CENTER FOR DRUG EVALUATION AND RESEARCH

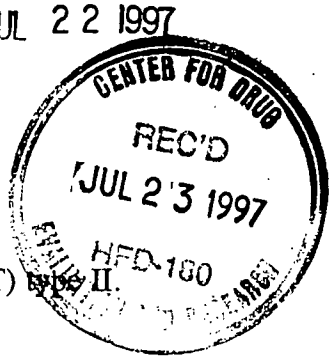
APPLICATION NUMBER: 020807

STATISTICAL REVIEW(S)

Dubeau

STATISTICAL REVIEW & EVALUATION
(Addendum)

Date: JUL 22 1997



NDA# 20-807

Applicant: ClinTrials Research

Drug Name: Refludan® (Lepirudin/HBW 023)

Indication: Treatment of heparin associated thrombocytopenia (HAT) type II.

Drug Classification: 1P

Statistical Reviewer: A. J. Sankoh, Ph.D. APPEARS THIS WAY ON ORIGINAL

Clinical Reviewer: The statistical issues addressed in this review have been discussed with the medical reviewer, L. Talarico, M.D.

Date of Document: May 15, 1997; **Date Received by Reviewer:** May 20, 1997

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Keywords/Phrases: Composite endpoint; confidence intervals; historical control; open label; pooled efficacy data.

BACKGROUND

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This review pertains to additional material (a second pivotal study #NR13, protocol HBW 023/7MN-301 WC) submitted by the sponsor (5/15/97), and a meta-analysis of the efficacy data of this second study and those of the first study (#B-7) contained in the review completed on 4/9/97, in heparin-associated thrombocytopenia (HAT) type II patients.

As in the completed review, this submission consists of a single open-label, non-randomized study (protocol #NR-13 in support of the efficacy and safety of HBW 023 (Refludan) in the treatment of HAT type II). Additional information in the form of historical control is provided for comparison purposes.

STUDY NR13 (Conducted from 7/95 to 4/96)

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As in study B7, this is an open-label, multi center study comparing a historical 120 patient population to 116 patients with HAT type II enrolled into one of three recombinant hirudin (r-hirudin) intravenous infusion groups. The three groups are (a) treatment of arterial or venous thromboembolism with and without thrombolysis (66 patients), (b) prophylaxis of arterial or

venous thromboembolism (43 patients), and (c) anticoagulation during cardiopulmonary bypass (CPB) surgery (4 patients).

Patients generally qualified for this study if they were at least 18 years of age and had a definite need for parenteral antithrombotic therapy or prophylaxis and a definite laboratory confirmation of HAT type II.

The two different indication groups included are those with a drop in platelet count during heparin therapy to a value $< 100 \times 10^9/l$ or by $\geq 30\%$ of their baseline value prior to heparin therapy (described as **acute HAT type II or indication group I** patients), and patients with normal platelet count but a known prior history of HAT type II, who are scheduled for a medical intervention necessitating parenteral anticoagulation (described as **latent type II or indication group II** patients).

Three treatment regimens (A, B, C) were proposed and used in this study as follows

1. Treatment regimen A (in treatment of arterial or venous thromboembolism) administered as

A1: initial iv bolus of 0.4 mg/kg/body weight (bw) followed by continuous iv infusion of 0.15 mg/kg bw for 2-10 days for patients without concomitant thrombolytic therapy;

A2: initial iv bolus of 0.2 mg/kg/body weight (bw) followed by continuous iv infusion of 0.1 mg/kg bw for 2-10 days for patients with concomitant thrombolytic therapy;

2. treatment regimen B (in prophylaxis of arterial or venous thromboembolism) administered as continuous iv infusion of 0.1 mg/kg bw/hr for 2-10 days; and

3. treatment regimen C (in anticoagulation during cardiopulmonary bypass (CPB)) administered as priming bolus (primary HLM) of 0.2 mg/kg/bw followed by an initial iv bolus of 0.25 mg/kg bw, and an additional bolus of 5 mg to maintain ecarin clotting time (ECT > 40 s; as per 10/18/95 protocol amendment), and/or activated coagulation time (ACT > 350 s) during CPB.

Treatment duration ranged from 2-58 days with a median duration of 10 days. A follow-up period of 24 days (or 14 days after HBW 023 therapy, if treatment duration exceeded 10 days) was also included in the study.

1.2.0 SPONSOR'S PLANNED ANALYSES & ANALYSIS METHODS

Study Objectives and Efficacy Endpoints

The primary objective of the study was to demonstrate that treatment of HAT type II patients with intravenous (iv) HBW 023 results in a clinically relevant increase in diminished platelet

counts or in maintenance of normal baseline platelet counts while providing effective anticoagulation.

The secondary objective of the study was to demonstrate that treatment of HAT type II patients with iv HBW 023 results in a clinically relevant benefit in the incidences of arterial or venous thromboembolic complications (TECs), major bleeding complications, surgical interventions/ limb amputations, and deaths.

The primary efficacy endpoint, as per original protocol specification, was the maintenance of normal baseline or increase in platelet counts during effective coagulation, and the secondary efficacy endpoint was combined incidence of venous TECs, limb amputations and deaths.

Sample Size Determination

The study was designed to show that the proportion of patients who attain the primary objective (stated above) exceeds $p_0=20\%$. Assuming a true response rate of $p_1=40\%$, a sample size of 42 patient population (from 30-50 centers) was required to achieve statistical significance at the one-sided 5% level of significance with at least 90% power. With allowance for a 15% dropout rate, a minimum of 50 patients was postulated. In order to increase safety information in patients with HAT type II, a decision was later (protocol amendment #1, 10/18/95) made to increase the sample size from 50 to 100 patients. A sample size of 100 patients was postulated for estimation of 95% confidence interval (of width not greater than 20%) for bleed events.

Following a meeting between the sponsor and the Agency, it was agreed that the primary efficacy endpoint of maintenance of normal baseline or increase in platelet counts (in the first study, #B7) is a surrogate endpoint, and would therefore be considered a secondary endpoint. The secondary efficacy endpoint of combined incidence of venous TECs, limb amputations, and deaths should be considered the primary endpoint. For ease of reference and comparison of efficacy results, this combined incidence event rate is also treated as the primary endpoint in this second study. As in study #B7, from the 116 patient database in this prospective second study, the primary analysis in support of the indication of HAT type II be based on patients diagnosed with HAT type II with ongoing thrombosis.

Sponsor's methods of analysis are as described in the first study (#B7).

Comparison With Historical Control

The prospective study data were to be compared to an historical control of HAT type II patients not treated with recombinant hirudin. The historical control group for this second study (#NR13) is the same as that of the first study (#B7).

Only cases with available information beyond the date of HAT type II diagnosis were to be

included in the historical control population. Exclusion criteria were similar to those for the prospective study HBW 023. Of the 182 (147 from principal investigator (PI), Prof. Greinacher, and 35 from other two sources) screened patients, 120 were described as evaluables and 91 of the evaluables were patients with ongoing thrombosis, and these qualified for the historical comparison. A total of 116 (65 A1, 4 A2, 43 B and 4 C) patients from 47 centers entered the prospective study NR13 (see Table 1 below for patient disposition by center); 59 (51%) of these were eligible for comparison with the historical control. Note that among the 59 patients with ongoing thrombosis (patients receiving treatment regimens A1 and A2) in the prospective study, 41 (73%) had TECs prior to HAT confirmation, compared to 89% in the historical control group (see Table 2 below).

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Table 1/Patient Disposition Per Center/Source

# Enrolled Per Center (n)	Prospective Study								Historical Control	
	1	2	3	4	5	8	10	21	PI	Others
# of Centers W/n (%)	29 (62%)	5 (11%)	3 (6%)	1 (2%)	5 (11%)	1 (2%)	1 (2%)	1 (2%)	147(81%)	35(19%)

The study report indicated that the primary comparison of the combined event rate of new TECs, limb amputations, and deaths was based on the time when HAT

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Sponsor's analyses indicated the two groups (i.e., HBW 023 and historical control) were comparable with respect to prior use of heparin, time period between onset of clinical symptoms and laboratory confirmation of HAT, and other baseline characteristics (see Table 2 below). This reviewer's analyses indicate that there were significantly more patients aged 65 years and over in the historical control group (56%) than in the prospective study (NR13) group (32%); Fisher's exact 2-sided p-value = .0047, and more TECs in the historical control group (89%) than in the prospective study (NR13) group (73%) during heparin therapy but before confirmation of HAT type II; Fisher's exact 2-sided p-value=.0266 (most of these TECs were of venous distal type; Fisher's exact =.0499 for the distal types). If necessary, the impact of this difference on the observed effectiveness results will be investigated in a subgroup analysis in the reviewer's comments section.

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Table 2/Comparison of Baseline Characteristics of Eligible Patients: Prospective vs Historical Control Study (HAT Type II)

Data Set/ Treatment	Male/Female (%)	Age<65/≥65 (%) [Mean Age]	Platelet # at Heparin HBW=52; Histori=73	Platelet # at HAT HBW=56;Histori=80	TECs Before HAT Confirmed
HBW #NR13: N=59	26/33 (44/56%)	40/19 (68/32%) [Mean =58 yrs]	Median=221 [Mean=245;SD=120]	Median=70 [Mean=126;SD=141]	41/56 (73%)
Historical Control: N=91	32/59 (35/65%)	40/51 (44/56%) [Mean =64 yrs]	Median=231 [Mean=249; SD=108]	Median=63 [Mean=102;SD=109]	80/90 (89%)

TTT=Time to thrombocytopenia; R HBW=N for prospective study; H=N for historical control study.

All eligible patients (100% HBW 023 NR13 vs 100% historical control) were on heparin/ heparinoid treatment prior to trial initiation. The most frequent observed types of thrombo-embolic complications (70% HBW 023 NR13 vs 88% historical, overall) were arterial-peripheral (39% HBW 023 NR13 vs 21% historical control), venous proximal (44% HBW 023

NR13 vs 29% historical), venous distal (46% HBW 023 NR13 vs 66% historical), and pulmonary embolism (46% HBW 023 vs 44% historical). Median treatment duration was 10 days for A1 and 9 days for A2.

Summary of Sponsor's Efficacy Analysis Results & Reviewer's Comments

Table 3/Analysis Results of Combined & Separate Endpoints (TECs, Limb Amputations, or Death) After HAT Confirmation

Endpoint/ Study	Study NR13 (R)	Historical (H)	Difference: R-H
Cumulative Combined Event Rate[1] by Wk1, Wk3, Wk4, Wk5, Wk6*:	23.7, 35.8, 35.8, 35.8, 51.8	21.5, 36.1, 43.1, 52.0, 55.5	+2.2, -0.3, -7.3, -16.2, -3.7 **2p=.758** (Log-rank); **.897** (Wilcox)
Pre-specified Other Analyses			
Combined Amputation & Death by Wk1, Wk3, Wk4, Wk6, Wk6*:	10.2, 20.3, 20.3, 20.3, 20.3	4.5, 12.4, 17.4, 23.4, 36.2	+2.3, +7.9, +2.9, -3.1, -15.9 **2p=.623** (Log-rank); **.306** (Wilcox)
Mortality Rate Estimates: by Wk1, Wk3, Wk4, Wk6, Wk7	6.8, 11.9, 11.9, 11.9, 11.9	2.3, 6.2, 13.5, 16.2, 25.0	+4.5, +5.7, -1.6, -4.3, -13.1 **2p=.772** (Log-rank); **.455** (Wilcox)
New TEC Rate Estimates: by Wk1, Wk3, Wk4, Wk6, Wk7	17.4, 21.3, 21.3, 47.5, 45.5	19.2, 26.0, 31.1, 34.9, 34.9	-1.8, -4.7, -9.8, +12.6, +12.9 **2p=.637** (Log-rank); **.567** (Wilcox)
Limb Amputation Rate Estimates: by Wk1, Wk3, Wk4, Wk6, Wk7	3.6, 9.1, 9.1, 9.1, 9.1	2.2, 6.4, 6.4, 10.3, 14.6	+1.4, +2.7, +2.7,-1.2, -5.5 **2p=.926** (Log-rank); **.637** (Wilcox)

1: rates are by Kaplan-Meier Estimates; *: see Figures below for week by week comparisons; data are from Tables C.2.13-2.19 of Vol 15.4

Reviewer's Comments

The sponsor's analysis results summarized in Table 3 above indicate that patients treated with lepirudin had no significant advantage over those in the historical control group regarding the combined incidences of death or limb amputation or thromboembolic complications (TECs) experienced. This lack of significant benefit from lepirudin as compared to the historical control group supported by the non-separating graphical displays of combined event rates by the two groups, and the overlapping corresponding 95% confidence limits of the combined cumulative (Kaplan-Meier) estimates of the event rates at all time points [see Figures below]. This lack of benefit is further supported by the crude combined event rate estimates (see bottom of Table 4); the exact 2-sided p-value on the difference on event rates is .651 with a mere absolute difference of 4%; the 95% CI on the difference in proportion is (-.21, +.13), clearly containing zero. The 95% CI crude estimate for protocol-specified 20% expected combined event rate are identical and both contained 20%; (27%, 53%) for HBW 023 NR13 and (33%, 54%) for historical control group. In addition, neither of the three components of the combined endpoints (mortality, limb amputations and TECs) show any meaningful numerical advantage in favor of lepirudin (see bottom of Table 3).

The sponsor's hazard ratio (estimates) by Cox regression analysis result also indicate no HBW 023 advantage over the historical control group. The unadjusted and adjusted (for pre-specified prognostic factors such as TECs, age< or ≥65 years, sex, etc) hazard (or risk) ratios are respectively .922 and .940 with corresponding 2-sided p-values of .7599 and .8302; both corresponding 95% CIs contained one [(.548, 1.553) and (.534, 1.655), respectively].

Note that the sponsor's Cox regression analysis results described above seem to suggest that prognostic factors such as TECs, age, sex, etc., do not significantly impact the observed

effectiveness results in this study. But as indicated earlier, this reviewer's analysis results indicate that there were significantly more patients aged 65 years and over in the historical control group (56%) than in the prospective study (NR13) group (32%); Fisher's exact 2-sided p-value=.0047, and more TECs in the historical control group (89%) than in the prospective study (NR13) group (73%) during heparin therapy but before confirmation of HAT type II; Fisher's exact 2-sided p-value=.0266 (most of these TECs were of venous distal type; Fisher's exact =.0499 for the distal types). However, given the lack of overall significant treatment benefit, no subgroup analyses will be performed by this reviewer.

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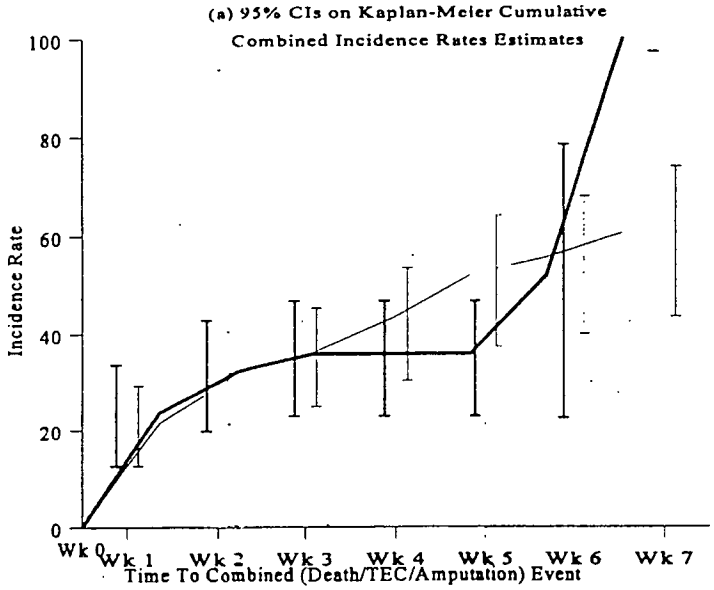

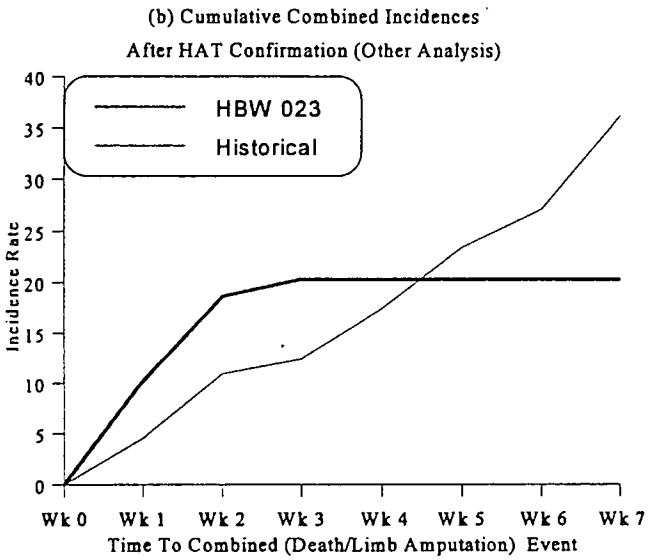

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Table 4/Subgroup Analysis Results for Combined & Separate Events (TECs, Limb Amputations, or Death) by Reviewer

	HBW 023 (R)		Historical (H)		Difference (R-H)	
Combined Event	Rate	95% CI on p	Rate	95% CI on p	Rate	95% CI on Difference
	23/59 (.39)	[.27, .53]	39/91 (.43)	[.33, .54]	-.04	[+.21, -.13]; 2p=.651
Deaths Only	8/59 (.14)	[.06, .25]	11/91 (.12)	[.06, .21]	+.02	[-.12, +.17]; 2p=.851
Limb Amputations Only	5/59 (.09)	[.03, .19]	8/91 (.09)	[.04, .17]	-.00	[-.13, +.13]; 2p=.967
TECs Only	14/59 (.24)	[.14, .37]	25/91 (.27)	[.19, .38]	-.04	[-.20, +.12]; 2p=.126

Note: p_0=.20

Summary of Safety Events

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Overall, there were significantly more cumulative bleeding incidences in the HBW 023 group than in the historical control group. The table below summarizes bleeding incidences since HAT confirmation in three different ways (p-values are by sponsor's analyses).

Table 5/ Cumulative Bleeding Events Since HAT Confirmation

	HBW 023 NR13 (N=59)		Historical Control (N=91)		
	# at Risk	Cumulative Incidence	# at Risk	Cumulative Incidence	
Documented Bleeding					
Day 7	40	33%	72	11%	
Day 14	33	37%	56	17%	
Day 28	11	43%	25	21%	
Log-rank 2-sided p-value					**.0009 against HBW 023**
Bleeding/Transfusions					
Day 7	35	43%	59	23%	
Day 14	28	47%	47	27%	
Day 28	8	54%	20	30%	
Log-rank 2-sided p-value					**.0025 against HBW 023**
Bleeding Requiring transfusions					
Day 7	47	19%	77	5%	
Day 14	41	23%	62	7%	
Day 28	17	23%	29	7%	
Log-rank 2-sided p-value					**.0024 against HBW 023**

Note that the minimum age requirement for entry into this trial is 18 years; the pediatric implication of this drug is therefore not clear.

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II. SUMMARY OF FIRST STUDY (B7) EFFICACY RESULTS (See 4/9/97 Review for Details)

Summary of Sponsor's Efficacy Analysis Results & Reviewer's Comments/ Study B7

Table 6/Analysis Results of Combined & Separate Endpoints (TECs, Limb Amputations, or Death) After HAT Confirmation

Endpoint/ Study	HBW 023 (R)	Historical (H)	Difference: R-H
Cumulative Combined Event Rate by Wk1, Wk3, Wk4, Wk6, Wk6*:	9.3, 20.4, 20.4, 20.4, 20.4	21.5, 36.1, 43.1, 52.0, 55.5	-12.2, -15.7, -22.7, -31.6, -40.0 **Log-rank 2p=.014** (Overall Curve)
Pre-specified Other Analyses			
Combined Amputation & Death by Wk1, Wk3, Wk4, Wk6, Wk7*:	1.9, 7.5, 7.5, 7.5, 7.5	4.5, 12.4, 17.4, 23.4, 36.2	-2.6, -4.9, -9.9, -15.9, -28.7 **Log-rank 2p=.121** (Overall Curve)
Mortality Rate Estimates: by 3 Wks, 4 Wks, 7 Wks	5.6, 5.6, 5.6	6.2, 13.5, 25.0	-0.6, -7.9, -19.4 **Log-rank 2p=.312** (Overall Curve)
New TEC Rate Estimates: by 1 Wk, 2 Wks, 3 Wks, 7 Wks	9.3, 13.0, 14.9, 14.9	19.2, 22.9, 26.0, 34.9	-9.9, -9-9, -11.1, -20.0 **Log-rank 2p=.079** (Overall Curve)
Limb Amputation Rate Estimates: by 2 Wks, after 2 Wks	3.7, Unchanged	6.4, 14.6, Unchanged	-2.7, -10.9, ... **Log-rank 2p=.386** (Overall Curve)

*: see Figures below for week by week comparisons; note, data are from Appendix II.5.1, II.5.5, and Tables C.26-C.2.9 of submission

Reviewer's Comments

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Sponsor's analysis results summarized in Table 3 above indicate that compared to the historical control group, patients treated with lepirudin experienced significantly less combined incidences of death or limb amputation or thromboembolic complications (TECs). These

significant findings are supported by the clear separation of the graphical displays of combined event rates in the prospective study HBW 023 (R) versus the historical control study (H), and non-overlapping corresponding 95% confidence limits of the combined cumulative (Kaplan-Meier) estimates of the event rates after week 4 [see Figure (c) below]. This is further supported by the crude combined event rate estimates (see bottom of Table 6); the exact 2-sided p-value on the difference on event rates is .0104 with an absolute difference of 22.5% in favor of lepirudin; the 95% CI on the difference in proportion is (-.3897, -.0576). The pre-specified 20% expected combined event rate is contained in the 95% CI crude estimate for HBW 023 (10.6%, 33.5%), but not for the historical control group (32.5%, 53.7%). Also, all three components of the combined endpoints (mortality, limb amputations and TECs) show numerical benefit in favor of lepirudin (see bottom of Table 3).

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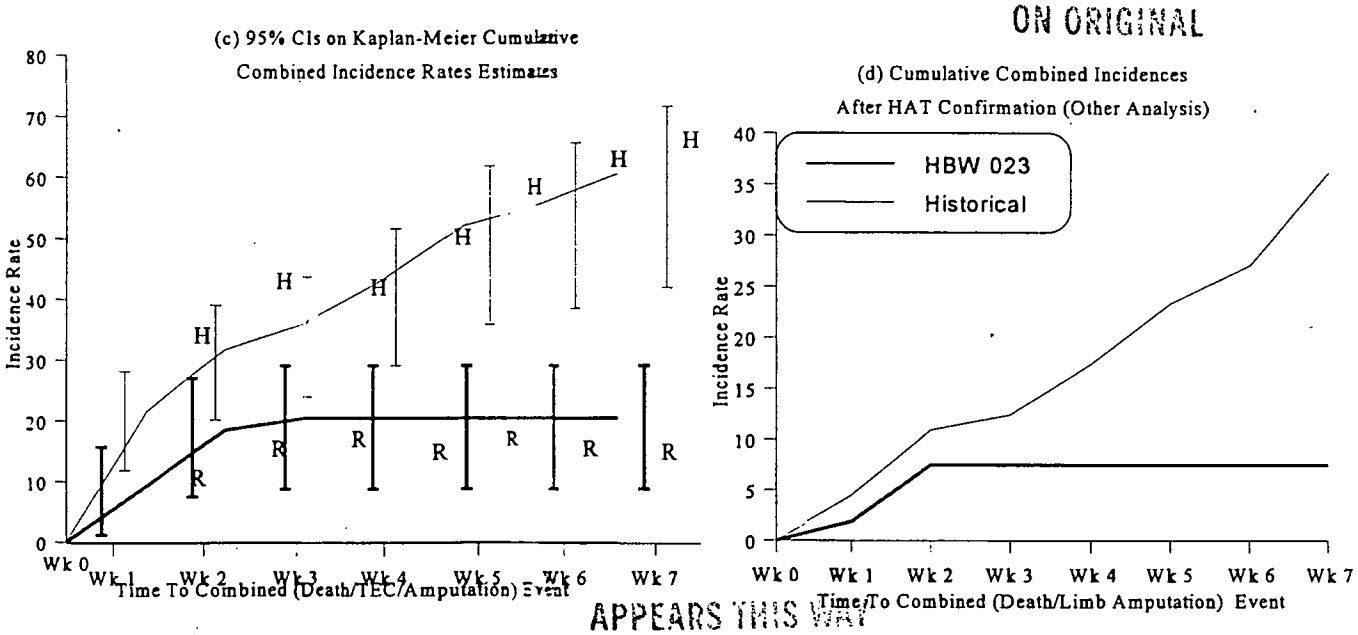

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Sponsor's hazard ratio (estimates) by Cox regression analysis result also indicate that patients in the prospective study experienced significantly less events than those in the historical group; the unadjusted and adjusted (for pre-specified prognostic factors such as TECs, age < or ≥65 years, sex, etc) hazard (or risk) ratios are respectively .443 and .439 with corresponding 2-sided p-values of .0119 and .0189; the corresponding 95% CIs are respectively (.225, .871) and (.211, .910).

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This reviewer's analysis results (see study B7 completed review, 4/9/97 for more details) indicate that there were significantly more 65 years and older patients in the historical control than in the prospective study group (Fisher's exact 2-sided p-value=.039). Table 4 below summarizes the results of gender and age subgroup analyses by this reviewer. The results in this table seem to indicate that there is (an overall) age impact on the observed effectiveness result. Optimal treatment benefit is observed in the ≥ 65 years subgroup; 28% absolute treatment difference, 2-sided p-value=.033 (favoring the prospective study group), compared with a 17% absolute treatment difference, 2-sided p-value=.148 (favoring the prospective study group) for patients in the < 65 years old subgroup. Even though no imbalance was detected between males and females (Fisher's exact 2-sided p-value=.463), optimal refludan

treatment benefit also appears to derive primarily from the female subgroup of patients; given the relatively small number of patients in these subgroups, these subgroup analysis results should be interpreted with caution.

It should be noted that in all analyses performed by sponsor and this reviewer, patients in HBW 023 prospective study group enjoyed at least a numerical advantage over those in the historical control group. This is indicated by the non-overlapping 95% CIs after week 4 (Figure (c) above) and the consistently left (of zero) skewed 95% CIs on the absolute difference (refludan - historical); see Table 4.

Table 7/Subgroup Analysis Results for Combined & Separate Events (TECs, Limb Amputations, or Death) by Reviewer

	HBW 023 (R)		Historical (H)		Difference (R-H)	
Combined Event	**Rate**	**95% CI on p**	**Rate**	**95% CI on p**	**Rate**	**95% CI on Difference**
Age <65 yrs	7/34 (.21)	[.09, .38]	15/40 (.38)	[.23, .54]	-.17	[-.41, .06]; 2p=.148
≥ 65 yrs	4/21 (.19)	[.06, .42]	24/51 (.47)	[.33, .62]	-.28	[-.52, -.02]; 2p=.033
Sex : Males	4/15 (.27)	[.08, .55]	14/32 (.44)	[.26, .62]	-.17	[-.49, .14]; 2p=.283
Females	7/39 (.18)	[.08, .34]	25/59 (.42)	[.30, .56]	-.24	[-.45, -.05]; 2p=.018
Overall Combined	**11/54 (.20)**	**[.11, .34]**	**39/91 (.43)**	**[.33, .54]**	**-.23**	**[-.39, -.06]; 2p=.010**
Deaths Only	3/54 (.06)	[.01, .15]	11/91 (.12)	[.06, .21]	-.06	[-.19, .09]; 2p=.372
Limb Amputations Only	2/54 (.04)	[.00, .13]	8/91 (.09)	[.04, .17]	-.05	[-.17, .07]; 2p=.452
TECs Only	8/54 (.15)	[.07, .27]	25/91 (.27)	[.19, .38]	-.12	[-.28, .03]; 2p=.126

Note: p_0=.20

Note that patient #1001 in center 10 (treatment regimen A1) had an event (limb amputation) but was excluded from the efficacy analyses due to missing platelet counts. The inclusion of this patient in the efficacy analyses, however, does not lead to a change in the direction of or conclusion based on observed statistical evidence: overall combined (crude) rate is 12/55 (22%) for HBW 023 vs 39/91 (44%) for historical control with a .0153 exact 2-sided p-value on absolute difference of 21%, and a 95% CI of (-37% , -4%).

III. Combined Efficacy Results (First and Second Studies)

Table 8 below summarizes sponsor's efficacy results for the combined crude incidence rates of deaths, limb amputations and new TECs after HAT confirmation. For the pooled efficacy results between the two studies, 95% CI and the corresponding 2-sided p-values are provided for the 'pooled' treatment effect difference (Diff) under heading "Pooled Results". It can be seen from this that the null hypothesis of zero treatment effect difference is not rejected; 95% CI on pooled treatment difference is (-32%, 5%) with 2-sided p-value of .095. Thus, the pooled data failed to show that patients treated with lepirudin experienced significantly fewer incidences of death or limb amputation or thromboembolic complications (TECs) than those in the historical control. This lack of significant combined lepirudin efficacy data advantage over the historical control group is supported by the overlapping corresponding 95% confidence limits of the combined cumulative (Kaplan-Meier) estimates of the event rates at almost all

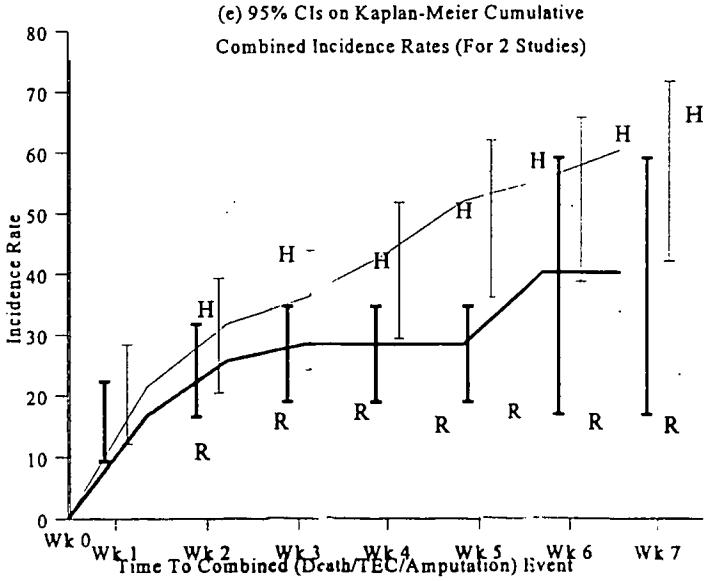
time points, despite the clear separation of the two curves [Figure (e) below], and the inclusion of zero in the 95% CI for the pooled data [see Figure (f) below].

Table 8/ Summary of Designs and Efficacy Results

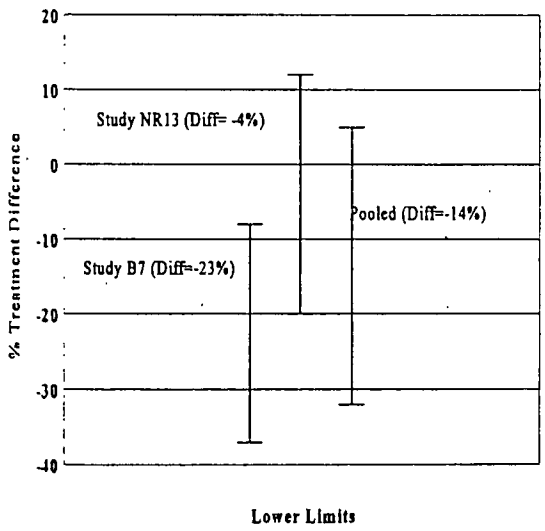
	Study HBW 023 #B7 (10/92 to 06/94)		Study HBW 023 #NR13 (7/95 to 4/96)		
Objective	The primary objective of the study was to demonstrate that treatment of HAT type II patients with intravenous (iv) HBW 023 results in a clinically relevant increase in diminished platelet counts or in maintenance of normal baseline platelet counts while providing effective anticoagulation.				
Study Type	OL, NR, HC, MD, (58 centers)		OL, NR, HC, MD, MC (47 centers)		
Dosing	Two dosing regimens: A1, A2 (for patients with ongoing thrombosis)				
Eligible N (male/female): Other Demographics	N=54 (15/39) vs Historical control N= 91 (32/59). Mean Age=57 yrs; Median Platelet at Hep=241; TECs before HAT=82%, TCH=94%; MTLD=7.7		N=59 (26/33) vs Historical control N=91 (32/59) Mean Age=64 yrs; Median Platelet at Hep=221; TECs Before HAT=73%, TCH=94%, MTLD=6.0		
Primary Endpoint	The primary efficacy endpoint is combined incidence of venous TECs, limb amputations and deaths.				
Combined Crude Rates Efficacy Results (Reviewer's)	Diff: R-HC	Study #B7 95% CI	Diff: R-HC	Study #NR13 95% CI	Pooled Results (graph e) Diff (δ) MH 95% CI
Death/Limb/New TECs	-23%	(-39%, -6%); 2p=.010	-4%	(-21%, 13%); 2p=.651 →	-14% (-32%, 5%)/
Deaths Only	-6%	(-19%, 9%); 2p=.372	2%	(-12%, 17%); 2p=.851	2-sided p-value=.095
Limb Amputations Only	-5%	(-17%, 7%); 2p=.452	0%	(-13%, 13%); 2p=.967	for testing the hypothesis
New TECs Only	-12%	(-28%, 3%); 2p=.126	-4%	(-20%, 12%); 2p=.655	H_0: δ=0 (trt difference)

2-sided p-value for Breslow-Day test for homogeneity of (i.e., common) odds ratios (OR)=.079 (Zelen's exact=.124); MH=Mantel Haenszel. OL=open-label; HC=historical control; MC=multi center. NR=Non-randomized; Diff=Treatment effect difference; MD=multi doses. TCH=thrombocytopenia during Heparin but before HAT confirmed; MTLD=mean time to lab diagnosis of HAT (8.4 in historical).

(e) 95% CIs on Kaplan-Meier Cumulative Combined Incidence Rates (For 2 Studies)



(f) 95% CI Estimates on Difference



The combined or pooled treatment difference of -14% (Refludan - Historical Control Group) is primarily due study #B7.

CONCLUSIONS

In this reviewer's assessment, the efficacy data in this submission do not provide convincing confirmatory efficacy evidence that patients treated with lepirudin had a significant efficacious advantage over those in the historical control group for the following reasons:

1. Study #B7 (conducted between 10/92 and 6/93) provides strong support for the claim of refludan (lepirudin) effectiveness in the treatment of heparin associated thrombocytopenia (HAT) type II patients in this trial.

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ON ORIGINAL

2. However, study #NR13 (conducted between 7/95 and 4/96) does not provide support for sponsor's claim that refludan (lepirudin) is effective in the treatment of heparin associated thrombocytopenia (HAT) type II in this trial.

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ON ORIGINAL

3. The combined efficacy data from the two pivotal studies provide borderline results in support of the effectiveness of lepirudin in the treatment of heparin associated thrombocytopenia.

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ON ORIGINAL

4. It should be noted that similar patient population profiles were used in these two studies (#B7 & NR13). Furthermore, the same historical control patient population was used in both studies. It is, therefore, highly disturbing to this reviewer that study #NR13 (started and completed (7/95 to 4/96) within two years after the completion of study #B7) failed to replicate the strong effectiveness findings of study #B7 conducted between 10/92 and 06/94. That two almost identical studies (conducted only two years apart) could arrive at two such diametrically opposing conclusions is especially troubling when viewed in the light of the advent of the single study submission.

APPEARS THIS WAY
ON ORIGINAL

A. J. Sankoh, Ph. D.
/S/ 7/21/97
Mathematical Statistician

Concur:
Dr. Huque /S/ 7/22/97
for Dr. Smith /S/ 7/22/97

cc: Archival NDA # 20-807
HFD - 180
HFD - 180/Dr. Fredd
HFD - 180/Dr. Talarico
HFD - 180/ Folkendt/Dubeau
HFD - 344/Dr. Lisook
HFD - 720/Dr. Smith
HFD - 720/Dr. Huque
HFD - 720/Dr. Sankoh

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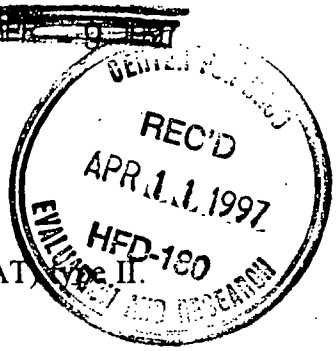
STATISTICAL REVIEW & EVALUATION

Date:



NDA# 20-807

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Applicant: ClinTrials Research

Drug Name: Refludan® (Lepiridun/HBW 023)

Indication: Treatment of heparin associated thrombocytopenia (HAT) type II.

Drug Classification: 1P

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Statistical Reviewer: A. J. Sankoh, Ph.D.

Clinical Reviewer: The statistical issues addressed in this review have been discussed with the medical reviewer, L. Talarico, M.D.

Date of Document: December 31, 1996; **Date Received by Reviewer:** January 15, 1997

45-Day Meeting: December 31, 1996; **Filing Date:** February 25, 1997.

Volumes Reviewed: 1.1, 1.144 - 1.154: December 31, 1996.

APPEARS THIS WAY
ON ORIGINAL

User Fee Due Date: June 29, 1997

Keywords/Phrases: Composite endpoint; confidence intervals; historical control; open label; single study submission.

APPEARS THIS WAY
ON ORIGINAL

BACKGROUND

Experiments demonstrating that heparin treatment unexpectedly decreased platelet counts in animals were first reported in the 1940s. Since then, clinical observations have revealed that heparin associated thrombocytopenia (HAT) is a relatively common adverse effect of heparin therapy, occurring in approximately of patients who receive this drug. HAT has been reported after administration of all types of unfractionated heparin and low molecular weight heparin (LMWH). However, higher incidences of thrombocytopenia with bovine heparin (4.2% to 10.7%) have been reported as compared to porcine heparin (.7% to 5.6%).

Two types of HAT have been described, each having a distinct etiology: 1) HAT type I is characterized by a relatively mild thrombocytopenia of early onset (i.e., within the first few days of heparin therapy). It usually resolves without cessation of heparin. This type of HAT is believed to be caused by an intrinsic proaggregatory effect of heparin; 2) HAT type II is more severe and usually occurs after 7-10 days of heparin therapy. Platelet counts often drop to values below 80 G/l, in rare cases even to values below 10 G/l. If heparin therapy is

continued, thrombocytopenia persists; after discontinuation of heparin administration, platelet counts normalize within 5-7 days. HAT type II is caused by an immune mechanism. In majority of the cases, the antigen is formed by multimolecular complexes of sulfated oligosaccharides (e.g. heparin) and platelet factor 4 (PF4). Several antibodies bind to this antigen and form immune-complexes, which bind to platelets via their Fc receptor (CD 32). This bind results in platelet activation, reduced platelet survival, and thrombocytopenia. Patients suffering from HAT type II have an increased risk of multiple thromboembolic complications which frequently results in crippling disability, e.g., limb amputation or even death.

In general, four diagnostic tests are available for laboratory confirmation of HAT type II.

No anticoagulation treatment is approved in any European country for patients suffering from HAT type II. LMWH, heparinoids (e.g., danaparoid) and several other drugs (e.g., ancroid) have been used with varying success.

Hirudin is a promising antithrombotic substance which is naturally produced by the salivary glands of the medicinal leech (*hirudo medicinalis*). Hirudin is the most potent and specific thrombin inhibitor currently known. It acts independently of cofactors, such as antithrombin III, and, unlike heparin, it is not inactivated by platelet factor 4 and may thus be more effective in the presence of platelet-rich thrombin. Hirudin also inhibits clot-bound thrombin which is protected from inhibition by heparin.

HBW 023 is a recombinant hirudin (r-hirudin) produced in yeast cells (Saccharonmyces cerevisiae) with a molecular weight of approximately 7,000 Dalton. The inhibition constant of HBW 023 for thrombin is in the picomolar range. After intravenous administration, the mean terminal half-life is approximately one hour. The elimination of hirudin occurs mainly via the kidneys, with about 50% of the administered activity being excreted in urine.

Approximately 1,000 patients have already been treated with HBW 023 in Phase II and Phase III clinical studies. Indications tested were adjunctive anticoagulation to thrombolysis for acute myocardial infarction, therapy of unstable angina pectoris, prevention of reischemia after percutaneous transluminal coronary angioplasty (PTCA) for unstable angina pectoris, antithrombotic therapy of deep venous thrombosis (DVT), and prevention of clotting in the hemodialysis circuit.

This submission consists of a single study (protocol #B-7 submitted to IND 46, 875S/N, 014) in support of the efficacy and safety of HBW 023 (Refludan) in the treatment of HAT type II.

Additional information in the form of historical control are provided for comparison purpose.

STUDY B7 (Conducted between 10/22/92 and 06/30/94)

This is an open-label, multi center study comparing a historical 120 patient population to 82 patients with HAT type II enrolled into one of three recombinant hirudin (r-hirudin) intravenous infusion groups. The three groups are (a) treatment of arterial or venous thromboembolism with and without thrombolysis (56 patients), (b) prophylaxis of arterial or venous thromboembolism (18 patients), and anticoagulation during cardiopulmonary bypass (CPB) surgery (8 patients).

Patients generally qualified for this study if they were at least 18 years of age and had a definite need for parenteral antithrombotic therapy or prophylaxis and a definite laboratory confirmation of HAT type II.

The two different indication groups included are those with a drop in platelet count during heparin therapy to a value $< 100 \times 10^9$/l or by $\geq 30\%$ of their baseline value prior to heparin therapy (described as **acute HAT type II or indication group I** patients), and patients with normal platelet count but a known prior history of HAT type II, who are scheduled for a medical intervention necessitating parenteral anticoagulation (described as **latent type II or indication group II** patients).

Three treatment regimens (A, B, C) were proposed and used in this study as follows (as per 08/18/1994 protocol amendment)

1. Treatment regimen A (in treatment of arterial or venous thromboembolism) administered as

A1: initial iv bolus of 0.4 mg/kg/body weight (bw) followed by continuous iv infusion of 0.15 mg/kg bw for 2-10 days for patients without concomitant thrombolytic therapy;

A2: initial iv bolus of 0.2 mg/kg/body weight (bw) followed by continuous iv infusion of 0.1 mg/kg bw for 2-10 days for patients with concomitant thrombolytic therapy;

2. treatment regimen B (in prophylaxis of arterial or venous thromboembolism) administered as continuous iv infusion of 0.1 mg/kg bw/hr for 2-10 days; and

3. treatment regimen C (in anticoagulation during cardiopulmonary bypass (CPB)) administered as priming bolus (primary HLM) of 0.2 mg/kg/bw followed by an initial iv bolus of 0.25 mg/kg bw, and an additional bolus of 5 mg to maintain ecarin clotting time (ECT > 250 s) and/or activated coagulation time (ACT > 350 s) during CPB.

The study report indicated that these dosing regimens are based upon the doses and preliminary results of phase II studies carried out with HBW 023 for treatment of unstable angina pectoris

(HBW 023/7MN-201UA), prevention of reischemia after PTCA for acute unstable angina pectoris (HBW 023/7MN-201AP), as adjunctive therapy to thrombolysis for acute MI (HBW 023/7MN-201MI, 7MN-202MI, 7MN-203MI), and as antithrombotic therapy for DVT (HBW 023/7F--201TH, 7F--202MI, 7MN-201TH).

Treatment duration ranged from 2-58 days with a median duration of 10 days. A follow-up period of 24 days (or 14 days after HBW 023 therapy, if treatment duration exceeded 10 days) was also included in the study.

1.2.0 SPONSOR'S PLANNED ANALYSES & ANALYSIS METHODS

Study Objectives and Efficacy Endpoints

The primary objective of the study was to demonstrate that treatment of HAT type II patients with intravenous (iv) HBW 023 results in a clinically relevant increase in diminished platelet counts or in maintenance of normal baseline platelet counts while providing effective anticoagulation.

The secondary objective of the study was to demonstrate that treatment of HAT type II patients with iv HBW 023 results in a clinically relevant benefit in the incidences of new thromboembolic complications (TECs), major bleeding complications, surgical interventions/ limb amputations, and deaths in patients with ongoing thrombosis.

The primary efficacy endpoint, as per original protocol specification, was the maintenance of normal baseline or increase in platelet counts during effective coagulation, and the secondary efficacy endpoint was combined incidence of venous TECs, limb amputations and deaths.

Sample Size Determination

The study was designed to show that the proportion of patients who attain the primary objective (stated above) exceeds $p_0=20\%$. Assuming a true response rate of $p_1=40\%$, a sample size of 42 patient population (from 30-40 centers) was required to achieve statistical significance at the one-sided 5% level of significance with at least 90% power. With allowance for a 15% dropout rate, a minimum of 50 patients was postulated. In order to increase safety information in patients with HAT type II, a decision was later (protocol amendment #2) made to increase the sample size from 50 to 80 patients.

Following a meeting between the sponsor and the Agency, it was agreed that the primary efficacy endpoint of maintenance of normal baseline or increase in platelet counts is a surrogate endpoint, and would therefore be considered a secondary endpoint. The secondary efficacy endpoint of combined incidence of venous TECs, limb amputations, and deaths should be considered the primary endpoint. The reasoning argument being that a primary mortality type endpoint would provide best support for consideration of a single study for approval. It was further agreed that from the 82 patient database in the prospective study HBW 023 (sponsor

conducted Phase III study), the primary analysis in support of the indication of HAT type II be based on patients diagnosed with HAT type II with ongoing thrombosis.

The study report contained in volume 1.145 indicated that a one-sided binomial test at 5% level of significance was used to test whether the proportion of responders exceeded the prespecified 20% limit; a two-sided 95% confidence interval (CI) for the proportion of responders was calculated according to Pearson and Clopper. The study report also indicated that cumulative incidences of clinical events were estimated using the Kaplan-Meier method and that comparisons between the HBW 023 treatment group and the historical control group were performed by means of log-rank tests and Wilcoxon tests; incidences of the combined endpoint (TECs, amputations, and deaths) were also analyzed using a Cox regression model.

Comparison With Historical Control

The prospective study data were to be compared to an historical control of HAT type II patients not treated with recombinant hirudin. Patients screened for inclusion into the historical control population were obtained from a registry of cases established by the Principal Investigator (PI; N=147), and from collections of cases established by other three different investigators. However, the study report indicated that due to logistic reasons, only patients from two of the collections of cases were screened (N=35). These three remaining sources (with N=182 patients) had in common laboratory diagnoses of HAT performed by the PI with the same assay (HIPAA) used in the prospective study HBW 023 (except for 8 historical control patients with a positive PAA in whom HIPAA was not performed). Of these 182, 91 (50%) were eligible for the historical control comparison.

The objective of the historical comparison was to evaluate the impact of treatment with HBW 023 on combined incidence of death, limb amputation and new TECs, as well as the incidence of bleeding. In addition, comparisons of the individual rates of death, limb amputations, and new thromboembolic complications as well as the incidence of bleeds were to be performed. The date of laboratory confirmation of HAT type II was considered to be the most appropriate starting point for this purpose.

Only cases with available information beyond the date of HAT type II diagnosis were to be included in the historical control population (exclusion criteria were similar to those for the prospective study HBW 023).

A total of 82 (51 A1, 5 A2, 18 B and 8 C) patients from 58 centers entered the prospective study (see Table 1 below for patient disposition by center). Fifty-four (66%) of these, with ongoing thrombosis, were on regimens A1 (highest claimed dose) or A2 and were eligible for comparison with the historical control. Among the excluded, 17 were on regimen B (without ongoing thrombosis), 8 had CPB, 2 did not satisfy the protocol inclusion criterion of ≤21 days between onset of symptoms and lab confirmation of HAT type II.

Table 1/Patient Disposition Per Center/Source

# Enrolled Per Center (n)	Prospective Study					Historical Control	
	1	2	3	4	5	9	PI	Others
# of Centers W/n (%)	46 (78.3%)	3 (5.2%)	4 (6.9%)	3 (5.2%)	1 (1.7%)	1 (1.7%)	147(80.8%)	35(19.2%)

The study report indicated that the primary comparison of the combined event rate of new TECs, limb amputations, and deaths was based on the time when HAT was confirmed by HIPAA.

Sponsor's analyses indicated the two groups were comparable with respect to prior use of heparin, time period between onset of clinical symptoms and laboratory confirmation of HAT [mean time to lab diagnosis=7.7 days (SD=5.2) for HBW 023 and 8.4 days (SD=4.9) for historical control], and other baseline characteristics (see Table 2 below). This reviewer's analyses indicate that there were significantly more patients aged 65 and over in the historical control group (56%) than in the prospective study group (44%); Fisher's exact 2-sided p-value=.039. The impact of this difference on the observed effectiveness results will be investigated in a subgroup analysis in the reviewer's comments section.

Table 2/Comparison of Baseline Characteristics of Eligible Patients: Prospective vs Historical Control Study

Data Set/ Treatment	Male/Female (%)	Age<65/≥65 (%) [Mean: Eligibles]	Platelet # at Heparin HBW=51; Histori=73	Platelet # at HAT HBW=51; Histori=73	TTT R=50; H=88
HBW 023: N=54	15/39 (28/72%)	34/20 (63/37%) [Mean Age=57 yrs]	Median=241 [Mean=281; SD=143]	Median=68 [Mean=131; SD=143]	Q_1=6; Q_2=9 Q_3=12
Historical Control: N=91	32/59 (35/65%)	40/51 (44/56%) [Mean Age=64 yrs]	Median=231 [Mean=249; SD=108]	Median=63 [Mean=102; SD=109]	Q_1=8; Q_2=11 Q_3=14

TTT=Time to thrombocytopenia; R/HBW=N for prospective study; H=N for historical control study; Q (i=1, 2, 3) denote quartiles.

Almost all eligible patients (98% HBW 023, 100% historical control) were on heparin/ heparinoid treatment prior to trial initiation. The most frequent observed types of thrombo-embolic complications (82% HBW 023 vs 89% historical, overall) were venous distal (77% HBW 023 vs 66% historical), pulmonary embolism (52% HBW 023 vs 44% historical), venous promial (50% HBW 023 vs 29% historical) and arterial peripheral (32% HBW 023 vs 21% historical). Median treatment duration was 10 days for A1 and 9 days for A2.

Summary of Sponsor's Efficacy Analysis Results & Reviewer's Comments

Table 3/Analysis Results of Combined & Separate Endpoints (TECs, Limb Amputations, or Death) After HAT Confirmation

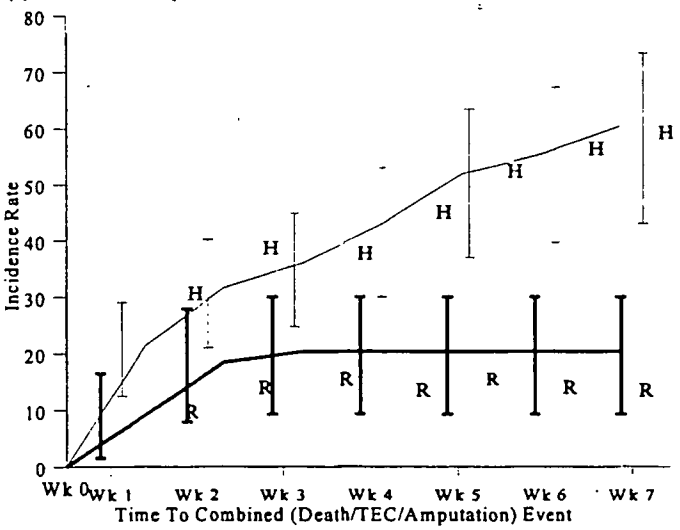
Endpoint/ Study	HBW 023 (R)	Historical (H)	Difference: R-H
Cumulative Combined Event Rate by Wk1, Wk3, Wk4, Wk6, Wk7*:	9.3, 20.4, 20.4, 20.4, 20.4	21.5, 36.1, 43.1, 52.0, 60.4	-12.2, -15.7, -22.7, -31.6, -40.0 **Log-rank 2p=.014** (Overall Curve)
Pre-specified Other Analyses			
Combined Amputation & Death by Wk1, Wk3, Wk4, Wk6, Wk7*:	1.9, 7.5, 7.5, 7.5, 7.5	4.5, 12.4, 17.4, 23.4, 36.2	-2.6, -4.9, -9.9, -15.9, -28.7 **Log-rank** 2p=.121 (Overall Curve)
Mortality Rate Estimates: by 3 Wks, 4 Wks, 7 Wks	5.6, 5.6, 5.6	6.2, 13.5, 25.0	-0.6, -7.9, -19.4 **Log-rank** 2p=.312 (Overall Curve)
New TEC Rate Estimates: by 1 Wk, 2 Wks, 3 Wks, 7 Wks	9.3, 13.0, 14.9, 14.9	19.2, 22.9, 26.0, 34.9	-9.9, -9-9, -11.1, -20.0 **Log-rank** 2p=.079 (Overall Curve)
Limb Amputation Rate Estimates: by 2 Wks, after 2 Wks	3.7, Unchanged	6.4, 14.6, Unchanged	-2.7, -10.9, ... **Log-rank** 2p=.386 (Overall Curve)

*: see Figures below for week by week comparisons; note, data are from Appendix II.5.1, II.5.5, and Tables C.26-C.2.9 of submission

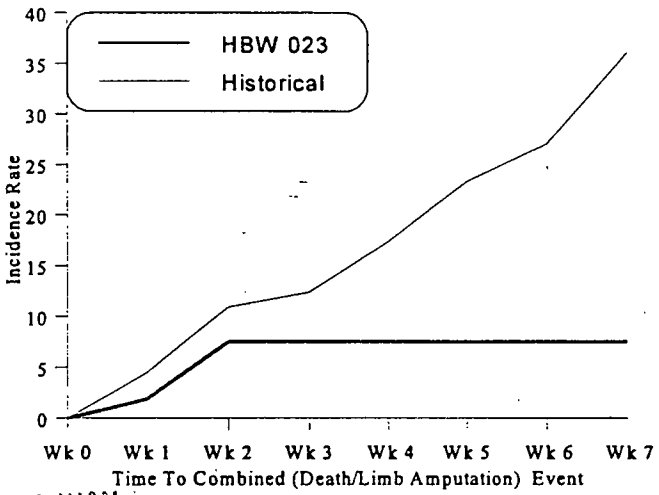
Reviewer's Comments

Sponsor's analysis results summarized in Table 3 above indicate that compared to the historical control group, patients treated with lepirudin experienced significantly less combined incidences of death or limb amputation or thromboembolic complications (TECs). These significant findings are supported by the clear separation of the graphical displays of combined event rates in the prospective study HBW 023 (R) versus the historical control study (H), and non-overlapping corresponding 95% confidence limits of the combined cumulative (Kaplan-Meier) estimates of the event rates after week 4 [see Figure (a) below]. This is further supported by the crude combined event rate estimates (see bottom of Table 4); the exact 2-sided p-value on the difference on event rates is .0104 with an absolute difference of 22.5% in favor of lepirudin; the 95% CI on the difference in proportion is (-.3897, -.0576). The pre-specified 20% expected combined event rate is contained in the 95% CI crude estimate for HBW 023 (10.6%, 33.5%), but not for the historical control group (32.5%, 53.7%). Also, all three components of the combined endpoints (mortality, limb amputations and TECs) show numerical benefit in favor of lepirudin (see bottom of Table 3).

(a) 95% CIs on Kaplan-Meier Cumulative Combined Incidence Rates



(b) Cumulative Combined Incidences After HAT Confirmation (Other Analysis)



Sponsor's hazard ratio (estimates) by Cox regression analysis result also indicate that patients in the prospective study experienced significantly less events than those in the historical group; the unadjusted and adjusted (for pre-specified prognostic factors such as TECs, age < or ≥65 years, sex, etc) hazard (or risk) ratios are respectively .443 and .439 with corresponding 2-sided p-values of .0119 and .0189; the corresponding 95% CIs are respectively (.225, .871) and (.211, .910).

As indicated earlier, this reviewer's analysis results indicate that there were significantly more 65 years and older patients in the historical control than in the prospective study group (Fisher's exact 2-sided p-value=.039). Table 4 below summarizes the results of gender and age subgroup analyses by this reviewer. The results in this table seem to indicate that there is

(an overall) age impact on the observed effectiveness result. Optimal treatment benefit is observed in the ≥ 65 years subgroup; 28% absolute treatment difference, 2-sided p-value=.033 (favoring the prospective study group), compared with a 17% absolute treatment difference, 2-sided p-value=.148 (favoring the prospective study group) for patients in the < 65 years old subgroup. Even though no imbalance was detected between males and females (Fisher's exact 2-sided p-value=.463), optimal refludan treatment benefit also appears to derive primarily from the female subgroup of patients; given the relatively small number of patients in these subgroups, these subgroup analysis results should be interpreted with caution.

It should be noted that in all analyses performed by sponsor and this reviewer, patients in HBW 023 prospective study group enjoyed at least a numerical advantage over those in the historical control group. This is indicated by the non-overlapping 95% CIs after week 4 (Figure (a) above) and the consistently left (of zero) skewed 95% CIs on the absolute difference (refludan - historical); see Table 4.

Table 4/Subgroup Analysis Results for Combined & Separate Events (TECs, Limb Amputations, or Death) by Reviewer

	HBW 023 (R)		Historical (H)		Difference (R-H)	
Combined Event	**Rate**	**95% CI on p**	**Rate**	**95% CI on p**	**Rate**	**95% CI on Difference**
Age <65 yrs	7/34 (.21)	[.09, .38]	15/40 (.38)	[.23, .54]	-.17	[-.41, .06]; 2p=.148
≥ 65 yrs	4/21 (.19)	[.06, .42]	24/51 (.47)	[.33, .62]	-.28	[-.52, -.02]; 2p=.033
Sex : Males	4/15 (.27)	[.08, .55]	14/32 (.44)	[.26, .62]	-.17	[-.49, .14]; 2p=.283
Females	7/39 (.18)	[.08, .34]	25/59 (.42)	[.30, .56]	-.24	[-.45, -.05]; 2p=.018
Overall Combined	**11/54 (.20)**	**[.11, .34]**	**39/91 (.43)**	**[.33, .54]**	**-.23**	**[-.39, -.06]; 2p=.010**
Deaths Only	3/54 (.06)	[.01, .15]	11/91 (.12)	[.06, .21]	-.06	[-.19, .09]; 2p=.372
Limb Amputations Only	2/54 (.04)	[.00, .13]	8/91 (.09)	[.04, .17]	-.05	[-.17, .07]; 2p=.452
TECs Only	8/54 (.15)	[.07, .27]	25/91 (.27)	[.19, .38]	-.12	[-.28, .03]; 2p=.126

Note: p_0=.20

Note that patient #1001 in center 10 (treatment regimen A1) had an event (limb amputation) but was excluded from the efficacy analyses due to missing platelet counts. The inclusion of this patient in the efficacy analyses, however, does not lead to a change in the direction of or conclusion based on observed statistical evidence; overall combined (crude) rate is 12/55 (22%) for HBW 023 vs 39/91 (44%) for historical control with a .0153 exact 2-sided p-value on absolute difference of 21%, and a 95% CI of (-37% , -4%).

Sponsor's analysis results also indicated that patients who entered the study with below normal platelet count (67% in treatment regimen A1 and 40% in treatment regimen A2) generally experienced a significant increase in their platelet count (≥107 G/l) during the treatment phase (71% in A1 and 100% in A2). The table below summaries these findings.

		Median Platelet Count			
Regimen	N	Baseline	Final	Difference	Wilcoxon 2p
A1	49	76.0	320	180	<.0001
A2	5	138.0	462	329	.0625

(an overall) age impact on the observed effectiveness result. Optimal treatment benefit is observed in the ≥ 65 years subgroup; 28% absolute treatment difference, 2-sided p-value=.033 (favoring the prospective study group), compared with a 17% absolute treatment difference, 2-sided p-value=.148 (favoring the prospective study group) for patients in the < 65 years old subgroup. Even though no imbalance was detected between males and females (Fisher's exact 2-sided p-value=.463), optimal refludan treatment benefit also appears to derive primarily from the female subgroup of patients; given the relatively small number of patients in these subgroups, these subgroup analysis results should be interpreted with caution.

It should be noted that in all analyses performed by sponsor and this reviewer, patients in HBW 023 prospective study group enjoyed at least a numerical advantage over those in the historical control group. This is indicated by the non-overlapping 95% CIs after week 4 (Figure (a) above) and the consistently left (of zero) skewed 95% CIs on the absolute difference (refludan - historical); see Table 4.

Table 4/Subgroup Analysis Results for Combined & Separate Events (TECs, Limb Amputations, or Death) by Reviewer

	HBW 023 (R)	Historical (H)	Difference (R-H)	
Combined Event	**Rate 95% CI on p**	**Rate 95% CI on p**	**Rate**	**95% CI on Difference**
Age <65 yrs	7/34 (.21) [.09, .38]	15/40 (.38) [.23, .54]	-.17	[-.41, .06]; 2p=.148
≥ 65 yrs	4/21 (.19) [.06, .42]	24/51 (.47) [.33, .62]	-.28	[-.52, -.02]; 2p=.033
Sex : Males	4/15 (.27) [.08, .55]	14/32 (.44) [.26, .62]	-.17	[-.49, .14]; 2p=.283
Females	7/39 (.18) [.08, .34]	25/59 (.42) [.30, .56]	-.24	[-.45, -.05]; 2p=.018
Overall Combined	**11/54 (.20) [.11, .34]**	**39/91 (.43) [.33, .54]**	**-.23**	**[-.39, -.06]; 2p=.010**
Deaths Only	3/54 (.06) [.01, .15]	11/91 (.12) [.06, .21]	-.06	[-.19, .09]; 2p=.372
Limb Amputations Only	2/54 (.04) [.00, .13]	8/91 (.09) [.04, .17]	-.05	[-.17, .07]; 2p=.452
TECs Only	8/54 (.15) [.07, .27]	25/91 (.27) [.19, .38]	-.12	[-.28, .03]; 2p=.126

Note: p_0=.20

Note that patient #1001 in center 10 (treatment regimen A1) had an event (limb amputation) but was excluded from the efficacy analyses due to missing platelet counts. The inclusion of this patient in the efficacy analyses, however, does not lead to a change in the direction of or conclusion based on observed statistical evidence; overall combined (crude) rate is 12/55 (22%) for HBW 023 vs 39/91 (44%) for historical control with a .0153 exact 2-sided p-value on absolute difference of 21%, and a 95% CI of (-37% , -4%).

Sponsor's analysis results also indicated that patients who entered the study with below normal platelet count (67% in treatment regimen A1 and 40% in treatment regimen A2) generally experienced a significant increase in their platelet count (≥107 G/l) during the treatment phase (71% in A1 and 100% in A2). The table below summaries these findings.

		Median Platelet Count			
Regimen	N	Baseline	Final	Difference	Wilcoxon 2p
A1	49	76.0	320	180	<.0001
A2	5	138.0	462	329	.0625

Summary of Safety Events

Overall, 18/56 (32%) bleeding events were reported (for treatment regimen A1 and A2). Seven (7/56=13%) of these were described as major and 15 (15/56=27%) were described as minor bleeds, respectively. Among major bleeds, none were males, 14% (=5/36) were 65 years old or younger and 22% (=2/9) were on thromboembolytic drug.

A total of 31/56 (=55%) adverse events (AEs) were reported among patients in treatment regimen A1 and A2; 19 of these were described as possibly drug related. Fifteen of the AEs (15/31=48%) were described as serious. Three deaths were reported (none considered drug related). For the historical control group, 10/91 (=11%) major bleeding events (hemorrhage and/or GI hemorrhage) were reported.

The minimum age requirement for entry into this trial is 18 years; the pediatric implication of this drug is therefore not clear.

OVERALL CONCLUSION

In this reviewer's assessment, the efficacy data in this single study submission provide adequate support for the claim of refludan (lepirudin) effectiveness in the treatment of heparin associated thrombocytopenia (HAT) type II patients.

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Concur:
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