8. SUMMARY AND CONCLUSIONS

The clinical development program of lepirudin in ACS was aimed at determining the efficacy and safety of lepirudin relative to standard unfractionated heparin. The two main studies in the program were the 10,141-patient OASIS-2 study and the 909-patient OASIS-1 study.

Overall, the OASIS studies provide persuasive evidence that lepirudin (1) is superior to heparin in preventing the hard and objective clinical endpoints of CV death or new MI and CV death, new MI or refractory angina, (2) would be overwhelmingly superior to placebo in the prevention of such endpoints, (3) has an acceptable safety profile, and (4) produces net clinical benefit relative to heparin.

8.1 Efficacy vs. heparin

In OASIS-2, 17% fewer lepirudin than heparin patients experienced the primary outcome of CV death or new MI at 7 days (double composite endpoint: 3.5% vs. 4.2%; p=0.0714). The conclusion that this effect is real is based on the totality of evidence, i.e. the consistency and the plausibility of all aspects of the study results:

- The incidence of the key secondary outcome of CV death, new MI or refractory angina at 7 days was significantly reduced by 18% (triple composite endpoint: 5.5% vs. 6.7%; p=0.0138).

- The benefit with lepirudin was achieved during treatment and was significant at 72 hours for both composite endpoints. Thereafter, the absolute benefit was preserved. Thus, lepirudin had a beneficial effect while it was given, and this benefit was sustained in subsequent periods. There was no additional gain, but also no loss in benefit after the end of treatment. For compounds with a short half-life such as lepirudin, this finding is biologically plausible.

- The early beneficial effect of lepirudin on cardiovascular mortality was not counterbalanced by any adverse effects on non-cardiovascular mortality. The analyses including all-cause mortality rather than cardiovascular mortality provide identical results up to 7 days and slightly more favorable results for lepirudin at 35 days and 180 days.

- The need for early therapeutic interventions, namely revascularization procedures and thrombolytic therapy at 7 days, was significantly lower in the lepirudin group.

- Significantly fewer lepirudin patients than heparin patients developed radiological evidence of heart failure between 24 hours after randomization and 7 days. This finding is considered to be an indicator of the reduced rate of severe ischemic damage in lepirudin patients.

- The results of OASIS-2 are highly consistent with those of OASIS-1.

- The results of OASIS-2 are highly consistent with those of the non-ST elevation arm of the GUSTO-2b study.

Therefore, the beneficial impact of lepirudin on the primary endpoint is strengthened by clear and consistent reductions in the key secondary endpoint, the composite endpoints using all-cause death, the need for early therapeutic interventions, and the occurrence of radiological evidence of heart failure in OASIS-2 (internal consistency). Furthermore, it is corroborated by complementary positive results from OASIS-1 and GUSTO-2b non-ST (external consistency).

In summary, the totality of evidence clearly favors the superiority of lepirudin over heparin.

8.2 Efficacy vs. placebo

All results in OASIS-1 and OASIS-2 emerged from an active (lepirudin) vs. active (unfractionated heparin) comparison on top of aspirin in a multi-drug environment. To aid in the interpretation of the OASIS trials, the study results were compared with a putative placebo control (aspirin alone) in an analysis that integrated data from similarly designed, published studies of aspirin plus heparin vs. aspirin alone. A direct comparison indicated that lepirudin would reduce the risk of all-cause death or new MI at the end of treatment by more than 50% as compared to aspirin alone, with p-values in the range of 0.00023 to 0.00451. These results were corroborated by a variety of statistical approaches and sensitivity analyses.

8.3 Safety profile

Treatment with lepirudin in the OASIS studies was associated with a significant excess of **bleeding events** at 7 days that was almost exclusively accounted for by an excess of minor bleeds and non-life-threatening major bleeds. The majority of major bleeds were managed with transfusions. Importantly, there was no difference in life-threatening bleeds between treatments, and no hemorrhagic stroke occurred in the lepirudin groups of the OASIS studies during the critical first 7 days. Most major bleeds were spontaneous, the leading source being gastrointestinal. Major puncture site bleeds were uncommon, probably due the relatively low rates of early cardiac intervention. The risk of bleeding, in particular of major bleeding in association with the use of lepirudin was found to be comparable with that of other highly active antithrombotic compounds already approved for the treatment of ACS.

Concordant with the overall distribution of bleeding events, hemorrhagic adverse events that were serious or led to discontinuation of study medication were more frequent in the lepirudin group. The pattern of hemorrhagic adverse events in various subgroups of OASIS-2 was also reflective of the safety population as a whole. However, there were 2 lepirudin subgroups that deviated substantially from the general trend: patients with a body weight <50 kg and those with baseline serum creatinine values >1.5 mg/dL had markedly increased rates of hemorrhagic adverse events, suggesting that the dose of lepirudin should be adjusted downward in such patients.

There were no differences between treatments in the cumulative incidence of **stroke** up to 7 days, 35 days and 180 days. In the period from 8 days to 35 days in OASIS-2, the overall incidence of stroke was slightly higher in the lepirudin group than in the heparin group, with significantly more ischemic strokes on lepirudin and significantly more hemorrhagic strokes on heparin. There is no plausible biological explanation for these imbalances. It seems likely that this was a chance observation given the overall similarity between treatments in the incidences of stroke from randomization to 7 days and during the follow-up period, the absence of a similar finding in OASIS-1, and the consistency of the lepirudin stroke data with published literature data from other compounds.

There was essentially no difference between the treatments in the frequency and pattern of **non-hemorrhagic adverse events**. Heart arrest and shock were the most common non-hemorrhagic adverse events that were serious, fatal, or led to discontinuation of study medication. The frequency of allergic reactions was low and similar in both treatment groups.

Laboratory findings did not reveal any additional safety concerns beyond the observed increase in the risk of bleeding. In OASIS-1, antibody formation was observed in 13% of patients, but not correlated with allergic reactions.

8.4   Risk/benefit ratio

The integrated endpoints of all-cause death, new MI, disabling stroke, and life-threatening bleed (quadruple) and all-cause death, new MI, refractory angina, disabling stroke, and life-threatening bleed (quintuple) at 7 days were used to assess the net clinical benefit of lepirudin. 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. 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 observed increase in the rate of major bleeds requiring transfusion <4 units of blood or blood products is considered 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 of the overall population 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.

8.5   Therapeutic justification

Based on the study selection criteria and the presenting disease characteristics, the populations of the OASIS studies can be considered to be representative of a broad range of patients with a moderate profile of ACS. The study protocols were aimed at minimizing any disruption of standard practice patterns at the participating institutions. Therefore, the results of the OASIS studies can be considered to be widely generalizable to the overall population.

Based on a total of about 2 million hospitalizations and an incidence of 5% of in-hospital death or new MI, ACS account for about 100,000 deaths or new MIs per year in Europe and North America [1]. Against this background, even relatively small absolute risk reductions are epidemiologically meaningful. The absolute treatment benefit observed with lepirudin in the OASIS studies would translate into annual reductions of about 16,000 cases of death or MI or about 26,000 cases of death, MI, or refractory angina in Europe and North America.

The OASIS study results are comparable with those obtained with LMW heparins and GP IIb/IIIa inhibitors that have recently been studied and approved in this indication. Importantly, the effects of lepirudin are achieved by replacing a drug that is already established in the treatment of ACS, rather than by adding another adjunct to the current therapeutic arsenal.

Therefore, it can be concluded that there is a clear therapeutic justification for the use of lepirudin in the treatment of acute coronary syndromes: unstable angina and acute MI without ST elevation, in order to prevent CV death, new MI or refractory angina.

8.6   Recommended dosage and duration of therapy

Based on the findings of the OASIS studies, it is recommended that the treatment with lepirudin in ACS be started with an initial IV bolus of 0.4 mg/kg, followed by an IV infusion of 0.15 mg/kg/hour for 72 hours. The weight adjustment should be limited to a maximum of 100 kg (maximum bolus

dose: 40 mg, maximum infusion dose: 15 mg/hour). The treatment should be monitored using the aPTT, aiming to achieve aPTT values of 60–100 seconds during infusion. Dose adjustments should be done in steps of 20% of the initial dose.

The initial lepirudin dose (bolus and infusion) should be reduced by 50% in patients with baseline serum creatinine values between >1.5 mg/dL and 2.0 mg/dL. Treatment with lepirudin should not be started if the baseline serum creatinine level is >2.0 mg/dL. If serum creatinine values are found to be >1.5 to 2.5 mg/dL during treatment, the infusion dose should be reduced to 50% of the original rate and intensified serum creatinine and aPTT monitoring should be performed. If the serum creatinine level is found to be >2.5 mg/dL at any time during treatment, treatment with lepirudin should be discontinued.

In case of minor bleeding, the infusion should be interrupted for about 2 hours and then be restarted at a 20% lower infusion rate. In case of severe or major bleeding, the infusion must be terminated.