National PBM Drug Monograph
Exenatide (Byetta™)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

EXECUTIVE SUMMARY

- Exenatide is the first agent in a class known as incretin mimetics. Incretins enhance glucose-dependent insulin secretion from the pancreas, suppress inappropriately elevated glucagon secretion, delay gastric emptying, reduce appetite, preserve β-cell function, and increase β-cell mass.

- Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who have not achieved adequate glycemic control while using a sulfonylurea (SU) or metformin as monotherapy or combination therapy with a SU + metformin.

- There are three 30-week, randomized, double-blind, placebo-controlled trials. The combination of exenatide + SU, exenatide + metformin, and exenatide + SU + metformin was evaluated in each of the 3 studies respectively. There was a dose dependent decrease in HbA1c when exenatide was added to the oral agents. At the 5mcg bid dose, mean HbA1c decreased by 0.46% and 0.4% when added to monotherapy with SU or metformin respectively, and by 0.55% when added to combination therapy. At the 10mcg bid dose, mean HbA1c decreased by 0.86% and 0.8% when added to monotherapy with SU or metformin respectively, and by 0.77% when added to combination therapy. HbA1c increased by 0.1-0.2% in the placebo groups.

- There was a dose-dependent decrease in weight in the studies combining exenatide with oral monotherapy. The greatest decrease was seen in the exenatide + metformin study where weight decreased by -1.6kg, -2.8kg, and -0.3kg for 5mcg, 10mcg and placebo groups respectively. In the exenatide + SU study, weight decreased by -0.9kg, -1.6kg and -0.6kg for 5mcg, 10mcg, and placebo groups respectively. When exenatide was added to metformin + SU, the mean weight loss was -1.6kg with either dose compared to mean weight gain of 0.9kg in the placebo group.

- Results presented in an abstract show that the decrease in HbA1c is maintained and that there is continued weight loss after 82-weeks of therapy.

- Mild to moderate hypoglycemia occurred more frequently in the exenatide treatment groups when a sulfonylurea was included in the treatment regimen. In the exenatide + metformin study, the incidence was the same as the placebo group. There was only 1 reported case of severe hypoglycemia with exenatide.

- Nausea was the most commonly reported adverse event. The incidence was approximately 39% with the 5mcg dose and approximately 50% with the 10mcg dose compared to 7-23% in the placebo groups. Severe nausea was not dose-dependent and ranged from 2.7-6%. Vomiting occurred in 10-14.7% of patients receiving exenatide.

- The initial dose of exenatide is 5mcg twice daily administered within 60-minutes before the morning and evening meals. Exenatide should not be administered after a meal. After 1 month, the dose may be increased to 10mcg twice daily. Exenatide is administered subcutaneously in the thigh, abdomen, or upper arm.

INTRODUCTION

Incretins such as glucagon-like peptide-1(GLP-1) are naturally occurring hormones released from the GI tract in response to the ingestion of food. Meal-stimulated circulating levels of GLP-1 are reduced in type 2 diabetes. Exenatide is the first agent in a class known as incretin mimetics.

PHARMACOLOGY

GLP-1is released from the L-cells located in the distal ileum and colon, in response to food containing carbohydrates and fats. Incretins enhance glucose-dependent insulin secretion from the pancreas, suppress inappropriately elevated glucagon secretion, delay gastric emptying, reduce appetite, preserve β-cell function, and increase β-cell mass. Incretins do not suppress normal counter-regulatory increase in glucagon secretion during hypoglycemia.

GLP-1 has a plasma half-life of approximately 2 minutes; therefore, its utility as a pharmacologic agent is limited. Dipeptidyl peptase IV (DPP IV) is the enzyme responsible for metabolizing GLP-1. Exenatide has a longer half-life because it is not recognized by DPP IV making it suitable for clinical use. Exenatide is a 39-amino acid peptide incretin mimetic so named because it mimics the action of GLP-1. It is the synthetic version of exendin-4, an incretin mimetic isolated from the saliva of the Gila monster. Approximately 53% of the 39-amino acid sequence of GLP-1 is similar to exenatide.

PHARMACOKINETICS

The following pharmacokinetic parameters were derived from patients with type 2 diabetes following subcutaneous administration of 10mcg of exenatide. Bioequivalence is not affected by administration in the abdomen, arm, or thigh.[1]

Table 1: Pharmacokinetics of exenatide

Cmax	211pg/mL
Tmax (median)	2.1h
$AUC_{0-\infty}$	1036 pg • h/mL
Volume of distribution	28.3L
Metabolism/elimination	glomerular filtration followed by proteolytic degradation
Clearance	9.1 L/h
Terminal t1/2	2.4h

Mean values shown unless otherwise indicated
Information obtained from product package insert (April 2005)

The clearance of exenatide is not affected by mild-moderate renal insufficiency. Clearance is reduced to 0.9L/h in patients with endstage renal disease on dialysis. The manufacturer recommends that exenatide not be used in patients with endstage renal disease (ESRD) or severe renal impairment.

Exenatide has not been studied in patients with hepatic impairment. Given that this drug is predominantly renally eliminated, it is unlikely that the pharmacokinetics will be altered in the presence of hepatic impairment.

FDA INDICATIONS

Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who have not achieved adequate glycemic control while using a sulfonylurea or metformin as monotherapy or combination therapy with a sulfonylurea + metformin.

VA FORMULARY ALTERNATIVES

None

DOSAGE AND ADMINISTRATION

The initial dose of exenatide is 5mcg twice daily administered within 60-minutes before the morning and evening meals. Exenatide should not be administered after a meal. After 1 month, the dose may be increased to 10mcg twice daily. Exenatide is administered subcutaneously in the thigh, abdomen, or upper

arm. If a dose of exenatide is missed, skip the dose and take the next scheduled dose. The dose should not be increased to make up for the missed dose.

For patients who do not eat a morning meal, exenatide may be administered before the 2 major meals of the day provided the meals are separated by at least 6 hours. If the patient only eats 1 meal per day, exenatide can be given before that meal and before a snack as long as they are separated by at least 6 hours. (Information provided by Amylin)

For regimens that include a sulfonylurea, the dose of the sulfonylurea may be reduced to decrease the risk of hypoglycemia.

No dosage adjustment is needed for mild-moderate renal impairment (CrCl 30-80ml/min). The manufacturer recommends that exenatide not be used in patients with ESRD or CrCl < 30ml/min.

Each milliliter of solution contains 250mcg of exenatide and is available in prefilled pens (needles not included). The 5mcg pen delivers a fixed dose of 5mcg and the 10mcg pen a fixed dose of 10mcg.

- 5mcg per dose, 60 doses, 1.2ml prefilled pen
- 10mcg per dose, 60 doses, 2.4ml prefilled pen

Once used, the pen should be discarded after 30 days. Exenatide, whether unopened or in use should be stored in the refrigerator (36-46°F) and protected from light. The needle should be removed from the pen while stored to avoid leakage of drug or formation of air bubbles in cartridge.

EFFICACY

There are three 30-week, randomized, double-blind, placebo-controlled trials. Exenatide was added to therapy in patients who had not achieved glycemic goal with SU alone[2], metformin alone[3], and combination SU + metformin[4]. The primary endpoints were change in HbA1c and safety. Please see Appendix 1 for study details.

For all 3 studies, randomization was stratified according to HbA1c values at screening (<9.0% and ≥ 9.0%). The intent-to-treat (ITT) population, defined as all randomized patients with at least one dose of medication, was used for the efficacy and safety analysis. The evaluable population was used for determining the percentage of patients achieving a HbA1c ≤7%. Each study began with a 4-week single-blind, placebo lead-in period.

In the oral monotherapy trials, at least 300 subjects were needed to provide 90% power to detect a difference of 0.6% in change from baseline HbA1c between exenatide and placebo.[2, 3] In the combination SU + metformin study, at least 600 subjects were needed to provide 90% power to detect a difference of 0.5% in change from baseline HbA1c between exenatide and placebo.[4]

Patients were randomized to exenatide 5mcg, 10mcg, or placebo administered twice daily. Patients randomized to the 10mcg group were initially given 5mcg twice daily for 4 weeks, and then increased to 10mcg twice daily for the duration of the study.

Subjects could be withdrawn from the study if HbA1c increased by > 1.5% from baseline, HbA1c was ≥ 11.5% at weeks 18-24, if FBG was > 240mg/dl for ≥ 2 consecutive visits during weeks 18-24, or FBG as determined by self-monitoring of blood glucose, was > 260mg/dl for ≥ 2 weeks during weeks 18-24 and not due to a readily identifiable cause such as infection.

The mean decrease in HbA1c ranged from 0.4 to 0.55% with exenatide 5mcg, 0.77 to 0.86% with exenatide 10mcg and increased by a mean of 0.1 to 0.23% with placebo. The magnitude of decrease for each dose of exenatide was similar for all 3 studies.

Weight loss was seen in all 3 studies in the exenatide arms and was greatest in the metformin study at the 10mcg dose. Weight loss was sustained over the duration of the study. Additional information that would

be of interest, is what percentage of patients experienced weight loss, did any patients gain weight and if so how much.

Table 2: Change in HbA1c and weight

	Exenatide + SU			Exenatide + metformin			Exenatide + SU + metformin		
	5mcg	10mcg	Placebo	5mcg	10mcg	Placebo	5mcg	10mcg	Placebo
HbA1c	-0.46 ± 0.12	-0.86 ± 0.11	+0.12 ± 0.09	-0.4 ± 0.1	-0.8 ± 0.1	+0.1 ± 0.1	-0.55 ± 0.07	-0.77 ± 0.08	+0.23 0.07
Weight	-0.9 ± 0.3	-1.6 ± 0.3	-0.6 ± 0.3	-1.6 ± 0.4	-2.8 ± 0.5	-0.3 ±0.3	-1.6 ± 0.2	-1.6 ± 0.2	+0.9 ± 0.2

HbA1c was significantly lower for all exenatide groups versus placebo
Weight was significantly lower for all exenatide groups versus placebo except for exenatide 5mcg arm in the SU study

A subgroup of patients from DeFronzo et al. (n=36)[3] and Kendall et al. (n=77)[4] also underwent a standardized meal test to assess post-prandial glucose at weeks 0 (all taking placebo), 4, and 30. At weeks 4, and 30, the post-prandial glucose geometric mean $AUC_{15\text{-}180min}$ was approximately 34% lower compared to baseline with both exenatide doses. The $AUC_{15\text{-}180min}$ was 9% lower in the placebo group. The results from Kendall et al. are presented in table 3.

Table 3: Results of standardized meal test at 30 weeks (Kendall et al.)[4]

	5mcg	10mcg	Placebo
Baseline glucose $AUC_{15\text{-}180min}$	2089	2033	2090
Glucose $AUC_{15\text{-}180min}$	1584	1539	3087
Incremental glucose $AUC_{15\text{-}180min}$	-318 ± 49	-474 ± 87	-3.0 ± 72

Values are geometric mean
Units as mmol · min · l^{-1}

Patients who have not achieved glycemic control with oral agents will often be started on a single-nighttime dose of an intermediate or long-acting insulin. This type of regimen offers excellent glycemic lowering; however at the cost of some weight gain and risk of hypoglycemia. Exenatide 10mcg BID (n=283) or insulin glargine once daily (n=268) added to metformin + sulfonylurea was evaluated in a 26-week trial.[5, 7] Metformin + sulfonylurea were continued in both arms; however the dose of sulfonylurea could be reduced by 50% for patients experiencing hypoglycemia. Patients randomized to exenatide began with 5mcg twice daily for 4 weeks and then were increased to 10mcg twice daily. Patients randomized to insulin glargine began with 10units daily and were titrated in 2unit increments every 3 days, using a fixed-dose algorithm, to achieve a fasting blood glucose target of 100mg/dl (average dose 25units/day).

Baseline HbA1c was 8.2 ± 1.0 and 8.3 ± 1.0 for exenatide and glargine respectively. Mean reduction in HbA1c was similar for both groups. Mean fasting plasma glucose was approximately 30mg/dl lower in the glargine group. On average, the exenatide group lost weight whereas the glargine group gained weight. The rate of symptomatic hypoglycemia was similar between groups; however, nocturnal hypoglycemia was lower with exenatide (table 4). Four patients in each group experienced a severe hypoglycemic event, which was treated with administration of oral carbohydrates.

Table 4: Results of exenatide vs. glargine[5, 7]

	Exenatide	Insulin glargine
HbA1c (%)	-1.0 ± 0.1	-1.1 ±0.1
% achieving HbA1c ≤ 7%	48	46
Weight (kg)	-2.3 ± 0.2*	+1.8 ± 0.2
FPG (mg/dl)	-21.6 ± 3.6*	-52.2 ± 3.6
All hypoglycemia	6.0 ± 1.0	5.0 ± 1.1
Nocturnal hypoglycemia (events/patient-yr)	0.9 ± 0.4*	2.4 ± 0.4
% pts. achieving HbA1c ≤ 7% without nocturnal hypoglycemia	37%	28%
% dropouts	19%	10%

*significant vs. glargine

Long-term studies

Patients who completed any of the 3 pivotal trials (n=393) were entered into a 1-year open-label extension trial (data from abstract).[6] In the extension trial, all patients received exenatide 5mcg BID for 4 weeks followed by 10mcg BID. Patients continued the oral agents received as in the parent trials. The decrease in HbA1c was maintained at week 82. Weight progressively continued to decrease over time (table 5).

Table 5: Results of 82-week extension trial[6]

	Week 30			Week 82*
	Exenatide 5mg	**Exenatide 10mcg**	**Placebo**	**Exenatide 10mcg**
HbA1c (%)	-0.9 ± 0.1	-1.1 ± 0.1	+0.1 ± 0.1	-1.1 ± 0.1[95%CI: -1.3, -0.9]
Weight (kg)	-1.9 ± 0.3	-2.7 ± 0.4	-0.6 ± 0.3	-4.5 [95%CI: -5.5, -3.5]

Mean ± SE
*reduction from baseline

Lipid parameters were also analyzed in 265 patients. There was a small decrease in total cholesterol and LDL-C by a mean of 2.52mg/dl [95%CI -6.43, 1.39] and 1.41mg/dl [95%CI -4.99, 2.16] respectively. Triglycerides decreased by a mean of 36.94mg/dl [95%CI -55.96, -17.91] and HDL-C increased by a mean of 4.46mg/dl [95%CI 3.64, 5.27].[7]

ADVERSE EVENTS (See appendix 2)

The safety data base is made up of 1857 patients, 840 of whom received exenatide for ≥ 6months, and 272 for ≥ 12 months. Gastrointestinal complaints, most commonly nausea, were the most frequently reported adverse events. The incidence of nausea was dose-dependent and was consistently seen among the 3 clinical trials. Nausea occurred most frequently during weeks 0-8 and was generally mild-moderate in nature. Severe nausea ranged from 2.7-6% and withdrawal from the study due to nausea ranged from 1.8-4%. The combination of metformin and exenatide did not result in an increased incidence of nausea. Lastly, the weight loss seen with exenatide treatment was not attributed to nausea (see table 6).

Table 6: Weight loss and nausea

	Exenatide + SU			Exenatide + metformin			Exenatide + SU + metformin		
	5mcg	**10mcg**	**Placebo**	**5mcg**	**10mcg**	**Placebo**	**5mcg**	**10mcg**	**Placebo**
No nausea	-0.6 ± 3.0	-1.4 ± 3.6	-0.7± 3.1	-1.4± 0.4	-2.2 ± 0.7	-	-1.7 ± 0.2	-1.1 ± 0.3	-
≥ 1 episode of nausea	-1.3 ± 2.9	-1.7 ± 3.2	0.6 ± 4.7	-	-	-	-	-	-

Mean ± SD
(-) data not shown

Mild to moderate hypoglycemia occurred more frequently in the exenatide treatment groups when a SU was included in the treatment regimen. In the exenatide + metformin study, the incidence was the same as the placebo group. Among the 3 trials combined, there was only 1 case of severe hypoglycemia (exenatide 5mcg + SU + metformin) requiring the assistance of another individual; however, additional medical attention was not needed. One patient withdrew from the study due to hypoglycemia (exenatide 5mcg + SU).

Approximately 45% of the patients receiving exenatide were positive for anti-exenatide antibodies, with the majority of titers being in the low range (≤ 1/125). The presence of these titers did not appear to have a predictive effect on glycemic response or adverse events.

Safety parameters evaluated in each study included laboratory tests, physical exam, electrocardiogram, and vital signs. The results of these evaluations are not fully described in the study. For example, Buse et al reported that there were no significant changes in the physical exam and vital signs.[2] They found a mild-moderate transient increase in CPK in 12 patients. They also found a small but significant decrease in LDL-cholesterol and Apolipoprotein B. DeFronzo et al. reported no significant changes in cardiovascular, hepatic, renal, lipids, laboratory parameters, vital signs, and EKG.[3] Kendall et al., reported no significant changes in cardiovascular, pulmonary, hepatic, and renal parameters.[4]

CONTRAINDICATIONS/PRECAUTIONS

Exenatide is contraindicated in patients with hypersensitivity to the product or any of its components.

Precautions

- Exenatide should not be used in patients with type 1 diabetes
- Exenatide is not a substitute for insulin in patients requiring insulin
- Concurrent use of exenatide with insulin, thiazolidinediones, alpha-glucosidase inhibitors, and meglitinides has not been studied.
- Exenatide has not been studied in patients with severe gastrointestinal diseases, including gastroparesis and is not recommended for use in these patients.
- Exenatide is not recommended in patients with severe renal impairment

LOOK-ALIKE/SOUND-ALIKE DRUGS

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for trade name Byetta:
Diabeta® (glyburide) – both Byetta and Diabeta are used to treat diabetes; however, Diabeta is only available in an oral dosage form. Note that Byetta is dosed as 5 -10 mcg twice daily and Diabeta sometimes is dosed at 5-10mg twice daily.

LA/SA for exenatide:
Nateglinide (Stalix®) –also used to treat diabetes and is administered prior to meals; however, nateglinide is only available orally in 60mg and 120mg tablets.

Ethionamide – used to treat tuberculosis. Available in 250mg tablets.

DRUG INTERACTIONS

Table 7: Drug interactions

Drugs	Pharmacokinetic parameter
Digoxin 0.25mg once daily (days 1-12) Exenatide 10mcg bid (days 8-12)	Cmax of digoxin decreased by 17% Tmax delayed by approximately 2.5h Steady state digoxin AUC unchanged
Lovastatin 40mg single dose Exenatide 10mcg bid	AUC of lovastatin decreased by 40% Cmax decreased by 28% Tmax delayed by approximately 4h
Lisinopril (patients stabilized on 5-20mg/day) Exenatide 10mcg bid x 1 day	No change in steady-state Cmax or AUC of lisinopril Tmax delayed by 2h No changes in 24-h mean blood pressure
6-way crossover study Acetaminophen (APAP) 1000mg elixir single-dose and exenatide 10mcg single-dose. APAP administered at -1h, 0h, + 1h, +2h, and +4h relative to exenatide inj.	AUC_{0-12h} of acetaminophen decreased by 21%, 23%, 24%, and 14% (0h, + 1h, +2h, and +4h respectively) Cmax decreased by 37%, 56%, 54%, 41% (0h, + 1h, +2h, and +4h respectively) Tmax was 0.9h, 4.2h, 3.3h, 1.6h (0h, + 1h, +2h, and +4h respectively) AUC, Cmax, and Tmax of acetaminophen not significantly changed when given 1h before exenatide

Information obtained from product package insert (April 2005)
Soon D, Linnebjerg H, Chan C, et al. Effect of exenatide on digoxin pharmacokinetics. Clin Exper Pharmacol Physiol 2004; 31(suppl 1): A65 (abstract PO-047)
Kothare P, Linnebjerg H, Atkins M, et al. Effect of exenatide on lisinopril pharmacodynamics in patients treated for hypertension. Clin Pharmacol Ther 2005; 77 (2): P14 (abstract PI-24)
Blasé E, Taylor K, Gao HY, et al. Pharmacokinetics of an oral drug (acetaminophen) administered at various times in relation to subcutaneous injection of exenatide in healthy subjects. J Clin Pharmacol 2005; 45: 570-7.

As part of a post-marketing commitment, the FDA has recommended that the mechanism(s) of the lovastatin-exenatide interaction be investigated. Also, studies should be conducted on how exenatide impacts the bioavailability of those drugs that are instructed to be taken with food.

COST

The FSS price for a 30-day supply is $103.29 (5mcg) and $121.21 (10mcg). Pen needles are not included and must be obtained separately. Prices of other medications that are used as add-on when glycemic control using multi-drug oral therapy is inadequate are provided for comparison.

Table 8: Costs of other drugs used as add-on therapy to combination OHA

Drug	Dose	30-day supply	FSS cost (30 days)
Insulin glargine	Assumes average dose used in clinical trial of 25units/day	10ml vial	$26.70
NPH insulin	25units/day (dose extrapolated from glargine study)	10 ml vial	$6.85
Rosiglitazone	8mg	30 tablets	$60.90

CONCLUSIONS

Exenatide offers modest benefit in HbA1c lowering and weight outcomes in patients with type 2 diabetes poorly controlled on SU and/or metformin; however, it is less convenient to use than bedtime insulin and is significantly more costly than most insulin regimens.

More studies are needed comparing the addition of exenatide or other agents (e.g. NPH, long-acting analogs, short-acting agents, or TZDs) to existing oral regimens. Studies evaluating relevant diabetes-related outcomes are needed.

REFERENCES

1. Calara F, Taylor K, Han J, et al. A randomized, open-label, crossover study examining the effect of injection site on relative bioavailability of exenatide (synthetic exendin-4). Clin Ther 2005; 27: 210-215.

2. Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004; 27: 2628-2635.

3. Defronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005 May; 28(5):1092-100.

4. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005 May; 28(5):1083-91.

5. Heine RJ, Van Gaal LF, Johns D, et al. Comparison of exenatide and insulin glargine in MET and SU-treated patients with type 2 diabetes: exenatide achieved equivalent glycemic control, with weight reduction and less nocturnal hypoglycemia. Diabetes 2005; 54 (abstract 9-OR)

6. Blonde L, Han J, Mac S, et al. Exenatide (exendin-4) reduced A1c and weight over 82 weeks in overweight patients with type 2 diabetes. Diabetes 2005; 54 (abstract 477-P)

7. Byetta (exenatide). Academy of Managed Care Pharmacy (AMCP) dossier. Version 1.0 May 26, 2005

Prepared by: Debbie Khachikian, PharmD

Date: June 2005

APPENDIX: Clinical trials

<table>
<tr><th>STUDY</th><th>INCLUSION/EXCLUSION</th><th>DOSING</th><th>DEMOGRAPHICS/BASELINE VALUES</th><th>RESULTS</th></tr>
<tr>
<td>Buse 2004[2]
R DB, PC, PR
N=377
30-weeks

ITT population used for efficacy and safety analysis. The evaluable population was used for % of patients achieving HbA1c ≤ 7%.</td>
<td>Type 2 DM
22-76 years old
Treated with at least the maximally effective dose of a SU as monotherapy for ≥ 3 months prior to screening
FBG < 240mg/dl
BMI 27-45 kg/m^2
HbA1c 7.1-11%
Stable weight (±10%) for 3 months prior to screening

Used metformin, TZDs, insulin, alpha-glucosidase inhibitors or meglitinides, or weight loss drugs within the prior 3 months
Corticosteroids, drugs known to affect GI motility, transplant drugs
Evidence of clinically significant co-morbidities</td>
<td>Exenatide 5mcg bid + SU
Exenatide 10mcg bid + SU
Placebo + SU

Dose was administered subcutaneously within 15-minutes before morning and evening meals

Patients in the exenatide 10mcg group began with 5mcg bid for 4 weeks then were escalated to the 10mcg bid dose

In order to standardize, SU dose was adjusted to maximally effective dose (if needed) during placebo run-in

SU dose may be decreased by 50% for if: 1 documented hypoglycemic event or 2 undocumented or suspected hypoglycemic events. Further decrease was allowed if hypoglycemia continued.</td>
<td>Values for exenatide 5mcg / exenatide 10mcg / placebo

% male: 59.2% / 57.4% / 62.6%
Age (years): 55±10 / 56 ±11 / 55±11
% white: 61.6 / 59.7 / 66.7
% black: 16.8 / 16.3 / 9.8
% Hispanic: 18.4 / 21.7 / 21.1
Duration of DM (years): 6.3 ± 5.2 / 6.6 ± 6.6 / 5.7 ± 4.7
HbA1c (%): 8.5 ± 1.1 / 8.6 ± 1.2 / 8.7 ± 1.2
HbA1c (baseline < 9%): 7.8 ± 0.1 / 7.9 ± 0.1 / 7.9 ± 0.1
HbA1c (baseline ≥ 9.5%): 9.7 ± 0.1 / 10.0 ± 0.1 / 10.1 ± 0.1
% w/ baseline HbA1c < 9%: 63.2% / 64.3% / 62.6%
Weight (kg): 95 ± 22 / 95 ± 18 / 99 ± 18
BMI (kg/m^2): 33 ± 6 / 33 ± 6 / 34 ± 5

Mean ± SD
Mean ± SE for stratified HbA1c values</td>
<td>
<table>
<tr><th></th><th>Exenatide 5</th><th>Exenatide 10</th><th>Placebo</th></tr>
<tr><td>d/c (all)</td><td>24%</td><td>29.5%</td><td>39.8%</td></tr>
<tr><td>d/c due to AE</td><td>7.2%</td><td>10.1%</td><td>3.3%</td></tr>
<tr><td>d/c due to LOE</td><td>5.6%</td><td>4.7%</td><td>16.3%</td></tr>
<tr><td>HbA1c (%)</td><td>-0.46 ± 0.12*</td><td>-0.86 ± 0.11*</td><td>+0.12 ± 0.09</td></tr>
<tr><td>HbA1c (baseline < 9%)</td><td>-0.39 ± 0.12*</td><td>-0.65 ± 0.12*</td><td>+0.11 ± 0.12</td></tr>
<tr><td>HbA1c (baseline ≥ 9%)</td><td>-0.58 ± 0.24*</td><td>-1.22 ± 0.19*</td><td>+0.13 ± 0.17</td></tr>
<tr><td>% with HbA1c ≤ 7% (ITT/ evaluable pop.)</td><td>26.7%
32.6%*</td><td>34.2%
41.3%*</td><td>7.7%
8.8%</td></tr>
<tr><td>FPG (mg/dl)</td><td>-5.4 ± 3.6</td><td>-10.8 ± 5.4*</td><td>+7.2 ± 5.4</td></tr>
<tr><td>Weight (kg)</td><td>-0.9 ± 0.3</td><td>-1.6 ± 0.3*</td><td>-0.6 ± 0.3</td></tr>
</table>
*significant versus placebo
Mean ± SE
</td>
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19-78 years old
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BMI 27-45 kg/m^2
HbA1c 7.1-11%
Stable weight (±10%) for 3 months prior to screening

Used SU, TZDs, insulin, alpha-glucosidase inhibitors or meglitinides, or weight loss drugs within the prior 3 months
Corticosteroids, drugs known to affect GI motility, transplant drugs</td>
<td>Exenatide 5mcg bid + metformin
Exenatide 10mcg bid + metformin
Placebo + metformin

Dose was administered subcutaneously within 15-minutes before morning and evening meals

Patients in the exenatide 10mcg group began with 5mcg bid for 4 weeks then were escalated to the 10mcg bid dose

Metformin was continued at ≥ 1500mg daily</td>
<td>Values for exenatide 5mcg / exenatide 10mcg / placebo

% male: 51.8% / 60.2% / 59.3%
Age (years): 53±11 / 52 ±11 / 54±9
% white: 77.3 / 79.6 / 72.6
% black: 10.9 / 8.8 / 13.3
% Hispanic: 7.3 / 8.0 / 10.6
Duration of DM (years): 6.2 ± 5.9 / 4.9 ± 4.7 / 6.6 ± 6.1
HbA1c (%): 8.3 ± 1.1 / 8.2 ± 1.0 / 8.2 ± 1.0
Weight (kg): 100 ± 22 / 101 ± 20 / 100 ± 19
BMI (kg/m^2): 34 ± 6 / 34 ± 6 / 34 ± 6
Weight (baseline BMI <30): 80.8</td>
<td>
<table>
<tr><th></th><th>Exenatide 5</th><th>Exenatide 10</th><th>Placebo</th></tr>
<tr><td>d/c (all)</td><td>18.2%</td><td>17.7%</td><td>21.2%</td></tr>
<tr><td>d/c due to AE</td><td>3.6%</td><td>7.1%</td><td>0.9%</td></tr>
<tr><td>d/c due to LOE</td><td>4.5%</td><td>0.9%</td><td>8.0%</td></tr>
<tr><td>HbA1c (%)</td><td>-0.4 ± 0.1*</td><td>-0.8 ± 0.1*</td><td>+0.1 ±0.1</td></tr>
<tr><td>% with HbA1c ≤ 7% ITT/evaluable pop.)</td><td>27%
31.6%*</td><td>40%
46.4%*</td><td>11%
13.0%</td></tr>
<tr><td>FPG (md/dl)</td><td>-7.2 ± 4.6*</td><td>-10.1 ± 4.4*</td><td>+14.4 ± 4.2</td></tr>
<tr><td>Weight (kg)</td><td>-1.6 ± 0.4*</td><td>-2.8 ± 0.5*</td><td>-0.3 ± 0.3</td></tr>
<tr><td>Weight (baseline BMI<30)</td><td></td><td></td><td></td></tr>
<tr><td>Weight (baseline BMI ≥ 30)</td><td></td><td></td><td></td></tr>
</table>
*significant versus placebo
Mean ± SE
</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Evidence of clinically significant co-morbidities</td>
<td></td>
<td>± 2 / 84 ± 1.9 / 80.3 ± 2.2
Weight (baseline BMI ≥ 30): 108.3 ± 2.3 / 106.9 ± 2.2 / 105.8 ± 1.8
% w/ baseline BMI ≥ 30: 70% / 74% / 77%

Mean ± SD
Mean ± SE for stratified weight values</td>
<td></td>
</tr>
<tr>
<td>Kendall 2005[4]
R, DB, PC, PR
N=734

ITT population used for efficacy and safety analysis. The evaluable population was used for % of patients achieving HbA1c ≤ 7%.</td>
<td>Type 2 DM
22-77 years old
Treated with ≥ 1500mg of metformin AND at least the maximally effective dose of a SU for ≥ 3 months prior to screening
FBG < 240mg/dl
BMI 27-45 kg/m^2
HbA1c 7.1-11%
Stable weight (±10%) for 3 months prior to screening

Used TZDs, insulin, alpha-glucosidase inhibitors or meglitinides, or weight loss drugs within the prior 3 months
Corticosteroids, drugs known to affect GI motility, transplant drugs
Evidence of clinically significant co-morbidities</td>
<td>Exenatide 5mcg bid + SU + metformin
Exenatide 10mcg bid + SU + metformin
Placebo + SU +metformin

Dose was administered subcutaneously within 15-minutes before morning and evening meals

Patients in the exenatide 10mcg group began with 5mcg bid for 4 weeks then were escalated to the 10mcg bid dose

Metformin was continued at ≥ 1500mg daily

1:1 randomization (unblinded) to either maximum dose SU or minimum recommended SU dose

SU dose may be decreased by 50% for if: 1 documented hypoglycemic event or 2 undocumented or suspected hypoglycemic events. Further decrease was allowed if hypoglycemia continued.

Increase in SU dose was allowed for FBG > 124mg/dl during weeks 4-12. No further dosage increase was allowed after week 12.</td>
<td>Values for exenatide 5mcg / exenatide 10mcg / placebo

% male: 59.2% / 59.3% / 55.9%
Age (years): 55± 9 / 55±10 / 56±10
% white: 69/ 66.4 / 68.4
% black: 10.2 / 11.6 / 12.1
% Hispanic: 15.9 / 16.6/ 15.8
Duration of DM (years): 8.7 ± 5.9 / 8.7 ± 6.4 / 9.4 ± 6.2
HbA1c (%): 8.5 ± 1.0 / 8.5 ± 1.1 / 8.5 ± 1.0
HbA1c (baseline < 9%): 7.91 ± 0.04 / 7.92 ± 0.04 / 7.94 ± 0.04
HbA1c (baseline ≥ 9.5%): 9.75 ± 0.07 / 9.86 ± 0.07 / 9.75 ± 0.07
% w/ baseline HbA1c < 9%: 70.2% / 70.1%/ 69.6%
Weight (kg): 97 ± 19 / 98 ± 21 / 99 ± 19
BMI (kg/m^2): 33 ± 6 / 34 ± 6 / 34 ± 5

Mean ± SD
Mean ± SE for stratified HbA1c values</td>
<td>
<table>
<tr><th></th><th>Exenatide 5</th><th>Exenatide 10</th><th>Placebo</th></tr>
<tr><td>d/c (all)</td><td>15.9%</td><td>17.8%</td><td>23.9%</td></tr>
<tr><td>d/c due to AE</td><td>5.7%</td><td>9.1%</td><td>4.5%</td></tr>
<tr><td>d/c due to LOE</td><td>1.2%</td><td>0.8%</td><td>2.4%</td></tr>
<tr><td>HbA1c (%)</td><td>-0.55 ± 0.07*</td><td>-0.77 ± 0.08*</td><td>+0.23 ± 0.07</td></tr>
<tr><td>HbA1c (min SU)</td><td>-0.4 ± 0.1*</td><td>-0.6 ± 0.1*</td><td>+0.3 ± 0.1</td></tr>
<tr><td>HbA1c (max SU)</td><td>-0.7 ± 0.1*</td><td>-0.9 ± 0.1*</td><td>+0.2 ± 0.1</td></tr>
<tr><td>HbA1c (baseline < 9%)</td><td></td><td></td><td></td></tr>
<tr><td>HbA1c (baseline ≥ 9%)</td><td></td><td></td><td></td></tr>
<tr><td>% with HbA1c ≤ 7% (ITT/ evaluable)</td><td>24%*
27%*</td><td>30%*
34%*</td><td>7%
9%</td></tr>
<tr><td>FPG (mg/dl)</td><td>-9 ± 3.6*</td><td>-10.8 ± 3.6*</td><td>+14.4 ± 3.6</td></tr>
<tr><td>Weight (kg)</td><td>-1.6 ± 0.2*</td><td>-1.6 ± 0.2*</td><td>0.9 ± 0.2</td></tr>
</table>
*significant versus placebo
^values estimated from graph
Mean ± SE
</td>
</tr>
</table>

AE=adverse event, AUC=area under the curve, BID= twice daily, BMI= body mass index, DB= double-blind, d/c= discontinued, DM= diabetes mellitus, FBG= fasting blood glucose, ITT= intent-to-treat, LOE= lack of efficacy, PC= placebo-controlled, PR= parallel, R= randomized, SU= sulfonylureas, TZD= thiazolidinediones

Appendix 2: Treatment emergent adverse drug reactions

	Exenatide + SU			Exenatide + metformin			Exenatide + SU + metformin		
	Exenatide 5	**Exenatide 10**	**Placebo**	**Exenatide 5**	**Exenatide 10**	**Placebo**	**Exenatide 5**	**Exenatide 10**	**Placebo**
Serious adverse events	3%	4%	8%	4.5%	2.7%	3.5%	6%	5%	6%
Severe adverse events	-	-	-	11.8%	9.7%	8.8%	14%	12%	8%
Hypoglycemia	14%	36%	3%	5%	5%	5%	19.2%	27.8%	12.6%
Severe nausea	6%	5%	2%	2.7%	3.5%	1.8%	5%	3%	<1%
Withdrawal 2° nausea	2%	4%	0	1.8%	1.8%	-	2%	4%	<1%
Nausea	39%	51%	7%	36%	45%	23%	39.2%	48.5%	20.6%
Vomiting	10%	13%	2%	11%	12%	4%	14.7%	13.7%	4.5%
Diarrhea	11%	9%	4%	12%	16%	8%	10.2%	17.4%	6.5%
Constipation	2%	9%	3%	-	-	-	-	-	-
Headache	9%	8%	7%	-	-	-	11%	7.5%	4.9%
Dizziness	15%	15%	7%	9%	4%	6%	-	-	-
Feeling jittery	12%	15%	2%	-	-	-	8.6%	11.6%	6.9%
Increased sweating	2%	8%	1%	-	-	-	-	-	-
Weakness	6%	2%	3%	-	-	-	-	-	-
URI	-	-	-	14%	10%	11%	11.4%	17.4%	19.4%
Sinusitis	-	-	-	5%	6%	5%	-	-	-
Back pain	-	-	-	3%	6%	3%	-	-	-

URI=respiratory tract infection
(-) data not shown