3. DOSE FINDING

The dose finding for lepirudin in ACS is based on the two early Phase IIa studies (APT-1 and PTCA study) and the OASIS-1 study. In addition, dose-ranging information from three studies involving a total of 717 thrombolysed MI patients has been taken into account. The latter studies were described in the original NDA submission for HIT and will not further be considered in the context of this briefing document.

3.1 Phase IIa studies (APT-1 and PTCA study)

Design and dosage regimens. The APT-1 study was an open uncontrolled study that investigated the use of lepirudin for conservative treatment of unstable angina (N=43 patients). The PTCA study was a randomized heparin-controlled study that was performed in 61 patients undergoing interventional treatment (PTCA) for unstable angina.

Both studies were conducted in Europe in 1993, when the bleeding risk associated with the use of lepirudin was thought to be very low. Consequently, the upper end of the dose range tested in these studies was comparatively high.

In both studies, the lower-dose regimen of lepirudin consisted of a 0.3 mg/kg initial bolus and a 0.12 mg/kg/hour constant infusion; the higher-dose regimen consisted of a 0.5 mg/kg initial bolus and a 0.24 mg/kg/hour constant infusion.

The duration of therapy in APT-1 was 72 hours. In the PTCA study, the duration of the initial 0.12 or 0.24 mg/kg/hour infusion was 24 hours, but treatment was then continued for another 24 hours in both dose groups using a very low dose of lepirudin (0.04 mg/kg/hour; total infusion time: 48 hours). Patients in the unfractionated heparin treatment arm received a 150 IU/kg bolus followed by infusion of 20 IU/kg/hour from 0 – 24 hours and 7 IU/kg/hour from 25 – 48 hours.

Dose-response relationship. The Phase IIa studies were planned as feasibility studies, and the sample sizes of approximately 20 patients per treatment group were too small to detect a dose-response relationship based on clinical parameters. However, a dose-response relationship was detected for pharmacokinetics, pharmacodynamic response, and surrogate efficacy parameters.

In both studies, the lepirudin plasma concentrations and levels of aPTT prolongation during infusion were clearly dose-dependent:

- **Lepirudin plasma concentrations** 24 hours after start of infusion were markedly higher in patients receiving the higher-dose regimens than in those receiving the lower-dose regimens (APT-1, mean: 2.3 µg/mL vs. 1.6 µg/mL; PTCA study, median: 2.2 µg/mL vs. 1.0 µg/mL).
- The higher-dose regimens also consistently produced higher **aPTT ratios** than the lower-dose regimens (APT-1, mean at 24 h: 3.0 vs. 2.4; PTCA study, median at 24 h: 2.3 vs. 1.9).

As judged from lower levels of **troponin T**, a very sensitive marker of myocardial ischemia, following PTCA in the PTCA study, both dose regimens of lepirudin were superior to heparin, and the higher-dose regimen appeared to be slightly better than the lower-dose regimen in preventing periprocedural ischemia.

In both studies, there were few **bleeding events** and no dose-response relationship could be discerned. However, in APT-1, mean **hemoglobin** levels at the end of the study were 7% (1 g/dL) lower in patients who received the higher-dose regimen than in those who received the lower-dose regimen. Therefore, for safety reasons, it was decided to reduce the dosage of the infusion to be tested as the high-dose regimen in OASIS-1 from 0.24 to 0.20 mg/kg/hour.

3.2 OASIS-1

The most important dose-finding information comes from the OASIS-1 study, conducted in Canada between July 1994 and November 1996.

Originally, OASIS-1 was planned to compare three different dose regimens of lepirudin:

- low: 0.2 mg/kg bolus, 0.10 mg/kg/hour infusion
- medium: 0.4 mg/kg bolus, 0.15 mg/kg/hour infusion
- high: 0.6 mg/kg bolus, 0.20 mg/kg/hour infusion.

This approach would cover an X, 2X, and 3X range for the initial bolus, and an X, 1.5X, and 2X range for the infusion. However, this plan was reconsidered following the release of the results of the GUSTO-2a trial [48]. This trial investigated the same dose of desirudin, another recombinant hirudin, in ACS patients with and without concomitant thrombolytic therapy. The trial had to be halted because of an excess of intracerebral hemorrhagic events after 2,564 patients were enrolled. The overall incidence of hemorrhagic stroke tended to be higher in patients receiving desirudin (1.3%) compared with patients receiving heparin (0.7%). Importantly, the incidence was significantly higher in patients who received thrombolytic therapy (23/1,264 patients, 1.8%) than in those who did not (3/1,168 patients, 0.3%). Although the patients planned for inclusion in OASIS-1 were not expected to receive thrombolysis, it was considered appropriate to abandon the high-dose regimen of lepirudin before the study was initiated.

Pharmacokinetic and pharmacodynamic dose-response relationships. Like in the Phase IIa studies, there was a dose-response relationship for pharmacokinetics and the pharmacodynamic response in OASIS-1:

- **Median steady-state lepirudin plasma concentrations** during study infusion (determined in 395 patients participating in a coagulation substudy) were about 30% higher in the medium-dose group than in the low-dose group (1.4 µg/mL vs. 1.1-1.2 µg/mL). Six hours after stopping the infusion, median lepirudin plasma levels had returned to 0 µg/mL in both dose groups. The systemic clearance of lepirudin was slightly higher in the medium-dose group (126 mL/min) than in the low-dose group (108 mL/min).
- Median **aPTT** values during study infusion (data from all patients) were in the range of 71-72 seconds (aPTT ratio: 2.5) in the medium-dose group and 63-65 seconds (aPTT ratio: 2.2-2.3) in the low-dose group. In contrast, the aPTT values in the heparin group showed a much greater variability (median: 70-103 seconds, ratio: 2.4-3.2).

  In all three treatment groups, the median aPTT values in the post-infusion period exceeded the baseline level (aPTT ratio: 1.6-1.8), probably due to non-study heparin given after the end of study infusion.

- As assessed by the **need for dosage adjustments**, the level of anticoagulation was more stable in the medium-dose group than in the low-dose group. Patients in both lepirudin groups needed fewer dosage adjustments than patients in the heparin group.

OASIS-1: Dosage adjustments during study infusion (Safety population)

	% of patients		
	Heparin N=369	Low-dose lepirudin N=270	Med.-dose lepirudin N=265
No change	15%	56%	72%
Increase above baseline	32%	37%	17%
Decrease above baseline	47%	7%	11%
Increase and decrease	6%	1%	0%
Change within 20% of baseline	37%	11%	12%
Change >20% - 40% of baseline	29%	12%	8%
Change >40% of baseline	19%	21%	7%

Clinical efficacy parameters. Although OASIS-1 was only powered to detect major differences in clinical outcome between lepirudin and heparin, the study also indicated a dose-response relationship for lepirudin based on clinical efficacy parameters.

OASIS-1: Clinical efficacy findings from randomization to 7 days (MITT population)

Composite endpoint	% of patients with events			RR vs. heparin	
	Heparin N=371	Low-dose lepirudin N=271	Med.-dose lepirudin N=267	Low-dose	Medium-dose
CV death, new MI, refract. or severe angina [a]	15.6%	12.5%	9.4%	0.77	0.56
CV death, new MI or refractory angina	6.5%	4.4%	3.0%	0.67	0.45
CV death or new MI	4.9%	2.6%	2.6%	0.52	0.53

[a] The most important composite endpoint in the analysis of efficacy

Bleeding events. The findings for minor bleeds, major bleeds and hemorrhagic stroke up to 7 days are summarized as follows:

OASIS-1: Safety findings from randomization to 7 days (Safety population)

	% of patients with events		
	Heparin N=369	Low-dose lepirudin N=270	Med.-dose lepirudin N=265
Minor bleed	10.6%	16.3%	21.5%
Major bleed	1.1%	0.7%	1.1%
Hemorrhagic stroke	0%	0%	0%

There was a clear dose-response relationship for lepirudin based on minor bleeding events. In contrast, major bleeding rates at 7 days were low and similar across all 3 treatment groups.

Importantly, no hemorrhagic strokes were observed in OASIS-1. For more details, see *Section 6.3.1.*

No notable differences between the lepirudin groups could be discerned with respect to the occurrence of non-hemorrhagic adverse events.

3.3 Conclusion

The two Phase IIa studies suggested that there was a dose-response relationship for pharmacokinetics, pharmacodynamic response, and surrogate efficacy parameters (e.g. troponin T).

The evidence from the OASIS-1 study indicated that the medium-dose regimen tested (0.4 mg/kg bolus, 0.15 mg/kg/hour infusion) provides the most favorable risk-to-benefit ratio. The data showed a pharmacokinetic and pharmacodynamic dose-response relationship that was correlated with clinical outcome. The medium-dose regimen was consistently associated with lower incidences and greater risk reductions than the low-dose regimen for the majority of clinical efficacy endpoints, at the cost of higher minor bleeding rates. Although it was anticipated that the latter would translate into higher major bleeding rates with larger patient numbers, it was considered that the safety profile would still be acceptable in conjunction with the improved efficacy outcome. Therefore, the medium-dose regimen was chosen for further testing in Phase III.