CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-271

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #: 21-271

Drug:] [redacted]

Indication: [redacted]

Sponsor: Aventis Pharmaceutical Products, Inc.

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1. INTRODUCTION

This submission addresses the efficacy, safety and tolerability of desirudin (15 mg b.i.d.) compared with

a) unfractionated heparin (5000 IUD t.i.d.) (Protocol RH/E28)

and b) enoxaparin (40 mg) (Protocol RH/E25)

for prevention of deep vein thrombosis (which may lead to pulmonary embolism) in patients undergoing primary elective total hip replacement. Enoxaparin is an approved drug for the prevention of DVT in patients undergoing primary elective hip replacement. [redacted] is a widely accepted but not approved regimen.

This submission also contains a dose finding (10 mg, 15mg, 20 mg b.i.d.) study with unfractionated heparin as a control (RH/E23). In fact, desirudin 15 mg dose was chosen for studies RH/E28 and RH/E25 on the basis of study RH/E23. See medical review for the dose finding study RH/E23.

The study RH/E28 showed that desirudin 15 mg was significantly more effective (p-value

0.0001) in the prevention of thromboembolic events (TE) than unfractionated heparin in patients undergoing primary elective hip replacement. The study RH/E25 showed that desirudin 15 mg was significantly more effective (p-value 0.018) in the prevention of TE than enoxaparin 40 mg in heparin in patients undergoing primary elective hip replacement.

The rest of this review is organized as follows: Section 1 describes study RH/E28; Section 2 describes study RH/E25; and Section 3 summarizes the conclusions of this submission.

1. Study RH/E28

Study RH/E28 is a multi-center double-blind randomized unfractionated heparin-controlled trial evaluating the efficacy of desirudin (15 mg b.i.d.) in patients undergoing a primary elective total hip replacement.

Primary Objective:

The primary objective of this study was to compare the antithrombotic effect, the safety and tolerability of desirudin (15 mg b.i.d.) with unfractionated heparin in patients undergoing elective hip replacement.

Design

This study was a multi-center, double blind, parallel design, unfractionated heparin controlled trial . There were 11 centers consisting of 36-48 patients randomly allocated, in equal numbers, to one of the two treatments. Among 11 centers, there were three centers in Denmark and eight centers in Sweden.

Patient population:

The general patient population undergoing orthopedic surgery was considered to be at high risk of developing thromboembolic events, among which DVT occurs most frequently.
The trial population consisted of cooperative patients aged 18 years or older, weighing 50 kg or more, who underwent an unilateral primary elective total hip replacement (no revision) with a cemented or non-cemented prosthasis.

Sample Size:

It is expected that event (DVT) rate would be 25% with unfractionated heparin prophylaxis. To detect an absolute difference of 12.5% (i.e., a 50% percent reduction in the event rate under desirudin) a sample size of 168 patients per treatment group would be required with a significance level of 5% (two sided) and a power of 80%. The planned sample size for the study is 420 in total assuming that about 20% of patients would not be evaluable. The sample size was determined using two-sample binomial distribution.

Patient Disposition:

There were 445 patients randomized to two treatment groups: 220 to unfractionated heparin 5000 IU (t.i.d.) and 225 to desirudin 15 mg (b.i.d.). The following table gives the decomposition of different patient populations by treatment groups.

Table 1.1 (sponsor's): Disposition of Patients Enrolled: Number of Patients (extracted from Table 6.1.1, Volume 79 of submission)

Population	Unfractionated Heparin	Desirudin	Total
Total patients enrolled			452
Total Randomized	220	225	445
Total Completed	193	202	395
Per Protocol (evaluable)	177	174	351

Baseline Demographics

The sponsor summarized demographic characterstics (age, sex, smoker, weight, height, obesity) by treatment groups. There was no relevant difference between the treatment groups regarding demographic characterstics. Summary statistics for age, sex, and smoking status by treatment groups are given in the following table.

Table 1.2 (sponsor's): Disposition of Patients Enrolled By Demograhic Characterstics: Number (%) of Patients (extracted from Table 7.1.1-1, Volume 79 of submission)

Subgroup	Unfractionated Heparin N=220	Desirudin N=225	Total N=445
Age n			
Mean	68.2	68.6	68.4
<65 years	76	70	146
≥ 65 years	144	155	2 99
Sex			
Male	92 (41.8%)	94(41.8%)	186 (41.2%)
Female	128 (58.2%)	128 (58.2%)	259 (58.2)
Smoker			
No	180(81.8%)	183 (81.3%)	363 (81.6%)
Yes	40 (18.2%)	42 (18.7%)	82(18.4%)

Diagnosis and Criteria for Inclusion (trial population):

Consenting inpatients aged ≥ 18 years, weighting ≥ 50 kg, who underwent an unilateral elective total hip replacement.

Exclusion Criteria:
See medical review for exclusion criteria.

Treatment Allocation:

The sponsor mentioned in the protocol that in order to ensure random allocation each patient was to be given the lowest available patient number. The numbering started from one. A computer-generated randomization scheme was used to provide balanced blocks of patient numbers for each of the two treatment groups within each center. A block size of six was used and only complete blocks were to be distributed to the centers.

Duration of Trial Treatment:

The duration of trial treatment (prophylaxis) in each patient included the operation day and 7-10 post-operation days. A reserve pack for one additional day of prophylaxis was provided. Thus total individual trial duration was 8-11 (12) days.

Test Product, Dose and Mode of Administration

Desirudin

Dose:

Operation day: Desirudin 15 mg administered b.i.d. (within 30 minutes pre-op, and in the evening), placebo 2 hours pre-op and in the afternoon

Post-Operation day: Desirudin 15 mg administered b.i.d. (morning, evening), placebo in the afternoon.

Mode of Administration: Subcutaneous

Unfractionated Heparin comparative control and placebo:

Dose:

Operation day: Unfractionated heparin 5000 IU t.i.d. (2 hrs pre-operation, afternoon, evening), placebo within 30 minutes pre-operation.

Post-Operation days: t.i.d. (morning, afternoon, evening)

Mode of Administration: Subcutaneous

Methodology /Criteria of Evaluation:

Efficacy:

Presence of a confirmed thromboembolic event:

1. Deep venous Thrombosis (DVT) confirmed by bilateral ascending phlebography assessed centrally

2. Pulmonary Embolism (PE) confirmed by either by high probability ventilation/perfusion scan or pulmonary angiography

3. Death due to thromboembolic event confirmed by autopsy, or unexplained death in absence of autopsy

Desirudin was considered superior to unfractionated heparin if there was a clinically and statistically significant reduction in thromboembolic event rate during the prophylactic treatment period.

Safety and Tolerability:

Safety

Safety was evaluated on the basis of bleedings, bleeding complications, immunoallergic complications and other complications.

Bleedings:

Bleedings were categorized as:

Peri-operative: 12 hour period from the time operation started (i.e. first incision), which includes peri-operative drainage and transfusion requirements

Post-operative: 12 hours to post-op Day 6, i.e. transfusion requirements, blood recovered in the post-operative drainage

Bleeding Complications:

All bleeding complications (i.e., all bleeding considered to be abnormal for these kind of patients) would be recorded in the adverse experience section of the Case Report Form with a precise description if they were procedure related or spontaneous.

Immuno-allergic Complications:

Although the immunogenic potential of hirudin appears to be extremely low, patients should be

carefully observed during the course of the trial for possible allergic reactions including anaphylaxis.

Measurement of Tolerability:

Tolerability will be assessed on the basis of vital signs.

Statistical Methods:

Efficacy Analysis

The primary analysis would be based on the evaluable patient population

It was mentioned in the protocol that an intention-to-treat analysis would be performed using the last available assessment taken within 5 days of the end of the trial drug prophylaxis period. Inadequate venograms would be excluded. If central assessment was not available, the local assessment was taken.

The analysis would be performed using logistic regression with treatment and center as fixed factors. The test procedures would be two sided with a significance level of 5%. Confidence intervals would be given for the estimated odds ratio. Treatment by center interaction would be evaluated.

Analysis of Safety and Tolerability

Tolerability parameters would be summarized by treatments.

To compare the total amount of blood loss (pre-operative plus the volume of blood loss during the subsequent 6 days of prophylaxis) between the different treatments an analysis of variance would be performed using treatment and center as fixed factors. The analysis is based on patients who have been treated for at least 6 consecutive post-operative days

The comparison of the frequency of major and/or serious bleeding between the different groups would be based on a chi-square test.

Adverse experiences including severity and relation to treatment would be listed and summarized in frequency tables.

Laboratory data would be listed and abnormal findings would be highlighted. When appropriate, a systematic trend in changes would be evaluated.

All data would be reported in individual patient listing. Patient demographics and medical history would be analyzed by center to investigate differences among them.

1.1 Efficacy

The sponsor's efficacy evaluation was based on the number of thromboembolic events (DVT PE+Death). Table 1.3 summarizes the efficacy evaluaion for the Per-Protocol patient population.

Table 1.3 (sponsor's): Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period (%) for Per-Protocol Patient Population (Extracted from sponsor's Table 8.1.1-3, Volume 79)

Patient Population	Treatment			
	Unfractionated heparin	Desirudin 15 mg	p-value *	Odds ratio (95% CI)
Per-Protocol Population	41/177 (23.2 %)	13/174 (7.5%)	0.0001	0.27 (0.14, 0.52)

Note: *: p-value (likelihood ratio test) and the odds ratio were computed from Logistic regression model after adjusted for country

It is seen from the above table that desirudin is significantly more effective in preventing thromboembolic events in comparison to unfractionated heparin for the Per-Protocol population. Similar conclusions were reached for the randomized patient population.

Components:

The following table summarizes the thromboembolic event rates by components.

Table 1.4 (sponsor's): Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period (%) for Per-Protocol Patient Population (Extracted from sponsor's Table 8.1.1-7 and Table 8.1.1-8, Volume 79)

Event	Treatment		
	Unfractionated Heparin	Desirudin 15 mg	p-value *
Confirmed PE	0/177 (0%)	0/174 (0%)	-
Death	0/177 (0%)	0/174 (0%)	-
DVT	41/177 (23.2 %)	13/174 (7.5%)	0.0001
DVT Proximal	14/177 (7.91%)	3/174 (1.72%)	0.0005
DVT Distal	27/177 (15.25%)	10/174 (5.75%)	0.0032

Note: *: p-value (likelihood ratio test) computed from Logistic regression model after adjusted for country

The DVT rate in the desirudin group was significantly lower than the unfractionated heparin group. Similar conclusions were valid corresponding to proximal (p-value 0.005) and distal (p-value 0.011) DVT rates. There were no deaths in both treatment groups. There ware no PEs in either treatment group.

Subgroup Analyses:

This reviewer performed subgroup analyses with respect to gender, age-group and country for the evaluable patient population. There were no ethnic data in this submission. The subgroup analyses are summarized below.

Gender

This reviewer conducted treatment by gender interaction test using the logistic regression model with country, treatment group, gender and gender x treatment -group as fixed effects.

It was seen that there was no interaction (p-value 0.7686) between gender and the treatment groups. The following table summarizes the event rates in the two treatment groups by gender for the per-protocol patient population.

Table 1.5 (reviewer's):Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period for Per-Protocol Patient Population by Gender

Gender	Unfractionated Heparin	Desirudin	p-value*
Male	19/74 (25.68%)	5/73 (6.85%)	0.0015
Female	22/103 (21.36%)	8/101 (7.92%)	0.0065

Note: *: p-value (likelihood ratio test) computed from Logistic regression model after adjusted for country

It is seen that the desirudin treated group has significantly lower event rates in comparison to the heparin treated group for either sex.

Age Group

This reviewer conducted treatment by gender interaction test using the logistic regression model with country, treatment group, age-group (<65 and ≥ 65) and age-group x treatment-group as fixed effects. It was seen that there was no interaction (p-value 0.8885) between gender and the treatment groups. The following table summarizes the event rates in the two treatment groups by gender for the per-protocol patient population.

Table 1.6 (reviewer's):Proportion (%) of Patients with Confirmed Thromboembolic Events) During Prophylaxis Period for Per-Protocol Patient Population by Age-Group

Age-group	Unfractionated Heparin	Desirudin	p-value Fisher's exact
<65	12/61 (19.67 %)	3/53 (5.66%)	0.049
≥ 65	29/116 (25.0%)	10/121 (8.26 %)	0.007

It is seen from the above table that the desirudin treated group has significantly lower event rates than the heparin treated group in both age-group.

Country:

This reviewer conducted treatment by country interaction test using the logistic regression model with country, treatment group, and treatment-group x country as fixed effects.

It was seen that there was no interaction (p-value 0.7686) between country and the treatment groups.

The following table summarizes the event rates in the two treatment groups by country.

Table 1.6 (reviewer's): Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period for Per-Protocol Patient Population by Country

Gender	Unfractionated Heparin	Desirudin	p-value Fisher's exact
Denmark	6/33 (18.18 %)	2/33 (6.06 %)	0.258
Sweden	35/144 (24.31 %)	11/141 (7.8%)	0.00017

It is seen that desirudin group in Sweden has significantly lower TE rate than heparin treated group. However, desirudin group in Denmark also has numerical advantage over the heparin treated group.

1.2 Safety:

Adverse events:

The adverse events by severity are summarized by the treatment groups in the following table.

Table 1.7 (sponsor's/reviewer's): Number (%) of Patients with any Adverse Experiences During the Treatment Period for Randomized Patients (Extracted from Sponsor's Table 9.1-1, Volume 79)

Severity	Unfractionated Heparin (N=220)	Desirudin 15 mg (N=225)	p-value (Fisher's exact)
Mild	67 (30.5%)	62 (27.6%)	0.531
Moderate	31 (14.1)	43 (19.1%)	0.0183
Severe	20 (9.1%)	6 (2.7%)	0.042

There were significantly fewer severe bleedings in desirudin treated group in comparison to the heparin treated group. However, there were significantly more moderate bleedings in desirudin treated group in comparison to the heparin treated group. Note that the treatment groups were comparable [redacted] versus heparin rates: 23% versus 22%) when moderate and severe bleedings were combined. The treatment groups were also comparable with respect to the number of mild bleedings.

The sponsor mentioned that these findings were expected from the nature of the patient population and pharmacological action of the drugs tested. The sponsor also claimed that the adverse experiences reported in general were comparable to those observed in the population undergoing major orthopedic surgery.

The following table summarizes bleeding by categories.

Table 1.8 (sponsor's/reviewer's): Propotion (%) of Patients with Adverse Experiences by Bleeding Category During the Treatment Period for Randomized Patients (Extracted from Sponsor's Table 9.1.2-1, Volume 79)

Blood loss/Hematoma type	Unfractionated Heparin	Desirudin 40 mg	P-value (Fisher's exact)
Injection Site Hematoma	4/220 (1.8%)	4/225 (1.8%)	1.0
Wound hematoma/infection	11/220 (5.0%)	14/225 (6.2%)	0.682
Serious bleeding	6/218 (2.75%)	7/223 (3.14%)	1.0

It is seen that the bleeding rates are not significantly different between the two treatment groups. However, enoxapain treated group has numerical advantage over desirudin treated group in wound hematoma/infection and serious bleeding categories.

Safety Monitoring Results:

The total blood loss and transfusion requirements results are summarized in the following table

Table 1.9 (sponsor's): Total Blood Loss and Transfusion Requirements (extracted from sponsor's volume 79, page 8-32-4)

	Unfractionated Heparin (mean mL ± sd)	Desirudin 15 mg (mean mL ± sd)	p-value
Blood loss	1435 ± 745	1379 ± 594	0.95
Transfusion of red cells	750 ±490	798 ± 507	0.94

Transfusion of plasmaexpanders	641 ± 373	672 ±441	0.96

It is seen from above table that there were no significant differences between the treatment groups regarding blood loss, transfusion of concentrated red blood cells and plasma expanders during the peri and postoperative period. However, heparin treated group has numerical advantage over desirudin treated group regarding transfusion of red cells and transfusion of Plasmaexpanders.

Clinical Laboratory evaluations:

The sponsor reported that changes in the routine laboratory tests were comparable with those observed postoperatively in an elective hip replacement population. The abnormalities in liver enzymes generally observed post-operatively in this patient population were less pronounced with desirudin than with unfractionated heparin. SGOT, SGPT, Gamma-GT and Alkaline phosphatase were increased less postoperatively in desirudin group; and fewer patients had these enzymes increased above baseline at the end of treatment.

1.3 **Conclusions**

Efficacy:

The efficacy data in this study showed that desirudin 15 mg started preoperatively and administered s.c. twice daily in patients undergoing primary elective total hip replacement provided a significantly more effective prophylaxis of thromboembolic complications in comparison to unfractionated heparin.

Safety:

The safety data in this study showed that the safety profiles of desirudin 15 mg and enoxaparin 40 mg were mostly comparable. Although there were significantly more moderate bleedings in desirudin treated group in comparison to the heparin treated group, the two treatment groups were comparable when moderate bleedings and several were combined.

2. Study RH/E25

Study RH/E25 was a multicenter, double blind, randomized, enoxaparin (40 mg) controlled trial evaluating the efficacy and safety desirudin 15 mg in patients undergoing a primary elective total hip replacement.

Primary Objective:

The objective of this study was to compare the antithrombotic effect, the safety and tolerability of one dose level of desirudin 15 mg with one dose level of a low molecular weight heparin (LMWH), enoxaparin, in patients undergoing a primary elective total hip replacement.

Design:

This was an international, multicenter (Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland,) double-dummy-blind, randomized, parallel design, between patient trial, using desirudin 15 mg s.c. b.i.d. or 40 mg enoxaparin s.c., q.d.

Diagnosis and Criteria for Inclusion (Trial population):

Consenting inpatients aged ≥ 18 years, weighing ≥ 50kg, who underwent an unilateral primary elective total hip replacement

Number of Patients:

The following table summarizes patient disposition.

Table 2.1 (sponsor's): Disposition of Patients Enrolled: Number of Patients (extracted from Table 6.1.1, Volume 74)

Population	enoxaparin	Desirudin 15mg	Total
Enrolled			2086
Randomized	1036	1043	2079
Operated	1023	1028	2051
Completed	975	973	1948
Evaluable Primary Outcome	785	802	1587
Evaluable secondary outcome	768	773	1541
Eavaluable safety	1036	1043	2079

Sample Size Calculation:

The trial was planned to have a total sample size of 749 evaluable patients per treatment group, 1498 evaluable patients in total. The sample size calculation was based on the assumption that the incidence of major thromboembolic events is 6.5% under enoxaparin. With 1498 evaluable patients an absolute difference of at least 3.25% (i.e. 50% reduction in the event rate) could be detected in the desirudin 15 mg group with a significance level of 5% and a power of 80%. Based on experience in previous trials it was assumed that 25% of the patients randomized would be nonevaluable. Therefore, the trial was planned to have 2000 randomized patients. In total, 2079 patients were randomized and 1587 patients met the criteria for the primary analysis, 785 treated with enoxaparin and 802 treated with desirudin 15 mg. The sample size was determined using two-sample binomial distribution.

Baseline Demographics

The sponsor summarized demographic characterstics (age, sex, smoker, weight, height, obesity) by the treatment group. There was no relevant difference between the treatment groups regarding demographic characterstics. Summary statistics for age, sex, and smoking status by treatment are given in the following table.

Table 2.2 (sponsor's): Disposition of Randomized Patients by Age, Gender and Smoking Status: Number (%) of Patients (extracted from Table 7.1.1, Volume 74)

Subgroup	Enoxaparin 40 mg (N=1036)	Desirudin 15mg (N=1043)	Total (N=2079)
Age n			
Mean	65.7	65.3	65.5
<65 years	442 (43%)	469 (45%)	911 (44%)
≥ 65 years	594 (57%)	574 (55%)	1168 (56%)
Sex			
Male	414 (40%)	453 (43.4%)	867 (41.7%)
Female	622(60%)	590 (56.6%)	1212 (58.3%)
Smoker			
No	850 (82%)	886 (85%)	1736 (83.5%)
Yes	186 (18%)	157 (15%)	343 (16.5%)

Test Product, dose and mode of administration

Desirudin:

Mode of administration: Subcutaneous

Doses: operation day, b.i.d., within 30 min pre-op and evening;
Post-operation days b.i.d. in the morning and evening

Enoxaparin 40 mg (comparative control and placebo):

Mode of administration: Subcutaneous

Doses: Pre-operation day evening: enoxaparin 12 hours pre-op
Operation day: enoxaparin in the evening
Post-operation days: enoxaparin in the evening

Duration of treatment: 9-12 days: Starting 12 hours pre-op in the enoxaparin group and within 30 min pre-op in the desirudin 15 mg group and continuing for 7-10 post-operation days.

A reserve injection was provided for one additional day.

Criteria for Evaluations:

Efficacy

Primary outcome:

Presence of a confirmed major thromboembolic event (i.e. thrombus in popiteal vein or above, PE or death) during the prophylaxis period by one (or more) of the following criteria:

Proximal Deep Vein Thrombois (DVT) confirmed by a bilateral ascending phlebography assessed centrally

Pulmonary Embolism (PE) confirmed either by high probability ventillation /perfusion scan or pulmonary angiography or pulmonary embolectomy

Death due to thromboembolic event or unexplained death

Secondary Outcome:

Presence of a confirmed thromoboembolic event [overall DVT (distal or proximal), PE, or Death during the prophylaxis period assessed by one (or more) of the criteria described above

Safety:

Safety was mainly evaluated on the basis of peri- and post-operative transfusion requirements, adverse experiences and four main clinical laboratory parameters: hemoglobin, platelets, SGOT and SGPT.

Statistical Methods

The primary efficacy analysis was performed on the evaluable population using a linear logistic regression with treatment and countries are fixed factors.

2.1 Efficacy Results:

Table 2.3 summarizes the sponsor's primary efficacy evaluation for the evaluable patient population.

Table 2.3 (reviewer's/sponsor's): Proportion (%) With Confirmed Thromboembolic Events During Prophylaxis Period for Per-Protocol Patient Population (Extracted from sponsor's Tables 8.1.1 - 8.1.1-3, Volume 74)

Patient Population	Treatment			
	Enoxaparin 40 mg	Desirudin 15 mg	p-value	Odds ratio (95% CI)
Evaluable	60/785 (7.64 %)	39/802 (4.86%)	0. 018	0.61 (0.40, 0.92)

Note: p-value (likelihood ratio test) and the odds ratio were computed from Logistic regression model after adjusted for country

It is seen from the above table that desirudin is significantly more effective in preventing thromboembolic events than enoxaparin for the Per-Protocol population. Similar conclusions were reached for the randomized patient population.

The following table summarizes the event rates for the components of the primary outcome for per-protocol population.

Table 2.4 (reviewer's): Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylxis Period (%) for Primary (outcome) Evaluable Patient Population (Extracted from sponsor's Table 8.1.1-7and Table 8.1.1-8, Volume 74)

Component	Treatment		
	Enoxaparin 40 mg	Desirudin 15 mg	p-value
DVT Proximal	59/785 (7.52%)	36/802 (4.49%)	0.0088*
Confirmed PE	2/ 785 (0.025%) 1.00	2/802 (0.025%)	1.00**
Death	0/785 (0.0%)	1/802 (0.012%)	1.00**

Note: *: p-value (likelihood ratio test) computed from Logistic regression model after adjusted for country;
****: p-value computed from Fisher's exact**

The DVT (proximal) rate in the desirudin group is significantly lower than the enoxaparin group. The number of deaths and PEs are comparable in both treated groups.

Secondary Outcome and its Components:
The following table summarizes the event for the secondary outcome and its components based on per-protocol population.

Table 2.5 (sponsor's): Proportion(%) of Patients with Confirmed Thromboembolic Events (DVT, PE, Death) During Prophylaxis Period for Per-Protocol Patient Population (Extracted from sponsor's Table 8.2.1 Volume 74)

Events	Enoxaparin 40 mg	Desirudin 15 mg	p-value
At least one major event (DVT, PE, Death)	197/768 (25.65%)	145/773 (18.76%)	0.0009
DVT (overall)	196/768 (25.52%)	142/773 (18.37%)	0.0005
Confirmed PE	2/768 (.026%)	2/773 (0.026%)	1.0
Unexplained Death	0//768 (0.0 %)	1/773 (0.013%)	1.0

Note: *: p-value (likelihood ratio test) computed from Logistic regression model after adjusted for country
****: p-value computed from Fisher's exact**

It is seen from the above table that desirudin was significantly more effective in preventing thromboembolic events than enoxaparin for the per-protocol population.
It is also seen from the above table that desirudin was significantly more effective in preventing DVT than enoxaparin for the per-protocol population. The number of deaths and PEs were comparable in both treated groups.

Subgroup Analyses:
This reviewer performed subgroup analyses with respect to gender, age-group and country for the evaluable patient population. There were no ethnic data in this submission. The results are summarized below.

Gender
This reviewer conducted treatment by gender interaction test using the logistic regression model with country, treatment group, gender and gender x treatment -group as fixed effects.
It was seen that there was no interaction (p-value 0.8616) between gender and the treatment groups. The following table summarizes the event rates in the two treatment groups by gender for the per-protocol patient population.

Table 2.6 (reviewer's):Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period for Per-Protocol Patient Population by Gender

Gender	Enoxaparin 40 mg	Desirudin 15 mg	p-value *
Male	27/323 (8.36%)	20/355 (5.63%)	0.1592
Female	33/462 (7.14%)	19/447 (4.25%)	0.0592

Note: *: p-value (likelihood ratio test) computed from Logistic regression model after adjusted for country

It is seen that the desirudin treated group has lower event rates than the enoxaparin treated group for either sex.

Age Group

This reviewer conducted treatment by gender interaction test using the logistic regression model with country, treatment group, age-group (<65 and ≥ 65) and age-group x treatment-group as fixed effects. It was seen that there was interaction (p-value 0.0135) between gender and the treatment groups. The following table summarizes the event rates in the two treatment groups by gender for the per-protocol patient population.

Table 2.7 (reviewer's):Proportion (%) of Patients with Confirmed Thromboembolic Events) During Prophylaxis Period for Per-Protocol Patient Population by Age-Group

Age-group	Enoxaparin 40 mg	Desirudin 15mg	p-value *
<65	16/333 (4.35%)	16/368 (4.80%)	0.7181
≥ 65	44/452 (9.73%)	23/434 (5.30%)	0.0083

Note: *: p-value (likelihood ratio test) computed from Logistic regression model after adjusted for country

It is seen from the above table that the desirudin treated group had significantly lower event rates than the enoxaparin treated group for the patients who were older than 64 years. However, there was no significant difference in the event rates between the enoxaparin treated group and desirudin treated group for patients younger than 65 years.Note that the trial was not sized for testing the equality of the event rates for each group separately. There was imbalance in sample size in two treated groups (333 in enoxaparin group and 368 in desirudin group) corresponding to age group <65. The sample size for the age group <65 was also smaller than that of the age group ≥ 65. Further, there is a problem of testing multiple hypotheses because of many subgroup analyses. Therefore, it is not appropriate to conclude that desirudin is more effective in age group ≥ 65 than in age group <65.

Country:

This reviewer conducted treatment by country interaction test using the logistic regression model with country, treatment group, and treatment x country as fixed effects. It was seen that there was no interaction (p-value 0.5705) between country and the treatment groups. The following

table summarizes the event rates in the two treatment groups by country.

Table 2.8 (reviewer's): Proportion (%) of Patients with Confirmed Thromboembolic Events During Prophylaxis Period for Per-Protocol Patient Population by Country

Country	Enoxaparin 40 mg	Desirudin 15mg	p-value (Fisher's exact)
Austria	9/149 (6.04%)	4/143 (2.8%)	0.257
Belgium	7/70 (10.0%)	1/71 (1.41%)	0.033
Switzerland	4/48 (8.33%)	4/49 (8.16%)	1.00
Germany	7/85 (8.24%)	5/87 (5.75%)	0.564
Denmark	1/68 (1.47%)	2/71 (2.82%)	1.00
Spain	3/31 (9.68%)	3/32 (9.38%)	1.00
France	6/61 (9.84%)	9/70 (12.86%)	0.784
Italy	8/77 (10.39%)	4/78 (5.13%)	0.246
Netherlands	4/45 (8.89%)	2/53 (3.77%)	0.409
Sweden	11/151 (7.28%)	5/148 (3.38%)	0.198

Desirudin treated group in Belgium has significantly lower event rate than the enoxaparin treated group. Although the enoxaparin treated group in Denmark and France has numerical advantage over the desirudin treated group (1.47% versus 2.82%), the event rates were not significantly different. Desirudin treated group has numerical advantage over the enoxaparin treated group in rest of the countries. As there was no significant treatment by country interaction, the numerical difference in event rates in Denmark may have occurred by chance. In rest of the countries the difference in the event rates went along the same direction.

2.2 Safety Results:

Adverse Experiences:

The following table summarizes the adverse experiences by treatment group.

Table 2.9 (sponsor's/reviewer's): Number and Percentages of Patients with any Adverse experiences During the Treatment period for Randomized Patients (Extracted from Sponsor's Table 9.1-1, Volume 74)

Severity	Enoxaparin 40 mg (N=1036)	Desirudin 15 mg (N=1043)	P-value (Fisher's exact)

Mild	389 (37.5%)	368 (35.3%)	0.295
Moderate	310 (29.9)	316 (30.3%)	0.886
Severe	33 (3.2%)	53 (5.1%)	0.36

There were no significant differences between the treatment groups by the degree of severity of adverse experiences. However, there were numerically more moderate and severe adverse experiences in the desirudin group than the enoxaparin treated group.

The following table summarizes adverse experiences by bleeding categories.

Table 2.10 (sponsor's/reviewer's): Proportion (%) of Patients with Adverse Experiences by Bleeding Category During the Treatment Period for Randomized Patients (Extracted from Sponsor's Table 9.1-4, Volume 74)

Bleeding/Hematoma type	Enoxaparin 40 mg	Desirudin 40 mg	P-value (Fisher's exact)
Injection Site Hematoma	6/1023 (0.6%)	29/1028 (2.8%)	0.0103
Wound hematoma/infection	88/1023 (8.6%)	98/1028 (9.5%)	0.489
Major bleeding	2/1023 (0.2%)	8/1028 (0.8%)	0.109
Serious bleeding	20/1023 (2.0%)	20/1028 (1.9%)	1.0

It is seen that there were more injection-site hematoma bleedings in the desirudin group than enoxaparin treated group. There was no significant differences between the treatment groups regarding serious bleeding category. However, there were more events in the desirudin treated group than the enoxaparin treated group with respect to wound hematoma/infection and major bleeding categories.

Safety Monitoring Results:

The bleeding (blood loss) results are summarized in the following table.

Table 2.11 (sponsor's): Blood Loss for Randomized Patients (Extracted from Sponsor's Volume 74, Page 8-27-4)

Blood loss type	Enoxaparin 40 mg (mean ± sd)	Desirudin 15 mg (mean ± sd)	p-value
Peri-operative Blood loss	1076 ± 600 mL	1075 ± 619 mL	1.00
Total blood loss	1327 ± 675mL	1365 ± 710 mL	0.978
Blood loss >3500 mL	12/1023 (1.2%)	12/1028 (1.2%)	1.0

There were no significant blood losses between enoxaparin group and desirudin group. However, enoxaparin group has numerical advantage over desirudin group with respect to peri-opeartive blood loss and total blood loss.

Clinical Laboratory Evaluations:

The sponsor reported that tolerability parameters and routine laboratory tests were comparable to those observed post-operatively in an elective hip replacement population. SGOT, SGPT Gamma-GT and Alkaline phosphalase were increased less post-operatively in the desirudin group than in the enoxaparin group and fewer patients had these enzymes increased above upper limit at the end of the treatment.

2.3 Conclusions

Efficacy:

The efficacy data in this study showed that desirudin 15 mg started preoperatively and administered s.c. twice daily in patients undergoing primary elective total hip replacement provided a significantly more effective prophylaxis of thromboembolic complications in comparison to enoxaparin 40 mg.

Safety:

The safety data in this study showed that the safety profiles of desirudin 15 mg and enoxaparin

40 mg were comparable except for the injection site hematoma.

3. Conclusions

3.1 Study RH/E28

Efficacy:

The efficacy data submitted in study RH/E28 showed that desirudin 15 mg is significantly more effective (p-value 0.0001, odds ratio 0.27 with 95% confidence interval 0.14 –0.52, event rate 7.5% versus 23.5%) than heparin in preventing thromboembolic events (DVT, PE , and Death) in patients undergoing a primary elective total hip replacement.

Safety:

The safety data in this study showed that the safety profiles of desirudin 15 mg and enoxaparin 40 mg were mostly comparable.

3.2 Study RH/E25

Efficacy:

The efficacy data submitted in study RH/E25 showed that desirudin 15 mg is significantly more effective (p-value 0.018, odds ratio 0.61 with 95% confidence interval 0.4 –0.92, event rate 4.86% versus 7.64%) than heparin in preventing thromboembolic event (Proximal DVT, PE, Death) in patients undergoing a primary elective total hip replacement.

Safety:

There were significantly more (2.8% versus 0.6%; p-value 0.0103) injection site hematoma occurrence in the desirudin treated group than the enoxaparin treated group.

The safety data in this study showed that the safety profiles of desirudin 15 mg and enoxaparin 40 mg were comparable except for the injection site hematoma.

3.3 Overall Conclusions

The efficacy data in this submission showed that desirudin was significantly more effective than both active controls (unfractionated heparin and enoxaparin) in preventing thromboembolic events in patients undergoing a primary elective total hip replacement

Analyses of the efficacy data by age group showed mixed results. There was no interaction between age and the treatment groups in the heparin controlled study. On the other hand, there was interaction between age and the treatment groups in the enoxaparin controlled study. It is hard to interpret this interaction because of multiple hypotheses testing. Desirudin treated group had significantly lower event rates than the enoxaparin treated group for age group ≥ 65 where as enoxaparin treated group had numerical advantage over desirudin treated group for age group <65. However, it is not appropriate to conclude that desirudin is more effective in age group ≥ 65 than in age group <65.

The safety profiles for desirudin versus unfractionated heparin were comparable. However, the safety profiles for desirudin versus enoxaparin were comparable except for the injection site hematoma. This should be noted in the labeling of the drug.

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