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A 4-month Randomized Controlled Clinical Trial of Adjuvant Exenatide or Pramlintide Versus Insulin Alone in Pediatric Type 1 Diabetes Mellitus: Effect on Glycemic Control

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A 4-month Randomized Controlled Clinical Trial of Adjuvant Exenatide or Pramlintide Versus Insulin Alone in Pediatric Type 1 Diabetes Mellitus: Effect on Glycemic Control

by

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This study investigates the effects of 16 weeks of treatment with adjuvant Exenatide or Pramlintide versus insulin alone on glycemic control, as measured by glycated hemoglobin (HbA1C) and 1,5-Anhydroglucitol (1,5-AG), or GlycoMark, in pediatric Type 1 Diabetes Mellitus (T1DM). We present here the preliminary results (n=24) of a Phase III randomized clinical trial designed to compare the glycemic effects of using adjuvant Pramlintide or Exenatide versus insulin alone in pediatric T1DM. Sample size calculations estimated 21 patients per treatment arm (63 total) are needed. So far, 24 patients have been recruited from Texas Children's Hospital's main Diabetes Care Center or its outlying clinics in the Houston, TX area. Recruited patients were randomized to one of 3 treatment arms (Pramlintide + insulin, Exenatide + insulin, or insulin alone) and completed 16 weeks of treatment. HbA1C and 1,5-AG levels were the primary endpoints analyzed as measures of glycemic control. All statistical analyses were

done using two-sample t-tests assuming equal variance and paired two-sample t-tests performed in Excel. No statistical differences in ΔHbA1C or Δ1,5-AG were observed between each treatment arm and the insulin control arm. Similarly, no statistical differences in HbA1C or 1,5-AG were reported within each group from baseline to 16 weeks. These preliminary data suggest that addition of Pramlintide or Exenatide to insulin regimen of pediatric T1DM does not improve glycemic control. However, reevaluation of the results upon study completion is warranted.

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CHAPTER 1: BACKGROUND AND SIGNIFICANCE

Type 1 Diabetes Mellitus (T1DM) most commonly occurs following auto-immune destruction of the pancreatic islet B-cells[1]. This destruction leads to total insulin deficiency and hyperglycemia. Approximately 150,000 children less than 20 years of age have diabetes and 15,000 new cases of T1DM occur each year in children less than 20 years[2]. Non-Hispanic white youth have the highest incidence rates of T1DM, estimated at 23.6 cases per 100,000 person years with a peak incidence of 32.9 in the 10-14 year-old age group[2,3].

Tight glycemic control prevents and/or delays the onset and progression of diabetic complications such as retinopathy, nephropathy, neuropathy, and cardiovascular events[4-6]. The Framingham Heart Study identified diabetes as an independent risk factor for cardiovascular events[7]. Postprandial glucose control, specifically, is linked to atherosclerosis[8-10]. Tighter postprandial control may potentially prevent or reverse atherosclerosis in patients with T2DM[11], although more studies are needed in order to draw this conclusion. Postprandial control is of particular interest in T1DM since exogenous insulin is unable to counter postprandial hyperglucagonemia. Therefore patients with diabetes have a paradoxical surge of glucagon, which stimulates hepatic release of glucose after meals[12]. This results in postprandial hyperglycemia as a result of both oral glucose absorption and hepatic glucose release. Postprandial hyperglycemia may be due to amylin deficiency and/or GLP-1 dysregulation.

Amylin is a naturally occurring endogenous hormone that is co-secreted with insulin from the pancreatic islet B-cells[17]. Since the B-cells are destroyed in T1DM, these patients are both insulin and amylin deficient. Pramlintide, an amylin analogue, exerts its

postprandial glucose control in diabetic patients by inhibiting paradoxical glucagon release[12] and by delaying gastric emptying[18,19] and thus absorption of glucose into the bloodstream.

Glucagon-like Peptide 1 (GLP-1) is a hormone secreted by the intestinal cells in response to a meal. GLP-1 exerts its anti-diabetic properties by stimulating glucose-dependent insulin secretion from the pancreatic B-cells, inhibiting glucagon secretion, and delaying gastric emptying and gastric acid secretion[20-22]. Individuals with T1DM have reduced levels of GLP-1 in response to a meal[23] and administration of Exenatide, a synthetic GLP-1 analogue, improved prandial glucose excursions[21]. Exenatide acts to reduce postprandial glucose surges via delayed gastric emptying, glucose-dependent glucagon suppression, and glucose-dependent insulin release[20] . Our research group has previously performed a dose-seeking study with adjunctive Exenatide in adolescents with T1DM, which determined safe and effective pediatric doses ranging from 1.25 mcg to 2.5 mcg per prandial injection[24].

Currently, the standard assessment of glycemic control is glycated hemoglobin (HbA1C). As the glucose concentration rises in the blood, some glucose becomes non-enzymatically attached to the B-chain of hemoglobin A molecules and remains attached for the lifetime of the red blood cell (RBC). Thus, HbA1C values are considered an estimate of glycemic control over the past 2 to 3 months[13,14]. Another test that is less commonly used in the U.S. to assess postprandial glycemic control is the 1,5-Anhydroglucitol (1,5-AG), or GlycoMark, test[15]. 1,5-AG is a monosaccharide normally maintained at steady plasma levels and is almost entirely reabsorbed by the renal tubules[16]. During episodes of hyperglycemia, in which the renal threshold for glucose is

passed (~180mg/dL), glucose competitively competes with 1,5-AG for reabsorption in the renal tubules[16]. This competitive inhibition of reabsorption leads to renal excretion of 1,5-AG. Serum levels of 1,5-AG, therefore, decrease as BG levels rise above ~180 mg/dL. This inverse relationship between plasma levels of 1,5-AG and hyperglycemia provides an additional measure of glycemic control that is more specific to postprandial glucose levels. In Dungan et al., 1,5-AG levels differed between individuals with similar HbA1C values and suggested that differences in postprandial glucose control may exist among individuals with similar HbA1C values[15-16]. While HbA1C correlated most closely with mean plasma glucose level, 1,5-AG levels correlated most closely with AUC>180 ($r=-0.49$, $p=0.002$) and with mean post-meal maximum glucose values ($r=-0.5$, $p=0.008$)[16]. This suggests that individuals with moderate glycemic control, as measured by HbA1C, may differ in their postprandial glucose excursions and these differences may be detected by 1,5-AG levels.

Pramlintide has been shown to improve postprandial glucose control in T1DM[25-28]. Likewise, the few studies which have examined the effects of GLP-1 or Exenatide on postprandial glucose control in T1DM have shown promising results[21,29,30]. Neither of these medications is approved in children, but studies have shown efficacy of Pramlintide in children with T1DM[31-34] and Exenatide shows promise in prolonging B-cell mass and/or function in T1DM. This may make islet cell transplantations a more viable option for newly diagnosed cases of T1DM in the future[35,36]. If used in children with T1DM, these medications can potentially prevent or mitigate future complications of diabetes. To our knowledge, the effectiveness of these two drugs has never been compared, especially in adolescents with T1DM. Our study's main objective was to determine the

effect of Exenatide vs. Pramlintide adjuvant therapy on glycemic control in addition to insulin in adolescents with T1DM.

CHAPTER 2: MATERIALS AND METHODS

Subjects

The experimental protocol for this study was approved by the Institutional Review Board at Baylor College of Medicine. We report preliminary data of a larger study, which is still ongoing. We studied 24 subjects with the following characteristics. Eligible patients were approached at the Diabetes Care Center and other outlying clinics affiliated with Texas Children's Hospital, and given a consent packet to review if interested. The parents of prospective patients signed a written, informed consent and all study patients gave assent prior to enrollment. For those screened for the study, written consent was either obtained when approached in clinic or at the screening visit.

Inclusion criteria:

- subjects aged 12-21 years
- willing to give assent
- antibody positive (anti-insulin Ab, anti-GAD Ab, and/or ICA-512 Ab) T1DM for at least 1 year
- HbA1C less than 9.0% at screening
- Tanner stage 3 or higher on physical exam by a physician at screening
- currently on intensive insulin therapy—consisting of basal-bolus therapy with a long-acting insulin plus 3 or more short-acting injections per day OR pump therapy

Exclusion Criteria:

- a diagnosis of T2DM

- any medications, other than insulin, known to affect glycemic excursions or glucose concentrations
- any chronic illness other T1DM and hypothyroidism stabilized on medication (Synthroid)
- abnormal amylase, lipase or creatinine values (twice normal) at screening
- abnormal AST or ALT values (thrice normal) at screening
- an unsupportive family environment, as determined by clinicians and/or social workers
- pregnant or lactating mothers

Participants were enrolled from August 2009 through January 2010. A total of 30 participants consented to the study; however 2 withdrew their consent prior to the screening visit. Of the 28 who completed screening visits, all qualified for the study and were randomized to a treatment arm: 10 to Pramlintide, 10 to Exenatide, and 8 to insulin alone. Randomization to one of three treatment arms was accomplished through use of a randomization table stratified by high or low BMI. The randomization table was not concealed from study staff. During the study a total of 4 participants either withdrew or were dropped from the study. In the Pramlintide arm, 2 participants withdrew from the study after Visit 1. One withdrew primarily due to family stress from divorce and also reported nausea as a side effect. The other withdrew mainly due nausea and also reported scheduling difficulties. In the Exenatide arm, 1 participant withdrew due to social issues and involvement with alcohol. Additionally, 1 participant was dropped from the Exenatide arm due to non-compliance with insulin adjustments and blood sugar checks. This left a total of 24 subjects (8 per treatment arm) who completed the study.

Study Design

Screening Visit: After signing a written consent form, a screening visit was performed in the GCRC (General Clinical Research Center) at Texas Children's Hospital in Houston, TX. All patients were fasting for at least 8 hours. This visit included a medical history and physical exam. Fasting blood samples were collected for screening labs, which included HbA1C, amylase, lipase, AST, ALT, CBC, creatinine, lipid panel, and diabetic autoantibodies (ICA-512, anti-GAD, or anti-insulin). Urinary microalbumin tests were performed on all subjects and urinary pregnancy tests were performed in all female subjects. Study staff inserted a blinded continuous glucose monitor (CGM) sensor for the patient to wear for 3 days. Patients were asked to record activity and dietary information in a food diary and to check their blood sugar at least 3 times per day during the 3 days on the sensor.

Visit 1: At this visit, subjects were randomized into one of three possible groups using a random number table. Subjects had vital signs taken, waist circumference measurement, HbA1C, 1,5-AG, and a urine pregnancy tests (if female). DEXA was performed on this day to estimate total body fat. QOL questionnaires were administered at this visit. Patients were given a home blood glucose meter and GlucoMon unit, which transmits blood sugar readings and delivers them electronically by email to the PI, study staff, and parents. Patients were given study medication if randomized to one of the 2 treatment groups and their prandial insulin was adjusted in order to prevent hypoglycemia with adjuvant study medication initiation.

Exenatide dosing: Exenatide was started at 1.25 mcg as determined by previous Baylor protocol H-16488, which found this dose to be safe in older adolescents with

T1DM[24]. Exenatide was given subcutaneously twice a day (within 30 minutes after the start of breakfast and dinner). Exenatide dose was titrated to a maximum dose of 5 mcg with most patients titrated to 2.5 mcg or 5 mcg bid.

Pramlintide dosing: Previous studies in older adolescents were performed at Baylor College of Medicine, Houston, TX and results from these studies were used to calculate Pramlintide dosing[33,34]. Pramlintide was started at 15 mcg and titrated up to a maximum dose of 60 mcg. Subjects received Pramlintide subcutaneously twice a day (within 30 minutes after the start of the breakfast and dinner).

Initially, prandial insulin was reduced by 30% with Exenatide and Pramlintide injections per personal communications with Dr. David Maggs, Amylin pharmaceuticals. Basal insulin was not changed at initiation of study medication. Study medication was not mixed with insulin injections or given within 2 inches of insulin injections or pump insertion sties. Whenever possible, study medication titrations were completed by Visit 2 (1 month). Basal and pre-meal insulin doses were adjusted throughout the study as needed based on blood sugar meter readings.

Insulin monotherapy: Subjects randomized to insulin monotherapy continued on either long-acting and short-acting insulin analogs or subcutaneous insulin pump therapy. Basal and pre-meal insulin doses were adjusted throughout the study as needed based on blood sugar meter readings.

Visit 2 (1 month): Subjects had vital signs, waist circumference, HbA1C, 1,5-AG, and a urine pregnancy test (if female). Adherence to insulin/medication regimen, side effects, and adverse event reporting was obtained by subject interview and logbooks.

Visit 3 (4 months): Subjects underwent a medical history, physical examination, vital signs, waist circumference, HbA1C, blood draws, urine microalbumin, and a urine pregnancy test (if female). Adherence to insulin/medication regimen and adverse event reporting was obtained by subject interview and logbooks. DEXA scans, and QOL questionnaires were repeated at this visit. Fasting amylase, lipase, AST, ALT, CBC, creatinine, and lipid panel labs were repeated at this visit. Study staff inserted a blinded continuous glucose monitor (CGM) sensor for the patient to wear for 3 days. Patients were asked to record activity and dietary information in a food diary and to check their blood sugar at least 3 times per day during the 3 days on the sensor. Subjects received instructions regarding how to properly remove the sensor at home. The subject was instructed to discontinue Pramlintide or Exenatide after removal of the sensor.

Adjustments with insulin regimen were made as needed based on glucose meter measurements. Data was reviewed daily for weeks 1 and 2, and then once a week for weeks 3 and 4. Starting at week 5, data was reviewed once every two weeks for the remainder of the study. Patients were permitted to contact study staff for guidance in insulin and study medication adjustments in between scheduled review times; however, parents were encouraged to make their own insulin changes in between scheduled review times.

Statistical Analysis

Using an estimated SD for ΔHbA1C in pediatric T1DM of 0.6, a sample size of 17 patients in each study arm (51 total) was calculated to detect a 0.6% ΔHbA1C from baseline with a power of 80%. Estimating an attrition rate of 20%, we calculated 21

patients in each study arm (63 total) would be needed. In this thesis we present preliminary data from the first half of the study (n=24 out of 30 recruited).

Primary endpoints in this study were glycated hemoglobin (HbA1C) and 1,5-Anhydroglucitol (1,5-AG), or GlycoMark. The final study will utilize ANCOVA analysis and pair-wise multiple comparisons; however, the preliminary data presented in this paper were analyzed with two-sample t-tests, assuming equal variances.

CHAPTER 3: RESULTS

Baseline Characteristics

Baseline study characteristics were not different between treatment arms with respect to age, gender, ethnicity, duration of diabetes, total daily insulin, and HbA1C (Table 1). The insulin control treatment arm had slightly lower HbA1C values at baseline, but was not statistically significant when compared to the Pramlintide and Exenatide treatment arms (p=0.60 and P=0.40, respectively). The groups did differ on number of individuals receiving multiple daily injections (MDI) versus those on continuous subcutaneous insulin infusion (CSII), or pump therapy. In our study group, it was noted that males were much more likely to be on pump therapy (15/16 or 94%) compared to females (2/8 or 25%), but gender differences were distributed equally among treatment arms. Two of the males on pump therapy also received injections at some point during the study. One male temporarily went on injections until pump malfunctions were resolved. The other male received daily injections of Lantus for extra basal insulin in addition to his pump therapy. During the study, one male patient in the insulin control arm permanently switched basal insulin from Lantus to Detemir as recommended by the study physician.

HbA1C

Baseline HbA1C values used for analyses were averages of screening and Visit 1 HbA1Cs. This was done to minimize effects on HbA1C between screening and Visit 1, prior to study medication initiation. There were no significant differences in ΔHbA1C

from baseline to 4 months between adjuvant Pramlintide or Exenatide to insulin alone (Table 2 and Graphs 1-3). Paired two-sample t-tests within each treatment arm also showed no significant difference in HbA1C values from baseline to 4 months. The slight increase in HbA1C in treatment arms may have resulted from initial reduction of prandial insulin to avoid hypoglycemia during study medication titration. Almost all titrations were completed by Visit 2 (4 weeks). However, no differences were detected when Visit 2 was analyzed as baseline compared to Visit 3. While the three months between Visit 2 and Visit 3 may have been a sufficient duration to detect changes in HbA1C following titration, more time and/or more subjects might be necessary to detect a statistical difference. Of note, the sample sizes presented in this preliminary data do not have the power to detect a difference.

1,5-AG (Glycomark)

No significant differences in Δ1,5-AG levels between adjuvant Pramlintide or Exenatide and insulin alone were present (Table 3 and Graphs 4-6). Paired two-sample t-test within each treatment groups also showed no statistically significant changes from baseline to 4 months. Exenatide and insulin treatment groups showed slight trends towards improved 1,5-AG values, while Pramlintide showed a slight trend towards worsened 1,5-AG values. However, one cannot draw any conclusions from these results as the sample sizes are small and the variances were large in relation to detected differences. It was noted that our results correlated closely with 1,5-AG values in a previous study involving pediatric individuals with T1DM[37].

All statistical analyses were done on a per protocol basis. Had statistically significant differences been detected based on per protocol data, intent to treat analyses would have been performed to see if results were affected. Intent to treat analyses are planned for completed study data.

Daily Insulin Doses

It is important to note that insulin was initially reduced in the two treatment arms in order to prevent hypoglycemia in the postprandial period. There were no statistical differences in changes in total daily insulin (TDI) and bolus daily insulin (BDI) between treatment groups compared to insulin alone (Tables 4-5). However, the Pramlintide group showed a trend toward reduced total daily insulin over the 4 months of treatment compared to the increased trend in total daily insulin in the Exenatide and Insulin groups. Similarly, the Pramlintide group showed a trend toward reduced bolus daily insulin, while the Exenatide group showed a smaller decrease in bolus daily insulin. The insulin group showed a trend toward increased bolus daily insulin throughout the study. These trend differences could explain the differences in glycemic control between groups. In particular, these differences in insulin trends could explain Pramlintide's worsened trends in both HbA1C and 1,5-AG.

CHAPTER 4: DISCUSSION

The data collected and analyzed to date suggest that 4 months of Pramlintide or Exenatide treatment in addition to insulin does not improve overall glucose control, as measured by HbA1C, compared to insulin alone. Although this effect was not significant, sample size calculations based on these data suggest that with the addition of 134 subjects per treatment arm, statistical significance could be achieved. In contrast to our hypothesis, the effects of the amylin analogue Pramlintide appeared to worsen postprandial glucose control as measured by 1,5-AG. On the other hand, the GLP-1 analogue Exenatide appears to have no noticeable effect on postprandial control, as measured by 1,5-AG, compared to insulin alone. Although this effect was not significant, sample size calculations based on these data suggest that with the addition of 62 subjects per treatment arm we will be able to achieve statistical significance between Pramlintide and insulin groups. However, it would take approximately an additional 7000 individuals to detect a difference between Exenatide and insulin groups based on these data.

An important point to mention, however, is that in the Pramlintide and Exenatide groups the subjects received less insulin during the early stages of this study. This reduction in insulin dose, performed to prevent possible hypoglycemia in the postprandial period, might have affected not only overall glucose control, but also postprandial glucose control. It was in fact the pre-meal short-acting insulin bolus that was reduced. Further analysis of CGMS data is necessary to ascertain whether 1,5-AG accurately portrayed postprandial control. CGMS data might also detect changes in postprandial

control that may not have been detected by 1,5-AG either due to time restraints or secondary to the initial reduction in pre-meal insulin.

The difference between the effects of Pramlintide and Exenatide on the direction of the change in 1,5-AG may be due to the fact that Exenatide can exert a stimulatory effect on residual pancreatic β-cell insulin secretion, while Pramlintide does not influence insulin secretion. Yet, since the changes are very small, it is also possible that these two drugs have no meaningful effect in T1DM.

In conclusion, our preliminary data indicate that adequate insulin therapy is the fundamental means for good glucose control in T1DM and suggest that adjuvant therapies with amylin or GLP-1 analogues do not enhance postprandial glucose control in these patients. However, completion of this study and possibly future clinical trials with longer observation periods are warranted.

Table 1: Baseline Study Characteristics

	Pramlintide	Exenatide	Insulin
n	8	8	8
Age **mean ± SD** **(range)**	 15.0 ± 2.3 (12.6-18.2)	 15.4 ± 2.0 (13.3-19.0)	 14.6 ± 1.8 (12.8-17.7)
Gender (F/M)	3/5	2/6	3/5
Ethnicity **(C/H/B)**	 7/0/1	 7/0/1	 6/1/1
Duration T1DM **mean ± SD** **(range)**	 5.0 ± 3.0 (1.6-11.8)	 4.8 ± 3.5 (1.5-12.7)	 6.1 ± 4.0 (1.0-13.4)
IIM Treatment **(MDI/pump)**	 3/5	 0/8	 4/4
HbA1C screen **mean ± SD** **(range)**	 7.4% ± 0.7 (6.4-8.5)	 7.5% ± 0.8 (6.5-8.8)	 7.2% ± 0.8 (5.9-8.1)
Total Daily Insulin (units/kg) **Visit 1** **mean ± SD** **(range)**	 1.04 ± 0.35 (0.53-1.69)	 1.05 ± 0.32 (0.65-1.52)	 0.98 ± 0.30 (0.52-1.54)
BMI **(<95%, >95%)**	 6/2	 7/1	 7/1

Table 2: HbA1C Results

	Pramlintide	Exenatide	Insulin
HbA1C screening			
mean ± SD	7.4% ± 0.7	7.5% ± 0.8	7.2% ± 0.8
(range)	(6.4-8.5)	(6.5-8.8)	(5.9-8.1)
HbA1C Visit 1 (V1)			
mean ± SD	7.4% ± 0.9	7.5% ± 0.7	7.2% ± 0.9
(range)	(5.9-8.3)	(6.8-8.7)	(5.9-8.1)
HbA1C Visit 3 (V3)			
mean ± SD	7.6% ± 0.8	7.7% ± 1.0	7.2% ± 0.7
(range)	(6.2-8.7)	(6.2-9.1)	(6.3-8.0)
ΔHbA1C base to V3			
mean ± SD	0.2 ± 0.5	0.2 ± 0.6	-0.0 ± 0.4
(range)	(-0.75 to 0.9)	(-0.6 to 0.8)	(-0.55 to 0.5)
p-value *	p=0.41 (two-tailed)	p=0.41 (two-tailed)	
LSN per arm**	99	142	

*p-value of ΔHbA1C comparison between treatment group and insulin control group

**LSN=least significant number (sample size needed to detect statistical difference between treatment and control based on these data)

Table 3: 1,5-AG (Glycomark) Results

	Pramlintide	Exenatide	Insulin
1,5-AG Visit 1 (V1)			
mean ± SD	4.0% ± 1.7	4.2% ± 2.3	5.5% ± 3.0
(range)	(2.5-8.0)	(2.1-9.3)	(2.6-10.4)
1,5-AG Visit 3 (V3)			
mean ± SD	3.5% ± 1.3	4.5% ± 3.3	6.0% ± 3.3
(range)	(1.4-4.9)	(2.4-12.2)	(2.0-11.7)
Δ1,5-AG V1 to V3			
mean ± SD	-0.5 ± 1.5	0.4 ± 1.6	0.5 ± 2.1
p-value *	p=0.29 (two-tailed)	p=0.87 (two-tailed)	
LSN per arm**	70	6924	

*p-value of Δ1,5-AG comparison between treatment group and insulin control group

**LSN=least significant number (sample size needed to detect statistical difference between treatment and control based on these data)

Table 4: Total Daily Insulin (TDI) Results

	Pramlintide	Exenatide	Insulin
TDI Visit 1 (V1)			
mean ± SD	1.04 ± 0.35	1.05 ± 0.32	0.98 ± 0.30
(range)	(0.53-1.69)	(0.65-1.52)	(0.52-1.54)
TDI Visit 2 (V2)			
mean ± SD	1.02 ± 0.33	1.08 ± 0.30	0.99 ± 0.25
(range)	(0.57-1.47)	(0.65-1.62)	(0.63-1.35)
TDI Visit 3 (V3)			
mean ± SD	1.02 ± 0.31	1.12 ± 3.1	1.1 ± 0.40
(range)	(0.57-1.47)	(0.67-1.54)	(0.57-1.50)
ΔTDI V1 to V3			
mean ± SD	-0.01 ± 0.15	0.07 ± 0.21	0.12 ± 0.24
p-value *	p=0.21 (two-tailed)	p=0.69 (two-tailed)	

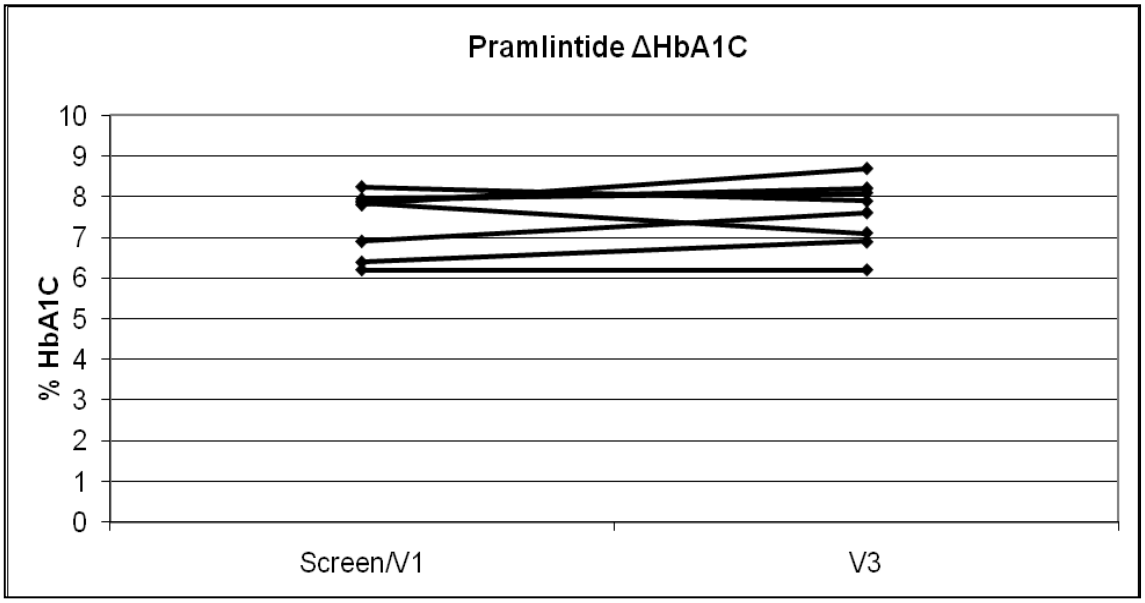
*p-value of ΔTDI comparison between treatment group and insulin control group

Table 5: Bolus Daily Insulin (BDI) Results

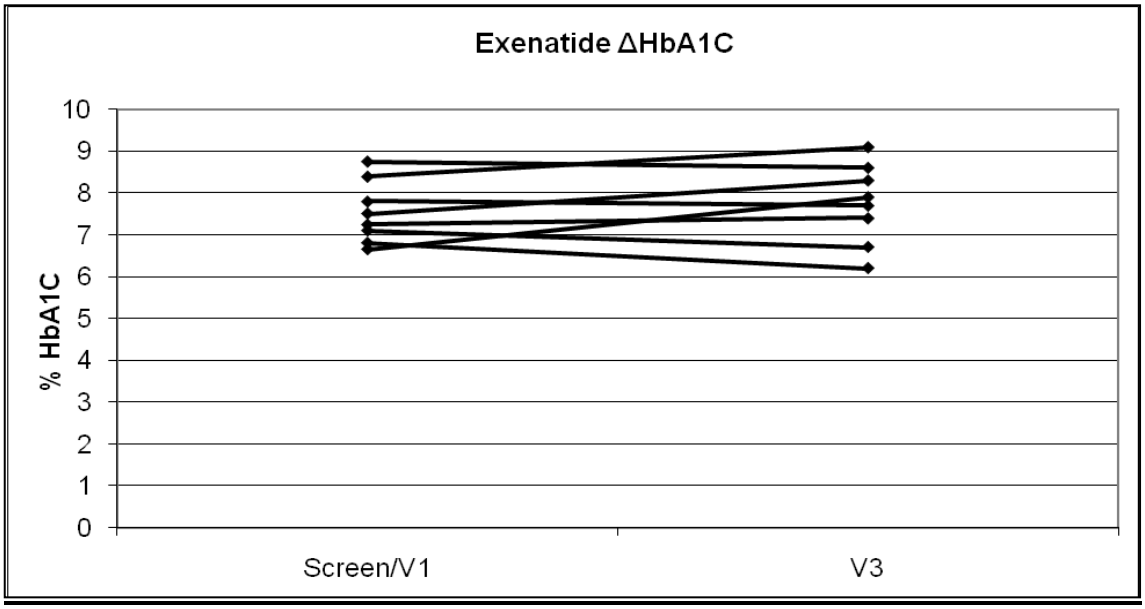
	Pramlintide	Exenatide	Insulin
BDI Visit 1 (V1)			
mean ± SD	0.42 ± 0.15	0.53 ± 0.28	0.47 ± 0.19
(range)	(0.18-0.57)	(0.21-1.00)	(0.26-0.69)
BDI Visit 2 (V2)			
mean ± SD	0.40 ± 0.19	0.53 ± 0.28	0.50 ± 0.25
(range)	(0.18-0.83)	(0.10-0.90)	(0.25-0.90)
BDI Visit 3 (V3)			
mean ± SD	0.38 ± 0.13	0.52 ± 0.32	0.52 ± 0.32
(range)	(0.22-0.60)	(0.09-0.92)	(0.19-1.03)
ΔBDI V1 to V3			
mean ± SD	-0.04 ± 0.14	-0.02 ± 0.19	0.05 ± 0.21
p-value *	p=0.34 (two-tailed)	p=0.51 (two-tailed)	

*p-value of ΔBDI comparison between treatment group and insulin control group

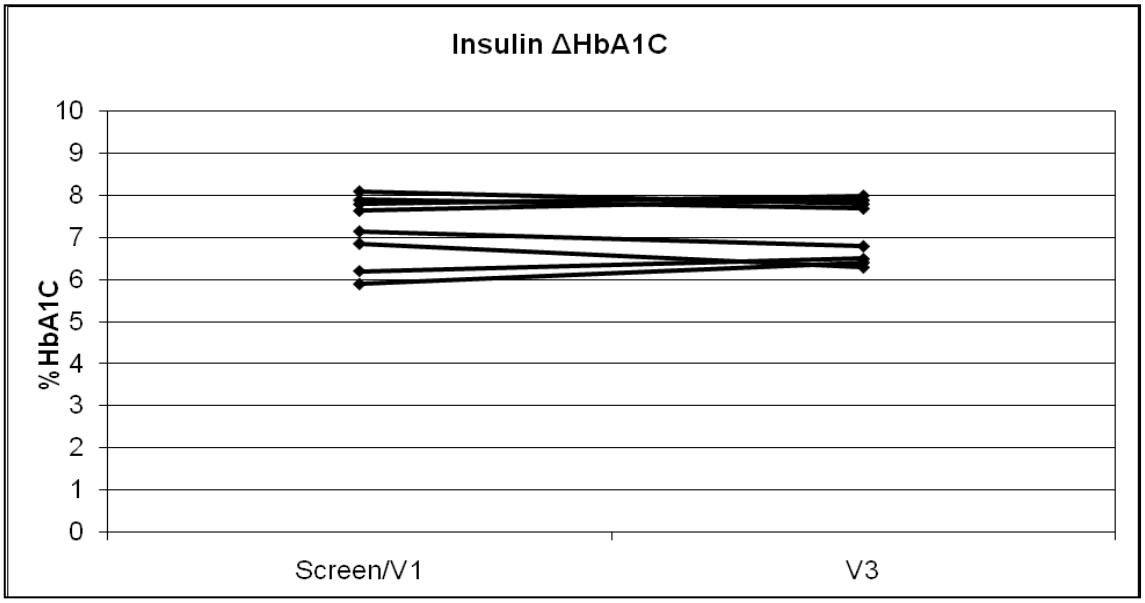
Graph 1: Pramlintide ΔHbA1C from baseline to V3



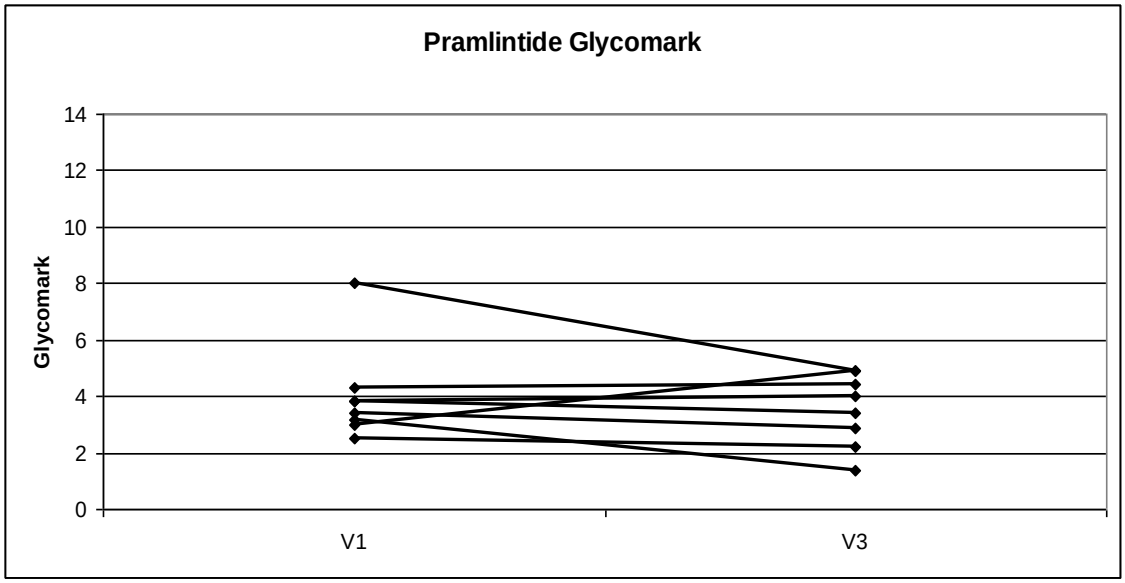
Graph 2: Exenatide ΔHbA1C from baseline to V3



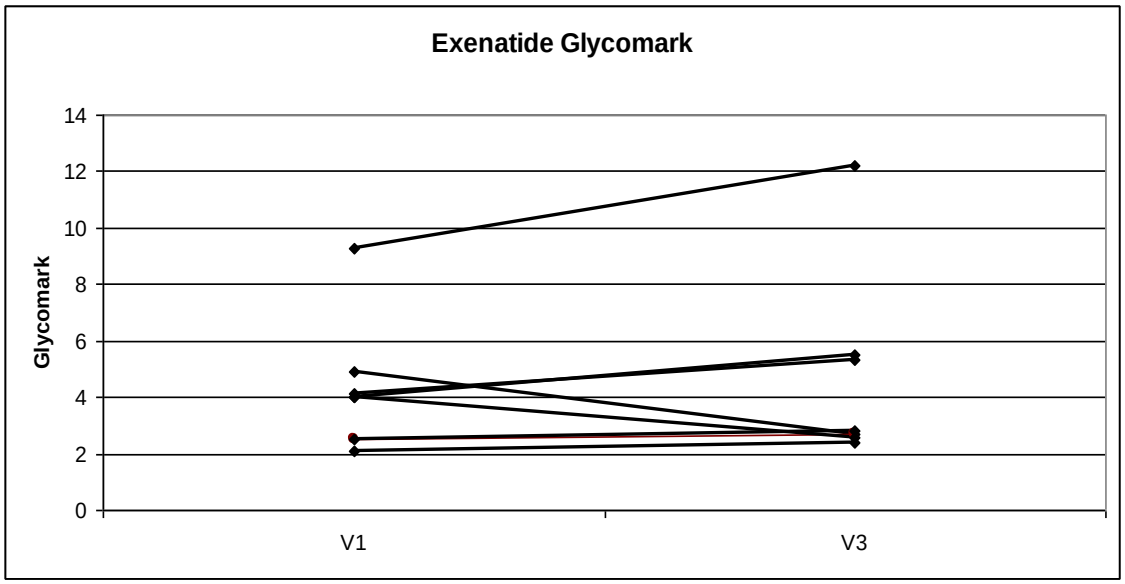
Graph 3: Insulin ΔHbA1C from baseline to V3



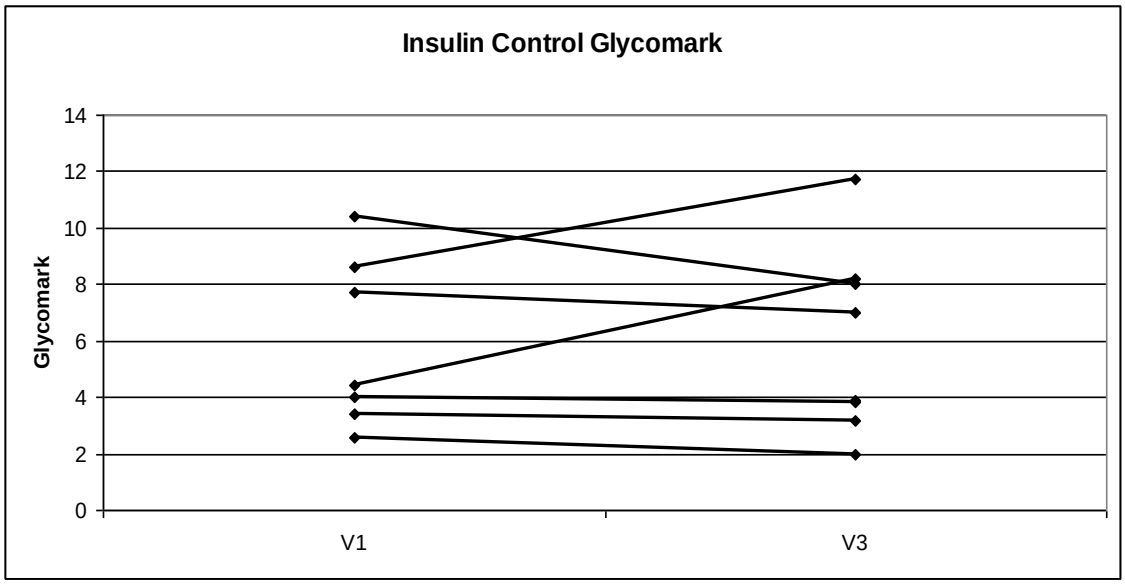
Graph 4: Pramlintide Δ1,5-AG (Glycomark) from V1 to V3



Graph 5: Exenatide Δ1,5-AG (Glycomark) from V1 to V3:



Graph 6: Insulin Δ1,5-AG (Glycomark) from V1 to V3



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Vita

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