



NOV 15 1996

## STATISTICAL REVIEW &amp; EVALUATIONS

NDA # 20-718

Applicant: COR Therapeutics Inc.

Drug Names: Integrilin™ (Intrifiban) Injection

Drug Classification: 1P

Indication: Prevention of acute coronary complications related to abrupt closure of treated coronary vessels in patients undergoing coronary angioplasty

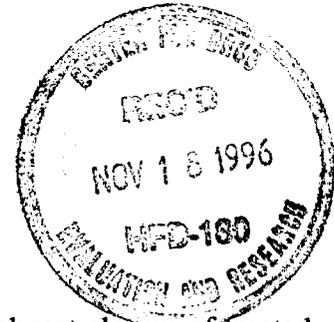
Statistical Reviewer: A. J. Sankoh, Ph.D.

Clinical Reviewer: The statistical issues addressed in this review have been discussed with the medical reviewer, L. Talarico, M.D.

Date of Document: April 02, 1996; Date received by reviewer: April 10, 1996

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Volumes Reviewed: 1.1, 1.109 - 6.39, 6.42-6.51: January 17, 1996.

MA. BACKGROUND

Abrupt closure is the major cause of adverse outcomes after coronary angioplasty. Aspirin is a relatively weak inhibitor of platelet aggregation compared with agents that block the fibrinogen receptor, glycoprotein (GP) IIb/IIIa. Integrilin has been studied as an antithrombotic therapeutic agent to reduce acute cardiac ischemic complications of coronary angioplasty. Integrilin acts by blocking the binding of fibrinogen to the platelet GP IIb/IIIa receptor complex, resulting in potent, specific inhibition of platelet aggregation and limiting thrombotic consequences of the procedure.

The sponsor has submitted one phase III pivotal study (IMPACT II, protocol # 93-014) in support of the efficacy and safety of Integrilin as an adjunct to heparin and aspirin for the prevention of acute cardiac ischemic complications (death, myocardial infarction (MI), need for urgent intervention) related to abrupt closure of the coronary vessel in patients undergoing coronary angioplasty (balloon angioplasty, directional atherectomy, transluminal extraction catheter atherectomy, rotational ablation angioplasty or excimer laser angioplasty).

target sample size.

Note that no statistical rationale is given (by the sponsor) for choosing the adjusted (per-comparison)  $\alpha$ -level of .035 as an appropriate upper bound for declaring statistical significance. This adjusted significance  $\alpha$ -level, however, seems to correspond to a Tukey, Ciminera and Heyes (TCH) adjusted significance  $\alpha$ -level [ $.0356 = 1 - (1 - .05)^{1/\sqrt{2}} = 1 - (.95)^{.7071}$ ] for two “highly correlated” comparisons [See Tukey, Ciminera & Heyes: *Biometrics* (1985), 295-301], or to any correlation based multiple endpoint adjustment (ad-hoc) method [see Dubey/ Armitage & Palmar: *Proceedings of the VIth/XIIth International Biometrics Conference (1985/1986)*] upon assuming a between treatment comparison correlation coefficient of 0.5 [under the null hypothesis, see Dunnett & Tamhane: *JASA* (1993); 162-170]. Note that by assuming an equi-correlation coefficient of 0.5, the average correlation coefficient is also 0.5, and the TCH and ad-hoc methods yield equivalent adjusted significance levels.

Note also that simulation results have shown that both of these adjustment methods lead to inflation of the Type I error rate, as can be seen from the results in Table 1 below. For two comparisons with (an assumed common) correlation coefficient of 0.5 between comparisons, the table below summarizes the simulated overall (attained) Type I error rates and the simulated per-comparison  $\alpha$ -levels for given nominal  $\alpha$ -levels for these two methods. For comparison purpose, corresponding simulation results for the Hochberg method are also provided. The table values are based on 100,000 normally simulated variates from a two treatment group clinical trial with 100 patients per treatment group. From these table values we note that a per-comparison  $\alpha$ -level of .035 would lead to an overall  $\alpha$ -level of .064 and not the .05 nominal level. To maintain the nominal .05 significance level, the per-comparison  $\alpha$ -level (prior to adjustment for interim analyses) should be  $\leq .0277$ , and not  $\leq .035$  as proposed by the sponsor.

Table 1/ Overall Type I Error Rate Protection for Equally Correlated Two Comparisons w/ $\rho = .5$

	Dubey/Armitage et al			Tukey et al			Hochberg		
Specified Nominal $\alpha$ -Level	.05	.039	.035	.05	.039	.035	.05	.039	.035
1 <sup>st</sup> Per-comparison $\alpha$ -Level	.035	.028	.024	.035	.028	.027	.028	.022	.020
2 <sup>nd</sup> Per-comparison $\alpha$ -Level	.035	.027	.024	.035	.027	.024	.028	.022	.020
Overall Attained $\alpha$ -Level	.064	.051	.046	.064	.051	.046	.047	.037	.033

(See Sankoh, Huque & Dubey, “Some comments on frequently used multiple endpoint adjustment methods in clinical trials”: Submitted to *Stats in Medicine*)

## INTERIM ANALYSIS

According to the protocol, two formal interim analyses (using O’Brien-Fleming stopping boundaries for early termination of the trial due to overwhelming efficacy evidence) were planned. The first of these was to be carried out following the 30-day follow-up of the first third of patients (n=1166), and the second following the first two-thirds of patients (n=2,333), respectively. The protocol also stated that to ensure the safety of the trial in the

early phase, one safety (only) analysis (to be conducted at approximately n=500 patients) would be distributed to the Data and Safety Monitoring Committee (DSMC). The DSMC was to be made up of five scientists (2 cardiologists, 1 hematologist, 1 statistician and 1 ethicist) independent of the sponsor, COR Therapeutics, Duke University and Cleveland Clinic. Also, two (2) additional statisticians, from Duke Coordinating Center (described as non-voting members) were in this committee.

However, the official DSMC minutes seem to suggest that four (4) formal interim analyses were actually carried out (on 6/2/94, 7/20/94, 8/31/94 and 9/29/94, with approximately 1033, 1600, 2309 and 2797 patients respectively), as per composite endpoint analysis results (see pages 118, 147, 173 and 199 of **Appendix H**). At each of these looks, comparative treatment analyses were carried out (treatment groups were coded as A, B and C corresponding to high, low dose and placebo respectively). This coding order was maintained at all 4 analyses (at the recommendation of the DSMC in their June 2, 1994 meeting). It, thus, appears that the result of the trial was known to all those who had access to the DSMC minutes (see **Attachment B**).

Furthermore, it appears that the pivotal study (IMPACT II) for this NDA submission was conducted in accordance with (amended) protocol IND [redacted] (see page 84, volume 1.1). In the statistical section of this amended protocol (IND [redacted]), the sponsor had submitted (for FDA review) a proposal to conduct an additional interim analysis (in addition to the 2 proposed in the original protocol design). The sponsor indicated that the purpose of the additional interim analysis was to "allow selection of one of the two integrilin dosing regimens for continued evaluation in the study. This (dose selection) was to be based on the recommendation of an independent Data and Safety Monitoring Committee". The FDA review advised against this amendment unless such additional analyses were treated as formal interim analyses with pre-specified appropriate stopping boundaries. The reason for this recommendation was that the proposed primary efficacy composite endpoint (incidence of death, MI and urgent emergency interventions) could also be viewed as a safety parameter. Thus any comparative analysis of the safety components of this composite endpoint of the trial provides direct comparative efficacy information.

It should also be noted that the completion of this study appears to pre-date the request for this amendment (to carry out additional interim analysis). The review for this IND amendment was completed on 10/11/95, and this pivotal study (IMPACT II) was initiated on January 1993 and completed on January 1995.

In response to this reviewer's request for more information on the number and details of the interim analyses actually carried out, the sponsor responded (08/09/96) that only the three (3) protocol specified (2 interim and a final) analyses were conducted. At a significance level of .039, **Table 2** below summarizes this reviewer's calculations of the appropriate stopping boundaries under both scenarios (3 and 4 comparative analyses) for the binary composite endpoint (incidence of death, MI or urgent/emergency revascularization) under the amended protocol design plan assuming a 33% reduction in failure rate (11% placebo and 7.4%

Integrilin with 80% power). Note that the planned sample sizes (n) reported in the table are for a two arm study design based on a three arm protocol specified planned analyses with 80% power at adjusted 2-sided significance level of .039 (see **Table 1** above), according to EaSt software. To obtain the required sample sizes for a three arm study, multiply the table values (n) by 3/2. Also included in the table are the achieved (post-hoc) powers of the study at the final analyses with 4010 patients per three arms.

**Table 2/ Appropriate Boundaries Under  $H_0$  for Interim Analyses with  $\beta = .2$ ,  $\alpha = .039$  & 33% Reduction**

Analysis	Boundaries For 4 Interim Analyses		Boundaries For 3 Interim Analyses	
	n O - F (p-value)	n Pocock (p-value)	n O - F (p-value)	n Pocock (p-value)
2. ( $\alpha_1$ )	689 (.00007)	689 (.01738)	778 (.00026)	778 (.019057)
3. ( $\alpha_2$ )	1067 (.00158)	1067 (.01107)	1556 (.00946)	1556 (.014913)
4. ( $\alpha_3$ )	1534 (.0085)	1534 (.01088)	2674 (.03475)	2674 (.014918)
4. ( $\alpha_4$ )	2674 (.03491)	2674 (.01462)		
Required n	2311	2628	2311	2628
P-H Power	85.4%	79.0%	85.4%	79.3%

Note all  $\alpha$ -levels are by EaSt Software; 33% reduction under placebo failure rate of 11% and treatment failure rate of 7.4%; P-H=post-hoc; O-F=O'Brien-Fleming Boundaries

Thus the appropriate significance level for declaring treatment effectiveness at the final analysis (with O'Brien-Fleming liberal boundaries) can not exceed .035 under the amended protocol sample size determination (for a 33% reduction in incidence rate).

Planned secondary analyses include a survival analysis of the time to the composite endpoint during the 30 day treatment period and time to the need for urgent intervention within 30 days using a log-rank test.

A primary safety analysis based on the ITT patient population was planned to examine the incidence of bleeding events, and other adverse events.

### **Patient Disposition & Baseline Characteristics**

**Table 3a** below summaries patient disposition by treatment group. A total of 4010 (1333 Integrilin high dose, 1349 Integrilin low dose and 1328 placebo) patients from 98 sites were randomized into this study. One hundred and thirty nine (47 Integrilin high dose, 49 Integrilin low dose and 43 placebo) of these did not receive any treatment drug. Twenty seven of the treated patients were unblinded for bleeding or drop in Hct/Hgb (3), need for CABG (12), thrombocytopenia (2) and other reasons (9).

**Table 3b** below summarizes some of the baseline characteristics among the three treatment groups. Except for race, the three treatment groups appear to be statistically balanced regarding most baseline characteristics, including smoking and other major risk factors at enrollment and by case report forms (CRFs). For race, however, there were significantly more

Caucasians in the Integrilin low dose treatment group than in any of the other treatment groups (Fisher's exact 2-sided p-value = .002 placebo vs low dose and .006 high vs low dose).

Table 3a/ Patient Disposition by Treatment Group

Category	High Dose	Low Dose	Placebo	Total
Randomized	1333 (33.24%)	1349 (33.64%)	1328 (33.12%)	4010 (100%)
Treated: Blinded	1276 (95.7%)	1294 (95.9%)	1274 (95.9%)	3844 (95.9%)
Unblinded	10 (0.8%)	6 (0.4%)	11 (0.8%)	27 (0.7%)
Evaluable	1022 (76.7%)	1069 (79.2%)	1032 (77.7%)	3123 (77.9%)

Extracted from sponsor's Table A-3, Vol 1.221, page 133

Table 3b/ Patient Characteristics Comparisons

Category	High Dose (1333)	Low Dose (1349)	Placebo (1328)
Male/Female (%)	1012/321 (76/24)	984/365 (73/27)	997/331 (75/25)
2-sided p vs Placebo (vs Low)	.620 (.084)	.217	
Caucasian/Others (%)	1208/120 (91/9)	1265/84 (94/6)	1199/127 (90/10)
2-sided p vs Placebo (vs Low)	.641 (.006)	.002	- Placebo vs
Weight: < 74 kg (%)	311/1333 (23%)	347/1349 (26%)	308/1328 (23%)
> 95 kg (%)	344/1333 (26%)	295/1349 (22%)	327/1328 (25%)
Age: < 50 yrs (%)	252/1333 (19%)	239/1349 (18%)	247/1328 (19%)
> 70 yrs (%)	259/1333 (19%)	306/1349 (23%)	266/1328 (20%)
High Risk at Enrollment (%)	545/1333 (41%)	553/1349 (41%)	555/1328 (42%)
High Risk Based on CRF (%)	509/1333 (38%)	514/1349 (38%)	510/1328 (38%)

Note: all p-values are Fisher's exact 2-sided p-values.

The impact of race on the observed effectiveness results will be investigated in a subgroup analysis.

### III SUMMARY OF EFFICACY ANALYSIS RESULTS & REVIEWER'S COMMENTS

Summarized in Table 4 below are the efficacy analysis results based on CEC assessed event rates at the 24-hour, 48-hour and 30-day time points. At each of these time points, the efficacy data was analyzed for the composite primary endpoint and for each of the four components of the primary endpoint: death, MI, urgent CABG and urgent coronary intervention. Sponsor's analyses are based on the odds ratio (OR), i.e., the odds of observing events in the treatment group relative to the placebo group. This reviewer has also provided analysis results based on treatment difference in the proportion of events.

Note that except for MI, incidence rates for death, urgent CABG and urgent coronary interventions components of the composite endpoint are very low (less than 3% even for placebo). The use of asymptotic theory for hypothesis testings in this case may not therefore be appropriate. This reviewer has therefore provided efficacy results (for OR and treatment

difference in proportions) using exact statistics methods. Where the results (by this reviewer) based on exact methods differ from those (by the sponsor) based on asymptotic theory only in the 3<sup>rd</sup> decimal place (e.g., .018 vs .014 in the case of placebo vs Integrilin high for the composite endpoint at the 24-hour time point), sponsor's analysis results (for OR) are provided in the table below; otherwise p-values based on exact methods are provided and are indicated by an underline. Provided in parentheses are these reviewer's analysis results based on differences in proportions of events between placebo and Integrilin (i.e., placebo - Integrilin).

Table 4/ Sponsor's ITT Analysis Results at 24- and 48- Hour and the Primary 30-Day Time points

Endpoint	At 24-Hour Time point			At 48-Hour Time point			At 30-Day Time point		
	Event (%)	OR (%Diff)	2-Sided* P-value	Events (%)	OR (%Diff)	2-Sided* P-value	Events (%)	OR (%Diff)	2-Sided* P-value
Composite: Placebo	123 (9.6)	Pla vs	Pla vs	131(10.2)	Pla vs	Pla vs	149(11.6)	Pla vs	Pla vs
Integrilin High	89 (6.9)	.70 (2.7)	<u>.014(.023)</u>	102 (7.9)	.76(2.3)	<u>.053(.063)</u>	128(10.0)	.84 (1.6)	<u>.201(.212)</u>
Integrilin Low	86 (6.6)	.67 (3.0)	<u>.006(.011)</u>	99 (7.6)	.73(2.6)	<u>.021(.035)</u>	118 (9.1)	.76 (2.5)	<u>.041(.050)</u>
Death: Placebo	1 (0.1)	Pla vs	Pla vs	4 (0.3)	Pla vs	Pla vs	14 (1.1)	Pla vs	Pla vs
Integrilin High	1 (0.1)	1.0 (0.0)	1.00 (.913)	5 (0.4)	1.3 (-.1)	<u>1.00(.928)</u>	11 (0.9)	.78 (0.2)	<u>.687 (.631)</u>
Integrilin Low	0 (0.0)	UD(0.1)	.237 (.714)	1 (0.1)	.25 (0.2)	<u>.367(.444)</u>	6 (0.5)	.42 (0.6)	<u>.108 (.175)</u>
MI: Placebo	90 (7.0)	Pla vs	Pla vs	95 (7.4)	Pla vs	Pla vs	106(8.2)	Pla vs	Pla vs
Integrilin High	66 (5.1)	.72 (1.9)	<u>.056(.069)</u>	75 (5.8)	.78 (1.6)	<u>.130(.146)</u>	90 (7.0)	.84 (1.2)	<u>.263(.275)</u>
Integrilin Low	71 (5.5)	.77 (1.6)	<u>.141(.158)</u>	77 (5.9)	.79 (1.5)	<u>.155(.174)</u>	86 (6.6)	.79(1.6)	<u>.131(.152)</u>
Urgent CABG: Placebo	28 (2.2)	Pla vs	Pla vs	30 (2.3)	Pla vs	Pla vs	36 (2.8)	Pla vs	Pla vs
Integrilin High	13 (1.0)	.46 (1.2)	<u>.026(.058)</u>	16 (1.2)	.53 (1.1)	<u>.052(.076)</u>	26 (2.0)	.72 (0.8)	<u>.246(.273)</u>
Integrilin Low	13 (1.0)	.45 (1.2)	<u>.023(.047)</u>	15 (1.2)	.49 (1.1)	<u>.031(.058)</u>	19 (1.5)	.52 (1.3)	<u>.025(.048)</u>
Coronary inter: Placebo	22 (1.7)	Pla vs	Pla vs	24 (1.9)	Pla vs	Pla vs	37 (2.9)	Pla vs	Pla vs
Integrilin High	13 (1.0)	.59 (0.7)	<u>.178(.213)</u>	20 (1.6)	.83 (0.3)	<u>.647(.609)</u>	36 (2.8)	.97 (0.1)	<u>.997(.894)</u>
Integrilin Low	11 (0.8)	.49 (0.9)	<u>.073(.121)</u>	23 (1.8)	.95 (0.1)	<u>.968(.914)</u>	35 (2.7)	.93 (0.2)	<u>.865(.823)</u>

Sponsor's results extracted from Tables E-1 thru E-4; \*: reviewer's results (underlined and/or in parentheses) are by STATXACT; UD=undefined OR (due to zero event rate for Integrilin)

### Reviewer's Comments

Based on odds ratio (OR) statistics, the observed p-value (unadjusted for multiple comparisons and/or interim analyses) for treatment effectiveness in comparison to placebo with respect to the composite endpoint at the 30-day primary time point is **.041** (borderline result in comparison to sponsor pre-specified .035 level for pairwise comparisons) in favor of the low Integrilin dose and .201 for the high Integrilin dose, indicating a numerical but not statistical Integrilin high dose advantage over placebo. The corresponding Integrilin low dose versus placebo comparison observed 2-sided p-values for the individual components of the composite endpoints are .108 for deaths, .131 for MIs, **.025** for urgent CABG and .865 for coronary interventions. Thus except for urgent CABG, all of these observed 2-sided p-values at the 30-day time point are higher than the required .035 nominal significance level needed to guard against inflation of the Type I error probability due to multiple comparisons (and interim analyses; see **Tables 1 & 2** on pages 4 and 6 respectively).

It thus appears that the only Integrilin (low dose) statistically significant therapeutic advantage

over placebo after adjusting observed p-values for multiple treatment comparisons is with respect to urgent CABG events. That is, the observed therapeutic benefit regarding the composite endpoint appears to be primarily due to urgent CABG events. Removing the events due to urgent CABG from the analysis of the composite endpoint indicate no Integrilin advantage over placebo, as can be seen below.

**CEC Assessed Events for Composite Endpoint Excluding Urgent CABG the 24-Hour & 30-Day Time points**

	At 24-Hour Time point		At 30-Day Time point	
	Placebo	Low Dose	Placebo	Low Dose
Event (%)	95/1285 (7.4%)	73/1300 (5.6%)	113/1285(8.8)	99/1300(7.6)
OR (% Diff)	Pla vs	.745 (1.8)	Pla vs	.855 (1.2)
Unadjusted P-value	Pla vs	.079 (.093)	Pla vs	.308 (.336)

**Secondary Analysis Results**

The 6-month follow-up time point analysis results, summarized in **Table 5** below, suggest no long term Integrilin statistical advantage over placebo.

**Table 5/ Sponsor's ITT Analysis Results at the 6-Month Follow-Up Time point**

Comparison/Endpoint	Death/MI	Death/MI/Inte <sup>1</sup>	Death	MI	CABG	Angio*
Placebo: Rate (%)	151 (11.7%)	403 (31.4%)	28 (2.2%)	141 (11.0%)	122 (9.5%)	240 (18.7%)
Integrilin High Dose: Rate (%)	130 (10.1%)	379 (29.5%)	21 (1.6%)	119 (9.3%)	112 (8.7%)	231 (18.0%)
Integrilin Low Dose: Rate (%)	136 (10.5%)	393 (30.2%)	23 (1.8%)	124 (9.5%)	124 (9.5%)	233 (17.9%)
<b>Placebo vs High Dose:</b>						
Odds Ratio (% Difference)	.845 (1.6)	.914 (1.9)	.745 (0.6)	.827 (1.7)	.907 (0.8)	.953(0.7)
2-sided P-value (on difference)	.204 (.214)	.318 (.316)	.386 (.400)	.1681(.179)	.533 (.524)	.677 (.659)
<b>Placebo vs Low Dose:</b>						
Odds Ratio (% Difference)	.877 (1.3)	.948 (1.2)	.809(0.4)	.856 (1.5)	1.00 (0.0)	.951(0.8)
2-sided P-value (difference)	.327 (.345)	.562 (.554)	.544(.584)	.255 (.270)	1.00 (.989)	.656 (.648)

Rates are from sponsor's Tables 7-9, 7-10 & 7-11; all p-values are exact (by reviewer); inte: any intervention; \*: Repeat angioplasty.

Note that sponsor's time-to-event secondary analysis results are consistent with the event rate primary analysis results, as can be seen below. The asymptotic 2-sided p-values for both rank tests (log-rank test, which places more weight on later survival times and the Wilcoxon test, which places more weight on earlier survival times) for homogeneity of survival curves across strata of .034 is equivalent to that obtained in sponsor's primary analysis. Time-to-event proportional hazard regression (Phreg) analyses that account for informative censoring yield similar result.

**Sponsor's Asymptotic Time-To-Event Analysis Results (2-sided p-values) at 30-Day Primary Time points**

	Log-Rank	Wilcoxon	Wald's Statistic (Phreg)
Pla vs High Dose	.179	.164	.172
Pla vs Low Dose	.034	.034	.035

## SOME SUBGROUP ANALYSES

Table 3b above indicates that there were significantly more Caucasians in the low Integrilin dose than in the placebo treatment group. We now investigate the impact of this imbalance on the observed overall effectiveness results via subgroup analyses. Table 6 below summarizes some subgroup analysis results. From these table results we observe that both the Caucasian and male subgroup efficacy data analysis results are consistent with the overall efficacy data summarized in Table 4 (page 10) above regarding the effectiveness of the low Integrilin dose. However, the low Integrilin dose is only shown effective for the subgroup of patients with low risk factor at randomization and not for the high risk factor subgroup. The high Integrilin dose is shown to have no advantage over placebo in any of these subgroup analyses.

Table 6/ Subgroup Analysis Results at the 24-hour and 30-day timepoints for Composite Endpoint Only

Comparison/Endpoint	Race*		Gender*		Risk Factor (At Randomization)	
	Caucasians	Others	Males	Females	High Risk	Elective
<b>24-Hour</b> : Placebo: Rate (%)	116 (10.0%)	7 (5.6%)	95 (9.8%)	28 (8.9%)	46/555 (8.3%)	77/773 (10.0%)
High Dose: Rate (%)	80 (6.9%)	9 (7.6%)	70 (7.2%)	19 (6.2%)	36/545 (6.6%)	53/788 (6.7%)
Low Dose: Rate (%)	82 (6.7%)	4 (5.0%)	61 (6.4%)	25 (7.2%)	36/553 (6.5%)	50/796 (6.3%)
<b>% Difference (p-value):</b>						
Placebo - High	3.1 (.013)	-2.0 (.653)	2.6 (.058)	2.7 (.298)	1.7 (.356)	3.2 (.038)
Placebo - Low	3.3 (.008)	0.6 (.916)	3.4 (.014)	1.7 (.507)	1.8 (.346)	3.7 (.015)
<b>30-Day</b> : Placebo: Rate (%)	139 (12.0%)	10 (8.0%)	113 (11.6%)	36 (11.4%)	57/555(10.3%)	92/773 (18.0%)
High Dose: Rate (%)	117 (10.1%)	11 (9.2%)	97 (9.9%)	31 (10.1%)	51/545 (9.4%)	77/788 (15.1%)
Low Dose: Rate (%)	112 (9.2%)	6 (7.5%)	81 (8.5%)	37 (10.6%)	57/553(10.3%)	61/796 (11.9%)
<b>% Difference (p-value):</b>						
Placebo - High	1.9 (.824)	-1.2 (.824)	-0.1 (.252)	-0.7 (.680)	0.9 (.673)	2.1 (.228)
Placebo - Low	2.8 (.037)	0.5 (.928)	1.3 (.037)	0.8 (.780)	0.0 (.989)	4.2 (.010)

Rates are from sponsor's Tables 7-13 and 7-20; all p-values are exact (by reviewer); \*: sample sizes based on all treated patients population.

Although there was no apparent statistically significant imbalance among the three treatment groups regarding smokers and non-smokers at baseline, sponsor's subgroup analysis results at the 30-Day time point summarized in Table 7 below seem to suggest that both doses of integrilin are numerically inferior to placebo among current smokers; p-values are exact 2-sided p-values by this reviewer. The smokers subgroup analysis results should, however, be interpreted with caution because of the relatively small sample sizes.

Table 7/Other Subgroup Analysis Results of the Composite Endpoint at the 24-Hour & 30-Day Time points

Subgroup	At 24-Hour Time point			At 30-Day Time point		
	Placebo (23%)	High Dose (24%)	Low Dose (25%)	Placebo (23%)	High Dose (24%)	Low Dose (25%)
<b>Smokers (%)</b>						
n (Event rate)	295 (8.1%)	303 (6.9%)	323 (7.4%)	<b>295 (9.5%)</b>	<b>303 (10.2%)</b>	<b>323 (10.8%)</b>
OR (% Diff)	Pla vs	.841(1.2)	.906 (0.7)	<b>Pla vs</b>	<b>1.09 (-0.7)</b>	<b>1.16 (-1.3)</b>
Unadjusted P-val	Pla vs	.687 (.676)	.858 (.803)	<b>Pla vs</b>	<b>.869 (.826)</b>	<b>.677 (.654)</b>
<b>Non-smokers (%) (77%)</b>		(76%)	(75%)	(77%)	(76%)	(75%)
n (Event rate)	981 (10.0%)	971 (7.0%)	969 (6.2%)	<b>981 (12.2%)</b>	<b>971 (10.0%)</b>	<b>969 (8.2%)</b>
OR (% Diff)	Pla vs	.679(3.0)	.595 (3.8)	<b>Pla vs</b>	<b>.593 (2.2)</b>	<b>.637 (4.0)</b>
Unadjusted P-val	Pla vs	.022 (.029)	.003 (.006)	<b>Pla vs</b>	<b>.132 (.150)</b>	<b>.004 (.007)</b>

Note: -ve difference indicates a numerical advantage in favor of placebo; Data extracted from page 223 of Appendix S, Vol 299.

## IV SUMMARY OF SAFETY DATA AT THE 30-DAY TIMEPOINT

**Table 8** below summarizes the incidence of CEC adjudicated bleeding complications in the all treated patients population. The data indicate significantly more (minor) bleeding complications in the Integrilin high dose than in the placebo treatment group (Mantel-Haenszel 2-sided p-value = .003 for overall bleeds and .002 for minor bleeds). Overall, there is no significant difference in bleeding complications between placebo and Integrilin low dose; numerically, there are more minor bleeding complications in the Integrilin low dose than in the placebo treatment group. There are no significant difference among the treatment groups regarding major bleeding complications. Among bleeding complications classified as insignificant, however, there were statistically more complications in the low dose than in the placebo treatment group.

**Table 8/ Incidence of CEC-Adjudicated Bleeding Complications For The 30-Day Time point**

Treatment (Sample Size)	Major + Minor [%]	Major [%]	Minor [%]	Insignificant [%]	Unresolved [%]
Placebo (N=1230)	170 [13.8%]	55 [4.5%]	115 [9.3%]	567 [46.1%]	55 [4.5%]
High Dose (N=1245)	235 [18.9%]	58 [4.7%]	177 [14.2%]	620 [49.8%]	41 [3.3%]
Low Dose (N=1249)	201 [16.1%]	55 [4.4%]	146 [11.7%]	650 [52.0%]	51 [4.1%]
<b>% Difference (p-value):</b>					
Placebo - High Dose	-5.1 (.003)	-0.2 ()	-4.9 (.002)	-3.7 (.068)	1.2 ()
Placebo - Low Dose	-2.3 (.140)	0.1 ()	-2.4 (.067)	-5.9 (.005)	0.4 ()

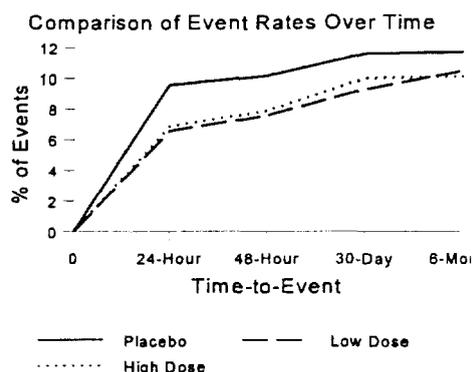
Rates are from sponsor's Table S-1; Note: -ve differences indicate numerically worse integrilin bleeding profile.

## REVIEWER'S COMMENTS AND CONCLUSION

The efficacy data in the single IMPACT II study suggest only some short term efficacy benefit in favor of Integrilin low dose as discussed in the following:

1. Regarding the primary composite efficacy endpoint, the efficacy data indicate Integrilin low dose is effective at the 24-hour time point (observed exact 2-sided p-value based on difference in proportions = .011) and at the 48-hour time point (observed exact 2-sided p-value based on difference in proportions = .035); but that at the 30-day primary time point, Integrilin low dose is only marginally better than placebo (observed exact 2-sided p-value based on difference in proportions = .050). The efficacy data indicate no Integrilin low dose advantage over placebo at the 6-month secondary time point (observed exact 2-sided p-value based on difference in proportions = .648). For Integrilin high dose, the only Integrilin advantage over placebo is at the 24-hour time point; no Integrilin high dose advantages are indicated at the 48-hour, 30-day, or 6-month time points. [See graph below.]

This seems to suggest that any observed Integrilin benefit is short lived. In other words, the observed Integrilin (low dose) advantage over placebo regarding the primary composite efficacy endpoints is due to events that occurred early on in the treatment period (i.e., at the 24-hour time point). This argument is supported by the almost parallel survival curves after the 8-hour time point according to the sponsor's survival analyses (see sponsor's survival curves in Attachment A).



2. For the 30-day primary time point, the unadjusted 2-sided p-value for the difference in the proportion of events in the all treated patient population (deaths, MIs or procedures) between placebo and the low dose is .05 (far above the sponsor pre-specified .035 level for pairwise comparisons); the corresponding p-values for the individual components of the composite endpoints are .048 for urgent CABG, .175 for deaths and .152 for MIs (see summary of results on next page). When adjusted for multiple comparisons, these p-values are respectively .070 for the composite endpoint and .067 for urgent CABG.

The observed Integrilin low dose advantage over placebo is even less impressive for the all randomized patient population (compared with the all treated patient population) results reported above; for this (all randomized) patient population, the unadjusted exact 2-sided p-value for the difference in the proportions of events [151/1328 (11.3%) placebo vs 124/1349 (9.2%) Integrilin low dose] for the primary composite endpoint at the 30-day primary time point is .087 (.073 for odds ratios).

Note that this pre-specified .035 per comparison  $\alpha$ -level is somewhat liberal and leads to inflated overall type I error rate of .064 instead of the nominal .05 (see Table 1 on page 4). Furthermore, it only takes 2 additional Integrilin low dose events to nullify the above observed (undadjusted) Integrilin low dose statistical advantage over placebo (at the 30-day primary time point):

	Placebo	Low Dose	OR (% Diff)	Exact 2-sided p-value
Rate (%)	149/1286 (11.6)	118/1300 (9.08)	.761 (2.52)	.0413 (.0496)
	149/1286 (11.6)	119/1300 (9.15)	.768 (2.45)	.0485 (.0577)
	149/1286 (11.6)	120/1300 (9.23)	.775 (2.37)	.0568 (.0668)

3. On excluding events related to urgent CABG, even the results at the 24-hour time point is no longer significant at the pre-specified significance level of .035 (exact 2-sided p-value = .079 for odds ratios and .093 for difference in proportions). This suggests that the observed effectiveness result for the primary composite efficacy endpoint is mainly driven by this particular event type.

4. In all the subgroups analyzed (see Tables 6 & 7 on page 10), Integrilin seems to enjoy an advantage over placebo only when the placebo (crude) rates are  $\geq 10\%$ . Furthermore, this is

only so in low risk subgroups; for instance, for smokers and high risk subgroups of patients at randomization, Integrilin seems to have no advantage over placebo (see table below).

**Summary of Efficacy Results by CEC Adjudicated Incidence Rates: Placebo vs Low Dose Integrilin**

	24-Hour		48-Hour		30-Day		6-Month	
	% Diff	p-val*						
<b>All Treated Pts: (Pla - Integ)</b>								
<b>Composite Endpoint:</b>	<b>3.0</b>	<b>.011</b>	<b>2.6</b>	<b>.035</b>	<b>2.5</b>	<b>.050</b>	<b>1.2</b>	<b>.554</b>
		(.016)#		(.049)#		(.070)#		
<b>Without Urgent CABG</b>	<b>1.8</b>	<b>.093</b>	<b>1.4</b>	<b>.214</b>	<b>1.2</b>	<b>.336</b>		
Urgent CABG alone	1.2	.047	1.1	.058	1.3	.048	(.067)#	
Deaths alone	0.1	.714	0.2	.444	0.6	.175		
MI alone	1.6	.158	1.5	.174	1.6	.152		

**Subgroup Analyses for Primary Composite Endpoint: (Pla - Integ)**

High Risk Factor:	1.8	.346			0.0	.989		
Elective:	3.7	.015			4.2	.010		
Smokers:	0.7	.803			-1.3	.657		
Non-smokers:	3.8	.006			4.0	.007		

\*: exact 2-sided p-values (unadjusted for multiple comparisons and interim analyses); # adjusted for multiple comparisons.

**OVERALL CONCLUSION**

The efficacy data in the single study IMPACT II suggests some effectiveness evidence in favor of Integrilin low dose. However, given only one study, and the lack of long term advantage over placebo (even at the 30-day primary time point), the demonstration of effectiveness results is not substantial enough for this review to conclude that even the low dose is effective in this trial.

A. J. Sankoh, Ph.D.

11/01/96

Mathematical Statistician

Concur:

Dr. Huque

u 11/01/96

Dr. Smith

11/7/96

cc: Archival NDA # 20-718  
HFD - 180  
HFD - 180/Dr. Fredd  
HFD - 180/Dr. Talarico  
HFD - 180/Ms. Dubeau  
HFD - 344/Dr. Lisook  
HFD - 720/Dr. Smith  
HFD - 720/Dr. Huque  
HFD - 720/Dr. Sankoh  
HFD - 720 File Copy  
Sankoh/x73090/AJS/11-01-96.

**ATTACHMENT A**

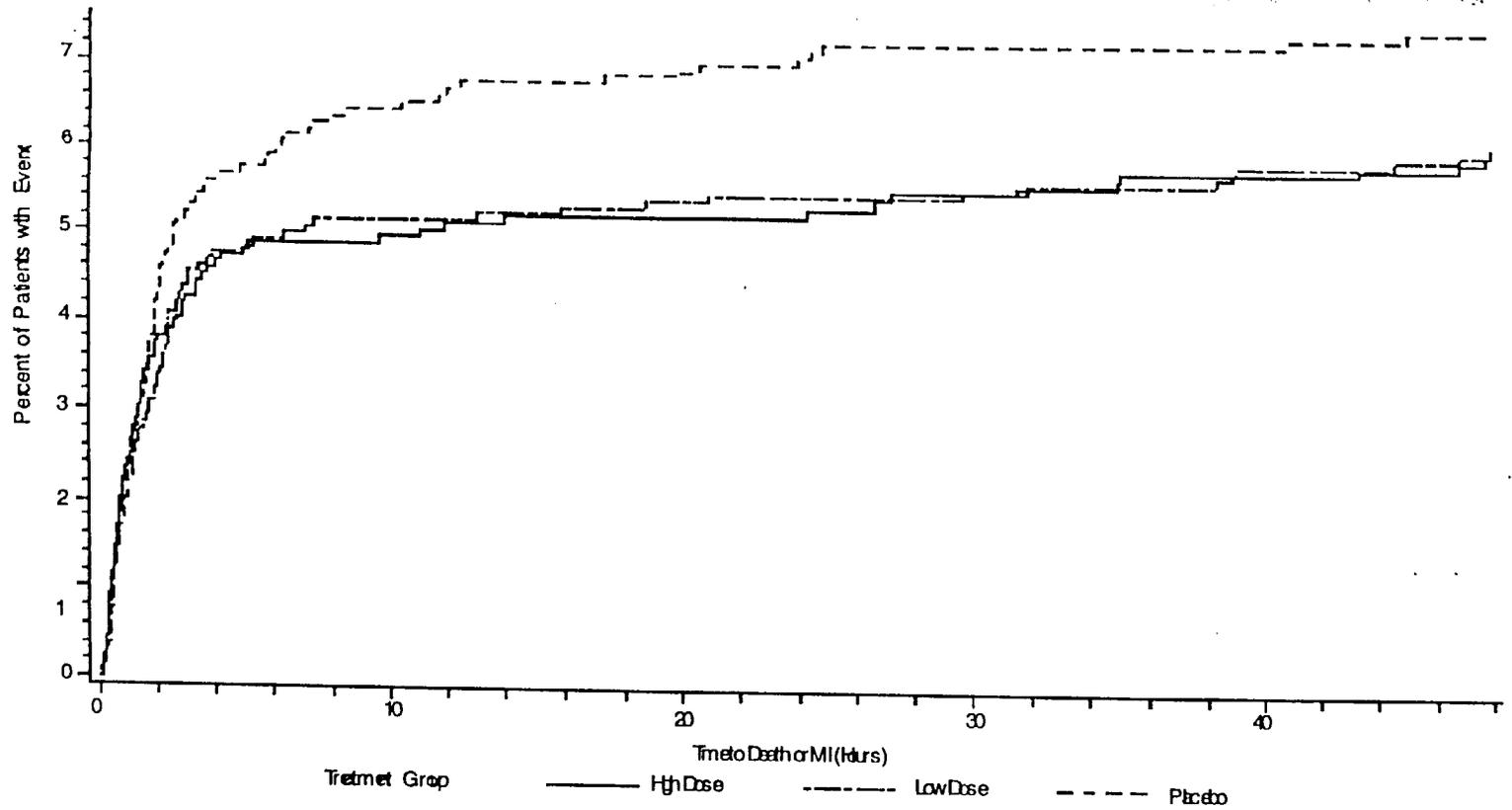


Figure 12-1: Frequency of Composite Endpoint at 48 Hours (Treated Patients Only)

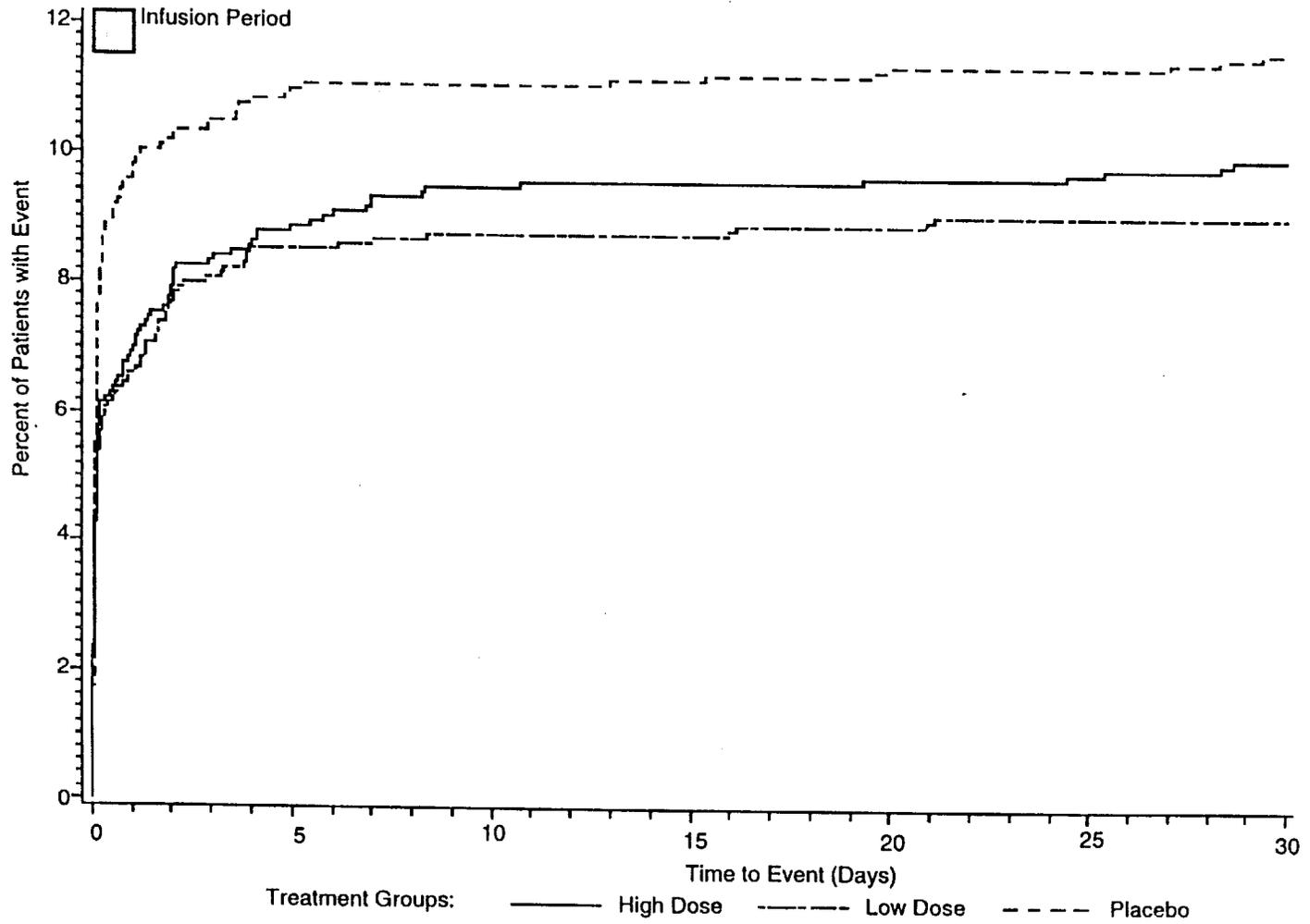


Figure 12-7: Frequency of Composite Endpoint at 30 Days (Treated Patients Only)

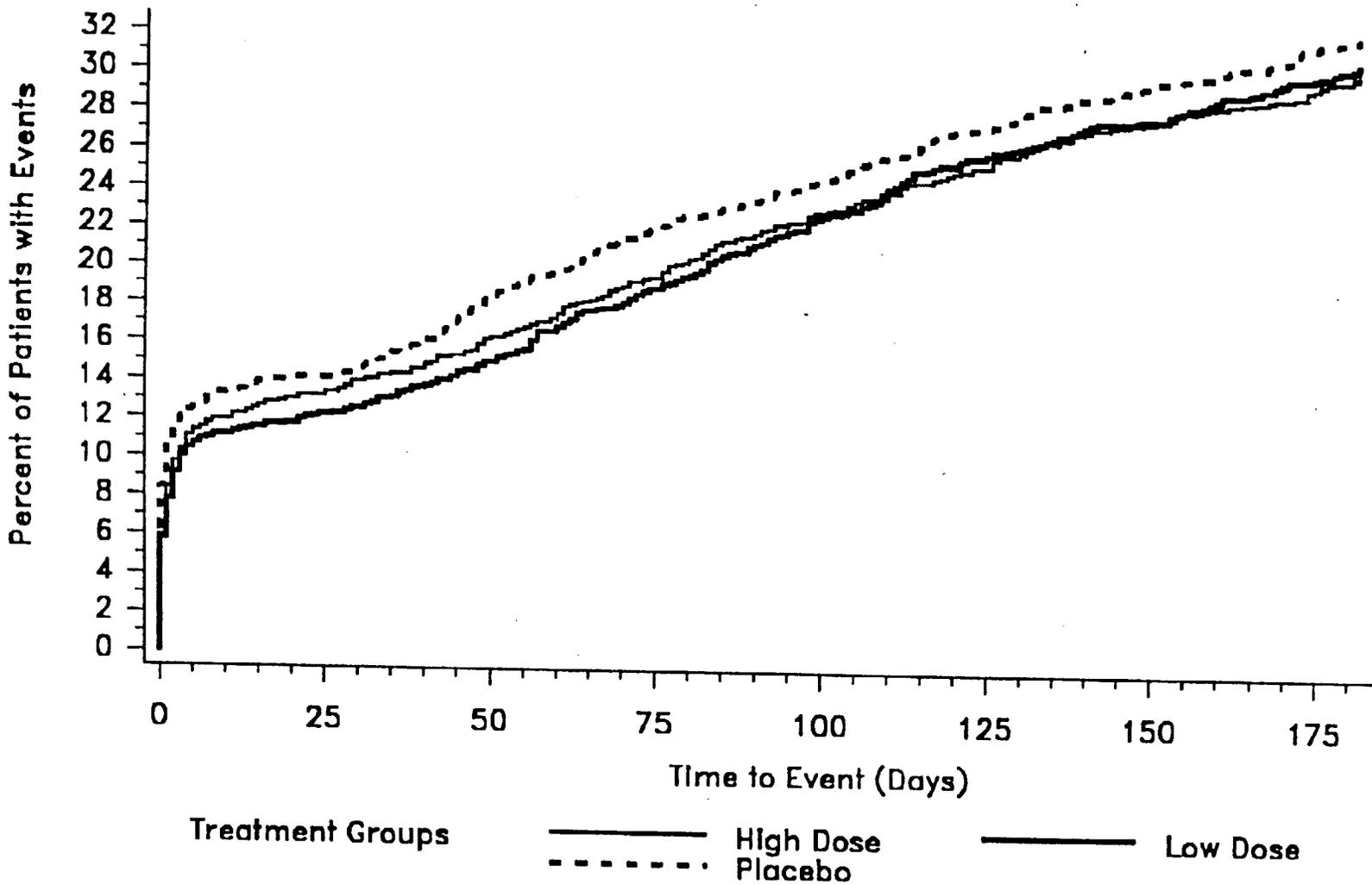


Figure 12-25: Frequency of Composite Endpoint at 6 Months (Treated Patients Only)

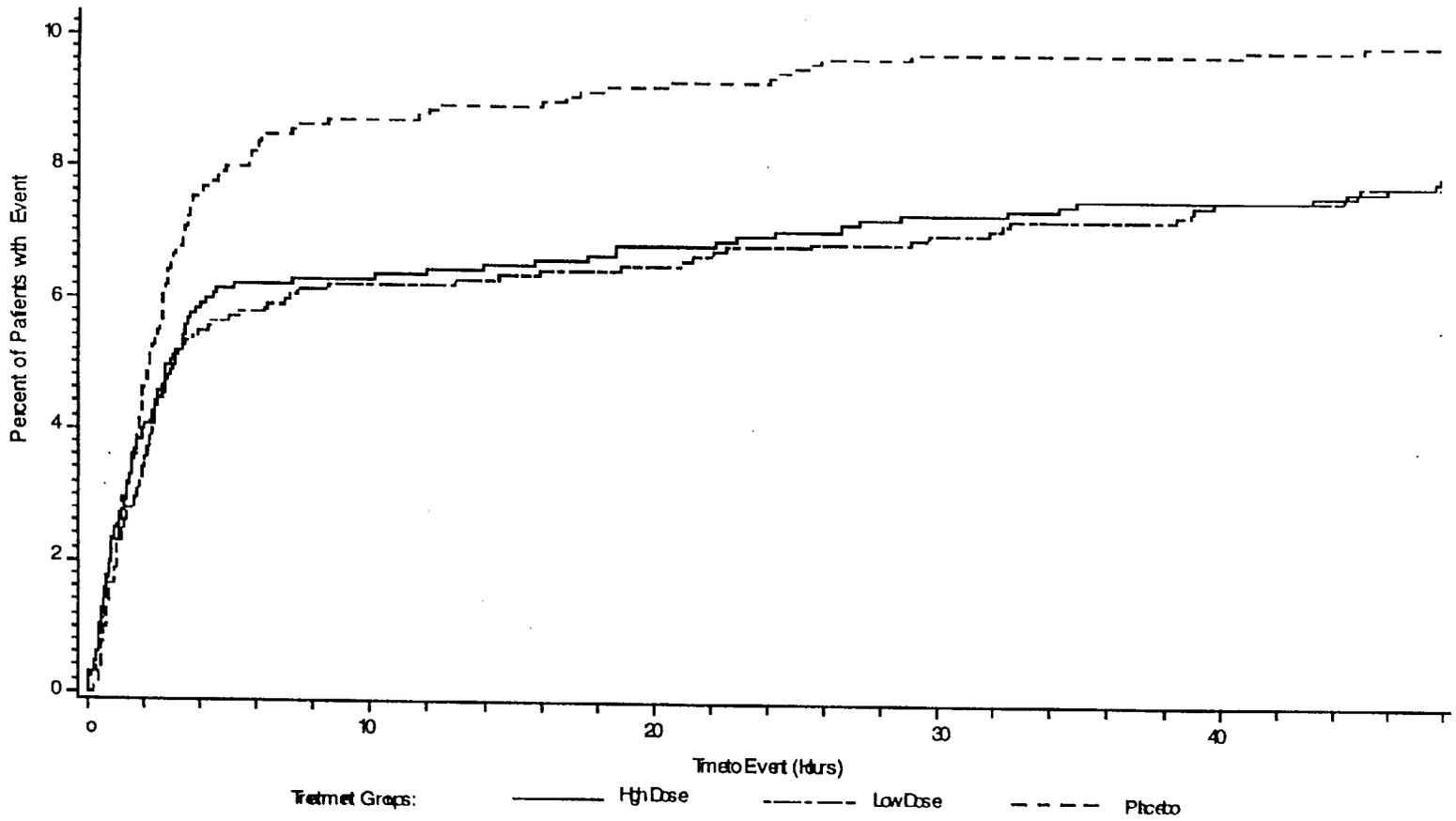


Figure 12-43: Frequency of Composite Endpoint at 48 Hours (All Randomized)

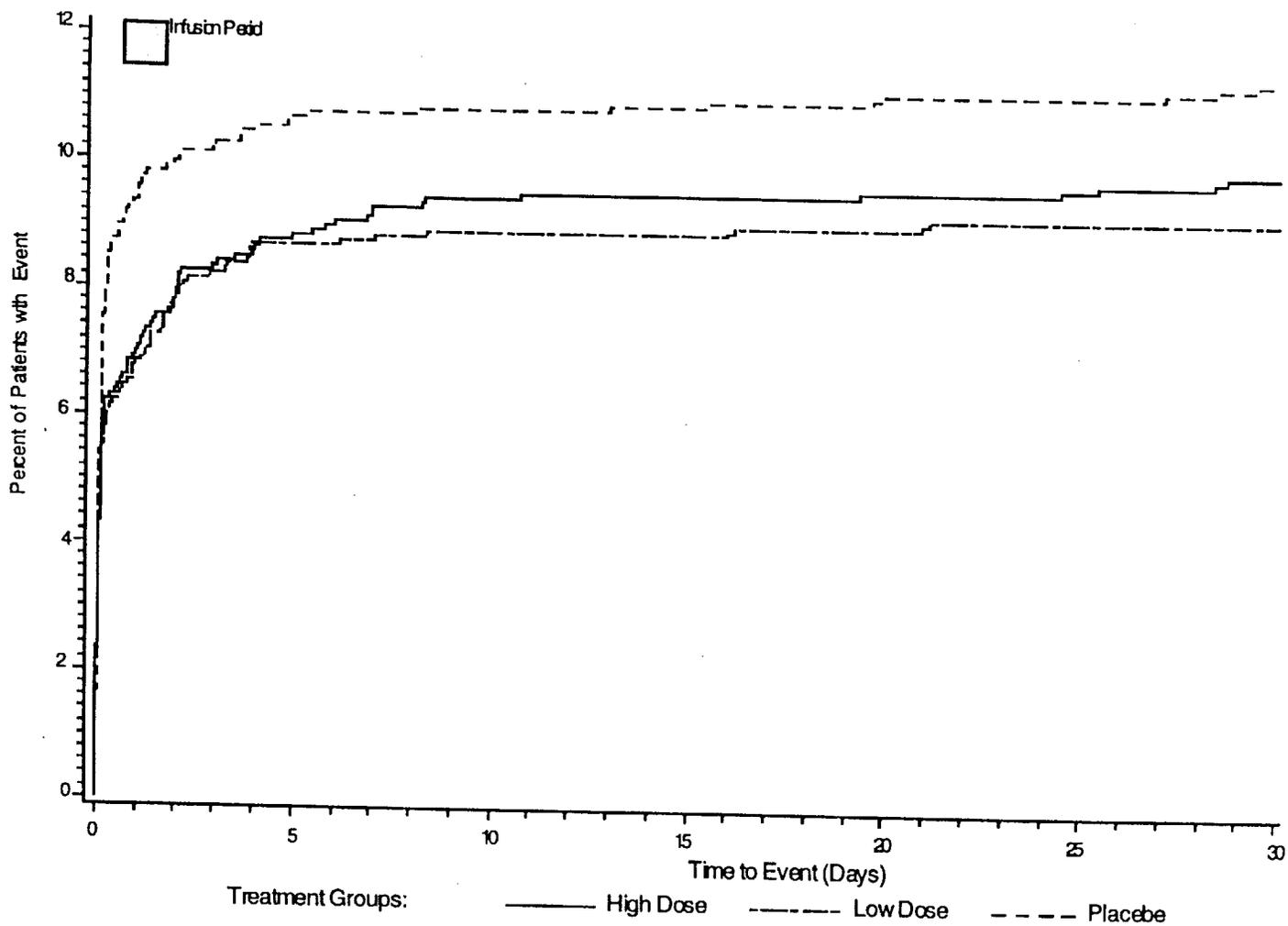


Figure 12-45: Frequency of Composite Endpoint at 30 Days (All Randomized)

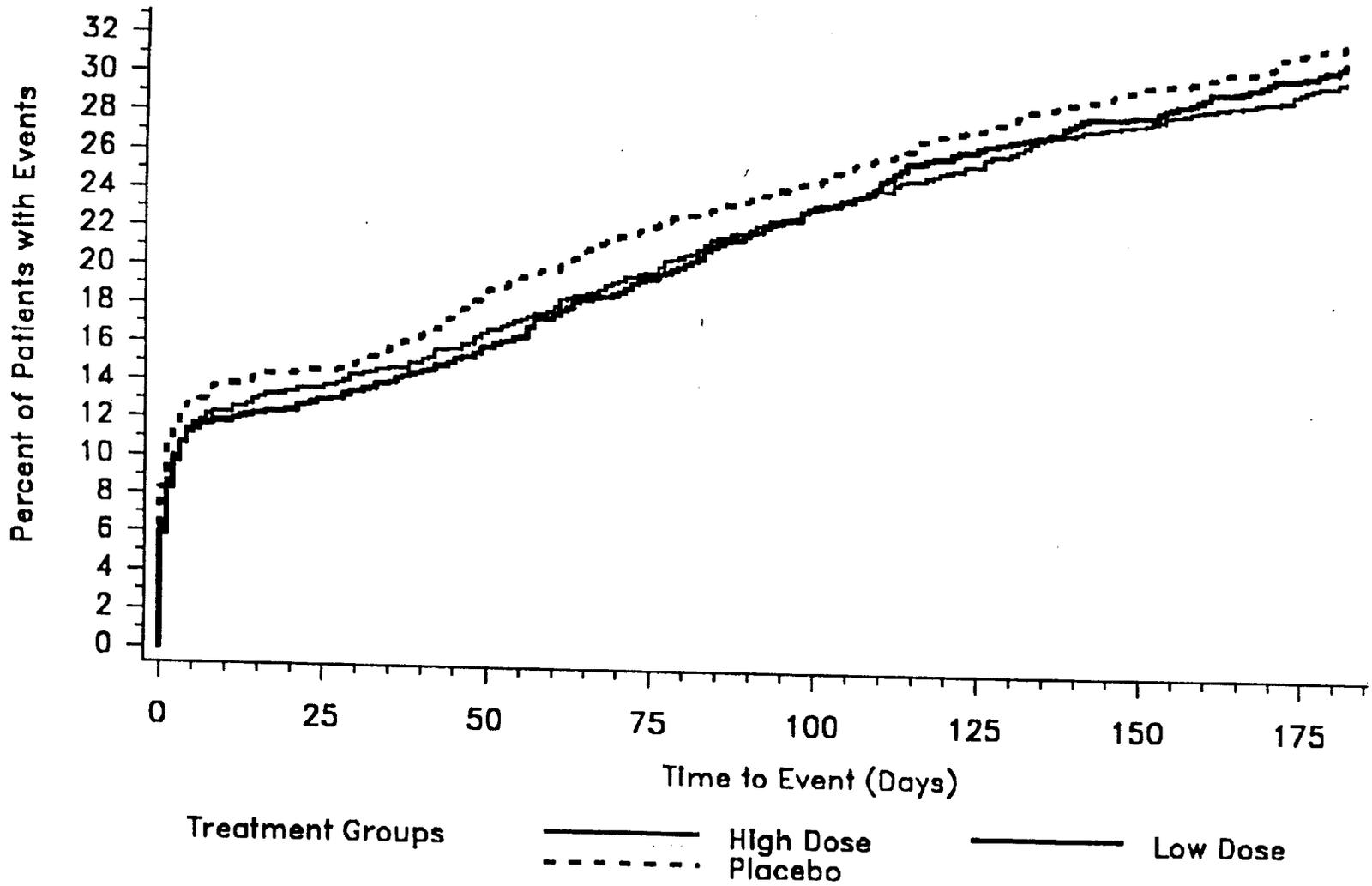


Figure 12-51: Frequency of Composite Endpoint at 6 Months (All Randomized Patients)

**ATTACHMENT B**

**MEETINGS OF THE IMPACT-II DATA AND SAFETY MONITORING COMMITTEE**

**June 2, 1994**

**July 20, 1994**

**August 31, 1994**

**September 7, 1994**

**September 29, 1994**

**The meeting on September 7 was a follow-up meeting to the August 31 meeting. No updated endpoint information was provided to the members at this follow-up meeting. Thus, the committee reviewed endpoint data on 4 occasions.**

**Due to availability of members, meetings were held by telephone conference call.**

MINUTES TO IMPACT II DATA AND SAFETY MONITORING  
COMMITTEE CONFERENCE CALL

June 2, 1994

Participants:

Entire call:

Edward Davis  
David Faxon  
Alan Guerci

Kerry Lee  
Kristina Sigmon  
Douglas Weaver

Nonconfidential portion:

Robert Califf  
Michael Kitt

James Tcheng ??

Nonconfidential Portion

Rob Califf and Michael Kitt provided some introductory remarks, summarizing the progress of the study to date. It was reported that we are enrolling approximately 100 patients per week, with a goal of increasing enrollment to 120-130 patients per week. Other than the desire to increase the rate of enrollment, the trial was reported to be going well with no unexpected problems. Enrollment is now projected to be completed the second week in November, although COR Therapeutics would like to see enrollment finished by the end of September.

It was discussed that this conference call represented the meeting designated in the protocol to evaluate information on the first 500 patients to reach 30 days. The next meeting will be the official efficacy evaluation of the first 1/3 of patients reaching 30 days.

Alan Guerci asked about the effect of the IMPACT II doses of Integrelin on bleeding times. Michael Kitt responded that bleeding times tended to be approximately 12-18 minutes, as presented by Bob Harrington at the ACC Meetings in Atlanta.

Rob Califf stated that there had been complaints about the length of the case report form.

Michael Kitt reported that COR Therapeutics is reporting deaths to the FDA on a quarterly basis. These reports, along with other IND safety reports, will continue to be sent to the chairperson, David Faxon.

At the conclusion of the nonconfidential portion of the conference call, Rob Califf, Michael Kitt, and James Tcheng terminated their participation.

Confidential Portion

The committee reported that they had not been receiving their weekly enrollment update, as described in the SOP for the DSMC. Kristina Sigmon will explore this problem.

At the request of David Faxon, Kristina Sigmon and Kerry Lee described the flow of data in the trial. Concern was voiced by the committee members that the Clinical Endpoints Committee (CEC) had not reviewed any cases yet, so adjudicated endpoint determinations were not available for the DSMC to review. Kerry Lee echoed this concern and stated that we were trying to accelerate the process.

Douglas Weaver felt that the committee needed to concentrate their review on the unmonitored, in-hospital safety summary form information, otherwise the trial would be

completed before review could be helpful. It was noted that for the last planned interim review after 2/3 of the patients reached 30 days, enrollment in the trial would be nearly over before the meeting would be held. Therefore, it was decided that the last analysis would be generated at the time that 2/3 of patients had been enrolled.

Alan Guerci requested that the committee members receive copies of the various data collection forms. It was agreed that they would be provided.

Edward Davis stated that he was not sure that a safety committee should be masked to the identity of each treatment group. Kerry Lee responded that we would be able to reveal the identity of any treatment arm if the committee felt it needed to have the information. The committee could request this information at any of the reviews. David Faxon and Douglas Weaver felt that this provided adequate flexibility.

It was requested and agreed upon that we retain the order of treatments in the documents from meeting to meeting. Thus, treatment A will always be treatment A, treatment B will always be treatment B, etc.

Edward Davis expressed the desire to have p-values presented as part of the analyses, and asked whether there was a plan to provide this. Kerry Lee responded that for the primary endpoint, it was part of the statistical plans to provide statistically comparative information. In addition, if the committee felt they needed other statistically comparative information, the coordinating center would be responsive. If we were to conduct extensive statistical testing, he expressed concern about the potential for misinterpretation due to the multiplicity of comparisons. His recommendation would be to perform statistical tests on the primary endpoint. He stated that if it were requested, we would provide additional testing, but generally would discourage it. David Faxon requested that analysis be performed at the next meeting on the primary endpoint and major bleeding measures. Kerry Lee stated that this was planned.

David Faxon noted that many of the peak ACT levels were higher than the upper limit set in the protocol (350 sec). It was decided that the committee would voice a concern about this issue, though they conceded that it may have little effect.

All members stated that they saw no safety concerns.

Douglas Weaver asked why we had not provided the composite efficacy endpoint as part of this analysis. Kerry Lee responded that the spirit of this initial analysis was a focus on safety, but that in future analyses it will be provided.

However, there was the suspicion that the overall event rate might be lower than hypothesized in the protocol. For this reason, the committee was informed of the overall event rate in the trial (7.9%). It was noted that the EPIC event rate had been higher (12.9%), but both Drs. Weaver and Faxon pointed out that EPIC enrolled a higher risk population.

Douglas Weaver expressed the desire to respond quickly to the Steering Committee about this issue. Kerry Lee agreed, and stated that the next analysis would provide the needed information.

Dates were tentatively selected for the next 2 meetings: the second week in July and the first week in August.

## OUTCOMES TO 30 DAYS

	<u>Treatment A</u> n=214	<u>Treatment B</u> n=213	<u>Treatment C</u> n=222	<u>Combined</u> n=649
Death	4 (1.9%)	2 (0.9%)	4 (1.8%)	10 (1.5%)
MI	6 (2.8%)	8 (3.8%)	8 (3.6%)	22 (3.4%)
CABG	7 (3.3%)	2 (0.9%)	9 (4.1%)	18 (2.8%)
Emergency/Urgent	2 (0.9%)	2 (0.9%)	2 (0.9%)	6 (0.9%)
Elective	9 (4.2%)	4 (1.9%)	12 (5.4%)	25 (3.9%)
Any				
Repeat Coronary Intervention	4 (1.9%)	4 (1.9%)	8 (3.6%)	16 (2.5%)
Emergency/Urgent	6 (2.8%)	3 (1.4%)	6 (2.7%)	15 (2.3%)
Elective	10 (4.7%)	7 (3.3%)	13 (5.9%)	30 (4.6%)
Any				
Stent Placement	2 (0.9%)	0 (0%)	0 (0%)	2 (0.3%)
Endpoint*	1 (0.5%)	8 (3.8%)	7 (3.2%)	16 (2.5%)
Non-endpoint	3 (1.4%)	8 (3.8%)	7 (3.2%)	18 (2.8%)
Any				

\*Stents that meet the endpoint definition are those placed for true abrupt closure (TIMI 0 or 1 flow) at the primary intervention.

## COMPOSITE ENDPOINT

	<u>Treatment A</u>	<u>Treatment B</u>	<u>Treatment C</u>	<u>Combined</u>
	<u>n=342</u>	<u>n=346</u>	<u>n=345</u>	<u>n=1033</u>
To Discharge	20 (5.9%)	15 (4.4%)	25 (7.3%)	60 (5.9%)
	<u>n=214</u>	<u>n=213</u>	<u>n=222</u>	<u>n=649</u>
To 30 Days*	18 (8.4%)	15 (7.0%)	18 (8.1%)	51 (7.9%)

\*Primary efficacy endpoint of trial.

The composite endpoint consists of death, MI, emergency/urgent CABG, repeat emergency/urgent coronary intervention, or endpoint stent placement.

MINUTES TO IMPACT II DATA AND SAFETY MONITORING  
COMMITTEE CONFERENCE CALL  
July 20, 1994

Participants:

David Faxon  
Alan Guerci  
Kerry Lee

Kristina Sigmon  
Douglas Weaver

Two members, Edward Davis and Joseph Loscalzo, were unable to participate in this second review of data. The members agreed to review the analyses and speak to the absent members if there were any concerns. Kristina Sigmon agreed to send the packet of information to the absent members.

The primary concern was the lack of Clinical Endpoints Committee (CEC) review. Kerry Lee agreed that this was a problem, and promised to do everything possible to speed the review process along.

There was some question about why the rate of abrupt closure was apparently low, since it was supposed to be including transient abrupt closure. Alan Guerci felt that it should be 2-3 times higher if that were the case, and that this must represent abrupt closure at the end of the procedure.

The members all felt reasonably comfortable with the bleeding rates. There was slight concern about the levels of stroke felt by Doug Weaver, who advised that we watch the events case by case to see what happens. It was requested that for the next meeting descriptions of all intracranial bleeds be assembled into a document, listed by coded treatment arm. Others then requested that non-hemorrhagic strokes and deaths be summarized in a document also.

The significant comparison of the TIMI bleeding classification between Treatments A and C was discussed. Kerry Lee explained that the significance level of 0.011 arose because of differences between the two groups with respect to minor bleeding, not major bleeding. It was felt that the difference was probably not clinically important.

The transfusion rates were felt to be encouraging.

The committee then voiced a concern that the composite event rate was lower than hypothesized in the protocol. It was decided to look more closely at the event rates in a meeting in late August.

For the next meeting, the committee needs adjudicated CEC data, as well as a comparison of how the site and CEC readings compare. It was requested that the CEC review the potential MI subjects first.

At the close of the call a meeting during the week of August 29th was planned, pending availability of the other members.

## OUTCOMES TO 30 DAYS

	<u>Treatment A</u>	<u>Treatment B</u>	<u>Treatment C</u>	<u>Combined</u>
	<u>n=375</u>	<u>n=382</u>	<u>n=387</u>	<u>n=1144</u>
Death	4 (1.1%)	2 (0.5%)	8 (2.1%)	14 (1.2%)
MI	9 (2.4%)	13 (3.4%)	12 (3.1%)	34 (3.0%)
CABG				
Emergency/Urgent	8 (2.1%)	4 (1.1%)	14 (3.6%)	26 (2.3%)
Elective	4 (1.1%)	13 (3.4%)	4 (1.0%)	21 (1.8%)
Any	12 (3.2%)	17 (4.5%)	18 (4.7%)	47 (4.1%)
Repeat Coronary Intervention				
Emergency/Urgent	6 (1.6%)	11 (2.9%)	10 (2.6%)	27 (2.4%)
Elective	12 (3.2%)	8 (2.1%)	7 (1.8%)	27 (2.4%)
Any	18 (4.8%)	18 (4.7%)	16 (4.1%)	52 (4.6%)
Stent Placement				
Endpoint*	2 (0.5%)	0 (0%)	2 (0.5%)	4 (0.4%)
Non-endpoint	8 (2.1%)	13 (3.4%)	17 (4.4%)	38 (3.3%)
Any	11 (2.9%)	13 (3.4%)	19 (4.9%)	43 (3.8%)

\*Stents that meet the endpoint definition are those placed for true abrupt closure (TIMI 0 or 1 flow) at the primary intervention.

## COMPOSITE ENDPOINT

	<u>Treatment A</u>	<u>Treatment B</u>	<u>Treatment C</u>	<u>Combined</u>
	<u>n=528</u>	<u>n=535</u>	<u>n=537</u>	<u>n=1600</u>
To Discharge	27 (5.1%)	27 (5.1%)	34 (6.3%)	88 (5.5%)
	<u>n=375</u>	<u>n=382</u>	<u>n=387</u>	<u>n=1144</u>
To 30 Days*	23 (6.1%)	24 (6.3%)	30 (7.8%)	77 (6.7%)

\*Primary efficacy endpoint of trial.

The composite endpoint consists of death, MI, emergency/urgent CABG, repeat emergency/urgent coronary intervention, or endpoint stent placement.

MINUTES TO IMPACT II DATA AND SAFETY MONITORING  
COMMITTEE CONFERENCE CALL  
August 31, 1994

Participants:

Edward Davis  
David Faxon  
Alan Guerci

Kerry Lee  
Kristina Sigmon  
Douglas Weaver

The previous minutes were reviewed and, with one minor change, were accepted.

Enrollment was reported to be approximately 133 patients per week, with a target date to end enrollment on October 1. However, with the current enrollment trends it appears that enrollment is likely to finish during the middle of October.

The quantity of available data from the Clinical Endpoints Committee is 357 patients. The committee would have liked to have more, but this was viewed as an improvement over the last analysis, in which none was available.

The committee considered the percentages of major and minor bleeding as reasonable. It was observed that the differences in bleeding were attributable to differences in minor bleeding. There were no concerns about the transfusion rate.

The frequency of patients experiencing platelet counts less than 100,000 was a little surprising (2.6%), but it was observed to be the same frequency across all treatment groups.

In reviewing the in-hospital and 30-day endpoint data, the committee noted consistent trends in the difference between treatments A and C. It was noted that the absolute rate of MI remained low. Kerry Lee predicted that, based on our experience, the absolute number of MIs may increase as more of the data is reviewed by the Clinical Endpoints Committee. It was also noted that the overall event rates were still lower than expected.

The table displaying the consistency of data sources was then reviewed. Kerry Lee stated that, as we might expect, the MI rate was slightly increased from safety summary to monitored CRF, and from monitored CRF to Clinical Endpoints Committee Review.

The efficacy comparison of high dose Integrelin vs placebo was presented graphically by drawing a plot to display the boundaries to achieve a statistically significant result. The test statistic for each analysis that has been performed is plotted on this figure, so that one can see where the test statistic falls relative to boundaries (that mimic O'Brien-Fleming bounds). Kerry Lee and Edward Davis explained how to interpret this diagram. Edward Davis cautioned that, in prior studies, he has seen the test statistic nearly cross a boundary and on a subsequent analysis it had dropped.

Conditional power calculations were also presented. Kerry Lee explained that these values for power took into account the differences observed thus far. He continued to state that for the original proposed hypothesis (of detecting a 33% reduction from a placebo event rate of 11%) we had good power. In addition, even if we were to observe event rates similar to what we are currently observing (5.0% in High dose Integrelin vs 7.9% in placebo, a 37% reduction) our power was quite good. However, if the overall difference becomes lower, we could have inadequate power to detect a difference.

OUTCOMES TO 30 DAYS

	<u>Treatment A</u>	<u>Treatment B</u>	<u>Treatment C</u>	<u>Combined</u>
	<u>n=575</u>	<u>n=585</u>	<u>n=585</u>	<u>n=1745</u>
Death**	4 (0.7%)	5 (0.9%)	11 (1.9%)	20 (1.2%)
MI	14 (2.4%)	17 (2.9%)	20 (3.4%)	51 (2.9%)
CABG				
Emergency/Urgent	10 (1.7%)	10 (1.7%)	17 (2.9%)	37 (2.1%)
Elective	9 (1.6%)	18 (3.1%)	10 (1.7%)	37 (2.1%)
Any	19 (3.3%)	28 (4.8%)	28 (4.8%)	75 (4.3%)
Repeat Coronary Intervention				
Emergency/Urgent	6 (1.0%)	16 (2.7%)	14 (2.4%)	36 (2.1%)
Elective	14 (2.4%)	12 (2.1%)	15 (2.6%)	41 (2.4%)
Any	20 (3.5%)	26 (4.5%)	27 (4.6%)	73 (4.2%)
Stent Placement				
Endpoint*	1 (0.2%)	1 (0.2%)	2 (0.3%)	4 (0.2%)
Non-endpoint	16 (2.8%)	20 (3.4%)	20 (3.4%)	56 (3.2%)
Any	20 (3.5%)	21 (3.6%)	23 (3.9%)	64 (3.7%)

\*Stents that meet the endpoint definition are those placed for true abrupt closure (TIMI 0 or 1 flow) at the primary intervention.

\*\*2 additional deaths have recently been reported, 1 in Treatment A and 1 in Treatment C.

## COMPOSITE ENDPOINT

	<u>Treatment A</u>	<u>Treatment B</u>	<u>Treatment C</u>	<u>Combined</u>
	<u>n=764</u>	<u>n=781</u>	<u>n=764</u>	<u>n=2309</u>
To Discharge	31 (4.1%)	38 (4.9%)	46 (6.0%)	115 (5.0%)
	<u>n=575</u>	<u>n=585</u>	<u>n=585</u>	<u>n=1745</u>
To 30 Days*	29 (5.0%)	39 (6.7%)	46 (7.9%)	114 (6.5%)

\*Primary efficacy endpoint of trial.

The composite endpoint consists of death, MI, emergency/urgent CABG, repeat emergency/urgent coronary intervention, or endpoint stent placement.

**CONSISTENCY OF DATA SOURCES**  
Case Report Forms with CEC Reviews

**CONFIDENTIAL**

	<u>differ</u>	<u>CRF yes</u> <u>CEC no</u>	<u>CRF no</u> <u>CEC yes</u>
Major bleeding	3/491 (0.6%)	0	3
Death	0/519 (0%)	0	0
MI	5/519 (1.0%)	1	4
Emergency/urgent CABG	0/518 (0%)	0	0
Emergency/urgent repeat intervention	1/519 (0.2%)	0	1
Stent placement (endpoint)	1/519 (0.2%)	0	1

Underlying event rates:

	<u>CRF</u>	<u>CEC</u>
Major bleeding	9 (1.8%)	12 (2.4%)
Death	3 (0.6%)	3 (0.6%)
MI	14 (2.7%)	17 (3.2%)
Emergency/urgent CABG	5 (1.0%)	5 (1.0%)
Emergency/urgent repeat intervention	5 (1.0%)	6 (1.2%)
Stent placement (endpoint)	0 (0%)	1 (0.2%)

MINUTES TO IMPACT II DATA AND SAFETY MONITORING  
COMMITTEE CONFERENCE CALL  
September 29, 1994

Participants:

Edward Davis  
David Faxon  
Alan Guerci

Kerry Lee  
Kristina Sigmon  
Douglas Weaver

The committee began the meeting by reviewing the information on bleeding complications. A slight gradient was noted in those patients that received more than 2 units of PRBCs; however, all members agreed there were no concerns regarding bleeding.

The outcome data was noted to be trended in a gradient from Treatment A to Treatment C. Dr. Weaver pointed out that treatment B was starting to look more like Treatment A. Kerry Lee pointed out to the group that the low dose could come out quite favorable in the end, particularly if there were any safety concern with regard to the rate of transfusion. An approximate reduction in the primary efficacy endpoint of 1/3 was observed in this analysis.

Dr. Guerci asked whether the analysis plan allowed the merging of Treatments A and B if no difference evolves between the two groups. Dr. Lee responded that this was not part of the primary analysis plan. However, he stated that ultimately they could be pooled for purposes of interpretation if it turned out to be appropriate. Some discussion occurred with regard to the possible effect of pooling data from treatments A and B and the role this could play if the trial were extended. It was felt that pooling the two arms, if similar, could be helpful.

Dr. Lee pointed out that, since the last look at the data, the significance level of high dose versus placebo remained similar ( $p=0.048$  previously,  $p=0.058$  at present). However, the difference between the low dose arm and placebo had become more significant ( $p=0.18$ ). The Z statistic stands approximately the same as last time, but now the committee is viewing 62% of the data (it was 50% last time).

The conditional power analysis was discussed. Dr. Lee informed the committee that with the current results, the trial is slightly underpowered. A sample size of 4000 patients would yield just slightly over 80% power. Dr. Weaver felt that, at a minimum, it would be wise to extend the trial to 4000 patients. Drs. Faxon and Guerci stated that their bias was to recommend extension to 4000 patients. Although there was discussion to recommend an increase to over 4000 to bring additional security should the event rate fluctuate or decrease, the conclusion was that in order to apply the trial design with 80% power an increase to 4000 patients would be recommended. This would be consistent with the "ground rules" going in. Dr. Faxon elicited Dr. Lee's opinion regarding whether the decision was reasonable, and he agreed that it was.

The possibility of taking an additional look in 1 month was discussed briefly, but was dismissed. Dr. Faxon felt that this analysis should be the final look at the data.

Drs. Guerci and Weaver asked whether they would be entitled to see the data after this analysis. Dr. Faxon stated that he felt that the committee's role was completed.

Dr. Lee thanked the group for their careful consideration and their time.

	<u>Treatment A</u>	<u>Treatment B</u>	<u>Treatment C</u>	<u>Combined</u>
	<u>n=704</u>	<u>n=724</u>	<u>n=733</u>	<u>n=2161</u>
Death**	6 (0.9%)	5 (0.7%)	12 (1.6%)	23 (1.1%)
MI	15 (2.1%)	18 (2.5%)	26 (3.6%)	59 (2.7%)
CABG				
Emergency/Urgent	13 (1.9%)	11 (1.5%)	19 (2.6%)	43 (2.0%)
Elective	11 (1.6%)	20 (2.8%)	13 (1.8%)	44 (2.0%)
Any	24 (3.4%)	31 (4.3%)	33 (4.5%)	88 (4.1%)
Repeat Coronary Intervention				
Emergency/Urgent	7 (1.0%)	18 (2.5%)	16 (2.2%)	41 (1.9%)
Elective	18 (2.6%)	16 (2.2%)	17 (2.3%)	51 (2.4%)
Any	25 (3.6%)	32 (4.4%)	30 (4.1%)	87 (4.0%)
Stent Placement				
Endpoint*	1 (0.1%)	0 (0%)	4 (0.6%)	5 (0.2%)
Non-endpoint	20 (2.8%)	26 (3.6%)	22 (3.0%)	68 (3.2%)
Any	24 (3.4%)	28 (3.9%)	31 (4.2%)	83 (3.8%)
Death or MI	20 (2.8%)	23 (3.2%)	34 (4.6%)	77 (3.6%)

\*Stents that meet the endpoint definition are those placed for true abrupt closure (TIMI 0 or 1 flow) at the primary intervention.

\*\*2 additional deaths have recently been reported, 1 in Treatment A and 1 in Treatment C.

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COMPOSITE ENDPOINT

	<u>Treatment A</u>	<u>Treatment B</u>	<u>Treatment C</u>	<u>Combined</u>
	<u>n=922</u>	<u>n=931</u>	<u>n=944</u>	<u>n=2797</u>
To Discharge	37 (4.0%)	42 (4.5%)	60 (6.4%)	139 (5.0%)
	<u>n=704</u>	<u>n=724</u>	<u>n=733</u>	<u>n=2161</u>
To 30 Days*	35 (5.0%)	41 (5.7%)	54 (7.4%)	130 (6.0%)

\*Primary efficacy endpoint of trial.

The composite endpoint consists of death, MI, emergency/urgent CABG, repeat emergency/urgent coronary intervention, or endpoint stent placement.

NDA 20-718

**Sponsor:** COR Therapeutics Inc.

**Drug Name:** Integrilin™(Intrifiban) Injection

**Indication:** Prevention of acute coronary complications related to abrupt closure of treated coronary vessels in patients undergoing coronary angioplasty



**Subject:** Request for SAS data - clinical trial #93-014(IMPACT II)

Please provide SAS data set on 3½ inch diskettes (or on a readable CD ROM compatible with Window95) readable by SAS/PC (Window Version 6.10). This data set is requested for the primary efficacy endpoint which is a composite endpoint. This data set should include all randomized patients data on the composite and its components along with other information as shown in the following list. [ If the data do not fit into one diskette then include data on 3 separate diskettes, one for each treatment group.]

Center #

Country

Patient #

Treatment group (with dosage)

Date and time of randomization

Date and time treatment began

Key demographic information:

a) disease classification at entry: unstable angina, MI, others

b) disease classification according to the EPIC trial

c) gender and age

d) any other key baseline or demographic variable of clinical significance for the indication.

Date and time of the (first) event

Type of the event (1 = death (any cause), 2 = MI, 3 = urgent or emergency coronary revascularization)

Time-to-event from the time of randomization

Time-to-event from the time treatment began

Censoring information (e.g., patient dropout, lost to follow-up) 1 = yes, 2 = no

Date and time of censoring

Time-to-censoring

Primary reason for censoring (1 =, 2 =, ..., etc)

Patient randomized but excluded from the intention-to-treat analysis (1 = yes, 2 = no)

Primary reason for such an exclusion (1 =, 2 =, ..., etc)

Patient excluded from the per-protocol analyses (1 = yes, 2 = no)

Primary reason for such an exclusion (1 =, 2 =, ..., etc)

Please include all data up to 30 days after randomization. Please also provide a hard copy listing of the first 100 patients along with the definitions of the data codes. Also test the readability of data by SAS/PC (6.10) before sending and please include instructions for loading the data files (with extension '.SD2').

M. F. Huque, Ph.D.  
Mathematical Statistician (Team Leader)

cc: Archival NDA #20-718  
HFD-180  
HFD-180/Dr. Fredd  
HFD-180/Dr. Talarico  
HFD-180/Ms. Dubeau  
HFD-720/Dr. Smith  
HFD-720/Dr. Huque  
HFD-720/Dr. Sankoh  
HFD-720/File Copy  
Huque/301-827-3114/Dec. 12, 1996/a:n20718.req