CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-718

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DEC 2 ? 1997

NDA: 20-718
Applicant: COR Therapeutics Inc.
Name of Drug: Integrilin (Eptifibatide Injection)
Document Reviewed: Volumes 2.1, and 2.67 to 2.86
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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 α=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.(α=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 α level of significance for the final analysis would have to be adjusted for that change in the interim analysis plan. However, since the nominal α 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 α level=0.05), the final analysis would be tested under a level of significance α=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 α=0.05. It was assumed that the proportions of the two binomial populations were π_1=0.080 (placebo) and π_2=0.064 (integrilin).

This reviewer has also used the East software to obtain the actual α 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 α=0.05 . The results of analysis, shown in Table B below, indicate that **the third analysis (which is the final one) should use an α=0.0478.**

Table B. Nominal critical values and the α 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 Chi-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 α=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 α=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.

Walid A. Nuri, Ph.D.
Mathematical Statistician

This review consists of 6 pages.

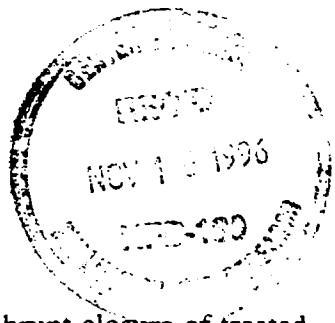
Concur:
Dr. Mahjoob 12/19/97
Dr. Chi 12/19/97

cc: Orig. NDA 20-718
HFD-110/Dr. Hammond
HFD-110/Ms. McDonald
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Nuri
Chron:
W A Nuri: 594-5303 DB I; 12-19-97: DISC10/intgrln1.wpd

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW & 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

45-Day Meeting and Filing Date: May 15, 1996.

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

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 athrectomy, rotational ablation angioplasty or excimer laser angioplasty).

I STUDY PROTOCOL #93-014 (Placebo controlled)

1.1 STUDY DESIGN

This is described in the protocol as a multi-center, double-blind, three parallel groups, placebo controlled, randomized trial in patients undergoing coronary angioplasty with an FDA-approved device (balloon angioplasty, directional atherectomy, transluminal extraction catheter athrectomy, rotational ablation angioplasty or excimer laser angioplasty). Following coronary angioplasty procedure, patients were to be followed until hospital discharge and re-evaluated at 30 days after enrollment for the occurrence of death, MI, urgent or emergency coronary revascularization.

Patients qualified for this trial if they were scheduled to undergo elective urgent, or emergency coronary angioplasty with an FDA-approved percutaneous coronary interventional. Patients exclusion criteria included a history of bleeding diathesis, history of stroke, history of gastrointestinal bleeding, severe hypertension, major surgery within six weeks of enrollment, pregnancy, known prothrombin time of 1.2 above control, known hematocrit $< 30\%$ or known platelet count $< 100{,}000/mm^3$, and known creatine > 4.0 mg/dl.

All qualifying patients were to have pre-treatment complete medical history, blood count, partial thromboplastin time, prothrombin time, CK, CK-MB, chemistry, urinalysis with microscopic exam, 12-lead electrocardiogram assessments. Post-treatment assessments of vital signs (taken immediately upon arrival and hourly for four hours at 6, 12, 18 and 24 hours after the procedure), daily physical exams, platelet counts at 1, 6, 12 and 24 hours after initial bolus infusion of study drug and CK, CK-MB assays at 6, 12 and 24 hours after initial bolus infusion of study medication.

A 30-day post randomization follow-up assessment that included an interval medical history, complete blood count and a physical was to be performed on all patients; a 6-month follow-up on major events such as death, MI, re-hospitalization for cardiac events, and coronary revascularization was also planned.

Sample Size Estimation/ Randomization Schemes

A sample size of 3500 randomized patients (1166 per treatment group) from 80 centers was planned to detect a 33% reduction in treatment failure (from 11% placebo rate to 7.4% integrilin rate with 80% power using a 2-sided α-level of .05. Patients enrollment was to be based on a stratified randomization strategy where the randomization strata are high risk (unstable angina or acute myocardial infarction) and low risk (all other patients). Within each stratum, patients were to be randomized (by telephone calls to the Duke Coordinating Center Randomization Facility) in a 1:1:1 ratio to either receive Integrilin bolus 135 μg/kg followed by a 0.5 μg/kg per minute infusion, or Integrilin bolus 135 μg/kg followed by a 0.75 μg/kg per minute infusion, or a matching placebo bolus followed by a matching placebo infusion for 20-

24 hours. All patients were concurrently on aspirin and heparin.

Study Objectives and Primary Endpoints

The primary objectives of this study are

1) to determine the efficacy of two different dosing regimens of Integrilin versus placebo in patients undergoing coronary angioplasty in reducing the incidence of death, MI, and need for urgent or emergency coronary revascularization in the first 30 days following enrollment, and

2) to determine the safety of Integrilin when used in patients undergoing coronary angioplasty.

The primary efficacy endpoint is a composite endpoint consisting the first occurrence of any one of these three events: all cause mortality, myocardial infarction and urgent or emergency coronary revascularization. Evidence of clinical benefit was to be assessed by comparing treatment groups with respect to this composite endpoint at 30 days after randomization. For this endpoint, death is defined as all-cause mortality where cause of death was to be adjudicated by an independent primary endpoint committee.

A number of secondary efficacy composite clinical endpoints were also considered for events occurring in the 6-month follow-up time-point following initial angioplasty procedure.

1.2.0 SPONSOR'S PLANNED ANALYSES & ANALYSIS METHODS

PRIMARY EFFICACY ANALYSIS

The purpose of the primary analysis (as per protocol amendment) was to assess whether a significant difference exists in the incidence of the primary composite clinical endpoint between the placebo arm and either or both of the Integrilin arms. The primary efficacy endpoint analysis was to be performed after an adjudication of outcome events by a Clinical Events Committee (CEC). This analysis was to be based on all randomized patients (i.e., on an intent-to-treat [ITT] patient population). The planned analysis was pairwise comparisons of high and low doses of integrilin to placebo using chi-square analysis method.

To guard against inflation of the nominal .05 significance level due to multiple comparisons, a reduced (per-comparison) significance level of $< .035$ was planned (as per 12/03/93 protocol amendment; original protocol specified a Bonferroni adjusted α-level of .017). Integrilin effectiveness was claimed if either of the control vs Integrilin pairwise tests were significant. Thus the postulated significance levels at each of the two planned interim analyses were .00007 (for the first) and .0074 (for the second). To supplement the efficacy comparisons at the interim analyses, the (amended) protocol indicated that conditional power calculations based on the data observed to that point and the hypothesized treatment differences were to be provided to the Data Safety Monitoring Committee (DSMC) for use in monitoring the adequacy of the

target sample size.

Note that no statistical rationale is given (by the sponsor) for choosing the adjusted (per-comparison) α-level of .035 as an appropriate upper bound for declaring statistical significance. This adjusted significance α-level, however, seems to correspond to a Tukey, Ciminera and Heyes (TCH) adjusted significance α-level [$.0356 = 1-(1-.05)^{1/\wedge 2} = 1-(.95)^{.7071}$] 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 summaries the simulated overall (attained) Type I error rates and the simulated per-comparison α-levels for given nominal α-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 α-level of .035 would lead to an overall α-level of .064 and not the .05 nominal level. To maintain the nominal .05 significance level, the per-comparison α-level (prior to adjustment for interim analyses) should be ≤.0277, and not ≤.035 as proposed by the sponsor.

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

	Dubey/Armitage et al			**Tukey et al**			**Hochberg**		
Specified Nominal α-Level	**.05**	**.039**	**.035**	**.05**	**.039**	**.035**	**.05**	**.039**	**.035**
1st Per-comparison α-Level	.035	.028	.024	.035	.028	.027	.028	.022	.020
2nd Per-comparison α-Level	.035	.027	.024	.035	.027	.024	.028	.022	.020
Overall Attained α-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 (see page 84, volume 1.1). In the statistical section of this amended protocol 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 studied (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 summaries 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

	Boundaries For 4 Interim Analyses		Boundaries For 3 Interim Analyses	
Analysis	n O - F (p-value)	n Pocock (p-value)	n O - F (p-value)	n Pocock (p-value)
2. (α_1)	689 (.00007)	689 (.01738)	778 (.00026)	778 (.019057)
3. (α_2)	1067 (.00158)	1067 (.01107)	1556 (.00946)	1556 (.014913)
4. (α_3)	1534 (.0085)	1534 (.01088)	2674 (.03475)	2674 (.014918)
4. (α_4)	2674 (.03491)	2674 (.01462)		
Required n	2311	2628	2311	2628
P-H Power	85.4%	79.0%	85.4%	79.3%

Note all α-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), thrombocythemia (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 3rd 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									
Integrilin Low									
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									
Integrilin Low									
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									
Integrilin Low									
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									
Integrilin Low									
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									
Integrilin Low									

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[1]	Death	MI	CABG	Angio*
Placebo: Rate (%) Integrilin High Dose: Rate (%) Integrilin Low Dose: Rate (%)	151 (11.7%)	403 (31.4%)	28 (2.2%)	141 (11.0%)	122 (9.5%)	240 (18.7%)
Placebo vs High Dose: Odds Ratio (% Difference) 2-sided P-value (on difference)	 .845 (1.6) .204 (.214)	 .914 (1.9) .318 (.316)	 .745 (0.6) .386 (.400)	 .827 (1.7) .1681(.179)	 .907 (0.8) .533 (.524)	 .953(0.7) .677 (.659)
Placebo vs Low Dose: Odds Ratio (% Difference) 2-sided P-value (difference)	 .877 (1.3) .327 (.345)	 .948 (1.2) .562 (.554)	 .809(0.4) .544(.584)	 .856 (1.5) .255 (.270)	 1.00 (0.0) 1.00 (.989)	 .951(0.8) .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
24-Hour: 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 (%)						
Low Dose: Rate (%)						
% Difference (p-value):						
Placebo - High						
Placebo - Low						
30-Day : 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 (%)						
Low Dose: Rate (%)						
% Difference (p-value):						
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	High Dose	Low Dose	Placebo	High Dose	Low Dose
Smokers (%)	(23%)	(24%)	(25%)	(23%)	(24%)	(25%)
n (Event rate)	295 (8.1%)	303 (6.9%)	323 (7.4%)	**295 (9.5%)**	**303 (10.2%)**	**323 (10.8%)**
OR (% Diff)	Pla vs	.841(1.2)	.906 (0.7)	**Pla vs**	**1.09 (-0.7)**	**1.16 (-1.3)**
Unadjusted P-val	Pla vs	.687 (.676)	.858 (.803)	**Pla vs**	**.869 (.826)**	**.677 (.654)**
Non-smokers (%)	(77%)	(76%)	(75%)	(77%)	(76%)	(75%)
n (Event rate)	981 (10.0%)	971 (7.0%)	969 (6.2%)	**981 (12.2%)**	**971 (10.0%)**	**969 (8.2%)**
OR (% Diff)	Pla vs	.679(3.0)	.595 (3.8)	**Pla vs**	**.593 (2.2)**	**.637 (4.0)**
Unadjusted P-val	Pla vs	.022 (.029)	.003 (.006)	**Pla vs**	**.132 (.150)**	**.004 (.007)**

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 summaries 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-Haeszel 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)					
Low Dose (N=1249)					
% Difference (p-value):					
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 ()

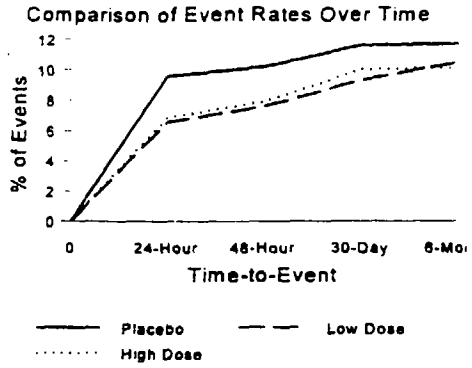
Rates are from sponsor's Table S-1; Note: -ve differences indicate numerically worse integrilin bleeding profile.

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 suggests 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 α-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 (undajusted) 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*	% Diff	p-val*	% Diff	p-val*	% Diff	p-val*
All Treated Pts: (Pla - Integ)								
Composite Endpoint:	**3.0**	**.011** (.016)#	**2.6**	**.035** (.049)#	**2.5**	**.050** (**.070**)#	**1.2**	**.554**
Without Urgent CABG	**1.8**	**.093**	**1.4**	**.214**	**1.2**	**.336**		
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 /Huque 11/01/96

Dr. Smith N 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.

STATISTICAL STABILITY REVIEW & EVALUATIONS

NDA # 20-718

NOV 1 5 1996

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: L. Talarico, M.D; **Chemist**: Al-Hakim, Ph.D.

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

45-Day Meeting and Filing Date: May 15, 1996.

Volumes Reviewed: 1.12 - 1.15: January 17, 1996.

I. Introduction

The sponsor has submitted analysis results of the stability data at the proposed labeled storage of 2-8°C (5°C stability data) to project shelf life. Linear regression analyses of the stability data were performed for the recovery of integrilin versus time for integrilin injection, 2 mg/mL lots D0014A, E0019A, E0021A and E0028A and .75 mg/mL lots D0018, E0020A, E0024A and H0032A. The 5°C stability data are summarized in the table below.

Summarized in **Table 2** through **Table 4** are the results of sponsor's analysis results for testing for the poolability across all lots within each strength by an analysis of covariance (Table 2), for testing the testing the equality of zero-time intercepts (or batch effect) and regression slopes (or time-by-batch interaction effects) across the lots by linear regression model methods (Table 3) using the standard statistical procedures described in the FDA "Guidelines for submitting Documentation for Stability of Human Drugs and Biologics". The level of significance used for each test is .25. A significance level of $p>0.25$ for both the main effect (batch) and interaction effect (time-by-batch) for all lots in a particular strength would suggest the use of a linear regression model based on the pooled slope and zero-time intercept of all these lots. If $p<0.25$ for batch but $p>0.25$ for time-by-batch interaction effect, then a linear regression model was to be run for each lot within that strength using the pooled slopes for all of these lots and the zero-time-intercept of the individual lots. If both significance levels of for batch and slopes for each

lot within each strength failed this minimum criterion test (i.e., $p<0.25$), separate linear regression models were to be run for each lot within each strength.

The general linear regression model in either case is $y=ax+b$, where y is the integrilin recovery in mg/mL, x is the time in months, a is the slop of the regression line and b is the intercept of the regression line.

Table 1/ Integrilin Recovery from Integrilin Injection Stored at 5°C (mg/mL)

Lot Number	Length of Storage in Months						
	0	3	6	9	12	18	24
2 mg/mL Lots							
D0014A	1.99	2.05	2.00	1.97	1.96	1.96	2.07
E0019A	2.02	2.02	2.02	2.01	1.96	1.96	
E0021A	1.99	1.99	2.00	1.96	1.96		
E0028A	2.07	1.90	2.03	1.99	2.02		
.75 mg/mL Lots							
D0018A	0.742	0.737	0.696	0.734	0.743	0.720	0.734
E0020A	0.760	0.756	0.762	0.757	0.768	0.769	
E0024A	0.767	0.777	0.765	0.744	0.755		
H0032A	0.799	0.786	0.777	0.778			

II. Sponsor's Analysis Results and Reviewer's Comments

Based on the analysis methods described above, and using the data summarized in **Table 1** above, sponsor's analysis of covariance results are summarized in **Table 2**.

Table 2/ Sponsor's Covariance Analysis Results (2-Sided p-values)

Strength	Batch	Time-by-Batch
2 mg/mL	.7993	.9285
.75 mg/mL	.0001	.2761

The results summarized in Table 2 above indicate that for the 2.0 mg/mL strength, linear regression can be performed on the pooled slopes and intercepts. For the .75 mg/mL strength, linear regression analysis can be performed on pooled slopes ($P>0.25$) but separate intercepts ($p<0.25$). This reviewer's examination of the submitted SAS data sets did not contradict these findings.

Sponsor's regression analyses results for both strength are summarized in **Table 3.**

For both the 2.0 mg/mL and .75 mg/mL strengths, predicted recoveries and 2-sided 90% confidence were compiled on all lots for up to and including 36 months. That is, the lower 90% confidence limit is equivalent to a 1-sided 95% confidence limit.

Table 3/ Sponsor's Linear Regression Analysis Results for 2 mg/mL Lots

Strength/ Lot Number	Intercept (mg/mL)	Intercept Standard Error	Slope (mg/mL/mon)	Slope Standard Error
2 mg/mL: Pooled Lots Results	1.99638	0.147768	0.0002958	0.001476
.75 mg/mL: Results by Lot #				
D0018A	0.73179	0.006620	-0 .000297	0.004563
E0020A	0.73638	0.006620	-0 .000297	0.004563
E0024A	0.76298	0.006620	-0 .000297	0.004563
H0032A	0.78603	0.006620	-0 .000297	0.004563

The regression analysis results are summarized in attached **Table 4** (for the 2.0 mg/mL strength) **Tables 6** through **9** (for the .75 mg/mL strength). The corresponding graphical displays (attached) are given in **Figure 1** (for the 2.0 mg/mL strength) and **Figures 2** through **5** (for the .75 mg/mL strength) see Attachment #2 for sponsor's analyses (100 mL lots).

The predicted recoveries and the 1-sided lower 95% confidence limits for both strength project a shelf-life greater than 36 months. This reviewer's analyese of the submitted SAS data set did not contradict these findings. In this reviewer's assessment, therefore, the stability data submitted by the sponsor support the currently proposed 24 month shelf-life.

A. J. Sankoh, Ph. D.

10/30/96

Mathematical Statistician

Concur:

Dr. Huque Huque 10/30/96

Dr. Smith NSmith 11/1/96

cc: Archival NDA # 20-333
HFD - 180
HFD - 180/Dr. Fredd
HFD - 180/Dr. Talarico
HFD - 180/Dr. Al-Hakim
HFD - 180/Ms. Dubeau
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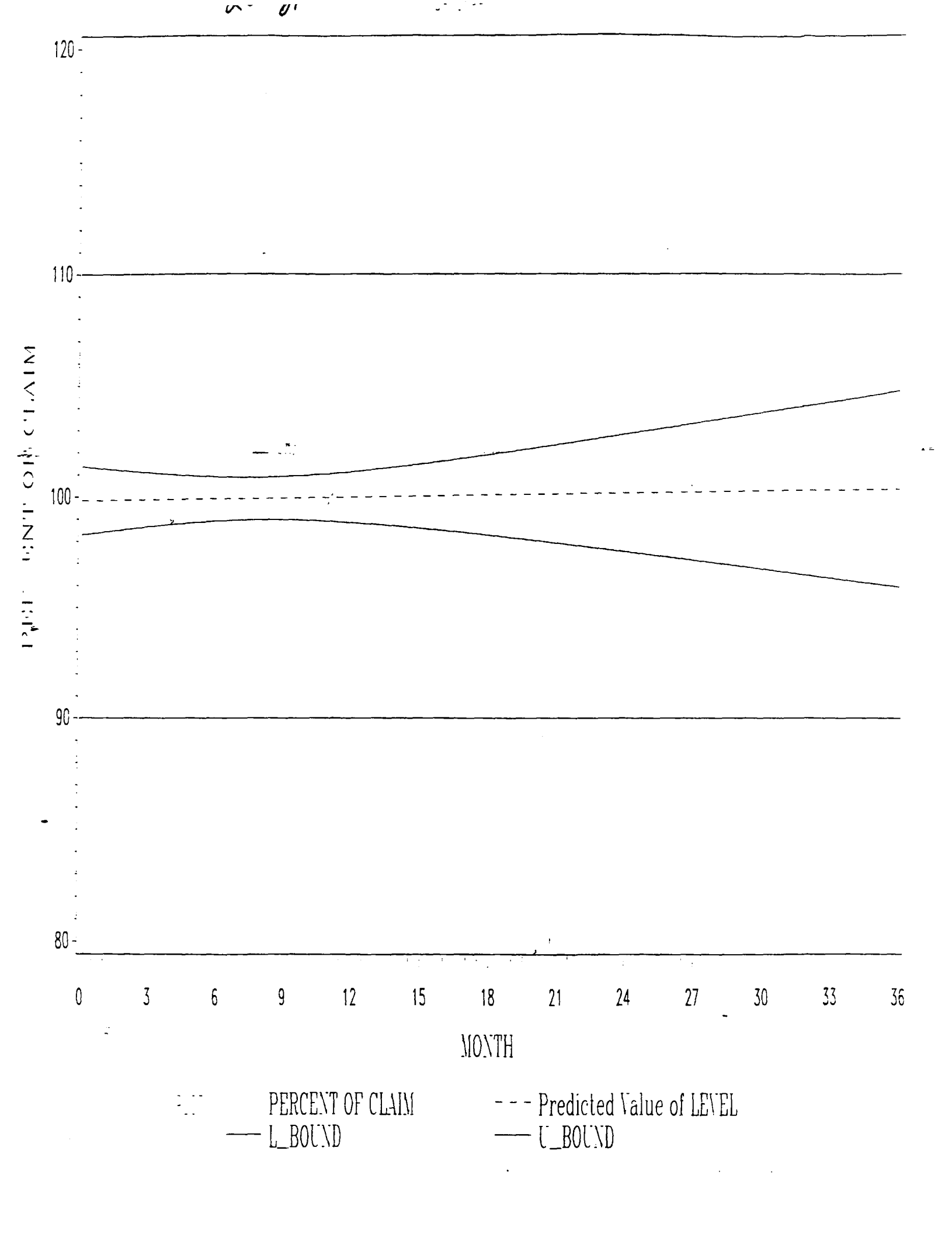
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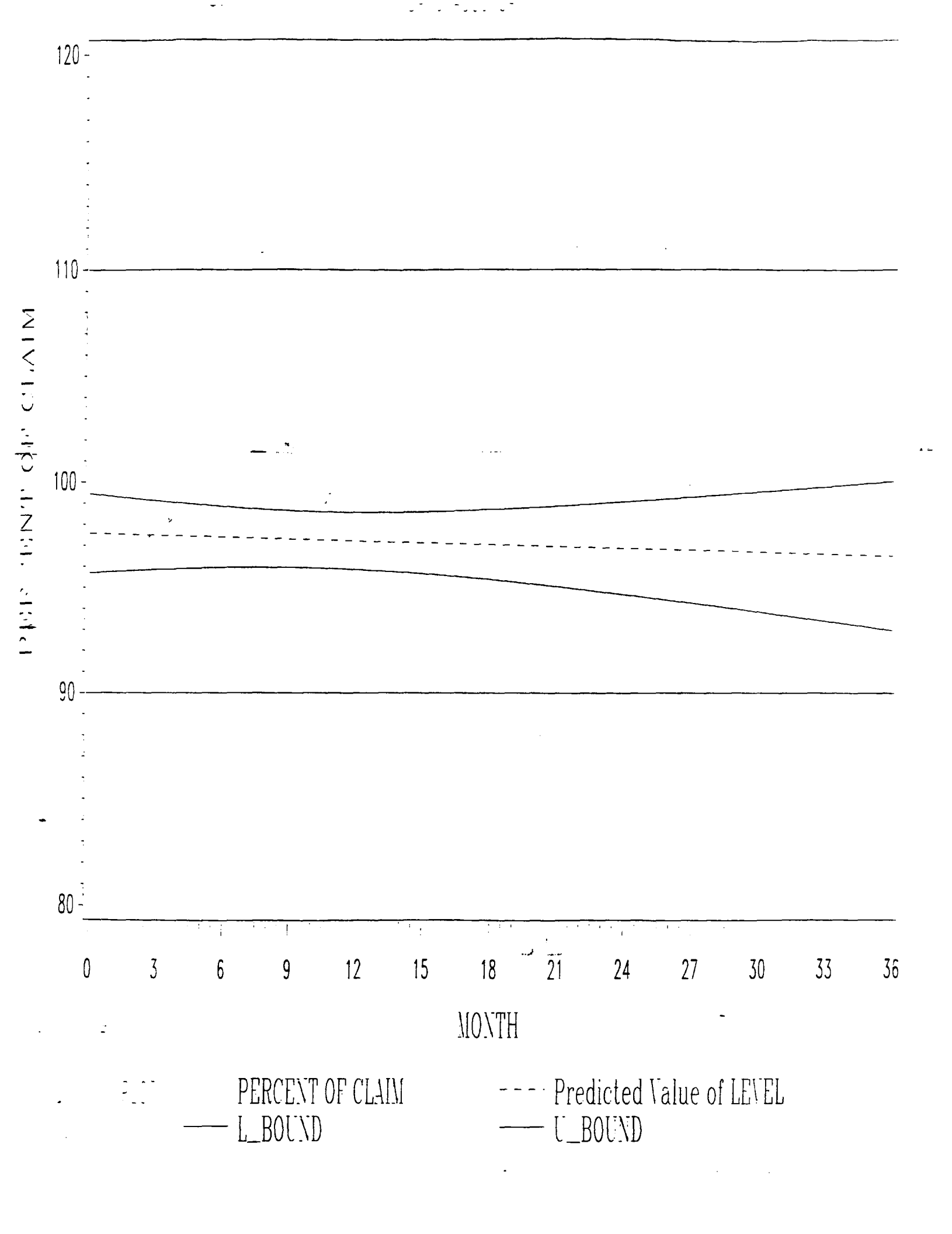
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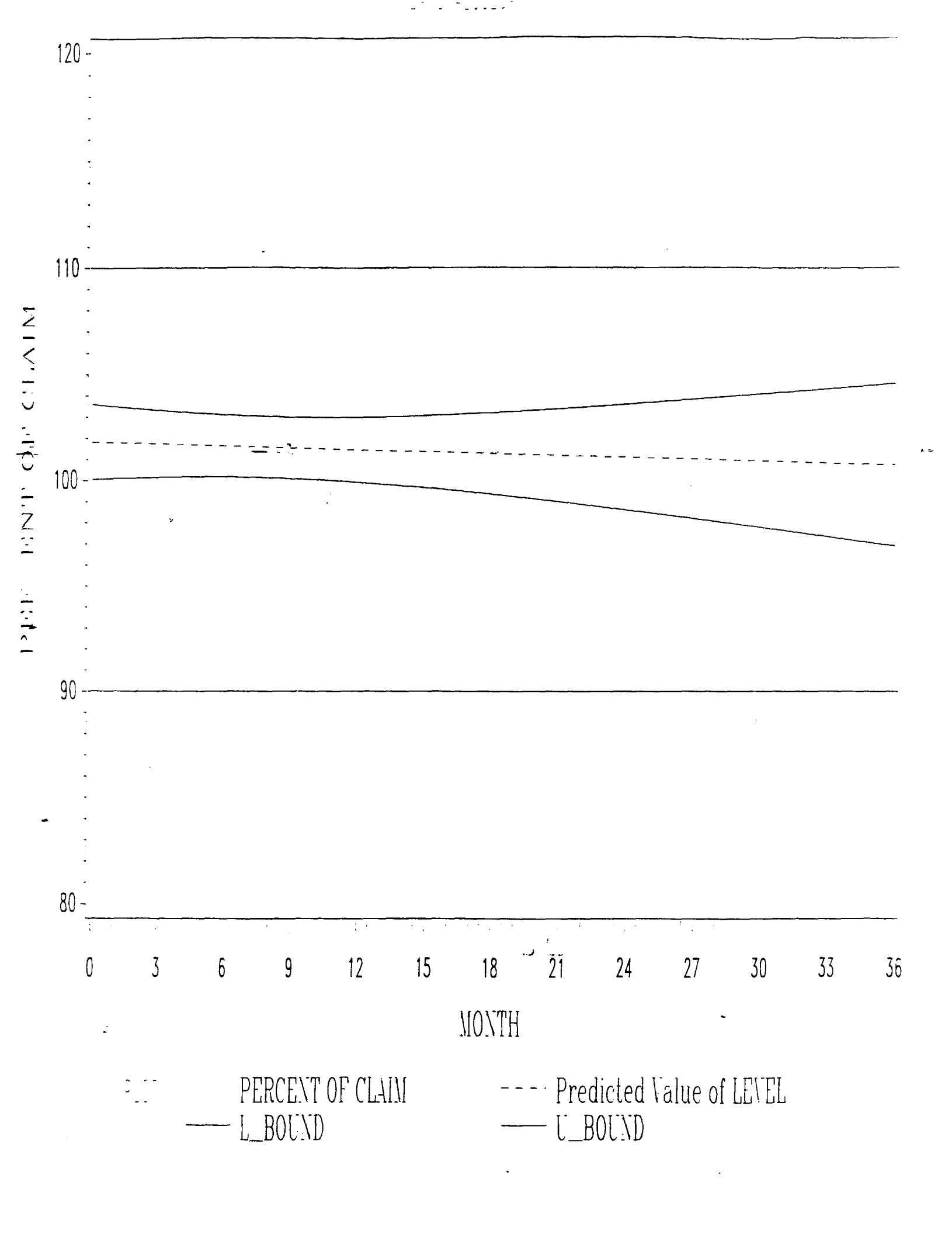
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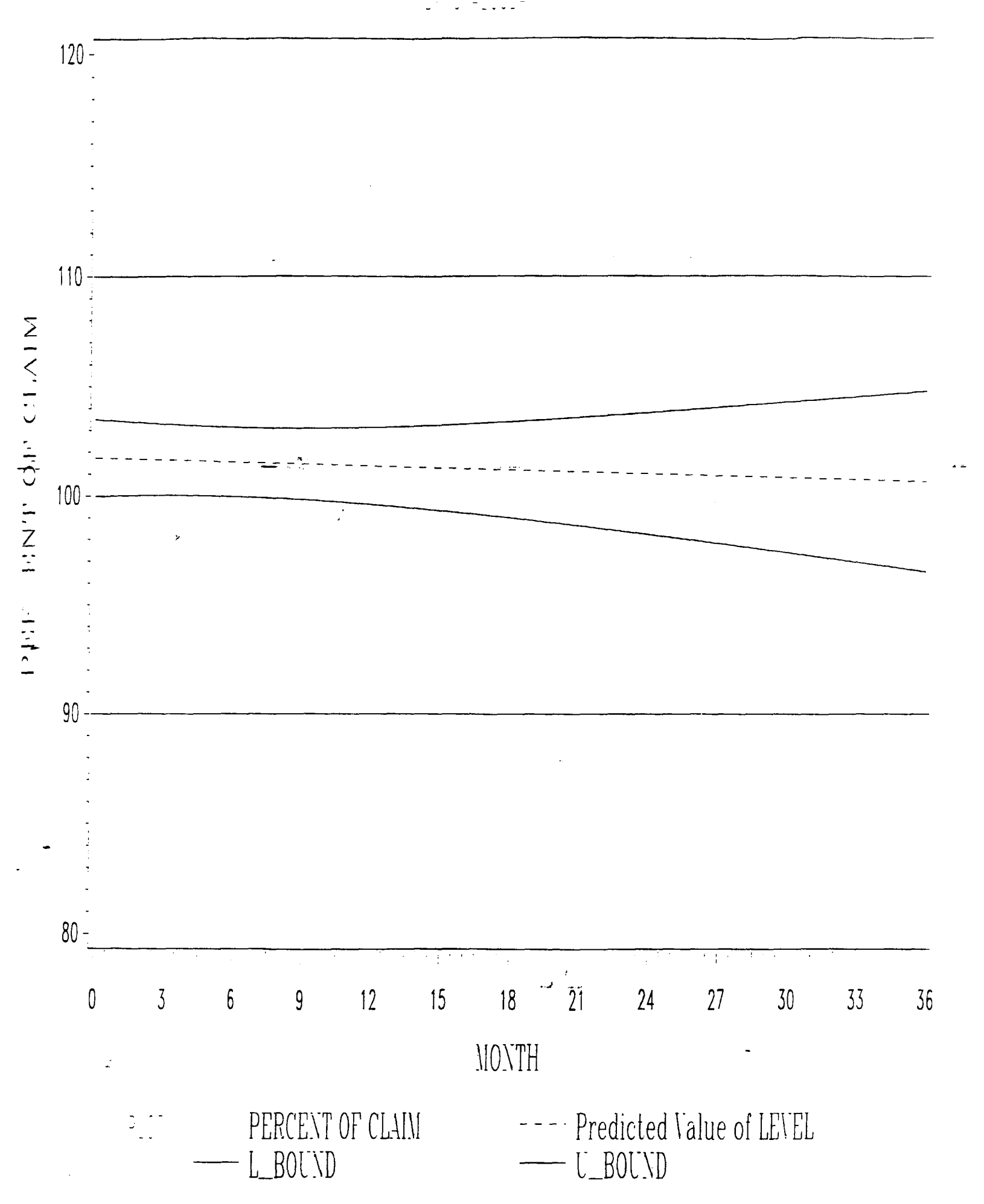
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Sponsor's Analyses

ATTACHMENTS #2

Tables 4-9
Figures 1-5

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9 pages

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-718 Date: **Dec. 29, 1997**

Applicant: COR Therapeutics, Inc..

Name of drug: Integrilin (intrifiban) Injection.

Documents reviewed: Documents dated 9/30/1997, 12/5/1997, and 12/18/97. Data on diskettes submitted by the sponsor.

I. Introduction: In this NDA Supplement, the firm has requested an expiry period of 18 months for Integrilin Injection 2.0 mg/mL and 0.75 mg/mL with a labeled storage condition at 25 °C.

In this stability study, the two types of Assay data (percent label strength and percent of initial) and Total Degradants for the two strengths (2.0 mg/mL and 0.75 mg/mL) were submitted by the sponsor on diskettes. Following a discussion with the reviewing chemist, Dr. Al-Hakim, this stability review is focused on the results from the Assay data of percent label strength and Total Degradants for both strengths: 2.0 mg/mL and 0.75 mg/mL.

II. Design

Number of Strength: 2;
Integrilin Injection 2.0 mg/mL and Integrilin Injection 0.75 mg/mL.

Number of package types:
One Package Type (named Package Type I) for each of the two strengths.

Tested Parameters for each strength:
Integrilin Assay and Total Degradants.

Temperature: 25 °C.

Specification limits:

Number of Lots for each strength: 5 lots for Integrilin Injection 2.0 mg/mL and lots for

Integrilin Injection 0.75 mg/mL.

Strength	Lot Number
Integrilin Injection 2.0 mg/mL	E0028A, H0048A, H0061A, H0062A, and K0069A.
Integrilin Injection 0.75 mg/mL	H0032A, H0049A, H0050A, H0051A, H0052A, H0064A, K0066A, and K0070A.

Sampling Times: For temperature at 25°C, the observation time points for each lot by strength are listed below.

Strength: Integrilin Injection 2.0 mg/mL

LOT ID.	Observed Time Points (Month)
E0028A	0, 3, 6, 9, 12, 18, 24, and 30.
H0048A	0, 1, 2, 3, 6, 9, 12, and 18.
H0061A	0, 3, 6, 9, 12, and 18.
H0062A	0, 3, 6, 9, 12, and 18.
K0069A	0, 3, 6, 9, and 12.

Strength: Integrilin Injection 0.75 mg/mL

LOT ID.	Observed Time Points (Month)
H0032A	0, 3, 6, 9, 12, 18, and 24.
H0049A	0, 1, 2, 3, 6, 9, 12, 18, and 24.
H0050A	0, 1, 2, 3, 6, 9, 12, and 18.
H0051A	0, 1, 2, 3, 6, 9, 12, and 18.
H0052A	0, 1, 2, 3, 6, 9, 12, and 18.
H0064A	0, 3, 6, 9, and 12.
K0066A	0, 3, 6, 9, and 12.
K0070A	0, 3, 6, 9, and 12.

III. Sponsor's and Reviewer's Analysis

III.a: Statistical Methods

The sponsor analyzed Total Degradant data using the SAS program developed by the Division of Biometrics, FDA for both strengths: 2.0 mg/mL and 0.75 mg/mL. The procedures consist of the following two steps.

Step 1: Model selection (Test for pooling of stability batch data).

An assessment is made as to whether or not the degradation curves, considering all individual batches separately, are similar. If the degradation curves are similar, it is desirable to pool the data in order to obtain more precise estimates of expiration dating periods. Batch similarity of the degradation curves is assessed by fitting linear regression models to the data, and applying statistical tests for equality of slopes and/or zero-time intercepts to these models. The following two conditions must be satisfied to allow such pooling of the data.

a) The test of the hypothesis that a model with separate intercepts and separate slopes (H_1) fits the data better than a model with separate intercepts and common slope (H_0) should have a p-value of 0.25 or greater, (equality of slopes) and,

b) The test of the hypothesis that a model with separate intercepts and the estimated common slope (H_1) fits the data better than a model with common intercept and common slope (H_0) should have a p-value of 0.25 or greater (equality of intercepts given parallel lines).

The rationale for using p-value of 0.25 for tests of this nature is presented in the paper of Bancroft "Analysis and inference for incompletely specified models involving the use of preliminary test of significance", Biometrics, pp. 427-442 (1964).

At the end of step 1, one of the following models is selected for the degradation model,

a) separate intercepts and separate slopes,
b) separate intercepts and common slope,
c) common intercept and common slope.

Step 2: Construction of the 95% lower, or 95% upper, or 95% two-sided confidence intervals for the mean degradation curve.

The 95% lower, or a 95% upper, or two-sided confidence intervals are constructed for the mean degradation curve based on model selected at step 1.

III.b: Acceptance criteria

In order to have an acceptable potency level of the assay under test, the 95% lower confidence bound should be above the lower specification limit and the 95% upper confidence bound should be below the upper specification limit when both upper and lower specification limits are required. However, if only one specification limit is needed, then either the 95% lower confidence bound should be above the lower specification limit or the 95% upper confidence bound should be below the upper specification limit.

III.c:Data analysis and results

This reviewer estimates the expiration dates by applying the SAS program developed by the Division of Biometrics, FDA to Assay data (Label Strength) submitted by the sponsor for both strengths: 2.0 mg/mL and 0.75 mg/mL. The expiration dates of the tested parameters with regard to Assay estimated by this reviewer and Total Degradants estimated by the sponsor for each of two strengths, are presented in Table 3.1 (below).

Table 3.1 Estimated Expiration Dates Of the Tested Parameters

Strength: Integrilin Injection 0.75 mg/mL

Tested Parameters	Estimated Expiration Date (Month)
Assay	29
Total Degradant	29

Strength: Integrilin Injection 2.0 mg/mL

Tested Parameters	Estimated Expiration Date (Month)
Assay	21
Total Degradant	27

IV. Reviewer's Summary

Based on the results of the stability analyses and the conservative principle, the expiration date for each of the two strengths is summarized in Table 4.1 (Below).

Table 4.1 (Reviewer's) The estimated expiration dates for the two strengths

Strength	Estimated Expiration Date (Month)
Integrilin Injection 0.75 mg/mL	29
Integrilin Injection 2.0 mg/mL	21

Table 4.1 indicates that the stability data collected from Package Type I stored at 25°C, submitted by the sponsor on data diskettes, support an expiration date of 18 months for both of the two strengths, Integrilin Injection 2.0 mg/mL and Integrilin Injection 0.75 mg/mL.

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Sankoh 12/29/97

Dr. Smith

cc: Original NDA# 20-718
HFD-180/Dr. Talarico
HFD-180/Dr. Al-Hakim
HFD-180/Ms. DuBeau
HFD-720/Dr. Smith
HFD-720/Dr. Sankoh
HFD-720/Dr. Chen
HFD-720 File Copy