CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-271

MEDICAL REVIEW(S)

Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Review

NDA:	21-271[N 000, BZ, SU, BZ]
Sponsor:	Aventis Pharmaceuticals Products Inc.
Drug Product:	[redacted] (desirudin, RPR205511, CGP39393)
Date submitted:	June 28, 2000, October 11, 2000, November 14,2000, December 19, 2000, March 27, 2001
Date Received:	June 29, 2000, October 12, 2000, November 15, 2000, December 20, 2000, March 28, 2001
Date assigned:	June 30, 2000, October 16, 2000, November 16, 2000, December 20, 2000, March 29, 2001
Review Completed:	May 11, 2001
Reviewer:	Ann T. Farrell MD

Executive Summary:

I. Recommendations

A. The sponsor submitted an application for [redacted] desirudin, a direct thrombin inhibitor/anticoagulant, to support the claim that desirudin 15 mg subcutaneously administered every 12 hours for 8-12 days is effective for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement. The sponsor has demonstrated that the benefits of desirudin outweigh the risks and that the application is approvable from a clinical standpoint.

In the pivotal studies for desirudin approval, the sponsor compared the efficacy of desirudin to active comparator (unfractionated heparin and enoxaparin) at established or appropriate doses. Desirudin was significantly better for prophylaxis than either enoxaparin or heparin. The efficacy result demonstrated is consistent with desirudin's pharmacodynamic effect of prolongation of the peak and trough APTT observed in dose ranging trials.

A major concern for anticoagulant use is the risk of bleeding. During the pivotal trials, similar rates for bleeding were seen with desirudin and the active comparator. No life-threatening or unusual adverse events, which would preclude use of this drug product, were noted during the conduct of these trials. Potential benefits of this product include:

1) Proven efficacy for prophylaxis against deep vein thrombosis in patients undergoing elective hip replacement
2) Use in those individuals who have an allergy to heparin, low molecular weight heparins, or heparinoids

Potential risks of this product include:

1) bleeding
2) allergic reactions
3) increased wound secretion

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4) hypotension
5) local reaction

B. 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
6) The sponsor should provide safety information from the time of initial marketing (Malaysia – November 1995) to start of Safety Update (May 1, 1999).

II. Summary of Clinical Findings

The sponsor has submitted this NDA for (desirudin), a direct thrombin inhibitor administered by subcutaneous injection for the following indication:

> Prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.

Other drug products approved for the same indication are listed in the table below.

Current Drug Products Approved for thromboprophylaxis in hip replacement surgery

Drug	Administration Route/Drug Classification	Approved population	Approved indication
dalteparin	Subcutaneous/ low molecular weight heparin	Adult	Prophylaxis of deep vein thrombosis(DVT), which may lead to pulmonary embolism in patients undergoing hip replacement surgery
danaparoid	Subcutaneous/ heparinoid	Adult	Prophylaxis of post-operative deep vein thrombosis(DVT), which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery
enoxaparin	Subcutaneous/ low molecular weight heparin	Adult	Prevention of deep vein thrombosis(DVT), which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery
heparin	Parenteral/unfractionated heparin	Adult	Anticoagulant therapy in prophylaxis of venous thromboembolism and its extension
warfarin	Oral/anticoagulant	Adult	Prophylaxis of venous thromboembolism and its extension

Reviewer's table

In support of this indication, the sponsor submitted one uncontrolled, open-label, phase II, dose ranging study (RH/PT 3) and three multicenter, randomized, double-blind, phase III trials (RH/E 23, RH/E 25, and RH/E 28) for deep vein thromboprophylaxis in patients undergoing hip replacement surgery. The RH/E 25 and RH/E 28 studies are the pivotal trials for this indication. The RH/PT3 and RH/E 23 studies are supportive trials. All of these non-U.S. studies involved subcutaneous administration of desirudin.

RH/PT3

The RH/PT3 study was a single center, open label, dose-ranging trial to assess safety of desirudin in patients undergoing an elective hip replacement. Forty-eight patients aged 48 to 85 years undergoing their first elective hip replacement were entered. The trial was initially designed to test the safety and efficacy of three dose regimens of desirudin (10 mg, 20 mg, and 40 mg bid). Patients were treated for 7-12 days. After all three patients randomized at the 40 mg dose level had major bleeds, the protocol was changed. The 40 mg dose was terminated and a 15 mg dose level was added. In the trial, thromboembolic events for desirudin 10 mg were 5/12 (41.7%), for desirudin 15 mg were 1/11 (9%), and for desirudin 20mg were 2/20 (10%). The rate of major bleeding for desirudin 10 mg was 0%, for desirudin 15 mg was 8.3%, for desirudin 20 mg was 4.8%, and for desirudin 40 mg was 100%. Peak APTT prolongation increased with increasing dose of desirudin. Transaminase elevation increased with increasing dose level.

RH/E 23 trial

The RH/E 23 trial was a multicenter, double-blinded, randomized, heparin-controlled, dose ranging trial that randomized 1119 patients who were scheduled to undergo elective unilateral hip replacement surgery. Important inclusion criteria were body weight over 50 kg and serum creatinine < 2.0 mg/dl. Important exclusion criteria included pregnancy. Patients were randomized to desirudin 10 mg every 12 hours, desirudin 15 mg every 12 hours, desirudin 20 mg every 12 hours or unfractionated heparin 5000 units tid and treated for approximately 10 days. The primary efficacy endpoint was the incidence of objectively verified thromboembolic events (venographically demonstrated, positive ventilation/perfusion scan, positive pulmonary angiogram or autopsy) on Day 10 $\pm$ 1 in the per-protocol population. The per-protocol population consisted of those patients who had at least 80% compliance with the protocol study medication, were not major protocol violators, did not have a negative phlebography performed before day 9, did not have a phlebography that was performed after Day 11, and had their phlebography reviewed centrally. Primary efficacy results for the per-protocol population for desirudin 10 mg were 51/213 (23.9%), for desirudin 15 mg were 36/196 (18.4%), for desirudin 20mg were 37/209 (17.7%), and for unfractionated heparin were 75/219 (34.2%). Of note is that the prolongation of peak and trough APTT were observed for all desirudin groups, but not in the heparin group. It is possible that the difference in degree of anticoagulation may have contributed to the greater efficacy of desirudin. The major safety concern for this trial was hemorrhage. Total hemorrhages for desirudin 10 mg were 73/283 (25.8%), for desirudin 15 mg were 96/277 (34.7%), for desirudin 20mg were 95/282 (33.7%), and for unfractionated heparin were 76/278 (27.3%). The rate of major hemorrhage for desirudin 10 mg was 1/283 (0.4%), for desirudin 15 mg was 2/277 (0.7%), for desirudin 20mg was 1/282 (0.4%), and for unfractionated heparin was 0/278 (0%).

RH/E 25

The RH/E 25 trial was a multicenter, double-blinded, randomized, enoxaparin-controlled trial that randomized 2079 patients who were scheduled to undergo elective unilateral hip replacement surgery. Important inclusion criteria were body weight over 50 kg and serum creatinine below the clinic's upper limit of normal. Important exclusion criteria included pregnancy. Patients were randomized to desirudin 15 mg every 12 hours or enoxaparin 40mg

daily and treated for a mean of 10 days. The primary efficacy endpoint was the incidence of objectively verified thromboembolic events (venographically demonstrated proximal DVT, positive ventilation/perfusion scan, positive pulmonary angiogram or autopsy or unexplained death) in the per-protocol population. The venogram had to be performed after Day 8 and within one day of discontinuing study medication (Day 13 at the latest). The per-protocol population consisted of those patients who had at least 80% compliance with the protocol study medication, were not major protocol violators, did not have a negative phlebography performed before day 8, did not have a phlebography that was performed after Day 12, did not have an inadequate venogram, and had their phlebography reviewed centrally. Primary efficacy results for the per-protocol population in the desirudin 15 mg group were 39/802 (4.9%) and in the enoxaparin group were 61/785 (7.8%), the difference was significant at $p<0.02$. The secondary efficacy endpoint included all categories in the primary efficacy endpoint plus distal DVT. The secondary efficacy results for the evaluable population in the desirudin 15 mg group were 145/773 (18.8%) and in the enoxaparin group were 198/768 (25.8%), the difference was significant at $p<0.01$. The major safety concern for this trial was hemorrhage. Total hemorrhages for desirudin 15 mg were 155/1028 (15.1%) and for enoxaparin were 116/1043 (11.1%).

RH/E 28

The RH/E 28 trial was a multicenter, double-blinded, randomized, unfractionated heparin-controlled trial that randomized 445 patients who were scheduled to undergo elective unilateral hip replacement surgery. Important inclusion criteria were body weight over 50 kg and serum creatinine below the clinic's upper limit of normal. Important exclusion criteria included pregnancy. Patients were randomized to desirudin 15 mg every 12 hours or unfractionated heparin 5000 units tid and were treated for mean of 8.8 days. The primary efficacy endpoint was the incidence of objectively verified thromboembolic events (venographically demonstrated proximal DVT, positive ventilation/perfusion scan, positive pulmonary angiogram or autopsy or unexplained death) in the per-protocol population. The venogram had to be performed after Day 8 and within one day of discontinuing study medication (Day 13 at the latest). The per-protocol population consisted of those patients who had at least 80% compliance with the protocol study medication, were not major protocol violators, did not have a negative phlebography performed before day 8, did not have a phlebography that was performed after Day 12, did not have an inadequate venogram, and had their phlebography reviewed centrally. Primary efficacy results for the per-protocol population for desirudin 15 mg were 13/174 (7.5%) and for heparin were 41/177 (23.2%), the difference was significant at $p<0.001$. The secondary efficacy results for the per-protocol population involved a comparison of the individual components of the primary composite endpoint. In all categories the desirudin treatment group had a lower incidence of thromboembolic events. The major safety concern for this trial was hemorrhage. Total hemorrhages for desirudin 15 mg were 38/343 (11.1%) and for unfractionated heparin were 44/379 (11.6%).

Summary of Efficacy

The clinical trials demonstrated the efficacy of desirudin for prophylaxis against DVT in patients undergoing hip replacement surgery in the population studied for 8-12 days. Desirudin was compared to appropriately dosed, approved or established active comparators in patients undergoing unilateral elective hip replacement.

The population studied had the following characteristics:

1) Caucasian
2) weighing $\geq$ 50 kg
3) normal renal function

The sponsor has not provided any clinical data concerning the use of the drug in non-Caucasian patients or pregnant patients.

Summary of Safety

Major safety concerns identified during the preclinical phase included the fact that desirudin is renally excreted, data suggests that desirudin is teratogenic, and no data exists on the use of desirudin on patients with hepatic impairment. Side effects seen with anticoagulants and drugs of the hirudin family were observed. These side effects include hemorrhage and antibody formation.

The pharmacokinetic/pharmacodynamic trial conducted in renally impaired subjects suggests that the dose must be reduced in patients with moderate to severely impaired renal function and that the APTT level must be followed in these patients. For details, please see the Agency's Clinical Pharmacology and Biopharmaceutics Review dated March 2001.

The phase I trials involved approximately 500 patient exposures. The phase II and phase III (intravenous administration) for cardiology use involved approximately 10,500 exposures (number of patients). The phase II and III clinical trials (subcutaneous administration) were conducted in 2157 patients with normal renal function treated for 8-12 days. The major safety issue identified during the clinical trials was bleeding. In clinical trials the incidence of overall bleeding associated with desirudin (29.4%) was more frequent than with unfractionated heparin (22.2%) however less than that seen for enoxaparin (32.9%). Overall risk of hemorrhage appeared to be greater in patients who were obese, had underlying cardiovascular disease, had diabetes mellitus, had spinal or epidural anesthesia, or used antiplatelet drugs. The most common serous adverse event was major bleed and the desirudin incidence (2.9%) was the same as the active comparators (unfractionated heparin 2.9% and enoxaparin 3.0%).

The following adverse reactions were seen with greater frequency for the desirudin treatment group compared with the active comparators: edema of legs (4%), increased wound secretion (9%), hypotension (7%), and nausea (12%). Statistically significant differences were observed for increased wound secretion and hypotension with regard to both comparators (unfractionated heparin and enoxaparin). 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.

The sponsor studied drug-drug interactions with DDAVP, piroxicam, aspirin, unfractionated heparin, and warfarin. DDAVP was demonstrated to partially reverse the prolongation of APTT in 12 healthy volunteers. However, partial reversal of APTT does not imply apply ability to control hemorrhage in the clinical setting. No information was provided on use of DDAVP to control hemorrhage in patients undergoing elective hip replacement. Concomitant use of piroxicam did not prolong the bleeding time or APTT. Concomitant use of aspirin did not prolong the APTT. Concomitant use of heparin did prolong the APTT more than would have been expected with desirudin alone. Concomitant use of warfarin did prolong the PT and APTT, however the trial was too short to make statements about safety. The trial was also not designed to give the physician guidance about switching patients on other anticoagulant therapy to desirudin.

The post-marketing safety information from Europe includes one case of a patient who experienced mental confusion and subsequently had a positive rechallenge with desirudin. Several other patients experienced life-threatening and fatal hemorrhages in the setting of being switched from one anticoagulant (low molecular weight heparin or oral anticoagulant) to desirudin.

The submission did not contain a race analysis because nearly all patients included in the clinical trials were Caucasian. The gender analysis did not demonstrate any significant differences in efficacy or safety between the genders. Information on use of desirudin in the geriatric population did not indicate a significant difference in either efficacy or safety for those 65 years and over compared with those under 65 years. The submission lacks information about use in hepatically impaired patients. The label for the drug product from a safety perspective needs to include a black box warning for spinal/epidural hematomas. In addition, changes to the label need to be made to reflect the results in the renal impairment study and to provide dosage information for renally impaired and elderly patients. The label should clearly inform about the teratogenic effects seen in the animal studies. The indication being sought is not seen in pediatric patients, thus studies for this population are not needed and the label should reflect the lack of information in this area.

Table of Contents

Abbreviations

Abbreviations	Text
AE	Adverse Event
AP	Administrative Problems
APTT	Activated Partial Thromboplastin Time
BID or bid	Twice daily
BSE	Bovine spongioform encephalopathy
CPMP	Committee for Proprietary Medicinal Products
DVT	Deep Venous Thrombosis
EMEA	European Agency for the Evaluation of Medicinal Products
IV or iv	Intravenous
hr	hour
kg	kilogram
mg	milligram
Ml	milliliter
NA	Not applicable
NC	Non-compliant patient
NG	Not given
NOS	Not Otherwise Specified
PCI	Percutaneous Coronary Intervention
PT	Prothrombin time
PTCA	Percutaneous transluminal coronary angioplasty
PE	Pulmonary embolism
PX	Ineligible for Protocol
SAE	Serious Adverse Event

SC or sc	subcutaneous
SPC	Summary of Product Characteristics
TID or tid	Three times daily
TT	Thrombin time
VTE	Venous Thromboembolism
WC	Withdrew Consent

Reviewer's Table

Definitions

Word	Definitions
Intent-To-Treat (1)	All patients with an adequate phlebography or confirmed thromboembolic event.
Intent-To-Treat (2)	All randomized patients.
Per-protocol	All patients who receive study medication as outlined in the protocol and who receive radiologic testing as outlined in the protocol schedule.

Reviewer's table

Clinical Review

I. Introduction and Background:

The sponsor has submitted NDA 21271 (desirudin,), a direct thrombin inhibitor for the following indication:

Prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.

Desirudin is a direct thrombin inhibitor, which can inactivate clot-bound thrombin as well as free thrombin. The planned drug regimen is desirudin 15 mg injected subcutaneously every 12 hours for up to 12 days.

Other drug products approved for the same indication are listed in the table below.

Current Drug Products Approved for thromboprophylaxis in hip replacement surgery

Drug	Administration Route/Drug Classification	Approved population	Approved indication
dalteparin	Subcutaneous/ low molecular weight heparin	Adult	Prophylaxis of deep vein thrombosis(DVT), which may lead to pulmonary embolism in patients undergoing hip replacement surgery
danaparoid	Subcutaneous/ heparinoid	Adult	Prophylaxis of post-operative deep vein thrombosis(DVT), which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery
enoxaparin	Subcutaneous/ low molecular weight heparin	Adult	Prevention of deep vein thrombosis(DVT), which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery
heparin	Parenteral/unfractionated heparin	Adult	Anticoagulant therapy in prophylaxis of venous thromboembolism and its extension
warfarin	Oral/anticoagulant	Adult	Prophylaxis of venous thromboembolism and its extension

Reviewer's table

In support of this indication, the sponsor submitted one uncontrolled, open-label, phase II, dose ranging study (RH/PT 3) and three multicenter, randomized, double-blind, phase III trials (RH/E 23, RH/E 25, and RH/E 28) for deep vein thromboprophylaxis in patients undergoing hip replacement surgery.

The sponsor also submitted synopses of trials conducted with intravenous administration of desirudin for a possible cardiac indication. From 1990 to 1995, the sponsor pursued a

cardiology indication for use of desirudin as an anticoagulant in patients with unstable angina, myocardial infarction, or undergoing PCI. However, two phase III clinical trials were terminated for safety reasons (TIMI 9A and GUSTO IIA). Hemorrhagic complications were higher compared with heparin in most phase II and phase III cardiology clinical trials. Several patients experienced an intracranial hemorrhage prompting discontinuation of the trial. The dose regimen used in the terminated cardiology trials was 0.6mg/kg intravenous bolus followed by 0.2 mg/kg/hr continuous intravenous infusion. The cardiology dose regimen administers a total daily dose that is nearly 10 times higher than the sponsor's proposed dose of desirudin for thromboprophylaxis (15 mg bid).

Foreign Marketing

The tables below show dates of marketing approval and dates of submission for this drug product in non-U.S. countries. This drug has not been withdrawn from any country. The label has not been revised in any country, however the Summary of Product Characteristics has been revised to strengthen the text on renal insufficiency, detailed recommendations when switching from oral anticoagulants, and interactions with agents that interfere with platelet function.

Approved Countries

Countries	Indication	Date	Dosage(s)
European Union	Prevention of deep venous thrombosis in patients undergoing elective hip and knee replacement surgery.	July 9, 1997	15 mg b.i.d.
Australia	Prevention of venous thromboembolism after elective hip replacement.	Nov 11, 1996	15 mg b.i.d.
New Zealand	Prevention of thromboembolic complications after orthopaedic surgery	Nov 28, 1996	15 mg b.i.d.
South Africa	Prevention of deep vein thrombosis in elective hip replacement surgery, in patients over 50kg body mass.	July 24, 1998	15 mg b.i.d.
Switzerland	Prevention of thromboembolic complications after orthopaedic surgery	Dec 5, 1997	15 mg b.i.d.
Czech Republic	Prevention of venous thromboembolism after hip and knee replacement.	June 16, 1999	15 mg b.i.d.
Brazil	Prevention of venous thromboembolism after elective hip replacement.	Aug 16, 1999	15 mg b.i.d.
Hungaria	Prevention of venous thromboembolism after elective hip replacement.	Sept 9, 1999	15 mg b.i.d.
Norway	Prevention of venous thromboembolism after elective hip replacement.	July 1, 1999	15 mg b.i.d.
Uruguay	Prevention of venous thromboembolism after elective hip replacement.	Aug 27, 1999	15 mg b.i.d.

Submissions

Countries	Indication	Date	Dosage(s)
[redacted]			

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Other pharmacologically related agents

Other pharmacologically related agents under study include lepirudin (a recombinant hirudin) approved for use in patients with heparin induced thrombocytopenia and associated

thromboembolic disease and bivalirudin (a synthetic hirudin) approved for use as an anticoagulant in patients undergoing PTCA.

II. Clinically Relevant Findings from Preclinical Sciences

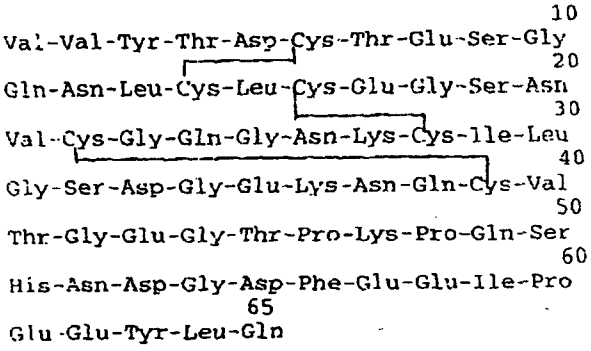
Drug Substance/Active Substance and Chemistry, Manufacturing and Control:

For further details, see the Agency's Chemistry, Manufacturing and Control Review dated April 9, 2001.

- The drug substance: CGP 39393: recombinant hirudin or desirudin produced in *Saccharomyces cerevisiae* is manufactured by Novartis AG (Ciba Geigy AG).

Recombinant hirudin, rHirudin, CGP 39393 or desirudin is a recombinant protein produced in the *Saccharomyces cerevisiae* strain TR1456 transformed with plasmid pDP34/GAPFL-YHIR. The protein contains a single polypeptide chain of 65 amino acids with 3 disulfide bridges. .

Fig. 1: Amino acid sequence of recombinant hirudin (CGP 39393)



The nomenclature of the active ingredient follows.

- USAN/WHO formula name: Desirudin
- Laboratory Codes: CGP 39393
- Trivial Names: Recombinant hirudin, rHirudin, r[Tyr^{63}]-hirudin sequence variant 1, rDesulfato hirudin
- Proprietary: REVASC™

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- The lyophilized drug product is [redacted] (recombinant hirudin) 15 mg dry substance is packaged in vials with mannitol 15mg/0.5 ml (3%) solvent for parenteral use in ampules.

F1 and F4 formulations

The sponsor used the F1 formulation during the conduct of the trials and currently in Europe is marketing the F4 formulation, [redacted] The sponsor's table below outlines the differences between the formulations.

Composition of the old (F1) and new (F4) formulations of desirudin for s.c. application

	Old Formulation (F1) (+2 to +8°C)	New Formulation (F4) (Room Temperature)
Desirudin	15 mg	15 mg
Mannitol	[redacted]	[redacted]
MgCl2 (anhydrous)	[redacted]	[redacted]
Reconstitution	0.5 mL 3% mannitol	0.5 mL 3% mannitol

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For the F4 formulation, the shelf-life of the dry substance is 24 months when stored below 25^0 C and protected from light. The shelf-life of the mannitol solvent is 36 months when stored below 25^0 C. Once reconstituted the solution is physically, chemically, and biologically stable in a vial for 24 hours at ambient temperature.

In a clinical bioequivalence study comparing the F1 formulation (used in the clinical trials) and the F4 formulation (currently marketed) in 12 healthy male volunteers, the two formulations appeared similar. (See "Section III. Human Pharmacokinetics and Pharmacodynamics" below).

Microbiology

No bacterial, fungal or wild type yeast contaminants have been detected.

Production of Drug Substance

[redacted]

Stability studies have indicated that recombinant hirudin is stable for 24 months and is suitable for use in the finished product when stored in the freezer at –15 to –20 ° C.

Preclinical Pharmacology and Toxicology Information:

Desirudin is a direct thrombin inhibitor which can inactivate clot-bound thrombin as well as free thrombin. The planned drug regimen is desirudin 15 mg injected subcutaneously every 12 hours for up to 12 days.

Desirudin was studied in mice, rats, dogs, and monkeys and in in vitro studies to evaluate the pharmacologic action and toxicity.

In-vitro studies

Stability: No deterioration of biological activity was detectable in human plasma at either 37^{0}C or 4^{0}C at six hours.

Hemostasis: In vitro enzymological studies demonstrated that desirudin is a selective inhibitor of thrombin. Studies performed on other serine proteases including digestive enzymes, coagulation pathways, and complement proteins did not demonstrate significant inhibition by desirudin. Platelet aggregation induced by thrombin is inhibited; however platelet aggregation induced by other agents was not affected. Of all coagulation parameters tested, the thrombin time was the most sensitive to desirudin. Since prolongation of the thrombin time was dependent upon the thrombin concentration used, and the stability of the thrombin in solution, the sponsor chose to use the APTT to monitor the effect of desirudin in clinical trials.

In vivo studies

Subcutaneous administration to rats produced rapid absorption and the APTT reached a plateau at 15 minutes, with an anticoagulant effect lasting 2-4 hours. Administration to nephrectomized rats prolonged the anticoagulant effect.

Venous thrombosis induced in the venae cavae of rats by administration of tissue thromboplastin followed by a 10 minute period of stasis could be reduced by administration of desirudin. In the rat model of thrombosis, desirudin inhibited thrombus formation. The inhibition was dose dependent.

Intravenously administered desirudin's prolongation of the bleeding time in rats suggested that DDAVP, recombinant FVIII and Vueffe may moderate desirudin's effect on primary hemostasis.

Acute toxicity studies were performed by single dose intravenous bolus in mice, rats, dogs, and monkeys. Doses were limited by volume and solubility constraints. No deaths occurred and desirudin was not acutely toxic at doses up to 300mg/kg. One cynomologus monkey treated with desirudin (100mg/kg) had anemia. One dog treated with desirudin (30mg/kg) had traces of blood in feces. [redacted]

Chronic toxicity studies were performed in rats, dogs, and monkeys. The sponsor's table below shows the studies performed.

Table 7 - SUBCHRONIC TOXICITY STUDIES

Species	Strain/Breed	Initial Group	Route of Administration	Vehicle	Doses mg/kg/day (except as noted)	Duration	Ref
Rat	Td: RAII(SPF)	5M	Subcutaneous	5% glucose	60	10 days	6
Rat	Td: RAII(SPF)	15M + 15F	Subcutaneous	5% glucose	0, 20 (0, 60 stopped)	28 days + 1 month recovery	7
Rat	Td: RAII(SPF)	10M + 10F plus 5/sex for recovery in control & HD grps	Subcutaneous	Glucose/PEG 4000/mannitol	0, 2.5, 5, 10	3 months + 1 month recovery	8
Dog	Beagle	1M + 1F	Intravenous Bolus 1/day	5% dextrose	10 for 4 days 20 for 1 day 30 for 5 days	10 days (total)	9
Dog	Beagle	3M + 3F	Intravenous Bolus 1/day	5% glucose	0, 20	1 month	10
Dog	Beagle	3M + 3F 6M + 6F in 25 mg/kg grp	Intravenous Bolus 1/day	Glucose/PEG 4000/mannitol	0, 10, 25	3 months + 1 month recovery	11
Dog	Beagle	3 M	Continuous intravenous infusion 24 hr/day	4% mannitol/ 0.9% NaCl	0, 1, 4 mg/kg/hr	7 days	12
Monkey (Cyno)		3M + 3F	Continuous intravenous infusion 24 hr/day	4% mannitol/ 0.9% NaCl	0, 1, 4 mg/kg/hr	14 days	13

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The major side effects associated with desirudin administration in the one-month and three-month rat studies were injection site hemorrhage, inflammation, and hematomas. In the one-month study, mortality due to anemia and blood loss occurred at 20 and 60 mg/kg/day dose levels. In the three-month study, two deaths occurred in the 10 mg/kg/day due to hematoma and excessive bleeding. Hematomas were noted in all dose groups in the three-month study. No systemic toxicity was observed.

In the continuous intravenous infusion study for 7 days in the dog, there was hemorrhage at low dose (1mg/kg/day) with hemorrhage and anemia noted in the higher dose group (4 mg/kg). In the continuous infusion study for 14 days in the monkey there were hemorrhage and deaths in the 1 mg/kg and 4 mg/kg groups. In the three month dog study, two dogs (one each in the 10 mg/kg and 25 mg/kg groups) either died or were euthanized as a consequence of bleeding. Arteritis was also noted in some dogs in the three month study prompting additional immunological studies.

Immunotoxicological Effect in the Dog

These studies were undertaken after arteritis was noted in the major organs in the dog. The sponsor's table below outlines the trials conducted.

Table 8 SPECIAL TOXICITY STUDIES (IMMUNOGENICITY)

Species	Group Size	Dose & Route of Administration	Injection Paradigm	Endpoints	Result	Ref
Rabbit	5 M + 5 F	2 mg/kg IV	10 daily injections & boosters at 4 and 8 weeks	Skin testing and antibody determinations	Negative	18
Dog	3 M + 3 F	2 mg/kg IV	10 daily injections & boosters at 4 and 8 weeks	Skin testing and antibody determinations	Increase in specific antibodies & IgG titer	19
Baboon	1 M & 1F	2 mg/kg IV	10 daily injections & boosters on days 38 and 66	Skin testing	Negative	20
Guinea pig	10 M 5 M in control grp	2 mg IV 2 mg subcut. with Freunc's Adjuvant	3 times per week, total 10 Biweekly, total 3 times	Active systemic anaphylaxis (ASA) Passive cutaneous anaphylaxis (PCA)	ASA & PCA positive only with desirudin plus Freund's adjuvant	21

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The studies conducted in the dog demonstrated an increase in specific antibodies and IgG titer. The studies conducted with the guinea pig demonstrated an increase in antibodies only when desirudin was administered concurrently with Freud's Adjuvant.

Reviewer's Comment: The clinical significance of these findings is uncertain.

Reproduction Studies

The sponsor's table below outlines the studies undertaken for fertility, reproduction, and teratogenicity. No effects on fertility or reproduction were noted however there were abnormalities noted in the teratogenicity studies.

Reviewer's Comment: The table below illustrates teratogenic findings across two species. The sponsor states that the non-reproducibility of the findings in the rabbits (lack of spina bifida in second rabbit trial) reassures that desirudin does not have a direct effect on fetal development. However, this reviewer disagrees with that statement. From the table below teratogenic abnormalities were noted in 10% (5/50) rats and 16% (9/56) rabbits. All teratogenic effects observed were defects in closure either of the abdominal wall or spinal canal.

DEVELOPMENTAL TOXICITY STUDIES (SEGMENT II)

Species/Strain	Group Size	Route of Administration	Dose mg/kg	Fetal Malformations
Rat/ Tif:RAIf (SPF hybrid	24 F	Subcutaneous	0 1 5 10 (gd 6-15)	One fetus at 1 mg/kg/day had incomplete closure of the abdominal wall. Low incidence of omphalocele at 5 mg/kg/day (1 fetus) and 10 mg/kg/day (2 fetuses).
Rat/ Crl:COB CD(SD) BR	26 F	Subcutaneous	0 5 10 15 (gd 6-15)	No omphaloceles at 5 or 10 mg/kg/day Only 1 omphalocele at 15 mg/kg/day.
Rabbit/ NZW	16 F	IV	0 0.6 2 6 (gd 6-18)	1 fetus with sacral spina bifida in each of the low and mid-dose groups and 6 fetuses (5 litters) with sacral spina bifida at the high dose.
Rabbit/ NZW	40 F	IV	0 (gd 7-19) 6 (gd 7-13) 6 (gd 14-19) 6 (gd (7-19)	No sacral spina bifidas Two fetuses (2 litters) had gastroschischis in the group that was administered 6 mg/kg/day from gd 7-13.

Sponsor's table volume 1.1 p.3-1-183

Desirudin showed no evidence of a mutagenicity or clastogenic effect in:

1) Salmonella/Mammalian microsome mutagenicity test
2) testing performed with Chinese hamster cells and
3) in vitro micronucleus test in the rat

Absorption, Distribution, Metabolism, and Excretion

In rats following subcutaneous desirudin administration, peak plasma concentrations were obtained within 0.7 hours. Bioavailability with subcutaneous administration compared with intravenous administration was 83%. The plasma elimination half-lives in the rat and dog ranged from 0.43 to 0.71 hours. Elevated plasma concentrations of desirudin were found in some dogs at the end of the three-month toxicology study where desirudin was given by intravenous bolus injection daily. The sponsor attributed this to desirudin-antibody complexes, however no definite proof was given. Distribution studies showed that desirudin was distributed into the extracellular space of rats, dogs, and cynomolgus monkeys. Intravenous administration of radioactively labeled recombinant hirudin demonstrated that the hirudin concentrations in the amniotic fluid was 0.015 percent of maternal plasma levels. After intravenous administration of desirudin, unmetabolized desirudin was demonstrated in the urine. In rats after intravenous bolus injection 14% was recovered in the urine compared with 44% recovered after higher doses were administered. The study in nephrectomized rats using desirudin demonstrated that APTT values remained elevated past 24 hours. This study suggested renal excretion.

III. Human Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and Pharmacodynamics data was obtained from 503 patients who participated in Phase I clinical trials. In these trials, desirudin was given by the cutaneous, intravenous, and subcutaneous routes.

The table below shows the studies used to determine pharmacodynamic effect.

Studies Used to Study Pharmacodynamic effect of desirudin

Administration Route	Study
Intravenous bolus	RH/ET 1, RH/ET 7, RH/E 10, HIR-001
Intravenous infusion	RH/ET 2, RH/ET 5, HIR-001
Subcutaneous	RH/ET 3, RH/ET 6, RH/ET 8, RH/ET 9, RH/E 10

Reviewer's Table

The sponsor chose the APTT to monitor the pharmacodynamic effect in trials because the thrombin test was considered too sensitive.

Single Subcutaneous Administration in Healthy Volunteers
Subcutaneous administration resulted in dose dependent prolongation of the APTT, which was detected 30 minutes after administration. The peak effect was noted from 30 minutes to 4 hours after dosing and the APTT returned to normal within 24 hours. The time to reach peak effect ranged between 1.5 to 2.5 hours post-dose in most cases.

The table below shows the mean maximum APTT prolongation values obtained with subcutaneous administration in healthy volunteers.

Reviewer's Comment: The table below illustrates that with subcutaneously administered doses as low as 0.1 mg/kg desirudin APTT values are prolonged. The proposed 15 mg sc dose corresponds to 0.5 mg/kg.

Table 1. Mean (± SD) maximum aPTT prolongation values (multiple of baseline) following a single sc. injection of desirudin in healthy volunteers

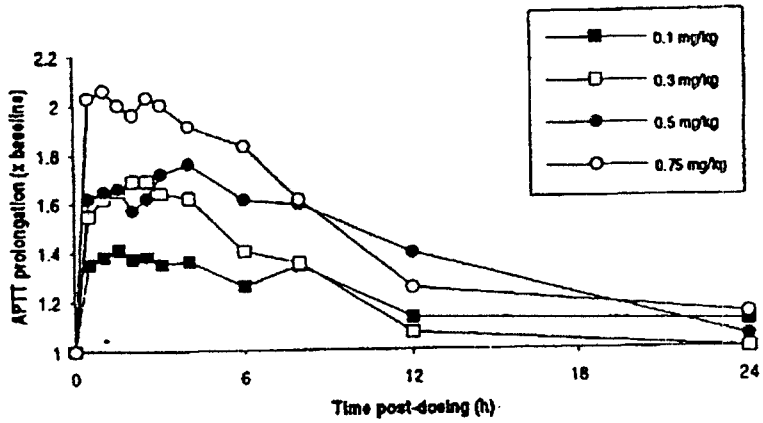
Trial RH/ET 8 (n=4)		Trial RH/ET 3 (n=8)	
Dose (mg/mL)	aPTT prolongation (x baseline)	Dose (mg/mL)	aPTT prolongation (x baseline)
0.1	1.41 (0.07)	0.1	1.47 (0.11)
0.3	1.72 (0.15)	0.2	1.51 (0.12)
0.5	1.82 (0.24)	0.3	1.86 (0.19)
0.75	2.07 (0.17)	0.4	2.00 (0.10)

Sponsor's table volume 1.1 p.3-1-205-206

The graph below illustrates the mean APTT prolongation following subcutaneous administration.

Reviewer's Comment: For the 0.5 mg/kg subcutaneous administration, prolonged APTT values between 1.4-1.6 times the baseline could be observed at 12 hours.

Mean aPTT prolongation (multiple of baseline) following a single sc. injection of desirudin in 4 healthy volunteers (Trial RH/ET 8)



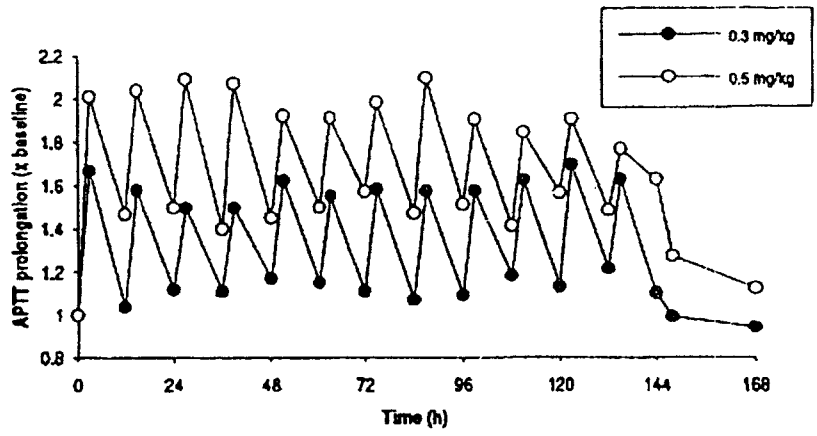
Sponsor s graph volume 1.1 p.3-1-205

Multiple Subcutaneous Dosing

Repeated doses of desirudin at 0.3 or 0.5 mg/kg were administered every 12 hours for six days. The sponsor's graph below shows the results.

Reviewer's Comment: The results below illustrate that at the 0.5mg/kg dosing level, the healthy volunteers are anticoagulated to APTT approximately 1.5 times the baseline at 12 hours (trough levels for the every 12hr regimen).

Mean aPTT prolongation (multiple of baseline) following repeated twice daily sc. injection of desirudin for 6 consecutive days in 4 healthy volunteers (Trial RH/ET 9)



Sponsor's graph volume 1.1 p. 3-1-206

Bleeding times after subcutaneous injection did not differ from the normal range.

Two trials involving patients undergoing hip replacement obtained pharmacodynamic laboratory data. Laboratory parameters obtained from these dose ranging trials demonstrated prolongation of the APTT value from baseline during conduct of the trial. These trials are discussed in greater detail under the clinical trials section.

Information on trials conducted in the elderly, in renal failure patients, coadministration of other medications is discussed later in the review under Use in Special Populations.

Pharmacokinetics

Clinical Studies of Pharmacokinetics of desirudin

Administration Route	Study
Intravenous bolus	RH/ET 1, RH/ET 7, RH/E 10
Intravenous infusion	RH/ET 2, RH/ET 5
Subcutaneous	RH/ET 3, RH/ET 6, RH/ET 8, RH/ET 9, RH/E 10

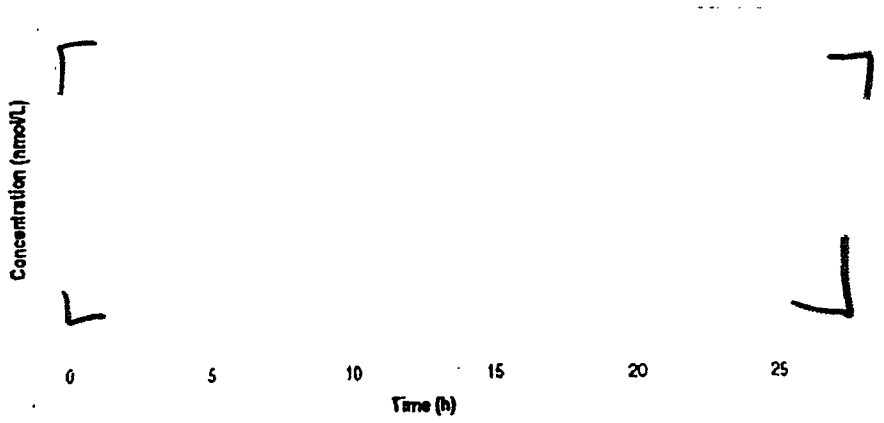
Reviewer's Table

Absorption
Single dose and multiple dose subcutaneous administration studies demonstrated that t_{max} occurred approximately 1 to 3 hours after initial dosing. Plasma concentration curves demonstrated a plateau effect due to prolonged absorption from the injection site. Maximum concentration levels and area under the curve were dose-proportional.

Metabolism and Elimination
Animal and human studies suggest that little systemic enzymatic degradation of desirudin occurs. Biotransformation was evaluated after intravenous administration in six healthy male volunteers. Metabolites of desirudin missing one or two C-terminal amino acids were recovered in the urine; this accounted for 7% of the total desirudin dose administered. Intravenous administration of radioactive I^{125} showed that the majority of radioactivity was recovered in the kidney (80%). Immunohistochemical staining showed that desirudin was almost always localized in the kidney and not in the liver, lung, or heart. In the kidney, staining was most intense in the proximal tubules, moderate in the distal tubules, and weakest in the medullary tubules. Desirudin was observed in endocytic vesicles and/or lysozomes suggesting uptake from the tubular lumen by endocytosis. No biliary excretion was demonstrated in the rat.

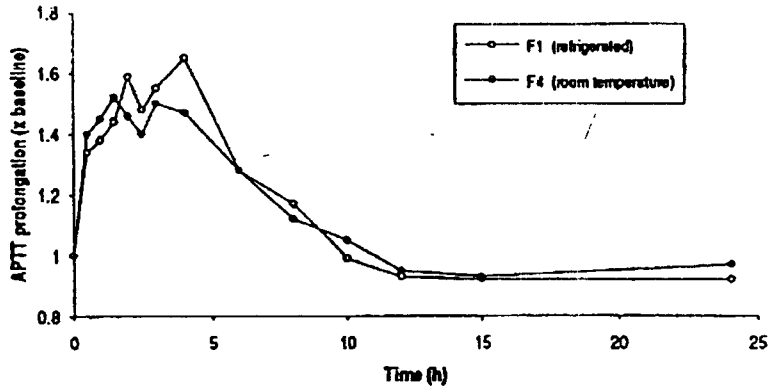
After subcutaneous administration to humans, the mean terminal $t_{1/2}$ was approximately 2.4 to 3.7 hours. In humans, the total urinary excretion of intact desirudin was 40-50% with C-terminal metabolites accounting for 7%.
The sponsor conducted a clinical bioequivalence study to compare the F1 formulation (used in the clinical trials) and the F4 formulation (currently marketed) in 12 healthy male volunteers. The two formulations appeared similar. The sponsor's graphs below illustrate the results of plasma desirudin concentrations and APTT values in this study.

Plasma pharmacokinetics following single s.c. administration of 15 mg desirudin as formulation F1 (stored at +2 to +8°C) and formulation F4 (stored at room temperature) in 12 healthy volunteers each (Trial RH/E 36).



Sponsor's graph volume 1.1 p.3-1-231

Mean aPTT prolongation (multiple of baseline) following single s.c. administration of 15 mg desirudin as formulation F1 (stored at +2 to +8°C) and formulation F4 (stored at room temperature) in 12 healthy volunteers each (Trial RH/E 36).



Sponsor's graph volume 1.1 p.3-1-232

The sponsor's table below compares the pharmacokinetic and pharmacodynamic parameters of the two formulations.

Reviewer's Comment: The F1 and F4 formulations show similar pharmacokinetic and pharmacodynamic properties.

APPEARS THIS WAY
ON ORIGINAL

Pharmacokinetic and pharmacodynamic parameters following administration of the old (F1) and new (F4) s.c. formulation of desirudin to 12 healthy volunteers (Trial RH/E 36).

Parameters (Unit)	Old Formulation (F1) (+2 to +8°C)	New Formulation (F4) (Room Temperature)
tmax (median, h)	2.0	2.5
Cmax (nmol/l)	38.5 ± 9.1	35.7 ± 6.1
AUCinf (nmol·h/L)	211 ± 27	204 ± 30
Peak aPTT (s)	68.5 ± 17.2	61.5 ± 8.5
Peak aPTT (X baseline)	1.89 ± 0.39	1.67 ± 0.18
AUC of aPTT (s·h)	1097 ± 107	1065 ± 82.1

Sponsor's table volume 1.1 p.3-1-232

IV. Clinical Data and Sources

The sources of data used in this review were the following:

a) NDA review volumes
b) SAS datasets
c) Correspondence between the Agency and the sponsor
d) Literature reports

Tables describing the types of trials, number of subjects enrolled, dose regimen can be found in the Appendix. The phase I trials involved approximately 500 patients exposed to desirudin, using subcutaneous and intravenous administration routes. The phase II and phase III trials for cardiology indication involved approximately 10,500 desirudin individual patient exposures using the intravenous administration route. The phase II and III clinical trials for prophylaxis of thromboembolism indication were conducted in 2157 patients with normal renal function treated for 8-12 days using the subcutaneous administration route. Information on patient demographics is presented in the sponsor's tables below.

Reviewer's Comment: These demographic characteristics reflect the patient population likely to receive the drug after it is marketed.

Table 5.3-1: Demographic Characteristics of 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 (%)
Age (Yrs)						
N; N Missing	295; 0	1561; 0	303; 0	2159; 0	501; 0	1036; 0
<45	7 (2.4)	43 (2.8)	4 (1.3)	54 (2.5)	9 (1.8)	30 (2.9)
45-54	25 (8.5)	164 (10.5)	33 (10.9)	222 (10.3)	43 (8.6)	106 (10.2)
55-64	91 (30.8)	439 (28.1)	86 (28.4)	616 (28.5)	134 (26.7)	306 (29.5)
65-74	115 (39.0)	587 (37.6)	118 (38.9)	820 (38.0)	184 (36.7)	399 (38.5)
≥75	57 (19.3)	328 (21.0)	62 (20.5)	447 (20.7)	131 (26.1)	195 (18.8)
<65	123 (41.7)	646 (41.4)	123 (40.6)	892 (41.3)	186 (37.1)	442 (42.7)
≥65	172 (58.3)	915 (58.6)	180 (59.4)	1267 (58.7)	315 (62.9)	594 (57.3)
Mean; SD	66.0; 9.72	66.0; 10.14	66.4; 9.69	66.1; 10.02	67.4; 9.86	65.7; 10.07
Minimum; Maximum	37; 90	27; 90	31; 90	27; 90	25; 86	18; 87

continued

Table 5.3-1: Demographic Characteristics of Patients in Treatment Groupings 1 and 2 (continued)

	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 (%)
Sex						
Male	108 (35.9)	663 (42.5)	116 (38.3)	885 (41.0)	193 (38.5)	414 (40.0)
Female	189 (64.1)	898 (57.5)	187 (61.7)	1274 (59.0)	308 (61.5)	622 (60.0)
Height (cm)						
N; N Missing*	292; 3	1555; 6	302; 1	2149; 10	497; 4	1033; 3
Mean; SD	166.5; 8.21	167.1; 8.53	166.4 ; 8.72	166.9 ; 8.52	167.2; 8.91	167.0; 8.44
Minimum; Maximum	140; 193	135; 196	142; 197	135; 197	141; 195	140; 195
Weight (kg)						
N; N missing	295; 0	1560; 1	303; 0	2158; 1	499 2	1036; 0
Mean; SD	73.7; 12.99	74.1; 12.86	73.3; 13.20	74.0; 12.92	73.2; 13 56	74.6; 13.17
Minimum; Maximum	50; 121	42; 121	40; 117	40, 121	47; 130	43;128
Body Mass Index (kg/m²)*						
N; N missing	292; 3	1555; 6	302; 1	2149; 10	496; 5	1033; 3
Mean; SD	26.5; 4.06	26.5; 3 88	26.4; 3.92	26.5; 3.91	26.1; 3.81	26.7; 3.93
Minimum; Maximum	19; 45	18; 45	16; 39	16; 45	18; 41	17; 44

* Missing category excluded from percentages.

* Body Mass Index = weight (kg)/height (m^2).

Cross Reference: Appendix 1. Table 3.1 and 3.2.

Sponsor's table volume 1.85 pp.8-38-327-328

The sponsor's tables below give information on concomitant illnesses.

Reviewer's Comment: The table below shows that no patients with renal insufficiency were given desirudin and that 3 patients with hepatic insufficiency were given desirudin.

Table 5.3-2: Clinical Characteristics of Patients in Treatment Grouping 1

	Desirudin 15 mg bid N=1561 n (%)	Unfractionated Heparin 5000 IU tid N=501 n (%)	Enoxaparin 40 mg qd N=1036 n (%)
Obesity*			
Yes	626 (40)	170 (34)	431 (42)
No	929 (60)	326 (66)	602 (58)
Missing*	6	5	3
Cardiovascular Disease†			
Yes	201 (13)	70 (14)	116 (11)
No	1360 (87)	431 (86)	920 (89)
Diabetes Mellitus			
Yes	82 (5)	24 (5)	56 (5)
No	1479 (95)	477 (95)	980 (95)
Malignancy‡			
Yes	59 (4)	16 (3)	37 (4)
No	1502 (96)	485 (97)	999 (96)
Renal Insufficiency‡‡			
Yes	0	0	2 (<1)
No	1561 (100)	501 (100)	1034 (100)
Hepatic Insufficiency§§			
Yes	2 (<1)	1 (<1)	1 (<1)
No	1559 (100)	500 (100)	1035 (100)

continued

Table 5.3-2: Clinical Characteristics of Patients in Treatment Grouping 1 (continued)

	Desirudin 15 mg bid N=1561 n (%)	Unfractionated Heparin 5000 IU tid N=501 n (%)	Enoxaparin 40 mg qd N=1036 n (%)
Concomitant Medications[88]			
Class 1	1163 (75)	295 (59)	844 (81)
Class 2	534 (34)	89 (18)	497 (48)
Anticoagulant[1]	440 (28)	70 (14)	413 (39.9)
Anticoagulant[2]	34 (2)	5 (1)	22 (2)
Class 3	1217 (78)	331 (66)	888 (86)
Class 4	344 (22)	170 (34)	148 (14)

* Obesity was defined as men having a body mass index >27.2 and women having a body mass index >26.9.
- Missing category excluded from the calculation of percentages.
Cardiovascular disease included the following medical history preferred terms: angina pectoris, aortic stenosis, arteriosclerosis, cardiac failure, cardiac failure left, cardiomegaly, coronary artery disease NOS, fibrillation atrial, fibrillation cardiac, heart valve disorders, myocardial infarction, and myocardial ischemia.
§ Malignancy included the following medical history preferred terms: carcinoma, carcinoma prostate, carcinoma uterine, colon carcinoma, leukemia lymphyocytic, lymphoma malignant, neoplasm brain malignant, neoplasm breast female, neoplasm breast malignant female, neoplasm GI, neoplasm hepatic, neoplasm malignant, neoplasm NOS, neoplasm ovarian malignant, neoplasm urinary tract, neoplasm uterine, skin neoplasm malignant, and tumor skin.
~ Renal insufficiency was defined as patients having a baseline creatinine level > 180 µmol/L.
~~ Hepatic insufficiency was defined as patients having a baseline bilirubin > 35 µmol/L.
Class 1: nonsteroidal antiinflammatory drugs, antiplatelets, and plasma expanders; Class 2: anticoagulants; Class 3: nonsteroidal antiinflammatory drugs, antiplatelets, plasma expanders, and anticoagulants; Class 4: Patients who were not a member of Class 3.
1 Includes patients who took any anticoagulant after the start of treatment through the last day of study medication.
2 Includes patients who took any anticoagulant after the start of treatment thrcugh the day prior to the last day of study medication.

Cross Reference: Appendix 1: Tables 3.5, 6.3, and 6.4.

Sponsor's table volume 1.85 pp.8-38-330-331

The sponsor provided information about worldwide exposure from May 1, 1999 to September 1, 2000. The sponsor did not provide information about exposure from when desirudin was first approved in Malaysia in November 1995. The sponsor estimates that the worldwide patient exposure from May 1, 1999 to September 1, 2000 is approximately 5800 patients. During that period the sponsor received 32 safety reports. Twenty-four of these were considered serious and 6 patients died. Detailed information on the post-marketing experience is located in the Integrated Summary of Safety.

The sponsor provided published articles on trials conducted in support of the indication.

IV. Clinical Review Methods

The clinical trial reports for the two pivotal trials and one dose ranging trial were scrutinized for adherence to study protocol, data accuracy, missing data, endpoints and all adverse events. The key efficacy and safety tables were double-checked by comparing the clinical

trial reports with the SAS datasets. No efficacy analyses were recomputed except for the removal of centers where the investigator did not return a financial disclosure form. No problems were encountered using the electronically submitted data.

The protocols were submitted to IND (34046).

The Division of Scientific Investigation (DSI) audit has been completed. DSI was requested to visit Center 1 in Austria and Center 4 in France from RH/E 25 trial. Center 1 in Austria was chosen for the following two reasons:

1) one of the largest centers
2) [redacted] did not provide financial disclosure forms

Center 4 in France was chosen because 67% of patients were excluded from the per-protocol analyses and no reason for exclusion was provided for most of these patients. For details see the center efficacy results in the appendix.

The DSI audit letters signed by Dr. John R. Martin revealed that Center 4 conducted the trial with adherence "to all pertinent federal regulations and/or good clinical investigational practices." The DSI audit letter signed by Dr. John R. Martin revealed that there were protocol violations, which were not felt to affect the reliability of the sponsor's data.

Ethics

Informed consent forms were provided for RH/E 25 and RH/E 28. The informed consent forms did provide information on risks associated with the medication. No informed consent form could be located for RH/E 23 or RH/PT 3. All study patients were treated according to standard of care. The active comparator used in clinical trials was an approved product or an established active comparator, which was appropriately dosed in patients undergoing unilateral elective hip replacement.

Financial Disclosure

Four investigators did not submit a financial disclosure form. The sponsor submitted a form detailing attempts to reach those investigators. The investigators and the trials in which they participated in are listed in the table below.

Investigators who did not provide financial disclosure information

Investigator	Trials
[redacted]	RH/E 23, RH/E 25
[redacted]	RH/E 25
[redacted]	RH/E 23 (form for this trial not provided however, others for RH/E 25, RH/E 28 were)
[redacted]	RH/E 25
[redacted]	RH/E 25, RH/E 28

Reviewer's table

All other investigators provided signed forms, which stated no financial conflict of interest.

Percentage of evaluable patients in trials by Selected Investigators

Trial/Investigator	RH/E 23 (N=837)	RH/E 25 (N=1587)	RH/E 28 (N=351)
[redacted]	143 (12.8%)	154 (9.7%)	N/A
[redacted]	N/A	64 (4%)	N/A
[redacted]	80 (9.6%)	N/A	N/A
[redacted]	N/A	139 (16.6%)	N/A
[redacted]	N/A	58 (3.7%)	43 (12.3%)
Total contribution of patients	223 (26.7%)	415 (26.1%)	43 (10.9%)

Reviewer's table

The patients enrolled by the investigators who did not sign financial disclosure forms are unlikely to have contributed to the outcome of the trial for the following reasons:

1) trials were conducted in a double-blind, double-dummy fashion
2) the trials were randomized
3) central assessors evaluated the venograms and ventilation/perfusion scans used for the final endpoints

This reviewer's re-analysis of RH/E 25 and RH/E 28 is shown in the table blow. RH/E 23 was not re-analyzed because this trial was the dose-determining trial.

Reviewer's Comment: As shown in the tables below, removing those centers where the investigator did not sign a financial disclosure form does not appear to affect the study efficacy outcome.

Original Primary Efficacy Results of RH/E 25 and RH/E 28 (including all centers)

Trial	Active comparator	Comparator event rate	Desirudin event rate
RH/E 25	Enoxaparin	61/785 (7.8%)	39/802 (4.9%)
RH/E 28	Heparin	41/177 (23.2%)	13/174 (7.5%)

Reviewer's table

Reviewer's Reanalysis of RH/E 25 and RH/E 28

Trial	Active comparator	Comparator event rate	Desirudin event rate
RH/E 25	Enoxaparin	47/571 (8.2%)	30/598 (5%)
RH/E 28	Heparin	35/157 (22.3%)	13/151 (8.6%)

Reviewer's table

VI. Review of Efficacy

RH/PT 3 – Uncontrolled Trial

Reviewer's Conclusion regarding RH/PT 3

This single center, open label, dose-ranging trial served to determine the desirudin dose used for the larger RH/E 23 trial. From a safety standpoint the 40-mg desirudin dose was associated with increased major bleeding. From an efficacy standpoint the 10-mg desirudin dose was associated with increased thromboembolic events compared with the other two dose groups. The major efficacy and safety event rates were approximately the same for the 15-mg and 20-mg dose groups.

The trial design was a single center, open label, dose-ranging trial to assess safety of desirudin in patients undergoing an elective hip replacement.

The trial period ran from April 1991 to December 1991.

Amendments to the protocol
Three amendments were made to the original protocol.

Amendment #1 (May 23, 1991)
This amendment modified the inclusion criteria:

1) to broaden the weight requirement to include individuals between 45 and 100 Kg
2) to include non-cemented prosthesis in addition to cemented prosthesis

Amendment #2 (September 3, 1991)

This amendment modified the protocol to stop 40 mg dose level. The stopping criteria permitted increased patient assignment to 20 mg dose level if 3 major bleeding episodes were observed in the 40 mg dose group.

Amendment #3 (September 12, 1991)
This amendment modified the protocol to extend the trial in order to assign 12 patients to the 15-mg dose group.
Main objective:
The main objective of this trial was to assess the safety of varying doses of desirudin primarily with respect to incidence of major bleeding in 36 patients.

Doses Administered
The sponsor's description of drug administration is given below.

The schedule of administration is as follows:

OPERATION DAY

10, 20 or 40 mg CGP 39 393	2 hours preoperatively (i.e. between 7 a.m. and 11 a.m.)
10, 20 or 40 mg CGP 39 393	in the evening (i.e. between 7 p.m. and midnight)

POST-OPERATION DAYS 1 to 9

10, 20 or 40 mg CGP 39 393	in the morning (i.e. between 7 a.m. and 9 a.m.)
10, 20 or 40 mg CGP 39 393	in the evening (i.e. between 7 p.m. and 9 p.m.)

Sponsor's text volume 1.81 p.8-34-109

Inclusion and Exclusion criteria

The sponsor's inclusion and exclusion criteria for RH/PT 3 are listed below.

INCLUSION CRITERIA

36 cooperative male or female 50 to 85-year old inpatients weighting between 50 to 90 kg, never previously exposed to hirudin (natural or recombinant), who have to undergo a first elective total hip replacement with a cemented prosthesis will be included after their informed consent

has been recorded. All patients should have a normal response to a collagen-induced platelet aggregation test (final concentration of 3 to 5 µg/mL).

EXCLUSION CRITERIA

Physiological states, previous and/or concomitant medical conditions

a) General exclusion criteria:

- Allergy to natural or recombinant hirudins (i.e. isoforms)
- Women in child-bearing potential

b) Cardiovascular and haematologic exclusion criteria:

- Acute internal or external haemorrhage
- Recent severe trauma (within the past 3 months)
- Major surgery, biopsy or puncture of a non-compressible vessel (within the past month)
- History of gastrointestinal or pulmonary bleeding
- History of intracranial or intraocular bleeding (including diabetic [haemorrhagic] retinopathy)
- Recent stroke (within the past 6 months)
- History of previous thromboembolic disease
- Recent (within the past month) cardiopulmonary resuscitation manoeuvres
- Pericarditis
- Severe or non-controlled hypertension, defined as a diastolic and/or systolic blood pressure over 100 and 180 mmHg, respectively
- Known left heart thrombus
- Bacterial endocarditis
- Haemostatic disorders (congenital or acquired, e.g. liver disease)
- Thrombocytopenia (< 100,000 platelets/mm^3)

c) Other exclusion criteria:

- Acute or chronic renal impairment (defined as an increase of serum creatinine above 1.5 mg/100 mL [130 µmol/L] or a fall in creatinine clearance below 90 mL/min)
- Ulcerative cutaneous lesions
- Known cavitary lung disease
- Known inflammatory bowel disease
- Breast feeding
- Known allergy to iodine

Previous and concomitant treatments

- The use of any drugs known to affect normal vascular integrity, and/or coagulation parameters, and/or platelet function (e.g. heparins, oral anticoagulants, thrombolytic agents, dextrans, cephalosporins, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, dipyramidole, sulphinpyrazone, ticlopidine, melphalan, vincristine, l-asparaginase) is prohibited within 14 days prior to the start of the trial and during the whole trial period.

- The use of any investigational drug (including rechirudin) within 28 days prior to the start of the trial is prohibited.

Sponsor's text volume 1.81 p.8-34-111 - 113

Definition of Major Bleeding
The sponsor's description of major bleeding is given below.

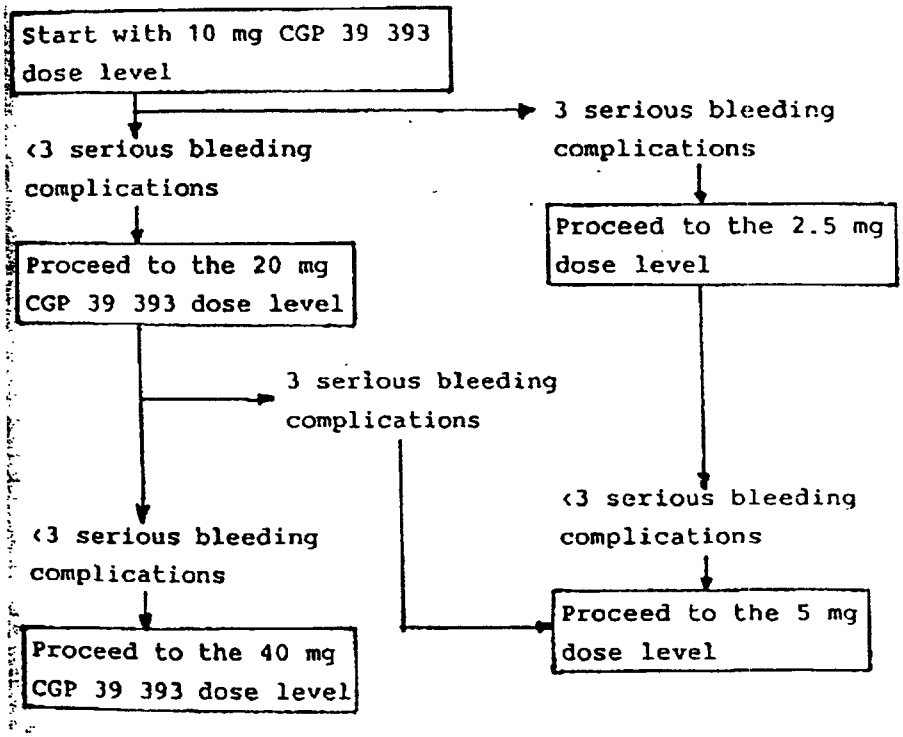
Major bleeding complications are:

* any bleeding whenever intracerebral, intraocular, intraspinal or retroperitoneal
* a decrease in haemoglobin level (preoperative level - postoperative level at one week [Post-operation Day 6]) greater or equal to 50 g/L
* peroperative transfusion requirements > 2500 mL whole blood or 5 units of concentrated red cell packs
* total (i.e. per- and postoperative up to Post-operation Day 6) requirements > 3500 mL whole blood or 7 units of concentrated red cell packs
* total blood loss (peroperative blood loss plus postoperative drainage at Post-operation Day 6) > 3500 mL

Sponsor's text volume 1.81 p.8-34-115

Flow of trial

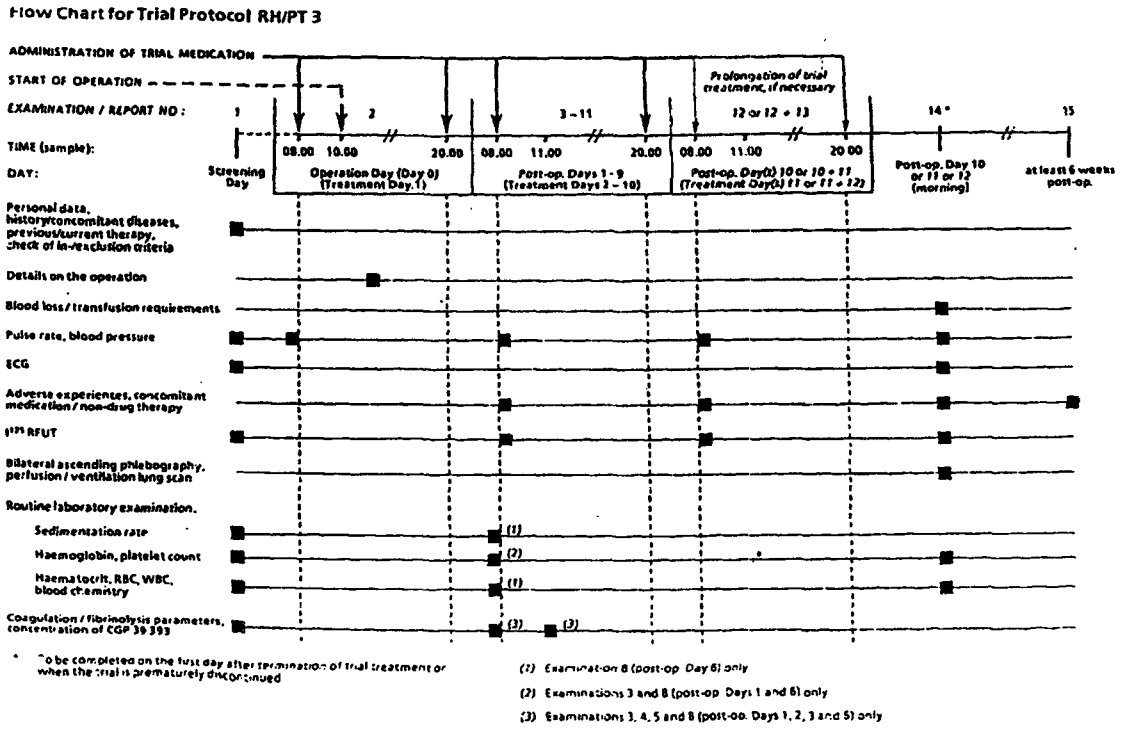
The next two sponsor's diagrams illustrate the flow of the protocol. The first shows the safety feature (major bleeding) built into the trial.



Sponsor's diagram volume 1.81 p.8-34-108

Reviewer's Comment: This trial was amended because the flow diagram did not provide for the occurrence of 3 major bleeds at the 40 mg dose level.

The diagram below shows the timing of procedures for this trial.



Sponsor's diagram Volume 1.81 p.8-34-133

Demographics

Forty-eight patients were entered into the trial. The mean age was 69.6 years with a range of 48 to 84. The mean weight was 71.7 kg with a range of 53-100 kg. Fourteen patients were smokers. Thirty-three patients were female and fifteen were male.

Protocol violations and deviations

Several patients received their pre-op injections incorrectly. Four patients received their first injection during or after the operation. One patient received 20 mg instead of 15 mg on post-op day 3.
Two patients had ages less than the inclusion criteria of 50 years (i.e. 48 and 49 years).
Eight patients had hypertension outside the range in the exclusion criteria. Four patients had a prior history of a thrombosis.

Premature Discontinuations
Nine patients were prematurely discontinued. Two patients (10 mg and 20 mg) withdrew because of development of a deep venous thrombosis. Three patients withdrew because they were discharged from the hospital early. One patient withdrew consent. Three patients withdrew because of major bleeding.

Efficacy and Safety
The sponsor's tables below highlight the efficacy and major safety concerns during the trial. The first table shows the thromboembolic rate during the trial. The fifteen mg dose had the lowest rate.

Reviewer's Comment: The table below only includes thromboembolic events occurring during the prophylaxis period. Three patients (one patient in each treatment group) experienced a DVT after the prophylaxis period.

Summary of verified thromboembolic events occurring during the prophylaxis period

Thromboembolic complication	10 mg CGP 39 393 (N = 12)	15 mg CGP 39 393 (N = 11)**	20 mg CGP 39 393 (N = 20)***
Events			
Deep-vein thrombosis (n):	5	1	2
Pulmonary embolism (n):	2	0	1*
Total number of thrombo-embolic complications	7	1	3
Patients			
Total number of patients with thromboembolic events	5 (41.7 %)	1 (9 %)	2 (10 %)
95 % Confidence limit:	15.2 % - 72.3 %	0.23 % - 41.3 %	1.2 % to 31.7 %

* Excluding one patient (Pat.No. 2013) with a borderline perfusion/ventilation lung scan.
** One patient (Pat.No. 1511) withdrew consent so phlebography and perfusion/ventilation lung scan were not performed.
*** One patient (Pat.No. 2015) withdrew consent on post-operation day 8 so phlebography and perfusion/ventilation lung scan were not performed.

Sponsor's table volume 1.81 p. 34-56

The next table shows the major safety concerns during this trial. Major bleeding was observed in six patients (all three 40 mg, two 15 mg, and one 20 mg desirudin patients). No patient experienced an intracerebral, intraocular, intraspinal or retroperitoneal bleed. All major bleeding was reported as > 3500 ml blood loss and/or transfusion. No immune or allergic reactions were noted.

TABLE 6: NUMBER OF PATIENTS WITH HAEMATOMA , MAJOR BLEEDING, SUSPICION OF ALLERGIC REACTION

Treatm. Group	Haematoma	Major Bleeding	Immune/Allergic Reaction
10 mg	n = 12	n = 12	n = 12
(N = 12)	no 12 (100%)	no 12 (100%)	no 12 (100%)
	yes 0 (0.0%)	yes 0 (0.0%)	yes 0 (0.0%)
15 mg	n = 12	n = 12	n = 12
(N = 12)	no 12 (100%)	no 11 (91.7%)	no 12 (100%)
	yes 0 (0.0%)	yes 1 (8.3%)	yes 0 (0.0%)
20 mg	n = 21	n = 21	n = 21
(N = 21)	no 19 (90.5%)	no 20 (95.2%)	no 21 (100%)
	yes 2 (9.5%)	yes 1 (4.8%)	yes 0 (0.0%)
40 mg	n = 3	n = 3	n = 3
(N = 3)	no 3 (100%)	no 0 (0.0%)	no 3 (100%)
	yes 0 (0.0%)	yes 3 (100%)	yes 0 (0.0%)

Sponsor's table volume 1.81 p.8-34-81

Laboratory Parameters
At peak, the APTT values were noted to be approximately 1.20 times the APTT baseline in the groups. The mean peak APTT levels compared to baseline were noted to be 1.34 (10 mg), 1.32 (15 mg) and 1.55 (20 mg). Eighteen patients experienced an elevation of their transaminases. These eighteen patients included 3 patients in the 10-mg group, 8 patients in the 15-mg group, and 7 patients in the 20-mg group. Three patients (15-mg, and 2 20-mg patients) had elevations of their transaminases (one patient at the 15-mg dose level and 2 patients at 20-mg dose level) greater than 3 times the upper limit of normal.

EKG abnormalities
One patient experienced new onset atrial flutter during the clinical trial.

Trial: RH/E 23
Reviewer's Conclusion regarding RH/E 23

The sponsor conducted a multicenter, randomized, double-blind, dose-ranging trial comparing varying doses of desirudin with heparin. Overall, the heparin treatment group had a higher primary event rate (DVT, PE, and Death) compared with the desirudin treatment groups. This result may be due to the fact that the desirudin patients were anticoagulated to a greater degree during the trial (i.e. peak and trough APTT levels were different from baseline compared to APTT levels for heparin). There was no significant efficacy difference between the 15-mg and 20-mg desirudin treatment groups. A greater percentage of patients in the 20 mg desirudin group needed a transfusion compared with the 15 mg desirudin group.

Design:
The trial was a multicenter, double-blind, randomized, heparin controlled, dose-finding trial evaluating the safety and efficacy of three CGP39393 dose levels (10 mg, 15 mg, and 20 mg bid) in patients undergoing an elective total hip replacement

Time period:
Trial was conducted from May 1992 to August 1993.

Amendments to trial:
There were several amendments to the original study protocol.

Reviewer's Comment: None of these amendments impacted the outcome of the trial.

The amendments were:
First – July 24, 1991
This reviewer could not locate this version of the protocol however this version predated the start of the trial.

Second- October 25, 1991
Since the first version could not be located it is difficult to say what the changes were to the protocol. This version of the protocol states that 1080 patients will be recruited from 14 centers to ensure 872 evaluable patients, assuming a 20% dropout rate.

February 21, 1992
This amendment described changes to the outward packaging of the syringes and reconstitution of desirudin. Following reconstitution of desirudin, the drug product was to be administered immediately.

April 21,1992
This amendment allowed for additional blood sampling to be performed at one site in Germany to test whether shortened platelet induced thrombin generation time or increased platelet adhesiveness to glass are predictive of post-operative thromboses.

May 25, 1992
This amendment increased the number of participants in the Safety and Data Monitoring Committee. The amendment also included minor changes to maintain the blind of the trial as much as possible. The statistician had access to the treatment allocation codes. If necessary the information held by the statistician and the information held by other committee members could be combined to allow committee members to know what a single patient's allocation was.

July 27, 1992

1) This amendment changed: The inclusion criteria now stated only unilateral hip replacement patients are eligible.
2) The distinction between peri-operative and post-operative bleeding was better defined.
3) The protocol was clarified with respect to information on measuring hematoma size.

Inclusion/exclusion criteria
The sponsor's inclusion and exclusion criteria are listed below.

INCLUSION CRITERIA

Cooperative inpatients aged over 21 years weighing over 50 kg, who have to undergo an elective total hip replacement (i.e. no

revision) with a cemented or non-cemented prosthesis are eligible after their informed consent has been recorded.

4.2 EXCLUSION CRITERIA

4.2.1 General exclusion criteria:

- Allergy to natural or recombinant hirudins (i.e. isoforms)
- 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).
- Previous hip surgery on the same side (within last 6 months)

4.2.2 Cardiovascular and haematologic exclusion criteria:

- Known haemostatic disorders (congenital or acquired, e.g. liver disease) including thrombocytopenia (< 100 x 10^9 platelets/L)
- History of serious bleeding (within the last 3 months)
- Recent severe trauma (within the past 3 months)
- Major surgery, biopsy or puncture of a non-compressible vessel (within the past month)
- History of gastrointestinal or pulmonary bleeding (within the last 3 months)
- History of intracranial or intraocular bleeding (including diabetic [haemorrhagic] retinopathy)
- Recent stroke (within the past 6 months)
- Uncontrolled hypertension

4.2.3 Other exclusion criteria:

- Renal impairment (defined as an increase of serum creatinine above 2.0 mg/dL [180 µmol/L])
- Known inflammatory bowel disease
- Contra-indication to contrast media
- Haemorrhagic or technical problems during administration of regional block anaesthesia

Sponsor's volume 1.72 pp. 014-015

Treatment administration:

Desirudin was administered 5 minutes pre-op and on the evening of surgery followed by bid administration. Heparin was administered 2 hours pre-op, in the afternoon and evening after surgery followed by tid administration. Matching placebo injections were given to maintain the blind.

Randomization:
Fixed block randomization was used with eight subjects in each block.

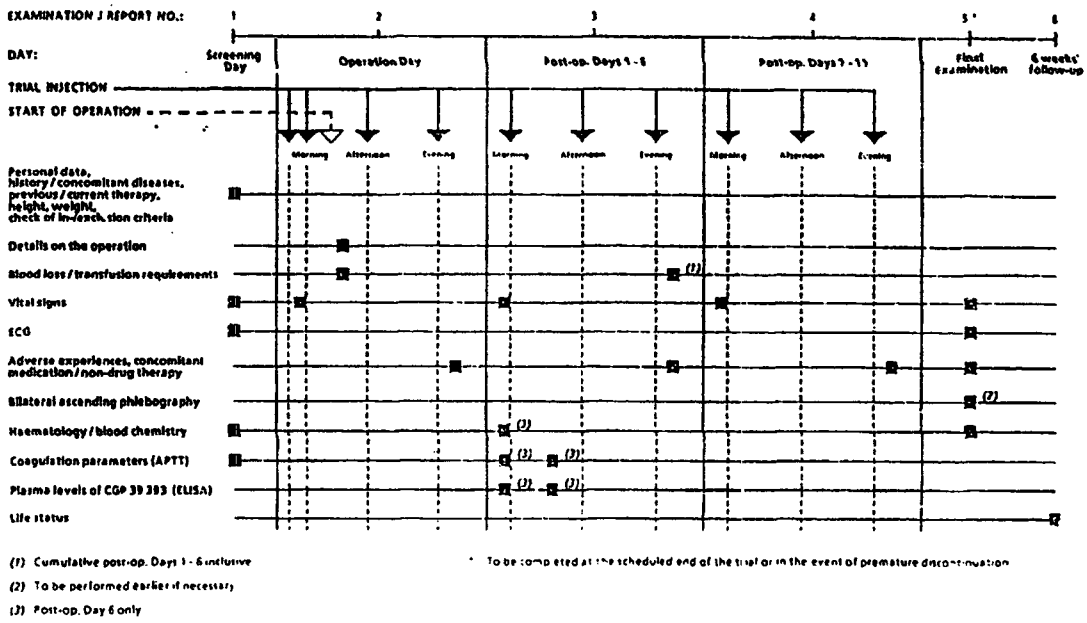
Concomitant medication
The following medications were prohibited: heparins other than study medication, oral anticoagulants, thrombolytic agents, dextran, long acting non-steroidal anti-inflammatory agents, aspirin, dipyridamole, sulphinpyrazone, and ticlopidine for the 7 days preceding the trial and during the trial. Subjects were not permitted to receive antineoplastic agents within the prior six months. The following anti-inflammatory medications could be administered within 7 days before the trial or during the trial: diclofenac, ibuprofen, sulindac, paracetamol, and dextro-propoxyphene.

The use of investigational agents within 30 days of this trial was also prohibited.

Flow of trial
The flow of the trial is listed in the sponsor's text and diagram below.

CGP 39 393 (REC-HIRUDIN)

Flow Chart for Trial Protocol RH/E 23



(1) Cumulative post-op. Days 1 - 5 inclusive
(2) To be performed earlier if necessary
(3) Post-op. Day 6 only
* To be completed at the scheduled end of the trial or in the event of premature discontinuation

Sponsor's volume 1.72 pp. 045

Efficacy Measurements

Bilateral Ascending Venography
The protocol required the procedure to be performed on post-operative day 10 (± 1 day) in all patients who did not manifest clinical evidence of a deep venous thrombosis earlier in the trial.
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

Efficacy

Patients are counted only once.
Primary efficacy was defined by the absence of a confirmed thromboembolic event:

1) bilateral ascending phlebography performed at the end of the prophylaxis period and assessed centrally
2) high probability ventilation/perfusion scan
3) pulmonary angiogram
4) autopsy

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

1) phlebography is performed before day 9 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) major protocol violation occurs
   a) use of oral anticoagulants, thrombolytics, or dextrans
   b) less than 80% compliance

Statistical analysis

Primary outcome
The main outcome is the presence of a confirmed thromboembolic event. In the case of death without an autopsy, the outcome was considered positive.
The main analysis was to be logistic regression with treatment and center as fixed factors and a two-sided test procedure with an overall significance level of 5%. The 95% confidence intervals was to be given for the estimated log odds ratio for each comparison.

Secondary outcome

The CGP 39393 dose response relationship regarding efficacy was analyzed using logistic regression with dose and center as fixed factors. In addition severity of outcome will be assessed (death > pulmonary embolism > DVT (proximal) > DVT (distal)).

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:

1) fall in hemoglobin of at least 2 gms/dl or
2) transfusion of $\geq$ 2 units packed red cells in the post-operative period or

3) retroperitoneal or
4) intracranial or
5) into a prosthetic joint

Serious bleeding was defined as:

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 exceed 7 units
3) total blood loss up to post-op day 6 exceeds 3500 ml

Results:

The trial was conducted in 17 centers in 7 countries (1 center in Austria, 2 centers in Denmark, 5 centers in Germany, 3 centers in Great Britain, 2 centers in Italy, 2 centers in The Netherlands, and 2 centers in Sweden). During the trial unforeseen difficulties caused the sponsor to add centers and permit increased enrollment at other centers in order to complete the trial within 11 months. Difficulties that arose included:

1) approval of protocol delayed in Germany because of phlebographic technique
2) lower than anticipated recruitment in the United Kingdom
3) temporary followed by permanent discontinuation of trial in the United Kingdom (Belfast) because of excessive bleeding seen for all treatment groups (including heparin treatment group)

Reviewer's Comment: Germany contributed the greatest number of patients (227 patients total, 20.3% of all patients) followed by Sweden (224 patients total, 20.2% of all patients).

Completed Patient Contribution to study RH/E 23 by Center

	Desirudin (10 mg)	Desirudin (15 mg)	Desirudin (20mg)	Heparin	Total
Center	N/G	N/G	N/G	N/G	1119
Austria	34	33	35	35	143 (12.8%)
Denmark- Center 1	20	19	20	20	79 (7.1%)
Denmark - Center 2	20	20	20	19	79 (7.1%)
Germany Center 3	1	2	1	0	4 (0.4%)
Germany- Center 4	14	14	14	14	56 (5%)
Germany –Center 7	28	28	28	28	112 (10%)
Germany – Center 8	4	4	4	4	16 (1.4%)
Germany – Center 9	10	10	10	9	39 (3.5%)
Great Britain – Center 1	29	28	29	30	116 (10.4%)
Great Britain - Center 2	8	8	9	8	33 (3%)
Great Britain – Center 3	6	4	6	6	22 (2%)
Italy – Center 1	20	20	20	20	80 (7.1%)
Italy – Center 2	20	20	20	19	79 (7.1%)
Netherlands – Center 1	8	8	8	10	38 (3.4%)
Netherlands – Center 2	2	0	1	0	3 (0.3%)
Sweden –Center 1	25	25	24	25	99 (8.8%)
Sweden –Center 2	32	31	32	30	125 (11.2%)

Reviewer's table

Code Numbers Broken during Conduct of Trial

Fifteen codes were broken by the investigator for serious adverse events in 12 patients. One surgeon broke the code and did not agree to the patient's continuing participation in the trial. One patient was given additional prophylaxis. One patient experienced an allergic reaction (received desirudin). In 53 cases, the code was broken in Great Britain and Italy to comply with the reporting of serious adverse events.

Reviewer's Comment: Codes were broken for all doses and treatment types.

Number of Times Code broken for Study RH/E 23

Treatment	Number of patients
Desirudin 10mg	12
Desirudin 15mg	15
Desirudin 20mg	19
Heparin	20

Reviewer's table

Duration of Treatment and Treatment during Trial

The sponsor's table, Duration of treatment in Days with Per-Protocol population is shown below.

Reviewer's Comment: The duration of treatment did not differ between treatment groups.

DURATION OF TREATMENT IN DAYS
(DATASET: PER-PROTOCOL POPULATION)

CENTER: ALL CENTERS

	Unfractionated Heparin	CGP 39 393			TOTAL
	Dose 5000 IU N = 219	Dose 10 mg N = 213	Dose 15 mg N = 196	Dose 20 mg N = 209	N = 837
Duration of prophylaxis period					
n	219	213	196	209	837
Mean (SD)	10.4 (0.9)	10.4 (1.0)	10.5 (1.1)	10.4 (1.0)	10.4 (1.0)
Median	10.0	10.0	10.0	10.0	10.0
Range	8.0 - 12.0	8.0 - 12.0	2.0 - 12.0	6.0 - 12.0	2.0 - 12.0
Q1-Q3	10.0 - 11.0	10.0 - 11.0	10.0 - 11.0	10.0 - 11.0	10.0 - 11.0
< 4 days	0 (0.0 %)	0 (0.0 %)	1 (0.5 %)	0 (0.0 %)	1 (0.1%)
5-8 days	2 (0.9 %)	1 (0.5 %)	1 (0.5 %)	2 (1.0 %)	6 (0.7%)
9-10 days	119 (54.3 %)	118 (55.4 %)	108 (55.1 %)	110 (52.6 %)	455 (54.4%)
11-12 days	98 (44.7 %)	94 (44.1 %)	86 (43.9 %)	97 (46.4 %)	375 (44.8%)
Number of patients with missing active injection(s) on the operation day	10	5	9	1	25

Sponsor's table volume 1.70 p.8-23-231

The next two sponsor's tables illustrate summary patient APTT values that occurred during the trial.

Reviewer's Comment: Both tables illustrate that the patients in the heparin treatment group did not experience a change in their trough or peak APTT values during the trial compared with baseline whereas the desirudin treatment groups did.

Table 8.2.2-1:

Trough APTT (absolute and relative to baseline)

APTT (secs)		Unfractionated Heparin 5000 IU	CGP 39 393 10 mg	CGP 39 393 15 mg	CGP 39 393 20 mg
baseline	N	147	141	145	133
	Mean	37.65	37.82	37.59	37.98
	Median	37.10	37.40	36.70	37.60
	SD	[illegible]	4.48	4.54	7.68
	Range				
	Q1 - Q3	34.80 - 40.30	34.30 - 39.60	34.80 - 39.80	34.80 - 39.90
trough	N	147	141	145	133
	Mean	37.26	41.33	42.76	44.26
	Median	36.50	40.30	41.10	42.90
	SD	6.36	7.67	[illegible]	7.68
	Range				.90
	Q1 - Q3	33.90 - 39.30	36.00 - 44.70	37.20 - 46.30	38.60 - 48.10
trough/baseline	N	147	141	145	133
	Mean	0.99	1.09	1.14	1.17
	Median	0.98	1.07	1.11	1.14
	SD	0.10	0.14	0.17	[illegible]
	Range				
	Q1 - Q3	0.92 - 1.03	1.01 - 1.16	1.03 - 1.22	1.06 - 1.28

Only patients with a valid baseline and trough measurement are included.
Valid baseline measurement: lab sample taken within 14 days before 1st injection.
Valid trough measurement: lab sample taken at post op day 5 - 7 within 9 - 15 hours after previous (evening) injection.

Sponsor's table volume 1.70 p.8-23-286

Table 8.2.2-2:

Peak APTT (absolute and relative to baseline)

APTT (secs)		Unfractionated Heparin 5000 IU	CGP 39 393 10 mg	CGP 39 393 15 mg	CGP 39 393 20 mg
baseline	N	204	198	202	196
	Mean	39.07	39.43	39.64	39.78
	Median	37.60	37.95	37.35	37.85
	SD	7.38	10.81	10.88	[illegible]
	Range				
	Q1 - Q3	35.40 - 41.70	35.20 - 40.80	35.19 - 40.78	35.05 - 40.58
peak	N	204	198	202	196
	Mean	39.01	49.39	53.87	55.67
	Median	37.80	47.70	51.30	52.80
	SD	7.17	9.80	15.83	12.54
	Range				
	Q1 - Q3	34.80 - 41.50	43.80 - 53.60	46.20 - 58.00	48.25 - 59.55
peak/baseline	N	204	198	202	196
	Mean	1.01	1.27	1.38	1.42
	Median	1.00	1.26	1.37	1.40
	SD	0.17	0.20	0.29	0.28
	Range				
	Q1 - Q3	0.93 - 1.05	1.16 - 1.37	1.25 - 1.48	1.28 - 1.57

Only patients with a valid baseline and peak measurement are included.
Valid baseline measurement: lab sample taken within 14 days before 1st injection.
Valid peak measurement: lab sample taken at post op day 5 - 7 within 1.5 - 3 hours after previous (morning) injection.

Sponsor's table volume 1.70 p.8-23-287

Demographics

There were no differences between treatment groups in age, sex, smoking history, height, and weight. Women constituted 62% of the randomized study population.

Risk Factors

There were no differences between treatment groups in risk factors. Sixty-four percent of randomized patients had one or more risk factors for thrombosis.

Past Medical History

There were no significant differences between treatment groups in past medical history. The heparin treatment group had the lowest incidence of hypertension and the 20mg desirudin group had the highest (21.3% and 30.1% respectively).

Concomitant medication including anesthesia, Physical Examination, and Operation

There were no significant differences between treatment groups. The protocol-designated injections were given to the patients on schedule for all treatment groups.

Efficacy Categories

Reviewer's Comment: Although the sponsor listed three efficacy categories in the study report, the protocol was never amended to provide for intent-to-treat 1 and intent-to-treat 2. This reviewer cannot find a separate statistical analysis plan, which defined these terms. The study report states that patients with no or an inadequate phlebography were excluded from the per-protocol and intent-to-treat 1 analyses. The study report defines the intent-to-treat 2 population as all randomized.

The majority of patients who did not complete the trial due to an adverse experience had bleeding as the reason.

There are small discrepancies in this table. For instance- all major protocol violators should have been excluded from the per-protocol analysis. Under the category title "Use of excluded medication" as a reason for exclusion from the per-protocol analysis the total number of patients is 29 compared with 33 for protocol violations –major.

Number of Patients study RH/E23

	Desirudin (10 mg)	Desirudin (15 mg)	Desirudin (20mg)	Heparin	Total
Enrolled	N/G	N/G	N/G	N/G	1203[1]
Randomized	283	277	282	277	1119[1]
Completed	265	253	248	263	1029
Did not complete	18	24	34	15	91 (9%)
Abnormal laboratory value	1	0	0	0	1
Abnormal test procedure	0	1	1	2	4
Administrative problems	4	3	5	2	14
Adverse Experience	6	16	15	7	43 (4.5%)
Death[2]	0	0	1	0	1
Protocol criteria not met	2	2	8	0	12
Trial treatment not required	0	0	2	0	2
Withdrawal of consent	5	2	2	4	13
Excluded from Per-protocol analysis[3]	70 (24.7%)	81 (29.2%)	73 (25.9%)	58 (20.9%)	282 (25.2%)
No operation	2	2	5	0	9 (0.9%)
Operation performed					
Phlebography not performed/no confirmed thromboembolic event	26	32	40	22	117 (10.5%)
Phlebography performed but...					
Central reading inadequate	32	40	23	26	121 (10.8%)
Not performed within one day after trial medication stopped	1	1	0	2	4
Only unilateral performed in a patient with two legs and no confirmed DVT	3	3	8	4	18 (1.8%)
Performed before day 8 and no confirmed DVT	2	2	3	3	10
Use of excluded medication	9	4	9	7	29 (2.6%)
Protocol violations- major (concomitant medications)	10	5	9	9	33
Protocol violations- minor (concomitant medications)	6	8	1	5	20
Included in Efficacy analyses					
Efficacy analyses					
Per-protocol	213	196	209	219	837

Intent-to-treat 1	223	202	218	229	872
Intent-to-treat 2	283	277	282	277	1119

[1] One patient randomized twice.
[2] This individual included in all analyses.
[3] Patients may be counted more than once.
Reviewer's table

Efficacy

The sponsor's primary efficacy analysis for the per-protocol population is shown below.

Reviewer's Comment: The heparin treatment group had the highest event rate. The 95% confidence intervals did not overlap for the two higher desirudin treatment groups compared with heparin for the per-protocol population.

TABLE 8.1.1-1:

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

CENTER: ALL CENTERS

Thromboembolic Event	Unfractionated Heparin	CGP 39 393			TOTAL
	Dose 5000 IU N = 219	Dose 10 mg N = 213	Dose 15 mg N = 196	Dose 20 mg N = 209	N = 837
DEEP VENOUS THROMBOSIS (based on central reading)	75 (34.2 %)	51 (23.9 %)	36 (18.4 %)	37 (17.7 %)	199 (23.8%)
PULMONARY EMBOLISM (confirmed #)	0 (0.0 %)	0 (0.0 %)	1 (0.5 %)	0 (0.0 %)	1 (0.1%)
Death ##	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.5 %)	1 (0.1%)
Total Number of Events	75 (34.2 %)	51 (23.9 %)	37 (18.9 %)	38 (18.2 %)	201 (24.0%)
Total Number of Patients with at least one event	75 (34.2 %)	51 (23.9 %)	37 (18.9 %)	38 (18.2 %)	201 (24.0%)
95% Confidence Interval	28.0 % - 40.9 %	18.4 % - 30.3 %	13.7 % - 25.1 %	13.2 % - 24.1 %	21.2 % - 27.1 %
Comparing CGP 39393 versus unfractionated heparin:					
relative risk reduction		30.08 %	44.88 %	46.91 %	
absolute risk reduction		10.30 %	15.37 %	16.06 %	

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

Sponsor's table volume 1.70 pp. 8-23-269

Reviewer's Comment: The results were similar for the intent-to-treat (1) and intent-to-treat (2) populations. When each center was reviewed one of the desirudin treatment groups always had a lower incidence rate than the heparin treatment group.

Reading Concurrence for Study RH/E 23

The sponsor has provided a table of the central assessment compared with the local assessment.

Reviewer's Comment: There were more cases where the central assessors called the films inadequate and the local assessors called the film as demonstrating DVT or no DVT. Nearly one-third of the central assessor read cases of DVT were missed by the local readers. There was greater concordance between the central readers and the local readers for the finding of no DVT.

PHLEBOGRAPHY: LOCAL VERSUS CENTRAL ASSESSMENT

Central Assessment	Local Assessment				
	DVT	No DVT	Inadequate	Missing	All
DVT	127	68	10		205
No DVT	21	589	53	2	665
Inadequate	9	82	30		121
Missing					
All	157	739	93	2	991

NOTE: DVT = DEEP VENOUS THROMBOSIS

Sponsor's table volume 1.70 p. 8-23-273

Reported Deaths and Pulmonary Emboli in the treatment period and follow-up period
The sponsor's stable is shown below.

Reviewer's Comment: The patient who died of a cerebrovascular event is not included in the tables above because the event occurred during the follow up period. Only patients 53 and 721 were included in the per-protocol analysis. There were more reported events in the heparin treatment group than in the desirudin treatment groups combined.

TABLE 8.1.1-12

REPORTED DEATHS OR PULMONARY EMBOLISMS DURING THE PROPHYLAXIS TREATMENT PERIOD OR FOLLOW-UP PERIOD (DATASET: RANDOMISED PATIENTS)

Treatment Center	Patno	Age	Sex	End of Treatment Period —Visit— No	Date	Event reported as Adverse Experience Preferred Term	Patient died	Onset date	Confirmation of Pulmonary Embolism according to the Protocol no/yes	Perfusion lung scan	Ventilation lung scan	Pulmonary angiography
CGP 39395 10 MG												
A -CENTER 1	149	74	f	5		EMBOLISM PULMONARY		24071992	NO			
I -CENTER 2	1188	69	f	2		EMBOLISM PULMONARY		17061993	NO			
ML-CENTER 1	399	77	m	5		CEREBROVASCULAR DISORDER	YES	14031993				
CGP 39395 15 MG												
GB-CENTER 1	53	72	f	4		xxx			YES	positive	mismatch	
CGP 39395 20 MG												
A -CENTER 1	721	66	m	3		FIBRILLATION VENTRICULAR	YES	21101992				
A -CENTER 1	777	65	m	5		EMBOLISM PULMONARY		05111992	NO	positive	no mismatch	negative
UH 5000 IU												
D -CENTER 7	303	78	f	5		EMBOLISM PULMONARY		12011993	NO	positive		
DK-CENTER 1	197	80	f	5		EMBOLISM PULMONARY		14091992	NO			
DK-CENTER 2	182	82	f	5		EMBOLISM PULMONARY		26101992	NO			
GB-CENTER 3	520	62	f	5		EMBOLISM PULMONARY		20111992	NO			
S -CENTER 1	805	63	f	5		EMBOLISM PULMONARY		27011993	NO			
S -CENTER 2	1119	72	f	5		EMBOLISM PULMONARY		18041993	NO			

UH: unfractionated heparin

xxx: No adverse experience linked to pulmonary embolism reported

Note: Patient 53 and Patient 721 are included in the per-protocol analysis.
Patients with an event reported after the end of treatment or non-confirmed are not included in the per-protocol analysis
Based on the autopsy, patient 721 died due to a pulmonary embolism

Sponsor's table volume 1.70 p.8-23-280

Reported Thrombophlebitis and Deep Venous Thromboses During the Follow-up Period

The sponsor's table on follow up DVT and thrombophlebitis events is shown in the table below.

Reviewer's Comment: There are no significant differences between treatment groups.

DEEP VENOUS THROMBOSIS AND THROMBOPHLEBITIS REPORTED DURING THE FOLLOW-UP PERIOD (i.e ONSET DURING FOLLOW-UP)
(DATASET: RANDOMISED PATIENTS)

Treatment Center	Patno	Age	Sex	End of prophylaxis visit No	End of prophylaxis visit Date	Event reported as Adverse Experience in the follow-up Report: Verbatim Term	Onset date	Severity grade	Relationship to treatment
CGP 39393 10 MG									
DK-CENTER 2	174	61	f	5		SUSPICION OF_DVT	03111992	mild	probable
S -CENTER 1	212	67	m	2		DEEP VENOUS THROMBOSIS	25051992	moderate	not related
CGP 39393 15 MG									
S -CENTER 2	829	65	f	5		DEEP VENOUS THROMBOSIS	15021993	moderate	highly prob.
CGP 39393 20 MG									
D -CENTER 4	677	45	f	5		DEEP VENOUS THROMBOSIS TO LEFT CALVE	10051993	moderate	unlikely
I -CENTER 2	1185	67	m	5		THROMBOPHLEBITIS LEFT LEG	03061993	mild	possible
S -CENTER 1	804	54	m	5		DVT	27011993	moderate	unlikely
UH 5000 IU									
D -CENTER 4	675	52	f	5		DEEP VEIN THROMBOSIS LEFT LEG	15051993	mild	unlikely
S -CENTER 2	608	58	m	5		DEEP VENOUS THROMBOSIS	20061993	severe	possible

UH: Unfractionated Heparin

Sponsor's table volume 1.70 p.8-23-281

Safety

Overall 75% of patients reported adverse experiences regardless of treatment group. The most frequent adverse event was hemorrhage NOS. The sponsor's tables for all adverse events occurring during this trial are listed in Appendix 3.

Hemorrhage
Below is a table illustrating hemorrhage rates during the trial.

Reviewer's comment: There is not much difference between treatment groups.

Hemorrhages reported in evaluable patients during the RH/E 23 trial

	Desirudin 10 mg (N=283)	Desirudin 15 mg (N=277)	Desirudin 20 mg (N=282)	Heparin (N=278)
Minor	64 (22.7%)	85 (30.7%)	82 (29.1%)	67 (24.1%)
Serious	8	9	12	9
Major	1	2	1	0
Total patients	73 (25.8%)	96 (34.7%)	95 (33.7%)	76 (27.3%)

Reviewer's table

Serious Adverse Events
The sponsor's table below demonstrates the event rate in each treatment group.

Reviewer's Comment: There is no significant difference between heparin and desirudin treatment groups. Bleeding rates increase with increasing dose of desirudin.

RH/E 23 (n = 1120)*	10 mg	15 mg	20 mg	Heparin	Total
CVA (Cerebral Vascular Accident)	1	3	0	1	5
CVS (Cardio Vascular Sytem)	3	1	3	2	9
DEATH	1	0	3	1	5
THROMBOEMBOLISM					
- Deep Vein Thrombosis	14	8	7	35	64
- Pulmonary Embolism	3	1	2	3	9
NOS (Not otherwise specified)	1	6	13	9	29
BLEEDING					
- Surgical Bleeding	7	8	8	7	30
- Wound bleeding	2	4	3	1	10
- Wound leakage	1	1	0	0	2
- Haematoma	0	5	3	0	8
- Haemorrhage	0	1	1	0	2
- Haematuria (Catheter)	0	0	2	0	2
IMMUNOALLERGY	0	1	0	0	1
TOTAL	34	40	47	60	181
181 events in 155 patients					

*includes patient 888 which was randomized twice.

Sponsor's table volume 1.70 pp.8-23-166

The sponsor's table below shows patients excluded from the sponsor's Serious Adverse Events Table for Study RH/E23.

Reviewer's Comment: The table below lists those individuals who were not included in the table above because they had prematurely discontinued from the trial. Two patients have allergic reactions, which prematurely discontinue them from the trial.

Patients excluded from the sponsor's Serious Adverse Events Table for 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

Blood Loss and Transfusion Requirements

There was no significant difference between treatment groups for the median peri-operative (1L) and post-operative blood loss (200-300mL). The table below shows the percentages of patients requiring transfusions.

Reviewer's Comment: There was no significant difference between treatment groups for peri-operative transfusion. Post-operatively the 20-mg desirudin treatment group had the greatest number of patients receiving either whole blood or packed red blood cells.

Percentages of Patients Requiring Transfusions During RH/E 23

Transfusion Type	Heparin	Desirudin 10 mg	Desirudin 15 mg	Desirudin 20 mg
Peri-operative				
Whole blood	17%	19.6%	17.5%	20.7%
Packed Red Blood Cells	53.6%	51.6%	57.8%	51.4%
Plasma Expanders	79%	76.9%	78.2%	78.3%
Post-operative				
Whole blood	5.2%	9.1%	9.3%	14.4%
Packed Red Blood Cells	25.5%	25%	26.6%	33.3%
Plasma Expanders	18%	18.5%	18.9%	22.2%

Reviewer's table

Deaths (During and After RH/E 23 trial)

One patient died during the conduct of the trial. One desirudin patient died from a pulmonary embolism/ventricular fibrillation on post-op day 1.

Four patients died after the trial. One heparin patient (a re-enrollment patient) died of bronchopneumonia/ emphysema, and myocardial ischemia post-op day 14. One desirudin patient developed a stroke fifteen days after the last injection. This patient died fifteen days after development of the stroke or one month after the last injection. Another desirudin patient died 2.5 months after the initial surgery from a pulmonary embolism and a deep venous thrombosis. Another desirudin patient died 2 months after completion of the study from breast cancer.

Center Discontinuation

One center in the United Kingdom withdrew from the trial because of excessive bleeding. The bleeding was observed in heparin patients as well as desirudin patients as shown in the sponsor's table below. The sponsor's investigation did not reveal a causative factor.

Discontinuation for Bleeding in Belfast Center (Sponsor's table for RH/E 23)

PAT NO	TRIAL DRUG	OP DATE	ADVERSE EVENT	PERI-OP BLOOD LOSS (ml)	POST-OP BLOOD LOSS (ml)	TRANS-FUSION
505	CGP 10 mg		Extensive bruising	311	790	No
506	CGP 15 mg		Large haematoma	197	627	No
507	Unfract. Heparin		Wound bleeding, extensive bruising	607	1040	1 unit post-op
513	CGP 20 mg		Wound bleeding	290	1100	2 units post-op
515	CGP 20 mg		Wound bleeding	266	590	No
510	CGP 15 mg		Bruising, wound bleeding	268	590	3 units post-op

Sponsor's table volume 1.70 p.8-23-167

Laboratory Parameters

There was no significant difference in the number of patients in each treatment group experiencing an abnormal hemoglobin value, platelet count, or change in either SGOT or SGPT values.

Reviewer's Comment: Although there was no significant difference noted, some laboratory parameters had a high percentage of missing values (e.g. SGPT values at the end of treatment were missing for 37% of patients treated with 20-mg desirudin.)

Trial: RH/E 25

Reviewer's Conclusion regarding RH/E 25

The sponsor conducted a multicenter, double-blind, randomized, active comparator controlled trial comparing the efficacy of 15 mg of CGP39393 with enoxaparin in patients undergoing a primary elective total hip replacement. Overall, the enoxaparin treatment group had a higher primary event rate (proximal DVT, PE, and Death) compared with the desirudin treatment groups ($p < 0.02$). Similar results were observed for the secondary event rate (proximal and distal DVT, PE, and Death) ($p< 0.01$). 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 all subgroups. The study results were driven by differences in DVT rates. There was no difference in PE or death rates between the treatment groups. The treatment-by-country analysis demonstrated that desirudin was associated with fewer thromboembolic events in 7/10 countries. There was no significant difference in safety between the desirudin and enoxaparin treatment groups.

Design:
The trial was a multicenter, double-blind, randomized, active comparator controlled trial comparing the efficacy of one dose of CGP39393 with enoxaparin in patients undergoing a primary elective total hip replacement.

Time period: Trial was conducted from April 13, 1994 to November 27, 1995.

There were several amendments to the original study protocol. All amendments were made prior to start of the trial. The first and second applied to Germany only. The third applied to France only. The first two German amendments would not have significantly impacted the outcome of the trial. The third amendment had the possibility of unblinding an individual patient and affecting the safety outcome of the trial.

Amendment #1, dated December 23, 1993, added the following contraindication to the exclusion criteria: Contraindication to Contrast media.

Amendment #2, dated December 23, 1993, changed the inclusion criteria from age $\geq$ 18 years to age $\geq$ 40 years.

Amendment #3, dated December 23, 1993, clarified a section on the pre-operative injections. The investigator was instructed to give a test injection and instructions for a pre-operative APTT test to be taken prior to surgery (at least three hours after the "test injection"). The lab was instructed not to give out the APTT test result but could indicate whether an individual patient could go to the operating room or not based on the APTT from the test injection. If the patient had a peak APTT level > 2 times the upper limit of normal after the test injection, then the investigator would be informed to discontinue the patient from the trial.
The test injection was then followed by the first trial injection.

Reviewer's Comment: The test injection could potentially have prematurely removed some patients with a higher than desired APTT response after the test dose (particularly CGP 39393). This premature discontinuation of some patients could have affected safety results.

Inclusion and Exclusion Criteria

INCLUSION CRITERIA

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

- **age ≥ 18 years**
- **weight ≥ 50 kg**
- **an unilateral operation**

EXCLUSION CRITERIA

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

General

- Amputees of one leg
- Bilateral hip operation
- Previous surgery or fracture of lower extremities 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. antithrombin III, protein C or protein S deficiencies. liver disease) including thrombocytopenia (< 100 x 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
- Cerebral ischaemic attacks (within the last 6 months)
- Hypertension (i.e. diastolic blood pressure constantly > 110 mm Hg)

Previous Treatments / Concomitant Medications and Therapies

- The use of the following drugs are prohibited within 7 days prior to the start of surgery and during the trial drug prophylaxis period:
  - Heparins (except that used in the present trial, or in connection with the intraoperative salvage of red blood cells)
  - Oral anticoagulants
  - Thrombolytic agents
  - Dextrans or plasma expanders interfering with coagulation (e.g. low-molecular weight hydroxyethylamidon i.v. solution)
  - Long-acting nonsteroidal anti-inflammatory drugs (defined as those requiring a greater than seven day washout period)
  - Acetylsalicylic acid > 325 mg / day
  - Dipyridamole
  - Sulphinpyrazone
  - Ticlopidine

- 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 serum creatinine above the upper limit of the clinic)
- Known inflammatory bowels disease
- Contraindication to contrast media e.g. documented history of allergy or renal impairment severe enough to make phlebography dangerous
- Contra-indications to Enoxaparin which are not already covered by the above list (for further details, see package leaflet , Addendum 6).
- 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 table volume 1.76 pp.8-29-16, 17, 18

Treatment Administration:
CGP 39393
Dose – 15 mg sc bid

Enoxaparin
Dose – 40 mg sc qd

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

Pre-operation day:

CGP 39 393 group:	Evening	Placebo (LMWH)	(12 hours, pre-op.)
LMWH group:	Evening	LMWH	(12 hours, pre-op.)

Operation day: (Injections should be given at least six hours apart)

CGP 39 393 group:	Morning	CGP 39 393	(within 30 min.pre-op.)*
	Evening	CGP 39 393	
		Placebo (LMWH)	
LMWH group:	Morning	Placebo (CGP 39 393)	(within 30 min.pre-op.)*
	Evening	Placebo (CGP 39 393)	
		LMWH	

*but after regional block anaesthesia if used.

APPEARS THIS WAY
ON ORIGINAL