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Exenatide ER in patients with Type 1 diabetes with and without residual insulin production

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Abstract

Background: Glucagon-like peptide-1 receptor agonists (GLP1RA) have activity that may benefit patients with Type 1 diabetes (T1D). Studies of GLP1RAs in T1D had mixed outcomes possibly because their effects in patients with residual insulin production were not been specifically addressed.

Methods: We performed a randomized placebo controlled trial of exenatide ER in participants with T1D with and without detectable levels of C-peptide. Seventy-nine participants were randomized to exenatide ER 2 mcg weekly or placebo, stratified by the presence or absence of detectable C-peptide levels. The primary outcome was the difference in HbA1c levels at 24 weeks. Participants were followed for another 6 months off study drug.

Results: At week 24, the time of the primary outcome, the HbA1c level was (LS mean (95% CI)) 7.76%(7.42, 8.10) vs. 8.0% (7.64, 8.35) in the drug vs placebo treatment groups (p=0.08). At week12 the HbA1c levels were(exenatide ER: 7.71% (7.37, 8.05) vs placebo: 8.05% (7.7, 8.4))(p=0.01)).The improvement at week 12 was driven mainly by those with detectable levels of C-peptide. Those treated with exenatide ER lost weight at 12 and 24 weeks compared to placebo ($p<0.001$ and $p=0.007$). The total dose of insulin was lower, but not when corrected for body weight, and was not affected by residual insulin production. Adverse events were more frequent with exenatide ER, but hypoglycemia was not increased.

Conclusion: Treatment with exenatide ER may have short-term benefits in some individuals with T1D who are overweight or with detectable levels of C-peptide, but short term improvements were not sustained. ClinicalTrials.gov: NCT01928329

Introduction

Glucagon-like peptide1 receptor agonists (GLP1RA) have become widely used for treatment of Type 2 diabetes[1-4]. Their metabolic actions involve augmenting glucose stimulated insulin release, inhibition of glucagon secretion, and slowed gastric emptying. The drug class has been found to have additional therapeutic benefits such as weight loss and reduced major cardiovascular disease events in several large randomized controlled trials[5].

The metabolic properties of these agents might also be of value for patients with Type 1 diabetes (T1D) particularly those with residual insulin production. Many patients, even those with long standing T1D, may have detectable levels of C-peptide well beyond the new onset period[6,7]. Tropic effects of exendin-4 on β cells were shown in rodents after partial pancreatectomy, and synergy with immune therapy at the time of diabetes onset enhanced insulin content of β cells[8,9]. Data from human studies have identified impaired function of residual β cells in patients with T1D, thus further supporting a potential use of GLP1RAs in these patients[10].

However, the results from previous clinical trials of GLP1RA in patients with T1D were inconclusive. Sarkar et al reported that exenatide treatment given 4x daily for 6 months in adults with T1D improved insulin sensitivity, assessed by hyperinsulinemic-euglycemic clamp, and reduced postprandial glucose levels, although fasting glucose levels were increased[11]. In the ADJUNCT ONE study, liraglutide, administered once daily at 3 dosing levels, added to insulin therapy in patients with T1D reduced HbA1c levels, total daily insulin dose and body weight but

increased the rates of hypoglycemia and hyperglycemia with ketosis[12]. Similar data were reported in the ADJUNCT TWO, evaluating 1.2 or 1.8 mg/d of Liraglutide added to capped insulin therapy[13]. Recently, short acting exenatide did not improve HbA1c levels when given for 26 weeks as add-on therapy to insulin treated patients with T1D.[14]

A possible reason for these inconclusive data is that the metabolic effects of GLP1RAs, particularly the augmentation of insulin production, might only be of value to patients with residual insulin production. In the ADJUNCT ONE trial, those with detectable C-peptide at baseline had improved responses to liraglutide compared to those without[12]. In an earlier study, we analyzed the acute metabolic effects of exenatide in patients with T1D during mixed meal tolerance tests and observed a marked improvement in glucose excursion in response to oral but not to intravenous glucose[15]. In those with residual insulin production, there was a relative increase in insulin secreted in response to glucose, most likely related to the reduced glucose excursion, since the total amount of insulin secreted did not change with exenatide. To date, the metabolic effects of GLP1RAs specifically comparing patients with T1D with and without residual insulin production, have not been directly studied. In addition, newer agents with weekly dosing may have a greater impact on fasting blood sugars and decreased burden of use.

We therefore conducted a randomized placebo-controlled trial to determine whether the long acting GLP-1 receptor agonist, exenatide ER, affected metabolic control in patients with stable management of T1D and whether there were differences in the responses in patients with

and without detectable levels of endogenous insulin production, i.e. with detectable C-peptide levels.

Research Design and Methods:

Trial Design: A randomized double-blind Phase 2b study of 2 mg Exenatide ER subcutaneously weekly or matched placebo for 24 weeks in patients with T1D was conducted at 7 academic sites in the US between September 2013 and November 2017. The clinical trial was approved by the IRBs at each of the clinical sites and the participants signed written consent. The trial was registered in ClinicalTrials.gov: NCT01928329.

Eligible participants were 18 years and older with "stable" T1D of at least 2 years duration (defined as insulin requirement < 0.9 U/kg/d, a HbA1c of < 9.0% and absence of diabetic ketoacidosis in the past 6 months)(SupplementalTable 1). Exclusion criteria included pregnancy, a personal or family history of MEN2, history of pancreatitis, gastroparesis or other GI disturbances, abnormal liver function tests, renal impairment, active infection, use of other anti-diabetic medications other than insulin, or a history of severe hypoglycemia.

A total of 79 patients were enrolled. They were screened for detectable levels of C-peptide in response to a mixed meal tolerance test (MMTT) performed with a liquid meal (Boost) using described methods[22]: 33 participants had a level during the test of $\geq$ 0.05 ng/ml and 46 had levels < 0.05 ng/ml (0.017 nmol/L)(the lower limit of detection in the C-peptide assay)(Figure 1, Supplemental Table 1). The participants were randomized 1:1 to treatment arms within the two strata. The two treatment arms were exenatide ER 2 mcg/wk sc or matched placebo sc. The patient was asked to reduce insulin by half after initiating study drug and then to

change the dosing in discussion with their physician. At week 24 the participants discontinued the study drug and were followed for another 24 weeks.

Compliance was assessed by query by the study staff at each visit. Diabetes management was left to the patients' care providers - All received "intensive" management of their diabetes in line with the current ADA standards[23].

Drug discontinuation was specified in the study protocol: nausea or vomiting that precluded adherence to diet, 3 severe hypoglycemic reactions on separate days (requiring assistance from another individual), weight loss of $\geq$ 5 kg from baseline, or any grade 3 or higher adverse event that prevented completion of the treatments.

Assessments: After the screening visit, the participants were seen at weeks 2, 4, 12, 24, 38 and 52. C-peptide and glucose levels were measured during the 120 min MMTT at weeks 12, 24, and 52. The average insulin use per day was determined from patient diaries that recorded insulin use for 3 days prior to a study visit. The insulin use was expressed as the total units or units/kg/d. Hypoglycemia was graded according to the CTCAE criteria (version 4). Hypoglycemia was captured from patient diaries with glucose measurements up to 6x daily for 3 days prior to study visits or with symptoms. Severe hypoglycemia was designated if assistance from others was required for recovery, resulted in hospitalization, or seizure.

Two hr mixed meal tolerance tests (MMTTs) were performed at each study visit. HbA1c and C-peptide (Tosoh assay) levels were measured at the Northwest Lipid Research Laboratory.

In a subgroup of participants, glucagon levels were measured with the Millipore assay (n=29) and GLP and GIP by ELISA (n=35) in the Yale Diabetes Center Core Laboratory.

Outcome measures and statistical analysis: The primary outcome was a comparison of the HbA1c levels, corrected for the baseline, between the two treatment arms at 24 weeks. Prespecified secondary outcomes at 24 weeks included: change in weight, change in total daily insulin dose, the C-peptide and glucose responses during the MMTTs, the frequency of hypoglycemia, and other adverse events with a comparison within and between participants with and without detectable C-peptide at entry.

The original target sample size calculation was based on repeated measures of HbA1c in patients with T1D in our clinic in which the standard deviation (SD) of the HbA1c level was 1.25% and the correlation between measurements of HbA1c, performed 24 weeks apart was 0.88. A sample size of 54 subjects per group would have provided 90% power to detect a difference of HbA1c of 0.4% between the study arms. Because of rates of enrollment, the original planned 120 participants was reduced to 79 participants. This gave us 79% power to detect a difference of 0.40% in HbA1c.

The final analysis involved all enrolled subjects. A likelihood-based ignorable analysis using a linear mixed model was used to compare HbA1c between groups[24,25]. The analysis assumed that missing data occurred at random. Fixed effects for treatment arm, time (12, 24, and 52 weeks), and the interaction of treatment with time were tested with additional fixed effects for baseline covariates (baseline A1c, detectable/non-detectable baseline C-peptide, site, gender,

race, BMI). A linear model compared the least squares means of exenatide ER to placebo at 24 weeks between groups at the two-sided 0.05 significance level. In subgroup analysis to determine whether presence of residual insulin production affected treatment response, 2 and 3 way interactions of that stratification factor with treatment and time were evaluated using a multiple degree of freedom likelihood ratio test at the 0.10 significance level. Linear mixed effect models similar to those described above were used to evaluate continuous secondary outcomes. For hypoglycemic events, the number of months that an individual was on and off study drug was used to calculate an event rate (rate = total events/total months). To compare these rates between treatment arms, the Mann-Whitney test was used. The number of patients that experienced severe adverse events on and off study drug were compared using Fisher's exact test. Adjustments were not made for multiple comparisons for secondary outcomes.

Role of the funding source: The funders were not involved in the design or execution of the study, collection of the data, writing of the manuscript, participation in the Data Safety Monitoring Board, or the decision to submit the manuscript for publication.

Results:

Study participants: The baseline characteristics and flow of participants in the trial are shown in Figure 1 and Supplemental Table 1. Of the 79 enrolled participants, five patients were randomized but never received study drug due to either withdrawal of consent (4 patients) or investigator's decision to remove one participant after randomization but before administration of study drug. Twenty-one participants (28%) discontinued the study drug during the first 6 months. The reasons cited for discontinuation were: adverse events (8, 11% overall in drug treated and placebo groups, respectively), withdrawn consent or ineligibility (6, 8% overall), weight loss >5 kg (5, 7% overall) unrelated illness (heart disease) (1, 1% overall) and non-compliance with insulin regimen (1, 1% overall).

The study participants' age at T1D diagnosis ranged from 2 to 50 years of age. Their baseline body weight was (mean(SD)) 83.7 (21.7) kg in exenatide ER and 84.13 (22.6) in placebo groups. There were not significant differences in baseline characteristics between those randomized to exenatide ER vs placebo treatment. The mean (SD) baseline HbA1c (7.60% (± 0.82)), and daily insulin use (0.59(0.18)U/kg/day) were consistent with features of individuals with long standing T1D. Insulin delivery methods were similar in the two treatment arms: 20 (25.3%) were using multiple daily injections and 58 (73.4%) were using pumps.

Overall, 42% (33) had detectable C-peptide levels at screening (Supplemental Table 1B). These participants had shorter duration of T1D (mean(SD): 14.9 (10.9) yrs) compared to those without detectable C-peptide levels (22.8 (10.3yrs))(p=0.002). Among those with detectable C-

peptide, those randomized to exenatide ER treatment had a significantly lower HbA1c at baseline (p=0.03) but otherwise there were not significant differences between the subgroups.

Primary outcome: At the primary endpoint, week 24, the effects of exenatide ER were not statistically different compared to placebo (group differences (95% CI) -0.237(0.50, 0.03), (LS mean (95% CI))(exenatide ER:7.76%(7.42, 8.10) vs placebo: 8.0% (7.64, 8.35), p=0.08) (Figure 2A). Exenatide ER treatment did have a rapid initial effect on the HbA1c. There was a significant decline in the active drug arm from the baseline to 12 weeks (LS mean(95%CI):-0.179% (-.352, -.004)), and a difference in the HbA1c levels of 7.71% (7.37, 8.05) vs 8.05% (7.7, 8.4)) between exenatide ER and placebo respectively (p=0.01). In the observational follow-up at week 52, 24 weeks after study drug discontinuation, the HbA1c level increased in the exenatide ER group to the pretreatment levels

The decline in the HbA1c at 12 weeks was largely driven by those with detectable C-peptide (mean (95% CI) -0.51%(-0.827, -0.184)), p=0.0025 vs baseline) vs those without detectable C-peptide (-0.143%(-0.447, 0.162) but the differences between those with and without C-peptide were not statistically significant at that time (0.363 (-0.08, 0.806), p=0.107) or at 24 weeks (-0.101%(-0.68, 0.479), p=0.73)(Figure 2B). At 52 weeks, the declines in HbA1c from the baseline were < 0.1% in both subgroups.

Secondary outcomes: Daily insulin dose declined significantly at 12 weeks in the exenatide ER group compared to the baseline (p=0.04)(Figure 3A). At the same time, the total daily insulin dose increased in the placebo group, leading to a significantly difference at week 24 when the

two treatment arms were compared (p=0.025). The difference between the treatment arms continued even at 52 weeks due to an increase in insulin use among those originally assigned to placebo treatment (p<0.001).

At both week 12 and 24, those treated with exenatide ER lost more weight from the baseline compared to placebo (group differences (mean (95%CI)) -2.93(-4.33, -1.5)kg p<0.0001, and -2.38(-4.11, -0.644), p=0.0078, respectively)(Figure 3B). At 52 weeks, the median weight loss in both treatment arms was < 1 kg compared to the baseline weight (exenatide ER -0.176(-2,1.65)kg and placebo 0.52(-1.45, 2.49)).

When the insulin dose was corrected for the body weight, there was not a significant difference with exenatide ER treatment compared to placebo (Figure 3C). The presence or absence of detectable C-peptide did not have a significant effect on the change in insulin dose either total U/d or U/kg/d with treatment at 12, 24, or 52 weeks (Figure 3D). In contrast to that reported for patients with T2D[3], we did not find a significant relationship between the change in weight and the change in A1c (Supplemental Figures 1A,B).

The glucose response during the MMTT improved significantly, from the baseline, at 24 weeks in the exenatide ER treated subjects (p=0.04, Figure 4A). However, there was not a significant difference from the glucose AUCs in the exenatide ER vs placebo treated participants at any of the time points. Among those without detectable C-peptide, the glucose AUC declined from the baseline at 24 weeks (p=0.04) and was significantly lower than those with detectable C-peptide at 52 weeks (p=0.04)(Figure 4B). To determine whether the exenatide ER treatment

improved insulin secretory responses, we analyzed the effects of exenatide ER on C-peptide responses during the MMTT in those with detectable levels at baseline. The differences between the two treatment arms were not significantly different at the baseline or 3 time points but there was a trend for improvement in the C-peptide at 12 weeks between the treatment groups (group difference=0..000374 (-0.00004, 0.000791) p=0.08). This was due primarily to a decline in the placebo group from the baseline (-0.0003(-0.00061, 0.000012)p=0.06) and there was a significant decline in the placebo group at week 52 (p=0.04) in the placebo group (Figure 4C). Our previous studies had suggested an improvement in the C-peptide/glucose ratio with short acting exenatide, but we did not find a significant change or difference between treatment arms with exenatide ER treatment (Figure 4D).

Plasma glucagon levels were measured before and after therapy with exenatide ER in 9 participants. The glucagon levels did not show a clear pattern of response either in the AUC during the MMTT or the peak value. In these same participants we did not detect a change in the plasma GIP or GLP levels (Supplemental Figure 2).

The frequencies of hypoglycemic events are summarized in Table 1. Hypoglycemia was classified using ADA criteria[23]. To standardize these measures, the number of months that an individual was on and off study drug is used to calculate an event rate (rate = total events/total months). While on drug, the placebo treatment arm had higher mean and median rates of minor, major and total hypoglycemic events compared to the intervention arm but the frequency of these events was not significantly different. While off study drug (months 6-12), the placebo treatment

arm continued to have higher mean and median rates of minor, major and total hypoglycemic events but were again not significantly different. The frequency and severity hypoglycemic events were not evenly distributed among the participants. One individual, treated with exenatide ER had 115 events. Another exenatide ER treated participant had a grade 3 major event with loss of consciousness.

Adverse events: While on study drug, 38 out of 39 active drug participants (97.4%) experienced at least 1 adverse event while in the placebo group, a total of 28 out of 35 participants (80.0%) experienced at least 1 adverse event (Supplemental Table 2)(p=0.02). There was a significant difference between the drug group (n=22, 56.4%) and placebo (n=8, 22.9%) with respect to gastrointestinal disorders. Skin manifestations were more frequent in the exenatide ER group. but overall, there were no significant differences between the treatment groups in the other organ class categories nor with respect to Grade 3 and Grade 4 events.

While off study drug, 29 out of 37 original exenatide ER treated participants (78.4%) experienced at least 1 adverse event in the active treatment arm while those originally treated with placebo, 25 out of 26 participants (96.2%) experienced at least 1 adverse event (p=0.069). A greater proportion of those in the placebo group (n=22, 84.6%) compared to the active treatment group (n=23, 62.2%) experienced adverse events related to metabolism and nutrition disorders. There were no significant differences between the treatment groups on other organ class specific adverse events, nor on Grade 3 or Grade 4 adverse events during the off study drug phase.

There was a total of 8 serious adverse events, 6 in the exenatide ER arm while taking study drug and 2 in the placebo group. One of the events in the exenatide ER arm involved ketoacidosis. The most frequent serious events were hypoglycemia. These are shown in Supplemental Table 3. Of the SAEs all except for the hypoglycemia were considered unrelated to study drug.

Discussion

We tested whether treatment with exenatide ER for 24 weeks would improve glycemic control in patients with T1D on stable insulin regimens, and the role of residual C-peptide in determining the responses. Because the GLP-1 receptor agonists improve endogenous glucose-stimulated insulin secretion, we postulated that the effects of the drug would be greater in those with residual insulin production compared to those in whom C-peptide was undetectable. We found that the primary endpoint of the trial, a comparison of the change in HbA1c levels at 24 weeks was not significantly different when all T1D patients were compared to placebo treatment, but we did find improvement between the treatment arms in the HbA1c levels at 12 weeks after starting drug therapy. There was not a lasting effect on HbA1c as levels 6 months after the study drug ended were similar in the two study arms suggesting the continued presence of drug was needed for metabolic effects. The drug treatment caused weight loss which resolved when the treatment was discontinued. Total insulin use declined but when corrected for the weight, there was not a significant difference between the groups or from the baseline suggesting that the exenatide ER treatment did not improve insulin sensitivity. Hypoglycemia was common in all study participants and there were more severe hypoglycemic events in the exenatide ER-treated participants although the rate was low overall. The frequency of skin manifestations from the exenatide ER injections was higher than placebo. There was an episode of DKA and 3 episodes of hypoglycemia that were classified as SAEs in the exenatide ER arm. Other adverse events were similar in the two treatment arms.

The improvement in the HbA1c level at 12 weeks was seen in those with and without residual insulin production at study entry but the effect was greater in those with detectable C-peptide. Other measures, such as insulin use or glucose AUC during the MMTTs were not different in those with and without residual insulin production. Because the GLP-1 receptor agonists are known to augment insulin production we predicted a greater treatment effect in those with residual insulin secretion but similar to our acute studies, the metabolic effects of the drug were not limited to those with residual insulin secretion[2,15]. Our findings were similar even when we separately analyzed those with the highest levels of C-peptide at baseline (not shown). Interestingly, we found a trend in improved C-peptide responses in the exenatide ER treated vs placebo treated participants in terms of stimulated responses in the treatment group but also compared to the decline in the placebo group. This is most likely explained by the relatively short duration of diabetes in those with detectable C-peptide and the ongoing decline over 1 year reflective of the natural history of the disease. Therefore, together with the HbA1c data our findings suggest but does not conclusively indicate that the drug may have additional benefit in those with residual β cell function.

The adverse events were consistent with the experience of GLP-1 receptor agonists in T2D but the rates of hypoglycemia overall were higher[3,4,26]. We observed other differences compared to the described effects in patients with T2D. First, exenatide ER had been shown to reduce glucagon levels in patients with T2D but we did not observe this during the provocative studies[3]. This may reflect a relative insensitivity or dysregulation of α cells in patients with T1D

to the effects of the agonist which had been seen in acute studies[15]. In addition, we did not see a relationship between weight loss and the improvement in A1c or insulin use. There may be additional effects of the drug on insulin sensitivity in patients with both forms of diabetes as suggested by Rother et al[27].

Our findings differ from other studies of GLP-1 receptor agonist in patients with T1D. In the ADJUNCT 1 trial, addition of liraglutide to insulin therapy reduced HbA1c levels, total insulin dose, and body weight but also increased the rates of symptomatic hypoglycemia and hyperglycemia with ketosis[12]. In the ADJUNCT TWO trial, liraglutide, added to capped insulin, reduced HbA1c levels, body weight and insulin requirements but with higher rates of hypoglycemia and ketosis[13]. The differences between the adverse events this study and the ADJUNCT trials may reflect our reduction in exogenous insulin treatment when the study drug was initiated or possibly the differing pharmacokinetics of the GLP1RAs give once weekly vs daily. Indeed, with acute administration of exenatide we found flattening of the glucose response during a MMTT which was not seen herein[15]. Our findings suggest a more robust response of HbA1c than was seen in the recently reported trial of exenatide, given 3x daily to patients with T1D.[14]

The observed rates of hypoglycemia were high but not higher in the exenatide ER vs placebo arms but there were 6 severe hypoglycemic in 3 exenatide ER treated participants. The rates were higher on the exenatide ER treated group vs off study drug. This suggests that the reduced need for exogenous insulin may not affect the rates of hypoglycemia overall, but there

may be particular individuals at high risk for hypoglycemia when exenatide ER is given in addition to insulin.

In the absence of clear enhancement of insulin secretion, reduced glucagon release, and change in insulin sensitivity with the exenatide ER, the basis for the improvement in HbA1c after 12 weeks remains unexplained. It is possible that the metabolic effects that we had seen with the acute administration of exenatide also occurred with the long acting formulation of the drug but were more modest and that our assays to detect these effects were limited by the sample size or there was tachyphylaxis to the long term GLP1RA exposure. It is also possible that other mechanisms are involved such as slowing gastric emptying or changes in dietary patterns in response to the GI AEs that resulted in improved glycemic control, in the short term. Finally, GLP1RAs have been found to have anti-inflammatory effects which could account for improved metabolic control[28]. However, we did not find changes in immune cells (CD4, CD8) or markers of cell activation (RAGE expression) with exenatide ER treatment (not shown)[29].

There are a number of limitations of the study. The total sample size was insufficient to detect a difference in the HbA1c level that we had originally planned. In addition, not all of the participants completed the 6 month follow up visit to determine whether any effects of the drug treatment may have persisted. Second, our study design did not entail a treat-to-target regimen or capped insulin dose that had been used in the ADJUNCT trials and therefore, the management of the participants may have varied based on the care provider. Finally, the patients were heterogeneous reflected by the shorter duration of disease in those with residual insulin

production which may have affected the management patterns or the responses to the drug. Nonetheless, the patients are reflective of patients seen in practice with clinical features such as increased BMI and residual insulin production, that might suggest the appropriateness of a GLP-1 receptor agonist for treatment.

In conclusion, in this clinical trial of exenatide ER in patients with T1D, we did not find a significant improvement in HbA1c after 6 months of treatment but the HbA1c was significantly reduced after 12 weeks. The effects of the drug treatment in the short term were more pronounced in those with residual insulin production but not significantly different from those without detectable C-peptide. Weight loss was common, but the rates of hypoglycemia were similar in the two treatment arms. We conclude that adjunctive treatment with exenatide ER may have value in some individuals with T1D – mainly those with obesity and in whom there is residual insulin production, but the short term improvements are not sustained. The reduced dependence on exogenous insulin without increased rates of hypoglycemia may make this adjunctive therapy attractive but caution should be exercised in view of the higher rates of hypoglycemia in some patients. In addition, the emerging beneficial effects of the GLP1RAs on cardiovascular and renal disease suggest there may additional benefits of these agents, but further studies will be needed to determine whether these other beneficial effects are common to T1D[18-21].

Authors contributions: KCH wrote the protocol, collected and conducted the study, analyzed data and wrote the manuscript; JR and JD collected and analyzed data and wrote the manuscript; DB, JG, SEG, PAG, JM, LHP, RPB, and RSW conducted the study, collected data and wrote the manuscript.

Conflicts of Interest: The authors do not have conflicts of interest to declare.

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Figure legends

Figure 1: CONSORT diagram showing flow through the clinical study.

Figure 2: Effects of exenatide ER treatment on HbA1c levels: A: The HbA1c levels in the two treatment arms are shown at each study visit. There was a significant reduction in the HbA1c level in the exenatide ER group at 12 weeks (p=0.045) and the levels were significantly different from the placebo group (p= 0.01). However, at 24 weeks the differences between the groups were not statistically significant (p=0.08). B: In those with a detectable level of C-peptide at the baseline (C-pep≥0.05 ng/ml), there was a significant reduction, compared to the baseline in the HbA1c level at 12 weeks (p=0.0025) but not in those with undetectable C-peptide levels (C-pep < 0.05 ng/ml). The treatment changes in each subgroup taken from the linear mixed model are shown. All data shown are from the linear mixed model (mean+95% CI).

Figure 3: Effects of exenatide ER treatment on insulin use and weight: A: The total daily insulin use (U/d) in the two treatment arms are shown. There was a reduction in the use of insulin in the exenatide ER group at 12 weeks compared to the baseline (p=0.038). At 24 weeks the insulin use in the exenatide group was significantly less than in the placebo group (p=0.025)(mean+95%CI). At 52 weeks the insulin use in the placebo group was increased compared to the baseline (p=0.008) and was significantly greater than in the participants that were treated with exenatide ER during the first 6 mos (p=0.0009). B: There was significant loss in weight in the exenatide ER vs placebo treated participants at 12 (p=0.003) and 24 weeks (p=0.017). C: The insulin use is corrected for the body weight (U/kg/d). D: A comparison of the

treatment difference (vs placebo) in the use of insulin in those with and without detectable C-peptide at baseline. All data shown are from the linear mixed models (mean+95% CI).

Figure 4: Effects of exenatide ER treatment on glucose and C-peptide responses. A: There was a significant reduction in the glucose AUC at week 24 in the exenatide ER group compared to the baseline (p=0.04) but not compared to placebo (p=0.1). B: There was a significant improvement, compared to the baseline vs placebo, in the group without detectable C-peptide at week 24 (p=0.04). At 52 weeks there was a greater effect on the glucose AUC in the participants that did not have detectable C-peptide compared to the participants that did (p=0.04). C: The C-peptide AUC (in pmol/ml/min) was compared between the Exenatide-ER and placebo treated participants by linear mixed model at each of the study time points in those with detectable C-peptide levels at baseline. The data are shown as ln(AUC/120min+1). There was a significant decline at 52 weeks, compared to the baseline, in the subjects treated with placebo for the first 24 weeks (p=0.04). D: The C-peptide/glucose ratio was compared in the two treatment arms for those with detectable C-peptide levels at baseline. At 12 weeks the comparison of the exenatide ER vs placebo effect p=0.06. All data shown are mean (95%CI) from the linear mixed models.

Table 1: Hypoglycemic events**								
Timeframe	**Arm**	**Variable**	**N**	**Mean**	**Std Error**	**Median**	**Minimum***	**Maximum***
On Drug	**Exenatide ER**	Level 1 hypoglycemia event rate	39	2.07	0.44	1.00	0	11.33
		Level 2 hypoglycemia event rate	39	1.82	0.50	0.67	0	13.00
		Total Event Rate	39	3.89	0.88	1.33	0	21.67
	Placebo	Level 1 hypoglycemia event rate	35	2.60	0.54	1.60	0	13.00
		Level 2 hypoglycemia event rate	35	2.00	0.43	0.80	0	10.50
		Total Event Rate	35	4.59	0.94	2.33	0	23.50
Off Drug	**Exenatide ER**	Level 1 hypoglycemia event rate	37	1.09	0.29	0.17	0	8.33
		Level 2 hypoglycemia event rate	37	0.74	0.19	0.33	0	5.00
		Total Event Rate	37	1.83	0.45	0.50	0	11.17
	Placebo	Level 1 hypoglycemia event rate	26	1.81	0.53	0.50	0	12.50
		Level 2 hypoglycemia event rate	26	1.62	0.55	0.50	0	13.17
		Total Event Rate	26	3.43	1.05	1.00	0	25.67

* Events/study month/person

**Hypoglycemia was defined using ADA criteria (Level 1 between 55 and 70 mg/dl, Level 2 hypoglycemia $\leq$ 55 mg/dl)[23].

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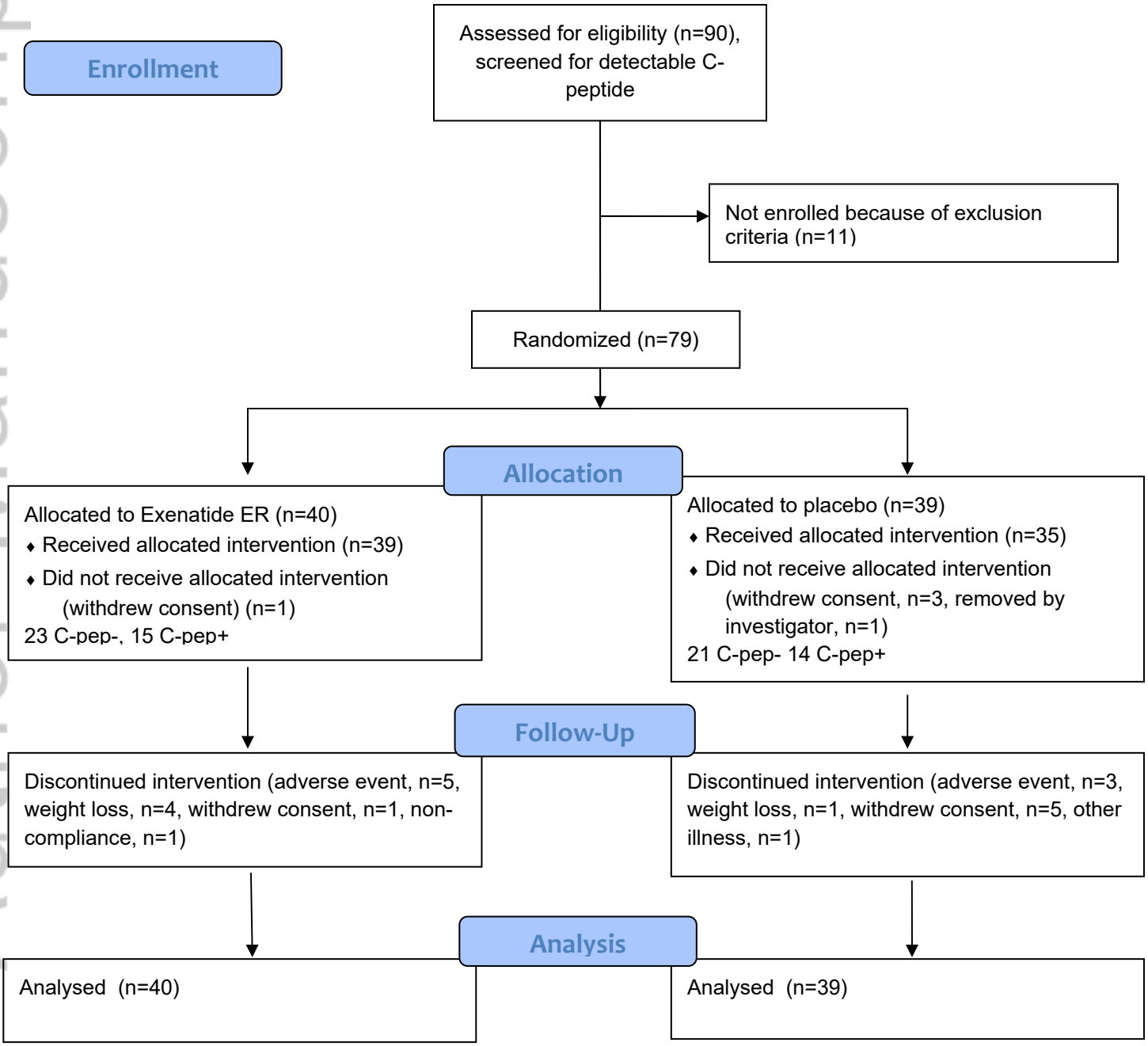
Figure 1: CONSORT Flow Diagram



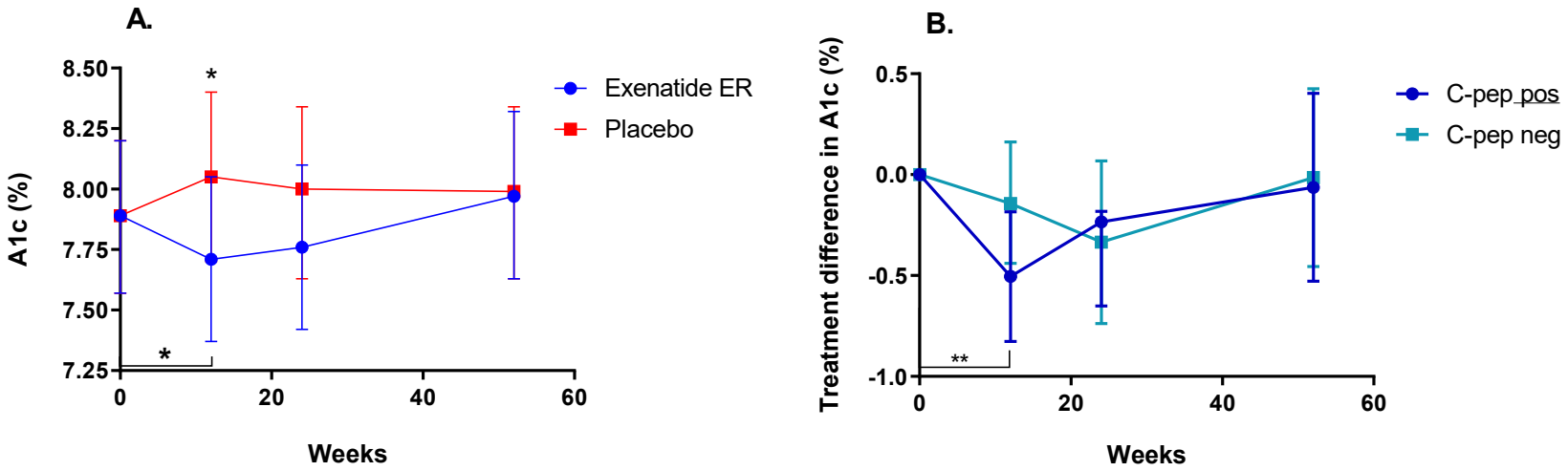
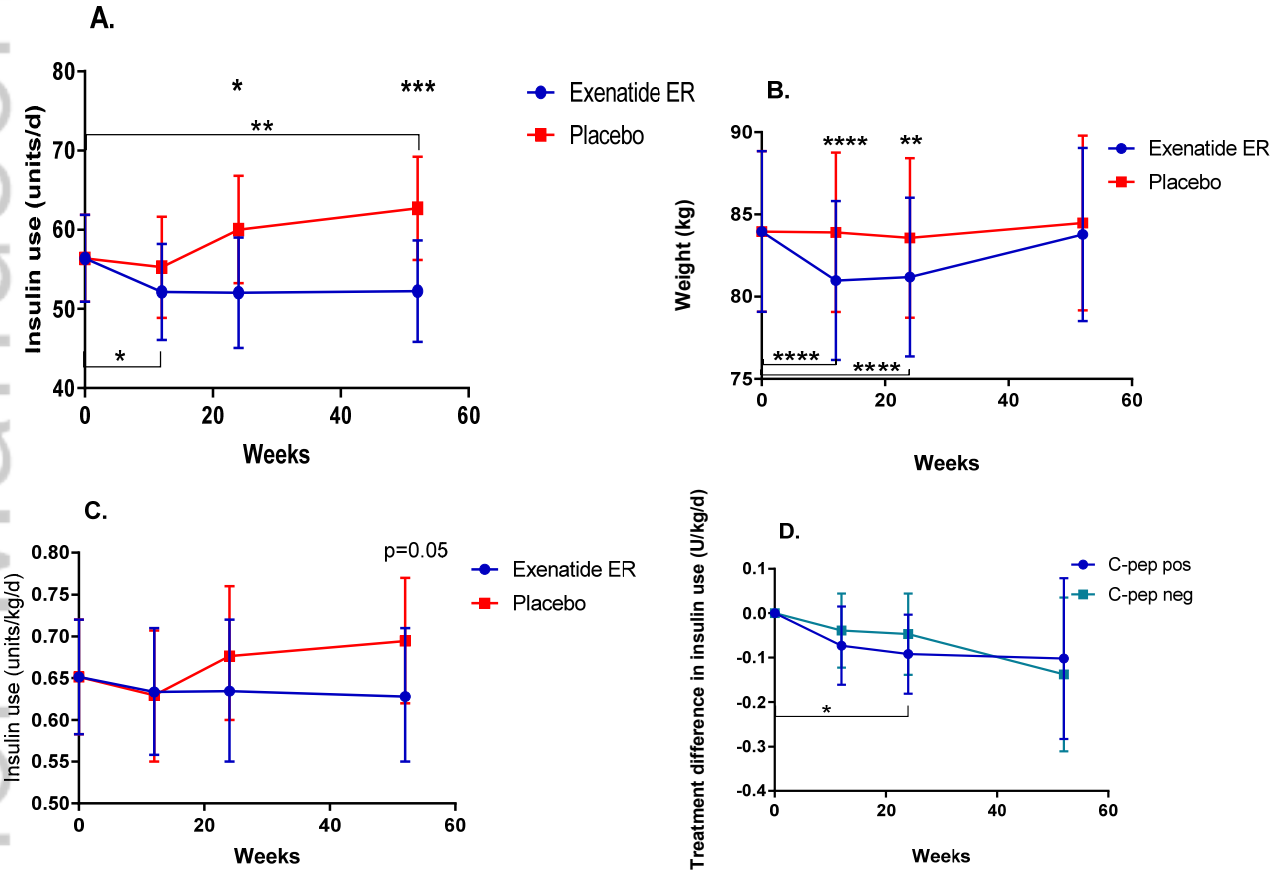


Figure 2

Figure 3



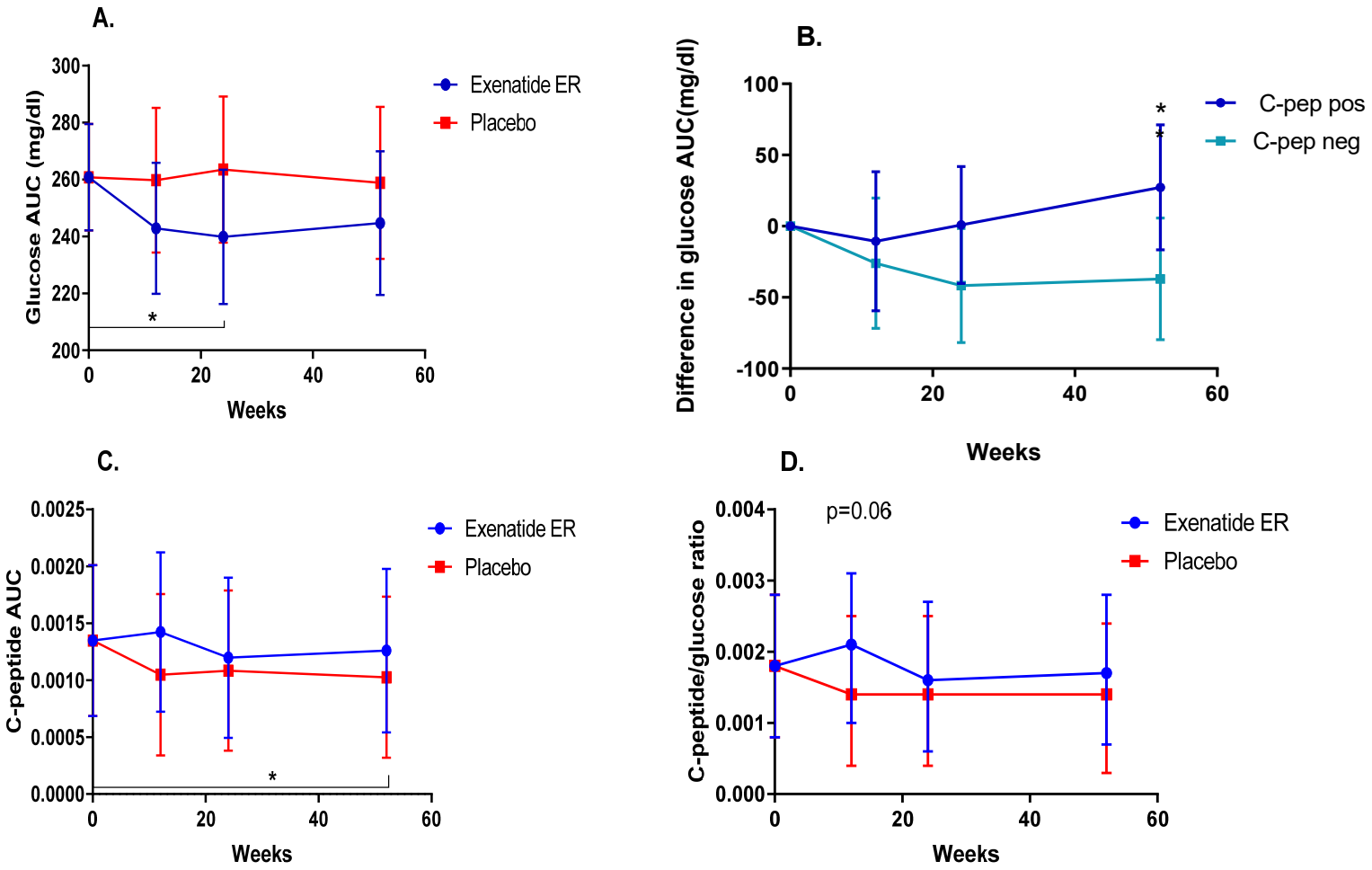


Figure 4