Appendix A

Summary of the Most Important OASIS-2 and OASIS-1&2 Efficacy Findings for the ITT population

(In OASIS-1, the MITT population is the same as the ITT population)

Table 1

OASIS-2: Key efficacy findings from randomization to 180 days (ITT population)

Composite endpoint Time period	N (%) patients with events Heparin N=5,058	 Lepirudin N=5,083	Relative risk [a] (95% CI)	p-value [b]
CV death or new MI				
72 hours	134 (2.6%)	103 (2.0%)	0.76 (0.59–0.99)	0.0342
7 days [c]	**213 (4.2%)**	**182 (3.6%)**	**0.84 (0.69–1.03)**	**0.0863**
35 days	379 (7.5%)	342 (6.7%)	0.89 (0.76–1.04))	0.1093
180 days	545 (10.8%)	521 (10.2%)	0.95 (0.83–1.07)	0.3219
CV death, new MI or refractory angina				
72 hours	202 (4.0%)	159 (3.1%)	0.78 (0.63–0.96)	0.0157
7 days [d]	**339 (6.7%)**	**284 (5.6%)**	**0.82 (0.70–0.97)**	**0.0163**
35 days	680 (13.4%)	639 (12.6%)	0.93 (0.82–1.04)	0.1705
180 days	1,064 (21.0%)	1,032 (20.3%)	0.96 (0.87–1.05)	0.3189

[a] Stratified by pooled center and treatment
[b] Corrected for center
[c] The primary analysis of efficacy
[d] The key secondary analysis of efficacy

Table 2

OASIS-2: Incidence of individual endpoint components (ITT population)

Time period Component [a]	N (%) patients with events Heparin N=5,058	 Lepirudin N=5,083
72 hours		
CV death	46 (0.9%)	41 (0.8%)
New MI	96 (1.9%)	72 (1.4%)
Refractory angina	77 (1.5%)	59 (1.2%)
7 days		
CV death	78 (1.5%)	71 (1.4%)
New MI	156 (3.1%)	131 (2.6%)
Refractory angina	141 (2.8%)	111 (2.2%)

[a] Most serious outcome

Table 3

OASIS-2: Absolute and relative benefit of lepirudin in comparison with heparin (ITT population)

Composite endpoint Time period	N (%) of patients with events Heparin N=5,058		Lepirudin N=5,083		Absolute benefit (%)	Rel. risk reduction (%) [a]
CV death or new MI						
72 hours	134	(2.6%)	103	(2.0%)	−0.62	24
7 days	213	(4.2%)	182	(3.6%)	−0.63	16
35 days	379	(7.5%)	342	(6.7%)	−0.76	11
180 days	545	(10.8%)	521	(10.2%)	−0.53	5
CV death, new MI or refractory angina						
72 hours	202	(4.0%)	159	(3.1%)	−0.87	22
7 days	339	(6.7%)	284	(5.6%)	−1.12	18
35 days	680	(13.4%)	639	(12.6%)	−0.87	7
180 days	1,064	(21.0%)	1,032	(20.3%)	−0.73	4

[a] Stratifed by pooled center and treatment

Figure 1

CV death or new MI to 7 days (ITT population)

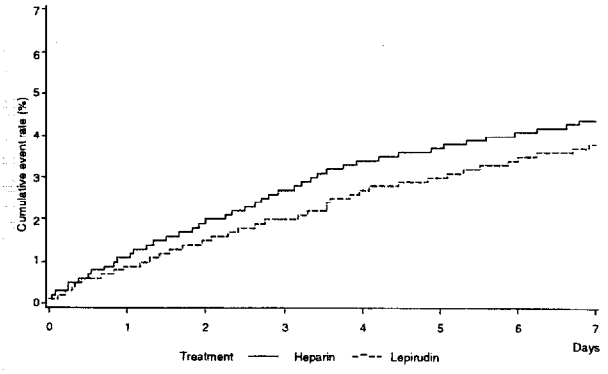

Figure 2

CV death, new MI or refract. angina to 7 days (ITT population)

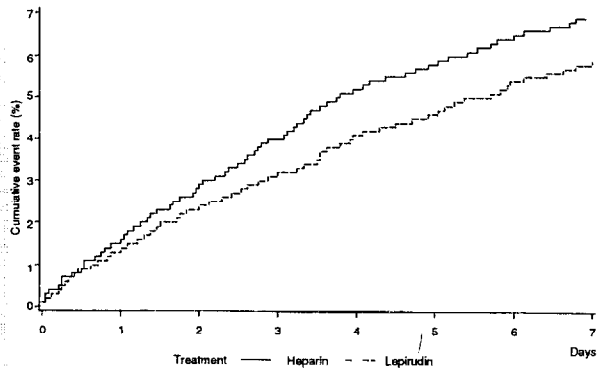

Table 4

OASIS-2: Efficacy findings, with all-cause death instead of CV death (ITT population)

Composite endpoint Time period	N (%) of patients with events Heparin N=5,058		Lepirudin N=5,083		Absolute benefit (%)	Rel. risk [a] reduction (%)	p-value [b]
All-cause death or new MI							
72 hours	134	(2.6%)	103	(2.0%)	–0.62	24	0.0342
7 days	213	(4.2%)	182	(3.6%)	–0.63	16	0.0863
35 days	387	(7.7%)	344	(6.8%)	–0.88	12	0.0681
180 days	572	(11.3%)	539	(10.6%)	–0.70	7	0.2003
All-cause death, new MI or refractory angina							
72 hours	202	(4.0%)	159	(3.1%)	–0.87	22	0.0157
7 days	339	(6.7%)	284	(5.6%)	–1.12	18	0.0163
35 days	688	(13.6%)	641	(12.6%)	–0.99	8	0.1221
180 days	1091	(21.6%)	1046	(20.6%)	–0.99	6	0.1849

[a] Stratified by pooled center and treatment [b] Corrected for center

Table 5

OASIS-2: Therapeutic cardiac interventions up to 7 days (ITT population)

Intervention	N (%) patients Heparin N=5,058		Lepirudin N=5,083		p-value
Any intervention, excluding cardiac cath.	**411**	**(8.1%)**	**351**	**(6.9%)**	**0.0198**
PCI	261	(5.2%)	216	(4.2%)	0.0303
CABG	98	(1.9%)	96	(1.9%)	0.8574
Thrombolysis	54	(1.1%)	44	(0.9%)	0.2985
Intra-aortic balloon pump	33	(0.7%)	33	(0.6%)	0.9840

Figure 3

OASIS-2: Numbers of patients undergoing PCI or CABG during or after end of study infusion (ITT population - data same as for MITT and Safety populations)

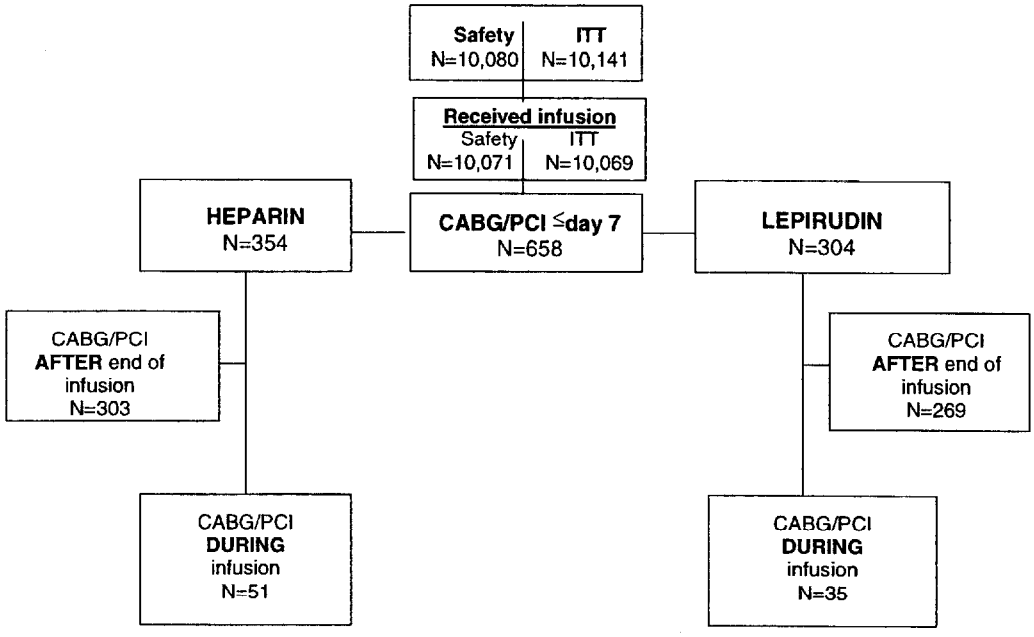

Table 6

OASIS-2: Efficacy and safety up to 7 days in patients undergoing PCI or CABG during study infusion (ITT population - data same as for MITTand Safety populations)

Endpoint	Heparin (N=51)			Lepirudin (N=35)		
	Patients with event			Patients with event		
	Total N (%) [a]	BEFORE intervention N (%) [a]	AFTER intervention N (%) [b]	Total N (%) [a]	BEFORE intervention N (%) [a]	AFTER intervention N (%) [b]
Efficacy (ITT)						
CV death/new MI	9 (17.6%)	5 (9.8%)	4 (8.7%)	2 (5.7%)	0	2 (5.7%)
CV death/new MI / ref. angina	16 (31.4%)	11 (21.6%)	5 (12.5%)	8 (22.9%)	6 (17.1%)	2 (6.9%)
Safety						
Minor bleed	14 (27.5%)	2 (3.9%)	12 (24.5%)	7 (20.0%)	1 (2.9%)	6 (17.6%)
Major bleed	0	0	0	0	0	0
Stroke	0	0	0	0	0	0

[a] Denominator for percents includes all patients undergoing PCI or CABG.

[b] Denominator for percents excludes patients who had an event of the respective type prior to intervention.

Table 7

OASIS-1&2 combined results (ITT populations)

Composite endpoint Time period	N (%) patients with events Heparin N=5,429	Lepirudin N=5,621	Absolute benefit (%)	Rel. risk reduction (%)	p-value
CV death or new MI [a]					
72 hours	144 (2.7%)	112 (2.0%)	−0.66	26	0.0200
7 days	231 (4.3%)	196 (3.5%)	−0.77	19	0.0334
35 days	410 (7.6%)	374 (6.7%)	−0.90	13	0.0541
End of study [b]	586 (10.8%)	564 (10.0%)	−0.76	8	0.1719
CV death, new MI or refractory angina [a]					
72 hours	217 (4.0%)	171 (3.0%)	−0.95	25	0.0059
7 days	363 (6.7%)	304 (5.4%)	−1.28	20	0.0052
35 days	719 (13.2%)	678 (12.1%)	−1.18	9	0.0829
End of study [b]	1,114 (20.5%)	1,082 (19.2%)	−1.27	7	0.1606

[a] Corrected for study and center within study

[b] 120 days in OASIS-1b and 180 days in OASIS-1a and OASIS-2

Table 8

Lepirudin (OASIS-1&2) versus putative placebo (aspirin alone) control
All-cause death or new MI – relative risk (95% confidence interval)
(ITT populations for observed RRs from OASIS data)

Time period	Observed RR Lepirudin : Heparin	Historical RR Heparin : Aspirin	Derived RR Lepirudin : Aspirin	p-value
72 hours	0.75 (0.58 – 0.96)	0.58 (0.40 – 0.85) [a]	0.44 (0.28 – 0.68)	0.00032
	0.75 (0.58 – 0.96)	0.35 (0.16 – 0.78) [b]	0.26 (0.11 – 0.60)	0.00161
	0.75 (0.58 – 0.96)	0.67 (0.44 – 1.02) [c]	0.50 (0.31 – 0.82)	0.00592
7 days	0.81 (0.67 – 0.98)	0.58 (0.40 – 0.85) [a]	0.47 (0.31 – 0.72)	0.00045
	0.81 (0.67 – 0.98)	0.35 (0.16 – 0.78) [b]	0.28 (0.13 – 0.64)	0.00242
	0.81 (0.67 – 0.98)	0.67 (0.44 – 1.02) [c]	0.54 (0.34 – 0.86)	0.00942

[a] Published meta-analysis (Oler) plus the FRISC and FRIC studies
[b] FRISC and FRIC studies alone
[c] Published meta-analysis (Oler) alone

Table 9

Lepirudin (OASIS-2) versus putative placebo (aspirin alone) control
All-cause death or new MI - relative risk (95% confidence interval)
(ITT populations for observed RRs from OASIS data)

Time period	Observed RR Lepirudin : Heparin	Historical RR Heparin : Aspirin	Derived RR Lepirudin : Aspirin	p-value
72 hours	0.76 (0.59 – 0.99)	0.58 (0.40 – 0.85) [a]	0.44 (0.28 – 0.70)	0.00045
	0.76 (0.59 – 0.99)	0.35 (0.16 – 0.78) [b]	0.27 (0.12 – 0.61)	0.00184
	0.76 (0.59 – 0.99)	0.67 (0.44 – 1.02) [c]	0.51 (0.31 – 0.83)	0.00737
7 days	0.84 (0.69 – 1.03)	0.58 (0.40 - 0.85) [a]	0.49 (0.32 – 0.75)	0.00096
	0.84 (0.69 – 1.03)	0.35 (0.16 – 0.78) [b]	0.29 (0.13 – 0.67)	0.00332
	0.84 (0.69 – 1.03)	0.67 (0.44 - 1.02) [c]	0.56 (0.35 – 0.90)	0.01555

[a] Published meta-analysis (Oler) plus the FRISC and FRIC studies
[b] FRISC and FRIC studies alone
[c] Published meta-analysis (Oler) alone

Table 10

OASIS-1&2: Integrated endpoints up to end of study (ITT populations)

Integrated endpoint Timepoint	N (%) of patients with events Heparin N=5,429		Lepirudin N=5,621		Absolute benefit (%)	Rel. risk reduction (%)	p-value
All-cause death, new MI, disabling stroke or life-threatening bleed [a]							
72 hours	156	(2.9%)	122	(2.2%)	–0.70	25	0.0167
7 days	253	(4.7%)	219	(3.9%)	–0.76	18	0.0406
35 days	457	(8.4%)	431	(7.7%)	–0.75	10	0.1266
End of study [b]	671	(12.4)	659	(11.7%)	–0.64	6	0.2727
All-cause death, new MI, refractory angina, disabling stroke or life-threatening bleed [a]							
72 hours	227	(4.2%)	181	(3.2%)	–0.96	24	0.0067
7 days	383	(7.1%)	324	(5.8%)	–1.29	19	0.0059
35 days	761	(14.0%)	730	(13.0%)	–1.03	8	0.1495
End of study [b]	1,191	(21.9%)	1,161	(20.7%)	–1.28	6	0.1616

[a] Corrected for study and center

[b] 120 days in OASIS-1b and 180 days in OASIS-1a and OASIS-2