CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:020807

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA No.:	20-807 AUG 1 0 1997
Sponsor:	Behringwerke AG AUG 1 9 1997
Drug:	HBW 023 (r-Hirudin, Lepirudin)
Class:	Antithrombin
Indications:	Treatment of immunologic type of heparin-associated thrombocytopenia (HAT type II or HAT-II)
Date of submission:	December 31, 1996
Date of Filing:	3-1-1997
Information Amendment:	May 13, 1997
Medical Reviewer:	Lilia Talarico, M.D.
Date of Review:	August 10, 1997

The Medical Review of NDA 20-807 will follow the outline described in the following Table of Content:

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Material reviewed: The clinical data of study B7 were provided in NDA vol. 1.1, 1.110-1.43, 1.55-1.70 of the NDA.

At the time of the submission of NDA 20-807, a second prospective study, (referred to as NR13), was ongoing in Germany. The preliminary results of this study were included in Section 8.VIII of vol.1.114 (Other Information) of the NDA. A follow-up was submitted on 4-30-1997 and the final report was submitted on 5-13-1997 in an Information Amendment. The clinical data of study NR13 were provided in NDA vol. 6.1-6.12.

I. INTRODUCTION AND BACKGROUND

Heparin-associated thrombocytopenia (HAT) is a complication of heparin therapy that occur in as many as 5% of patients receiving this drug. Two types of heparin-induced thrombocytopenia have been described: Type I (HAT-I) and Type II (HAT-II).
HAT-I is due to direct aggregation of platelets by heparin. The reduction in platelet counts is mild and not clinically significant. HAT-I occurs within the first few days of heparin therapy and resolves spontaneously despite continued heparin administration.
HAT-II occurs in of patients after days of heparin therapy and persists as long as heparin administration is continued. HAT-II is caused by an immune mechanism where the antigen consists of complexes of sulfated oligosaccharides (heparin) and platelet factor 4 (PF4). Several antibodies can bind to these antigens and form immune complexes which then bind to platelets via their Fc receptor (CD 32). Binding of immune complexes results in platelet activation, reduced platelet survival, and thrombocytopenia. HAT-II antibodies also activate endothelial cells by binding to endothelial heparin/heparan sulfate.

Contrary to other immune-mediated drug-induced thrombocytopenias which are associated with hemorrhagic events, HAT-II carries an increased risk of new thromboembolic complications (TEC) in as many as 30% of affected patients. In this patient population, TECs frequently result in severe disability, e.g., limb amputation in of cases, or even death in up to of patients. Bleeding events are less frequent than thrombotic complications, however, serious bleeding, including retroperitoneal hemorrhage, GI, intracerebral, and postoperative bleeding, has been described.

A recent review of 14 year experience of 127 HAT-II patients has recently been reviewed by T.E. Warkentin (American Journal of Medicine, vol 101: 502-507, Nov. 1996). In this review, 62 patients presented with isolated thrombocytopenia and 65 with thrombocytopenia and thrombosis. Both arterial and venous thromboses occurred (ratio 1:4); 26 patients with TECs had pulmonary emboli. A total of 51% of the patients presenting with isolated thrombocytopenia developed TECs over the subsequent 30 days despite discontinuation of heparin and recovery of thrombocytopenia. Institution of warfarin did not reduce the incidence of TECs. Mortality rates were similar in HAT-II

patients presenting with thrombosis (20%) or with isolated thrombocytopenia (21%).

HAT-II has been reported with the administration of any type of unfractionated heparin (UFH) and low molecular weight heparins (LMWH). The incidence of thrombocytopenia appears to be higher with bovine heparin as compared to porcine heparin . HAT-II can occur after i.v. and s.c. heparin administration, and even very low amounts of heparin, such as those used for flushing i.v. catheters or coating pulmonary catheters, may induce HAT-II. HAT-II and new TECs have occurred in patients receiving heparin for therapy of established thromboses as well as in patients receiving heparin for thromboprophylaxis of arterial or venous thromboses associated with high risk medical or surgical conditions.

Immune-mediated heparin-induced thrombocytopenia resolves upon discontinuation of heparin administration, however, for patients with HAT-II and TECs who require anticoagulant therapy, no alternate treatment is presently available. Low Molecular Weight Heparins (LMWH) cross-react with heparin antibody at rates that approaches Unfractionated Heparin (UFH). Danaparoid is a low sulfated heparinoid with a lower cross-reactivity with heparin antibody . However, the efficacy and safety of this compound in HAT-II have not been fully evaluated.

Hirudin is a 65 amino acid polypeptide naturally produced by the salivary gland of the medicinal leech (hirudo medicinalis). Hirudin is a direct and specific thrombin inhibitor. Unlike heparin, hirudin acts independently of cofactors such as AT-III, is not inactivated by platelet factor 4 (PF4) and therefore is more effective in the presence of platelet-rich thrombi than UFH, and, unlike UFH, it can inhibit clot-bound thrombin. Hirudin does not cross-react with anti-heparin antibodies.

HBW 023 is a recombinant hirudin (r-hirudin) produced from yeast cells (Saccharomyces cerevisiae) HBW 023 has a MW of about 7,000 Dalton and has inhibition constant for

thrombin in the picomolar range. After intravenous administration, the mean terminal half-life (T1/2 β) of HBW 023 is approximately one hour. The elimination of r-hirudin occurs mainly via the kidneys; about 50% of the activity is excreted in urine.

HBW 023 has been studied in more than 1000 patients in Phase II and Phase III clinical trials as adjunctive anticoagulation to thrombolysis for acute myocardial infarction (AMI), for therapy of unstable angina pectoris (UA), for prevention of recurrent ischemia after PTCA, for therapy of DVT, and for prevention of clotting in the hemodialysis circuit. Adverse events associated with HBW 023 treatment are: 1) bleeding (secondary to its anticoagulant effect), and, 2) allergic reactions (HBW 023 is a heterologous protein and thus, potentially immunogenic in man). Excessive bleeding has occurred particularly in patients receiving HBW 023 and concomitant thrombolytic and antiplatelet drugs.

Because of its documented anticoagulant activity and because of the lack of cross-reactivity with anti-heparin antibodies, HBW 023 has been evaluated in HAT-II patients who require immediate anticoagulation and for whom heparin or LMWH are contra-indicated. Clinical trials conducted by Behringwerke AG in Germany have evaluated HBW 023 in: 1) "Acute HAT-II" which includes patients presenting with thrombocytopenia (with or without associated new TECs) developed while on heparin therapy, and, 2) "Latent HAT-II" which includes patients with history of HAT-II, not currently thrombocytopenic, but in need of prophylactic anticoagulant therapy.

A clinical trial of HBW 023 (Study B7) was completed in Germany by Behringwerke in July 1995 to be submitted as an NDA for the approval of HBW 023 in the treatment of HAT-II patients requiring immediate anticoagulant therapy.

The study included 82 patients with HAT-II. The patients were enrolled in four groups: Group A1 included 51 patients with ongoing thrombosis; Group A2 included 5 patients with ongoing thrombosis receiving thrombolytic therapy; Group B included 18 patients with isolated thrombocytopenia; and Group C included 8 patients with "latent" HAT-II undergoing cardiopulmonary bypass (CPB) surgery.
All patients enrolled in the study were treated with HBW 023 because assignment to a placebo control was deemed unethical given the severity of HAT-II and the lack of active therapy for comparison.

The primary efficacy endpoints in study B7 were: 1) resolution of thrombocytopenia or maintenance of normal platelet counts, and 2) achievement and maintenance of adequate anticoagulation during treatment with HBW 023. Secondary endpoints were the incidence rates of recurrent or new TEC, limb amputation (due to TECs), and death due to any cause.

At a pre-NDA meeting with Behringwerke representatives on 4-11-1996, the Agency informed the sponsor that the protocol-specified primary endpoints were surrogate endpoints which did not necessarily reflect the clinical benefit of the treatment. The Agency, therefore, recommended that the clinical outcome of HAT-II study patients should be the primary objective of the study. Since all study patients had been treated with HBW 023, it was agreed that the clinical outcome HAT-II patients in study B7 could be compared with an historical control group consisting of patients HAT-II and TECs selected from a registry of patients treated according to individual hospital practice. Furthermore, it was also recommended that the efficacy comparison should focus on the group of patients with HAT-II and ongoing thrombosis which was either present at baseline as indication for heparin therapy or had developed during heparin therapy (Treatment regimen A1 and A2). The patients studied in the other subgroups, namely patients with isolated thrombocytopenia and latent HAT-II patients undergoing CPB surgery (treatment regimen B and C), were too few for meaningful analyses.

NDA 20-807 was submitted on 12-31-1996 for the approval of HBW 023 for anticoagulant therapy of HAT-II patients.
Due to the severity of the indication and lack of available therapy for HAT-II, NDA 20-807 was filed as Priority NDA.
At the time of the submission of NDA 20-807, a second prospective study, (referred to as NR13), was ongoing in Germany.
Preliminary results were included in the NDA submission and the final report of study NR13 was submitted on 5-13-1997.

Both studies were comparable for study design, primary and secondary objectives and treatment regimens. In each study the treated patients were compared to the same historical control.

All patients included in the two clinical trials were identified from the patients listings and tabulations. No discrepancies were detected for patients assignments and all efficacy or safety outcomes for each patient reported in the NDA were validated. The tables included in this review were either reproduced from the NDA or generated from the data provided in the study reports.

II) STUDY PROTOCOL

II.A. SUMMARY OF THE STUDY PROTOCOL

The same study protocol, including study design, primary and secondary objectives, treatment regimens, general study outline and organization was followed for the two prospective studies:

- STUDY HBW 023/7D-301WC (REFERRED TO AS STUDY B7)
- STUDY HBW 023/7MN-301WC (REFERRED TO AS STUDY NR 13)

Title of Studies: HBW 023(recombinant hirudin) for treatment of immunologic type of heparin-associated thrombocytopenia (HAT-II)

Principal Investigator: Prof. Dr. A. Greinacher

Study Design: Both studies were open, uncontrolled, prospective, multicenter trials conducted in Germany. Study B7 was conducted at 54 centers between March 1994 and July 1995. Study NR13 was conducted at 46 centers between July 1995 and April 1996.

The **primary objective** of the studies was to demonstrate that treatment of HAT-II patients with iv HBW 023 resulted in a clinically relevant increase in platelets counts or in the maintenance of normal baseline platelet counts, while providing effective anticoagulation.

The **secondary objectives** of the studies were to assess the efficacy and the safety of HBW 023 on the clinical endpoints of arterial or venous thromboembolic complications (TECs), major bleeding complications, surgical interventions/limb amputations, and death in patients with HAT-II.

In both studies, there were two groups of HAT-II patients:

> Group 1 (Acute HAT): Patients with a drop in platelet count occurring during heparin therapy to a value <100 G/l or by ≥ 30% of their baseline value prior to heparin therapy.
>
> Group 2 ("Latent" HAT): Patients with normal platelet count (>100 G/l) but with a known prior history of HAT, who were scheduled for a medical intervention necessitating parenteral anticoagulation.

Study medication and Dosage Regimen: INN: Lepirudin (proposed)
Drug Formulation: HBW 023 (Leu^1-Thr2-63-desulfohirudin) lyophilisate (50 mg/vial) for iv injection dissolved in 0.9% NaCl or water for injection.
HBW 023 Batch no. 17, 26, 27, 31, 030011, 115011 were used in Study B7. Thirty (30) patients were treated with HBW 023 derived from an upscaled production procedure.
HBW 023 Batch no. 119011 was used in Study NR13.
The following treatment regimens were used for the studies:

Treatment regimen A:

A1: treatment of HAT-II patients with arterial or venous TEC not receiving concomitant thrombolytics:
- initial i.v. bolus: 0.4mg/kg bw
- continuous infusion: 0.15 mg/kg/h for 2-10 days

A2: treatment of HAT-II patients with arterial or venous TECs receiving concomitant thrombolytics:
- initial i.v. bolus: 0.2 mg/kg b.w.
- continuous infusion of 0.1 mg/kg/h for 2-10 days

Treatment regimen B: prophylaxis of arterial or venous Thromboembolism:
- continuous infusion: 0.1 mg/kg b.w./h, 2-10 days

Treatment regimen C: anticoagulation during cardiopulmonary bypass (CPB):
- priming of Heart-Lung Machine: 0.2 mg/kg b.w.;
- initial i.v. bolus of 0.25 mg/kg b.w.;
- additional boluses: 5 mg (ECT >250" or ACT >350")

Dosage regimen were modified to maintain the patient's aPTT values

The treatment period was 2-10 days for regimens A and B. Therapy could be extended or repeated if clinically indicated.
In regimen C, treatment was limited to the duration of CPB, however, patients could be switched to regimen B if necessary.

HBW 023 was gradually reduced after starting oral anticoagulant (e.g., Marcumar; phenprocoumon or Coumadin) in patients requiring prolonged anticoagulation. The aPTT was maintained >1.5-fold baseline until the INR exceeded 2.5 (PT <50%) and HBW 023 could then be stopped.

The follow-up period was completed on Day 24 or two weeks after the end of HBW 023 therapy.

Study populations: In the two prospective studies B7 and NR13, all patients with laboratory or clinical diagnosis of HAT-II and a definite need for parenteral antithrombotic therapy were eligible for enrollment. No placebo or active control were used because of ethical considerations and lack of approved regimen.

Primary efficacy criteria: The primary efficacy criteria were the proportions of responders. A patient was considered to be a responder if both of the following criteria were fulfilled:

- The platelet counts increased or remained stable, depending on the indication group. In acute HAT-II (drop in platelet count during heparin therapy below 100 G/l or by ≥ 30% of their baseline value prior to heparin therapy), the platelet counts had to increase by at least 30% of the nadir value to a value >100 G/l on Day 10. In latent HAT-II (normal platelet count, i.e. ≥ 100 G/l, and prior history of HAT-II), the platelet counts had to be >100 G/l on Day 3 and 10.

- Effective anticoagulation during antithrombotic therapy with HBW 023 (until discontinuation of HBW 023 or initiation of alternative anticoagulation). For regimens A and B, the aPTT values were to be maintained >1.5-fold reference aPTT value, with a maximum of two dose adjustments for low aPTT values.
  For regimen C, the Ecarin clotting time (ECT) was to be maintained >250" during CPB. If required, additional boluses of HBW 023 could be administered during CPB.

Secondary efficacy criteria (clinical endpoints): The secondary efficacy criteria in both prospective studies (B7 and NR13) consisted of:

- Prevention of clinical endpoints, namely death, limb amputation and new thromboembolic complications.

Safety Evaluation: In both prospective studies, all patients were observed for adverse events. Evaluation of clinical variables and laboratory parameters were performed throughout the study period. Allergic reactions, bleeding events, arterial or venous TECs, surgical interventions and amputations, and deaths were documented in CRFs. Laboratory assessments included CBC, platelet count, serum creatinine, coagulation parameters PTT, PT (% activity relative to a normal plasma pool), thrombin-antithrombin III complex (TAT), prothrombin fragments F1.2) HBW 023 plasma level, thrombin-hirudin complex (THC), antibodies against hirudin, and anti-Xa activity (heparin/heparinoid).

Statistical Methods: A minimum response rate in platelet recovery of 20% was defined for evaluations of efficacy. A one-sided binominal test at a 5% level of significance was used to test whether the proportion of responders exceeded the prespecified limit of 20%. A two-sided 95% CI for the proportion of responders was calculated.

Analyses were performed on the "Per Protocol" and on the "Safety" populations. The Per-protocol population consisted of all patients who received at least 2 days of therapy with HBW 023 (except regimen C which was limited to the duration of CPB) and who were followed for at least 7 days. The "per-protocol" population was only used for the primary efficacy analysis. No center-specific analyses were performed due to the limited number of patients enrolled in most of the centers. The Safety population consisted of all patients who received at least one dose of HBW 023.

The following characteristics were used to describe the patient population:

- indication group, treatment regimen, underlying and/or concomitant diseases
- demographic
- baseline aPTT value and platelet count
- time to detection of thrombocytopenia, nadir of platelet count
- thromboembolic complications prior to start of HBW 023 treatment
- prior therapy with heparin/heparinoids, oral anticoagulants, and thrombolytics

Exploratory analyses: The average rates of combined endpoint (new TECs, limb amputations, or deaths) and individual endpoints during HBW 023 treatment were descriptively compared with average rates before HBW 023 treatment (after diagnosis of HAT,) and after HBW 023 treatment. The average event rate for a period was defined as:

$$\text{Average event rate in}_{\text{period}} = \frac{\text{total No. of events in period}_i}{\text{No. of patient days in period}_i}$$

Cumulative incidences of clinical events were estimated using the Kaplan-Meier method. Comparisons between the HBW 023 group and the historical control group were performed by means of log-rank tests and Wilcoxon tests. Incidences of the combined endpoint (TEC, amputations, and deaths) were subjected to a Cox regression analysis.

II.B. PROTOCOL AMENDMENTS

Amendment No. 1 (8-18-94) provided for 1) modification of treatment regimen for patients in regimen A2 receiving concomitant thrombolytics,
2) modification of aPTT target range
3) modification of document requirements

Amendment No.2 (12-7-1994) provided for 1) recruitment of additional patients to increase safety information, 2) use of upscaled HBW 023 production, 3) modifications of documentation and monitoring procedures, new location of principal investigator.

Amendment No.3 (2-14-1995) provided for: 1) the comparison with a historical control population to strengthen the assessment of the clinical data derived from the prospective trials, 2) the introduction of additional case report forms (CRFs) for documentation of surgical interventions.

II.C. HISTORICAL CONTROL

The historical control consisted of patients with confirmed HAT-II and thrombosis who were treated according to individual hospital practice. In each patient, the laboratory diagnosis of HAT was made by the Principal Investigator

The historical controls were selected from three registries of 182 patients with clinical information available beyond the date of laboratory diagnosis of HAT-II:

a) A registry of 147 consecutive cases between the end of 1989 and 1993 established by the Principal Investigator. Prof. Greinacher. at the Justus-Liebig University, Gielbe,
b) Twenty consecutive cases collected by Prof. Breithaupt, Justus-Liebig University. Giessen,
c) Fifteen consecutive cases collected by Dr. Randerath and Dr. Smeets, St.Bernhard Hospital, Kamp-Lintfolt.

Exclusion criteria for the historical control patients were: age <18 years, missing date of laboratory diagnosis of HAT-II, time between clinical and laboratory diagnosis of HAT-II greater than 21 days, and cardiopulmonary bypass (CPB) during the observation period.

In the prospective studies, all patients with ongoing thrombosis who received HBW 023 (treatment regimens A1 and A2) were eligible for comparison with the historical control for clinical events. The response criteria that were compared to the historical controls were:
- combined and individual rates of death, limb amputations, and new thromboembolic complications (TEC),
- rate of bleedings since confirmation of HAT-II diagnosis.

As secondary objective, the individual incidences of new TECs, limb amputations, and deaths in patients from the prospective studies and

from the historical group were also compared.

The data from the historical control were documented from the initiation of the heparin treatment under which HAT-II was diagnosed. The starting point of the observational period for the historical control group was chosen as the date of laboratory confirmation of HAT-II. However, all clinical events occurring on the day of HAT-II confirmation in the historical control were conservatively excluded since it could not be determined whether they had occurred before or after the laboratory confirmation of the diagnosis. The maximum length of the observation period for the historical control group was defined as 60 days from laboratory confirmation of HAT-II.

While the observation period for the primary efficacy in the prospective studies extended from the initiation of treatment with HBW 023 to Day 24 (or 14 days after end of HBW 023 treatment), the date of laboratory confirmation of HAT-II was selected as a comparable starting point for the comparison of clinical events with historical control. To account for differences in the lengths of observation periods, time-to-event analyses were performed.

Variables that were compared to the historical group included: demographic (age, gender); indication for heparin therapy; heparin regimen; platelet counts; TECs present prior to the start of observation period; and rates of clinical events during the study.

Cumulative incidences of combined endpoints were estimated using the K-M product-limit method. The historical control was compared to the HBW 023 groups for combined and individual endpoints by log-rank test.

Exploratory analyses included the analysis of combined efficacy endpoint of limb amputations and deaths, and the analysis according to first selected treatment after laboratory confirmation of HAT.

In the historical control, bleeding events were not recorded as consistently as in the prospective studies. Three definitions of bleeding were used in the historical control: documented bleeding, bleeding or transfusions, and bleeding requiring transfusion. For each of the three definitions, cumulative incidences were estimated using the K-M method. Time to bleeding was compared between HBW 023 groups and the historical control using the log-rank test.

III. CLINICAL TRIALS

III.A. STUDY B7

III.A.1. STUDY REPORT

Study Size: This prospective study was designed to show that the proportion of patients who achieved the primary objective (adequate anticoagulation and improvement or stability of platelet counts) exceeded 20%. With a true response rate of 40%, a sample size of 42 patients was needed for statistical significance (one-sided α=5%, β=90%). At least 50 patients had to be enrolled to allow for 15% drop-outs. The sample size was increased to 80 patients to enhance the safety evaluation.

Disposition of Patients: From March 1994 to July 1995, a total of 82 patients were enrolled in study B7. Each patient was assigned to one of four treatment regimens:

A1	(HBW 023 treatment without thrombolysis)	51 patients
A2	(HBW 023 treatment plus thrombolysis)	5 patients
B	(Thrombo-prophylaxis with HBW 023)	18 patients
C	(cardiopulmonary bypass with HBW 023)	8 patients

The patients' **Demographic and Background Characteristics** are summarized in the following table.

Demographic and background characteristics

	A1 N=51 (%)	A2 N=5 (%)	B N=18 (%)	C N=8 (%)
Sex				
Male	16 (31)	1 (20)	9 (50)	4 (50)
Female	35 (69)	4 (80)	9 (50)	4 (50)
Age				
median	60	41	61	72
range				
Underlying Disease				
Medical	24 (47)	4 (80)	12 (67)	2 (25)
Orthopedic	12 (24)	0	1 (6)	1 (13)
Trauma	4 (8)	0	0	0
Cardiovascular	1 (2)	0	2 (11)	7 (88)
Other	13 (25)	1 (20)	3 (17)	0
Laboratory Confirmation				
Acute HAT	47 (92)	4 (80)	13 (72)	2 (25)
Latent HAT	4 (8)	1 (20)	5 (28)	6 (75)

The median platelet count prior to the start of the reference heparin treatment, documented for 62 of the 66 patients with acute HAT-II, was 228 G/l (range 102 G/l- 903 G/l). The median nadir of platelets prior

to initiation of study treatment, available for 65 of the 66 acute HAT-II patients, was 31 G/l

The median time to detection of thrombocytopenia in the 82 patients was 10 days after start of heparin treatment.

The median baseline platelet count prior to the start of HBW 023 treatment was 71 G/l for patients with acute HAT and 194 G/l for patients with latent HAT-II.

All 56 patients in treatment regimens A1 and A2 had at least one TEC prior to start of HBW 023; 46 of the 56 patients (82.1%) experienced at least one TEC during heparin therapy. In the remaining 10 patients, TECs had either occurred before onset of heparin treatment (heparin indication) or during a heparin treatment break.

The most frequently observed TECs in the 56 patients in treatment regimens A-1 and A-2 are showed in the following table:

Types of TECs prior to start of study treatment (Treatment regimens A1 and A2)

Types of TECs	Patients with TECs N (%)	Patients with TECs Due to heparin N (%)
Cardiac	1 (1.8)	1 (1.8)
Arterial: cerebral	1 (1.8)	1 (1.8)
: coronary	2 (3.6)	2 (3.6)
: aortic	3 (5.4)	3 (5.4)
: iliac	4 (7.1)	4 (7.1)
: peripheral	14 (25.0)	13 (23.3)
Distal DVT	39 (69.6)	27 (48.2)
Proximal DVT	27 (48.2)	21 (37.5)
Pulmonary Embolism	28 (50.0)	20 (35.7)
Arterial-peripheral	14 (25.0)	13 (23.2)

Of the 18 patients in treatment regimen B, four (22.2%) had developed thromboembolic complications between the start of heparin treatment and the start of study treatment (# 2801, 3201, 3205, and 3903).

Forty-one patients (50.0%) had received exclusively unfractionated heparin (UFH) before initiation of study treatment; 33 of the remaining patients (40.2%) had received UFH and an additional heparin/heparinoid; the recent heparin treatment was not specified for six patients (7.3%).

Oral anticoagulation or platelet inhibitors were administered to 14 patients (17.1%) prior to the start of study treatment; nine (11.0%) of these patients received phenprocoumon and five (6.1%) received ASA. Nine (11.0%) patients received thrombolytics before entering the study.

The antithrombotic regimens used prior to HBW 023 therapy are summarized in the following table.

Treatment Regimen	Anticoagulants and antiplatelets administered prior to Study Treatment													
	None		UFH		Orgaran		UFH+LMWH		UFH+LMWH +Orgaran		ASA		Phen-procum	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
A-1 n=51	-	-	28	55	1	2	7	14	12	24	4	8	4	8
A-2 n= 5	-	-	3	60	-	-	-	-	2	40	-	-	1	20
B n=18	1	6	8	44	1	6	2	11	5	28	1	6	2	11
C n= 8	5	63	2	25	-	-	-	-	-	-	-	-	2	25
Total n=82	6	7	41	50	2	2	9	11	19	23	5	6	9	11

Concomitant illnesses and medication: The most frequently documented concomitant conditions were:

circulatory, mainly TECs and hypertension:	98.8%
endocrine, nutritional and metabolic (mainly DM):	37.8%
surgery, musculoskeletal system:	24.4%
surgery, cardiovascular system:	24.4%
respiratory system", mainly pneumonia	24.4%

All patients had multiple concomitant illnesses at study entry. All patients received concomitant medication during the study period, including antibiotics, analgesics, cardiac drugs, diuretics. Sixty-six patients (80.5%) received phenprocoumon during the study period; 4 patients (A1) also received thrombolytic treatment.

Protocol Violations: The protocol violations that occurred in 38 patients are summarized in the following table:

	Treatment Regimen			
	A1 N=51 (%)	A2 N=5 (%)	B N=18 (%)	C N=8 (%)
Inclusion/Exclusion Criteria:				
No Laboratory Diagnosis of HAT:	0	0	1 (6)	1 (13)
Delayed laboratory diagnosis	7 (14)	0	0	0
No Informed Consent	1 (2)	0	0	0
Study Treatment:				
Dosage Errors (high or low):	14 (27)	2 (40)	2 (11)	2 (25)
Treatment interruption:	1 (2)	0	0	
Treatment error prior/post CPB	0	0	0	5 (62)
Incomplete data	1 (2)	0	0	0
Measuring Times				
Day 10 Platelet count missing	0	0	1 (6)	0

Patient Discontinuations: Eight of the 82 patients (9.8%), discontinued treatment with HBW 023 prematurely because of a non-fatal adverse event (four), death/fatal adverse event (three), and planned colonoscopy (one). One of five patients who received a second treatment course discontinued the study drug prematurely due to hepatic insufficiency.

In 36 patients (43.9%), anticoagulation with HBW 023 was continued for more than 10 days due to overlapping anticoagulation with HBW 023 and phenprocoumon, ongoing immobilization of the patient, diagnostic or therapeutic interventions, continuing TEC, postoperative prophylactic anticoagulation, and adjuvant therapy to thrombolysis.

The median duration of treatment with HBW 023 was 10 days in treatment regimen A1 , 9 days in treatment regimen A2 15 days in treatment regimen B and 9 days in treatment regimen C . Seven patients in treatment C were switched to treatment B after cardiac surgery.

Missing Laboratory Tests Measurements: Patients with missing baseline values were excluded from the analysis of the specific laboratory parameters. The Day 10 platelet count was not available for 2 patients in treatment regimen B.

Baseline hematology data were not available for 2 patients in regimen A1 and for 1 patient in regimen C.
Baseline creatinine was not available for 8 patients in regimen A1, 3 patients in regimen A2, 1 patient in regimen B, and 2 patients in regimen C.

Baseline coagulation tests were missing for 1 patient in AI. Baseline TAT and F1+2 were missing for 12 patients in A1, 3 in B, and 3 in C. Baseline Hirudin and THC levels were missing for 12 patients in A1 and 2 patients in regimen B.

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III.A.2. PRIMARY EFFICACY: ANTICOAGULANT EFFECT AND EFFECT ON PLATELETS

Primary efficacy analyses were based on the time courses of platelets and aPTT for regimen AI, A2 and B, and on the time course of ECT for regimen C. Secondary efficacy analyses were based on clinical data (new TECs, limb amputations, and death).
Second treatment courses with HBW 023 were not subjected to efficacy analyses.

Number of patients included in analyses: The numbers of patients evaluable for efficacy analyses are summarized in the following table:

Evalualble patients

	Treatment regimen				
	A1	A2	B	C	Total
Number of patients enrolled	51	5	18	8	82
Primary efficacy evaluation (per protocol)	50	5	16	8	79
Secondary efficacy evaluation	51	5	18	8	82
Safety population	51	5	18	8	82

Three patients were excluded from primary efficacy evaluation because of missing platelet count at nadir or at Day 10. One of these patients received less than 48 hours of study medication because of a fatal adverse event.

All patients in group A1 are included in the secondary efficacy analysis of clinical events. The proportions of responders for primary efficacy criteria in each regimen are shown in the following table.

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Primary efficacy analysis-Proportion of responders

		Responders			
Treatment Regimen	Evaluable patients	Platelets N (%)	Anticoagulation N (%)	Combined N (%)	95%CI
A1	50	45 (90.0)	42 (84.0)	37 (74.0)	59.7-85.4
A2	5	5 (100)	3 (60.0)	3 (60.0)	14.7-94.7
B1	16	14 (87.5)	9 (56.3)	7 (43.8)	19.8-70.1
C	8	4 (50.0)	7 (87.5)	4 (50.0)	15.7-84.3
Total	79	68 (86.1)	61 (77.2)	51 (64.6)	53.0-75.0

The proportion of responders for platelet alone was 86.1%, while 77.2% achieved effective anticoagulation. The total proportion of responders (64.6%) was significantly greater than the prespecified 20% ($p<0.0001$). Most patients had discontinued heparin for at least 1 day, and 24 patients had received Orgaran for 2 days or longer prior to starting HBW 023.

Eighteen patients did not achieve effective anticoagulation, presumably due to inadequate dosing, inadequate dose adjustment, safety reasons, diagnostic procedure; excessive dose increases, insufficient aPTT prolongation despite dose increases. Seven (87.5%) of 8 patients in regimen C fulfilled the criteria of effective anticoagulation during CPB as assessed by the Ecarin Clotting Time (ECT).

For acute HAT-TT patients (regimens A1, A2 and B), the median platelet count increased during the first 7 days of therapy with HBW 023 to about 4-fold baseline value. Recovery of thrombocytopenia (platelet count >100.000/cmm) began after discontinuation of heparin; in fact, the platelet count had already improved in 20 of 62 patients with acute HAT-II at the time of initiation of HBW 023 therapy .
For latent HAT patients with normal platelet counts at baseline, median platelet count remained nearly constant during the first 10 days of treatment.

The time courses of platelets counts and aPTT are displayed in Figures B.2 and B9 (NDA v.1.114, p.5 and 15).

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Figure B.2: Time course of platelet count – acute HAT, median and quartiles by treatment regimen
2. linear scale
(cf. Table B.5.12, App. I.9, III.17)

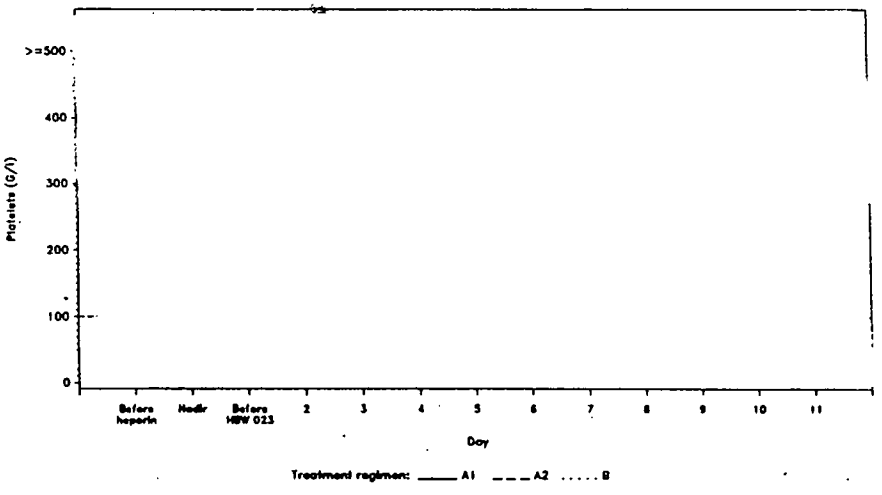

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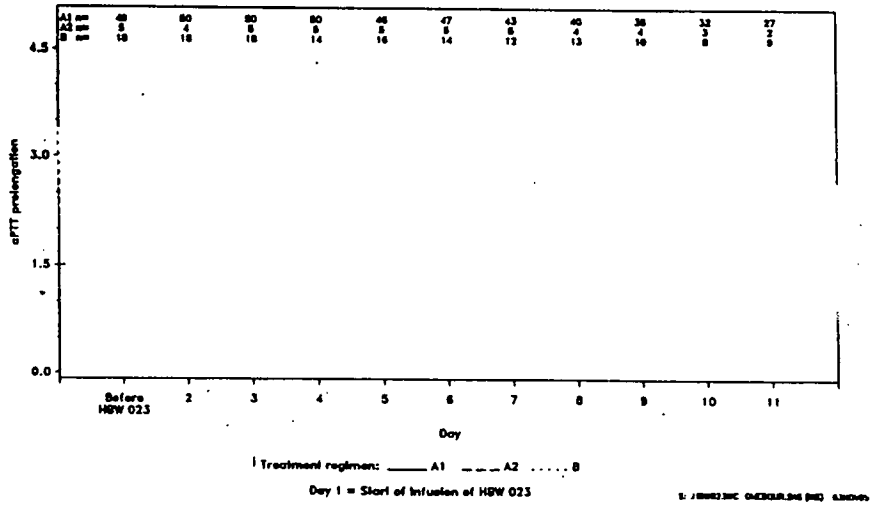
Figure B.9: Time course of aPTT prolongation, median and quartiles by treatment regimen
2. linear scale
(cf. App. I.1, I.8, III.16a)



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III.A.3. SECONDARY EFFICACY: CLINICAL EVENTS

Deaths, surgical interventions and new thromboembolic complications during the study period: The incidences of individual events and the combined incidences of deaths, limb amputations and new thromboembolic complications during the study period are summarized in the following table.

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Overall incidence of deaths, limp amputations, and new TECs (n=82)

Event	Patients with Events*		Time of First Occurrence					
			During HBW023		After HBW 023		Not assessable	
	N	%	N	%	N	%	N	%
Death	6	7.3	1	1.2	5	6.1	0	0
New TECs	8	9.8	2	2.4	5	6.1	1	1.2
Amputation	3	3.7	3	3.7	0	0.0	0	0.0
Combined	15	18.3	6	7.3	8	9.8	1	1.2

*Patients may have had more than one event.

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Two patients died of heart failure, 2 of sepsis, and 1 of multiorgan failure. One patient who died from heart failure on study day 16 had thrombosis of the jugular vein, SVC, and PE at autopsy.

The new TECs observed during the study period were arterial-peripheral in 4 cases, PE in 2 cases, proximal/distal DVT in 2 cases, and proximal DVT in 1 case. Two new arterial-peripheral TECs occurred during the treatment period.
In addition to three limb amputations, 16 patients (19.5%) underwent other surgical interventions.

The combined incidence of death, limb amputation, and new TECs by treatment regimen is summarized in the following table.

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Combined incidence of deaths, limb amputations, and new TEC

Treatment Regimen		Patients with Events*		Time of First Occurrence					
				During HBW023		After HBW 023		Not assessable	
		N	%	N	%	N	%	N	%
A1	n=51	7	13.7	3	5.9	4	7.8	0	0.0
A2	n= 5	0	0.0	0	0.0	0	0.0	0	0.0
B	n=18	8	44.4	3	16.7	4	22.2	1	5.6
C	n= 8	0	0.0	0	0,0	0	0.0	0	0.0
Total	n=82	15	18.3	6	7.3	8	9.8	1	1.2

*Patients may have had more than one event.

The rates of events were assessed in relation to treatment with HBW 023. The average event rates per patient day were calculated taking into account the length of the observation periods. The first period began with laboratory confirmation of HAT and continued until the start of study treatment. The overall rates of each clinical endpoints and of the combined endpoints are summarized in the following table:

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Average event rates per patient day period

Event	Number of evaluable pts.	Average event rate per patient day		
		Before HBW 023	During HBW 023	After HBW 023
Death	79	0,000	0.001	0.005
New TEC	78	0.034	0.002	0.005
Limb Amputation	79	0.005	0.003	0.000
Combined	78	0.039	0.006	0.008

The average combined event rates per day, by period and treatment regimen, are presented in the following table.

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Average event rates per patient day period and treatment

Treatment Regimen	Number of evaluable pts.	Average event rate per patient day		
		Before HBW 023	During HBW 023	After HBW 023
A1	51	0,079	0.005	0.007
A2	5	0.000	0.000	0.000
B	18	0.048	0.010	0.017
C	8	0.000	0.000	0.000
Total	82	0.039	0.006	0.008

Six patients (7.3%) died during the study period, one (1.2%) during treatment with HBW 023. Eight patients (9.8%) experienced a new TEC during the study, two of them (2.4%) on study treatment. Three patients (3.7%) underwent limb amputation during study treatment.

The combined incidence for TECs, amputations, and deaths) was 18.3% during the entire study period and 7.3% during the treatment period.

In treatment regimens A2 and C, no new TECs, limb amputations, or deaths were observed during the study. The average combined event rate per patient day in treatment regimen B was roughly two times higher than in regimen A1 during the treatment period; however, the number of patients in group B was small.

III.A.4. SAFETY ANALYSES

Safety analyses included all patients enrolled in the study, from the initiation of study medication to the end of follow up, including second treatment cycles. Only first treatment cycles were subjected to detailed laboratory analyses.

ADVERSE EVENTS: The overall incidence of bleeding and non-bleeding adverse events observed in the patient population of study B7 is summarized in the following table.

Number of patients with adverse events in prospective study

	A1 n(%)	A2 n(%)	B n(%)	C n(%)	Total n(%)
Patients Treated	51(100)	5(100)	18(100)	8(100)	82(100)
Adverse Events (AE)[2]	28(55)	3(60)	14(78)	3(38)	48(59)
Possibly related AE	19(37)	2(40)	5(28)	1(13)	27(33)
Bleeding Events[3]	17(33)	1(20)	6(33)	3(38)	27(33)
Serious AE (SAE)	13(25)	2(40)	9(50)	2(25)	26(32)
Fatal SAE	3(6)	--	3(17)	--	6(7)
.Heart Failure	1(2)	--	1(6)	--	2(2)
.Sepsis	1(2)	--	1(6)	--	2(2)
.Multiorgan Failure	1(2)	--	--	--	1(1)
.Heart Failure and TEC	--	--	1(6)	--	1(1)
Non-fatal SAE[4]	11(22)	2(40)	8(44)	2(25)	23(28)
.Major Bleeding	7(14)	--	2(11)	2(25)	11(13)
.TEC	3(6)	--	5(28)	--	8(10)
.Allergic Reaction	1(2)	1(20)	--	--	2(2)
.Kidney Failure	--	--	2(11)	--	2(2)
.Infection	1(2)	--	1(6)	--	2(2)
.PVD	1(2)	1(20)	--	--	2(2)

[1] A patient may have suffered more than one event
[2] Including serious adverse events
[3] Including major bleeding
[4] Occurring in more than one patient

SAE that were considered by the investigator to be possibly related were minor bleedings (seven patients), allergic reactions (two), superimposed infections (one), and arterial thrombosis (one). None of the fatal adverse events were considered to be possibly related to HBW 023 treatment or involved drug toxicity.

Bleeding events: Twenty-seven patients (32.9%) experienced at least one bleeding event during the study. Eleven patients (13.4%) had a total of 15 major bleeding events. Two patients had four and two major bleeding events respectively.
A total of 27 minor bleedings were reported in 22 patients. The most

frequent events were isolated drop in hemoglobin (seven events), hematuria (five events), hematoma at a puncture site (four events), and other hematoma (four events).
A listing of major and minor bleedings events by treatment regimen is provided in the following table.

Bleeding Events

Treatment Regimen	Number of patients	Major Bleeding N (%)	Minor Bleeding N (%)	Any Bleeding N (%)
A1	51	7 (13.7)	14 (27.5)	17 (33.3)
A2	5	0 (0.0)	1 (20.0)	1 (20.0)
B1	18	2 (11.2)	6 (33.3)	6 (33.3)
C	8	2 (25.0)	1 (12.5)	3 (37.5)
Total	82	11 (13.4)	22 (26.8)	27 (32.9)

No obvious differences in bleeding incidences were detected among treatment regimens. The incidence of major bleedings in the highest dose group A1 (7/51 patients = 13.7%) was comparable to that of the remaining treatment regimens (4/31 patients = 12.9%).

The following types of major bleedings were observed:

Bleeding at invasive sites (9 events in 7 patients)
- .peri- or post-operative bleeding (6 events)
- .bleeding at a catheter insertion site (2 events)
- .bleeding due to phenprocoumon-induced necroses (1 event)

Spontaneous bleeding (6 events in 5 patients)
- · urogenital bleeding (2 events)
- · organ bleeding (1 event)
- · soft tissue bleeding (1 event)
- · gastrointestinal bleeding (1 event)
- · diffuse bleeding (1 event)

No intracerebral bleeding occurred during the study. None of the observed major bleeding events were fatal. One patient experienced bleeding into pre-existing liver cyst during concomitant thrombolysis with urokinase.

Overall, major bleeding was more frequent in patients older than 65 years of age, in females, in patients treated with thrombolytics, in patients with Broca index >120, and in patients with hypertension.

The median aPTT at the time of major bleeding (15 events) was 69 seconds ; the median HBW 023 plasma level was 1099 ng/ml

Adverse Events: The most frequently observed adverse events, other than bleeding events, were the following:

Adverse events observed in more than two patients

	Number with Events		Number with possibly Related event		Number with severe event	
	N	%	N	%	N	%
TECs	8	9.8	1	1.2	4	4.9
Fever	8	9.8	4	4.9	1	1.2
Heart failure	4	4.9	0	0.0	3	3.7
PT increased	3	3.7	3	3.7	0	0.0
Pneumonia	3	3.7	0	0.0	1	1.2

Excluding bleeding events.

Forty-eight patients (58.5%) experienced adverse events. Of these, 27 patients had possibly related adverse events (Tables B.8.5 and B.8.6).

Allergic Reactions: Two patients experienced an allergic reaction (exanthema) during the study. One case recovered despite continued treatment, the second case had occurred five days after the end of study treatment and diminished after antibiotic therapy was changed.

Serious Adverse Events: Serious adverse events were reported for 26 patients (31.7%), nine were regarded as possibly related to HBW 023. Two patients in regimen B experienced kidney failure during the study. Both SAE were judged to be not related to HBW 023 treatment.

Six patients died, three each in groups A1 and B. None of the fatal events were considered to be associated with the study drug. Of the eight patients with AE resulting in permanent discontinuation of study drug, the AE was regarded as possibly related to HBW 023 in three. All drop-outs due to AE were counted as treatment failures.

The incidences of serious adverse events sorted by body system and the serious adverse events possibly related to study therapy that were documented for nine patients (11.0%) are listed in Table B.8.9 and B.8.10 (NDA v.1.113, p.160 and 161).

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Table 8.8.5: Incidence of adverse events by body system

(cf. App. 1.10)

		Treatment regimen									
		A1 (n=51)		A2 (n=5)		B (n=18)		C (n=8)		Total (n=82)	
Body System	Adverse Event	N	%	N	%	N	%	N	%	N	%
Body as a Whole	Abscess	1	2%	-		-		-		1	1%
	Fever	4	8%	1	20%	3	17%	-		8	10%
	Infection superimposed	1	2%	-		1	6%	-		2	2%
	LE syndrome	-		-		1	6%	-		1	1%
	Multi organ failure	1	2%	-		-		-		1	1%
	Necrosis	1	2%	-		-		-		1	1%
	Sepsis	1	2%	-		1	6%	-		2	2%
Cardiovascular System	AV block second degree	-		-		1	6%	-		1	1%
	Heart failure	1	2%	-		3	17%	-		4	5%
	Pericardial effusion	-		-		-		1	13%	1	1%
	Peripheral vascular disorder	1	2%	1	20%	-		-		2	2%
	Vasodilatation	1	2%	-		-		-		1	1%
Digestive System	Liver function test abnormal	-		-		1	6%	-		1	1%
Hemic and Lymphatic System	Prothrombin increased	2	4%	-		1	6%	-		3	4%
	Thrombocytopenia	-		-		1	6%	-		1	1%
Hemorrhage	Anemia	1	2%	-		-		-		1	1%
	Decreased hemoglobin	2	4%	-		4	22%	-		6	7%
	Epistaxis	2	4%	-		-		-		2	2%
	Hematuria	3	6%	1	20%	-		-		4	5%
	Hemoperitoneum	1	2%	-		-		1	13%	1	1%
	Hemoptysis	1	2%	-		-		-		1	1%
	Hemorrhage	7	14%	-		3	17%	1	13%	11	13%
	Hemorrhage of liver	1	2%	-		-		-		1	1%
	Hemothorax	-		-		-		1	13%	1	1%
	Injection site hemorrhage	4	8%	1	20%	-		-		5	6%
	Mouth hemorrhage	-		-		1	6%	-		1	1%
Hemorrhage	Petechia	1	2%	-		-		-		1	1%
	Rectal bleeding	2	4%	-		-		-		2	2%
	Subcutaneous hematoma	-		-		-		1	13%	1	1%
	Vaginal hemorrhage	1	2%	-		-		-		1	1%
Hypersensitivity	Allergic reaction	1	2%	1	20%	-		-		2	2%
Nervous System	Agitation	1	2%	-		-		-		1	1%
Respiratory System	Pneumonia	3	6%	-		-		-		3	4%
Skin and Appendages	Skin necrosis	1	2%	-		-		-		1	1%
	Vesiculobullous rash	1	2%	-		-		-		1	1%
Special Senses	Otitis media	1	2%	-		-		-		1	1%
Thromboembolism	Arterial thrombosis	1	2%	-		2	11%	-		3	4%
	Arterial thrombosis of the leg	1	2%	-		-		-		1	1%
	Deep thrombophlebitis	-		-		3	17%	-		3	4%
	Pulmonary embolus	1	2%	-		1	6%	-		2	2%
Urogenital System	Kidney failure	-		-		2	11%	-		2	2%

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Table 8.8.6: Incidence of possibly related adverse events by body system

(cf. App. 1.10)

		Treatment regimen									
		A1 (n=51)		A2 (n=5)		B (n=18)		C (n=8)		Total (n=82)	
Body System	Adverse Event	N	%	N	%	N	%	N	%	N	%
Body as a Whole	Abscess	1	2%	-		-		-		1	1%
	Fever	3	6%	1	20%	-		-		4	5%
	Infection superimposed	-		-		1	6%	-		1	1%
Cardiovascular System	Vasodilatation	1	2%	-		-		-		1	1%
Digestive System	Liver function test abnormal	-		-		1	6%	-		1	1%
Hemic and Lymphatic System	Prothrombin increased	2	4%	-		1	6%	-		3	4%
Hemorrhage	Anemia	1	2%	-		-		-		1	1%
	Epistaxis	2	4%	-		-		-		2	2%
	Hematuria	3	6%	1	20%	-		-		4	5%
	Hemoperitoneum	1	2%	-		-		-		1	1%
	Hemoptysis	1	2%	-		-		-		1	1%
	Hemorrhage	5	10%	-		1	6%	1	13%	7	9%
	Injection site hemorrhage	3	6%	1	20%	-		-		4	5%
	Mouth hemorrhage	-		-		1	6%	-		1	1%
	Rectal bleeding	2	4%	-		-		-		2	2%
	Vaginal hemorrhage	1	2%	-		-		-		1	1%
Hypersensitivity	Allergic reaction	1	2%	1	20%	-		-		2	2%
Nervous System	Agitation	1	2%	-		-		-		1	1%
Skin and Appendages	Skin necrosis	1	2%	-		-		-		1	1%
Thromboembolism	Arterial thrombosis	-		-		1	6%	-		1	1%

Treatment regimen: A1=treatment of thromboembolic complications (without conc. thrombolysis)
A2=treatment of thromboembolic complications (with conc. thrombolysis)
B =prophylaxis of new thromboembolic complications
C =anticoagulation during cardiopulmonary bypass

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Table 8.8.9: Incidence of serious adverse events by body system

(cf. App. 1.10)

		Treatment regimen									
		A1 (n=51)		A2 (n=5)		B (n=18)		C (n=8)		Total (n=82)	
Body System	Adverse Event	N	%	N	%	N	%	N	%	N	%
Body as a Whole	Infection superimposed	1	2%	-		1	6%	-		2	2%
	LE syndrome	-		-		1	6%	-		1	1%
	Multi organ failure	1	2%	-		-		-		1	1%
	Necrosis	1	2%	-		-		-		1	1%
	Sepsis	1	2%	-		1	6%	-		2	2%
Cardiovascular System	AV block second degree	-		-		1	6%	-		1	1%
	Heart failure	1	2%	-		2	11%	-		3	4%
	Peripheral vascular disorder	1	2%	1	20%	-		-		2	2%
Hemorrhage	Hemoperitoneum	1	2%	-		-		-		1	1%
	Hemorrhage	5	10%	-		2	11%	1	13%	8	10%
	Hemorrhage of liver	1	2%	-		-		-		1	1%
	Hemothorax	-		-		-		1	13%	1	1%
	Injection site hemorrhage	1	2%	-		-		-		1	1%
	Rectal bleeding	1	2%	-		-		-		1	1%
	Vaginal hemorrhage	1	2%	-		-		-		1	1%
Hypersensitivity	Allergic reaction	1	2%	1	20%	-		-		2	2%
Respiratory System	Pneumonia	1	2%	-		-		-		1	1%
Thromboembolism	Arterial thrombosis	1	2%	-		2	11%	-		3	4%
	Arterial thrombosis of the leg	1	2%	-		-		-		1	1%
	Deep thrombophlebitis	-		-		3	17%	-		3	4%
	Pulmonary embolus	1	2%	-		1	6%	-		2	2%
Urogenital System	Kidney failure	-		-		2	11%	-		2	2%

Treatment regimen: A1=treatment of thromboembolic complications (without conc. thrombolysis)
A2=treatment of thromboembolic complications (with conc. thrombolysis)
B =prophylaxis of new thromboembolic complications
C =anticoagulation during cardiopulmonary bypass

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Table 8.8.10: Incidence of possibly related serious adverse events by body system

(cf. App. 1.10)

		Treatment regimen									
		A1 (n=51)		A2 (n=5)		B (n=18)		C (n=8)		Total (n=82)	
Body System	Adverse Event	N	%	N	%	N	%	N	%	N	%
Body as a Whole	Infection superimposed	-		-		1	6%	-		1	1%
Hemorrhage	Hemoperitoneum	1	2%	-		-		-		1	1%
	Hemorrhage	3	6%	-		1	6%	1	13%	5	6%
	Rectal bleeding	1	2%	-		-		-		1	1%
	Vaginal hemorrhage	1	2%	-		-		-		1	1%
Hypersensitivity	Allergic reaction	1	2%	1	20%	-		-		2	2%
Thromboembolism	Arterial thrombosis	-		-		1	6%	-		1	1%

Treatment regimen: A1=treatment of thromboembolic complications (without conc. thrombolysis)
A2=treatment of thromboembolic complications (with conc. thrombolysis)
B =prophylaxis of new thromboembolic complications
C =anticoagulation during cardiopulmonary bypass

Fatal adverse events: Six patients (7.3%) died during the study, three of 51 patients in regimen A1 and three of 18 patients in regimen B. None of the deaths were considered to be drug-related.

Patients with fatal adverse events

Treatment Regimen	Patient	Fatal AE	Day of Onset
A1	1401	Heart Failure	13
	2301	Sepsis	5
	3103	Multiorgan Failure	13
B	1601	Sepsis	8
	1708	DVT*, PE*, Heart Failure	16
	3201	Heart Failure	3

* Findings of autopsy.

Drop-outs due to Adverse Events: The eight patients in whom the study therapy was prematurely discontinued due to an adverse event, are listed in table 8.8.15 (NDA v.1.113, p.172). All drop-put patients due to AEs were included in the treatment failures.

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Table 8.8.15: Discontinuations of study therapy due to adverse events by body system

[cf. App. 1.10]

		Treatment regimen									
		A1 (n=51)		A2 (n=5)		B (n=18)		C (n=8)		Total (n=82)	
Body System	Adverse Event	N	%	N	%	N	%	N	%	N	%
Body as a Whole	Infection superimposed	1	2%	-		1	6%	-		2	2%
	Multi organ failure	1	2%	-		-		-		1	1%
	Sepsis	1	2%	-		-		-		1	1%
Cardiovascular System	Heart failure	-		-		1	6%	-		1	1%
Hemic and Lymphatic System	Prothrombin increased	1	2%	-		1	6%	-		2	2%
Hemorrhage	Hemorrhage of liver	1	2%	-		-		-		1	1%
Thromboembolism	Arterial thrombosis	-		-		1	6%	-		1	1%
Urogenital System	Kidney failure	-		-		1	6%	-		1	1%

Per patient, more than one event may habe been reported as cause of discontinuation

Treatment regimen: A1=treatment of thromboembolic complications (without conc. thrombolysis)

Adverse Events during Second Treatment Courses: Three of five patients who underwent a second treatment course of HBW 023, experienced an adverse event during repeated treatment courses. One patient suffered three major bleedings (SAEs), one patient experienced fever and a drop in hemoglobin (both non-serious AEs), and one patient had recurrent mild skin lesions which disappeared during ongoing HBW 023 treatment.

Laboratory investigations: The following tests were assessed:

1) hematology and clinical chemistry
2) coagulation
3) hirudin plasma levels and THC levels
4) antibodies against hirudin
5) HBW 023 clearance.

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1) Hematology and clinical chemistry

Hemoglobin: The majority of patients entered the study with Hgb value below the normal range. Twenty-two (22) of the 78 patients (28%) with baseline value experienced a drop in Hgb of at least 1.2 mmol/l (2 g/dl) during treatment with HBW 023: six had major bleeding events and two had minor bleeding events.

Platelets: The time courses of platelet counts has been discussed in the efficacy evaluation.

Serum creatinine: Sixteen patients entered the study with a serum creatinine above normal: 7 patients in regimen A1, 6 in B, and 3 in C. Six patients had increase to levels >35 umol/l.

2) Coagulation

Activated partial thromboplastin time (aPTT): Median aPTT values increased between 1.5 and 3.0 fold the baseline value within 4 hours after initiation of study drug (first scheduled determination) and remained within this range during treatment. Median aPTT for regimen B were slightly lower because of the lower dose of HBW 023 administered. In regimen C, median aPTT values increased to 5.5 fold baseline at the start of CPB and in the baseline value after the end of surgery. The median aPTT values were not affected by the concomitant administered of phenprocoumon in treatment regimens A1, A2, and B. After cessation of HBW 023 treatment, median aPTT values in all regimens dropped to values slightly above baseline values.

Prothrombin Time: A consistent increase in Prothrombin Time (PT) was observed within the first four hours of treatment due to the direct anticoagulant effect of HBW 023 and remained prolonged in

most patients. The international normalized ratio (INR) was not routinely determined during the study.

Anti-Xa activity: In 21 patients, increased anti-Xa was observed at distinct time points during study treatment. One patient with elevated anti-FXa activity developed TEC. In seven patients, the increased anti-Xa may have been related to recent administration of Orgaran.

Thrombin-antithrombin complex (TAT): Baseline TAT levels were relatively high, particularly in groups A1 and A2 due to the ongoing thromboses. TAT values varied substantially during the study, nevertheless, TAT values decreased during the first 4 hours after initiation of HBW 023 treatment in treatment regimens A1, A2, and B and remained at a low level during treatment in all of these regimens.

Prothrombin Fragment F1+2: Baseline values were elevated and time courses showed a pattern as described for TAT.

3) Hirudin plasma levels and Thrombin-hirudin complexes (THC):

Lower levels were reported in regimen B. Considerable variability was also noted.

4) Antibodies against hirudin:

Thirty-eight patients (46.3%) developed positive anti-hirudin antibody (IgG) during the study. The first positive value was observed 6 days after the start of treatment. No IgE anti-hirudin antibodies were observed in the 8 patients with positive IgG antibody level tested. The formation of antibodies was not associated with clinical manifestations or with reduced hirudin plasma levels. However, in 5 patients, the HBW 023 maintenance dose had to be reduced to keep the aPTT stable. None of the four patients with persisting antibodies re-exposed to HBW 023 during a second treatment experienced allergic reaction. The follow-up test was positive in 6 patients (24%) retested at 120 to 477 days.

5) HBW 023 clearance:

The HBW 023 clearance decreased with age. Clearance at years was 17% lower, at age >70 years was about 40% lower. Females had about 25% lower clearance than males. The median HBW 023 clearance with serum creatinine (N=6) was about 20% lower than with values <100 umol/l (N=49). In patients with baseline serum creatinine of >133 umol/l (N=7), the median HBW 023 clearance was reduced by more than 50%.

III.B. CLINICAL TRIAL NR13

III.B.1. STUDY REPORT

Disposition of Patients: From July 1995 to April 1996, a total of 116 patients were enrolled in study NR13. As in study B7, each patient was assigned to one of four treatment regimens:

A1	(HBW 023 treatment without thrombolysis)	65 patients
A2	(HBW 023 treatment plus thrombolysis)	4 patients
B	(Thrombo-prophylaxis with HBW 023)	43 patients
C	(cardiopulmonary bypass with HBW 023)	4 patients

The patients' **Demographic and Background Characteristics** are summarized in the following table.

Demographic and background characteristics

	A1 N=65 (%)	A2 N=4 (%)	B N=43 (%)	C N=4 (%)
Sex				
Male	29 (45)	2 (50)	22 (51)	1 (25)
Female	36 (55)	2 (50)	21 (49)	3 (75)
Age				
median	56	44	62	64
range				
Underlying Disease				
Medical	33 (51)	2 (50)	15 (35)	0
Orthopedic	10 (15)	0	6 (14)	0
Trauma	9 (14)	1 (25)	2 (5)	0
Cardiovascular	2 (3)	0	4 (9)	4 (100)
Other	5 (8)	1 (25)	14 (33)	0
Laboratory Confirmation of HAT type II	64 (99)	5 (100)	42 (99)	3 (99)
Acute HAT	47 (92)	4 (80)	13 (72)	2 (25)
Latent HAT	1 (2)		3 (7)	1 (25)

The median platelet count prior to the start of the reference heparin treatment, documented for 106 of the 116 enrolled patients was 234 G/l
The median nadir of platelets prior to initiation of study treatment, available for 108 of the 116 patients, was 61 G/l
The median time to detection of thrombocytopenia in 106 patients was 13 days after start of heparin treatment.
The median baseline platelet count prior to the start of HBW 023 treatment available for 112 patients was 95 G/l

All 69 patients in treatment regimens A-1 and A-2 had at least one TEC prior to start of HBW 023; 59 of these patients (85.5%) experienced at least one TEC during heparin therapy. In the remaining 10 patients, TECs had either occurred before onset of heparin treatment (heparin indication) or during a heparin treatment break.
The most frequently observed TECs in the 56 patients in treatment regimens A-1 and A-2 are showed in the following table:

Types of TECs prior to start of study treatment

Types of TEC	Treatment regimens A-1 and A-2	
	No. of patients With TECs N (%)	TECs Due to heparin No. of patients N (%)
Distal DVT	45 (65)	29 (42)
Proximal DVT	39 (57)	32 (46)
Pulmonary Embolism	38 (55)	30 (44)
Arterial-peripheral	13 (19)	10 (15)

Of the 43 patients in treatment regimen B, 12 (27.9%) had developed thromboembolic complications between the start of heparin treatment and the start of study treatment. No patient in treatment regimen C developed TEC during heparin treatment.

Sixty patients (52%) had received only heparin (UH) before initiation of study treatment; 45 (39%) had received UH and an additional heparin/heparinoid (9 LMWH and 44 heparinoid).
Oral anticoagulation or platelet inhibitors were administered to 35 patients (30%) prior to study treatment: 23 (20%) received ASA and 14 (12%) received phenprocoumon. A total of 18 patients (16%) received thrombolytics before entering the study.

Antithrombotic regimens prior to HBW 023 therapy.

Treatment Regimen	Anticoagulants and antiplatelets administered prior to Study Treatment													
	None		UFH		Orgaran		UFH+LMWH		UFH+LMWH+ Orgaran		UHF+ Orgaran		LMWH	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
A-1 n=65	1	2	36	55	3	5	5	8	2	3	17	26	1	2
A-2 n= 4	-	-	3	50	-	-	-	-	-	-	2	50	-	-
B n=43	4	9	21	49	-	-	-	-	1	2	16	37	-	-
C n= 4	1	25	1	25	-	-	-	-	-	-	2	50	-	-
Total n=116	6	5	60	52	3	3	5	4	3	3	37	32	1	1

Concomitant Illnesses and Medication: All patients had multiple concomitant illnesses at study entry. Overall, patients in treatment group B appeared to have more concomitant illnesses than patients in the other treatment groups.

The most frequent concomitant conditions were:

circulatory, mainly TECs and hypertension:	97.4%
endocrine, nutritional and metabolic (mainly DM):	36.2%
surgery, musculoskeletal system:	21.0%
surgery, cardiovascular system:	39.7%
respiratory system", mainly pneumonia	26.7%

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Nearly all patients received concomitant medication during the study period. The most frequently administered classes of drugs were:

antithrombotic (ASA, phenprocoumon, thrombolytics):	93 (80.2%)
antacids:	69 (59.5%)
antibacterials and analgesics (each):	65 (56.0%)
analgesics	64 (55.2%)
plasma or perfusion solutions:	62 (53.4%)
cardiac therapy:	64 (55.2%)
diuretics:	52 (44.8%)
ophthalmologicals:	65 (56.0%)

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Seventy-five patients (64.7%) received phenprocoumon during the study period. One patient in treatment regimen A1 received thrombolytic treatment in addition to HBW 023 treatment.

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Protocol Violations: Fifty-eight patients (50%) received a modified HBW 023 regimen, most of them received reduced amounts of HBW 023 because of concomitant antithrombotic drugs, abnormal coagulation tests and increased risk of bleeding. All these patients were included in the efficacy analyses. Platelet counts at day 3 and/or 10 were missing for 15 patients and 3 patients received less than 48 hours of therapy. These patients were not included in the primary efficacy analysis.

Patient Discontinuations: Twenty-one patients (18.1%) discontinued treatment with HBW 023 prematurely because of non-fatal adverse event (eleven), death/fatal adverse event (seven), consent withdrawal (one) or other reasons (two). Two patients who received a second treatment course discontinued the study drug prematurely.

The median duration of treatment with HBW 023 was 13 days in treatment regimen A1 , 10 days in treatment regimen A2 (range 1-58 days), 8 days in treatment regimen B , and 1 day in treatment regimen C .
In 67 patients (57.8%), treatment was continued longer than 10 days due to patients' conditions.

III.B.2. PRIMARY EFFICACY: ANTICOAGULANT EFFECT AND EFFECT ON PLATELETS

Primary efficacy analyses were based on the time courses of platelets and aPTT for regimen AI, A2 and B, and on the time course of ECT for regimen C. Secondary efficacy analyses were based on clinical data (new TECs, limb amputations, and death). Second treatment courses with HBW 023 were not subjected to efficacy analyses.

Number of Patients included in Analyses: The numbers of patients evaluable for efficacy analyses are summarized in the following table:

Evalualble patients

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	Treatment regimen				
	A1	A2	B	C	Total
Number of patients enrolled	65	4	43	4	116
Primary efficacy evaluation (per protocol)	57	3	34	4	98
Secondary efficacy evaluation	65	4	43	4	116
Safety population	65	4	43	4	116

Fifteen patients were excluded from primary efficacy evaluation because of missing platelet count (nadir or D.10). Three additional patients received less than 48 hours of study medication. All patients in group A1 are included in the secondary efficacy analysis of clinical events.

Study Completion: 95 patients (81.9%) completed the study according to protocol while 21 (18.1%) patients discontinued treatment due to: non-fatal adverse events (11); death, fatal adverse events (7); consent withdrawal (1); need for further anticoagulation (1); persistent thrombocytopenia (1). The follow-up period was shortened for 37 patients (31.9%) due to death/fatal events (11); hospital discharge (10); other reasons (16).

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Dosage and Duration of Treatment: The median duration of treatment was 13 days in regimen A1, 10 days in regimen A2, 8 days in regimen B, and 1 day in regimen C. Treatment was given for more than 10 days to 67 patients due to severe disease requiring prolonged anticoagulation. As per protocol, the dose of HBW 023 was modified according to APTT.

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Primary Efficacy Endpoints: The proportions of responders for primary efficacy criteria (platelet response and anticoagulant effect) in each treatment regimen are shown in the following table.

Primary efficacy analysis-Proportion of responders

Treatment Regimen	Evaluable patients	Responders: Platelets N (%)	Anticoagulation N (%)	Combined N (%)	95%CI
A1	57	54 (94.7)	44 (77.2)	42 (73.7)	60.3-84.5
A2	3	3 (100)	1 (33.3)	1 (33.3)	0.8-90.6
B	34	30 (88.2)	23 (67.6	22 (64.7)	46.5-80.3
C	4	3 (75.0)	4 (100)	3 (75.0)	19.4-99.4
Total	98	90 (91.8)	72 (73.5)	68 (64.6)	59.3-78.3

The proportion of patients responding with regard to the platelet count alone was 91.8%, while 73.5% fulfilled the criterion for effective anticoagulation. The total proportion of responders (64.6%) was significantly greater than the prespecified margin of 20% ($p<0.0001$).

Patients in group C experienced transient decrease in platelet counts following cardiac surgery due to platelet consumption in the CPB circuit.

Twenty-six patients did not achieve effective anticoagulation presumably due to inadequate dosing, inadequate dose adjustment, safety reasons, diagnostic procedure; excessive dose increases, insufficient aPTT prolongation despite dose increases.

All patients in regimen C fulfilled the criteria of effective anticoagulation during CPB as assessed by the Ecarin Clotting Time.

For acute HAT-II patients (A1, A2 and B), the median platelet count increased by day 7 of therapy to about 4-fold baseline value. Most patients had discontinued heparin for at least 1 day, and 36 patients had received Orgaran for 2 days or longer prior to starting HBW 023. In fact, recovery of thrombocytopenia (platelet count >100.000/cmm) had already began at the time of initiation of HBW 023 therapy in 22 of the 64 patients with thrombocytopenia on admission.

For latent HAT=II patients with normal platelet counts at baseline, median counts remained nearly constant over treatment.

The time courses of platelets and aPTT relative to baseline for patients with acute HAT were similar to those shown in study B7 shown on page 18 of this review.

III.B.3. SECONDARY EFFICACY: CLINICAL EVENTS

Deaths, surgical interventions and new thromboembolic complications during the study period: The incidences of individual events and the combined incidences of deaths, limb amputations and new TECs during the study period are summarized in the following table (NDA v.6.3,p.79).

Overall incidence of deaths, limp amputations, and new TECs (n=82)

Event	Patients with Events*		Time of First Occurrence					
			Before HBW023		During HBW023		After HBW023	
	N	%	N	%	N	%	N	%
Death	11	9.5	-	-	6	5.2	5	4.3
New TECs	20	17.2	9	7.8	10	8.6	1	0.9
Amputation	10	8.6	1	0.9	7	6.0	2	1.7
Patients with events	33	28.4	9	7.8	18	15.5	6	5.2

*Patients may have had more than one event.

The causes of death were heart failure (two patients), sepsis (two patients), and multiorgan failure (three patients) and PE, apnea, shock, and ventricular fibrillation (one patient each).

The new TECs observed during the study period were PE in five cases, proximal DVT in two cases, arterial-peripheral in three cases, distal DVT in one case and arterial peripheral/arterial iliac in one case.

In addition to nine limb amputations, 38 patients (32.8%) underwent other surgical interventions.

The combined incidence of death, limb amputation, and new TECs by treatment regimen is summarized in the following table.

Combined incidence of deaths, limb amputations, and new TEC

Treatment Regimen		Patients with Events*		Time of First Occurrence					
				Before HBW023		During HBW 023		After HBW 023	
		N	%	N	%	N	%	N	%
A1	n=65	22	33.8	6	9.2	11	16.9	5	7.7
A2	n= 3	2	66.0	1	33.0	1	33.0	-	-
B	n=43	9	20.9	2	4.7	6	14.0	1	2.3
C	n= 5	0	0.0	0	0,0	0	0.0	0	0.0
Total Patients	n=116	33	28.4	9	7.7	18	15.5	6	5.2

*Patients may have had more than one event.

The event rates were assessed in relation to treatment with HBW 023. The average event rates per patient/day were calculated taking into account the length of the observation periods. The first period began with laboratory confirmation of HAT and continued until the start of study treatment. The overall rates of each clinical endpoints and of the combined endpoints are summarized in the following table:

Average event rates per patient day period

Event	Number of evaluable pts.	Average event rate per patient day		
		Before HBW 023	During HBW 023	After HBW 023
Death	107	0,000	0.004	0.004
New TEC	107	0.028	0.007	0.001
Limb Amputation	107	0.003	0.004	0.001
Combined	107	0.032	0.015	0.006

The average combined event rates per day by period and treatment regimen are presented in the following table (NDA v.6.4,p.188).

Average Combined Event Rates per Day by Period and Treatment

Treatment Regimen	Number of evaluable pts.	Average event rate per patient day		
		Before HBW 023	During HBW 023	After HBW 023
A1	65	0,053	0.015	0.007
A2	3	0.083	0.038	0.000
B	43	0.043	0.012	0.005
C	5	0.000	0.000	0.000
Total	116	0.032	0.015	0.005

During treatment, the average combined event rates in regimens A1, A2 and B were 0.015, 0.038 and 0.012, respectively.

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III.B.4. SAFETY ANALYSES

Safety analyses included all patients enrolled in the study, from the initiation of study medication to the end of follow up, including second treatment cycles. Only first treatment cycles were subjected to detailed laboratory analyses.

ADVERSE EVENTS: The overall incidence of bleeding and non-bleeding adverse events observed in the patient population of study NR13 is summarized in the following table.

Number of patients with adverse events in prospective study

Patients Treated[1]	A1 n(%) 65(100)	A2 n(%) 4(100)	B n(%) 43(100)	C n(%) 4(100)	Total n(%) 116(100)
Adverse Events (AE)[2]	41(63)	4(100)	20(65)	4(100)	77(66)
.Possibly related AE	23(35)	3(75)	16(37)	2(50)	44(38)
.Bleeding Events[3] (any)	27(41)	4(100)	22(51)	3(75)	56(48)
.Drug stopped for AE	7(11)	1(25)	11(26)	2(50)	21(18)
.Allergic Reaction	61(5)	--	1(6)	--	--
Serious AE (SAE)	21(32)	2(50)	20(47)	2(50)	45(39)
.Major Bleeding	6 (9)	1(25)	12(28)	2(50)	21(18)
Fatal SAE	7(11)	1(25)	3(7)	--	11(9)

[1] A patient may have suffered more than one event
[2] Including serious adverse events
[3] Including major bleeding
[4] Occurring in more than one patient

Non-Bleeding Adverse events: Seventy-seven patients (66%) experienced adverse events. Of these, 44 patients (38%) had possibly related adverse events. Serious adverse events were reported for 45 patients (39%), 19 of which were regarded as possibly related to HBW 023. Eleven patients died, 7 in treatment regimens A1, 1 in treatment A2, and 3 in treatment B. None of the fatal events were considered to be associated with the study drug. Of the 21 patients with adverse events which resulted in permanent discontinuation of study drug, the adverse event was regarded as possibly related to HBW 023 in 8. The most frequently observed adverse events, other than bleeding events, were the following (v.6.3, p.85):

Adverse events observed in more than two patients#

	Number with event		Number with possibly related event		Number with severe event	
	N	%	N	%	N	%
Fever	5	4.3	1	0.9	–	–
Infection	3	2.6	–	–	–	–
Multi organ failure	3	2.6	–	–	3	2.6
Sepsis	6	5.2	–	–	4	3.4
SGOT (ASAT) increased	6	5.2	6	5.2	–	–
Pneumonia	5	4.3	–	–	–	–
Rash	4	3.4	2	1.7	–	–
Occlusion/Thromboembolism	5	4.3	–	–	2	1.7
Pulmonary embolus	5	4.3	1	0.9	5	4.3
Thrombophlebitis	4	3.4	1	0.9	1	0.9

Excluding bleeding events.

Serious Adverse Events: Serious adverse events were reported for 45 patients (38.8%). Possibly related SAEs were documented in 19 patients (16.4%). The events are listed in the following table (NDA v.6.3, p.86).

Possibly drug-related serious adverse events (as judged by the investigator)

Treatment regimen	Patient	Adverse event	Day* of onset	Intensity	Onset relative to study treatment	Permanent discont. due to event
A1	109	Epistaxis	2	moderate	during	no
	208	Hemothorax	2	severe	during	no
	504	Hematuria	21	severe	during	no
	1301	Rash	2	moderate	during	no
	1705	Coronary thrombosis	2	severe	during	yes
	2001	Pulmonary embolus	5	severe	during	no
	2201	Thrombocytopenia	34	severe	during	yes
	4501	Hemorrhage	1	severe	during	no
A2	4502	Hemorrhage	1	severe	during	no
		Hemorrhage	1	severe	during	no
		Epistaxis	1	severe	during	no
B	114	Rectal bleeding	28	moderate	during	no
	501	Hemorrhage	1	moderate	during	no
		Hemorrhage	2	severe	during	yes
	602	Hemorrhage	10	moderate	during	no
	804	Hemothorax	25	moderate	during	yes
		Hematuria	25	moderate	during	yes
	1005	Epistaxis	8	moderate	during	no
	2205	Hemothorax	2	moderate	during	no
		Ventricular fibrillation	2	severe	during	no
		Hemorrhage	2	moderate	during	no
	2702	Hemorrhage	–	severe	–	no
	2703	Hemorrhage	2	severe	during	yes
		Hemorrhage	2	severe	during	no
C	701	Hemorrhage	1	moderate	during	yes
		Pericardial effusion	4	severe	after	no
	4301	Hemothorax	1	severe	during	yes
		Hemothorax	1	severe	during	yes

* Relative to start of study treatment (Day 1).