7. RISK/BENEFIT ASSESSMENT

In the OASIS studies, the efficacy assessment of lepirudin in ACS focused on the hard and objective clinical endpoints of CV death, new MI, and refractory angina necessitating an additional intervention. The combined results of OASIS-1&2 at 7 days (see *Section 4.3*, page 37) suggest that – per 100,000 patients treated with lepirudin instead of heparin – 799 fewer patients would experience CV death or new MI, and 1,306 fewer patients would experience CV death, new MI or refractory angina.

The safety assessment of the OASIS studies focused primarily on bleeding and stroke. Particular attention was paid to life-threatening and other major bleeding events, including hemorrhagic stroke, in the first 7 days after randomization. Driven by an unexpected imbalance against lepirudin in OASIS-2, ischemic strokes beyond 7 days were also analyzed extensively.

Since the main elements of the efficacy and safety assessments are not readily comparable in terms of severity, reversibility and clinical relevance, the following two integrated clinical endpoints were defined *post hoc* by adding non-cardiovascular death, disabling stroke and life-threatening bleed to the double and triple composite endpoints of the OASIS studies:

- Quadruple integrated endpoint: All-cause death, new MI, disabling stroke and life-threatening bleed
- Quintuple integrated endpoint: All-cause death, new MI, refractory angina, disabling stroke and life-threatening bleed. This endpoint was not included in the supplemental NDA dossier.

As the integrated endpoints consist of comparably hard, objective and mostly irreversible efficacy and safety components, they can be considered a direct and reliable quantitative measure of the net clinical benefit.

The combined 7-day results of OASIS-1&2 for these endpoints were investigated as the most important approach to assess the overall net clinical benefit of lepirudin.

OASIS-1&2: Integrated endpoints up to end of study (MITT populations) [a]

Integrated endpoint Timepoint	N (%) of patients with events Heparin N=5,404		Lepirudin N=5,583		Absolute benefit (%)	Rel. risk reduction (%)	p-value
Quadruple endpoint [b]							
72 hours	154	(2.9%)	118	(2.1%)	-0.74	27	0.0115
7 days	251	(4.6%)	215	(3.9%)	-0.79	18	0.0346
35 days	455	(8.4%)	426	(7.6%)	-0.79	11	0.1113
End of study [c]	667	(12.3%)	655	(11.7%)	-0.61	6	0.2950
Quintuple endpoint [b]							
72 hours	224	(4.1%)	176	(3.2%)	-0.99	25	0.0047
7 days	380	(7.0%)	319	(5.7%)	-1.32	20	0.0051
35 days	756	(14.0%)	724	(13.0%)	-1.02	8	0.1443
End of study [c]	1,182	(21.9%)	1,155	(20.7%)	-1.18	6	0.1879

[a] For ITT results see Table 10 of Appendix A
[b] Corrected for study and center
[c] 120 days in OASIS-1b and 180 days in OASIS-1a and OASIS-2

There is a clear and consistent net clinical benefit with lepirudin as compared to heparin. The results for the overall population of OASIS-1&2 suggest that – per 100,000 patients treated with lepirudin instead of heparin – 794 fewer patients would experience any of the events of the quadruple integrated endpoint and 1,318 patients would experience any of the events of the quintuple integrated endpoint. Thus, the magnitude of the net clinical benefit is very similar to that of the efficacy benefit shown for the double and triple composite endpoints. This indicates that the safety components of the integrated endpoint do not dilute the efficacy benefit achieved with lepirudin.

The most important additional safety components that are not represented in the integrated endpoint are minor and non-life-threatening major bleedings. Among these, major bleeds requiring transfusion of <4 units of blood or blood products are considered the most serious and important events. The observed increase in the rate of such major bleeds is taken as the medical cost to be paid for the benefit achieved with lepirudin. The results of the OASIS studies at 7 days suggest that – per 100,000 patients treated with lepirudin instead of heparin – 280 more patients would have to be transfused with <4 units of blood or blood products. However, this would be more than offset by the beneficial effects of lepirudin.