2. CLINICAL TRIAL PROGRAM FOR LEPIRUDIN IN ACS

2.1 Overview of the program

The clinical development program for lepirudin in ACS consisted of four clinical studies.

There were two adequate and well-controlled studies:

- **OASIS-1**: a partially blinded, randomized, heparin-controlled Phase IIb study: N=909
  (HBW 023/7CDN201UA)
- **OASIS-2**: a double-blind, randomized, heparin-controlled Phase IIIa study: N=10,141
  (HBW 023/7MN-302UA)

In addition, there were two Phase IIa feasibility studies:

- **APT-1**: an open-label, uncontrolled Phase IIa study: N=43
  (HBW 023/7MN-201UA)
- **PTCA study**: an open-label, randomized, heparin-controlled Phase IIa study: N=61
  (HBW 023/7MN-201AP)

The four studies comprised a total of 11,154 patients. Of these, 11,088 received at least one dose of study medication (lepirudin or heparin): 10,080 in OASIS-2, 904 in OASIS-1, 61 in the PTCA study, and 43 in APT-1.

The development program is greatly dominated by the OASIS studies, particularly OASIS-2. The dosage regimens tested in the OASIS studies were different from those tested in the Phase IIa studies. Furthermore, although the patient populations were very similar in the OASIS studies, they were slightly different in the Phase IIa studies. When presenting and discussing the findings, this briefing document therefore focuses on the data from the OASIS studies, with the primary emphasis on OASIS-2. The two Phase IIa feasibility studies were previously submitted in the original NDA (#20-807) and are considered only with respect to dose finding in this briefing document.

The findings of all four studies have been published [32, 33, 34, 35, 36, 37] or accepted for publication [38].

2.2 Study design of the OASIS studies

The OASIS studies were conducted by the Organization to Assess Strategies for Ischemic Syndromes (OASIS) investigators, under the leadership of the Canadian Cardiovascular Collaboration (CCC) chaired by Dr Salim Yusuf of McMaster University, Hamilton, Ontario, Canada.

2.2.1 OASIS-1

Design and dosage regimens. OASIS-1 was a prospective, partially blinded, randomized, heparin-controlled, parallel-group, partially factorial, multi-center trial of 909 patients from 31 centers in Canada (first patient in: July 1994, last patient out: November 1996). The study comprised two parts,

OASIS-1a and OASIS-1b, which took place sequentially, with 500 patients and 300 patients planned for each stage. Patients were randomized in a ratio of 4:3:3 within centers to receive standard unfractionated heparin or one of two dosages of lepirudin. While investigators knew whether heparin or lepirudin had been assigned to an individual patient, the exact dose of lepirudin was blinded. The bolus + infusion dosage regimens used were:

Treatment	IV bolus	IV infusion
Standard unfract. heparin:	5,000 U	1,200 U/hour for 72 hours (1,000 U/hour if body weight <60 kg)
Low-dose lepirudin:	0.2 mg/kg	0.10 mg/kg/hour for 72 hours
Medium-dose lepirudin:	0.4 mg/kg	0.15 mg/kg/hour for 72 hours

It was recommended that all patients take aspirin (325 mg/day while hospitalized and 80 mg to 325 mg/day after discharge from hospital).

In OASIS-1a, the initial bolus of lepirudin or heparin was to be omitted in patients on pre-study heparin if the baseline aPTT was >60 seconds. In OASIS-1b, the initial bolus of lepirudin or heparin was to be omitted in patients on pre-study heparin if the baseline aPTT was >60 seconds or if a heparin bolus had been administered in the 2 hours prior to randomization.

The IV infusion rate was to be adjusted to maintain the patient's aPTT levels within a target range of 60 to 100 seconds. If, in the lepirudin groups, the aPTT remained above 100 seconds after two dosage decreases, the infusion was to be discontinued. Similarly, in all treatment groups, if the patient's serum creatinine was >2.5 mg/dl (>220 µmol/l) at any point during the infusion, the infusion was to be discontinued; if it was 2.0 – ≤2.5 mg/dL, the dose was to be reduced by 20% and the creatinine level monitored again after 6 – 8 hours. Other possible reasons for stopping the study infusion prematurely were the occurrence of a major bleed, stroke or associated serious adverse event, the need for urgent PTCA or CABG, or the need to initiate therapy with a thrombolytic. Patients were hospitalized for at least the 72-hour infusion period. The primary follow-up visit was at 7 days, further follow-up visits were scheduled for 35 days and 4 months in OASIS-1b and for 35 days and 6 months in OASIS-1a.

Eligible patients were further randomized (1:1 within centers) to open-label treatment with either warfarin or standard therapy. During OASIS-1a, randomization was to take place 48 to 96 hours after the end of study infusion, and fixed low-intensity warfarin given for 6 months was tested. During OASIS-1b, warfarin randomization was to take place around 24 hours (range 12 to 36 hours) after starting the study infusion, and INR-adjusted moderate-intensity warfarin given for 3 months was tested. Additional follow-up visits were scheduled for warfarin patients.

Inclusion criteria. Adult patients with typical chest pain suspected to represent unstable angina or acute MI without persistent ST elevation at the presenting ECG were eligible for the study if they presented within 12 hours of the most recent of episode of chest pain or symptoms. ECG changes compatible with ischemia were desirable but not required for the diagnosis of unstable angina. In the absence of supportive or diagnostic ECG changes at entry in such patients, medical history strongly supporting the diagnosis that chest pain was due to myocardial ischemia was required (e.g. prior MI, chronic stable angina, revascularization procedure, cardiac catheterization showing significant coronary artery disease, or positive exercise test). Patients with suspected acute MI were eligible for inclusion if the pre-randomization ECG did not show typical ST elevation. This definition was consistent with the diagnosis of non-Q-wave MI characterized by ST depression, T-wave inversion, with minor ST elevation (<1 mm), or even a normal ECG.

Exclusion criteria. Major exclusion criteria were active bleeding or high risk of bleeding, recent major surgery or trauma, arterial puncture (within <24 hours), uncontrolled severe hypertension, coagulopathies, severe anemia, recent stroke (within <1 year), known renal impairment (e.g. serum creatinine >2.0 mg/dL), suspected acute MI with ST elevation, planned thrombolysis, PTCA within the previous 6 months, cardiogenic shock requiring inotropic agents, history of heparin-induced thrombocytopenia, and age over 85 years.

Efficacy outcomes and analyses. OASIS-1 investigated the effects of lepirudin compared to heparin using hard and objective composite clinical endpoints. Although there was no clearly prespecified primary efficacy outcome in OASIS-1, the composite endpoint of CV death, new MI, refractory or severe angina up to 7 days after randomization was considered the most important outcome in the analysis of efficacy, since it formed the basis of the sample size and power calculations. All analyses of efficacy were performed on the MITT population (all randomized patients who completed their 7-day efficacy assessment). Since all patients completed their 7-day assessment, the MITT population included all patients randomized, i.e. the MITT population is the same as the ITT population.

Endpoint definitions and adjudication process. The study protocol provided detailed definitions for all major clinical outcomes. The definitions were very similar or identical to those employed in OASIS-2 (see *Section 2.2.2*, page 7). The only relevant difference was that in contrast to OASIS-2, there was no definition of refractory angina post hospital discharge such as rehospitalization for angina in OASIS-1. This probably resulted in an underestimation of the incidence of refractory angina after hospital discharge, i.e. at timepoints beyond 7 days, in this study.

Only events that were reported as outcome events by the investigators on the basis of the full clinical picture were considered. The database was not systematically screened for further events. All deaths, MIs, and refractory and severe angina events reported by investigators were adjudicated by the blinded OASIS-1 Adjudication Committee. The adjudication results were binding for the final analyses.

Safety outcomes and analyses. The study placed particular emphasis on the collection of information on major and minor bleeds and stroke. Information on bleeds and strokes was collected throughout the trial, applying prespecified definitions (see *Section 6.1*, page 51). Information on AEs was collected over the entire study period. All major bleeds and strokes were reviewed by the blinded OASIS-1 Adjudication Committee. All analyses of safety were performed on the safety population (all randomized patients who received any lepirudin or heparin), according to the initial study medication administered.

Sample size estimation. It was planned to enroll 500 patients into OASIS-1a and 300 patients in OASIS-1b in 30 centers. Assuming an event rate of 16% in the heparin group and an alpha level of 5%, the total sample size of 800 patients would provide 80% power to detect a 43% relative risk reduction in the incidence of the composite endpoint of CV death, new MI, refractory or severe angina (comparison between a single dosage of lepirudin and heparin).

Statistical analysis plan. No statistical analysis plan was produced because the results of OASIS-1a were published in 1996 before Aventis (then Hoechst Marion Roussel, HMR) had access to the data. The sponsor was unblinded to the randomization codes of OASIS-1a on February 7, 1997 and to the randomization codes of OASIS-1b on February 6, 1998. As far as appropriate, the analysis of OASIS-1 followed the approaches in the OASIS-2 statistical analysis plan, which was finalized on June 23, 1998 (see *Section 2.2.2*, page 7). The initial analyses and publication were prepared independently of the sponsor by CCC.

Validity of the study. Although investigators knew whether heparin or lepirudin had been assigned to an individual patient, any potential bias associated with this was minimized by two processes. These were: (1) patients were randomized through a central call-in process which made it impossible for a treatment-specific bias to be introduced; and (2) all major clinical outcomes were centrally adjudicated by the blinded OASIS-1 Adjudication Committee, which made it highly unlikely that a treatment-specific misclassification bias would be introduced. While a bias due to systematic underreporting of clinical efficacy events could not be entirely excluded *a priori*, this was probably minimal since: (1) source data verification was performed in about 45% of all patients in OASIS-1 and did not reveal any evidence of relevant underreporting, and (2) systematic underreporting would probably have obscured the observed dose-response relationship for lepirudin described in *Section 3.2* (page 15).

2.2.2 OASIS-2

Design and dosage regimens. OASIS-2 was a double-blind, double-dummy, randomized, heparin-controlled, partially factorial, multicenter trial of 10,141 patients from 360 centers in 15 countries worldwide (first patient in: August 1996, last patient out: February 1999). The patients were randomized in a ratio of 1:1 to receive standard unfractionated heparin or lepirudin. The bolus + infusion dosage regimens used were:

Treatment	IV bolus	IV infusion
Standard unfract. heparin:	5,000 U	15 U/kg/hour for 72 hours
Medium-dose lepirudin:	0.4 mg/kg	0.15 mg/kg/hour for 72 hours

It was recommended that all patients take aspirin (325 mg per day while in hospital and 80 – 325 mg per day after discharge from hospital).

The initial bolus of lepirudin or heparin was to be omitted in patients on pre-study heparin if the baseline aPTT was >60 s or if a heparin bolus had been administered in the 2 hours prior to randomization.

The infusion rate of lepirudin or heparin was to be adjusted, starting 6 – 8 hours after the start of infusion, in order to keep the patient's aPTT within the stipulated target range of 60 – 100 seconds. If the aPTT remained high despite 2 adjustments, the study infusion was to be stopped. Similarly, if at any time during study infusion, the patient's serum creatinine was >2.5 mg/dL, the infusion of study medication was to be stopped; if it was 2.0 – ≤2.5 mg/dL, the dose was to be halved and the creatinine level monitored again after 6 – 8 hours. Other possible reasons for stopping the study infusion prematurely were the occurrence of a major bleed, stroke or associated serious adverse event, the need for urgent PTCA or CABG, or the need to initiate therapy with a thrombolytic or abciximab (ReoPro®). Patients were hospitalized for at least the 72-hour infusion period. The primary follow-up visit was at 7 days, further follow-up visits were scheduled for 35 days and 6 months.

The heparin infusion dose regimens differed slightly between the OASIS studies. While OASIS-1 used a semi-fixed regimen (see *Section 2.2.1*, page 4), OASIS-2 used a weight-adjusted regimen to facilitate blinding of study medication. In the most common range of 70–90 kg body weight, the two regimens resulted in very similar starting doses (OASIS-1: 1,200 U/hour, OASIS-2: 1,050 – 1,350 U/hour). Since the aPTT- and creatinine-based dose adjustment schedules used in the two studies were very similar, on-treatment differences in dosing were likely to be minimal.

Approximately 24 hours into the infusion, eligible patients were to be randomized to receive a 5-month open-label treatment with moderate-intensity warfarin or standard therapy (without warfarin), in a ratio of 1:1 ("warfarin substudy"). Additional follow-up visits were scheduled for warfarin-randomized patients.

Inclusion criteria. Adult patients with typical chest pain suspected to represent unstable angina or acute MI without persistent ST elevation were eligible for the study if they could be randomized within 12 hours from the onset of the most recent episode of chest pain. Admission ECG changes compatible with ischemia were required for all patients under the age of 60. Older patients could be included without ECG changes if they had other objective evidence of CAD such as history of prior MI, chronic stable angina, revascularization procedure, cardiac catheterization showing significant CAD, or positive exercise stress test.

Exclusion criteria. Major exclusion criteria were active bleeding or high risk of bleeding, recent stroke (<1 year), known renal impairment (e.g. serum creatinine >2.0 mg/dL), recent PTCA (<6 months), suspected acute MI with ST elevation, planned thrombolysis or direct PTCA, cardiogenic shock requiring inotropic agents, history of heparin-induced thrombocytopenia, and age over 85 years.

Efficacy outcomes. The primary efficacy outcome of OASIS-2 was the combined incidence of CV death or new MI ("double composite endpoint") up to 7 days after randomization. The key secondary efficacy outcome was the combined incidence of CV death, new MI, or refractory angina ("triple composite endpoint") up to 7 days. Other secondary outcomes included the incidences of these double and triple composite endpoints up to 72 hours, 35 days, and 6 months, the time to first occurrence of both composite endpoints, and the two composite endpoints including all-cause death instead of CV death at the same timepoints. Furthermore, the combined incidence of CV death, new MI, or refractory or severe angina and the incidences of cardiac interventions and radiological evidence of heart failure occurring more than 24 hours after randomization were assessed.

Timing of efficacy analyses. Performing the primary analysis of efficacy at 7 days was considered to be a reasonable compromise between an early assessment at the end of treatment and a late assessment at 35 days. The early assessment would be most powerful in terms of clinical benefit achieved, but would not capture two potential phenomena that might be observed early after cessation of treatment: (1) sustained treatment effects of hirudin after its clearance from plasma which are due to its ability to inactivate fibrin-bound thrombin [7, 39], and (2) rebound effects of both heparin [40] and hirudin [41]. The late assessment might be more consistent with methodological conventions in cardiology, but would lead to a substantial dilution of the expected relative risk reductions and, thus, decrease the power of the study. This would be expected to occur if the background incidences increased in a similar fashion over time, assuming no relevant differential effects between lepirudin and heparin beyond the early post-treatment phase.

Endpoint definitions and adjudication process. The study protocol provided detailed definitions for all major clinical outcomes (CV death; MI, subdivided into associated, new within 24 hours of randomization, and new beyond 24 hours of randomization; refractory angina; severe angina; recurrent angina) to guide the investigators in classifying cardiac events. Only events that were reported as outcome events by the investigators on the basis of the full clinical picture were considered. The database was not systematically screened for further events. All deaths, MIs, and refractory angina events reported by investigators were to be adjudicated by the blinded OASIS-2 Adjudication Committee. The adjudication results were binding for the final analyses.

The following specific definitions were applied:

- **CV deaths** were all deaths that were not clearly due to non-cardiovascular reasons, including deaths of unknown cause and deaths following cardiovascular procedures, whether directly or indirectly related to the procedure.

  Non-CV death was excluded from the primary and key secondary efficacy outcomes, since it was anticipated that lepirudin would have no potential to impact on this endpoint. This approach was considered to be justified based on the conservatism of the definition of CV death and the blinded adjudication of all deaths. All-cause mortality was, however, also considered in order to account for any unexpected trends in non-CV death. Furthermore, all fatal adverse events were the subject of safety investigations.

- **New MIs** occurring within 24 hours of randomization were separated from MIs associated with the index episode by the need for new typical clinical symptoms that were distinguishable from the presenting symptoms and either new ECG changes or new enzyme elevation. Beyond 24 hours, any two out of these three criteria were needed.

- To qualify as **refractory angina**, an episode of angina had to meet a triad of (1) typical chest pain occurring in the presence of optimum medical treatment with at least two anti-anginal agents, (2) new characteristic ECG changes associated with the pain, and (3) the urgent need for an additional intervention (thrombolytic therapy, insertion of an intra-aortic balloon pump, cardiac catheterization, PTCA, CABG, or transfer to another hospital for any of these interventions) by midnight of the following day. After discharge from hospital, rehospitalization for unstable angina was considered to be equivalent to refractory angina if ischemic ECG changes were present or the patient had to be admitted to a monitoring ward.

  The definition of refractory angina is very hard and objective as compared to various definitions applied in other recent studies in ACS [42, 43, 44, 45, 46, 47]. In contrast to OASIS-2, all these studies used refractory angina as a component of the *primary* efficacy outcome (see *Section 4.5.1*, page 42).

- The definition of **severe angina** was identical to that of refractory angina, except that it did not require an additional intervention. Also, there was no appropriate definition for severe angina after discharge from hospital. Severe angina data were not adjudicated in OASIS-2.

Safety outcomes. The study placed particular emphasis on the collection of information on major and minor bleeds and stroke. Information on bleeds and stroke was collected throughout the trial, applying prespecified definitions (see *Section 6.1*, page 51). All major bleeds and strokes were to be adjudicated by the blinded Adjudication Committee. The adjudication results were binding for the final analyses. For collection of adverse events (AEs), the study focused on the initial 7-day period: from randomization up to 7 days, all serious AEs and all unexpected non-serious AEs were to be documented; beyond day 7, information was to be recorded only for fatal AEs and unexpected serious AEs possibly related to study medication.

Sample size estimation. Based on the findings of the OASIS-1 study and the OASIS registry [16], it was estimated that the event rates in the heparin group for the primary efficacy outcome (CV death or new MI up to 7 days) and the key secondary efficacy outcome (CV death, new MI, or refractory angina up to 7 days) would be at least 5% and 8.7%, respectively. With these rates and an overall alpha level of 5%, a sample size of 10,000 patients would provide 80% power to detect a 23% relative risk reduction in the primary outcome and a 21% relative risk reduction in the key secondary outcome.

Analysis populations. Analyses of efficacy were performed on the following populations (as defined in the statistical analysis plan [SAP]):

- modified intention-to-treat (MITT): all randomized patients who received any lepirudin or heparin and completed their 7-day efficacy assessment (**primary analysis population**),
- intention-to-treat (ITT): all randomized patients, whether treated or not, and
- per-protocol: all MITT patients with no major protocol deviations.
  The prespecified major protocol deviations were: (1) normal baseline ECG and age <60 years at entry; (2) treatment with study medication initiated >14 hours after the onset of the qualifying episode of chest pain; and (3) receipt of study medication other than that initially administered.

The MITT and per-protocol populations were analyzed as initially treated, the ITT population was analyzed as randomized. Analyses of safety were performed on the safety population (all randomized patients who received any lepirudin or heparin).

The study protocol stated that the primary efficacy analysis would be performed on an ITT population without giving further specification. When preparing the SAP before unblinding of the study database, the use of the MITT population as the primary efficacy analysis population was considered to be justified and appropriate because the central call-in randomization process and the double-blind, double-dummy study design did not allow bias to be introduced. Therefore, it could be assumed that any events occurring prior to start of lepirudin or heparin would be randomly distributed between the groups and dilute the study results by adding noise. The requirement of a completed 7-day efficacy assessment in the MITT population minimized the need for assumptions and imputations. As reviewed in *Section 4.2.1.4* (page 23), the results were very similar and consistent across the populations.

Statistical methods. Relative risks for the double and triple composite efficacy endpoints at 72 hours, 7 days, 35 days and 180 days were based on a logistic regression model. Treatment groups were compared using the Mantel-Haenszel test (stratified by center, 4.8% significance level for primary analysis due to adjustment for interim analyses). Time-to-event analyses were performed using the Kaplan-Meier method and log-rank test. Subgroup analyses, non-parametric analyses of covariance, and logistic regression analyses were also performed.

Statistical analysis plan. The SAP was finalized on June 23, 1998. A copy of the final SAP was sent to the FDA on June 25, 1998. Aventis (then HMR) received the summary preliminary OASIS-2 results from CCC on June 27, 1998. A clarification to the SAP, dated January 7, 1999, incorporated final statistical programming specifications and minor clarifications to the SAP. This document was finalized prior to unblinding of the HMR database later the same day. In particular, it incorporated changes suggested in a letter from the FDA to HMR, dated October 28, 1998. The sponsor was unblinded to the randomization codes of OASIS-2 on January 7, 1999. The initial analyses and publication were prepared independently of the sponsor by CCC.

2.3 Characteristics of the patients in the OASIS studies

The table on the following page summarizes characteristics of the patients included in the OASIS studies.

Demographic characteristics. Demographic characteristics in the two OASIS studies were typical of patients with ACS. Although there were slightly fewer male patients in OASIS-2, there were no relevant differences in demographic characteristics between treatment groups in either study.

OASIS-1 and OASIS-2: Characteristics of the patients studied (MITT populations)

Characteristic	OASIS-1			OASIS-2	
	Heparin	Low-dose lepirudin	Medium-dose lepirudin	Heparin	Lepirudin
	N=371	N=271	N=267	N=5,033	N=5,045
Demographics					
Male	66%	65%	69%	62%	60%
Age (mean [SD], years)	65 (11)	64 (11)	64 (12)	64 (11)	64 (11)
Weight (mean [SD], kg)	78 (13)	78 (14)	78 (13)	77 (15)	76 (15)
Entry diagnosis					
Unstable angina	87%	87%	87%	88%	88%
MI without ST elevation	13%	13%	13%	12%	12%
Abnormal baseline ECG	84%	87%	79%	90%	91%
Type of abnormality [a]					
ST depression	33%	30%	35%	49%	49%
ST elevation	7%	6%	6%	3%	4%
T-wave inversion	29%	34%	32%	36%	37%
Other	30%	29%	27%	11%	10%
Location of abnormality [a]					
Any anterior	46%	50%	47%	56%	53%
Other	54%	49%	53%	44%	47%
Time from pain onset to randomization (mean, hours)	6.7	6.9	6.9	6.6	6.6
Relevant history					
Previous MI	45%	43%	48%	39%	39%
Revascularization procedure	29%	28%	34%	19%	18%
Other evidence of CAD	78%	79%	75%	55%	57%
Hypertension	46%	47%	44%	54%	53%
Current or former smoker	76%	73%	73%	64%	61%
Diabetes	19%	20%	20%	21%	21%
Stroke	6%	6%	7%	4%	4%
Previous medication [b]					
Aspirin	64%	63%	65%	64%	66%
Other antiplatelet	0%	0%	0%	4%	3%
Any non-study heparin	27%	30%	33%	24%	25%
Beta-blockers	35%	37%	34%	39%	40%
Nitrates	55%	56%	55%	66%	66%
Calcium antagonists	40%	39%	44%	33%	32%
ACE inhibitors	19%	18%	18%	30%	31%
Med. during study infusion [c]					
Aspirin	95%	97%	96%	94%	94%
Other antiplatelet	0%	0%	0%	5%	4%
Any non-study heparin	53%	50%	49%	3%	3%
Beta-blockers	76%	73%	71%	69%	68%
Nitrates	94%	96%	94%	92%	91%
Calcium antagonists	55%	57%	54%	33%	32%
ACE inhibitors	25%	28%	29%	39%	39%

[a] Percents based on number of patients with abnormal ECG at baseline
[b] OASIS-1: Concom. med. at hospital admission. OASIS-2: Med. in 2 days before randomization
[c] OASIS-1: Med. between hospital admission and discharge. OASIS-2: Med. betw. random. and end of infusion.

Primary disease. The primary disease characteristics of the patients were similar across the two studies. Most of the patients had an abnormal baseline ECG, although there were more patients with an abnormal baseline ECG in OASIS-2 than in OASIS-1. The remaining patients presented with a qualifying history of CAD (previous MI, revascularization procedure, or other evidence). While this was generally possible in OASIS-1, it was allowed as an entry criterion in OASIS-2 only in patients >60 years. Consistent with the disease pattern, the leading ECG changes were ST depression and T-wave inversion. The most prominent location of the ECG changes was anterior or anterolateral. Overall, these findings were similar across the treatment groups in each study, except that fewer lepirudin patients than heparin patients had anterior or anterolateral ECG changes in OASIS-2 (49% vs. 52%; p=0.0195). However, subgroup analyses performed for OASIS-2 indicated that anterior wall changes were not a prognostic indicator for outcome at 7 days (see *Section 4.2.2.3*, page 27).

Clinical presentation at randomization. At randomization, the majority of patients presented with suspected unstable angina; 13% of OASIS-1 patients and 12% of OASIS-2 patients were suspected to have an acute MI without persistent ST elevation. However, higher proportions of patients were finally diagnosed as having an MI associated with the event that led to randomization (OASIS-1: 21.5% OASIS-2: 19.0%; see also *Section 4.2.2.5*, page 31).

Other medical history and risk factors. Apart from the acute clinical symptoms and findings, the vast majority of patients presented with a medical history typical of patients with severe CAD. Within the studies, the individual factors were generally well balanced between treatment groups. In contrast, there were marked differences between OASIS-1 and OASIS-2 in the frequencies of previous revascularization procedures (about 30% in OASIS-1 as compared to about 20% in OASIS-2). These differences can probably be attributed to the different patterns of medical practice in the countries participating in the studies. While OASIS-1 was a purely Canadian study, OASIS-2 was a multinational trial with relevant contributions from countries known for low rates of invasive procedures (e.g. Eastern European countries). There were notable differences between the studies but not between the treatment groups within the studies in the frequency of hypertension, while there was no notable difference in the frequency of diabetes or stroke. In OASIS-2, fewer lepirudin patients than heparin patients were current or former smokers (61% vs. 64%). However, subgroup analyses performed for OASIS-2 indicated that smoking was not a prognostic indicator for outcome at 7 days (see *Section 4.2.2.3*, page 27).

Concomitant medication. As expected from the practice patterns in this setting, patients in both OASIS studies were taking concomitant medications frequently before, during and after study infusion. Aspirin was the most commonly used drug at any time. During study infusion, 96% of OASIS-1 patients and 94% of OASIS-2 patients were on aspirin, as recommended by the protocol. A further 4% of OASIS-2 patients received other anti-platelet agents during the infusion. Thus, a total of 98% of patients in both treatment groups in OASIS-2 were on active antiplatelet therapy during study infusion. This did not include GP IIb/IIIa inhibitors, since abciximab (ReoPro®) was specified as an indication for early termination of study medication in OASIS-2, and no other GP IIb/IIIa inhibitors had been approved for use in ACS patients at the time of the studies. Other medications frequently used concomitantly during study infusion included nitrates, beta-blockers, angiotensin-converting enzyme inhibitors and calcium antagonists. There were no marked differences between the treatment groups in the use of any of these concomitant medications.

2.4 Exposure to study medication in the OASIS studies

As described in *Sections 2.2.1* (OASIS-1) and *2.2.2* (OASIS-2), both lepirudin and heparin study medications were given as a combination of an IV bolus followed by a 72-hour IV infusion.

Overall, in the OASIS studies, 5,582 patients received at least one dose of lepirudin, as compared with 5,402 patients who received heparin as randomized study medication. The following table summarizes details of the use of the study medication.

OASIS-1 and OASIS-2: Study medication data

Characteristic	OASIS-1			OASIS-2	
	Heparin	Low-dose lepirudin	Medium-dose lepirudin	Heparin	Lepirudin
	N=369	N=270	N=265	N=5,033	N=5,045
Duration of study infusion					
Mean duration (hours)	68.3	64.5	62.8	67.5	66.0
% patients treated for >60 hours	86%	80%	79%	88%	85%
Dose adjustments (% patients)					
Any adjustment	85%	44%	28%	88%	52%
Multiple increases	33%	20%	7%	52%	13%
Multiple decreases	28%	1%	3%	23%	16%
Bidirectional adjustments	6%	1%	0%	16%	2%
Premature termination of study med.					
% patients terminated	18%	26%	27%	15%	18%
Most important reasons (% patients)					
aPTT out of range	0%	5%	3%	3%	6%
Urgent surgery/invas. procedure	5%	4%	3%	3%	2%
Bleeding/other AE	1%	2%	4%	2%	4%
Temp. interruption of study med.					
% patients with interruption >1 hr	10%	4%	4%	5%	5%

OASIS-1: Safety population; OASIS-2: MITT population

NOTE: As the OASIS-2 data presented in the table are for the MITT population, the table does not include the data for the two patients in OASIS-2 who received study medication but who did not have a complete 7-day efficacy assessment.

In both studies, the mean **duration of study infusion** was slightly shorter in lepirudin patients than in heparin patients. Fewer lepirudin patients than heparin patients required **dose adjustments** during study infusion. Furthermore, fewer lepirudin patients than heparin patients required multiple and bidirectional (up and down) dose adjustments. **Premature termination** of the study infusion occurred in more lepirudin patients than heparin patients. The most important reasons for early termination were aPTT out of range, urgent surgery/invasive procedure, and bleeding or other adverse event. The proportions of patients who completed the study infusion with **temporary interruptions** of >1 hour were low and similar between the treatment groups of both studies (except for the heparin group of OASIS-1 which had a higher proportion of such patients).