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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-332

Statistical Review(s)

Statistical Review and Evaluation
Clinical Studies

NDA#: 21-332/Class 1-S

Applicant: Amylin Pharmaceuticals, Inc.

Name of Drug: Symlin Injection (pramlintide acetate)

Documents Reviewed: Vols 240-241, 242-243, 244-246, 255-257, 258-259, 260-262
dated 12/7/2000

Medical Officer: Robert Misbin, M.D., HFD-510

Key Words: clinical studies, NDA review, multiple comparisons

Background

The sponsor has submitted six Phase III trials testing the efficacy of Symlin for the lowering of HbA_{1C} in patients with Type I and Type II diabetes. Three (3) trials enrolled patients with Type I (Trial 112: 52 weeks, Trial 117: 26 weeks, and Trial 121:52 weeks) and the other 3 with Type II diabetes (Trial 111:52 weeks), Trial 122: 52 weeks, and Trial 123:26 weeks). In all trials, patients were instructed to follow their "usual regimen" for insulin therapy although, in practice, insulin dose varied over time in many patients.

The primary endpoint in all studies was either the absolute or relative change in $\%HbA_{1C}$ for the last week of the respective study. Although the primary method of analysis was two-way ANOVA, there were changes made to the original protocols with respect to multiple comparison procedures which were then stated in the final Statistical Analysis Plans (SAP's) of each study report. Sample size documentation is scant. The protocols state only that sample sizes were based upon a treatment effect of an absolute .5% difference in decrease of HbA_{1c} between an active group and placebo.

Figure 1 (trial 117 completers) **displays the typical profile of group mean decreases in HbA_{1C} over time in the trials.** There is an initial rapid response by 4 weeks and a subsequent maintenance of group response relative to placebo or a tendency for means to "creep" up towards the placebo level of response.

The following table displays the sponsor's analyses of the major results for the mean decreases in HbA_{1C} in each treatment group for all 6 trials for both the ITT LOCF data set and the Evaluable patient data set. The latter included only completers whose last observation fell into a pre-specified time window. The text table at the top indicates four typical multiple comparison procedures together with the "history" of the designated plan for each trial (right hand column).

For completeness, the series of letters following the p-value indicates the multiple comparison procedure(s), which would result in a statistically significant difference from placebo at the .05 level. (S) Stepdown refers to the plan wherein the highest dose is tested first at the .05 level, and other doses are tested only if the highest dose is significantly different from placebo. (**H**) refers to a plan, which orders all the p-values for tests versus placebo and then declares statistical significance for individual doses using a different criterion for each rank of the p-values. (**B**) refers to the standard Bonferroni correction in which each test versus control is conducted at the .05/n level where "n" is the number of tests being conducted. (**F**) Fisher's LSD is the procedure in which individual tests versus control are made only if the global null hypothesis of equality of all treatment groups is rejected at the .05 level.

In the table, it is important to note that the tabled number for the Placebo group is the mean change from baseline. ***However, the tabled number for the Symlin groups is NOT the mean change from baseline but the mean difference from Placebo (wrt change from baseline)***. The table is displayed this way so that one may visually ascertain whether Symlin's groups' differences from placebo are in any way related to the placebo response in each trial.

Summary of Changes in Multiple Comparison Procedures

S=Stepdown
H=Hochberg
B=Regular Bonferroni
F=Fisher's LSD

112:Not Applicable
117:Prot-Hochberg SAP-Stepdown
121:Dropped 90 TID, Prot-Hochberg SAP-Fisher's LSD
111:Prot-Hochberg SAP-Hochberg
122:Dropped 60 TID, Prot Hochberg SAP-Fisher's LSD
123:Prot-Stepdown SAP-Stepdown

TYPE I

112 (N=480)

	PBO	30 TID & 60TID
week26 ITT	-.21	-.34(**.0002**)
EVAL	-.18	-.41(**.0001**)
week52 ITT	-.15	-.23(**.01**)
EVAL	-.12	-.26(**.007**)

117 (N=586)

	PBO	90 BID	60 TID	90 TID
week26 ITT	.09	-.23(.053)	-.32 (.007)**HBF**	-.19(.123)
EVAL	.08	-.10(.472)	-.27(.04)	-.20(.161)

121 (N=651)

	PBO	60 TID	60 QID
week26 ITT	-.18	-.25(.012)**SHBF**	-.25 (.013)**SHBF**
EVAL	-.21	-.30(.019)	-.18(.15)
week52 ITT	-.04	-.27(.001)**SHBF**	-.35(.001)**SHBF**
EVAL	.05	-.41(.004)**SHBF**	-.35(.012)**SHBF**

TYPE II

111 (N=538)

	PBO	30 TID	75 TID	150 TID
week26 ITT	-.34	-.13(.36)	-.38 (.004)**SHBF**	-.35(.01)**SHBF**
EVAL	-.41	-.10(.50)	-.36(.017)**SHBF**	-.35(.027)**SF**
week52 ITT	-.13	-.19(.22)	-.33 (.028)**S**	-.41(.007)**SHBF**
EVAL	-.21	-.13(.48)	-.25(.17)	-.39(.039)**S**

122 (N=656)

	PBO	90 BID	120 BID
week26 ITT	-.32	-.21(.053)	-.34(.002)**SHBF**
EVAL	-.31	-.23(.084)	-.40(.003)**SHBF**
week52 ITT	-.30	-.09(.44)	-.33(.004)**SHBF**
EVAL	-.24	-.19(.21)	-.49(.001)**SHBF**

123 (N=499)

	PBO	90 BID	120 BID	90 TID
week26 ITT	-.06	-.24(.075)	-.30 (.029)	-.24(.073)
EVAL	-.07	-.19(.20)	-.29(.048)	-.24(.112)

Discussion

Trial 112's design differed from the others in that all patients were initially randomized to placebo or 30 TID. After 20 weeks, patients on 30 TID with less than a 1% change from baseline in HbA_{1C} were randomized to either 30 TID or 60 TID. The analysis pooled the two active arms in order to compare Symlin to placebo.

Dropout rates in the **Type I** trials were substantial, the vast majority due to adverse events. In trial 112, the proportions of patients dropping out were 30% in both the Symlin and placebo groups. In trial 117, the average dropout rate was 28% in the Symlin groups and 12% in the placebo group. In trial 121, the average dropout rate in the Symlin groups was 42% and 33% in the placebo group. Dropout rates in the **Type II** trials were comparable to those in **Type I**, but adverse events played less of role.

Examination of the table above indicates that role of dropouts had only a minor influence on the statistical results. One might anticipate that the elevated dropout rates in the Symlin groups would prevent patients from carrying forward "good" decreases from baseline, thus depressing the treatment differences from placebo. But that is not a consistent finding in the table. On the other hand, statistical significance may be hard to reach in the completer subgroups (EVAL in the table above) because the sample sizes have decreased. All in all, the general agreement of results between the EVAL and ITT analyses in the table mitigate inferential problems with regard to Symlin's comparison to placebo. One must simply recognize that approximately 70%-75% of subjects who initiate treatment will still be on treatment after 26 to 52 weeks.

Fasting Glucose

Although Symlin's effect is supposed to be on postprandial glucose, it was of some interest to examine whether or not the change in fasting glucose to the end of study followed a dose response relationship in each trial. The following table illustrates that there is no relationship at all in either Type I or Type II patients. There were no cases of nominally statistically significant differences between any treatment arms in any trial.

TYPE I

112

PBO	30 TID
1.3	-4.9

117

PBO	90 BID	60 TID		90 TID
-6.1	-7.6	9.0	14.9	

121

PBO	60 TID	60 QID	90 TID
3.0	-21.9	-15.4	5.4

TYPE II

111

PBO	30 TID	75 TID	150 TID
-0.3	-1.5	-8.3	5.7

122

PBO	90 BID	60 TID	120 BID
-16.5	-12.2	-8.2	-14.7

123

PBO	90 BID	120 BID	90 TID
-2.7	-4.1	-10.3	-9.4

Relation Between **Change in Weight** and **Change in HbA_{1C}**

This question can arise in two major contexts: 1) Is there a statistical correlation between subjects' changes in weight and their respective changes in HbA_{1C} ***within a treatment group*** and 2) Is there essentially the same "treatment difference" between the Symlin and placebo subgroups defined by those who lose weight and those whose weight stayed the same or increased? In order to approach the latter question, this reviewer defined the **two strata distinguished by subjects who lost weight and those whose weight stayed the same or increased**. Only subjects who completed the trial were used. The following table displays the results: (Loss=weight loss, Gain=weight gain, and tabled number is mean change in HbA_{1C})

TYPE I

	Trial 112		Trial 117		Trial 121	
	Loss	Gain	Loss	Gain	Loss	Gain
Placebo	+.15	-.24	+.28	-.07	+.07	+.04
Symlin	-.31	-.50	-.13	-.15	-.18	-.57

TYPE II

	Trial 111		Trial 122		Trial 123	
	Loss	Gain	Loss	Gain	Loss	Gain
Placebo	-.12	-.42	-.03	-.20	-.23	-.08
Symlin	-.70	-.94	-.61	-.77	-.44	-.23

Note that in each trial in **Type II** diabetes, the differences between placebo and the highest Symlin dose are similar in each 'change in weight' stratum, suggesting that differences from placebo are not due solely to weight loss in subjects who are assigned to Symlin. In **Type I** diabetes, the interaction between treatment and weight change stratum is only quantitative, not qualitative. In general, throughout the six trials, placebo subjects **gained** an average of between 0 and 1 kg while patients on Symlin **lost** an average of between 0 and 1.5 kg. This pattern is also reflected in the fact that the average percentage of evaluable placebo patients over all six studies who lost weight was 38% while the respective percentage was 64% in evaluable patients in the highest Symlin dose groups.

As to question 1, it was found that there is essentially no correlation (R^2 essentially zero) between changes in weight and HbA_{1C} in the Symlin treatment groups.

Durable Responders

In some trials, the sponsor has defined a "durable responder" as one whose HbA_{1C} decreased from baseline by .5% (absolute) by 4 weeks and who had a decrease of at least of .5% at the end of the trial. The charts referred to below were derived using **evaluable patients, i.e. essentially all those who finished the trial**. Thus, the percentage of durable responders in this analysis is slightly higher than those reported by the sponsor because the sponsor used all randomized patients (ITT data set) as the denominator when computing the proportions. **Figure 2** displays the percentage of durable responders in each treatment group in each Type I diabetes study, while **Figure 3** displays the average *decrease* in HbA_{1C} in each of the respective responder subgroups. **Figures 4** and **5** display the analogous results in Type II diabetes.

Severe Hypoglycemic Events

Patients with Type I diabetes experienced a substantial number of severe hypoglycemic events. **Table 1** displays the sponsor's tables of incidences of events for each treatment group in each trial. **Figures 6, 7,** and **8** display the sponsor's Kaplan-Meier plots for the trials. Note that the majority of events occurred in the first month of the trials. The logrank statistic for trial 112 produced a p-value of .16, the global logrank p-value for trial 117 was .008, and that for trial 121 was .123. The following table displays nominal p-values for separate tests of each treatment

group versus placebo (insulin, only in each trial). Using the generalized Wilcoxon test yields slightly lower p-values due to its sensitivity to departures from the null hypothesis which occur as a result of events occurring early in the trial.

	112	
	30 TID	
	.16	
	121	
60 TID	60 QID	90 TID
.03	.11	.03
	117	
90 BID	60 TID	90 TID
.007	.24	.003

Discussion

An overview of the statistical results indicates statistically significant results for both the all randomized patient (ITT) data set and those who completed the studies (essentially the "evaluable") data set in all studies except study 123. There were two trials in which an arm was dropped. No issue of Type I error arises in these cases since the decision to withdraw the arms from consideration derived from other studies. Study 122 dropped the 60 TID arm because of results in trial 123. In trial 121, the 90 TID arm was dropped due to results of the 90 TID arm in trial 117.

The "failure" of trial 117 was due to the failure of the 90 TID arm to achieve a p-value of less than .05 , thus not allowing the testing of other doses as a consequence of changing the multiple comparisons plan from the Hochberg to the stepdown procedure. One way to approach this problem is to evaluate the Type I error associated with the *union* of the two rejection regions of the two procedures. With two active groups and a placebo, the Type I error is .065 taking into account the correlation of the two treatment comparisons. With three comparisons to placebo, the Type I error would be slightly more, but would require evaluation of a triple integral which is not available. At any rate, it is plausible that a reasonable rejection region derived from the union of rejection regions would include the nominal p-value of .007 achieved by the 60TID arm in trial 117.Allowing these technicalities, it appears that the substantial issues do not lie in whether or not Symlin has shown to be statistically different from placebo (since it clearly is in multiple

trials). Rather, questions should focus upon whether the distributions of HbA_{1C} decrease from baseline are clinically useful, or more precisely, which doses provide sufficient percentages of patients who achieve clinically relevant decreases from baseline over a clinically relevant time period.

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cc:
NDA# 21-332
HFD-510
HFD-510/RMisbin, DOrloff, JRhee
HFD-715/TSalhroot, DHoberman,CAnello

Mean Change in HbA1C over Time

Trial 117

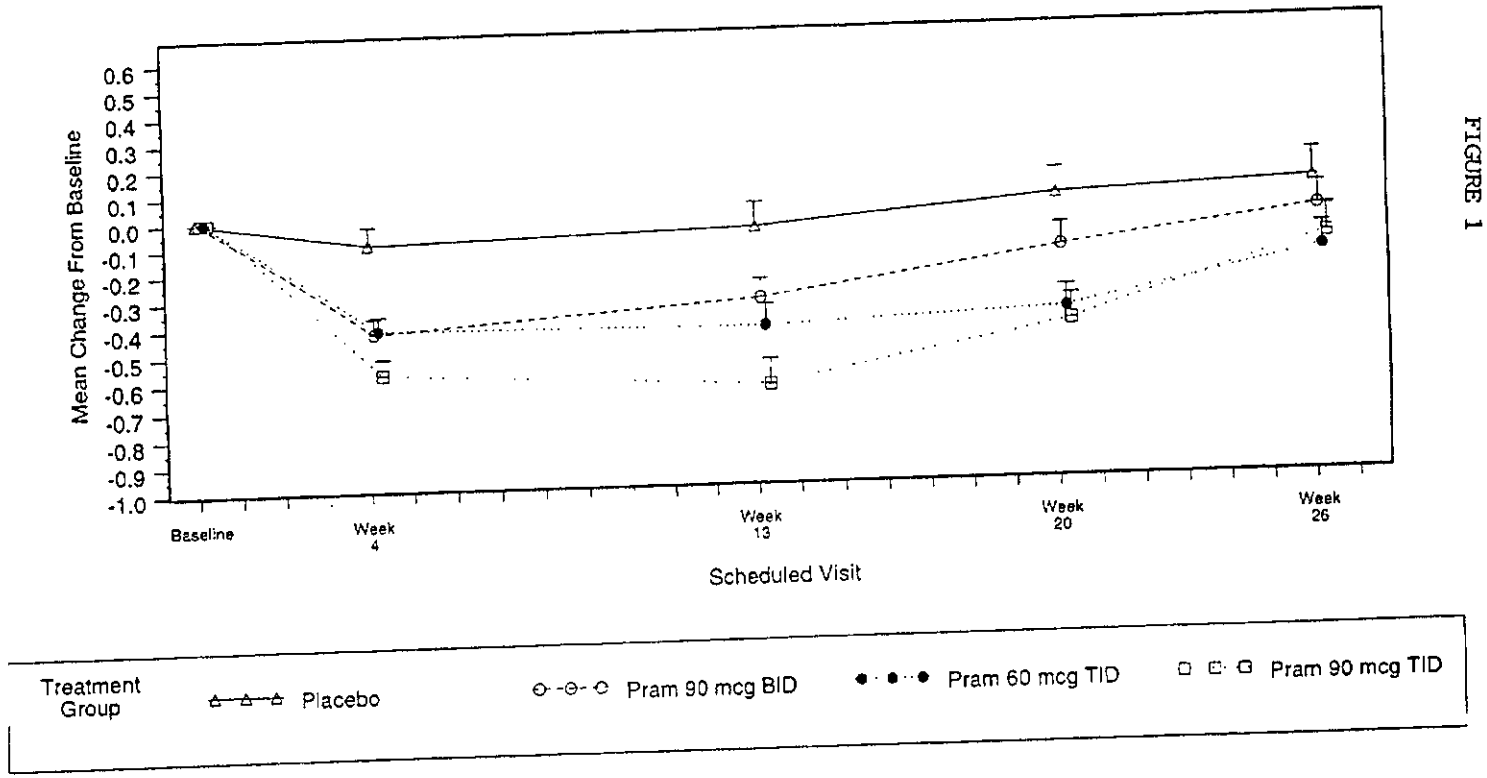


FIGURE 1

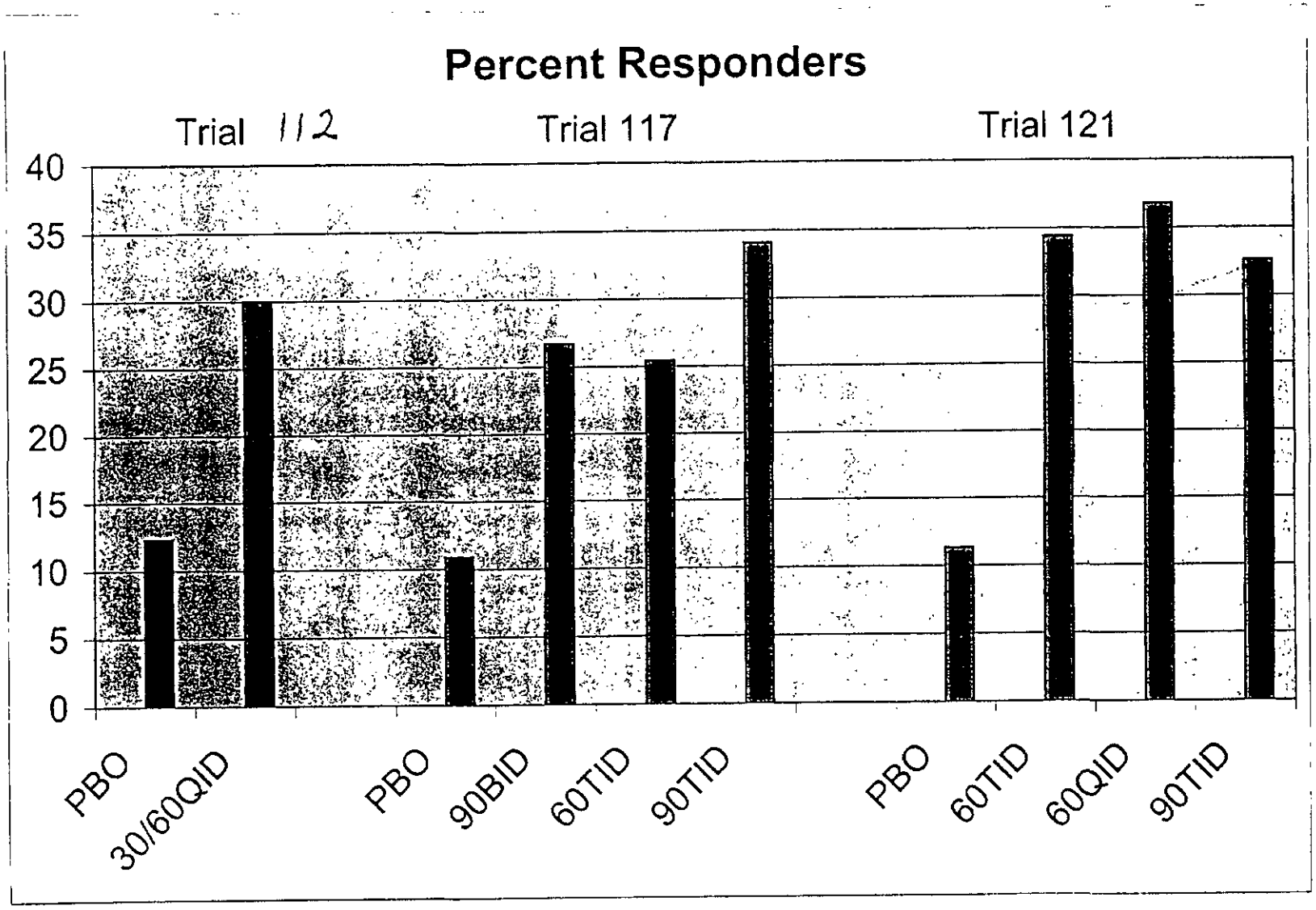

Percent Responders
Trial 112
Trial 117
Trial 121
40
35
30
25
20
15
10
5
0
PBO
30/60QID
PBO
90BID
60TID
90TID
PBO
60TID
60QID
90TID

FIGURE 2

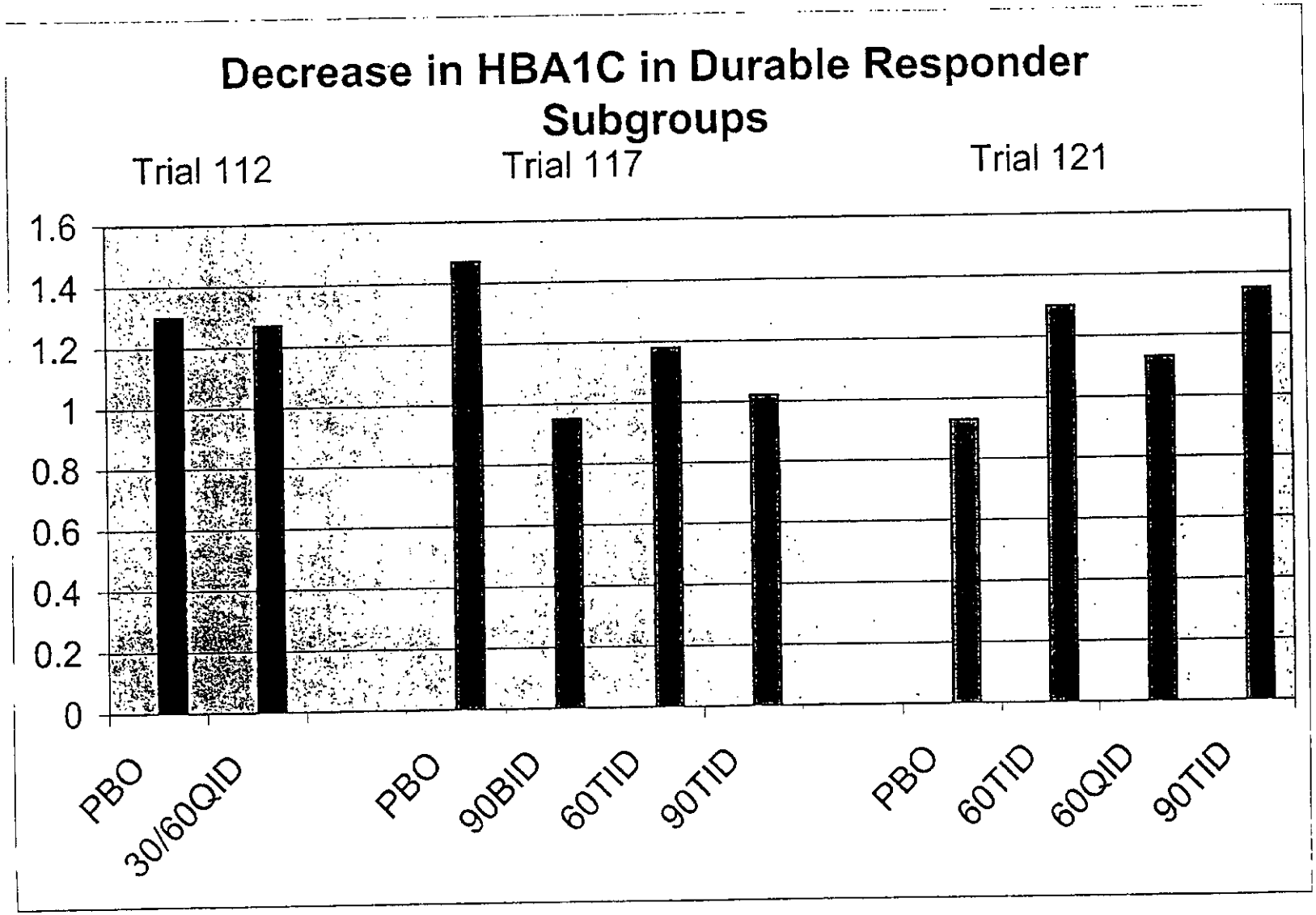

Decrease in HBA1C in Durable Responder Subgroups
Trial 112
Trial 117
Trial 121
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
PBO
30/60QID
PBO
90BID
60TID
90TID
PBO
60TID
60QID
90TID

FIGURE 3

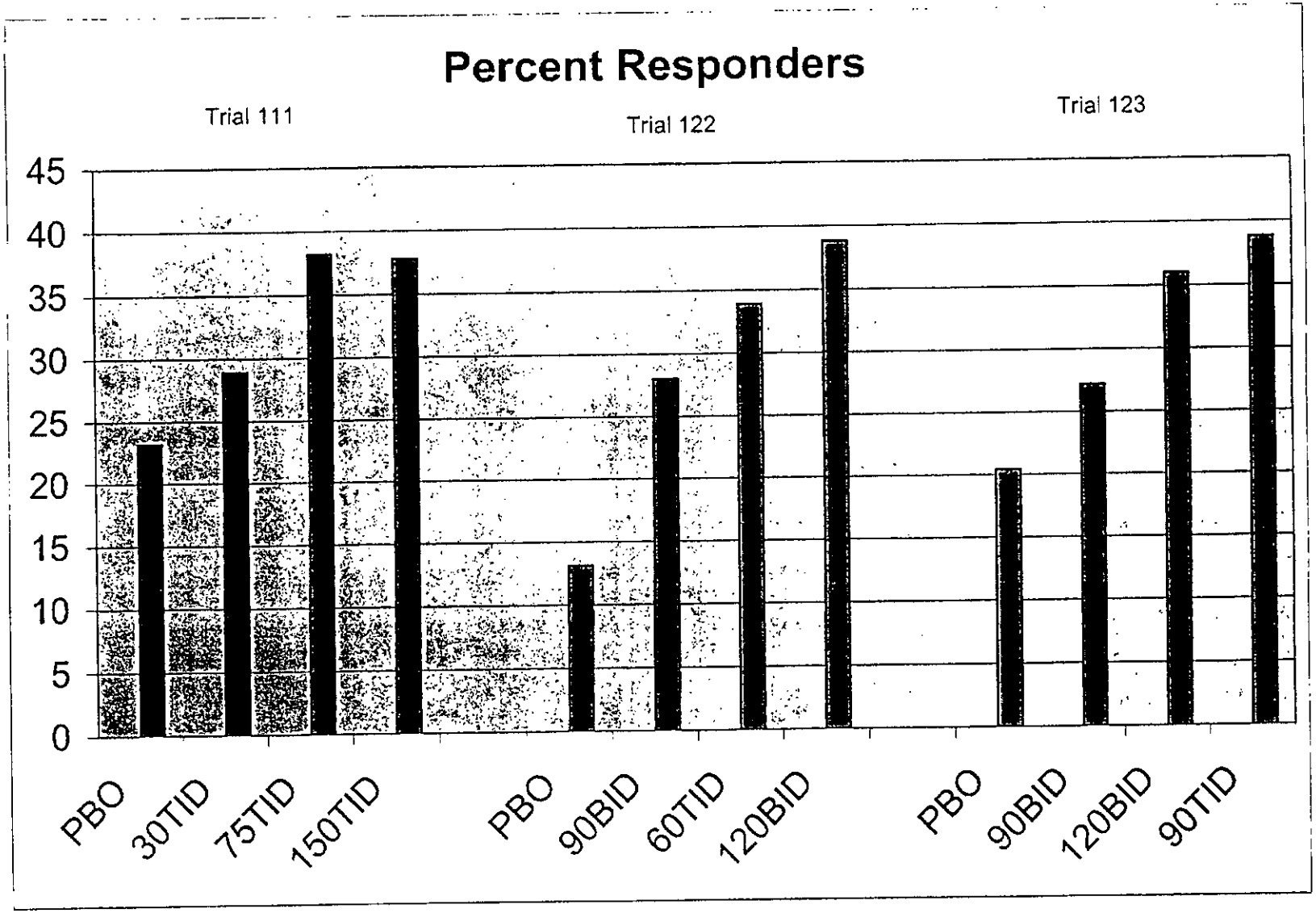

Percent Responders
Trial 111
Trial 122
Trial 123
45
40
35
30
25
20
15
10
5
0
PBO
30TID
75TID
150TID
PBO
90BID
60TID
120BID
PBO
90BID
120BID
90TID

FIGURE 4

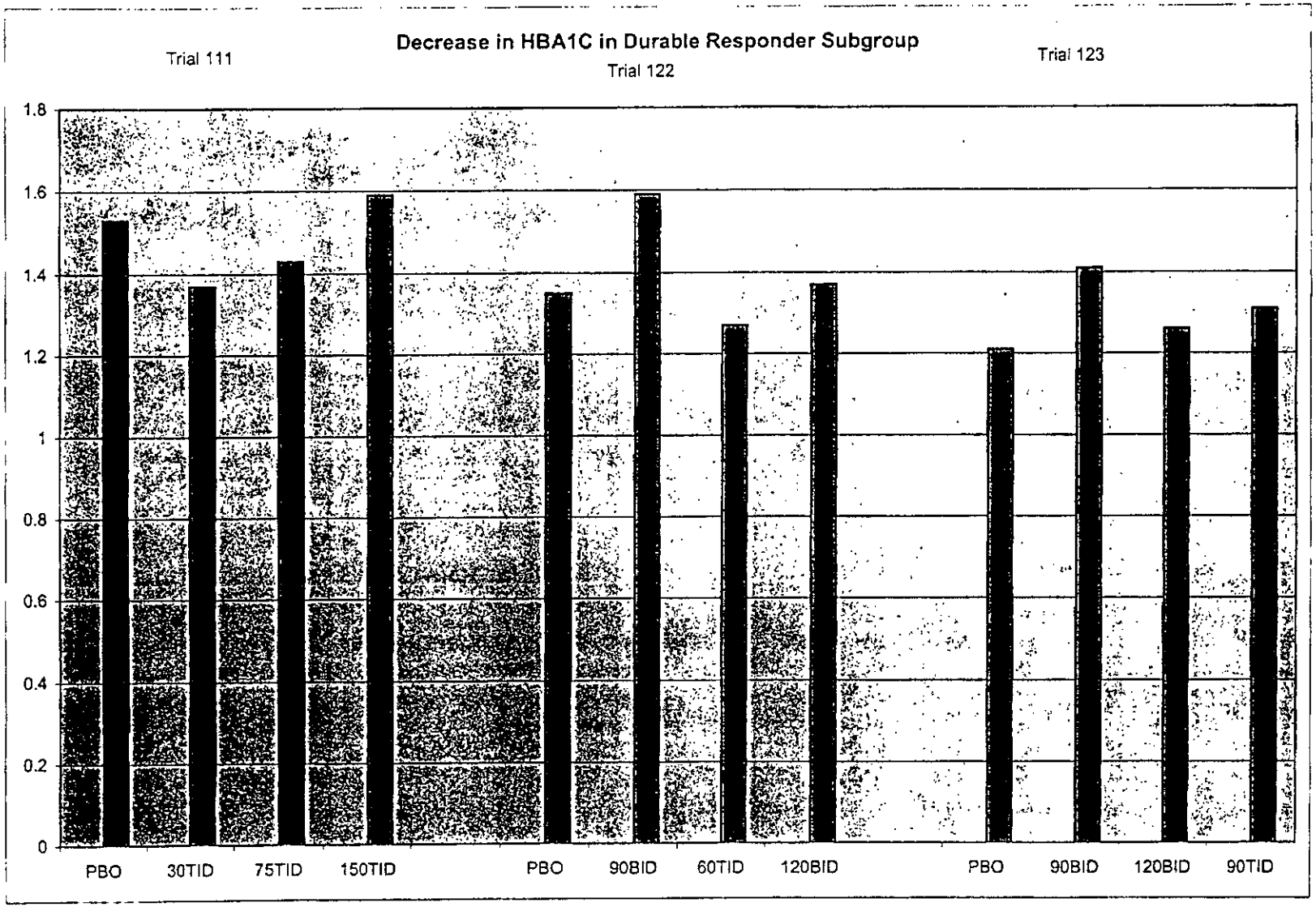

Decrease in HBA1C in Durable Responder Subgroup
Trial 111
Trial 122
Trial 123
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
PBO
30TID
75TID
150TID
PBO
90BID
60TID
120BID
PBO
90BID
120BID
90TID

FIGURE 5

TABLE 1

Trial 112

Kaplan-Meier Estimate of Severe Hypoglycemic Events: Survival Analysis
Population: Intent-to-Treat (N=480)

Variable	Treatment: Placebo (N=237)	Treatment: Pramlintide 30 µg (N=243)	p-value [1]
Subjects at Risk	237	243	0.1555
Subjects with Events	42	53	
Event Rate [2] (SE)	0.20 (0.03)	0.25 (0.03)	

1 Overall comparison of treatment groups using the log-rank test
2 The event rate is [1.0 - (Kaplan-Meier event-free rate at end of study)]
Note: 63 subjects receiving 30 µg pramlintide were re-randomized at week 20 to receive 60 µg pramlintide.

Trial 117

Proportion with Severe Hypoglycemic Events: Descriptive Statistics and Survival Analysis
(Population: Intent-to-Treat)
(Page 1 of 1)

Variable	Treatment Regimen: Placebo (N=147)	Pramlintide 90 µg QID (N=144)	Pramlintide 60 µg TID (N=148)	Pramlintide 90 µg TID (N=147)	p-value [1]
Subjects at Risk	147	144	148	147	0.0077
Subjects with Events	20	35	27	38	
Event Rate [2] (SE)	0.15 (0.030)	0.26 (0.038)	0.20 (0.034)	0.29 (0.040)	

[1] Overall comparison by using the log-rank test.
[2] The event rate is 1.0 - [Kaplan-Meier event-free rate at Week 26].

Trial 121

Proportion with Severe Hypoglycemic Events: Descriptive Statistics and Survival Analysis
(Population: Intent-to-Treat)
(Page 1 of 1)

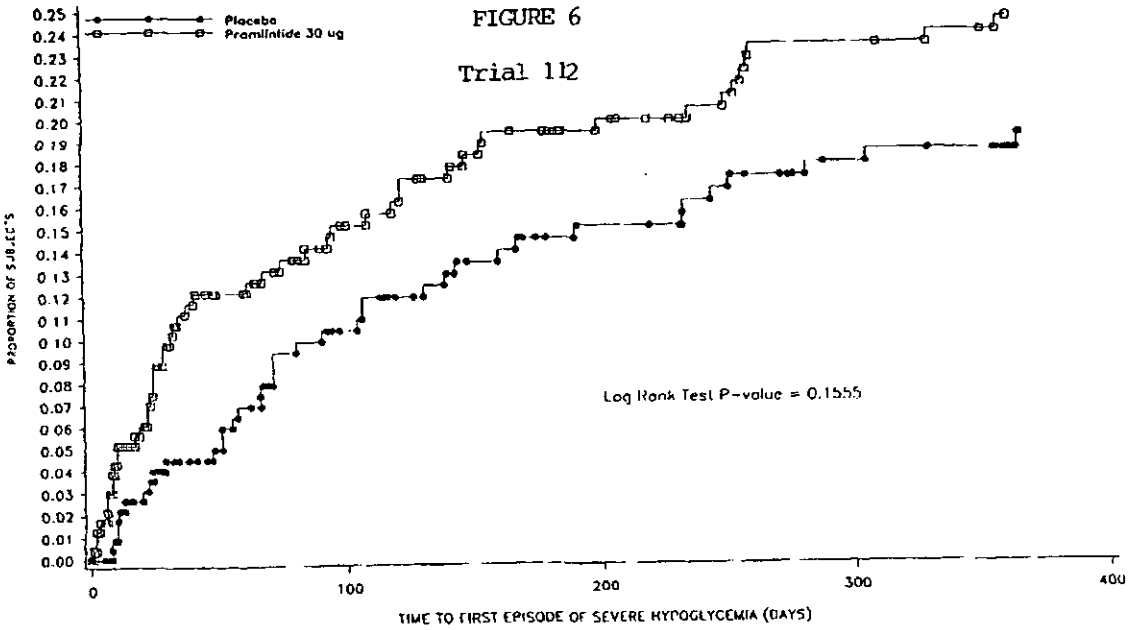
Variable	Treatment Regimen: Placebo (N=154)	Pramlintide 60 µg TID (N=164)	Pramlintide 60 µg QID (N=161)	Pramlintide 90 µg TID (N=172)
Subjects at Risk	154	164	161	172
Subjects with Events	34	49	45	49
Event Rate [1] (SE)	0.26 (0.039)	0.36 (0.042)	0.34 (0.042)	0.38 (0.045)

[1] The event rate is 1.0 - [Kaplan-Meier event-free rate at Week 26].

Kaplan–Meier Estimate of Proportion of Subjects with Severe Hypoglycemic Events
Population: Intent-to-Treat (N=480)

FIGURE 6

Trial 112



Note: 62 subjects receiving 30 ug pramlintide were re-randomized at week 20 to receive 60 ug pramlintide.

[redacted] Kaplan-Meier Estimate of Proportion With Severe Hypoglycemic Events
(Population: Intent-to-Treat)

FIGURE 7 (Trial 117)

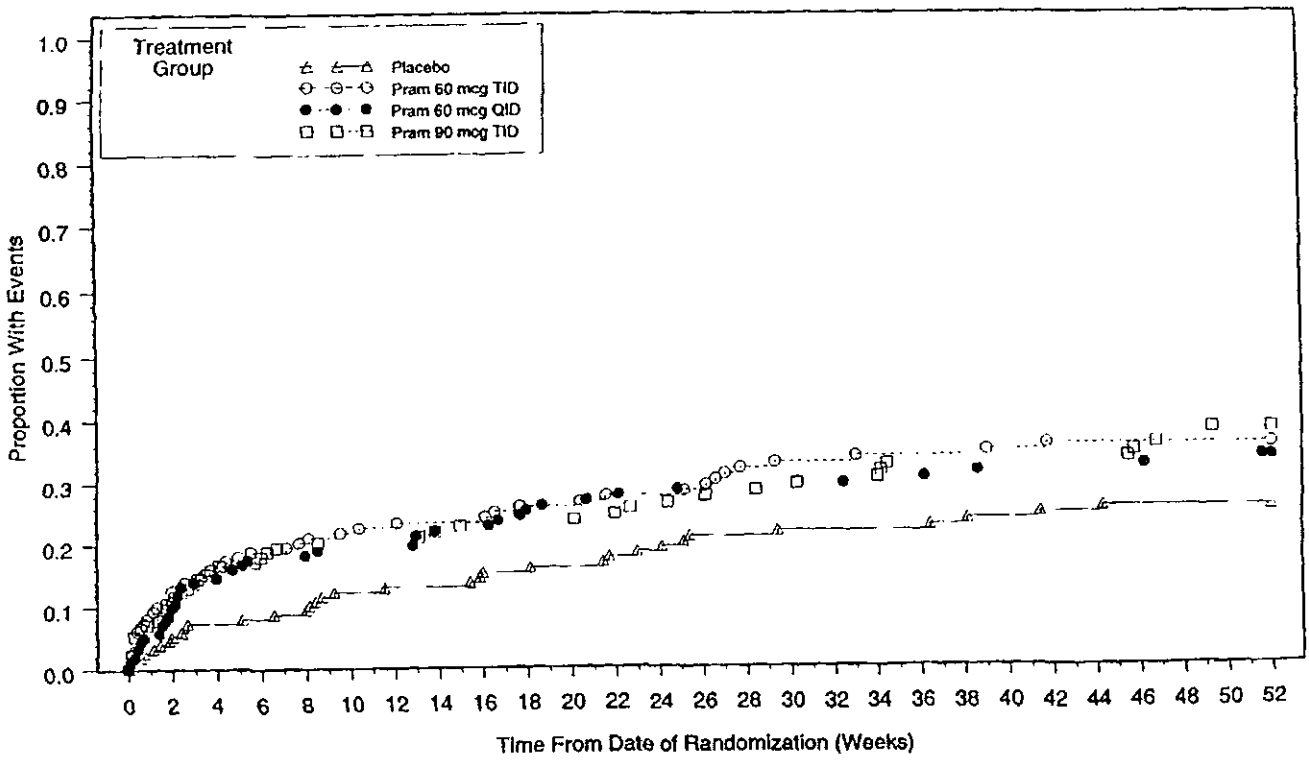
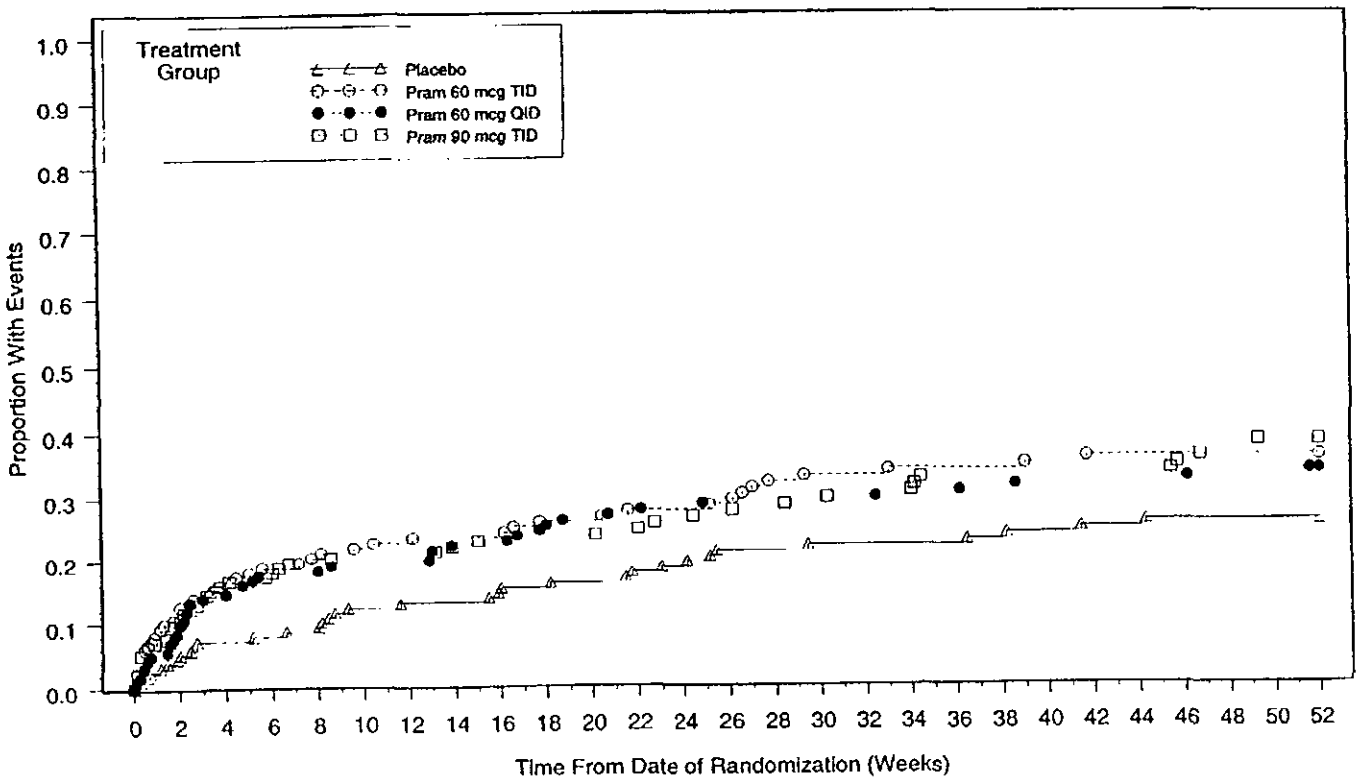


FIGURE 8

Trial 121

Figure of Kaplan-Meier Estimate of Proportion With Severe Hypoglycemic Events
(Population: Intent-to-Treat)



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