 female; ethnic origin not recorded	30-minute infusion

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Controlled Clinical Trials - Venous Active Control										
Protocol #; Investigators, Publications	Completion Status, Study Time Period	Location Product Code #	Full Report Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age, Mean, Range; Gender, Ethnic Origin	Duration of Treatment
RH/E24; [redacted] Not applicable	Completed; 18 January 1993 to 29 January 1993	TBD	TBD	TBD	Double-blind, randomized, parallel-design, heparin-controlled study	Inpatients at least 18 years of age, weighing not less than 50 kg, scheduled to undergo an elective unilateral total hip replacement (i.e., no revision) with a cemented or non-cemented prosthesis.	Desirudin/ Subcutaneous 15 mg; Unfractionated Heparin/ Subcutaneous 5000 IU	Desirudin: 7 Heparin: 3	66.5 years; 50 to 92 years, 3 males, 7 females; ethnic origin not recorded	Desirudin: single dose twice daily for 9 to 11 days. Heparin, single dose three times daily for 9 to 11 days
RH/E25; B. Eriksson; Eriksson BI, et al. The New England Journal of Medicine. 1997;337:1329-1335.	Completed; 13 April 1994 to 27 November 1995	TBD	TBD	TBD	Double-blind, randomized, heparin-controlled parallel study	Consenting patients, 18 years of age or older, weighing at least 50 kg, who underwent primary unilateral elective total hip replacement	Desirudin/ Subcutaneous 15 mg; Enoxaparin/ Subcutaneous 40 mg	Desirudin: 1043 Enoxaparin: 1036	65.5 years; 18 to 90 years, 867 male, 1212 female; ethnic origin not recorded	Desirudin: single dose twice daily for 9 to 12 days. Enoxaparin: single dose every day for 9 to 12 days
RH/E28; B. Eriksson; Eriksson BI, et al. American Journal of Bone and Joint Surgery. 1997;79:326-333.	Completed; 28 November 1993 to 23 August 1994	TBD	TBD	TBD	Double-blind, randomized, heparin-controlled parallel study	Consenting patients, 18 years of age or older, weighing at least 50 kg, with cemented or non-cemented prosthesis who underwent primary unilateral elective total hip replacement	Desirudin/ Subcutaneous 15 mg; Unfractionated Heparin/ Subcutaneous 5000 IU	Desirudin: 225 Heparin: 220	68.4 years, 34 to 89 years; 186 male, 259 female; ethnic origin not recorded	Desirudin: single dose twice daily for 8 to 12 days Heparin single dose three times daily for 8 to 12 days

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Controlled Clinical Trials - Venous
Active Control - Dose-Comparative

Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report; Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age; Mean; Range; Gender; Ethnic Origin	Duration of Treatment
RHVE23; B. Eriksson; Eriksson BI, et al. Lancet. 1996;347:635-639 Cofrancesco E,et al. Thrombosis and Haemostasis. 1997;77:267-269. Confrancesco E, et al. Thrombosis and Haemostasis. 1996;75:407-411. Confrancesco E, et al. Thrombosis and Haemostasis. 1998;79:509-510.	Completed; 05 May 1992 to 15 August 1993	TBD	TBD	TBD	Double-blind, randomized, dose-comparative, heparin-controlled parallel study	Consenting patients over 21 years, weighing over 50 kg, with a cemented or non-cemented prosthesis who underwent elective total hip replacement.	Desirudin/ Subcutaneous 10, 15, or 20 mg; Unfractionated Heparin/ Subcutaneous 5000 IU	Desirudin: 10 mg: 283 15 mg: 277 20 mg: 282 Heparin: 277	66.3 years; 25 to 90 years; 422 male, 697 female; ethnic origin not recorded	Desirudin: single dose twice daily for 8 to 12 days. Heparin: single dose three times daily for 8 to 12 days

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Uncontrolled Clinical Trials - Venous

Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report; Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age; Mean; Range; Gender; Ethnic Origin	Duration of Treatment
RHPT3; B. Eriksson; Eriksson BI, et al. Thrombosis and Haemostasis. 1994;72:227-231 Agnelli, et al. Thrombosis and Haemostasis. 1997;23:143-148.	Completed; 10 April 1991 to 17 December 1991	TBD	TBD	TBD	Open-label, non-randomized, dose-comparative study	Consenting patients between 50 and 85 years, weighing between 45 and 100 kg, in need of a first elective total hip replacement with a cemented or non-cemented prosthesis.	Desirudin/ Subcutaneous 10, 15, 20, or 40 mg	10 mg: 12 15 mg: 12 20 mg: 21 40 mg: 3	70.6 years; 48 to 84 years; 15 male, 33 female; ethnic origin not recorded	Single dose twice daily for 12 days

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Other Studies
Phase III - Controlled Clinical Trials

Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report; Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age; Mean; Range; Gender; Ethnic Origin	Duration of Treatment
US09A. E. Braunwald; Antman EM. Circulation. 1994;90:1624-1630	Completed; 25 August 1993 to 08 April 1994	TBD	TBD	TBD	Randomized, double-blind, heparin-controlled study	Male or female patients with suspected acute myocardial infarction, presenting within 12 hours of symptom onset, and eligible to receive thrombolytic therapy	Desirudin/ Intravenous 0.6 mg/kg and 0.2 mg/kg/h; Unfractionated Heparin/ Intravenous 5000 IU and 1000 IU/h or 1300 IU/h	Desirudin: 375 (1 patient random-ized twice) Heparin: 383	(Treated patients only) 61.7 years; 25 to 75 years; 501 male, 212 female; 605 white, 58 black, 9 oriental, 41 other	Desirudin: single dose followed by continuous infusion for at least 96 hours. Heparin: single dose followed by continuous infusion for at least 96 hours
US09B. E. Braunwald, Antman EM. Circulation. 1996;94:911-921.	Completed; 03 May 1994 to 05 September 1995	TBD	TBD	TBD	Randomized, double-blind, heparin-controlled study	Patients with suspected acute myocardial infarction, presenting within 12 hours of symptom onset, and eligible to receive thrombolytic therapy.	Desirudin/ Intravenous 0.1 mg/kg and 0.1 mg/kg/h; Unfractionated Heparin/ Intravenous 5000 IU and 1000 IU/h	Desirudin: 1511 Heparin: 1491	60.1 years; 25 to 75 years; 2247 male, 755 female; 2675 white, 150 black, 42 oriental, 135 other	Desirudin: single dose followed by continuous infusion for at least 96 hours. Heparin: single dose followed by continuous infusion for at least 96 hours

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Other Studies Phase III Controlled Clinical Trials										
Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report Data Listings:	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/Doses	Number of Patients Entered into Each Treatment	Age: Mean; Range;; Gender; Ethnic Origin	Duration of Treatment
US10A; Approximately 300 investigators; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Circulation. 1994;90:1631-1637.	Completed; 30 August 1993 to 09 April 1994	TBD	TBD	TBD	Double-blind, randomized, heparin- controlled study	Male or female patients with suspected acute coronary syndromes.	Desirudin/ Intravenous 0.6 mg/kg and 0.2 mg/kg/h; Unfractionated Heparin/ Intravenous 5000 IU and 1000 IU/h or 1300 IU/h	Desirudin: 1274 Heparin: 1291	(Treated patients only) 64.1 years; 25 to 75 years; 1745 male, 769 female; 2360 white, 84 black, 14 oriental, 55 other	Desirudin: single dose followed by continuous infusion for at least 3 days; Heparin: single dose followed by continuous infusion for at least 3 days

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Other Studies Phase III - Controlled Clinical Trials										
Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report: Data Listings:	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/Doses	Number of Patients Entered into Each Treatment	Age: Mean; Range; Gender; Ethnic Origin	Duration of Treatment
US10B; Several hundred investigators; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. The New England Journal of Medicine. 1996;335:775-782. Metz BK, et al. Journal of the American College of Cardiology. 1998;31:1493-1498. Jönssen B, et al. International Journal of Technocology Assessment in Healthcare. 1997;13:49-58.	Completed; 19 May 1994 to 17 November 1995	TBD	TBD	TBD	Double-blind, randomized, heparin- controlled study	Male or female patients who experienced symptoms of cardiac ischemia at rest within 12 hours of randomization with either transient or persistent ST-segment elevation or depression of at least 0.5 mm, or persistent definite T-wave inversion of at least 1 mm.	Desirudin/ Intravenous 0.1 mg/kg and 0.1 mg/kg/h; Unfractionated Heparin/ Intravenous 5000 IU and 1000 IU/h	Desirudin: 6069 Heparin: 6073	63.3 years; 25 to 75 years; 8479 male, 3662 female, 1 sex missing; 11392 white, 360 black 114 oriental, 273 other	Desirudin: single dose followed by continuous infusion for at least 3 days; Heparin single dose followed by continuous infusion for at least 3 days

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Other Studies Phase II - Controlled Clinical Trials										
Protocol #; Investigators Publications	Completion Status; Study Time Period	Location Product Code #	Full Report: Data Listings:	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age: Mean, Range; Gender; Ethnic Origin	Duration of Treatment
RH/ES2; P.W. Serruys; Serruys PW, et al. The New England Journal of Medicine. 1995;333:757-763.	Completed; 24 September 1992 to 23 December 1993	TBD	TBD	TBD	Double-blind, randomized, heparin- controlled study	Male or female patients aged 30 to 75 years with the development of the following conditions within the past three months: new onset of angina pectoris or worsening of the angina pattern (i.e., worsening of angina pattern by two classes according to the Canadian Cardiovascular Society classification), need for prescribing additional antianginal medication, and/or angina at rest.	Desirudin/ Intravenous and subcutaneous 40-mg dose followed by a 0.2 mg/kg/h infusion for 24 hours with or without 40-mg Desirudin injections twice daily; Unfractionated Heparin/ Intravenous 10,000 IU followed by a continuous infusion of 15 IU/kg/h with 5000 IU given one hour after the first dose	Desirudin: INF/INJ: 383 INF: 386 Heparin: 385	(Treated patients only) 58.0 years, 45 to 75 years; 896 male, 245 female; 1129 white, 2 black, 7 oriental, 3 other	Desirudin: single dose followed by a continuous infusion for 24 hours with or without single dose injections twice daily. Heparin: single dose followed by a continuous infusion with an additional dose

continued

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Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Other Studies
Phase II Controlled Clinical Trials

Protocol #; Investigators, Publications	Completion Status; Study Time Period	Location Product Code #	Full Report Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age: Mean; Range, Gender; Ethnic Origin	Duration of Treatment
RH/PT2: G Heyndrickx G.J. Laarman A.A. van de Bos H. Suryapranata I. Zijlstra; van den Bos, et al. Circulation. 1993;89:2058-2066.	Completed; 10 January 1991 to 17 June 1991	TBD	TBD	TBD	Double-blind, randomized, heparin-controlled study	Patients (30 to 75 years) with either single or multivessel coronary artery disease were considered for inclusion provided the following conditions were fulfilled: they were scheduled to undergo a percutaneous transluminal coronary angioplasty of one or more coronary vessels because of symptoms of stable angina pectoris, they were not on a heparin infusion, and they were never previously exposed to natural or recombinant hirudin.	Desirudin/ Intravenous 0.16 mg/kg/h; Heparin/ Intravenous 12 IU/kg/h	Desirudin: 77 Heparin: 41	58.3 years: 35.5 to 74.4 years; 91 male, 27 female; ethnic origin not recorded	Desirudin: single dose followed by a continuous infusion for 24 hours; Heparin: single dose followed by a continuous infusion for 24 hours

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Other Studies
Uncontrolled Clinical Trials

Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age: Mean; Range; Gender; Ethnic Origin	Duration of Treatment
US04; P. Bear, R. Califf, J.R. Bengtson, M. Mock, J. H. Chesebro, M. Cohen, B. George, H. Gold, D. Kereiakes, N. Kleiman, J.J. Popma, E. Topol; Topol, et al. Circulation. 1994;89:1557-1566. Rao AK, et al. Circulation. 1996;94:2389-2395.	Completed; 21 August 1991 to 01 June 1993	TBD	TBD	TBD	Open-label, ascending-dose study	Male or female inpatients between the ages of 21 and 75 years with ≥ 60 % narrowing of a major coronary artery, a diagnosis of unstable angina or non-Q-wave myocardial infarction and who had an episode of ischemic chest pain presumed to be myocardial in origin lasting at least 5 minutes.	Desirudin/ Intravenous 0.15 mg/kg then 0.05 mg/kg/h; 0.3 mg/kg then 0.10 mg/kg/h; 0.6 mg/kg then 0.20 mg/kg/h; 0.6 mg/kg then 0.30 mg/kg/h; 0.9 mg/kg then 0.30 mg/kg/h; Heparin/ Intravenous 5000 IU then 1000 IU/h	Desirudin: 0.15 mg/kg/0.05 mg/kg/h: 23 0.3 mg/kg/0.1 mg/kg/h: 23 0.6 mg/kg/0.2 mg/kg/h: 23 0.9 mg/kg/0.3 mg/kg/h: 3 0.6 mg/kg/0.3 mg/kg/h: 44 Heparin: 65-90 sec aPTT: 28 90-110 sec aPTT: 22	60.3 years; 31 to 75 years; 123 male, 43 female; 150 white, 11 black, 1 oriental, 4 other	Desirudin: single dose followed by a continuous infusion; Heparin: single dose followed by a continuous infusion

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Other Studies
Uncontrolled Clinical Trials

Protocol #, Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age: Mean; Range; Gender; Ethnic Origin	Duration of Treatment
US05; 15 investigators Cannon CP, et al. Journal of the American College of Cardiology. 1994;23:993-1003. Cannon CP, et al. American Journal of Cardiology. 1997;80:696-699.	Completed; 02 July 1991 to 13 January 1993	TBD	TBD	TBD	Open-label, ascending-dose study	Male and female inpatients between the ages of 21 and 75 years were eligible for enrollment. Patients must have had ischemic pain presumed to be myocardial in origin and of at least 30 minutes duration. The onset of symptoms leading to hospitalization must have been within six hours of the planned start of recombinant tissue plasminogen activator administration. Patients also had to exhibit new (or presumably new) ST-segment elevation of at least 0.1 mV in two continuous ECG leads or new (or presumably new) left bundle branch block. Female patients were required to be post-hysterectomy or at least one or more years post-menopausal or post-tubal ligation.	Desirudin/ Intravenous 0.15, 0.10, 0.30, or 0.60 mg/kg followed by 0.05, 0.1, or 0.2 mg/kg/h; rt-PA/ Intravenous 15 mg then 0.75 mg up to 50 mg max over 30 minutes, 0.5 mg/kg up to 35 mg max over 60 minutes; Heparin/ Intravenous 5000 U then 1000 IU/h	Desirudin: 0.15 mg/kg/0.05 mg/kg/h. 52 0.1 mg/kg/0.1 mg/kg/h: 34 0.3 mg/kg/0.1 mg/kg/h: 30 0.6 mg/kg/0.2 mg/kg/h: 51 rt-PA: 253 Heparin: 86	56.7 years; 21 to 75 years; 191 male, 62 female were enrolled: 210 white, 31 black, 12 other	Desirudin: ≤ 52 hours; Heparin: ≤ 171 hours

continued

Table 1-1: Summary of Studies in Clinical Development of Desirudin (continued)

Other Studies Uncontrolled Clinical Trials Protocol #; Investigators; Publications	Completion Status; Study Time Period	Location Product Code #	Full Report; Data Listings;	CRFs	Design	Criteria For Inclusion	Treatment/ Route of Administration/ Doses	Number of Patients Entered into Each Treatment	Age; Mean, Range; Gender; Ethnic Origin	Duration of Treatment
US07; 32 investigators; Lee LV. American Journal of Cardiology. 1995;75:7-13.	Completed; 11 August 1992 to 21 August 1993	TBD	TBD	TBD	Randomized, open-label, ascending-dose study	Male or female inpatients between the ages of 21 and 75 years, were eligible for enrollment. Patients must have had ischemic pain presumed to be myocardial in origin and of at least 30 minutes duration; the onset of symptoms leading to hospitalization must have occurred within six hours of planned initiation of streptokinase administration. Patients also had to exhibit new (or presumably new) ST-segment elevation of at least 0.1mV in two contiguous ECG leads or new (or presumably new) left bundle branch block.	Desirudin/ Intravenous 0.15 mg/kg then 0.05 mg/kg/hr. 0.3 mg/kg then 0.10 mg/kg/hr or 0.6 mg/kg then 0.20 mg/kg/hr. Heparin/ Intravenous 5000 IU then 1000 IU/h	Desirudin: 0.15 mg/kg/0.05 mg/kg/hr 55 0.3 mg/kg/0.1 mg/kg/h: 31 0.6 mg/kg/0.2 mg/kg/h: 36 Heparin: 71	(Age and ethnic origin data for treated patients only) 57.4; 31 to 75 years; 145 male, 47 female; 134 white, 24 black, 2 oriental, 25 other	Desirudin: single dose followed by a continuous infusion; Heparin: single dose followed by a continuous infusion

Sponsor's table volume 1.1 pp.3-1-250 – 3-1-268

Appendix 2

Country and Center Analysis- RH/E25 for the Primary Outcome

These tables are a compilation of data from several sources (sponsor's tables and SAS data sets).

Austria – Center 1 Results – [redacted]

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	84	84	168
Prophylaxis period completed	82	80	162
Discontinued prematurely	2	4	6
Death	1	0	1
Adverse Event	1	4 (1 PE, 1 MI)	5
Treated, but no operation	1 (AE)	0	1
Efficacy Analysis			
Per-protocol	78	76	154
Intent-to-Treat 1	78	76	154
Intent-to-Treat 2	84	84	168
Excluded from PP and ITT	6	8	14
Inadequate central reading	4	5	9
No operation	1	0	1
No phlebography	2	3	5
Phlebography performed at wrong time	0	1	1
Excluded from PP only	0	1	1
Inadequate central reading	0	1	1
Phlebography performed at wrong time	0	1	1
Efficacy Results			
Per-protocol	3 (3.8%)	1 (1.3%)	4
Intent-to-Treat 1	3 (3.8%)	1 (1.3%)	4
Intent-to-Treat 2	3 (3.6%)	1 (1.2%)	4

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

Austria – Center 2 Results – [redacted]

	Enoxaparin (number	Desirudin (number of	Total (number of

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	of patients)	patients)	patients)
Randomized	84	84	168
Prophylaxis period completed	84	84	168
Efficacy Analysis			
Per-protocol	72 (85.7%)	70 (83.3%)	139 (82.7%)
Intent-to-Treat 1	73 (86.9%)	70 (83.3%)	140 (83.3%)
Intent-to-Treat 2	84 (100%)	84 (100%)	
Excluded from PP and ITT*	11	14	25
Inadequate central reading	7	9	16
Missing information	1 (pt # 4727)	3 (pt # 4646, 4785, 7213)	4
No phlebography	3	2	5
Excluded, from PP only	1	0	1
Phlebography performed at the wrong time	1	0	1
Efficacy Results			
Per-protocol	6 (8.3%)	3 (4.3%)	9
Intent-to-Treat 1	6 (8.2%)	3 (4.3%)	9
Intent-to-Treat 2	6 (7.1%)	3 (3.6%)	9

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

Belgium – Center 1 Results–

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	27	27	54
Prophylaxis period completed	25	27	52
Discontinued prematurely	2	0	2
Adverse Event	1	0	1
Other reason	1 (PX)	0	1
Treated, but no operation	1	0	1
Efficacy Analysis			
Per-protocol	24 (88.9%)	26 (96.3%)	50 (92.6%)
Intent-to-Treat 1	24 (88.9%)	27 (100%)	51 (94.4%)
Intent-to-Treat 2	27 (100%)	27 (100%)	54 (100%)
Excluded from PP and ITT*	3	0	3
Inadequate central reading	1	0	1
No operation	1	0	1
No phlebography	2	0	2
Excluded from PP only	0	1	1
Randomized twice	0	1	1
Efficacy Results			
Per-protocol	2 (8.3%)	1 (3.8%)	3
Intent-to-Treat 1	2 (8.3%)	1 (3.7%)	3
Intent-to-Treat 2	2 (7.4%)	1 (3.7%)	3

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

Belgium – Center 3 Results–

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	32	32	64
Prophylaxis period completed	29	30	59
Discontinued prematurely	3	3	6
Other reason	3 (2 AP, 1 PX)	3 (2 AP, 1 WC)	6
Efficacy Analysis			
Per-protocol	22 (68.8%)	21 (65.6%)	43 (67.2%)
Intent-to-Treat 1	23 (71.9%)	22 (68.8%)	45 (70.3%)
Intent-to-Treat 2	32 (100%)	32 (100%)	64
Excluded from PP and ITT*	9	10	19
Inadequate central reading	0	1	1
Missing	3 (pt # 5033, 5044, 5108)	3 (pt # 5058, 5076, 5136)	6
No phlebography	6	6	12
Excluded from PP only	1	1	2
Phlebography performed at the wrong time	1	1	2
Efficacy Results			
Per-protocol	2 (9.1%)	0	2
Intent-to-Treat 1	2 (8.7%)	0	2