

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20718/S2

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

JUN 7 1999

NDA #: 20-718

Applicant: COR Therapeutics

Drug Name: Integrilin (eptifibatide)

Indication: PTCA and Unstable Angina

Document Reviewed: 10-day Response to "approvable" letter from Division of Cardio-Renal Drug Products (CDER REC'D date: May 10, 1999), NDA Supplements SE8-002 (BM) and SLR-003 (BM) (CDER REC'D date: May 20, 1999).

In the May 4, 1999 approvable letter, Division of Cardio-Renal Drug Products did not accept the sponsor's proposal that the six-month PURSUIT data be included in the CLINICAL STUDIES section of the Package Insert. According to Dr. Throckmorton's and Dr. Ganley's reviews, one problem with the sponsor's initial submission was that the follow-up was inadequate. Another problem was that it depended on the events reported by investigators and not on events adjudicated by the Clinical Events Committee.

In this submission the sponsor argued that the events by the investigators were confirmed by the chart reviews as defined prospectively and in accordance with similar trials with competing drugs. Regarding the issue of follow-up, the sponsor submitted SAS data base to justify that 96.9% of patients (n=10,611) were followed for 165 days or longer (this defined six month follow-up in the PURSUIT study). The sponsor proposed that the following paragraph be added to the Package Insert in the CLINICAL STUDIES section:

A secondary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (as reported by investigators) within 6 months of randomization. Based on data available from 96.9 percent of patients (n=10,611) who were followed for 165 days or longer, endpoint events were reduced from 13.6 percent with placebo to 12.1 percent with eptifibatide 180/2.0 (p=0.021 log rank) at the six-month timepoint.

This review pertains to the follow-up issue and the endpoint (Death/MI) analysis at 180 days and 146 days, requested by Dr. Throckmorton and Dr. Ganley.

REVIEWER'S EVALUATION

The comparison of integrilin 180/2.0 (180 µg/kg IV bolus followed by 2.0 µg/kg/min IV infusion for 72 hours) to placebo in patients underwent PTCA with respect to death/MI endpoint at six month from randomization was at issue. All the following tables are generated by this reviewer based on the SAS data base provided by the sponsor.

Six Month Follow-up

The distribution of follow-up duration is given in Table 1. Overall speaking, the integrilin group and the placebo group had a similar distribution of follow-up duration, though the eptifibatide 180/2.0 appeared to have slightly more early discontinuations.

Table 1. Distribution of follow-up duration by treatment group

	Eptifibatide 180/1.3* (n=1487)	Eptifibatide 180/2.0 (n=4722)	Placebo (n=4739)
Lost to follow-up	7 (0.47%)	30 (0.64%)	26 (0.55%)
< 120 days	0	4 (0.08%)	3 (0.06%)
120-149 days	6 (0.40%)	29 (0.61%)	21 (0.44%)
150-154 days	7 (0.47%)	24 (0.51%)	29 (0.61%)
155-159 days	8 (0.54%)	35 (0.74%)	29 (0.61%)
160-164 days	4 (0.27%)	34 (0.72%)	41 (0.81%)
165-169 days	36 (3.09%)	152 (3.22%)	154 (3.25%)
170-174 days	63 (4.24%)	218 (4.62%)	202 (4.26%)
175-179 days	85 (5.72%)	295 (6.25%)	291 (6.14%)
≥180 days or verified death	1261 (84.8%)	3901 (82.6%)	3943 (83.2%)

* this arm was terminated early

Six Month Endpoint Analysis

Table 2 shows that this reviewer analysis confirms with the sponsor's results. Table 3 shows that the slightly more early discontinuations in the eptifibatide group dampens the degree of statistical significance substantially.

Table 2. Incidence of Death/MI in all randomized patients at 6 months (analysis treating all discontinuations [follow-up duration < 166 days] as nonevents)

Eptifibate 180/2.0 (n=4722)	Placebo (n=4739)	Logrank p-value	Absolute Reduction	Relative Reduction	Hazard ratio (95% C.I.)
570 (12.1%)	643 (13.6%)	0.021	1.5%	11.0%	0.88 (0.78, 0.98)

Table 3. Incidence of Death/MI in all randomized patients at 6 months (analysis treating all discontinuations [follow-up duration < 166 days] as events)

Eptifibate 180/2.0 (n=4722)	Placebo (n=4739)	Logrank p-value	Absolute Reduction	Relative Reduction	Hazard ratio (95% C.I.)
732 (15.5%)	792 (16.7%)	0.076	1.2%	7.2%	0.91 (0.83, 1.01)

146 Days Endpoint Analysis

As shown in Table 4, the 146 days analysis seems to support that the eptifibatide group continued to have a smaller incidence of death/MI than the placebo group.

Table 4. Incidence of Death/MI in all randomized patients at 146 days (analysis treating all discontinuations [follow-up duration < 166 days] as nonevents)

Eptifibate 180/2.0 (n=4722)	Placebo (n=4739)	Logrank p-value	Absolute Reduction	Relative Reduction	Hazard ratio (95% C.I.)
543 (11.5%)	618 (13.0%)	0.016	1.5%	11.5%	0.87 (0.77, 0.97)

CONCLUSION

Based on the SAS data base provided by the sponsor, this reviewer's analyses at 146 days and at six months suggest that eptifibatide seemed to reduce death/MI events reported by the investigators after 30 days. At 146 days, the reduction is nominally statistically significant (p=0.016). At six months, the reduction appears to be of borderline significance (see Tables 2 and 3 for p-values). The validity of these analyses certainly depends upon the assumption that there is no bias in the investigator assessment of the endpoint. Thus, in my view, whether data collection beyond 30 days not blinded to treatment group (see page 4 of Dr. Throckmorton's review of 3/31/99) caused some unassessable bias is an important point of concern.

/S/

H.M. James Hung, Ph.D.
Acting Team 1 Leader

This review consists of 4 pages of text.