DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL TEAM LEADER'S REVIEW

NDA: NDA 20-807

Sponsor: Hoechst Marion Roussel, Inc.
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DRAFT

Drug name: Refludan (lepirudin (rDNA) for injection)

Indication: for anticoagulation in adult patients with acute coronary syndromes (unstable angina/acute MI without ST elevation) to reduce the rate of cardiovascular death, new myocardial infarction or refractory angina

Date submitted: July 9, 1999

Date received: July 12, 1999

Review completed: April 3, 2000

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Background and Rationale:
This submission is a supplemental NDA providing for use of Refludan for anticoagulation in adult patients with acute coronary syndromes. The sponsor proposes the following wording of the indication:

> "Refludan is indicated for anticoagulation in adult patients with acute coronary syndromes (unstable angina/acute myocardial infarction with ST elevation). In this setting, Refludan has been shown to decrease the rate of CV death or new MI (combined double endpoint), as well as the rate of CV death, new MI or refractory angina (combined triple endpoint).
>
> In patients with ACS, Refludan is intended for use with aspirin."

Refludan is a 65-amino acid polypeptide active as a highly specific, direct thrombin inhibitor. It is a recombinant analogue of natural hirudin, the most potent and specific thrombin inhibitor known. Currently, Refludan is indicated for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications (approved, March 6, 1998).

The anticoagulant action of Refludan is manifest as an increase in activated partial thromboplastin time (aPTT) and thrombin time (TT). Important features of lepirudin (a direct thrombin inhibitor) as compared to heparin (an indirect thrombin inhibitor) include:
- direct inhibition of thrombin independent of antithrombin III,
- highly specific binding almost exclusively to thrombin,

- is not inactivated by platelet factor 4,
- reduces growth of platelet-rich arterial thrombus on deeply injured artery and pre-existing mural thrombus,
- inhibits both free and fibrin-bound thrombin.

Effect of lepirudin is dependent on plasma levels of the drug which are dependent on renal function. The drug is 48% renally cleared with an initial half-life of about 10 minutes and a terminal half-life of about 1.3 hrs.

In this supplemental NDA the sponsor provides two clinical studies. These are OASIS-1, a randomized, partially-blinded, pilot trial of lepirudin versus heparin plus aspirin in 909 patients and OASIS-2, a randomized, double-blind trial of lepirudin plus aspirin versus heparin plus aspirin in 10,141 patients.

Abbreviations used in this review are listed in Appendix A.

OASIS-1 (HBW 023/7CDN-201UA):
Title: A phase III randomized comparative trial of hirudin [lepirudin] versus heparin and warfarin versus standard therapy for acute myocardial ischemia without ST elevation

This was a multicenter (31 sites in Canada), randomized, partially-blinded (overall allocation to heparin or lepirudin was open, but exact lepirudin dose was blinded), parallel groups pilot study comparing two doses of lepirudin (low and medium*) followed by warfarin to heparin followed by warfarin for treatment of patients with unstable angina and myocardial infarction without ST elevation. The study was done in two consecutive parts OASIS-1a and OASIS-1b). [*Note: Originally 3 doses of lepirudin had been planned: "low", "medium" and "high" but the high dose was dropped from the protocol prior to initiation of the study].

OASIS-1a: The aims of OASIS-1a were:
i)   To ensure that there are no important safety concerns (e.g. bleeding) with the use of lepirudin compared to heparin in the treatment of unstable angina and MI without ST elevation.
ii)   To assess the feasibility of giving lepirudin compared with heparin in patients with unstable angina and MI without ST elevation in a number of centers.
iii)   To compare the effects of different doses of lepirudin with a standard regimen of intravenous heparin on measures of efficacy:
  a)   clinical markers: recurrent angina, refractory angina, subsequent MI and cardiovascular death (although with a sample size of 250, only large differences between treatment groups are likely to be detectable).
  b)   to assess the effects of lepirudin versus heparin on coagulation parameters and pharmacokinetics: aPTT, thrombin/antithrombin III complex (TAT), D-dimer, heparin and lepirudin levels during and after cessation of therapy.
iv)   To assess the feasibility and safety of low dose warfarin started 5 to 7 days after randomization to heparin or lepirudin and continued for 6 months.

reference: from 5/20/94 protocol for OASIS-1, NDA Vol. 21.29

In OASIS–1a the early phase lepirudin or heparin regimen (given for 3 days) was followed by warfarin at a fixed dose of 3mg/day for the duration of study participation (6 months). The protocol identified the composite endpoint "cardiovascular death, infarction, and recurrent or refractory angina" as the endpoint that would be compared in the statistical

analyses comparing lepirudin versus heparin. The analyses were to be done at 7 days, 35 days, and 6 months (OASIS-1a)/4 months (OASIS-1b). The safety endpoint for statistical comparison was combined incidence of major bleeding and stroke. The lepirudin doses were to be compared to each other and to heparin. The endpoint for the standard therapy versus warfarin comparison was the combined incidence of cardiovascular death, myocardial infarction, and recurrent or refractory angina assessed at 35 days with another analysis done at 6 months after randomization. The clinical outcome measures and safety outcome measures are listed and defined in Appendix B of this review.

For the early phase treatment patients were randomized (3:3:4) The early phase treatments were:
- low dose intravenous lepirudin: initial bolus 0.2mg/kg followed by a constant infusion of 0.10 mg/kg/hr for 72 hrs
- medium dose intravenous lepirudin: initial bolus 0.4mg/kg followed by a constant infusion of 0.15 mg/kg/hr for 72 hrs
- heparin: initial bolus 5000 units followed by 1200 units/hr (or 1000 units/hr for patients with estimated body weight <60kg) titrated to increase aPTT to between 60 and 100 secs (about 2-3 time normal) for 72 hrs.

At completion of the early phase study infusion period (5 to 7 days) patients entered the warfarin assessment phase. Patients were randomized (1:1) to either standard therapy or warfarin (10mg on day of randomization followed by 3mg daily for at least 6 months). Additonally, all patients were recommended to receive aspirin 325 mg/day during hospitalization and 80-325mg/day at discharge continuing for at least 6 months. Followup was at 35 days, 2 months, 3 months and 6 months from the initial randomization.

This part of the study was initiated as a pilot study intended to enroll about 250 patients (5/20/94 protocol). The study size was changed twice after study enrollment had begun: increased to 500 (12/21/94 protocol) then stated as 600 patients (9/28/95 protocol).

OASIS-1b: This part of the study was added by protocol amendment (6/6/95 protocol).

> [Note: The rationale for this part of the pilot study appears to involve an evolving interpretation of results of earlier studies involving treatment of stroke and atrial fibrillation patients with warfarin. In OASIS-1a the literature is cited as showing benefits of "low dose warfarin" in preventing thromboembolic events and the warfarin doses in OASIS-1a are termed "low dose". In the 6/6/95 protocol the same literature is cited as showing benefits of "intermediate intensity warfarin" and the study warfarin dose proposed is termed "low intensity warfarin" in the 6/6/95 protocol and "of such an intensity" in the 9/28/95 protocol. No interim analysis of OASIS-1 is mentioned in any of the protocols; however, in the 9/28/95 protocol the sponsor discusses that the coagulation data from the OASIS pilot study indicate that in both the heparin and lepirudin groups though markers of coagulation (F1-2, TAT, and D-dimer levels) are suppressed during dosing; as early as 6 hours there is re-elevation of these markers (See Section 4 of the protocols)].

A total of 300 patients were to be enrolled (these were in addition to the 600 already enrolled or planned for enrollment into OASIS-1a). There is no indication that this stage of the pilot study was planned prior to the 6/6/95 protocol. The aims of OASIS-1b were as follows. [Differences from OASIS-1a are bolded].
i)   To ensure that there are no important safety concerns (e.g. bleeding) with the use of hirudin compared to heparin in the treatment of unstable angina and MI without ST elevation **when given in combination with warfarin.**

ii)   To compare the effects of different doses of lepirudin with a standard regimen of intravenous heparin on measures of efficacy:

    a)   clinical markers: recurrent angina, refractory angina, subesquent MI and cardiovascular death (although with a sample size of 300, only large differences between treatment groups are likely to be detectable).

    b)   to assess the effects of lepirudin versus heparin on coagulation parameters and pharmacokinetics: aPTT, thrombin antithrombin III complex (TAT), D-dimer, heparin and lepirudin levels during and after cessation of therapy.

iii)   To assess the feasibility and safety of low dose warfarin started **within 24 hours of** randomization to heparin or lepirudin and continued for 6 months. [Modified by protocol amendment 9/28/95 to say: *To assess the safety and feasibility of moderate intensity warfarin started about 24 hours after starting lepirudin, and continued for 3 months*].

iv)   **To assess the impact of warfarin on the "reactivation" of the coagulation parameters observed after cessation of IV anti-thrombin therapy.**

reference: from 6/6/95 OASIS-1 protocol, NDA Vol. 21.29

The design of OASIS-1b was similar to that of OASIS-1a with the following major exceptions:

- Patients were randomized to warfarin or standard therapy within 24 hours (rather than at completion of the initial infusion, 5-7 days after randomization);

- Warfarin was to be given as a loading dose of 10 mg given on day of randomization, followed by 3mg/day for 6 months. A further 9/28/95 amendment modified the warfarin regimen to be dose-adjusted to maintain INR at 2.0-2.5 and be continued for only 3 months.

- An additional clinical outcome measure "severe angina" was added. This was defined as "at least 2 episodes of recurrent ischemic chest pain during a 24 hour period while on optimal therapy, with documentation of new ECG changes associated with at least one episode of cardiac chest pain."

- Duration of warfarin treatment was decreased to 3 months with final followup visit at 4 months (9/28/95 protocol).

- Followup initially was at 35 days, 3 months, and 6 months (as for OASIS-1a) but was changed to 35 days, 2 months, 3 months and 4 months from the initial randomization (9/28/95 protocol).

Results: This study was conducted from July 1, 1994 through November 8, 1996. A total of 909 patients were randomized (601 into OASIS-1a; 308 into OASIS-1b) at 31 sites (1-96 patients per site). Demographic features of the patients enrolled are summarized in the following table:

OASIS-1: Demographics and Baseline Characteristics

	Lepirudin low (N = 271)	Lepirudin medium (N = 267)	Heparin (N = 371)	Total (N = 909)
Sex				
male	176 (65%)	183 (69%)	245 (66%)	604 (66%)
female	95 (35%)	84 (31%)	126 (34%)	305 (34%)
Age (yrs)				
mean	64	64	65	64
median	66	65	66	65
range	27-85	34-86	32-85	27-86
Smoker				
current	66 (24%)	72 (27%)	101 (27%)	239 (26%)
Clinical diagnosis at time of randomization:				
suspected unstable angina	235 (87%)	233 (87%)	321 (87%)	789 (87%)
suspected MI without ST elevation	36 (13%)	34 (13%)	50 (13%)	120 (13%)

Baseline ECG				
abnormal	235 (87%)	212 (79%)	311 (84%)	758 (83%)
normal	36 (13%)	55 (21%)	60 (16%)	151 (17%)
Related medical history				
previous MI	116 (43%)	128 (48%)	167 (45%)	411 (45%)
PTCA	35 (13%)	41 (15%	55 (15%)	131 (14%)
CABG surgery	50 (18%)	57 (21%0	66 (18%)	173 (19%)
exertional angina over prior month	174 (64%)	152 957%)	236 (64%)	562 (62%0
stroke	16 (6%)	19 (7%)	23 (6%)	58 (6%)
known hypertension	128 (47%)	118 (44%)	169 (46%)	415 (46%)
diabetes	55 (20%)	53 (20%)	70 (19%)	178 (20%)

from sponsor's tables, NDA Vol. 21.26,

Most patients (about 89%) had chest pain prior to hospital admission with pain starting about 3 hours prior to hospital admission. Percent of patients with normal baseline ECG was somewhat unbalanced, particularly in OASIS-1a, where more lepirudin medium patients had normal ECGs as compared to the other groups (23% vs. 11-16%). There were also slight imbalances in time from chest pain to hospital admission and duration of chest pain. Where ECG was abnormal at baseline, in about 30-35% of patients there was ST depression and about 29-34% had T-wave inversion in 2 or more leads. At hospital admission about 89% of patients were on some concomitant medication. About 64% were taking aspirin and 55% were on nitrate therapy. Demographic and baseline characteristics of patients in OASIS-1a and OASIS-1b were similar.

Disposition of patients for OASIS-1a and OASIS-1b combined is summarized in the following table:

OASIS-1: Disposition of Patients During the Infusion Period of the Study

	Lepirudin low	Lepirudin medium	Heparin	Total
Lepirudin versus Heparin phase				
Total randomized[a]	271	267	371	909
OASIS-1a	175	173	253	601
OASIS-1b	96	94	118	308
Did not receive study medication	1	2	2	5
Premature discontinuation before completion of infusion:				
surgery or invasive procedure	16	11	20	49
lack of efficacy, clinical event, AE, death (except bleed)	8	10	10	28
bleeding	4	6	1	11
Total	71	71	66	208
Completed infusion[b]	199	194	303	696
Warfarin versus Standard therapy phase:				
Randomized to warfarin	70 (26%)	69 (26%)	114 (31%)	253 (28%)
Randomized to standard therapy	80 (30%)	71 (27%)	102 (27%)	253 (28%)
Not randomized	121 (45%)	127 (48%)	155 (42%)	403 (44%)
Assessments Available (Completed study):				
Completed 7 days	269 (99%)	263 (99%)	367 (99%)	899 (99%)
Completed 35 days	263 (97%)	256 (96%)	359 (97%)	878 (97%)
Completed study	256 (94%)	252 (94%)	350 (94%)	858 (94%)

[a] all patients randomized had 7-day assessment completed and were included in the sponsor's ITT population
[b] about 36% of lepirudin low dose, 37% of lepirudin medium dose and 22% of heparin patients had infusion interrupted for more than 1 hour.

from sponsor's table NDA Vol. 21.26, Table 2 of study report.

The sponsor had estimated that about 2/3 of patients enrolled in the lepirudin versus heparin phase of the study would continue into the warfarin versus conventional therapy phase; however, less that half the patients randomized into the lepirudin versus heparin phase were randomized into the warfarin versus standard therapy phase.

Efficacy: The statistical plan in the protocol for OASIS-1 did not describe the population to be used in the statistical analyses for the study. Where sample sizes are referred to in the statistical discussion in the protocol, number for all patients randomized are used. In the study report three study populations are identified:
- **ITT:** All randomized patients, analyzed as randomized
- **Safety:** All randomized patients who received lepirudin or heparin, analyzed as randomized
- **Modified intention-to-treat (MITT):** All randomized patients who completed their 7-day efficacy assessment (whether or not they received study medication), analyzed as randomized The 7-day efficacy assessment was to be completed on or before day 7 of the study. If each of the questions relating to death, new MI and refractory angina were answered (or it could be discovered otherwise that the patient died or had a new MI before the end of day 7), the 7-day efficacy assessment was considered to be complete.
- **Warfarin subgroup:** All patients randomized (to either warfarin or standard care), analyzed as randomized.

The sponsor indicates that the ITT and MITT populations were identical (i.e., consisted of all patients randomized). However, it should be noted that for patients included in the MITT where the day 7 death and new MI information was obtained from sources other than the CRF, there apparently may have been no information regarding refractory angina. It cannot be discerned from the information provided how many patients had their day 7 death and new MI observation determined from sources other than the CRF.

The sponsor used the MITT population for all efficacy analyses. The adjudicated assessments were used in the analyses.

The sponsor's primary table of efficacy results is shown below for the lepirudin versus heparin comparison. It should be noted that the quadruple endpoint displayed is not the one specified in the protocol ("severe angina" is included instead of "recurrent angina").

Findings for CV death, new MI, refractory or severe angina

Composite endpoint Time from randomization	Treatment group [a]	Patients with events (%) [b]	Relative risk [c]	95% CI		p-value [c]
CV death, new MI, refractory or severe angina (Quadruple endpoint)						
72 hours	Lepirudin low	7.7%	0.62	0.36 -	1.08	0.0764
	Lepirudin medium	7.1%	0.57	0.32 -	1.00	0.0418
	Lepirudin combined	7.4%	0.60	0.38 -	0.94	0.0215
	Heparin	11.9%				
7 days	Lepirudin low	12.5%	0.77	0.49 -	1.22	0.2791
	Lepirudin medium	9.4%	0.56	0.34 -	0.92	0.0176
	Lepirudin combined	11.0%	0.66	0.45 -	0.98	0.0380
	Heparin	15.6%				
35 days	Lepirudin low	16.6%	0.81	0.54 -	1.22	0.3525
	Lepirudin medium	15.0%	0.72	0.47 -	1.10	0.0640
	Lepirudin combined	15.8%	0.77	0.54 -	1.08	0.0955
	Heparin	19.7%				
End of the study	Lepirudin low	18.5%	0.75	0.51 -	1.11	0.1676
	Lepirudin medium	17.2%	0.69	0.46 -	1.03	0.0331
	Lepirudin combined	17.8%	0.72	0.52 -	1.00	0.0352
	Heparin	23.2%				

[a] Lepirudin low: N = 271; lepirudin medium: N = 267; lepirudin combined: N = 538; heparin: N = 371.

[b] Absolute numbers of patients with events are presented in Tables 28 - 31.

[c] Relative risk was based on a logistic regression model (treatment) comparing each treatment group with heparin. The p-values were determined using the Mantel-Haenszel test stratified by center.

The sponsor's table below shows incidences of occurrence of individual clinical endpoints. Additional efficacy analyses done by the sponsor are included in Appendix C of this review.

OASIS-1: Cumulative Incidences of All Clinical Events*

Time Period Clinical Event	Number (%) of Patients					
	Lepirudin low		Lepirudin medium		Heparin	
	OASIS-1[#] (N = 271)	OASIS-1a; OASIS-1b^{+} [N = 175; N = 96]	OASIS-1[#] (N = 267)	OASIS-1a; OASIS-1b^{+} [N = 173; N = 94]	OASIS-1[#] (N = 371)	OASIS-1a; OASIS-1b^{+} [N = 253; N = 118]
Up to 72 hours:						
CV death	2 (0.7%)	[1.1%; 0%]	3 (1.1%)	[1.2%, 1.1%]	1 (0.3%)	[0.4%; 0%]
Non-CV death	0	--	0	--	0	--
New MI	4 (1.5%)	[1.7%; 1.0%]	4 (1.5%)	[1.2%; 2.1%]	10 (2.7%)	[2.8%; 2.5%
Refractory angina	3 (1.1%)	[1.1%; 1.0%]	0	[0]	5 (1.3%)	[1.6%; 0.8%]
Severe angina	14 (5.2%)	[5.7%; 4.2%]	16 (6.0%)	[6.4%;5.3%]	30 (8.1%)	[9.9%; 4.2%]
Recurrent angina	14 (5.2%)	[7.4%; 1.0%]	9 (3.4%)	[4.6%; 1.1%]	23 (6.2%)	] [8.7%; 0.8%]
Up to 7 days:						
CV death	2 (0.7%)	[1.1%; 0%]	4 (1.5%)	[1.2%; 2.1%]	3 (0.8%)	[1.2%; 0%]
Non-CV death	0	--	0	--	1 (0.3%)	[0.4%; 0%]
New MI	7 (2.6%)	[2.9%; 2.1%]	5 (1.9%)	[1.7%; 2.1%]	18 (4.9%)	[5.1%; 4.2%]
Refractory angina	5 (1.8%)	[1.7%; 2.1%]	1 (0.4%)	[0.6%; 0%]	7 (1.9%)	[2.4%; 0.8%]
Severe angina	25 (9.2%)	[10.9%; 6.3%]	19 (7.1%)	[7.5%; 6.4%]	39 (10.5%)	[12.6%; 5.9%]
Recurrent angina	16 (5.9%)	[7.4%; 3.1%]	12 (4.5%)	[6.4%; 1.1%]	24 (6.5%)	[9.1%; 0.8%]
Up to 35 days:						
CV death	6 (2.2%)	[1.7%; 3.1%]	11 (4.1%)	[4.6%; 3.2%]	10 (2.7%)	[3.2%; 1.7%]
Non-CV death	1 (0.4%)	[0%; 1.0%]	0	--	1 (0.3%)	[0.4%; 0%]
New MI	13 (4.8%)	[4.6%; 5.2%]	12 (4.5%)	[5.8%; 2.1%]	27 (7.3%)	[7.5%; 6.8%]
Refractory angina	7 (2.6%)	[2.3%; 3.1%]	3 (1.1%)	[1.2%; 1.1%]	10 (2.7%)	[3.6%; 0.8%]
Severe angina	31 (11.4%)	[12.0%; 10.4%]	26 (9.7%)	[9.8%; 9.6%]	44 (11.9%)	[14.6%; 5.9%]
Recurrent angina	26 (9.6%)	[10.3%; 8.3%]	26 (9.7%)	[11.0%; 7.4%]	31 (8.4%)	[10.7%; 3.4%]
Up to end of study:						
CV death	10 (3.7%)	[2.9%; 5.2%]	13 (4.9%)	[5.8%; 3.2%]	15 (4.0%)	[4.3%; 3.4%]
Non-CV death	1 (0.4%)	[0%; 1.0%]	1 (0.4%)	[0.6; 0%]	4 (1.1%)	[1.6%; 0%]
New MI	16 (5.9%)	[5.7%; 6.3%]	17 (6.4%)	[6.9%; 5.3%]	33 (8.9%)	[9.5%; 7.6%]
Refractory angina	7 (2.6%)	[2.3%; 3.1%]	3 (1.1%)	[1.2%; 1.1%]	12 (3.2%)	[4.3%; 0.8%]
Severe angina	32 (11.8%)	[12.6%; 10.4%]	27 (10.1%)	[10.4%; 9.6%]	48 (12.9%)	[16.2%; 5.9%
Recurrent angina	30 (11.1%)	[12.6%; 8.3%]	26 (9.7%)	[11.0%; 7.4%]	35 (9.4%)	[12.3%; 3.4%]

* some patients had more than one type of event. All events are counted
[#] values for OASIS-1a and OASIS-1b combined;   [+] values for OASIS-1a and OASIS-1b separately

reviewer's table, based on sponsor's Table 26 of OASIS-1 Study Report, NDA Vol. 21.26

Generally, frequency of outcomes for patients in OASIS-1a and OASIS-1b were similar. However, in all treatment groups the occurrence of recurrent angina at the 72 hours and 7 days assessment was more than twice as high in the OASIS-1a patients as in the OASIS-1b patients. In the heparin group, the OASIS-1a patients had a higher frequency of refractory angina, severe angina and recurrent angina as compared to the OASIS-1b patients throughout the study.

About 12% of patients overall had confirmed MI associated with presentation before randomization. An additional 9% of patients had associated MI confirmed after randomization. Distribution of these patients was similar across treatment groups, except that the medium dose lepirudin group had a somewhat lower rate of associated MI confirmed after randomization (6.4%) as compared to the other groups (10.0%, low dose lepirudin; 10.5%, heparin).

The most frequent clinical endpoints occurring after radomization in the study were associated MI (in 10.5% of patients overall), severe angina (in 9.1% of patients at 7 days), recurrent angina (in 5.7% of patients at 7 days) and new MI (in 3.3% of patients at 7 days). New MI, refractory angina, severe angina, and recurrent angina tended to be more frequent in the heparin group as compared to the lepirudin groups. The greatest amount of discrepancy between the investigators' assessments and the adjudicated assessments were with regard to classification of refractory angina (59% disagree) and severe angina (38% disagree).

All patients received some concomitant medication during hospitalization. About 96% of patients received aspirin; 52% received IV nitrates; 89% received other nitrates. In OASIS 1a about 56% of patients received some non-study IV heparin and in OASIS-1b about 36% of patients received non-study heparin. Two percent of patients received thrombolytic therapy (slightly more in heparin groups as compared to lepirudin) and 5% received non-study oral anticoagulants.

Though no interim analyses were specified in the protocol, two interim analyses were conducted. These were an analysis done 9/26/95 after 274 patients had been enrolled. This analysis focused on safety and the sponsor indicates that no analysis of acute MI, refractory or recurrent angina was done at this time. The study was deemed safe to proceed. A second interim analysis was done 7/1/97 after 601 patients had been enrolled. At this time OASIS-1a had been completed.

Safety: With regard to safety, the treatment groups were similar in incidence of major bleeds; however, incidence of minor bleeds tended to be slightly greater in the lepirudin groups. There were no documented hemorrhagic strokes. There were 9 ischemic strokes (4, lepirudin low; 3 lepirudin medium; 2 heparin). Five patients (3 heparin) had stroke "type uncertain". Frequency of bleeding adverse events is summarized in the sponsor's table below:

Table 55. Minor, major, life-threatening* and fatal bleeds by time period (Safety,N=904)

Type of bleed	Number (%) of patients			
	Lepirudin low	Lepirudin medium	Heparin	Total
OASIS-1	**N=270**	**N=265**	**N=369**	**N=904**
Number of patients with bleeding	67 (24.8%)	84 (31.7%)	72 (19.5%)	223 (24.7%)
Randomization to day 7				
Any bleed	46 (17.0%)	59 (22.3%)	41 (11.1%)	146 (16.2%)
Minor bleeds	44 (16.3%)	57 (21.5%)	39 (10.6%)	140 (15.5%)
Major bleeds	2 (0.7%)	3 (1.1%)	4 (1.1%)	9 (1.0%)
Life-threatening bleeds*	2 (0.7%)	2 (0.8%)	3 (0.8%)	7 (0.8%)
CRF life-threatening	2 (0.7%)	3 (1.1%)	1 (0.3%)	6 (0.7%)
Fatal bleeds	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)
Day 8 to day 35				
Any bleed	21 (7.8%)	20 (7.5%)	21 (5.7%)	62 (6.9%)
Minor bleeds	20 (7.4%)	19 (7.2%)	19 (5.1%)	58 (6.4%)
Major bleeds	1 (0.4%)	2 (0.8%)	3 (0.8%)	6 (0.7%)
Life-threatening bleeds*	1 (0.4%)	2 (0.8%)	2 (0.5%)	5 (0.6%)
CRF life-threatening	1 (0.4%)	0 (0.0%)	1 (0.3%)	2 (0.2%)
Fatal bleeds	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* Includes all fatal and intracranial bleeds and major bleeds requiring surgery or 4 or more units of blood or blood products

Hemorrhagic adverse events (mainly minor) occurring from randomization to day 7 were more frequent in the lepirudin groups as compared to the heparin group. Study drug infusion was discontinued in 5 (1.9%) lepirudin low patients, 7 (2.6%) lepirudin medium patients and 1 (0.3%) heparin patient due to hemorrhagic adverse events. Most frequent adverse events in all treatment groups were headache (28-34% of patients) and nausea (7.6-8.6% of patients). Most adverse events were mild in severity.

Reviewer's comments:

This study was designed to be a pilot study to help select a lepirudin dose and design a larger, appropriately sized, definitive efficacy trial of lepirudin for treatment of patients with unstable angina. However, the study does not appear to have been used as effectively as possible for that purpose. For example, no detailed statistical plan was prepared for OASIS-1. (The analyses presented in this NDA are based on the statistical analysis plan for OASIS-2, which was finalized 6/23/98 after OASIS-2 had been underway for 22 months and 4 months before study completion).

OASIS-1 has a number of deficiencies that limit its usefulness as a pivotal efficacy trial.

There are a number of confounding factors to be considered in evaluating this study. These included the following:

1. The study was not blinded and this may have allowed introduction of non-random elements (such as use of other concomitant therapies or interventions) into the study.

2. There were significant discrepancies between investigator assessments and adjudicated assessments for several of the angina endpoints.

3. Some patients (about 28%) were receiving heparin prior to randomization. (page 9 of 6/6/95 protocol).

4. After randomization treatment of patients with non-study anticoagulants and other interventions may have led to bias in the conduct of the study.

5. With increasing time on study the results become increasingly confounded by warfarin use. This should make it more difficult to distinguish among the treatment groups (all other things being equal).

OASIS-2 (HBW 023/7CMN-302UA):

Title: A phase III randomized comparative trial of hirudin [lepirudin] versus heparin and warfarin versus standard therapy for acute myocardial ischemia without ST elevation

OASIS-2 was designed based on the results from OASIS-1. It was planned as a randomized, double-blind, active control, parallel groups trial of lepirudin versus heparin started at randomization and given for 72 hours with a randomized substudy of warfarin versus standard treatment started at 24 hours (12-30 hours) after initiation of lepirudin or heparin treatment and continued for 5 months. All patients received aspirin (80 to 325mg/day). Lepirudin dose was 0.4mg/kg bolus followed by 0.15mg/kg/hr infusion. Standard intravenous heparin dose was 5,000 units bolus followed by 15 units/kg/hr infusion. Warfarin dosing was "moderate intensity warfarin (INR target of 2.5; range 2-3)". Standard therapy consisted of aspirin alone.

The study proposed to demonstrate superiority of lepirudin over the comparator for the primary outcome: CV death and new MI at 7 days. A sample size of 10,000 was planned. The secondary endpoint was CV death, new MI, and refractory angina at 7 days. Other endpoints included CV death, new MI and severe angina at 7 days and CV death and new MI at 35 days. A population size of 6,000 patients was planned for part 2. The primary outcome was combined CV death, new MI and stroke over 5 months and the secondary outcome was CV death, new MI, stroke, and readmission for unstable angina over 5 months. Followup assessments were done at 35 days and 6 months for all patients with additional followups at 3 and 5 months for patients participating in the warfarin substudy.

Definitions of some endpoints were modified from those used in OASIS-1.
• Acute pulmonary edema was dropped from the clinical symptoms of new MI

• ECG changes indicative of new MI was modified to say "new diagnostic ECG changes" and the definition of diagnostic ECG changes was modified to specify that changes were to be persistent,

• Definition of new CK enzyme changes was modified to include increases >20% above the previous value if CK-MB was already elevated.

• Definition of refractory angina was revised to be as follows: " new episode of ischemic chest pain (with documented characteristic ECG changes during pain) lasting >5 minutes occurring in the presence of "optimum" medical treatment and leading to an additional intervention such as thrombolytic therapy for threatened MI, or insertion of an intra-aortic balloon pump or a revascularization procedure (PTCA or CABG) within 7 days of the original randomization to heparin or lepirudin. Optimum treatment in this

context is defined as at least two anti-anginal treatments, one of which should be an IV nitrate (unless contraindicated). A twelve lead ECG documenting the ECG changes associated with this event will be required, From hospital discharge until 35 days, refractory angina is defined by the same criteria as readmission to hospital with unstable angina." This definition eliminated cardiac catherization within 24 hours and transfer to a tertiary care center within 48 hours of the onset of pain/symptoms from the listed examples of "additional interventions" and required that ischemic chest pain must be a **new episode** (not just recurrent pain). The definition was further modified in an amendment (6/22/97)to the protocol which:
- specified that ECG changes must be new and associated with pain.
- added to the list of interventions cardiac catherization or transfer for an intervention, regardless of whether or not the intervention is done.
- the additional interventions or transfer must occur by the end (i.e. midnight) of the next calendar day after a pain episode.
- the ischemic pain which leads to the documentation of refractory angina may occur until Day 35, not only Day 7, as long as it is within the initial hospitalization period (i.e. a randomizing hospital or a hospital the patient was transferred [to] from randomizing hospital).

- Severe angina was defined as at least **1** (instead of at least 2) episodes of recurrent ischemic chest pain lasting >5 minutes while on optimal medical therapy.

- For recurrent angina the clarification was added that ECG documentation was not needed for this event.

- A new definition "associated MI" was added. This was defined as suspected MI on admission with typical clinical history of acute coronary ischemia with subsequent diagnostic cardiac enzyme elevation or persistent ECG changes associated with these symptoms. There should be no further symptoms of MI (typical prolonged chest pain of >20 minutes or chest pain requiring narcotic analgesic) during the 24-hour period following randomization.

- A new definition "readmission to hospital with unstable angina" was added. This was defined as readmission to hospital (after initial hospitalization for study entry) over the following 6 months. Acceptable criteria include: a) Clinical symptoms of typical prolonged ischemic chest pain unresponsive to the patient's usual medications, leading to hospital admission, **and** b1) ECG changes consistent with acute myocardial ischemia (e.g. ST depression, minimal ST elevation not justifying the use of thrombolytic therapy, or T-wave inversion) or b2) admission to a monitoring unit (e.g. CCU, ICU, ICCU). Patients were to be subdivided into those who meet criteria a and b1, and those who meet criteria a and b2.

- A new definition of "stroke" was added. This was defined as the presence of a new focal neurologic deficit thought to be vascular in origin with signs or symptoms lasting greater than 24 hours. It was strongly suggested (but not required) that an imaging procedure such as CT or MRI be performed. These reports were to be reviewed to further classify the stroke as a definite intracranial hemorrhage or ischemic infarction.

- The definition of major bleeding was modified slightly so that any bleeding (whether overt or not) requiring transfusion of 2 or more units of packed red blood cells or equivalent was classified as major.

Provisions were made for central adjudication of clinical events including death classified by cause, MI, refractory angina, stroke, readmission for unstable angina, and major bleeds. The adjudicated results were to be used in the final analyses.

The 6/22/97 amendment also made some changes in the warfarin substudy to allow randomization of patients to be delayed up to 7 days due to emergency or semi-elective procedures and allowed patients scheduled for invasive procedures to have warfarin therapy interrupted for the procedure and restarted afterwards. Also, additional analyses were added for the warfarin substudy: (1) Clinical events in patients randomized to warfarin were to be examined overall versus standard therapy, and subgroup analysis would be conducted by whether warfarin was started during study infusion or after it was stopped. (It was expected that the impact of rebound clinical events would be seen only in the former group) and (2) Comparison of the combination of warfarin and lepirudin to warfarin and heparin on both the primary outcome and a composite that includes the secondary endpoints.

The statistical plan in the protocol specified that statistical analyses for lepirudin versus heparin would compare incidence rates of the main outcomes of CV death and new MI at 7 days by an intention to treat analysis." A 2-tailed p-value of 0.05 was to be considered significant. The intention-to-treat population was not explicitly identified. The secondary outcome of CV death, new MI and refractory angina was to be be considered statistically significant at a 2-tailed p value of 0.01. Mantel-Haenszel test (stratified by center) was to be used and the primary comparison was to be done at 7 days with other times being further comparisons. Combined CV death, new MI and severe angina was stated as an additional supportive outcome.

The Statistical Analysis Plan for OASIS-2, dated June 23, 1998 identified 5 study populations:
- **All randomized patients** (analyzed as treated, i.e., in treatment group of teratment initially received, except for patients who did not receive lepirudin/heparin study medication – they will be analyzed according to the treatment of the initial treatment pack number allocated by CCC).
- **Safety** – All randomized patients who received lepirudin/heparin study medication (analyzed as initially treated).
- **Modified intent-to-treate (MITT)** – All randomized patients who received lepirudin/heparin study medication and who had their 7-day event assessment completed (analyzed as initially treated).
- **Per-protocol (PP)** – All MITT with no major protocol deviations (analyzed as initially treated).
- **Warfarin subgroup** – efficacy and safety analyses – those randomized to warfarin/standard care (analyzed as randomized).

A 7-day event assessment was considered complete if either 1) on the 7-day form there must be an answer (yes/no) to each of the following three items: death, new MI and refractory angina; or 2) if the 7-day form was missing, but according to actual event forms

the patient either died, or suffered from a new MI before the end of day 7. [Reviewer's note: The source of the death and new MI information for patients is not identified in the data listings as being from "the 7-day form" or the "actual event forms". At any rate refractory angina would be captured only on the 7 day form].

The analysis plan identifies the adjudicated incidence of CV death or new MI at 7 days in the MITT population as the primary endpoint with CV death or new MI or refractory angina/re-hospitalization for unstable angina at 7 days as the key secondary endpoint. Treatment differences were to be tested using the MITT population. Additional analyses were to be done for other endpoints and other populations.

The protocol specified that three interim analyses would be done when about 25%, 50%, and 75% of patients had been randomized. Safety and efficacy variables would be analyzed at these points with the intent of (1) increasing sample size if event rates were lower than expected, (2) assessing safety, and (3) assessing whether the study should be stopped for efficacy (using combined endpoint of CV death and new MI with a prespecified stopping rule in place).

Results: This study was conducted from August 12, 1996 through February 27, 1999 at 360 sites in Canada, Europe, South America, Mexico, Australia, S. Africa, and the U.S. . A total of 10,141 patients were randomized (5083 to lepirudin, 5058 to heparin). About 19% of the patients were from Canada, 14% from Poland, and 10% were from Italy. All other countries enrolled less than 10% of the total patients. About 1% of patients were in the U.S. Demographic features of the patients enrolled are summarized in the following table:

OASIS-2: Demographics and Baseline Characteristics

	Lepirudin low	Heparin	Total
Sex			
male	3040 (60%)	3098 (62%)	6138 (61%)
female	2005 (40%)	1935 (38%)	3940 (39%)
Age (yrs)			
mean	64	64	64
median	65	65	65
range	22-86	26-85	22-86
Smoker			
current	1145 (23%)	1153 (23%)	2298 (23%)
Ethnic group			
Caucasian	4086 (81%)	4086 (81%)	8172 (81%)
Latin American	652 (13%)	658 (13%)	1310 (13%)
Other	307 (6%)	289 (6%)	596 (6%)
Clinical diagnosis at time of randomization:			
suspected unstable angina	4426 (88%)	4407 (88%)	8833 (88%)
suspected MI without ST elevation	618 (12%)	626 (12%)	1244 (12%)
Baseline ECG			
abnormal	4586 (91%)	4553 (90%)	9139 (91%)
normal	459 (9%)	480 (10%)	939 (9%)
Related medical history			
Previous MI	1968 (39%)	1941 (39%)	3909 (39%)
PTCA/atherectomy without stent	346 (7%)	365 (7%)	711 (7%)
PTCA/atherectomy with stent	85 (2%)	82 (2%)	167 (2%)
CABG surgery	614 (12%)	653 (13%)	1267 (13%0
CAD other evidence:	2854 (57%)	2765 (55%)	5619 (56%)
chronic stable angina	1942 (38%)	1920 (38%)	3862 (38%)
cardiac cath. showing significant CAD	898 (18%)	874 (17%)	1772 (18%)
positive stress test	590 (12%)	534 (11%)	1124 (11%)

other objective evidence	189 (4%)	179 (4%)	368 (4%)
Stroke	193 (4%)	223 (4%)	416 (4%)
Hypertension	2699 (53%)	2724 (54%)	5423 (54%)
Heart failure	414 (8%)	377 (7%)	791 (8%)
Diabetes	1060 (21%)	1056 (21%)	2116 (21%)

from sponsor's tables, NDA Vol. 21.3

Most patients (97%) had chest pain within 12 hours prior to admission (50% within 6 hrs; 47 % within 6-12 hrs). Most patients with abnormal ECG at baseline had ST depression (42%) or T-wave inversion (37%). About 90% of patients had used some conconmitant medication within 2 days prior to randomization. About 65% of patients were taking aspirin and about 58% were using non-IV nitrates. Forty percent of patients were on bets-blockers and 31% on ACE inhibitors. Generally, treatment groups were well-balanced with regard to baseline parameters. There were slightly fewer patients in the heparin group who had never smoked (39%, lepirudin; 36%, heparin). Location of ECG abnormality tended to be more in the anterior or anteriolateral leads as compared to the inferior or inferiolateral leads in the heparin group as compared to the leprirudin group (52% and 22% in the heparin group; 49% and 24% in the lepirudin group. Slightly more heparin than lepirudin patients had recent use of anti-platelet agents other than aspirin (4% vs. 3%). It is doubtful that any of these slight imbalances would have a significant effect on the study results.

Disposition of patients for OASIS-2 is summarized in the following table:

OASIS-2: Disposition of Patients During the Infusion Period of the Study

	Lepirudin	Heparin	Total
Lepirudin versus Heparin phase			
Total randomized[a]	5083	5058	10141
Did not receive study medication	unk	unk	61
Received study medication[a]	5047	5033	10080
MITT population[b]	5045	5033	10078
Premature discontinuation before completion of infusion:	927 (18%)	735 (15%)	1662 (17%)
aPTT out of range	294 (6%)	158 (3%)	452 (4%)
bleeding or other adverse event	176 (3%)	116 (2%)	292 (#%)
urgent surgery/invasive procedure	123 (2%)	147 (3%)	270 (3%)
other [d]	93 (2%)	81 (2%)	174 (2%)
technical problem /administrative error	79 (2%)	88 (2%)	167 (2%)
early discharge home	76 (2%)	64 (1%)	140 (1%)
consent withdrawn	40 (1%)	36 (1%)	76 (1%)
thrombolysis	21 (<1%)	31 (1%)	52 (1%)
serum creatinine >2.5mg/dl	21 (<1%)	13 (<1%)	34 (<1%)
Unspecified bleeding or other adverse event	4 (<1%)	1 (<1%)	5 (<1%)
Assessments Available (Completed study):			
Completed infusion[c] (72 hrs)	5006 (99%)	4987 (99%)	9993 (99%)
Completed 7 days	4971 (99%)	4951 (98%)	9922 (98%)
Completed 35 days	4863 (96%)	4826 (96%)	9689 (96%)
Completed study early (between 35 and 166 days)	53 (1%)	47 (1%)	100 (1%)
Completed study	4704 (93%)	4652 (92%)	9356 (93%)
Warfarin versus Standard therapy substudy[b]			
Randomized to warfarin	949 (19%)	963 (19%)	1912 (19%)
Randomized to standard therapy	950 (19%)	931 (18%)	1881 (19%)
Not randomized	3146 (62%)	3139 (63%)	6285 (62%)

[a] 10 lepirudin patients initially received heparin; and 5 heparin patients initially received lepirudin. The numbers under "received study medication" indicate initial treatment received by the patient.

[b] MITT = modified intention-to-treat

[c] includes 2 patients not in the MITT population; about 5% of lepirudin and 5% of heparin patients had infusion interrupted for more than 1 hour.

d largest categories: lack of efficacy, unspecified physician's decision

from sponsor's table NDA Vol. 21.3, Table 2 of study report.

About 18% of lepirudin patients and 15% of heparin patients discontinued intravenous study medication before completion of infusion. These discontinuations were about equally spaced over the 72 hour infusion period. About 5% of patients in both treatment groups had study drug infusion interrupted for more than 1 hour. The infusion rate was adjusted at some point in 52% of lepirudin patients [increased in 24%, decreased in 27%; increased and decreased in 2%] and in 88% of heparin patients [increased in 48%, decreased in 25% and increased and decreased in 16%]. About 9% of lepirudin patients and 9% of heparin patients had non-study heparin use within 2 hours prior to randomization. (About 28% of patients received some non-study heparin after presenting to the hospital but prior to randomization). About 16% of lepirudin patients and 18% of heparin patients received non study intravenous heparin within 24 hours after end of the study drug infusion.

A small number of patients (about 15) were randomized to one treatment but received the other initially (10 randomized to lepirudin received heparin initially; 5 randomized to heparin initially received lepirudin). Some of these were switched to the correct treatment later; at least one patient was inadvertently switched from the correct treatment to the other treatment. Apparently some additional switches occurred as well. These switches appear to have involved relatively small numbers of patients and switches occurred in both directions (5 from lepirudin to heparin; 10 from heparin to lepirudin). Though the study was blinded, the sponsor does not explain how the erroneous treatments were discovered.

Reasons for discontinuation from study prior to completion are summarized in the following table:

OASIS-2: Reasons for Premature Discontinuation from the Study

Reason	Number of Patients (%)		
	Lepirudin (N = 5045)	Heparin (N = 5033)	Total (N = 10078)
Randomization to end of study:			
Total	341 (7%)	381 (8%)	722 (7%)
Died	312 (6%)	348 (7%)	660 (7%)
Lost to followup	22 (<1%)	21 (<1%)	43 (<1%)
Withdrawal of consent	7 (<1%)	12 (<1%)	19 (<1%)
Randomization to day 7:			
Total	74 (1%)	82 (2%)	156 (2%)
Died	69 (1%)	77 (2%)	146 (1%)
Lost to followup	3 (<1%)	3 (<1%)	6 (<1%)
Withdrawal of consent	2 (<1%)	2 (<1%)	4 (<1%)
Day 8 to day 35:			
Total	108 (2%)	125 (2%)	233 (2%)
Died	100 (2%)	119 (2%)	219 (2%)
Lost to followup	7 (<1%)	4 (<1%)	11 (<1%)
Withdrawal of consent	1 (<1%)	2 (<1%)	3 (<1%)
Day 36 to end of study:			
Total	159 (3%)	174 (3%)	333 (3%)
Died	143 (3%)	152 (3%)	295 (3%)
Lost to followup	12 (<1%)	14 (<1%)	26 (<1%)
Withdrawal of consent	4 (<1%)	8 (<1%)	12 (<1%)

from sponsor's table, NDA Vol. 21.3, Table 6-7

Overall about 7% of patients discontinued study prematurely. The majority of these discontinuations (about 91%) were due to death of the patient. About half of these deaths occurred after day 35.

Efficacy: The sponsor's primary analysis of efficacy (CV death and new MI at 7 days) and key secondary efficacy analysis (CV death, new MI or refractory angina) are displayed in the sponsor's table below:

Findings for CV death or new MI and CV death, new MI, or refractory angina (MITT population)

Composite endpoint	Number of patients (%) with events				Relative risk[c] (95% CI)		p-value [d]
Time from randomization	Lepirudin N=5045		Heparin N=5033				
CV death or new MI							
72 hours	99	(2.0%)	132	(2.6%)	0.74	(0.57 – 0.97)	0.0229
7 days [a]	178	(3.5%)	211	(4.2%)	0.83	(0.68 – 1.02)	0.0714
35 days	337	(6.7%)	377	(7.5%)	0.88	(0.76 – 1.03)	0.0896
180 days	517	(10.2%)	541	(10.7%)	0.95	(0.83 – 1.08)	0.3377
CV death, new MI or refractory angina							
72 hours	154	(3.1%)	199	(4.0%)	0.76	(0.62 – 0.95)	0.0108
7 days [b]	279	(5.5%)	336	(6.7%)	0.82	(0.69 – 0.96)	0.0138
35 days	633	(12.5%)	675	(13.4%)	0.92	(0.82 – 1.04)	0.1600
180 days	1026	(20.3%)	1055	(21.0%)	0.96	(0.87 – 1.06)	0.3559

[a] The primary analysis of efficacy.

[b] The key secondary analysis of efficacy.

[c] Based on a logistic regression model.

[d] Based on a Mantel-Haenszel test stratified by center

A difference of 0.7% between lepirudin and heparin groups is seen in incidence (combined) of CV death or new MI. This difference was not found to be statistically significant (p = 0.071, sponsor's determination by Mantel-Haenszel test; p = 0.088, by Fisher's exact test [see FDA Statistical Review]). A comparable analysis using the ITT population shows an event rate of 182/5083 (3.6%) for the lepirudin group and 213/5058 (4.2%) for the heparin group. This difference is not statistically significant (p = 0.086, Mantel-Haenszel test; p = 0.111, Fisher's exact test). The sponsor's exclusion of 63 patients (33 lepirudin; 30 heparin) resulted in exclusion at 7 days of 10 events in the lepirudin group (2 CV death, 4 new MI, 4 refractory angina) and 5 events in the heparin group (1 CV death, 4 refractory angina) and at day 35 exclusion of 1 new MI in the lepirudin group. These exclusions favored lepirudin in the sponsor's statistical comparison. Analysis of combined CV death or new MI at 72 hours showed a statistically significant difference (p = 0.023 in the MITT population; p = 0.034 in the ITT population).

FDA Statistical Review points out that the efficacy result does not appear consistent across countries for the primary endpoint. Only in 7 of the 15 participating countries was there a numerical advantage in favor of lepirudin over heparin for the primary endpont.

For the key secondary endpoint of combined CV death, new MI or refractory angina, a difference between groups was seen at 7 days (p = 0.014, MITT; p = 0.016 ITT) and at 72 hrs (p = 0.011, MITT; p = 0.016 ITT). The prespecified statistical analysis stipulated that on this endpoint, a 2-tailed p-value of 0.01 was to be considered statistically significant (probably reflecting the fact that sample size for the study was determined based on the estimated combined rate of CV death or new MI and not on the higher combined rate of CV death, new MI or refractory angina).

Efficacy analyses in all the study populations are summarized in Appendix D.

When the efficacy results (7 days) were examined in the warfarin substudy patients, the sponsor found the following:

OASIS-2: Composite Efficacy Endpoints by Treatment and Warfarin Group (MITT Population)

	Lepirudin	Heparin
Warfarin		
CV death or new MI	20 (2.1%)	27 (2.8%)
CV death, new MI or refractory angina	29 (3.1%)	49 (5.1%)
Total patients	949	963
Standard Therapy		
CV death or new MI	24 (2.5%)	27 (2.9%)
CV death, new MI or refractory angina	36 (3.8%)	48 (5.2%)
Total patients	950	931
Not Randomized		
CV death or new MI	98 (4.3%)	119 (5.2%)
CV death, new MI or refractory angina	157 (6.9%)	187 (8.1%)
Total patients	2270	2296
No warfarin supplies*		
CV death or new MI	36 (4.1%)	38 (4.5%)
CV death, new MI or refractory angina	57 (6.5%)	52 (6.2%)
Total patients	876	843

* Presumably these were patients at centers where no patients were entered into the warfarin substudy because there were no warfarin supplies

reference: sponsor's table, NDA Vol. 21.3

Event rates were higher in the patients who were not randomized into the warfarin substudy even though they were at centers where warfarin was available. The time to event for these subgroups was not provided, so it is not clear whether more patients in the "not randomized" group had events prior to the time warfarin would have been started. Event rates in these subgroups at 72 hours were not provided.

Incidence of interventions other than catheterizations was significantly higher in the heparin group as compared to the lepirudin group up to day 7 (8.1% vs. 6.7%, p = 0.011) and incidence of PTCA/stent/atherectomy was higher in the heparin group as compared to the heparin group up to day 7 (5.1% vs. 4.2%, p = 0.025) and up to day 35 (12.9% vs. 11.5%, p = 0.023); otherwise, there did not appear to be significant differences between groups in interventions during the study.

The sponsor's table below shows incidences of occurrence of individual clinical endpoints.

OASIS-2: Cumulative Incidences of All Clinical Events in the Sponsor's Various Analysis Populations*

Time Period / Clinical Event	Number of Patients (%)							
	MITT (adjudicated)		MITT (investigator reported)		Per Protocol (adjudicated)		ITT (adjudicated)	
	Lepirudin (N=5045)	(N=5033)	Lepirudin (N=5045)	Heparin (N=5033)	Lepirudin (N=4927)	Heparin (N=4909)	Lepirudin (N=5083)	Heparin (N=5058)
Up to 72 hours:								
CV death	39 (0.8%)	45 (0.9%)	39 (0.8%)	45 (0.9%)	37 (0.8%)	44 (0.9%)	41 (0.8%)	46 (0.9%)
Non-CV death	0	0	0	0	0	0	0	0
New MI	70 (1.4%)	95 (1.9%)	73 (1.4%)	99 (2.0	68 (1.4%)	94 (1.9%)	72 (1.4%)	96 (1.9%)
Refractory angina	58 (1.1%)	76 (1.5%)	75 (1.5%)	87 (1.7%)	56 (1.1%)	75 (1.5%)	59 (1.2%)	77 (1.5%)
Up to 7 days:								
CV death	69 (1.4%)	77 (1.5%)	69 (1.4%)	77 (1.5%)	66 (1.3%)	75 (1.5%)	71 (1.4%)	78 (1.5%)
Non-CV death	0	0	0	0	0	0	0	0
New MI	129 (2.6%)	155 (3.1%)	133 (2.6%)	160 (3.2%)	126 (2.6%)	152 (3.1%)	131 (2.6%)	156 (3.1%)
Refractory angina	110 (2.2%)	140 (2.8%)	134 (2.7%)	156 (3.1%)	107 (2.2%0	136 (2.8%)	111 (2.2%)	141 (2.8%)
Up to 35 days:								
CV death	166 (3.3%)	188 (3.7%)	165 (3.3%)	186 (3.7%)	162 (3.3%)\	183 (3.7%)	168 (3.3%)	189 (3.7%)
Non-CV death	3 (0.1%)	8 (0.2%)	4 (0.1%)	10 (0.2%)	3 (0.1%)	5 (0.1%)	3 (0.1%)	8 (0.2%)
New MI	229 (4.5%)	246 (4.9%)	235 (4.7%)	256 (5.1%)	222 (4.5%)	242 (4.9%)	232 (4.6%)	247 (4.9%)
Refractory angina	337 (6.7%)	342 (6.8%)	366 (7.3%)	373 (7.4%)	329 (6.7%)	338 (6.9%)	338 (6.6%)	345 (6.8%)
Up to 180 days**								
CV death	294 (5.8%)	318 (6.3%)	283 (5.6%)	305 (6.1%)	286 (5.8%)	307 (6.3%)	295 (5.8%)	321 (6.3%)
Non-CV death	20 (0.4%)	30 (0.6%)	31 (0.6%)	43 (0.9%)	17 (0.3%)	26 (0.5%)	20 (0.4%)	30 (0.6%)
New MI	308 (6.1%)	319 (6.3%)	315 (6.2%)	330 (6.6%)	298 (6.0%)	314 (6.4%)	311 (6.1%)	320 (6.3%)
Refractory angina	596 (11.8%)	608 (12.1%)	629 (12.5%)	644 (12.8%)	580 (11.8%)	598 (12.2%)	599 (11.8%)	613 (12.1%)

* some patients had more than one type of event. All events are counted.
**a few patients were in for longer than 180 days

reviewer's table, based on sponsor's tables, NDA Vol. 21.3

About 11% of patients in both lepirudin and heparin treatment groups had confirmed MI associated with presentation before randomization. An additional 7.3% of lepirudin patients and 8.2% of heparin patients had associated MI confirmed after randomization.

The following table summarizes results using the most serious event experienced by each patient (i.e., each patient counted only once) and shows results counting "All cause" death and CV death. Seriousness is ranked: death (CV or non-CV) > new MI > refractory angina.

OASIS-2: Cumulative Incidences of Most Serious Clinical Outcome for Each Patient in the Sponsor's Various Analysis Populations*

	Number of Patients (%)							
	MITT (adjudicated)		MITT (investigator reported)		Per Protocol (adjudicated)		ITT (adjudicated)	
Time Period Clinical Event	Lepirudin (N=5045)	(N=5033)	Lepirudin (N=5045)	Heparin (N=5033)	Lepirudin (N=4927)	Heparin (N=4909)	Lepirudin (N=5083)	Heparin (N=5058)
Up to 72 hours:								
CV death	39 (0.8%)	45 (0.9%)	39 (0.8%)	45 (0.9%)	37 (0.8%)	44 (0.9%)	41 (0.8%)	46 (0.9%)
New MI	60 (1.2%)	87 (1.7%)	63 (1.2%)	90 (1.8%)	59 (1.2%)	86 (1.8%)	62 (1.2%)	88 (1.7%)
Refractory angina	55 (1.1%)	67 (1.3%)	70 (1.4%)	78 (1.5%)	53 (1.1%)	66 (1.3%)	56 (1.1%)	68 (1.3%)
Up to 7 days:								
CV death	69 (1.4%)	77 (1.5%)	69 (1.4%)	77 (1.5%)	66 (1.3%)	75 (1.5%)	71 (1.4%)	78 (1.5%)
New MI	109 (2.2%)	134 (2.7%)	113 (2.2%)	138 (2.7%)	108 (2.2%)	131 (2.7%)	111 (2.2%)	135 (2.7%)
Refractory angina	101 (2.0%)	125 (2.5%)	123 (2.4%)	141 (2.8%)	98 (2.0%)	123 (2.5%)	102 (2.0%)	126 (2.5%)
Up to 35 days:								
CV death	166 (3.3%)	188 (3.7%)	165 (3.3%)	186 (3.7%)	162 (3.3%)\	183 (3.7%)	168 (3.3%)	189 (3.7%)
New MI	171 (3.4%)	189 (3.8%)	176 (3.5%)	197 (3.9%)	167 (3.4%)	188 (3.8%)	174 (3.4%)	190 (3.8%)
Refractory angina	296 (5.9%)	298 (5.9%)	324 (6.4%)	324 (6.4%)	288 (5.8%)	296 (6.0%)	297 (5.8%)	301 (6.0%)
All cause death	169 (3.3%)	196 (3.9%)					171 (3.4%)	197 (3.9%)
New MI	170 (3.4%)	189 (3.8%)	ND	ND	ND	ND	173 (3.4%)	190 (3.8%)
Rfractory angina	296 (5.9%)	298 (5.9%)					297 (5.8%)	301 (6.0%)
Up to 180 days**								
CV death	294 (5.8%)	318 (6.3%)	283 (5.6%)	305 (6.1%)	286 (5.8%)	307 (6.3%)	295 (5.8%)	321 (6.3%)
New MI	223 (4.4%)	223 (4.4%)	227 (4.5%)	230 (4.6%)	217 (4.4%)	222 (4.5%)	226 (4.4%)	224 (4.4%)
Refractory angina	509 (10.1%)	514 (10.2%)	541 (10.7%)	542 (10.8%)	494 (10.0%)	507 (10.3%)	511 (10.1%)	519 (10.3%)
All cause death	314 (6.2%)	348 (6.9%)					315 (6.2%)	351 (6.9%)
New MI	221 (4.4%)	220 (4.4%)	ND	ND	ND	ND	224 (4.4%)	221 (4.4%)
Rfractory angina	505 (10.0%)	514 (10.2%)					507 (10.0%)	519 (10.3%)

* some patients had more than one type of event. Patients are counted only once (for most serious event). Up to 7 days there were no non-CV deaths
**a few patients were in for longer than 180 days
ND = not done
        reviewer's table, based on sponsor's tables, NDA Vol. 21.3

Safety: A total of 5045 patients received lepirudin in this study (mean infusion rate 0.14mg/kg/hr; mean duration 66 hrs) and 5033 patients received heparin (mean infusion rate 15U/kg/hr; mean duration 67.5 hrs). Occurrence of bleeding episodes in these patients is summarized in the sponsor's following table:

Bleeding episodes during OASIS-2

Time period	Number (%) of patients				p-value [a]
Bleeding type	Lepirudin N = 5047		Heparin N = 5033		
Any bleed	**721**	**(14.3%)**	**549**	**(10.9%)**	**0.0001**
Randomization to day 7					
Any bleed	441	(8.7%)	260	(5.2%)	0.0001
Minor bleed	389	(7.7%)	226	(4.5%)	0.0001
Major bleed	60	(1.2%)	37	(0.7%)	0.0243
Life-threatening [b]	21	(0.4%)	22	(0.4%)	0.8800
Intracranial bleed	2	(0.0%)	3	(0.1%)	0.6870
Surgery required	8	(0.2%)	7	(0.1%)	1.0000
CRF life-threatening [c]	23	(0.5%)	12	(0.2%)	0.0890
Fatal bleed	3	(0.1%)	4	(0.1%)	0.7261
Day 8 to day 35					
Any bleed	206	(4.1%)	204	(4.1%)	0.9598
Minor bleed	164	(3.2%)	160	(3.2%)	0.8655
Major bleed	50	(1.0%)	52	(1.0%)	0.8429
Life-threatening [b]	35	(0.7%)	28	(0.6%)	0.4486
Intracranial bleed	7	(0.1%)	12	(0.2%)	0.2621
Surgery required	17	(0.3%)	7	(0.1%)	0.0636
CRF life-threatening [c]	16	(0.3%)	15	(0.3%)	1.0000
Fatal bleed	6	(0.1%)	6	(0.1%)	1.0000
Day 36 to day 180					
Any bleed	161	(3.2%)	153	(3.0%)	0.6883
Minor bleed	118	(2.3%)	121	(2.4%)	0.8445
Major bleed	45	(0.9%)	35	(0.7%)	0.3124
Life-threatening [b]	31	(0.6%)	20	(0.4%)	0.1597
Intracranial bleed	15	(0.3%)	6	(0.1%)	0.0781
Surgery required	9	(0.2%)	7	(0.1%)	0.8035
CRF life-threatening [c]	19	(0.4%)	9	(0.2%)	0.0867
Fatal bleed	6	(0.1%)	3	(0.1%)	0.5076

[a] Fisher's Exact test

[b] Objective criteria: includes all fatal and intracranial bleeds and major bleeds requiring surgical intervention, transfusion of ≥ 4 units of blood or blood products, as defined in *Section 4.1.2.1 Bleeds.*

[c] Subjective assessment

Both major and minor bleeding episodes were more frequent in the lepirudin group at the 7 day assessment. Three bleeds in the lepirudin group and 4 bleeds in the heparin group were fatal. Seventy-two lepirudin patients (1.4%) and 58 heparin patients (1.2%) suffered stroke during this study. Relatively more of these events in the lepirudin group occurred after day 8 as compared to in the heparin group. There were 8 hemorrhagic strokes in the lepirudin group (7 occurred after day 35) and 10 hemorrhagic strokes in the heparin group (8 occurred before day 35). The following sponsor's table shows incidence of adverse events from randomization to day 7.

Patients with adverse events from randomization to day 7

Adverse event (AE)	Lepirudin		Heparin		Total		p-value[a]
	N = 5047		N = 5033		N = 10 080		
All adverse events							
Any AE	710	(14.1%)	548	(10.9%)	1258	(12.5%)	0.0001
Hemorrhagic AE	446	(8.8%)	263	(5.2%)	709	(7.0%)	0.0001
Non-hemorrhagic AE	348	(6.9%)	348	(6.9%)	696	(6.9%)	1.0000
Serious adverse events							
Any AE	200	(4.0%)	206	(4.1%)	406	(4.0%)	0.7613
Hemorrhagic AE	61	(1.2%)	40	(0.8%)	101	(1.0%)	0.0450
Non-hemorrhagic AE	151	(3.0%)	174	(3.5%)	325	(3.2%)	0.1948
Fatal adverse events							
Any AE	75	(1.5%)	87	(1.7%)	162	(1.6%)	0.3428
Hemorrhagic AE	4	(0.1%)	6	(0.1%)	10	(0.1%)	0.5481
Non-hemorrhagic AE	72	(1.4%)	82	(1.6%)	154	(1.5%)	0.4178
Adverse events resulting in discontinuation of infusion							
Any AE	187	(3.7%)	119	(2.4%)	306	(3.0%)	0.0001
Hemorrhagic AE	130	(2.6%)	53	(1.1%)	183	(1.8%)	0.0001
Non-hemorrhagic AE	62	(1.2%)	69	(1.4%)	131	(1.3%)	0.5394

[a] Fisher's Exact test

Significantly more adverse events leading to discontinuation of the infusion occurred in the lepirudin group. Most events leading to study drug discontinuation were hemorrhagic events in the lepirudin group (38 GI hemorrhage; 35 hematuria; 15 epistaxis; 13 injection site hemorrhage; 12 hemoptysis). Hemorrhagic events in the heparin group were similar but less frequent. In the heparin group most events leading to study drug discontinuation were non hemorrhagic events. Most frequently reported fatal adverse events in both treatment groups from randomization to day 7 were heart arrest (19 lepirudin; 16 heparin); MI (18 lepirudin; 20 heparin) and shock (17 lepirudin; 24 heparin). Six lepirudin patients and 3 heparin patients suffered serious allergic reactions by the day 7 assessment.

Reviewer's Comments: OASIS-2 was a large, randomized, double-blind, multicenter, multinational trial planned with benefit of a pilot study prior to initiating the study. It was designed as a superiority trial to demonstrate a benefit of lepirudin over heparin in preventing CV death and MI in during the first 7 days after initiation of therapy in patients presenting with unstable angina. The study clearly failed to meet its prespecified criteria for success based on the primary endpoint (combined CV death or new MI). Also, using the sponsor's prespecified 0.01 level of significance the study failed as well on the key secondary efficacy endpoint (combined CV death, new MI, or refractory angina).

Interpretation of the study results is complicated by several factors:

1. The study results are confounded by nonrandom selection of patients to participate in a substudy of warfarin versus standard care beginning 24 hours after initiation of

the lepirudin or heparin infusion. About 37% of patients participated in the warfarin substudy Selection of patients likely was influenced by factors, such as patient symptoms, bleeding or other events that that may have affected patient management and also may have affected the study endpoints.

2.   The use of warfarin beginning after 24 hours on lepirudin or heparin in a large fraction of the patients in the study complicates the interpretation of the events occurring after the first day of the study and could have significantly impacted the day 7 result.

3.   Additional interventions, such as use of non-study heparin, occurred during the study and could have affected outcomes.

4.   Definitions for some endpoints were changed during the study.

5.   It is not clear how well-protected the blind was during the study. In several instances patients were given the wrong treatment and somehow this was discovered and corrected during the infusion period. If the blind was weak, it is even more likely that interventions (such as use of other anticoagulants) that might affect the study outcomes may have been made in a non-random fashion in the study.

Discussion:
This application should be viewed essentially as submission of a single study to demonstrate efficacy of lepirudin for the desired indication. Study OASIS-1 is not acceptable as an adequate and well controlled study because: it was not blinded with regard to lepirudin dose; a number of protocol amendments that may have affected the outcome of the study were made after patient enrollment had begun (including changing the time of start of warfarin dosing and changing definitions of endpoints); there was no prospective plan for statistical analysis. While the results of OASIS-1 are consistent with a beneficial effect of lepirudin, the support is weak. Therefore, OASIS-2 must essentially stand on its own as an efficacy trial. The problems with OASIS-2, including non-random inclusion of some patients in a warfarin substudy, have been mentioned above. Additionally, a single trial for efficacy should demonstrate internal consistency and provide evidence that is robust and statistically convincing. It does not appear that OASIS-2 has met the criteria set forth in the May 1998 **Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Human Drug and Biological Products.**

The sponsor proposes to pool OASIS-1 and OASIS-2 to enhance the efficacy results. This is problematic for several reasons. As described above, OASIS-1 clearly is deficient with regard to design and conduct (e.g., open-label design, changes in treatment during the study [start time of warfarin in substudy], confounding non-study therapies, non-random selection of patients for participation in warfarin substudy). Definitions of some endpoints (e.g., refractory angina, severe angina, ECG changes indicative of new MI) were somewhat different in the two studies. Furthermore, the relative sizes of the two studies are not conducive to a pooled analysis (OASIS-1 had only about 1/10 as many patients enrolled as OASIS-2). The heparin regimens used in OASIS-1 and OASIS-2 were different. Also, the lepirudin dosing in half of the lepirudin patients in OASIS-1 (i.e., the "low dose" patients was not the same as in OASIS-2.

Finally, the sponsor puts forth the argument that using data from the literature in combination with the OASIS-2 data, it can be deduced that had placebo been present in OASIS-2, lepirudin would have been superior to placebo with regard to the primary endpoint. Statistical aspects of this approach are presented in the FDA Statistical Review. Difficulties with this approach include the fact that heparin is not labeled for this indication and though heparin is widely used in managing these patients the dosing regimen is not standardized.

These issues will be presented to the Cardiorenal Advisory Committee for discussion on May 2, 2000.

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APPENDIX A

List of Abbreviations

ACE	angiotensin converting enzyme
AE	adverse event
aPTT	activated partial thromboplastin time
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CCU	coronary care unit
CK	creatine kinase
CT	cat scan
CV	cardiovascular
ECG	electrocardiogram
INR	international normalized ratio
HIT	heparin-inducted thrombocytopenia
ICCU	intensive coronary care unit
ICU	iintensive care unit
ITT	intention-to-treat
IV	intravenous
MI	myocardial infarction
MITT	modified intention-to-treat
MRI	magnetic resonance imaging
NDA	new drug application
OASIS	Organization to Assess Strategies for Ischemic Syndromes
PT	prothrombin time
PTCA	percutaneous transluminal coronary angioplasty
TT	thrombin time

APPENDIX B

13. DESCRIPTION AND DEFINITION OF ENDPOINTS

The primary follow-up period in this study for the evaluation of the effects of hirudin will be 7 days. For warfarin and standard therapy, the same outcomes will be reviewed over 35 days. Follow-up assessments will be performed at 35 days and 6 months after randomization. The endpoints recorded after randomization will be as follows.

13.1 Clinical Outcome Measures

i)   **Cardiovascular Death:** to be subdivided by cause.

ii)   **New myocardial infarction after randomization:** This will be subdivided into subsequent infarction for patients with an entry diagnosis of suspected unstable angina, or reinfarction for patients with initial suspected MI without ST elevation. The criteria for new MI after randomization will be:

      a) **within 24 hours of randomization:** patients must have recurrent typical clinical symptoms, with either new enzyme elevation or new ECG changes,

      b) **beyond 24 hours:** two out of three criteria of clinical symptoms, new enzyme changes or ECG changes.

Clinical symptoms include typical prolonged ischemic chest pain lasting ≥ 20 minutes chest pain requiring narcotic analgesia or acute pulmonary edema.

Diagnostic ECG changes include new ST elevation, (eg ST elevation > 1 mm in two contiguous leads), new Q-waves, or other ECG changes consistent with myocardial infarction. ECG documentation of this event will be required.

Diagnostic enzyme elevations include a rise in CK above twice the upper limit of the reference range (or > 20% of the previous value if CK is already elevated), or a rise in CK-MB above the reference range. In the absence of these enzyme analyses being available in a particular centre, a rise of other less specific cardiac enzymes, as for CK above, will be adequate.

iii) **Refractory angina:** defined as recurrent ischemic chest pain (with documented characteristic ECG changes during pain) lasting > 5 minutes occurring in the presence of "optimum" medical treatment and requiring an additional intervention in the view of the responsible physician. Optimum treatment in this context is defined as at least two anti-anginal treatments, one of which should be an intravenous nitrate (unless nitrate therapy is contraindicated for some reason). An additional intervention will include: thrombolytic therapy for threatened MI, intra-aortic balloon pump, or cardiac catheterization within 24 hours, or transfer to a tertiary care centre within 48 hours of the onset of pain/symptoms (i.e. impending infarction).

iv) **Severe angina:** defined as at least 2 episodes of recurrent ischemic chest pain during a 24 hour period while on optimal therapy, with documentation of new ECG changes associated with at least one episode of cardiac chest pain.

v) **Recurrent angina:** defined as all other recurrent ischemic chest pain lasting more than five minutes which requires any increase in or addition of a new anti-anginal medication, with or without characteristic ECG changes. Patients who are on optimum treatment (as defined above) but who only require a narcotic analgesic for pain relief will be classified as having recurrent angina.

13.2 Safety Outcome Measures

i) All strokes will be recorded and classified as definite intracranial hemorrhage, definite ischemic stroke, or other (unclassified). Documentation by either CT or MRI scan, or autopsy report will be obtained wherever possible.

ii) All bleeding will be recorded, and will be classified as **major if:**
   - fatal or life-threatening
   - permanently or significantly disabling
   - an overt bleed requires transfusion of two or more units of packed red blood cells or equivalent

- surgical intervention is required
  or minor if any other bleeding including bleeding around puncture sites, subcutaneous bruising or hematomas occur.

iii) Other possible side effects of treatment (eg. rash, fever, rigors or allergic reactions). In this case, a plasma sample should be drawn, clearly identified with the patient ID and stored at -20°C.

APPENDIX C

Findings for CV death or new MI, CV death, new MI or refractory angina, and CV death, new MI, refractory, severe or recurrent angina

Composite endpoint Time from randomization	Treatment group [a]	Patients with events (%) [b]	Relative risk [c]	95% CI	p-value [c]
CV death or new MI (Double endpoint)					
72 hours	Lepirudin low	1.5%	0.54	0.17 - 1.74	0.2979
	Lepirudin medium	1.9%	0.69	0.23 - 2.04	0.4803
	Lepirudin combined	1.7%	0.61	0.25 - 1.53	0.2875
	Heparin	2.7%			
7 days	Lepirudin low	2.6%	0.52	0.21 - 1.26	0.1787
	Lepirudin medium	2.6%	0.53	0.22 - 1.28	0.1493
	Lepirudin combined	2.6%	0.52	0.26 - 1.07	0.0805
	Heparin	4.9%			
35 days	Lepirudin low	5.5%	0.64	0.34 - 1.22	0.2373
	Lepirudin medium	6.4%	0.75	0.40 - 1.38	0.3083
	Lepirudin combined	5.9%	0.69	0.42 - 1.16	0.1657
	Heparin	8.4%			
End of the study	Lepirudin low	7.4%	0.64	0.37 - 1.12	0.1561
	Lepirudin medium	8.6%	0.76	0.44 - 1.30	0.2862
	Lepirudin combined	8.0%	0.70	0.45 - 1.10	0.1261
	Heparin	11.1%			
CV death, new MI or refractory angina (Triple endpoint)					
72 hours	Lepirudin low	2.6%	0.63	0.25 - 1.57	0.3019
	Lepirudin medium	1.9%	0.45	0.16 - 1.26	0.1069
	Lepirudin combined	2.2%	0.54	0.25 - 1.17	0.1067
	Heparin	4.0%			
7 days	Lepirudin low	4.4%	0.67	0.33 - 1.36	0.3106
	Lepirudin medium	3.0%	0.45	0.20 - 1.01	0.0436
	Lepirudin combined	3.7%	0.56	0.30 - 1.03	0.0641
	Heparin	6.5%			
35 days	Lepirudin low	7.4%	0.68	0.39 - 1.19	0.2364
	Lepirudin medium	7.1%	0.65	0.37 - 1.16	0.1266
	Lepirudin combined	7.2%	0.67	0.42 - 1.06	0.0911
	Heparin	10.5%			
End of the study	Lepirudin low	9.2%	0.65	0.39 - 1.08	0.1291
	Lepirudin medium	9.4%	0.66	0.40 - 1.10	0.1040
	Lepirudin combined	9.3%	0.66	0.43 - 1.00	0.0536
	Heparin	13.5%			
CV death, new MI, refractory, severe or recurrent angina (Quintuple endpoint)					
72 hours	Lepirudin low	10.3%	0.62	0.38 - 1.01	0.0466
	Lepirudin medium	8.2%	0.48	0.29 - 0.81	0.0050
	Lepirudin combined	9.3%	0.55	0.37 - 0.83	0.0034
	Heparin	15.6%			
7 days	Lepirudin low	15.5%	0.79	0.52 - 1.20	0.2836
	Lepirudin medium	11.2%	0.54	0.34 - 0.86	0.0075
	Lepirudin combined	13.4%	0.66	0.46 - 0.95	0.0248
	Heparin	18.9%			
35 days	Lepirudin low	22.5%	0.91	0.63 - 1.31	0.6497
	Lepirudin medium	21.3%	0.85	0.58 - 1.24	0.2801
	Lepirudin combined	21.9%	0.88	0.64 - 1.20	0.3830
	Heparin	24.3%			
End of the study	Lepirudin low	25.5%	0.85	0.60 - 1.22	0.4292
	Lepirudin medium	23.2%	0.76	0.53 - 1.09	0.0816
	Lepirudin combined	24.3%	0.80	0.60 - 1.09	0.1325
	Heparin	28.6%			

[a] Lepirudin low: N = 271; lepirudin medium: N = 267; lepirudin combined: N = 538; heparin: N = 371.

[b] Absolute numbers of patients with events are presented in Tables 28 - 31.

[c] Relative risk was based on a logistic regression model (treatment) comparing each treatment group with heparin. The p-values were determined using the Mantel-Haenszel test stratified by center.

APPENDIX D

OASIS-2: Findings for CV Death or New MI and CV Death, New MI, or Refractory Angina

	Number of Patients (%)											
	MITT (adjudicated)			MITT (investigator reported)			Per Protocol (adjudicated)			ITT (adjudicated)		
	Lepirudin (N=5045)	Heparin (N=5033)	p-value	Lepirudin (N=5045)	Heparin (N=5033)	p-value	Lepirudin (N=4927)	Heparin (N=4909)	p-value	Lepirudin (N=5083)	Heparin (N=5058)	p=value
CV Death or New MI												
72 hours	99 (2.0%)	132 (2.6%)	0.0229	102 (2.0)	135 (2.7%)	0.0234	96 (1.9%)	130 (2.6%)	0.0179	103 (2.0%)	134 (2.6%)	0.0342
7 days	178 (3.5%)	211 (4.2%)	0.0714	182 (3.6%)	215 (4.3%)	0.0725	174 (3.5%)	206 (4.2%)	0.0743	182 (3.6%)	213 (4.2%)	0.0863
35 days	337 (6.7%)	277 (7.5%)	0.0896	341 (6.8%)	383 (7.6%)	0.0767	329 (6.7%)	371 (7.6%)	0.0700	342 (6.7%)	379 (7.5%)	0.1093
180 days	517 (10.2%)	541 (10.7%)	0.3377	510 (10.1%)	535 (10.6%)	0.3102	503 (10.2%)	529 (10.8%)	0.2910	521 (10.2%)	545 (10.8%)	0.3219
CV death, new MI or refractory angina												
72 hrs	154 (3.1%)	199 (4.0%)	0.0108	172 (3.4%)	213 (4.2%)	0.0269	149 (3.0%)	196 (4.0%)	0.0072	159 (3.1%)	202 (4.0%)	0.0157
7 days	279 (5.5%)	336 (6.7%)	0.0138	305 (6.0%)	356 (7.1%)	0.0366	272 (5.5%)	329 (6.7%)	0.0125	284 (5.6%)	339 (6.7%)	0.0163
35 days	633 (12.5%)	675 (13.4%)	0.1600	665 (13.2%)	707 (14.0%)	0.1787	617 (12.5%)	667 (13.6%)	0.0935	639 (12.6%)	680 (13.4%)	0.1705
180 days	1026 (20.3%)	1055 (21.0%)	0.3559	1051 (20.8%)	1077 (21.4%)	0.4106	997 (20.2%)	1036 (21.1%)	0.2349	1032 (20.3%)	1064 (21.0%)	0.3189

from sponsor's tables, NDA Vol. 21.3