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STATISTICAL REVIEW AND EVALUATION

NDA #: 20-807/SE1-004

Drug: Refludan [lepirudin (rDNA) for injection]

Indication: The use of Refludan for anticoagulation in adult patients with acute coronary syndromes (unstable angina/acute MI without ST elevation)

Sponsor: Hoechst Marion Roussel, Inc.

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INTRODUCTION

Refludan has been approved for use in the indication "anticoagulation in adult patients with heparin-associated thrombocytopenia (HAT) type II and thromboembolic disease mandating parenteral antithrombotics therapy." This submission presents the efficacy and safety data in support of the use of Refludan (IV bolus of 0.4 mg/kg body weight: IV infusion of .15 mg/kg/hour) for anticoagulation in adult patients with acute coronary syndromes (unstable angina/acute MI without ST elevation). The principal clinical study presented in support of Refludan for this indication is the Organization to Assess Strategies for Ischemic Syndromes-2 (OASIS-2) trial. Unfractionated heparin (IV infusion of 15 U/kg/hour) was used as an active comparator for Refludan although heparin is not an approved drug for the proposed indication. The data in OASIS-2 did not show statistical superiority of Refludan with respect to heparin at the 0.05 level of significance. However, the agency recommended (dated 10/28/98) that the final efficacy analysis results should be assessed at the 0.048 level of significance because there was plan for conducting interim analysis in the protocol. The protocol for OASIS-2 was not reviewed by the agency.

The sponsor claims that the proposed indication for Refludan is also supported by the efficacy results from a phase II dose finding (low dose, medium dose and heparin) study known as OASIS-1. The OASIS-1 study consisted of OASIS-1a and OASIS-1b. Note that the medium dose of OASIS-1 was the dose for OASIS-2. In OASIS-1, the medium dose Refludan was not

significantly more effective (p-value .1493) than heparin with respect to the primary endpoint (CV death or new MI) of OASIS-2. It must be emphasized that OASIS-1 was different from OASIS-2 (e.g,, doses, time of warfarin use, etc.).

The sponsor combined OASIS-1 and OASIS-2 to show the efficacy of Refludan. It was mentioned in the protocol that clincal, safety, and coagulation data from the OASIS-1 study as well as other information from other Refludan trials would be used to determine the dose of Refludan which would be compared with heparin in a larger and simpler trial of 8,000 to 10,000 patients. The plan to combine the two studies was not mentioned in the protocol of OASIS-2.

Because heparin is not an approved drug for the proposed indication and the data from OASIS-2 failed to show superiority of Refludan over heparin, the sponsor attempted to show the effectiveness of Refludan by comparing Refludan with imputed placebo based on historical data and simulation. Section 4 summarizes the placebo estimation from Oler et al. and FRISC/FRIC studies.

The rest of this review is organized as follows. Section 1 discusses study protocol of OASIS-2 including the sponsor's analysis and this reviewer's analysis; Section 2 discusses the analyses of data from OASIS-1; Section 3 summarizes a combined analysis of OASIS-2 and OASIS-1; and Section 5 summarizes the conclusions.

1.1 STUDY PROTOCOL OASIS-2 (Organization to Assess Strategies for Ischemic Syndromes)

The OASIS-2 trial was a double blind, randomized trial (1:1) of Refludan versus heparin in 10,141 patients in 15 countries. The patients were randomized with Refludan (bolus: 0.4 mg/kg infusion: 0.15 mg/kg/hour) or standard unfractionated heparin (bolus: 500 U, infusion; 15U/kg/hoour). Patients were to take aspirin (325 mg/day while in hospital and 80-325mg /day after discharge from hospital). The dosage of study medication was adjusted starting 6 to 8 hours after the start of infusion in order to keep the aPTT within the target range of 60 to 100 seconds. Additionally, infusion rates were adjusted for renal function where necessary. Approximately 24 hours into the infusion, eligible patients were randomized to a warfarin sub-study.

Eligible patients who consented was initially were randomized to one of two IV treatment groups (started immediately and continued for 72 hours):

1. Refludan (0.4 mg/kg bolus, 0.15mg/kg/hr infusion), or

2. Standard intravenous heparin (500u bolus, 15u/kg/hr infusion).

A subset of patients who met additional eligibility criteria (see below) and who consented to a

second randomization, approximately 24 hrs (between 12 and 30 hours) after starting Refludan or heparin treatment, was randomized to one of two groups:

1. Moderate intensity warfarin (INR target of 2.5; range 2-3) for 5 months as well as aspirin, or

2. Standard therapy (aspirin).

In patients who required an urgent invasive procedure, warfarin randomization was extended up to 5 days.

Eligibility:

See medical review for both inclusion and exclusion criteria.

Study Patients and Conduct:

A total of 10141 patients were randomized (ITT population). The protocol stated that the primary analysis would be based on ITT population. Out of 10141 ITT patients, 10080 randomized patients received study medication (safety population). Out of 10080 treated patients, 10078 patients had a 7-day assessment. The sponsored classified these 10078 patients as modified ITT (MITT) population. Although ITT analysis was the primary analysis recommended by the FDA (in a letter to the sponsor dated October 28, 1999), the sponsor felt that the MITT population was more appropriate because no method of imputation missing data was addressed in the protocol. The MITT population also reflects the first study infusion given to the patient. Note that the difference between the ITT population and the MITT population is 63 patients. The 30 heparin patients excluded from the MITT analysis had the following events: 1 CV death and 4 refractory angina. The 33 Refludan patients excluded from the MITT analysis had the following events: 2 CV death, 4 new MIs and 4 refractory angina.

The number of patients randomized into each treatment group and their outcome were as follows:

Table 1.1: Patient Accounting and Administration of Study Medication

	Refludan N(%)	Heparin N(%)	Total N(%)
Total Randomized (ITT Population)	5083	5058	10141
Patient Accounting (MITT population):	5045 (100%)	5033 (100%)	10078 (100%)
Early withdrawal from study*	341 (7%)	381 (8%)	722 (7%)
Total completion study	4704 (93%)	4652 (92%)	9356 (93%)
Administration of study Medication (safety population)			
Total treated:	5047 (100%)	5033 (100%)	10080 (100%)
Premature discontinuations	927 (18%)	735 (15%)	1662 (17%)
Randomized to warfarin:**	949 (19%)	964 (19%)	913 (19%)
Premature discontinuations***	369(39%)	377 (39%)	746 (39%)

*: Death, lost to follow-up or withdrawal of consent
**: Percentages based on the MITT population (N=10078)
***: Percentages based on the warfarin population (N=1912)

There were no relevant differences between the treatment groups with respect to demographic characterstics and medical history at randomization. The mean age was 64 years (range: 22 - 86). Sixty-one (61) percent of patients were male. The majority of patients (88%) had suspected unstable angina at randomization; the remainder had suspected MI without ST elevation. Eighty-five (85) percent of Refludan patients and 88% of heparin patients completed > 60 hours of IV infusion. The mean duration of IV infusion was 66.0 hours in the Refludan group and 67.5 hours in the heparin group. Fewer Refludan (52%) than heparin (88%) required changes in the rate of infusion. The patients' baseline characteristics (e.g., age, sex, and race) are summarized in Table A.1 in the Appendix.

Timetable

Approximately 360 centers in 15 countries participated in this study.
Recruitment of patients began in June 1996. Recruitment of 10,000 patients was expected to be finished by December 1997. Follow-up of all patients was completed by June 1998. The 7-day data were planned to be analyzed by June 1998. The follow-up data were cleaned and available by December. Final data clean up and statistical analyses were completed by June 1999.

STUDY OBJECTIVES:

The objective of OASIS-2 was to reliably evaluate:

Whether recombinant Refludan, a potent direct anti-thrombin agent, is superior to heparin in preventing cardiovascular (CV) death and new nonfatal myocardial infarction (MI) within 7 days in 10,000 patients with suspected unstable angina or suspected non-Q wave MI (without ST elevation on the presenting ECG).

The following secondary endpoints would also be considered:

To compare the effects of IV Refludan versus a standard regimen of IV heparin
On the secondary outcome:

i) CV death or new MI or refractory angina (triple composite endpoint) at 7 days
ii) CV death or new MI, or severe angina at 7 days
iv) CV death or new MI at 35 days.

Safety outcomes including major bleeds (especially fatal, intra-cranial bleeds and bleeds requiring surgical intervention) and other serious adverse events were examined at 7 days.

Purpose of warfarin sub-study:

The purpose of the warfarin substudy was to reliably evaluate whether five months of therapy with moderate intensity warfarin reduces the incidence of new MI, stroke and CV death in a subset of approximately 6000 patients. Analysis of safety outcomes including major bleeds (especially fatal, intra-cranial bleeds and bleeds requiring surgical intervention) and serious adverse events over 5 months would also be performed. However, since it was expected that warfarin would take about 3 days to have an anticoagulant effect, an efficacy analysis for the warfarin versus control would also be conducted after excluding the data from 3 days. However, this reviewer could not locate this analysis.

Randomization Procedures:

Randomization to Refludan or Heparin:

Randomization was by a toll-free call to a central 24-hr randomization. This took place without any undue delays (e.g. randomization was performed in the emergency room). After key entry data had been provided over the telephone, the patient was assigned to receive either heparin or Refludan, in a blind fashion. Study medications was held in each coronary care unit (or hospital pharmacy) along with all relevant instructions in pre-numbered, sealed treatment boxes. All patients who were randomized, were irrevocably in the study, whether or not they were subsequently found to be eligible, or actually received the allocated treatment, and were followed for six months or until death. Study treatment was initiated as soon as possible after randomization.

Randomization to warfarin or standard therapy

At about 24 hours (range between 12 to 30 hours) after starting Refludan or heparin, all patients were considered for randomization into the OASIS-2 warfarin sub-study unless a clear contraindication to or indication for warfarin was present. If it was likely that patients would undergo an urgent invasive procedure, such as angiography or PTCA, randomization to warfarin occurred within a period of 5 days from the initial randomization to heparin or Refludan. Randomization to warfarin or standard therapy was performed by a second telephone call to the randomization service.

Exclusion criteria for warfarin randomization

(i) Clear clinical indication for warfarin treatment as standard treatment
(ii) Major bleeding during the Refludan /heparin infusion
(iii) CABG surgery planned within 7 days of eligibility assessment for warfarin randomization
(iv) Normal coronary anatomy documented by coronary angiography since the initial randomization
(v) Any other known clear contraindication to warfarin.

Clinical Outcome Measure:

(i) Cardiovascular death: To be divided by cause
(ii) New myocardial infarction after randomization: The criteria for new MI after randomization was:

a) within 24 hours of radomization: patients had recurrent typical clinical systems with either new CK enzyme elevation or new diagnostic ECG changes beyond 24 hours from

hospitalization;

b) Two out of three criteria of clinical systems, new CK enzyme elevation or new persistent ECG changes.

(iii) Refractory Angina was defined as a new episode of ischemic chest pain (with documented characterstic ECG changes during pain) lasting > 5 minutes occurring in the presence of "optimum" medical treatment and leading to an additional intervention such as thrombolytic procedure (PTCA, CABG) within 7 days of the original randomization to heparin or Refludan. Optimum treatment in this context is defined as at least two anti-anginal treatments, one of which should be an IV nitrate (unless contraindicated). A twelve lead ECG documenting the ECG changes associated with this event will be required. From hospital discharge until 35 days, refractory angina is defined by the same criteria as readmission to hospital with unstable angina.

(iv) Severe Angina was defined as at least 1 episode of recurrent ischemic chest pain lasting > 5 minutes while an optimal medical therapy, with documentation of new ECG changes.

Study Size and Statistical Considerations:

Study Size:

Approximately 10,000 patients were planned to be randomized to heparin or Refludan. The randomization to each arm was expected to be equal. It was expected that at least two thirds of the initial cohort would be re-randomized to warfarin or standard therapy in equal proportions (about 3300 versus 3300). These sample sizes were likely to give adequate power to detect moderate but important differences in the primary clinical outcomes and safety outcomes.

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 o 7 days) would be at least 5% and 8.7%, respectively. With these rates and an overall significance level of 5%, the sample size of 10000 patients would provide 80% power to detect a 23% relative risk reduction in the primary outcome and 21% relative risk reduction in the secondary outcome (CV death, new MI or refractory angina).

Refludan vs. heparin

The main comparison between Refludan and heparin was to be made on CV death and new MI in seven days.

The secondary outcomes were the triple composite endpoint (CV death, new MI and severe angina at 7 days), and CV death and new MI at 35 days.

Differences in the rates of associated MI (stratified by entry diagnosis of suspected UA or acute MI without ST elevation) were also be examined. Also safety outcomes including major bleeds (especially fatal, intra-cranial bleeds, and bleeds requiring surgical intervention) and other serious adverse events were examined at seven days. A further analysis to explore a clinical rebound in thromboembolic events after cesation of intravenous antithromboetic therapy was also planned utilizing Cook and Lawless method.

Statistical Analysis

The aims of this study were to determine the efficacy and safety of Refludan versus heparin. Statistical analyses compared incidence rates of the main outcomes of CV death, and new MI at 7 days as defined by an intention to treat analysis and a 2-tailed p-value of .05 would be considered statistically significant. The secondary outcome of CV death, new MI and refractory angina would be considered statistically significant at a 2-tailed P-value of .01 (sponsor's S8-V8-P31). Also the combined safety endpoints of major bleeding and stroke would be contrasted. The Mantel-Haenszel test (stratified by center) would be used. Primary comparison and time to event analysis were performed at 7 days. Further comparisons would be made at 35 days and 6 months follow-up utilizing descriptive statistics. The sponsor wanted to conduct additional tests at the time of analysis.

Interim Analysis and Data Monitoring

The independent Data and Safety Monitoring Board (DSMB) monitored the progress of all aspects of the study and would ensure that the study met the highest standards of ethics and patients safety. In particular, the data on key study endpoints were to be monitored at regular intervals to ensure that the event rates met protocol projections. If the event rates in the heparin group (at 25% of recruitment) were lower than, the DSMB would recommend an increase in the number of patients recruited into the study to maintain the study power. These formal interim analyses were planned, occurring when 25%, 50%, and 75% of 7-day information was available. More frequent meetings were planned to be called on the advice of the DSMB chairperson who would receive reports for the monitoring of efficacy and safety for heparin and Refludan. However, the DSMB would take into account all available data from relevant studies to make decisions.

The DSMB monitored all aspects of the study, particularly with regard to safety. In addition, three interim analyses were performed when 25%, 50%, and 75% of the 7-day follow-up data were available. The conditions for early terminations on the grounds of proven efficacy were not fulfilled.

It is to be noted here that that in a memo to the sponsor (HMR), the GI division stated that the interim analysis plan was acceptable and the final efficacy analysis was to be done at .048 level of significance.

Monitoring for Efficacy:

For efficacy, the combined endpoint of CV and new MI was to be monitored using a modified Haybittle–Peto rule of four standard deviations in the first half of the study and 3 standard deviation of the second half. The boundary would have to be exceeded on at least two consecutive time points, 3 months apart. A similar monitoring rule would be used for evaluation of warfarin.

Analysis Population:

The following populations were defined for the purpose of analysis.

a) **Intent-to-treat (ITT):** All randomized patients, analyzed according to the treatment they were randomized.

b) **Safety:** All randomized patients who received Refludan or heparin, analyzed according to treatment initially received.

c) **Modified Intention to treat (MITT):** All safety patients who completed the 7-day efficacy assessment, analyzed according to treatment initially received. The 7-day efficacy assessment was considered complete if the patient died or had a new MI before the end of day 7, or if the 7-day event form had all these questions answered relating to death, new MI, and refractory angina.

Results of Interim Analyses (extracted form from sponsor's S8-V3-P84)

Three formal interim analyses were performed by the Independent Data and Safety Monitoring Board (DSMB), where approximately 25%, 50%, and 75% of the 7-day follow-up data were available (as planned in the study protocol). In addition, DSMB monitored the progress of all aspects of the trial, particularly patient safety. For this purpose, the CCC study statistician provided the DSMB with blinded and unblinded analyses. No HMR personnel or CC Project Office personnel other than the study statistician took part in or was informed of DSMB closed-session deliberations. The DSMB received monthly reports on major bleeds, strokes and other serious adverse events.

At the 25% recruitment point, the heparin primary endpoint (CV death or new MI) event rate was assessed to determine whether the endpoint event rate was met protocol projections (at least 5% percent in the heparin group). Based on the heparin event rate (lower heparin rate than the expected heparin event rate) at that time, the DSMB did not recommend a sample size increase.

It was also possible for the trial to be stopped early due to proven efficacy. At the three interim analyses, the pre-specified testing levels employed were p= .00006, .00006 and .00270, respectively(the areas of a standard normal distribution beyond +/-4, +/-4 and +/-3). However, it was also anticipated that if the significance level was reached, a repeat analysis after a further 3 months recruitment would also be required to be significant at the same level for the study to be terminated early on the grounds of proven efficacy. This would mean that the accumulated type I error up to the final analysis was much less than the sum of the individual alphas.

A simulation study of 200,000 OASIS-2 studies under the null hypothesis (various event rates assumed) examined the effect of conducting these interim analyses on the final testing level. If a p-value correction were to be made based on these findings (using event rates of 4-6%), then a final testing level of .048 would preserve the overall type I error rate 5%.

Pooling of Centers for Analyses:

Although the pooling of centers was not mentioned in the protocol, an amendment of the protocol was made (January 6, 1999) to pool the centers. The sponsor mentioned that the pooling of centers was necessary to certain statistical procedures (logistic regression or proportion hazards analyses) which rely on asymptotics for large sample theory to hold. Prior to unblinding, a listing of number of patients and number of events by center was created. When possible, if sufficient numbers within a country allowed subdivisions within the country, the list was distributed to the respective local coordinators. Based upon number of events and geographical considerations, the local coordinators grouped the centers aiming that 10 events were observed per regions. As a result, there were 34 pooled centers (out of 360 centers), 8 from Canada, 3 from Australia, 3 from Italy, 3 from Germany, 6 from Poland, 2 from Argentina and 1 each from USA, South Africa, Israel, Hungary, Scotland and Ireland combined, England and Wales combined, Brazil, Mexico, and Greece.

1.2 Efficacy Results:

Primary Endpoint

The primary efficacy endpoint of the study was the 2-component composite endpoint (CV death or new MI) at 7-day. The Mantel-Haenszel test (stratified by center) was used for differences between groups in the primary endpoint. A point estimate and 95% confidence interval for the relative risk was computed using a logistic regression model using pooled

center.

The sponsor analyzed the primary endpoint for MITT, ITT and per protocol populations. Note that the sponsor did not randomize the patients within each center separately. The results were summarized in the following table.

Table 1.3: Efficacy Results for the Primary Endpoint (CV Death or new MI up to 7-day) (extracted from sponsor's S8-V3-P290 Tables 7-49 and S8-V3-P269 7-32)

Population	Proportion (%) of patients with events		Relative risk: Refludan vs heparin (95% CI) (logistic)	P-value
	Refludan	heparin		M-H
MITT	178/5045 (3.5%)	211/ 5033 (4.2%)	.83 (.68-1.02)	.0714
ITT	182/5083 (3.6%)	213/5058 (4.2%)	.84 (.69 – 1.03)	.0863

Note: M-H: Mantel-Haenszel test; logistic: logistic regression

It is seen from the above table that Refludan was not significantly more effective than heparin for the treatment of UA using the pre-specified primary endpoint CV death or new MI upto 7 days. Because there were three interim analyses performed during the conduct of OASIS-2, the agency (dated October 28, 1998) suggested the p-value for the test corresponding to the primary endpoint needed to be compared at the 0.048 level.

According to protocol, it was expected that the event rates in the heparin group for the primary efficacy outcome (CV death or new MI up to 7 days) would be at least 5%. It was also expected that a 23% relative risk reduction would occur in the primary outcome. However, it is seen from the above table that estimated heparin event rate was 4.2 % and estimated relative risk reduction is 16%. The sponsor mentioned that as a consequence of observed heparin rate (4.2%), the statistical significance for the primary analysis did not reach the pre-specified level.

Although, the primary interest in OASIS-2 was to analyze the double composite endpoint (CV death or MI) at day 7, the sponsor also analyzed CV death or MI at day-35 and day-180. These results also failed to show a significant benefit of Refludan over heparin.

Exploration of Robustness Analysis of the Primary endpoint (Worst case analyses)

The sponsor conducted some additional methods of imputation for the ITT analysis of patients

who did not have a 7-day assessment completed or who had an early assessment.

In the first method, patients with no or early 7-day assessments were given a value of 0.036 for Refludan and 0.042 for heparin, these being the event rates in the ITT population. The observed no-event cases were given a value 0 and event cases a value of 1. A modifed Mantel-Haenszel test incorporating these imputations was used to test for difference between groups. The effect on the p-value for the ITT analysis for the primary endpoint was extremely minimal: The p-value was reduced from 0.0863 to 0.0856 (extracted from sponsor'' S8-V18-P-107).

In the second, "worst case" approach, no or early 7-day assessment Refludan patients were given a value of 2 times 0.036 (0.072), while the heparin patients were assumed event free (0 value imputed). The results of this "worst case" analysis showed an increase from 0.0863 to 0.0910 (extracted from sponsor's S8-V18-P-107).

Time to Event Analyses for the Primary Endpoint

In the primary composite endpoint (CV death or new MI at 7-day) for the MITT population, the Gehan-Wilcoxon test (stratified by center) failed to show that Refludan was significantly more effective (p-value .0629) than heparin (extracted from sponsnor's Appendix C.2.1: Summary 21 S8-V25-P122).

1.2 Other Analyses of the Primary Endpoint

The sponsor conducted non-parametric analyses of covariance for the double composite endpoint of CV death or new MI at 7 days. The sponsor claimed that these analyses were conducted to reduce the variance for estimates of treatment effect (and thereby increase the power of the analysis) and to adjust for any random imbalances between treatment groups with respect to the covariates (thereby allowing the comparison of treatments with any covariate imbalance removed).

The centers were accounted for in the model, as were the following analysis plan-defined covariates:

a) Age (< = 65 years, > 65 years)
b) Baseline ECG (ST depression vs. other findings)
c) Previous MI (yes or no)
d) Current smokers (vs. never or former)
e) History of heart failure (yes or no).

Prior to unblinding, the following 6 covariates were found to be independently predictive of

outcome at 7 days:

a) ECG abnormal/normal
b) Baseline ECG (ST depression vs. other findings)
c) Diabetic history
d) Diagnosis at entry (suspected UA or non-q wave MI)
e) Age (< = 65 years, > 65 years)
f) Sex.

The sponsor also conducted a third analysis on the combined set of covariates (9 covariates in total, since two covariates were common to both analyses).

The results for the between comparison of CV death or new MI at 7 days obtained from the analyses of covariance were reported in the following table.

Table 1.4: Efficacy Results for the Primary Endpoint Based on Covariate Analyses (CV Death or new MI up to 7-day) (extracted from sponsor's S8-V3-P108)

Time from randomization (statistic)	Covariate Model		
	Pre-defined (5 covariates)	Predictive (6 covariates)	Combined (9 covariates)
7 days:			
Estimated difference (absolute)	.71%	.69%	.7%
95% CI (absolute)	(-.04, 1.44)	(-.05, 1.44)	(-.05, 1.45)
p-value	.0635	.0699	.0665
7 days:			
Estimated difference (absolute)	.95%	.91%	.94%
95% CI (absolute)	(-.04, 1.94)	(-.08, 1.91)	(-.05, 1.93)
p-value	.0628	.0738	.0656

At 7 days, all three covariance analyses failed to show that Refludan was significantly more effective than heparin with respect to the double composite endpoint (CV death or new MI).

1.3 Secondary Endpoints

One of the secondary endpoints of OASIS-2 is the triple composite endpoint (CV death or MI or Refractory angina). The results of this secondary endpoint are summarized below.

Table 1.5: Efficacy Results for the Secondary (CV Death or new MI or Refractory Angina up to 7-day) (extracted from sponsor's S8-V3-P290, Table 7-32)

Population	Proportion (%) of Patients with Events		Relative risk (95% CI) (logistic)	P-value	
	Refludan	heparin		M-H	Fisher's (reviewer's)
MITT	279/5045 (5.5%)	336/5033 (6.7%)	.82 (.69-.96)	.0138	.018
ITT	284/5083 (5.6%)	339/5058 (6.7%)	.82 (.70 - .97)	.0163	.021

Note: M-H: Mantel-Haenszel test; logistic: logistic regression

The above analyses suggested that Refludan was significantly more effective than heparin at the 0.05 level with respect to the triple composite endpoint for the treatment of UA. However, Refludan was not significantly more effective than heparin at the pre-specified level 0.01.

Other Secondary Endpoints

The other secondary endpoint of interest are 1) death (all causes) or MI and 2) death or new MI or refractory angina. The results of these two secondary endpoints were summarized below.

Table 1.6: Efficacy Results for Other Endpoints (up to 7-day) for the ITT Population (extracted from sponsor's S8-V3-P290, Table 7-53)

Endpoint	Proportion (%) of Patients with Events		Relative risk (95% CI) (Logistic)	P-value
	Refludan	heparin		M-H
Death or new MI	182/5083 (3.6%)	213/5058 (4.2%)	.84 (.69-1.03)	.0863
Death or new MI or Refractory Angina	284/5083 (5.6%)	339/5058 (6.7%)	.82 (.70 - .97)	.0163

Note: M-H: Mantel-Haenszel test; logistic: logistic regression

It is seen that Refludan was significantly more effective than heparin at .05 level for the triple composite endpoint (death or MI or Refractory angina). However, the test was not significant at the 0.01 level specified in the protocol. The sponsor did not mention why this secondary endpoint would be tested at 0.01 level. However, according to an amendment made on June 23, 1998, all the secondary analyses would be tested at 0.05 level because these analyses were for supportive purpose only.

Components

The agency advised (dated October 28, 1999) the sponsor to analyze the contribution of each component of the composite endpoint. The efficacy results for each component were summarized below.

Table 1.7 (Reviewer's): Efficacy Results for the Components up to 7-day for the ITT Population (extracted from sponsor's S8-V3-P238, Table 7-4)

Components	**Proportion (%) of patients with events**		**Relative risk** (95% CI)	**P-value** (Fisher's exact)
	Refludan	heparin		
CV death	71/5083 (1.4%)	78/5058 (1.5%)	.906 (.66 – 1.25)	.56
New MI	136/5083 (2.7%)	161/5058 (3.2)	.84 (.67 – 1.05)	.14
Refractory Angina	135/5083 (2.7%)	157/5058 (3.1%)	.86 (.68 – 1.07)	.19

It is seen from the above table that Refludan was not significantly more effective than heparin corresponding to any component of the Primary endpoint or the triple composite endpoint. Note that the trial was not sized for testing significance of each component separately.

Analyses by Country

Only in one country (Israel) among the 15 countries, Refludan was significantly more effective (relative risk .36) than heparin with respect to the primary endpoint. The p-value for consistency of treatment effect across the countries was .6279. However, only in seven of the 15 countries, the Refludin treated group did have numerical advantage over the heparin treated group.

Warfarin Sub-study

It was expected that two-thirds of study patients would enter the warfarin substudy and be randomized to either warfarin or control. One day after initiating Refludan or heparin intravenous infusion, the patients would be assigned on a random basis to receive, for a period of 5 months, standard therapy or a treatment with warfarin tablets. The primary outcome cluster would include: CV death, new MI, and stroke in 5 months. The secondary outcome cluster would include: CV death, new MI, stroke, and readmission to hospital for UA at 5 months. Note that warfarin has been used for several decades and has been found to prevent blood clots.

A total of 3793 (38%) patients were randomized in the warfarin sub-study: 949 of 1899 Refludan patients and 963 of 1894 heparin patients received warfarin. The remaining patients in each group received standard therapy. Recruitment into the warfarin substudy was at least 30% less than foreseen in the protocol, reducing statistical power of the study to detect differences in treatment effect between treatment groups. In addition warfarin therapy was frequently discontinued prematurely (39% of the warfarin patients) in Refludan and heparin groups. The sponsor claimed that there was also some evidence of bias in the selection of patients for the warfarin randomization. The decision to include patients in the warfarin randomization was largely based on the physician's assessment of a patient's suitability for inclusion. As a result the purpose (to reliably evaluate whether five months of therapy with moderate intensity warfarin reduces the incidence of new MI, stroke and CV death in a subset of approximately 6000 patients) warfarin substudy was not achieved.

Although it was mentioned in the protocol that the patients would be given warfarin on the 5th day after the study drug was administered, in practice patients were given warfarin within one day of the administration of the study drug. The study patients, who were not randomized to warfarin (an anticoagulant) at the second randomization, suggests a separate analysis because these patients would show the treatment differences in the absence of warfarin. Note that the patients who were randomized to receive warfarin after 24 hours of receiving the study drugs also requires a separate analysis because warfarin may have delayed the CV death or MI (CV

death or MI or refractory angina) to these patients during six days. Analyses of the primary outcome (CV death or new MI up to day 7) for OASIS-2 trial were summarized in the following table.

Table 1.8 (reviewer's: Efficacy Results for the Primary Endpoint (CV Death or new MI up to 7-day) for the ITT population

Population	Proportion (%) of patients with events		Relative risk: Refludan vs heparin (95% CI) (M-H)	P-value	
	Refludan	heparin		M-H	Fisher's exact
Warfarin	24/949 (2.53%)	29/964 (3.01%)	.85 (.493-1.467)	.56	.578
No Warfarin	171/4134 (4.14%)	197/4094 (4.81%)	.858 (.702, 1.048)	.133	.15

Note: M-H: Mantel-Haenszel test

It is seen from the above table that the patients, who did not receive warfarin, had a risk reduction (Refludan + nonwarfarin vs. heparin+ nonwarfarin) of 14% whereas the patients, who did receive warfarin, had a risk reduction (Refludan+ warfarin vs. heparin + warfarin) of 15%. Within each treatment group (Refludan or heparin), warfarin treated patients had a lower incidence of CV death or new MI at 7 days compared to nonwarfarin treated patients. Patients previously randomized to Refludan and included in the warfarin substudy had a lower incidence of CV death or new MI at 7 days compared to heparin treated patients . However, the incidence of CV death or new MI at 7 days was lowest in warfarin-randomized Refludan patients. The sponsor did not provide direct warfarin to standard therapy comparisons because the sponsor did not consider these comparisons to be directly relevant the efficacy and safety of Refludan (see S8-V18-P108).

Analyses of a secondary outcome (CV death or MI or refractory angina up to day 7) for OASIS-2 trial were summarized in the following table.

Table 1.9 (reviewer's): Efficacy Results for the Secondary (CV Death or new MI or Refractory Angina up to 7-day) for the ITT population

Population	Proportion (%) of Patients with Events		Relative risk (95% CI) (M-H)	P-value	
	Refludan	heparin		M-H	Fisher's
warfarin	37/948 (3.90%)	55/964 (5.74%)	.679 (.449 -1.028)	.067	.07
No warfarin	288/4134 (6.97%)	318/4094 (7.77%)	.896 (.769 - 1.045)	.161	.177

Note: M-H: Mantel-Haenszel test

It is seen from the above table that the patients who did not receive warfarin had a risk reduction of 10% whereas the patient who did receive warfarin had a risk reduction of 32%. The significance of this secondary endpoint in OASIS-2 trial was mainly attributed to the patients who had warfarin within 7 day of assessment. It is worth noting that warfarin patients did better than nonwarfarin patients with in each treatment (Refludan or heparin) group.

Subgroup Analyses

The sponsor analyzed twenty-six baseline factors to explore potential differences in the treatment effect across population subgroups. Treatment effects were assessed for CV death or new MI at 7 day through estimation of Refludan versus heparin relative risk in each subgroup. A level of p-value ($<= .10$) was used to screen for statistical evidence of inconsistency of treatment effects across subgroups (treatment by subgroup interaction test). To assist in the review of treatment differences, the primary event rate in each subgroup was calculated and differences in the event rate across subgroups were tested. Some of the subgroup analyses (age, sex, and race) were included in the following Table A.2 in the appendix. Overall, the analyses showed consistency of the treatment effects across population subgroups except diabetic patients. The diabetic patients tended to respond less (p-value 0.0516) well to Refludan than to heparin.

1.4 Safety Analysis:

Bleeds:

721 (14.3%) Refludan patients and 549 (10.9%) heparin patients reported bleeding episodes during the study (p=.0001). The difference between treatment groups was largely observed between randomization and day 7.

Table 1.10: Bleeding episodes from randomization to day 7 (extracted from sponsor's S8-V3-P127)

Blood-type	Number of Patients		P-value*
	Refludan	Heparin	
Any blood	444 (8.7%)	260 (5.2%)	.0001
Minor bleed	389 (7.7%)	226 (4.5%)	.0001
Major bleed	60 (1.2%)	37 (.7%)	.0243
Life threatening*	21 (.4%)	22 (.4%)	.8800
Intracranial	2 (0.%)	3(0.1%)	.6870
Surgery required	8 (.2%)	7(.1%)	1.000
Fatal	3(.1%)	4 (.1%)	.7261

Note: *Objective criteria: include all fatal and intra-cranial bleeds requiring intervention or transfusion of > + 4 units of blood or blood products; ** Fisher's exact.

Although, the incidence of bleeding episodes from randomization to day 7 was higher in the Refludan group than the heparin group, the sponsor claimed that further investigation of major bleeds revealed that during this period there was no difference between treatment groups with respect to life-threatening bleeds (objective definition), intra-cranial bleeds, bleeds requiring surgical intervention or fatal bleeds. The difference between treatment groups from randomization to day 7 was almost exclusively accounted for by an excess of minor bleeds and non-life threatening, clinically manageable major bleeds. After day 7, the overall bleeding rates in the two treatment groups were very similar. The proportion of Refludan patients with aPTT values > =100 seconds was higher in patients with a major bleed up to 72 hours than in patients without a major bleed in this period.

Strokes:

The incidence of strokes during OASIS-2 was as follows:

Table 1.11: Strokes during OASIS-2 (extracted from sponsor's S8-V3-P130)

Cumulative Occurrence Time Period: Stroke Type	Number(%) of patients		P-value*
	Refludan (N=5047)	Heparin (N=5033)	
Cumulative Occurrence from randomization to:			
Day 7	14 (.3%)	14(.3%)	1.000
Day 35	41 (.8%)	30 (.6%)	.2335
Day 180	72 (1.4%)	58 (1.2%)	.2511
Randomization to Day 7:			
Any stroke	14 (.3%)	14 (.3%)	1.000
Hemorrhagic	0 (0.0%)	1 (0.0%)	.4933
Ischemic	12 (.2%)	11(.2%)	1.000
Type uncertain	2 (0.0%)	2 (0.0%)	1.000
Day 8 to day 35			
Any stroke	27 (.5%)	16 (.3%)	.1255
Hemorehagic	1 (0.0%)	7(0.1%)	.0387
Ischemic	23 (.5%)	4(.1%)	.0003
Type uncertain			
Day 36 to day 180:			
Any stroke	31 (.6%)	28 (.6%)	.7943
Hemorrhagic	7 (.15)	2 (0.0%)	.1795
Ischemic	17 (.3%)	23 (.5%)	.3473
Type uncertain	7 (.1%)	3(.1%)	.3435

Note: *: Fisher's exact

The cumulative incidence of stroke was comparable between treatment groups across all time periods. Up to day 7, the incidence of stroke was low and identical in both treatment groups. No patient in the Refludan group and one patient in the heparin group experienced a hemorhhagic stroke. Between day 8 and day 35, the incidence of stroke was slightly higher in the Refludan group than in the heparin group (.5% vs. .3%; p-value = .1255). With respect to the individual types of stroke, there was an imbalance with more ischemic strokes in the Refludan group (.5% vs. .1%; p-value: .00003) and more hemorrhagic strokes in the heparin group (7 (.1%) vs. 1 (0.0%)); p-value: .0387). The sponsor claims that there is no biologically plausible explanation for these imbalances in a time period well beyond the end of the study medication. Beyond day 35, no differences were observed between the treatment groups.

Non-hemorrhagic Adverse Events:

There were only small differences between the treatments in the incidence of non-hemorrhagic adverse event s(serious and non-serious). The incidences of both serious allergic reactions were low and comparable with both treatment groups.

Subgroup Analyses:

Subgroup analyses did not yield evidence of difference in the reporting pattern of hemorrhagic or non-hemorrhagic adverse events in most of the subgroup tested. However, the sponsor claims that Refludan patients with a body weight < 50 kg or creatinine values > 1.5 mg/dl had markedly higher rates of hemorrrhagic adverse events, indicating that Refludan dose adjustments (in contrast to what was done in OASIS-2) should include weights below 50 kg, and start at a creatinine threshold of 1.5 mg /dl.

2 OASIS-1

OASIS-1 trial is a dose finding trial with an enrollment of 909 patients. The study was a multi-center, prospective, randomized, partially blinded, parallel-group comparison of IV refludan, conducted in 909 patients at 31 centers in Canada. An initial hospitalization phase was followed by a 4 to 6 month follow-up phase. This pilot study comprised two parts, OASIS-1a and OASIS-1b, which are sequentially conducted, with 500 patients and 300 patients planned in each stage. Patients were randomized to receive a 2-hour with a standard heparin (bolus: 5000 U, infusion: 1000 -1200 U/hour) or two different doses of Refludan (lower dose: bolus .2 mg/kg, infusion .10 mg/kg/hour; medium dose: bolus .4 mg/kg, infusion .15 mg/kg/hour) in addition to aspirin. While investigators knew whether heparin or refludan had been assigned to an individual patients, the exact dose of refludan was blinded. See the medical review for a detailed discussion about OASIS-1.

The primary analysis of efficacy was quadruple endpoint of CV death, new MI, refractory angina, or severe angina at day 7.

In the following table, analyses of medium dose Refludan versus heparin are reported.

Table 2.1: Comparisons of Refludan (medium) versus heparin in OASIS-1 for ITT population (extracted from sponsor's S8-V64-P320, Table 28)

Endpoint	Refludan (N=267)	Heparin (N=371)	Refludan vs. Heparin: RR (95% CI) (logistic regression)	P-value	
				M-H	Fisher's (reviewer's)
CV Death or new MI (primary endpoint of OASIS-2)	7/267 (2.62%)	18/371 (4.85%)	.53 (.22-1.28)	.1493	.214
CV death or new MI or refractory angina	8/267 (3.0%)	24/371 (6.47%)	.45 (.20-1.01)	.0436	.065
CV death or new MI or refractory angina or severe angina (primary endpoint)	25/267 (9.36%)	58/371 (15.63)%	.56 (.34-.92)	.0176	.023

Note: M-H: Mantel-Haenszel test

It can be seen the medium dose Refludan was not significantly better than heparin in reducing CV death or MI in OASIS-1. However, both triple and quadruple (primary) endpoints were significant.

Analyses of low dose Refludan versus heparin are summarized.

Table 2.3: Comparisons of Refludan (low) versus heparin in OASIS-1 for ITT population (extracted from sponsor's S8-V64-P320, Table 28)

Endpoint	Refludan (low dose) (N=271)	Heparin (N=371)	Refludan vs Heparin: RR (95% CI) (logistic regression)	P-value
				M-H
CV Death or new MI (primary endpoint of OASIS-2)	7/271 (2.58%)	18/371 (4.85%)	.52 (.21-1.26)	.1787
CV death or new MI or refractory angina	12/271 (4.43%)	24/371 (6.47%)	.67 (.33-1.36)	.3106
CV death or MI or refractory angina or severe angina (primary endpoint)	34/271 (12.55%)	58/371 (15.63)%	.77 (.49-1.22)	.2781

Note: M-H: Mantel-Haenszel

It can be seen that Refludan was not significantly more effective than heparin with respect to any of the three composite endpoints. It can be seen from Table 2.3 and Table 2.4 that for only the double composite endpoint (CV death or new MI), the low dose Refludan event rate is lower than medium dose dose Refludan event rate.

The efficacy results for Refludan (low + medium) versus heparin are summarized in the following Table.

Table 2.4: Comparisons of Refludan (low + medium) versus heparin in OASIS-1 for ITT population (extracted from sponsor's S8-V64-P320, Table 28)

Endpoint	Refludan (low+medium) (N=538)	Heparin (N=371)	Refludan vs Heparin: RR (95% CI) (logistic regression)	P-value M-H
CV Death or new MI	14/538 (2.6%)	18/371 (4.85%)	.52 (.26-1.07)	.0805
CV death or new MI or refractory angina	20 /538(3.72%)	24/371(6.47%)	.56 (.30-1.03)	.0641
CV death or new MI or refractory angina or severe angina (primary endpoint)	59/538 (10.97 %)	58/371(15.63)%	.66 (.45-.98)	.038

The sponsor claimed that OASIS-1 was a pilot study and p-values are for descriptive purpose rather than formal hypothesis testing. Comparison of the two Refludan treated groups (low and medium) revealed a dose dependent effect, with medium dose Refludan consistently numerically more effective than heparin corresponding to the triple (CV death or new MI or refractory angina) and quadruple (CV death or new MI or refractory angina or severe angina) endpoints. The medium dose Refludan was not significantly more effective than heparin with respect to the double composite endpoint (CV death or MI), although there was numerical advantage of medium dose Refludan over heparin. As mentioned earlier that the low dose Refludan event rate is lower than medium dose dose Refludan event rate. Thus the pooled (low + medium) Refludan event rate becomes lower than medium dose Refludan even rate. By pooling low dose and medium dose Refludan in OASIS-1 study, it was possible to lower the p-value corresponding to the double composite endpoint (CV death or new MI) from 0.15 (medium dose) to 0.08 (pooled). Therefore, there could be an advantage to Refludan by combining the pooled (low +medium) rate of OASIS-1 trial with the OASIS-2 trial whose Refludan dose was the medium dose of OASIS-1 trial.

Warfarin substudy

The efficacy analyses of OASIS-1 trial by warfarin treated group and nonwarfarin treated group were summarized in the following table.

Table 2.2 (reviewer's): Efficacy Results for the double composite endpoint (CV Death or new MI up to 7-day) for the ITT population in OASIS-1.

Population	Proportion (%) of Patients with Events		Relative risk (95% CI) (M-H)	P-value
	Refludan	heparin		Fisher's exact
warfarin	2/69 (2.9%)	4/114(3.51%)	.826 (.155 -4.392)	1.0
No warfarin	5/198(2.53%)	14/257 (5.45%)	.464 (.170- 1.265)	.157

It is seen from the above table that the estimated relative risk (Refludan versus heparin) was much smaller in the nonwarfarin treated group than in the warfarin treated group (53% risk reduction in the nonwarfarin group and 17% percent in warfarin treated group).

Note that about two thirds of the patients in OASIS-1 trial (OASIS-1a) were administered warfarin after 5 days of the study drugs were given whereas one third of the patients in OASIS-1 trial (OASIS-1b) were administered warfarin after 24 hours of the study drugs were given.

3 Combined Analysis of OASIS-1 and OASIS-2

It was not mentioned in the protocol of OASIS-2 whether the efficacy data from OASIS -1 would be combined withOASIS-2 trial. Note that the two trials did not have the same primary endpoint. If OASIS-1 and OASIS-2 are to be combined, it is logical that the data from the medium dose of OASIS-1 should be combined with the data from OASIS-2 because the Refludan dose of OASIS-2 was the medium dose of Refludan in OASIS-1.

The efficacy results from the combined OASIS-1 and OASIS-2 trials were summarized in the following table.

Table 3.1 (reviewer's): Comparisons of Refludan versus heparin when OASIS-1 and OASIS-2 (ITT) Combined

Endpoint	Refludan (low+ medium) Vs. heparin		Refludan (medium) Vs. heparin		Refludan (low) Vs. heparin	
	RR (95% CI) (Logit)	P-value CMH (Fisher's/BD)	RR (95% CI) (Logit)	P-value CMH (Fisher's/BD)	RR (95% CI) (Logit)	P-value CMH (Fisher's/BD)
CV Death or new MI	.822 (.682, .99)	.039 (.038/.203)	.83 (.688, 1.005)	.053 (.058/.308)	.83 (.688,1.004)	.052 (.052/.292)
CV death or new MI or refractory angina	.814 (.70, .94)	.006 (.005/.224)	.816 (.70, .95)	.007 (.008/.144)	.826 (.71, .96)	.011 (.013/.578)

Note: CMH: Cochran-Mantel-Haenszel test; BD: Breslow-Day

It is seen from the above table that medium dose Refludan was not significantly more effective than heparin with respect to the double composite endpoint (CV death or MI) when the trials were combined. It can be seen that for the double composite endpoint, low dose Refludan is slightly better than medium dose Refludan.

The medium dose Refludan was significantly more effective than heparin with respect to the triple composite endpoint (CV death or MI or refractory angina) when the trials were combined.

The sponsor combined the outcomes OASIS-1 (a dose finding phase II trial) and OASIS-2 trials for the MITT population although the Refludan doses were not the same in the two trials. For example, in OASIS-1 there were two doses: low dose and medium dose whereas in OASIS-2 there is only one dose (medium). The outcomes of the two doses of OASIS-1 were combined to make a single outcome (RR = .52; 95% CI for RR: .26 – 1.07). The p-value of the combined analysis of OASIS-1 and OASIS-2 for the primary end-point of this submission (from sponsor's S8-V59-P-77) was .0268 with relative risk .80 (95% CI for RR .057-.97).

It is worth mentioning that OASIS-1 and OASIS-2 were not combinable because:

a) the former was a phase 2 trial consisting of two dissimilar trials (OASIS-1a and OASIS-1b) whereas the later was a phase III clinical trial

b) heparin dose regimen in OASIS-1 was not the same as in OASIS-1
c) the two trials (OASIS-1 and OASIS-2) were not similar with respect to primary endpoints
d) the definitions of angina in the two trials (OASIS-1 and OASIS-2) were different
e) concomitant medications uses were also different in the two trials (OASIS-1 and OASIS-2)
f) Plan to combine the pooled data of the two doses (low and medium) in OASIS-1 trial with the data of OASIS-2 trial was not specified in the protocol
g) The two doses of Refludan in OASIS-1 trial were not blinded.

3.1 Combined Analysis of OASIS-1 and OASIS-2 by Warfarin and Nonwarfarin Patients

Efficacy analyses of the primary endpoint (new MI or CV death) of OASIS-2 by the patients randomized to warfarin and not to nonwarfarin were summarized in the following table.

Table 3.2: Comparisons of Refludan versus heparin according to warfarin randomization when OASIS-1 and OASIS-2 was combined (medium dose)

Endpoint	Refludan vs. heparin: RR (95% CI) (logit)	P-value	
		M-H	Breslow-Day
Randomized to warfarin	.839 (.505-1.39)	.499	.984
Not randomized to warfarin	.840 (.690 - 1.022)	.074	.229

Note: M-H: Mantel-Haenszel test

Although the estimated risk reductions are almost the same in warfarin and nonwrafarin treated groups, the borderline significance (p-value .053 corresponding to medium dose in Table 3.1) of medium dose Refludan over heparin in the overall combined analysis of OASIS-1 and OASIS-2 trials was attributed to the patients who were not randomized to warfarin.

The p-value of the Breslow-Day test for the homogenity of odd ratios in warfarin treated group was .984. This suggests that the odd ratios in the two studies are homogeneous.

4. Comparison with Imputed Placebo

The objective of this section was to examine whether or not Refludan is more effective than placebo in reducing death or new MI among patients receiving standard care (aspirin) for treatment of UA. Statistical methods for the hypothetical placebo comparison were applied to the double-composite endpoint of death or new MI over the 7-day post-randomized periods. The sponsor used two approaches (direct method and simulation method) to address the

problem. However, only the direct method will be discussed in this review because the direct method is based on the historical data.

The sponsor claims that the direct method is a natural extension of methodology used for meta-analyses, combines Refludan data with historical data from heparin studies to derive the relative risk for Refludan versus placebo (aspirin alone). The sponsor calculated the relative risk for Refludan versus placebo as the product of two terms:

(1) the relative risk of Refludan versus heparin and
(2) the relative risk for heparin versus placebo.
The product of relative risks is additive in logarithmic scale, and because the two sets of studies are statistically independent, the variance of the sum of the natural logs is equal to the sum of their variances. Assuming that log transformed risks are normally distributed, a hypothetical relative risk and corresponding confidence interval were then constructed for Refludan versus placebo.

The sponsor combined OASIS-1 and OASIS-2 to derive relative risk for Refludan versus aspirin. In this combined analysis of OASIS-1 and OASIS -2, the outcomes of low dose and medium dose in OASIS-1 are combined together. Note that the medium dose of OASIS-1 is the dose of OASIS-2. In addition, the two sub-studies (OASIS-1a and OASIS-1b) are not identical. Therefore, because it is more appropriate, in this review only OASIS-2 would be used to compare with hypothetical placebo.

4.1 Placebo Estimation

a) Using Historical Data:
The sponsor claims that the most comprehensive overview of studies comparing heparin plus aspirin to aspirin alone in UA was performed in 1996 by Oler et al. Six studies involving a total of 1353 patients met the inclusion criteria for the meta-analysis and provided information regarding the risk of death or MI during randomized treatment with heparin plus aspirin versus aspirin alone. Rate ratios from each study were used as measures of effect in these analyses. The total numbers of patient outcomes in both aspirin and aspirin plus heparin groups were recorded in 2x2 tables. To improve bias and precision properties, 0.5 was added to every cell in any table containing a zero. Relative risks (RRS) with 95% confidence intervals (CIs) were calculated individually for each study. These findings are summarized in the table below.

Table 4.1: Oler's Meta Analysis of Six Trials extracted from sponsor's S8-V60-P269)

Source	Heparin plus aspirin	Aspirin	Relative Risk (95% CI)
Theroux et al. (1988)	2/122 (2%)	4/21 (3%)	.50 (.18 - 2.68)
RISC group, 1990	3/210(1%)	7/189 (4%)	.39 (.18 - 1.47)
Cohen et al. (1990)	0/37(0%)	1/32 (3%)	.29 (.06 - 6.87)
Cohen et al. (1994)	4/105(4%)	9/109 (8%)	.48 (.24 - 1.45)
Holdright et al. (1994)	42/154(27%)	40/131 (31%)	.89 (.68 - 1.29)
Gurfinkel et al.(1995)	4/70 (6%)	7/73 (10%)	.60 (.29 - 1.95)
Pooled Studies	**55/698 (8%)**	**68/655 (10%)**	**.67 (.44 - 1.02)**

The findings of each of the 6 trials demonstrated a trend toward improved outcome during treatment with heparin plus aspirin compared to aspirin alone, but none of the findings reached statistical significance.

The summary measures of effect in the meta analysis for double endpoint (death or MI) is the odds ratio (OR). Since the sample cross product has a highly skewed distribution, its natural log transformation is appropriate for purposes of estimation and hypotheses testing. The summary effect measures or estimated overall RR, was calculated using the DerSimonian and Laird model which uses a random effects model to incorporate variance between study findings in a weighted average of rate ratios.

The incidence of death or new MI during heparin therapy was 7.9% (55/698) in patients treated with heparin plus aspirin versus 10.4% (68/655) in the patients treated with aspirin alone. The summary (from meta analysis) of relative risk (RR) of death or MI during randomized treatment is .67 (95% CI: .44 - 1.02, p-value = .06 for testing the null hypothesis that the expected RR is unity) in patients treated with aspirin plus heparin with those treated with aspirin alone. The result of test of heterogeneity was not statistically significant (p-value .78).

The evidence from the Oler meta-analysis suggested that heparin reduced the risk over aspirin by about one third. Relative risks within individual studies ranged from .29 to .89.

Incorporating Data from Recent Studies:

The sponsor claims that FRISC and FRIC were the only two additional studies that met criteria for the meta-analysis and allowed an indirect calculation of relative risk for heparin plus aspirin versus aspirin alone in patients with unstable angina. In FRISC, dalteparin plus aspirin was compared to aspirin alone where as in FRIC, dalteparin plus aspirin was compared to heparin plus aspirin. The two studies were combined for comparison of aspirin alone and heparin plus aspirin groups as follows.

Table 4.2: Combining Dalteprin Studies for Inclusion in Meta Analysis (extracted from sponsor's S8-V60-P270)

Parameter	FRISC dalteprin: aspirin:	FRIC daltepirn:heparin:	(FRISC and FRIC) heparin : aspirin
Relative Risk (95% CI)	.37 (.20 - .68)	1.07 (.63 - 1.8)	.35 (.16 - .78)

Pooling of a) and b)

In the following, the sponsor combined the results of FRISC and FRIC studies with the estimate of RR(H:A) from the meta analysis (by Oler et al.):

FRISC/FRIC: log (RR(H:A))+/- S.E. (log (RR(H:A))) = -1.062 +/- .41
Historical Data: log (RR(H:A))+/- S.E. (log (RR(H:A))) = -.401 +/- .21

Now combining relative risks by weighting (using inverse variance):

log(RR(H:A)) =-.538 and SE (log(RR(H:A)))=.19.

Therefore RR(H:A)=.584 with 95% CI (.40, .85). By incorporating results of more recent studies in the meta analysis, the pooled estimate of relative risk for heparin versus aspirin was lowered from the value reported by Oler et al. (.67) to .58, with p-value 0.005.

Table 4.3: Refludan (OASIS-2) versus hypothetical placebo (aspirin alone) control For All-cause Death or New MI (extracted from sponsor's S8-V59-P83)

Up to 7 days	Observed RR: Refludan:heparin	Historical RR: Heparin:aspirin	Derived RR: Refludan:aspirin	P-value
Published meta analysis (Oler) plus FRISC and FRIC studies	.83 (.68-1.02)	.58 (.40 - .85)	.481 (.314 - .738)	.00081
Published meta analysis (Oler)	.83 (.68-1.02)	.67 (.44-1.02)	.556 (.349 - .887)	.0137

Results based on this direct approach to calculation of relative risk seems to indicate that Refludan would have performed significantly better than aspirin alone in preventing death and MI among patients with UA.

4.2 Sensitivity Analysis

The sponsor estimated placebo (aspirin) using two sources a) Oler et al. and b) Oler et al + FRISC/FRIC studies. In this subsection, we estimate placebo using only FRISC/FRIC studies. We will provide an analysis based on treatment effect size (absolute difference of the event rates) and corresponding 95% confidence interval. We will also conduct a sensitivity analysis by determining how many more events in dalteparin group in FRISC study would make the estimated benefit (Refludan versus placebo) substantially different from that it is.

A meta analysis using FRIC, FRISC and OASIS-2 trials based on proportion difference is described in the following table.

Table 4.4: Historical Analysis Using FRIC and FRISC

Study	Rates (Death or MI)		Difference	95% CI for the difference of rates
FRIC	Dalteparin + aspirin (n= 751)	heparin + aspirin (n= 731)		(-.0162, .0223)
	29/751 (3.9%)	26/731 (3.6%)	.3%	
FRISC	Dalteparin + aspirin (n= 741)	aspirin alone (n= 757)		(-.0478, -.01214)
	13/741 (1.8%)	36/757 (4.8%)	-3%	
OASIS-2	Refludan + aspirin (n= 5083)	heparin + aspirin (n=5028)		
	182/5083(3.6%)	213/5028(4.2%)	-.6%	(-.014113, .000999)
FRISC - FRIC			-3.3% (heparin - aspirin)	(-.0593, -.00656)
OASIS-2 + (FRISC – FRIC)			-3.9% (Refludan - aspirin)	(-.06694, -.01229)

It is seen from the above table that heparin is significantly more effective (3.3%) than placebo. The meta analysis also suggests that Refludan is significantly more effective (almost 4%) than hypothetical placebo (aspirin).

Note that FRIC study showed that dalteparin is significantly more effective than placebo and the FRISC study showed that dalteparin is not significantly more effective than placebo. In the following, we will vary dalteparin events in FRISC study to examine the sensitivity of the placebo estimation.

First, we change the dalteparin events in FRISC study from 13 to 21. We summarize the results in the following table.

Table 4.5: Historical Analysis Using FRIC and FRISC (Changing Dalteparin Events in FRISC from 13 to 21)

Study	Rates (Death or MI)		Difference	95% CI for the difference of rates
FRIC	Dalteparin + Aspirin (n= 751)	Heparin + aspirin (n= 731)		(-.0162, .0223)
	29/751 (3.9%)	26/731 (3.6%)	.3%	
FRISC	Dalteparin + Aspirin (n= 741)	aspirin alone (n= 757)		(-.03852, .000087)
	21/741 (2.83%)	36/757 (4.8%)	-1.92%	
OASIS-2	Refludan + aspirin (n= 5083)	Heparin + aspirin (n=5028)		
	182/5083 (3.6%)	213/5028 (4.2%)	-.6%	(-.014113 , .000999)
FRISC - FRIC			-2.23% (heparin – aspirin)	(-.0495, .00499)
OASIS-2 + (FRISC –FRIC)			-2.88% (Refludan -aspirin)	(-.0571, -.000538)

An addition of 8 events to dalteparin arm in FRISC study resulted in reduction of dalteparin versus aspirin event rate from 3 percent to 1.92%. This indicates that dalteparin has

numercal advantage over aspirin if we add 8 events to dalteparin arm. The additional 8 events in dalteparin arm resulted in reduction of heparin vesrsus aspirin event rate from 3.3% to 2.33%. This indicates that heparin has numerical advantage over aspirin. The reduction in derived Refludan versus placebo (hypothetical) event rate is from 3.9% to 2.88%. However, it appears from the 95% confidence interval (see Table 4.5) that Refludan treated patients still have significant benefit over placebo (hypothetical) treated patients.

Next, we change dalteparin events in FRISC study from 13 to 22. We describe the results in the following table.

Table 4.6: Historical Analysis Using FRIC and FRISC (Changing Dalteparin Events in FRISC from 13 to 22)

Study	Rates (Death or MI)		Difference	95% CI for the difference of rates
FRIC	Dalteparin + aspirin (n= 751)	Heparin + aspirin (n= 731)		(-.0162, .0223)
	29/751 (3.9%)	26/731 (3.6%)	.3%	
FRISC	Dalteparin + aspirin (n= 741)	aspirin alone (n= 757)		(-.03734, .00160)
	22/741 (2.97%)	36/757 (4.8%)	-1.78%	
OASIS-2	Refludan + aspirin (n= 5083)	Heparin + aspirin (n=5028)		(-.014113 , .000999)
	182/5083 (3.6%)	213/5028 (4.2%)	-.6%	
FRISC - FRIC			-2.09% (heparin – aspirin)	(-.048289, .006408)
OASIS-2 + (FRISC – FRIC)			-2.74% (Refludan - aspirin)	(-.05587, .000927)

In the following, we discuss the changes under this new scenario (one more event than the first scenario) with respect to the first scenario (addition of 8 event in dalteparin arm of FRISC study).

Additional one event (i.e., an addition of nine events to the FRISC study) to dalteparin arm in FRISC study resulted in reduction of dalteparin versus aspirin event rate from 1.92% percent to 1.72%. This again indicates that dalteparin has numercal advantage over aspirin if we add events to dalteparin arm. The additional one event in dalteparin arm resulted in reduction of heparin vesrsus aspirin event rate from 2.23 % to 2.09%. This also indicates that heparin has numerical advantage over aspirin. The reduction in derived Refludan versus placebo (hypothetical) event rate is from 2.88% to 2.74%. However, it appears from the 95% confidence interval (see Table 4.5) that Refludan treated patients does have numerical advantage over placebo (hypothetical) treated patients.

5. Conclusions

5.1 Efficacy:

Primary Endpoint

a) The protocol defined primary endpoint in OASIS-2 (the only phase III study) was the two component endpoint of CV death or new MI at 7-day follow-up for the intent to treat patients (ITT: all-randomized patients data base). However, the sponsor considered the two-component endpoint of CV death or new MI at 7-day follow-up for the patients who completed their 7-day assessment (Modified ITT or MITT). The sponsor obtained a p-value of .0714 (Refludan versus heparin; relative risk: .83, 95 % CI for relative risk: .68 - 1.02) for the MITT population. The corresponding p-value for the ITT population is .0863 (relative risk .84, 95% CI for relative risk: .69-1.03). Thus, the efficacy data in OASIS-2 showed that Refludan was not significantly more effective than heparin (see Table 1.3) for the treatment of unstable angina at the 0.05 level. Because, there were three interim analyses performed in this trial, the final analysis for Refludan versus heparin was recommended (by the GI division, a letter dated 10/28/98) to be compared at .048 level.

b) The sponsor combined the outcomes OASIS-1 (a dose finding phase II trial) and OASIS-2 trials for the MITT population although the Refludan doses are not the same in the two trials. In OASIS-1 there are two doses: low dose and medium dose whereas in OASIS-2 there is only one dose (medium). The outcomes of the two doses of OASIS-1 are pooled together to make a single outcome (RR = .52; 95% CI for RR: .26 - 1.07). The p-value of the combined analysis of OASIS-1 and OASIS-2 for the primary end-point of this submission (from sponsor's S8-V59-P-77) was .0268 with relative risk .80 (95% CI for RR .057-.97). It is worth mentioning that in OASIS-1 trial the estimated event rate for the medium dose of Refludan is higher than the estimated event rate for low dose of Refludan with respect to the double endpoint (CV death or new MI).

This reviewer combined OASIS-1 (medium dose) and OASIS-2 for the ITT population. The efficacy result showed that Refludan was not significantly more effective (CMH p-value 0.053;

RR: .83 with 95% confidence interval (.688, 1.005)). Note that this p-value requires an adjustment for the fact that there were three interim analyses. Also an adjustment for the two OASIS analyses is also required.

c) The sponsor made an implicit comparison to aspirin with Refludan for the double composite endpoint of death or new MI over the 7-day post-randomized periods.

The sponsor considered two different sources (FRISC/FRIC and Oler et al.) to obtain heparin versus aspirin comparisons. The sponsor also combined FRISC/FRIC and Oler et al. to obtain Heparin versus placebo comparison. Based on the heparin versus aspirin comparisons, the sponsor derived relative risk of Refludan versus aspirin. The derived relative risk .481 (see Table 4.3) of Refludan versus aspirin suggests that Refludan may have performed better than aspirin alone in preventing death or new MI among patients with UA.

Note that comparison with imputed placebo was a post-hoc analysis. Oler's meta analysis showed that heparin was not significantly better than aspirin for the treatment of unstable angina. On the other hand FRISC/FRIC studies showed that heparin was significantly more effective than aspirin for the treatment of UA. The meta analysis of Oler et al. + FRISC/FRIC +OASIS-2 studies produced even more significant results than meta analysis of Oler et al.+ OASIS-2. See Table 4.3 for a detailed analysis.

The sensitivity analysis reported in Section 4.2 (Table 4.6) suggests that Refludan could be significantly less effective than hypothetical placebo when heparin was not significantly more effective than aspirin. Note that the effectiveness of heparin with respect to placebo (aspirin) was derived from the outcomes two nonrandomized arms of FRIC and FRISC trials. Note also that the meta analysis of Oler et. al + OASIS-2 suggested that Refludan was significantly more effective than placebo although heparin was not significantly more effective than aspirin.

5.2 **Safety**

The Refludan treated group in OASIS-2 experienced significantly more bleeding events (i.e., any bleed, minor bleed, and major bleed) than the heparin treated group. Although the incidence of bleeding episodes from randomization to day 7 was higher in the Refludan group than the heparin group, the sponsor claimed that further investigation of major bleeds revealed that during this period there was no difference between treatment groups with respect to life-threatening bleeds (objective definition), intra-cranial bleeds, bleeds requiring surgical intervention or fatal bleeds.

The cumulative incidence of stroke was comparable between treatment groups across all time periods. There were only small differences between the treatments in the incidence of non-hemorrhagic adverse events (serious and non-serious).

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APPENDIX

Table A.1:Baseline demographic characteristics for MITT population

In OASIS-2 (extracted from sponsor's S8-V3-P219)

Characterstic	Statistic	Refludan	heparin	Total	p-value
Sex		N=5045			
	N(%)	3040(60%)	3098 (62%)	6138 (61%)	.1825
Male	N(%)	2005(40%)	1935 (38%)	3940 (39%)	
Female					
Age	N Mean(SD)	5045 64(11)	5033 64(11)	10078 64(11)	.5069
<=65	N(%)	2523 (50%)	2554 (51%)	5077 (50%)	
>65	N(%)	2522(50%)	2479(49%)	5001(50%)	
Ethnic group					
Caucasian	N(%)	4086(81%)	4086 (81%)	8172 (81%)	
South Asian	N(%)	71 (1%)	57(1%)	128 (1%)	
Latin American	N(%)	652 (13%)	658 (13%	1310 (13%)	
Black	N(%)	37 (1%)	40 (1%)	77 (1%)	
Other Asian	N(%)	104 (2%)	94(2%)	198 (2%)	
Other	N(%)	95 (2%)	98 (2%)	193 (2%)	

Table A.2: Subgroup Analyses of CV Death or New MI at 7-day for MITT population (extracted from sponsor's S8-V3-P11)

Subgroup	Event rate across Subgroups		Treatment effect across subgroups	
	p-value	Event rate	p-value	Relative risk
Age: <=65 >65	.0023	3.3% 4.4%	.3072	.73 .92
Sex: Male Female	.0061	4.3% 3.3%	.7759	.82 .87
Race: Caucasian Latin American Black, South/other Asian/Other	.8919	4.0 3.4 3.7	.47	.80 .92 1.38