

Eptifibatide/Statistical
Review PURSUIT |

STATISTICAL REVIEW AND EVALUATION

NDA: 20-718

DEC 27 1997

Applicant: COR Therapeutics Inc.

Name of Drug: Integrilin (Eptifibatide Injection)

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1. INTRODUCTION

The protocol of the integrilin trial had gone through 6 amendments and had started on the basis of randomizing patients with unstable angina or non-Q wave myocardial infraction into three arms: placebo, integrilin 135/1.25, and 135/1.30 (μg per kg bolus / infusion rate of μg per kg per minute). The **efficacy** assessment was based on a pooled comparison of the integrilin arms versus placebo arm. After the recruitment of 118 patients, the trial was terminated, which is now called Pre-PURSUIT trial. Amendment 2 of this protocol stated that the integrilin trial be continued with some changes in the inclusion criteria for patients described above that would now be randomized to three arms: placebo, integrilin (180/1.3, 180/2.0). Amendment 2 added the option of discontinuing the low dose integrilin arm, after approximately 2100 patients have been recruited, if the Data and Safety Monitoring Committee (**DSMC**) found no substantial difference in bleeding and stroke profiles between the two integrilin doses. Amendment 2 also changed the primary analysis from a pooled comparison of the integrilin arms versus placebo arm to a **pairwise** comparison of a single-dose arm versus placebo. Thus, the Pre-PERSUIT trial is considered a separate trial from the one specified in amendment 2 (with 4 additional amendments) which is now called the PURSUIT trial.

This review discusses the results of the "PURSUIT" trial, which was a multi-center, randomized, double-blind, placebo-controlled, parallel trial to compare the **efficacy** and safety of eptifibatide to placebo in reducing the incidence of death and/or myocardial infraction (MI) in patients with unstable angina/Q-wave MI (UA/NOMI). The primary **efficacy** endpoint was the incidence of death and/or myocardial infraction (MI). The incidence of MI was adjudicated by an independent blinded Clinical Events Committee (CEC).

2. THE PURSUIT TRIAL

The protocol of the PURSUIT trial stated that a maximum of 9382 patients will be recruited, based on a two-arm trial (integrilin and placebo) with 4791 patients in each arm, so that a statistical test will have a power of 80% to detect a 20% reduction in primary events (MI or death) between placebo (8.0%) and the integriln group (6.4%),.

The protocol stated that three interim analyses plus a final analysis will be planned after 1/6, 1/3, and 2/3 of the patients have been accrued. The first interim look was only for safety

assessment. In addition to that, and after 300 patients have been recruited, the DSMC will review the data to determine if patients >75 years of age should not be excluded from the study. The plan of the interim analysis was based on comparing the proportions of two treatment groups using a normal approximation for a two-sided test with a significance level $\alpha=0.05$. The O'Brien Fleming Boundaries with early rejection for the null hypothesis or the alternative hypothesis was used. This interim analysis plan is summarized in Table A given below.

Table A. The sponsor's plan for the interim analysis for two treatment groups using a normal approximation for a two-sided test for comparing two independent proportions. ($\alpha=0.05$)

Interim Analysis	Number. of Patientts	Process Time	Type of Analysis	Nominal Critical Level to Reject	
				Null Hypothesis	Alt. Hypothesis
1	1400(2100 total)*	1/6 ⁺	Safety	4.58	-1.48
2	3127	1/3	Efficacy	3.54	-0.10
3	4528	2/3	Efficacy	2.35	1.24
4	9382	1.0	Efficacy	1.96	1.96

* 2100 is the total number of patients, including patients of the low dose integrilin group that was planned to be dropped.

+ An approximate figure

In the final count, the PURSUIT trial had enrolled patients from 27 different countries located at four different regions (North America, Western Europe, Eastern Europe, and Latin America) to be randomized into three groups: integrilin 180/1.3, 180/2.0, and placebo. The total number of patients that were randomized was 10,948: 1487 to 180/1.3 arm (which was later discontinued), 4722 to 180/2.0 arm, and 4739 to placebo.

After an enrollment of 3218 patients, the DSMC voted that the enrollment be continued but, only for the high integrilin dose (180/2.0) and placebo. At that time the first interim analysis for the primary endpoint was conducted, using a total of 1232 patients that were enrolled in the high dose and placebo arms. The second interim analysis for the primary endpoint was conducted using 4528 patients (out of a total of 8363 patients that were enrolled in the study) who were enrolled in the integrilin and placebo arms. The DSMC recommended that the trial neither stopped nor extended. The third interim analysis for efficacy was not implemented. Thus, the sponsor considered that, as was stated in the final report, *"the trial had been conducted as if the planned analyses have been actually 3 interim analyses. Consequently, the nominal a level of significance for the final analysis would have to be adjusted for that change in the interim analysis plan. However, since the nominal a level for the final analysis in the new plan is not much different than if the originally planned fourth interim analysis was performed (two-sided nominal a level=0.05), the final analysis would be tested under a level of significance $\alpha=0.05$ ".*

3. REVIEWER'S COMMENTS

As stated above, the protocol planned to have three interim analyses for efficacy plus a final analysis but, according to the sponsor's statistical report, the third interim analysis was not conducted. In this case the third interim analysis was considered as the final analysis at which 9381 patients were recruited to the trial.

The sponsor had used the East software (East) to obtain the critical values for 4 interim looks, using the O'Brien-Fleming's spending function for α for a two-sided test for comparing two independent binomial populations under $\alpha=0.05$. It was assumed that the proportions of the two binomial populations were $\pi_1=0.080$ (placebo) and $\pi_2=0.064$ (integrilin).

This reviewer has also used the East software to obtain the actual a level that should be used for each of the three analyses that the sponsor has actually conducted for a two-sided test for comparing two binomial proportions under a level of significance $\alpha=0.05$. The results of analysis, shown in Table B below, indicate that **the third analysis (which is the final one) should use an $\alpha=0.0478$.**

Table B. Nominal critical values and the a levels that correspond to the recruited number of patients at each interim analysis (calculated by the reviewer).

Interim Analysis	Number. of Subjects	Process Time	Nominal Values for Rejecting H_0		Amount of α to be used
			Critical Value	α	
1	1232	0.1362	4.616	0.0000	0.0000
2	4528	0.5004	2.750	0.0056	0.0056
3	9381	1.0000	1.932	0.0534	0.0478

Although the protocol stated that the primary analysis would be based on all randomized patients (i.e. the intent-to-treat (ITT) analysis), the sponsor's report has put the emphasis on the "treated as randomized" analysis. This reviewer has checked the sponsor's analysis, using the submitted data, for the primary endpoint based on the unadjusted Chi-square test (as stated in the protocol). The sponsor apparently has employed the odd ratio test to compare the proportions of the primary events between placebo and integrilin groups. The sponsor's results for the ITT and the treated as randomized analyses are shown in Table C below.

Table C. The results of the sponsor's analysis for the primary endpoint, using the ITT and the treated as randomized analyses..

Analysis	Number of Primary Events		p-value
	Placebo (N=4697)	Integrilin (N=4680)	
ITT	745	672	0.042
Treated As Randomized	743	667	0.034

As stated in the protocol, the primary endpoint was to be analyzed by comparing the proportions of two independent populations. This means that a test should be used to compare two binomial populations corresponding to the integrilin and placebo groups. There are a number of statistical tests that can be applied for this purpose and since the protocol did not specify which test would be considered for analysis, this reviewer has conducted four widely used tests for comparison. These are the Pearson Chi-square, the **likelihood** test, Fisher's exact test and a test for odd ratios of two binomial proportions. The results of the four tests, using **StatXact3 software** of CYTEL Corporation for both the exact and the asymptotic tests, **are** summarized in Table D below.

Table D. Asymptotic and exact tests for the comparing two binomial population.
(carried out by the reviewer)

Analysis	Test	P-Value	
		Asymptotic*	Exact
ITT	(1) Pearson's CI-G-Square	0.0424	0.0437
	(2) Fisher's Exact Test	0.0424	0.0437
	(3) Likelihood Ratio Test	0.0423	0.0437
	(4) Odd Ratio	0.0425	0.0454
Treated As Randomized	(1) Pearson's ChiSquare	0.0339	0.0351
	(2) Fisher's Exact Test	0.0339	0.0351
	(3) Likelihood Ratio Test	0.0339	0.0351
	(4) Odd Ratio	0.0340	0.0364

The asymptotic p-value is the tail value of a Chi-square distribution with 1 degree of freedom based on the observed value of the test statistic for each method.

The results of Table D show that these tests produce almost the same p-values for both the asymptotic and the exact p-values. However, in comparing two binomial proportions one should consider the exact p-values rather than the asymptotic ones of these test. Thus, by

considering the sponsor's choice of the odd ratio test **the exact p-value for the ITT analysis is 0.0454, which is to be compared to a significance level $\alpha=0.0478$** as described above.

In addition to the above discussion, and by examining the results of the four regions that were considered in the PURSUIT study, there seems to be some differences in the event rates of the primary endpoint among these different regions (as can be seen from Table E below) so that one may need to apply a test that would adjust for these differences. In this case the Cochran-Mantel-Haenszel test seems appropriate.

Table E. Number of events for the primary endpoint by region,
 EE=Eastern Europe, LA=Latin America, NA=North America
 WE=Western Europe. (calculated by the reviewer)

Region	Group	No.of Patients	No. Of Events	Percent
EE	Placebo	769	153	19.9
	Integrilin	762	160	21.0
LA	Placebo	196	30	15.3
	Integrilin	197	32	16.2
NA	Placebo	1901	287	15.1
	Integrilin	1887	221	11.7
WE	Placebo	1831	273	14.9
	Integrilin	1834	254	13.8

This reviewer has carried out the Cochran-Mantel-Haenszel test and the p-values found for the ITT and the treated as randomized analyses are 0.043 and 0.034, respectively. Referring to the above discussion, these p-values should be compared to $\alpha=0.0478$, and thus these results indicate significant difference in the proportions of primary endpoint between integrilin and placebo, after controlling for the differences in the primary events among the four regions.

In conclusion, the results of the PURSUIT trial seem to support the sponsor's claim that integrilin has significantly reduced the event rate of MI or death over placebo (within 30 days of treatment) in patients with unstable angina or non-Q wave myocardial infraction.

This review consists of 6 pages.

Concur:

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