Liraglutide (Victoza®) National PBM Drug Monograph

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- Liraglutide is a glucagon-like peptide-1(GLP-1) agonist approved for use in adults with type 2 diabetes mellitus.
- Liraglutide is not recommended as first-line therapy for patients inadequately controlled on diet and exercise.
- There are 6 published Phase 3 trials (LEAD trials).
  - Liraglutide + glimepiride vs. rosiglitazone + glimepiride vs. placebo + glimepiride (26-weeks)
  - Liraglutide + metformin vs. glimepiride + metformin vs. placebo + metformin (26-weeks)
  - Liraglutide vs. glimepiride (52-weeks)
  - Liraglutide + metformin + rosiglitazone vs. placebo + metformin + rosiglitazone (26-weeks)
  - Liraglutide + metformin + glimepiride vs. insulin glargine + metformin + glimepiride vs. placebo + metformin + glimepiride (26-weeks)
  - Liraglutide + oral hypoglycemic agents vs. exenatide + oral hypoglycemic agents (26-weeks)

  And 1 published trial that is not part of the LEAD trials
  - Liraglutide + metformin vs. sitagliptin + metformin (26-weeks)
- Liraglutide has not been studied in combination with insulin.
- Liraglutide is administered once daily as a subcutaneous injection.
- On average, liraglutide reduces A1C by 0.8-1.1% when used as monotherapy or as part of a 2-drug regimen. When used as part of a 3-drug regimen, average reduction in A1C was 1.3-1.5%. There is little to no difference between the 1.2mg and 1.8mg dose of liraglutide. The addition of liraglutide versus insulin glargine (average dose 24 units/day) to metformin + SU resulted in a mean decrease in A1C of 1.3% and 1.1% respectively. Liraglutide reduced A1C by 1.1% compared to 0.8% with exenatide when either drug was combined with oral hypoglycemic agents. For those with inadequate glycemic control on metformin monotherapy, mean A1C was reduced by 1.2 and 1.5% for the 1.2mg and 1.8mg doses respectively.
- Mean weight loss ranged from 2-2.8kg when liraglutide was used as monotherapy or combined with metformin. The weight loss benefit was mitigated when liraglutide was combined with a SU. Mean weight loss ranged from 1.0-1.8kg when liraglutide was used as triple therapy with metformin + SU or metformin + rosiglitazone. In the liraglutide versus insulin glargine study, patients lost an average of 1.8kg with liraglutide and gained an average of 1.6kg with insulin glargine. There was no significant difference in mean weight loss between liraglutide and exenatide.
- There are 3 extension trials showing that improvement in glycemic parameters and weight loss was maintained.
- Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2.
- The most common adverse events were GI-related which occurred more frequently in the liraglutide groups (41%) compared to the comparator groups (17%). Adverse events included nausea, vomiting, diarrhea, dyspepsia and constipation. The frequency of events tended to be dose-related and lessened over time.

- Hypoglycemia was uncommon and the majority of cases considered minor. Hypoglycemia occurred more often when combined with a sulfonylurea. Therefore, the manufacturer suggests reducing the dose of concomitantly-administered insulin secretagogues to reduce the risk of hypoglycemia. Interestingly there was no difference in frequency of minor events between liraglutide and insulin glargine; however, there were 6 major events in the liraglutide group and none in the glargine group. In the liraglutide versus exenatide trial there were fewer events in the liraglutide group (1.93 vs. 2.6 events/pt-year).

- Pancreatitis has been reported with other incretin drugs. In the LEAD trials, the rate of pancreatitis in the liraglutide and comparator groups was 2.2 versus 0.6 cases per 1000 patient-years respectively. Some patients had other risk factors for pancreatitis (e.g., history of cholelithiasis, alcohol abuse). Liraglutide has not been adequately studied in patients with a history of a pancreatitis.

- C-cell hyperplasia and neoplasia were seen in pre-clinical studies using rodents; however, these findings were not observed in monkeys. C-cells comprise a very small fraction of the thyroid in humans, but are abundant in rodents. The function of the C-cell is to synthesize and release calcitonin Because of the preclinical findings in rodents, calcitonin levels were monitored in the Phase 3 clinical trials.

    - Mean serum calcitonin levels were within normal limits during treatment for all treatment groups. In trials with measurements out to 5-6 months, a shift from normal calcitonin value to above the upper limit of the reference range occurred in 1.9% of liraglutide 1.8mg groups and 0.8-1.1% in the liraglutide 0.6mg, 1.2mg, and comparator groups. In trials with calcitonin measurements out to 12 months, 1.3% (1.8mg), 0.6% (1.2mg), 0 (placebo), and 1.0% (active-comparator) had values that increased to outside the upper limit.

    - There were 6 reports of C-cell hyperplasia among the patients in the LEAD trials (5 liraglutide; 1 active comparator). In the liraglutide groups, 4 out 5 had elevated calcitonin levels at baseline and throughout the studies and 1 developed an increased level while on therapy.

    - The rates of benign thyroid neoplasms were 7.0 and 2.5 events/1000-patient years for liraglutide and non-liraglutide groups respectively. Papillary thyroid cancer was diagnosed in 5 liraglutide-treated patients and in 1 patient in the comparator group (1.6 and 0.6 events/1000-patient years for liraglutide and non-liraglutide groups respectively). There was 1 case of medullary thyroid carcinoma (MTC) reported in a patient from a comparator group. This patient had a pre-treatment calcitonin level > 1000ng/ml.

    - Post-marketing requirements include: 5-year prospective epidemiological study to determine incidence of thyroid cancer among patients exposed to liraglutide; medullary thyroid carcinoma case series registry for at least 15years; additional studies in mice to evaluate potential risk of MTC in humans.

- As part of the Risk Evaluation and Mitigation Strategies (REMS) Program, a medication guide is required to be dispensed with each liraglutide prescription to inform providers and patients about the risk of acute pancreatitis and the potential risk of medullary thyroid carcinoma.

- Across all 3 doses of liraglutide, approximately 8-9% of patients were positive for liraglutide antibodies. The presence of antibodies did not appear to alter the glucose-lowering effect or the likelihood of having an immunologic reaction.

- The FDA determined there was no evidence of excess cardiovascular risk associated with liraglutide. However, the FDA is requiring that a post-marketing study be conducted. A 5-year trial is planned to evaluate cardiovascular outcomes with liraglutide in a higher risk population. The trial is expected to be completed September 2015 and submission of the complete report in April 2016.

- Liraglutide has a low potential for drug interactions via the cytochrome P450 pathways or interactions involving protein binding. Because liraglutide delays gastric emptying, there is a potential that co-administered oral drugs may be affected.
- The acquisition cost of liraglutide exceeds that of exenatide, the DPP-4 inhibitors, and TZDs (Table 9).

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. Liraglutide is the second agent in a class known as incretin mimetics.

Pharmacology/ Pharmacokinetics

GLP-1 is 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-4 (DPP-4) is the enzyme responsible for metabolizing GLP-1. Liraglutide is a human GLP-1 analog with a longer half-life than native GLP-1. Liraglutide has 97% homology to the amino acid sequence of native GLP-1. The structure of native GLP-1 has been modified; replacing lysine with arginine at position 34 and attaching a C16 fatty acid chain to lysine at position 26.

Table 1: Pharmacokinetics of Liraglutide

Absolute bioavailability following SQ injection	~ 55%
Cmax	35 ng/mL (after 0.6mg given SQ)
Tmax (median)	8-12h (after 0.6mg given SQ)
AUC	960 ng·h /mL(after 0.6mg given SQ)
Volume of distribution	13L (after 0.6mg given SQ) 0.07L (after IV administration)
Metabolism/elimination	metabolized by endogenous peptidases without a specific organ as a major route of elimination
Clearance	1.2 L/h after single dose
Elinination half-life (t1/2)	13h
Protein binding	>98% (primarily to albumin)

Data obtained from product package insert

FDA-Approved Indications

Liraglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise
- Has not been studied sufficiently in patients with a history of pancreatitis. Use caution
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with insulin.

Current VA Formulary Alternatives

None in this class

Dosage and Administration

- Administer once daily at any time of day, independently of meals
- Inject subcutaneously in the abdomen, thigh or upper arm
- The injection site and timing can be changed without dose adjustment

- Initiate at 0.6 mg per day for one week. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg
- When initiating liraglutide, consider reducing the dose of concomitantly-administered insulin secretagogues to reduce the risk of hypoglycemia
- No dosage adjustment is recommended for patients with renal or hepatic impairment. Because of limited experience cautious use in these patient populations is advised. The product labeling in the EU recommends that liraglutide currently cannot be recommended for use in moderate-severe renal impairment (including ESRD) and hepatic failure due to limited experience.

Risk Evaluation and Mitigation Strategies (REMS) Program
A medication guide is required to be dispensed with each liraglutide prescription. The goals are to:

- Inform providers about the risk of acute pancreatitis and the potential risk of medullary thyroid carcinoma associated with liraglutide
- Inform patients about the serious risks associated with liraglutide

Dosage Form/Strength

Liraglutide is available as a solution for subcutaneous injection in a pre-filled, multi-dose pen. Each pen delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL). It is available in packages containing 2 pens and 3 pens. Prior to first use, liraglutide should be refrigerated (36°F to 46°F). Once in use, liraglutide can be stored for 30 days at room temperature (59°F to 86°F) or in a refrigerator.

Efficacy

Glycemic control(A1C, fasting and post-prandial glucose)[1-6, 15]
Liraglutide reduced A1C as shown in Table 3. The mean baseline A1C in the clinical trials ranged from 8.2 to 8.5%. Duration of diabetes ranged from 5.4 to 9.4 years. In the combination trials, the majority of patients were receiving prior combination therapy. Those entering the trial on prior monotherapy had a greater decrease in A1C than those on prior combination therapy as were those previously treated with diet and exercise only. Similar to other drugs used to treat diabetes, the decrease in A1C is greater for those who had a baseline A1C of ≥ 10%. There was very little difference in A1C reduction between the 1.2mg and 1.6mg doses.

For patients with inadequate glycemic control on their prestudy oral drugs, the combination of liraglutide + glimepiride resulted in a greater decrease in mean A1C than rosiglitazone + glimepiride (-1.1 vs. -0.44%). The dose of rosiglitazone was 4mg daily and was not titrated to the maximum of 8mg daily. In LEAD-2, mean A1C was reduced to a similar extent (-1.0%) by liraglutide + metformin or glimepiride + metformin.

In LEAD-3, monotherapy with liraglutide resulted in a greater mean decrease in A1C than monotherapy with glimepiride. In LEAD-4, triple therapy with liraglutide + metformin + rosiglitazone decreased mean A1C by 1.5% compared to a 0.5% decrease with a 2-drug regimen of metformin + rosiglitazone.

LEAD-5 compared the combination of liraglutide or glargine with metformin + glimepiride. The dose of insulin glargine (mean 24 units daily) was titrated using the ATLANTUS protocol[14] (this does not use a treat-to-target method). The mean decrease in A1C was 1.3% with liraglutide and 1.1% with glargine.

The addition of liraglutide or exenatide to background oral antidiabetic drugs (metformin, SU, or both) was compared in LEAD-6. The mean decrease in A1C was 1.1% with liraglutide and 0.8% with exenatide.

In an open-label study of patients who had inadequate glycemic control on metformin, the addition of liraglutide decreased mean A1C by 1.2 and 1.5% for the 1.2mg and 1.8mg doses respectively, while the addition of sitagliptin 100mg reduced mean A1C by 0.9%. The greater reduction in A1C with liraglutide in this study compared to the

study by Nauck (LEAD-2) might be because in the LEAD-2 study, more than 60% of patients were on prior 2-drug therapy and had a longer duration of DM whereas in the Pratley study, patients had to have inadequate glycemic control on metformin monotherapy. Therefore, switching patients from one 2-drug regimen to another 2-drug regimen may not result in as great a reduction in A1C than when a second drug is added to a monotherapy regimen.[15]

Changes in fasting and post-prandial glucose followed a pattern similar to changes in A1C. Decrease in FPG was seen during the first 2 weeks. Post-prandial glucose was reduced similarly after each meal. In LEAD-6, liraglutide reduced FPG to a greater degree than exenatide; conversely, exenatide reduced PPG more than liraglutide.

Body Weight[1-6, 15]

Average weight loss was approximately 2-2.5kg when liraglutide was given as monotherapy and 2.6-3.8kg when combined with metformin (see table 3). When combined with sulfonylureas, there was a slight increase in mean weight with the 1.2mg dose (+0.3kg) and slight decrease in mean weight with the 1.8mg dose (-0.2kg).

In a triple therapy regimen including liraglutide, metformin, and rosiglitazone, the mean change in weight for the 1.2mg and 1.8mg dose was -1.0kg and -2.0kg respectively. In another trial, triple therapy with liraglutide 1.8mg + metformin + glimepiride resulted in a mean weight change of -1.8kg.

In the liraglutide versus insulin glargine study, patients lost an average of 1.8kg with liraglutide and gained an average of 1.6kg with insulin glargine.

Mean weight loss for liraglutide or exenatide added to oral hypoglycemic agents (SU, metformin, or both) was 3.2 and 2.9kg respectively (difference not significant). The proportion of patients who lost weight was similar (78% and 76% respectively).

Two trials stated that weight loss was independent of nausea; however, in LEAD-5 a small number of patients with sustained nausea (n=8) seemed to have greater weight loss (-3.2kg).[2, 5]

In the monotherapy trial, weight loss in the first 16 weeks was sustained throughout the 52-week study. Patients with > 7 days of nausea had a mean weight change of -3.24kg (1.2mg), -3.39kg (1.8), and -1.43kg (glimepiride). In comparison, those who had ≤ 7days of nausea had a weight loss of -1.85kg, -2.26kg, and +1.22kg respectively (difference not significant).[3]

The relationship between weight loss and A1C was assessed in LEAD-6. Those with weight loss had a mean decrease in A1C of 1.3% with liraglutide and 0.9% with exenatide. Those who did not lose weight had a mean decrease in A1C of 1.0% and 0.5% respectively. The difference in A1C reduction between those with and without weight loss was not significant.

Weight loss generally occurred within the first 12 weeks and was maintained thereafter. In LEAD studies 2-5, approximately 19-33% of patients receiving liraglutide had weight loss of 5% or greater.[10]

Lipids[1-6, 15]

A meta-analysis of the LEAD trials using liraglutide 1.8mg showed that mean change in total cholesterol, LDL-C, HDL-C and triglycerides were -5.0mg/dL, -7.7mg/dL, -1.5mg/dL, and -17.7mg/dL respectively.[11] However, results for individual trials were variable as shown in table 2.

Table 2: Liraglutide and Lipids

	Treatment Arms	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Triglycerides(mg/dL)
Marre LEAD-1	LIR 1.2mg + GLIM	-5.06*	-2.36*	-0.84	-17.64
	LIR 1.8mg + GLIM	-11.99*^	-8.09*	-1.57*	-14.72
	GLIM + RSG	+7.42	+4.43	+0.75	+1.73
	GLIM + PBO	+0.64	-1.33	-0.06	+7.78
Nauck LEAD-2	LIR 1.2mg + MET	+0.68	+5.92	+0.29^	-25.38^
	LIR 1.8mg + MET	-1.26	+4.59	-0.56	-24.59^
	MET + GLIM	+1.78	+7.35	-0.09	-14.52
	MET + PBO	+2.13	+3.40	-1.8	+15.56
Garber LEAD-3	LIR 1.2mg	+1.47	-2.43	-3.83	-7.55
	LIR 1.8mg	-2.51	-4.09	-3.88	-14.40
	GLIM 8mg	+0.68	-2.89	-3.94	+2.26
Zinman LEAD-4	LIR 1.2mg + MET +RSG	-8.2	-10.99^	-1.13	-33.81^
	LIR 1.8mg + MET + RSG	-7.64	-8.72	-1.68	-28.54
	MET + RSG+PBO	-7.7	-4.03	-1.35	-11.74
Russell-Jones LEAD-5	LIR 1.8mg + MET+ GLIM	-2.36	+4.19	-2.32	-21.79
	GLA + MET + GLIM	+2.77	+9.15	-2.07	-19.52
	MET + GLIM	-0.96	+5.22	-1.03	-17.45
Buse LEAD-6	LIR 1.8mg + OHA	-7.73	-17	-1.5	-36.3*
	EXE 10mcg BID + OHA	-3.48	-15.5	-1.9	-20.4
Pratley	LIR1.2mg + MET	-1.16	+3.1	0	-16.83
	LIR1.8mg + MET	-6.57*	+1.93	0	-38.1
	SIT100mg + MET	-0.77	+5.03	0	-35.43

EXEN=exenatide; HDL-C= high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; LIR=liraglutide; MET=metformin; OHA=oral hypoglycemia agent; RSG=rosiglitazone; SIT=sitagliptin; TC=total cholesterol; TG=triglycerides
*significant vs. comparator
^Significant vs. placebo

Blood Pressure and Pulse Rate[1-6, 15]

Treatment with liraglutide resulted in mean decrease in systolic blood pressure ranging from 0.6 – 6.7mmHg (Table 3). The greatest reduction was seen when liraglutide was combined with rosiglitazone and metformin. In general, there was no significant change in diastolic blood pressure. Pulse rate increased by 2-4 beats/minute and may possibly be a compensatory response to the decrease in blood pressure.

Extension Trials

There are 3 open-label extensions trials from LEAD trials: LEAD-2 (to complete 104 weeks), LEAD-3 (to complete 104 weeks and 156 weeks), and LEAD-6 (to complete 40 weeks and 78 weeks). See table 3 and appendix for more details.

Eighty-nine percent of patients (n=780) completing 26-weeks of the LEAD-2 trial entered the extension. Among these, 68% completed 2 years. Patient continued the treatment to which they were originally randomized. Change in A1C from baseline was not shown; however, A1C at endpoint for liraglutide + metformin was similar to glimepiride + metformin (mean range 7.38 – 7.44). Change in weight was maintained.[11]

Data from LEAD-3 (104 weeks) are available. Among the 487 patients completing the 52-week parent study, 440 entered the extension and 321 completed 2 years. Patients continued receiving the same treatment to which they were originally randomized. Improvement in glycemic parameters and weight loss was maintained.[7]

Data from LEAD-6 (40weeks) are available. All patients (n=389) completing the 26-week parent study entered the extension for an additional 14 weeks with 97% completing this phase. Those originally randomized to liraglutide continued liraglutide and those originally randomized to exenatide were switched to liraglutide. Improvement in glycemic parameters and weight loss was maintained in the group remaining on liraglutide. In the group switched from exenatide to liraglutide, additional improvement in these parameters was noted.[8, 9]

Table 3: Results of Selected Parameters

Study	Duration	Patients	Treatment arms	Change in A1C (%)§	A1C < 7% (%)	Change in FPG (mg/dL)	Change in PPG (mg/dL)‡	Baseline weight (kg)	Change in weight (kg)	Change in SBP (mmHg)
Marre (LEAD-1)	26-weeks	Inadequate control on OHA	LIR 0.6mg + GLIM	-0.60	24	-13	-32.4	82.6	+0.7	-0.9
			LIR 1.2mg + GLIM	-1.08	35	-28.3	-45	80	+0.3	-2.6
			LIR 1.8mg + GLIM	-1.13	42	-28.6	-48.6	83	-0.2	-2.8
			GLIM + RSG	-0.44	22	-15.8	-32.4	80.6	+2.1	-0.9
			GLIM + PBO	+0.23	8	+18.2	-7.2	81.9	-0.1	-2.3
Nauck (LEAD-2)	26-weeks	Inadequate control on OHA	LIR 0.6mg + MET	-0.7± 0.1	28	-19.8	-30.8	Not reported	-1.8	-0.6
			LIR 1.2mg + MET	-1.0± 0.1	35.3	-28.8	-41.4		-2.6	-2.8
			LIR 1.8mg + MET	-1.0± 0.1	42.4	-30.6	-46.8		-2.8	-2.3
			MET + GLIM	-1.0± 0.1	36.3	-23.4	-45		+1.0	+0.4
			MET + PBO	+0.1± 0.1	10.8	+7.2	-10.8		-1.5	-1.8
Garber (LEAD-3)	52-weeks	Drug-treatment naïve or on monotx with OHA up to ½ max dose	LIR 1.2mg	-0.84±1.23	42.8	-15.1	-30.8	92.5	-2.05	-2.12
			LIR 1.8mg	-1.14±1.24	50.9	-25.6	-37.4	92.8	-2.45	-3.64
			GLIM 8mg	-0.51±1.2	27.8	-5.2	-2.5	93.4	+1.12	-0.69
Zinman (LEAD-4)	26-weeks	Inadequate control on OHA	LIR 1.2mg + MET +RSG	−1.5±0.1	57.5	-40	-47	Not reported	-1.0	-6.7
			LIR 1.8mg + MET + RSG	−1.5±0.1	53.7	-44	-49		-2.0	-5.6
			MET + RSG	−0.5±0.1	28.1	-8	-14		+0.6	-1.1
Russell-Jones (LEAD-5)	26-weeks	Inadequate control on OHA	LIR 1.8 + MET+GLIM	-1.33 ± 0.09	53	-27.9	-32.4	85.5	-1.81	-3.97
			MET+GLIM	-0.24 ± 0.11	15	+9.54	+0.54	85.7	-0.42	+0.54
			Glargine+MET+GLIM	-1.09 ± 0.09	46	-32.2	-29	85	+1.62	-1.44
Buse (LEAD-6)	26-weeks	Inadequate control metformin, SU or both	LIR 1.8mg + OHA	-1.12 ± 0.08	54	-29	-24/-18†	93.1	-3.24	-2.51
			EXEN 10mcg BID + OHA	-0.79 ± 0.08	43	-10.8		93	-2.87	-2.0
LEAD-2 extension	104-weeks	Inadequate control on OHA	LIR 0.6mg + MET	7.74	19.7	Not reported	Not reported		-2.1	Not reported
			LIR 1.2mg + MET	7.44	29.9				-3.0	
			LIR 1.8mg + MET	7.38	31.1				-2.9	
			MET + GLIM	7.49	23.5				+0.68	
			MET + PBO	8.12	10.8				Not reported	
LEAD-3 extension	104-weeks	Drug-treatment naïve or on monotx with OHA up to ½ max dose	LIR 1.2mg	-0.9	53.3	-23.6	-34		-2.3	-0.01
			LIR 1.8mg	-1.1	58	-27.1	-46.6		-2.8	+0.15
			GLIM 8mg	-0.6	37	-6.2	-32.8		+1.0	+0.21
LEAD-6 extension	40-weeks	Inadequate control metformin, SU or both	LIR→LIR	-0.1±0.04	61	-3.6	Not reported		-0.4	-2.2
			EXE →LIR	-0.3±0.04	57	-16.2			-0.9	-3.8
Pratley	26-weeks	Inadequate control on metformin	LIR1.2mg + MET	-1.24	2.75^	-33.7	Not reported	93.7	-2.86	-0.55
			LIR1.8mg + MET	-1.5	4.50^	-38.5		94.6	-3.38	-0.72
			SIT100mg + MET	-0.9		-14.9		93.1	-0.96	-0.94

EXEN=exenatide; FPG-fasting plasma glucose; GLIM-glimepiride; LIR=liraglutide; MET=metformin; OHA=oral hypoglycemia agent; PBO=placebo; PPG=post-prandial glucose; RSG=rosiglitazone; SBP=systolic blood pressure; SIT=sitagliptin; SU=sulfonylurea

‡Determined using self-measured 7 or 8 point plasma glucose profile

†Values shown as estimated treatment difference after breakfast/dinner. Exenatide reduced PPG more than liraglutide.

§For the LEAD-2 extension trial, final A1C (not change in A1C) was shown

^ Value shown is odd ratio versus sitagliptin

Adverse Events (Safety Data)

The frequency of adverse events and withdrawal from study due to adverse events and deaths are shown in table 4. The percentage of patients reporting ≥ 1 adverse event in the liraglutide groups is slightly higher than the comparator arms. In LEAD trials 2, 3, 4, and 5 more patients receiving liraglutide withdrew from the trial due to adverse events. In the head-to-head trial of liraglutide versus exenatide, fewer patients in the liraglutide group withdrew due to adverse events. There were 5 deaths in the liraglutide groups (including 1 patient from a Phase III trial conducted in Japan) and 4 in the comparator groups.

Table 4: Frequency of Adverse Events[8, 10, 11, 15]

	Treatment Arms	≥1 AE (%)	Serious AEs (%)	Discontinued due to AE (%)	Deaths
LEAD-1	LIR 0.6mg + GLIM	-	3	-	None
	LIR 1.2mg + GLIM	69	4	4.8	
	LIR 1.8mg + GLIM	70	5	3.8	
	GLIM + RSG	62	3	3	
	GLIM + PBO	64	3	5.3	
LEAD-2	LIR 0.6mg + MET	-	-	-	1 patient in LIR 1.2mg group (liver cirrhosis, hepatocellular CA)
	LIR 1.2mg + MET	70	5.8	10	
	LIR 1.8mg + MET	74	3.7	12	
	MET + GLIM	61	4.1	3	
	MET + PBO	66	3.3	2	
LEAD-3	LIR 1.2mg	83	6.4 (16pts; 18 events)	10	1 patient in LIR 1.8mg group (acute pancreatic, colon CA) 1 patient in GLIM 8mg group (MVA)
	LIR 1.8mg	79	3.3 (8 pts; 9 events)	7.3	
	GLIM 8mg	71	5.2 (13 pts; 17 events)	6	
LEAD-4	LIR 1.2mg + MET +RSG	84	4.5 (8 pts; 8 events)	6	None
	LIR 1.8mg + MET + RSG	83	3.9 (7 pts; 10 events)	15	
	MET + RSG	70	6.9 (12 pts; 13 events)	3	
LEAD-5	LIR 1.8mg + MET+ GLIM	66	4	4.7	1 patient in LIR group (renal cell CA) 2 patients in comparator group (AMI)
	GLA + MET + GLIM	55	7	2.1	
	MET + GLIM	56	7	0.9	
LEAD-6	LIR 1.8mg + OHA	75	5.1	9.8	None
	EXE 10mcg BID + OHA	79	2.6	13.4	
LEAD-6 Extension	LIR→LIR	37.6	5 pts; 8 events	0	1 patient in LIR group (stroke)
	EXE →LIR	37.4	4pts; 7 events	3.2	1 patient from EXE→LIR (MI)1
Pratley	LIR 1.2mg + MET	66	3.0	6.2	None
	LIR 1.8mg + MET	73	3.0	6.8	N=1(pancreatic CA dx on day 11)
	SIT + MET	58	2.0	1.8	N=1(MI on day 48)

AE=adverse events; EXEN=exenatide; GLIM-glimepiride; LIR=liraglutide; MET=metformin; OHA=oral hypoglycemia agent; PBO=placebo; RSG=rosiglitazone; SIT=sitagliptin; SU=sulfonylurea

Adverse GI effects[10-11, 15]

In the LEAD trials (LEAD-6 excluded), adverse GI events were reported in 41% and 17% of liraglutide- and comparator-treated groups respectively and tended to be dose-related. The most common GI adverse events included nausea, vomiting, diarrhea, dyspepsia and constipation. Approximately 13% of liraglutide-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. The incidence of nausea decreased over time. In LEAD-4, nausea was transient with 216 events occurring during weeks 1-4 and 65 events during weeks 4-26. In LEAD-5, the incidence of nausea decreased to 1.5% after 14 weeks of treatment.

Overall, 5% of liraglutide-treated patients and 0.5% of those in the comparator groups withdrew from the study due to adverse GI events. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

Initially, the incidence of nausea was similar between liraglutide and exenatide, but less persistent with liraglutide over time. The proportion of those with nausea by week 6 was 8.1% with liraglutide and 15.8% with exenatide. By week 26 it was 3% and 9% for liraglutide and exenatide respectively.[6]

Table 5: Percent patients experiencing ≥ 1 adverse GI event(s) [10,11, 15]

	Treatment Arms	Nausea (%)	Vomiting (%)	Diarrhea (%)	Study withdrawal due to adverse GI event (%)
Marre (LEAD-1)	LIR 0.6mg + GLIM	NR	NR	NR	Nausea (0.9-2.2%) Vomiting (0.4 – 0.9%) Diarrhea (0-1.3%) Range of withdrawals shown across all groups
	LIR 1.2mg + GLIM	10.5	4.4	7.9	
	LIR 1.8mg + GLIM	7	NR	NR	
	GLIM + RSG	3	NR	NR	
	GLIM + PBO	2	NR	NR	
Nauck (LEAD-2)	LIR 0.6mg + MET	11	5-7 (all LIR)	10	1
	LIR 1.2mg + MET	16		8	5
	LIR 1.8mg + MET	19		15	8
	MET + GLIM	NR	1	4	0
	MET + PBO	4	1	4	0
Garber (LEAD-3)	LIR 1.2mg	27.5	12.4	15.5	4
	LIR 1.8mg	29.3	9.3	18.7	2
	GLIM 8mg	8.5	3.6	8.9	0
Zinman (LEAD-4)	LIR 1.2mg + MET +RSG	29	7	NR	3
	LIR 1.8mg + MET + RSG	40	17	NR	11
	MET + RSG	NR	NR	NR	0
Russell-Jones (LEAD-5)	LIR 1.8 + MET+GLIM	13.9	6.5	10	N=4
	MET+GLIM	3.5	3.5	5.3	0
	Glargine+MET+GLIM	1.3	0.4	1.3	0
Buse (LEAD-6)	LIR 1.8mg + OHA	25.5	6.0	12.3	8.1
	EXEN 10mcg BID + OHA	28	9.9	12.1	9.5
LEAD-3 extension (total 2 yrs)	LIR 1.2mg/1.8mg	30	NR	20-25	0
	GLIM 8mg	NR		10	
LEAD-6 extension (total 40wks)	LIR→LIR	1.5†	2.0		Nausea (0.5%)
	EXE →LIR	3.2†	0.5		
Pratley	LIR 1.2mg + MET	21	8	7	NR
	LIR 1.8mg + MET	27	10	11	
	SIT + MET	5	4	5	

EXEN=exenatide; GLIM-glimepiride; LIR=liraglutide; MET=metformin; NR= not reported; OHA=oral hypoglycemia agent; PBO=placebo; RSG=rosiglitazone; SIT=sitagliptin; SU=sulfonylurea
†Incidence shown is for nausea and diarrhea

Hypoglycemia[10-11]

Most cases of hypoglycemia were considered minor. Major hypoglycemia requiring assistance of another person occurred in 7 liraglutide-treated patients (2.6 cases per 1000 patient-years). Among these 7 patients, 6 were receiving a sulfonylurea concomitantly.

Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in extension trials. Both patients were receiving liraglutide, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

There was no difference in frequency of minor events between liraglutide and insulin glargine; however, there were 6 major events in the liraglutide group and none in the glargine group. In the liraglutide versus exenatide trial there were fewer events in the liraglutide group (1.93 vs. 2.6 events/patient-year).

Table 6: Frequency of Hypoglycemia[10-11]

	Treatment Arms	Minor hypoglycemia % (events/patient-year)	Major hypoglycemia	Comments
Marre LEAD-1	LIR 0.6mg + GLIM LIR 1.2mg + GLIM LIR 1.8mg + GLIM GLIM + RSG GLIM + PBO	5.2 (0.17) 9.2 (0.51)* 8.1 (0.47)* 4.3 (0.12) 2.6 (0.17)	LIR 1.8 + GLIM (n=1)	Major hypo case occurred 9 days after treatment was started. Third party assistance was needed. Dose of GLIM was reduced from 4mg to 3mg.
Nauck LEAD-2	LIR 1.2mg + MET LIR 1.8mg + MET MET + GLIM MET + PBO	All LIR 3.6 (0.05)* 22.3 (0.87) 2.5 (0.06)	LIR1.2 + MET (n=1)	Event occurred during hospitalization and after insulin infusion
Garber LEAD-3	LIR 1.2mg LIR 1.8mg GLIM 8mg	12 (0.30 events/yr)* 8 (0.25 events/yr)* 24 (1.96 events/yr)	No major hypoglycemic events reported	
Zinman LEAD-4	LIR 1.2mg + MET +RSG LIR 1.8mg + MET + RSG MET + RSG	9.0 (0.4) 7.9 (0.6)^ 5.1 (0.2)	No major hypoglycemic events reported	
Russell-Jones LEAD-5	LIR 1.8mg + MET+ GLIM GLA + MET + GLIM MET + GLIM	27.4 (1.2) 28.9 (1.3) 16.7 (1.0)	2.2 (0.06 events/pt-yr) 0 0	5 patients (6 events) had major hypo in the LIR group (1 required medical assistance). None were nocturnal
Buse LEAD-6	LIR 1.8mg + OHA† EXE 10mcg BID + OHA†	26 (1.93)* 34 (2.6)	0 (n=2)	The 2 cases occurred in patients receiving exenatide + SU
LEAD-2 extension (total 2 yrs)	LIR 1.2mg + MET LIR 1.8mg + MET MET + GLIM MET + PBO	0.15 0.15 1.60‡ 0.16	Not reported	
LEAD-3 extension (total 2 yrs)	LIR 1.2mg LIR 1.8mg GLIM 8mg	0.21* 0.22* 1.75	0 1 0	Major hypoglycemia occurred following administration of regular insulin during a diagnostic test
LEAD-6 extension (total 40wks)	LIR1.8mg→LIR1.8mg EXEN→LIR1.8mg	0.7 1.3	1 0	
Pratley	LIR 1.2mg + MET LIR 1.8mg + MET SIT+MET	5 (0.178) 5 (0.370) 5 (0.106)	1 0 0	Blood glucose was 64.8; no seizure or coma occurred

EXEN=exenatide; GLIM-glimepiride; LIR=liraglutide; MET=metformin; OHA=oral hypoglycemia agent; PBO=placebo; RSG=rosiglitazone; SIT=sitagliptin; SU=sulfonylurea
†metformin, sulfonylurea, or metformin + sulfonylurea
*Significant vs. comparator
^Significant vs. placebo
‡Significant vs. all liraglutide doses

Pancreatitis[10, 15]

In the LEAD trials, there were 7 cases of pancreatitis among liraglutide-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Among the 7 liraglutide cases, 5 were reported as acute pancreatitis and 2 were reported as chronic pancreatitis. Pancreatitis with necrosis leading to death was observed in 1 patient; however, clinical causality could not be established.

Some patients had other risk factors for pancreatitis (e.g., history of cholelithiasis, alcohol abuse). There are no conclusive data establishing a risk of pancreatitis with liraglutide treatment. Table 7 shows the reported cases of pancreatitis from the LEAD trials.

In LEAD-1, five patients with prior histories of pancreatitis entered the study. None of these patients developed pancreatitis during the study. Liraglutide has not been studied sufficiently in patients with a history of a pancreatitis.

Table 7: Reports of Pancreatitis [10, 15]

	Liraglutide groups	Comparators	Comments
LEAD-1	LIR 0.6mg + glimerpiride (n=1)	0	Chronic pancreatitis reported after 157 days of liraglutide; continued therapy and completed trial
LEAD-2	LIR 1.2mg + metformin (n=1)	Glimepiride + metformin (n=1)	Acute pancreatitis reported after 50 days of liraglutide and 63 days of comparator. Patient in comparator group had elevated TG (>1500mg/dl) prior to the event. Both were withdrawn from the study. Both were hospitalized for 1 week and recovered
LEAD-3	LIR 1.2mg (n=1) LIR 1.8mg (n=2)	0	Acute pancreatitis was reported after 197 days of therapy (LIR 1.2mg) and this patient continued in the study. Patient had history of regular alcohol use. Acute pancreatitis was reported after 333 days of therapy (LIR 1.8mg). This patient was withdrawn from the trial. Both patients recovered. Acute pancreatitis reported after 669 days. Patient died. Autopsy showed acute and chronic pancreatitis and cholelithiasis
LEAD-4	0	0	
LEAD-5	0	0	
LEAD-6	LIR 1.8mg (n=2)	0	Chronic pancreatitis reported after 88 days of liraglutide. Patient continued trial Acute pancreatitis reported after 419 days. Patient recovered. This case was reported after the cut-off of the 120-day Safety Update
Pratley	0	0	

The manufacturer recommends after initiation of liraglutide and after dose increases, to observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, liraglutide and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, liraglutide should not be restarted. Use with caution in patients with a history of pancreatitis.

Calcitonin

C-cell hyperplasia and neoplasia were seen in pre-clinical studies using rodents; however, these findings were not observed in monkeys. C-cells comprise a very small fraction of the thyroid in humans, but are abundant in rodents. The function of the C-cell is to synthesize and release calcitonin. It was found that GLP-1 agonists can activate rodent C-cells causing calcitonin release. Continued activation could lead to C-cell proliferation in rodents. Spontaneous development of C-cell tumors is common in rats. GLP-1 receptors are found in rodent C-cells, but have not been definitively identified in human C-cells.[10]

Because of the preclinical findings in rodents, calcitonin levels were monitored in the Phase 3 clinical trials. Calcitonin levels were measured approximately every 3 months during the studies including 2 extension trials. The normal reference range for the calcitonin assay used in the clinical trials was 0.7-5.0ng/ml (females) and 0.7-8.4ng/ml (males).

> Mean serum calcitonin levels were higher in liraglutide-treated patients compared to placebo, but not compared to those receiving an active comparator. Mean values were approximately 1.0ng/ml (between group treatment-difference $\leq$ 0.1ng/ml).[12]
>
> A shift from normal calcitonin value to above the upper limit of the reference range occurred in 1.9% receiving liraglutide 1.8mg. In the liraglutide 0.6mg and 1.2mg and comparator groups 0.8 to 1.1% of patients had a shift in calcitonin value from normal to above the upper limit of normal. Calcitonin measurements were made out to 5-6 months. [12]
>
> In trials with calcitonin measurements out to 12 months, 1.3% (1.8mg), 0.6% (1.2mg), 0 (placebo), and 1.0% (active-comparator) had values that increased to outside the upper limit.[12]

C-cell hyperplasia
There were 6 reports of C-cell hyperplasia among the patients in the LEAD trials. Five of these reports were in patients receiving liraglutide and 1 was in the active comparator group. In the liraglutide groups, 4 out 5 had elevated calcitonin levels at baseline and throughout the studies and 1 developed an increased level while on therapy.[12]

Thyroid Neoplasms[10]
Thyroid neoplasms were the most commonly reported neoplasm adverse event. Approximately 80% were benign nodules. The rates of benign thyroid neoplasms were 7.0 and 2.5 events/1000-patient years for liraglutide and non-liraglutide groups respectively.

Papillary thyroid cancer was diagnosed in 5 liraglutide-treated patients and in 1 patient in the comparator group. The rates of papillary thyroid cancer were 1.6 and 0.6 events/1000-patient years for liraglutide and non-liraglutide groups respectively. All but one patient had an elevated calcitonin level at baseline. The diagnosis in 4 of the 6 cases was papillary microcarcinoma. The clinical importance of papillary microcarcinoma is uncertain because there are few data evaluating outcomes.

There was 1 case of medullary thyroid carcinoma reported in a patient from a comparator group. This patient had a pre-treatment calcitonin level > 1000ng/ml.

Post-marketing requirements:
- A five-year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to liraglutide.
- Medullary thyroid carcinoma case series registry of at least 15 years
- Additional animal studies in mice to further evaluate the potential risk of medullary thyroid cancer in humans.

Other thyroid adverse events[10]
There was no difference in the rate of endocrine disorders (e.g., goiter, hypo- or hyperthyroidism, autoimmune thyroiditis, etc.) between liraglutide (10.2 events/1000-patients years) and non-lirglutide groups (10.7 events/1000-patient years).

The rates of abnormal thyroid-related blood tests were 13.8 and 8.2 events/1000-patients years for liraglutide and non-liraglutide groups respectively.

Liraglutide antibodies
In the 26-week LEAD trials, the percentage of patients who were positive for liraglutide antibodies at the end of treatment were 9.2%, 8.2%, and 8.1% for LIR0.6, LIR1.2, and LIR1.8mg respectively. The presence of antibodies did not appear to alter the glucose-lowering effect of liraglutide.[10]

Infections occurred in 40% of patients who were positive for liraglutide antibodies compared to 36% who received liraglutide, but were antibody negative, and 34-35% in the comparator groups. Specifically, non-serious upper respiratory tract infections occurred in 11% those with liraglutide antibodies and 5-7% in all other groups.[12]

Events that are potentially immunologically-related (e.g., urticaria, angioedema) occurred in 0.8% of liraglutide-treated patients versus 0.4% of comparator-treated patients. Urticaria accounted for most of these events. All but 1 immunologically-related event was considered non-serious. There was 1 case of angioneurotic edema deemed serious that occurred within minutes of administration of an oral spray antibiotic. Those who developed liraglutide antibodies were not more likely to have an immunologic reaction compared to those who did not develop antibodies. [12]

Cardiovascular Safety
In December 2008, the FDA issued guidance on characterizing cardiovascular safety for new diabetes therapies. Because, the liraglutide application for approval was submitted prior to December 2008, the manufacturer had not designed trials according to the guidance. The FDA did perform an analysis of major cardiovascular adverse events (MACE) on the available data. The FDA recommends that point estimates and 95% confidence limits be calculated comparing the incidence of events with the investigational drug to that occurring in the control group. If pre-marketing data showed an upper bound of the 95% CI to be < 1.8, the new agent could be approved without additional pre-approval commitment for assessing cardiovascular safety.

Most point estimates in the main analyses were less than 1 with the upper bound of the 95% CI < 1.8. The FDA determined there was no evidence of excess cardiovascular risk associated with liraglutide. However, the FDA is requiring that a post-marketing study be conducted.[10]

A 5-year trial is planned to evaluate cardiovascular outcomes with liraglutide in a higher risk population. The trial is expected to be completed September 2015 and submission of the complete report in April 2016.

Cardiac Electrophysiology (QTc)
The effect of liraglutide on QTc interval was evaluated in healthy volunteers (n=51) in a randomized placebo-controlled, double-blind crossover study. Liraglutide 0.6, 1.2, 1.8mg and placebo were each given once daily for 7 days. Four different models for QT correction were used. Baseline subtracted difference in QTc interval was not found to increase compared to placebo when measured at various time points. There were no QTc values above 500ms or QTc increase of > 60ms.[13]

Contraindications
Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2.

Warnings and Precautions
Liraglutide has the following black box warning

WARNING: RISK OF THYROID C-CELL TUMORS Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Sentinel Events
No data

Look-alike/Sound-alike (LASA) Error Risk Potential
As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion.

Using the 4 data sources mentioned above, no LASA names were listed for liraglutide or brand name Victoza. Based on clinical judgment Vidaza™ might be considered as a candidate for LASA confusion; however, the potential for mix-up is expected to be low due to the different dose and indications. Vidaza (used for myelodysplastic syndromes) comes as a 100mg injection that needs to be reconstituted whereas Victoza comes as 3mL pre-filled pens (6mg/mL).

Drug Interactions[12]

Liraglutide has a low potential for drug interactions via the cytochrome P450 pathways or interactions involving protein binding. Because liraglutide delays gastric emptying, there is a potential that co-administered oral drugs may be affected.

The drug-drug interaction studies were performed at steady state with liraglutide1.8 mg/day. Administration of the interacting drugs was timed so that Cmax of liraglutide (8-12 h) would coincide with the absorption peak of the co-administered drugs. The co-administered drugs were given as a single dose. There were no significant interactions requiring a dosage adjustment.

Table 8: Effect of liraglutide on the pharmacokinetics of co-administered drugs[12]

	Digoxin 1mg	Lisinopril 20mg	Atorvastatin 40mg	Acetaminophen 1000mg	Griseofulvin 500mg	Ethinylestradiol 0.03 mg/ levonorgestrel 0.15 mg
Cmax	↓31%	↓27%	↓38%	↓31%	↑37%	↓12% (EES)/↓13% (LEV)
AUC	↓16%	↓15%	No change	No change	No change	No change (EES)/ ↑18% (LEV)
Time to Tmax	Delayed by 1/2h	Delayed by 2h	Delayed by 2h	Delayed up to 15 min	No change	Delayed by 1.5h (both)

AUC=area under the curve; Cmax=maximum concentration; EES= ethinylestradiol; LEV= levonorgestrel; Tmax=time to maximum concentration

Cost

Table 9: VA Acquisition Cost

	Usual daily dose	Dosing Frequency	Cost/day	Cost/month
Liraglutide	1.2mg	Once daily	$6.00	$180.25
	1.8mg		$9.00	$270.37
Exenatide	5mcg	Twice daily	$4.22	$119.34
	10mcg		$4.96	$140.24
Sitagliptin	50mg	Once daily	$3.78	$113.50
	100mg		$3.75	$112.50
Saxagliptin	2.5mg	Once daily	$4.28	$128.40
	5mg		$4.09	$122.70
Pioglitazone	15mg	Once daily	$2.62	$78.60
	30mg		$4.00	$120.10
	45mg		$4.30	$128.98
Rosiglitazone	4mg	Once or twice daily	$2.26	$67.90
	8mg		$4.08	$122.40

Does not take into account tablet splitting of rosiglitazone 8mg or twice daily dosing of the 2mg and 4mg tablets
Prices accessed March 2010

Conclusions

Liraglutide offers another option for add-on therapy when oral agents (i.e. metformin, sulfonylureas, TZDs) no longer provide adequate glycemic control. Of interest to the VA is how liraglutide compare to insulin or exenatide when added to 2 oral agents. Apart from its effect on weight, it does not appear to offer a significant advantage over insulin glargine at the doses used in the trial. In comparison to exenatide, liraglutide reduced A1C slightly more, had fewer minor hypoglycemic events, less persistent nausea, and is dosed once daily.

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Appendix 1: Liraglutide Studies

<table>
<tr><th>Study</th><th>Inclusion/Exclusion</th><th>Dosage</th><th>Demographics/Baseline values</th><th>Results</th></tr>
<tr>
<td>Marre 2009
LEAD-1
R, DB, DD, PC
26-week
N=1041

ITT (≥ 1 dose taken)

Conducted primarily in Europe and Asia</td>
<td><u>Inclusions:</u>
Type 2 DM
18-80 years old
HbA1c 7-11% on OHA monotherapy ≥ 3 months
HbA1c 7-10% on OHA combination therapy ≥ 3 months
BMI ≤ 45kg/m2

<u>Exclusions:</u>
Used insulin during previous 3 months
Impaired liver/renal fx
BP ≥ 180/100mmHg
Cancer
Other meds that can affect glucose</td>
<td>LIR 0.6mg + GLIM 2-4mg
LIR 1.2mg + GLIM 2-4mg
LIR 1.8mg + GLIM 2-4mg
Placebo + GLIM 2-4mg
GLIM 2-4mg + RSG 4mg

All drugs taken once daily</td>
<td><u>Values for LIR 0.6; LIR 1.2; LIR 1.8; PBO; RSG respectively</u>

Age (years): 55.7±9.9; 57.7±9; 55.6±10; 54.7± 10; 56 ± 9.8
Male (%): 54; 45; 53; 47; 47
BMI (kg/m2): 30.± 5; 29.8±5.1; 30±5.1; 30.3± 5.4; 29.4 ± 4.8
Weight (kg): 82.6± 17.7; 80 ± 17.1; 83 ± 18.1; 81.9 ± 17.1; 80.6 ± 17
DM duration (years): 6.5; 6.7; 6.5; 6.5; 6.6
HbA1c (%): 8.4±1.0; 8.5±1.1; 8.5±0.9; 8.4±1.0; 8.4±1.0
FPG (mg/dL): 180 ±43.2; 176.4± 48.6; 174.6 ±43.2; 171 ±36; 178.2 ± 45
Monotherapy (%): 30; 31; 27; 32; 32

Mean ±SD unless otherwise noted</td>
<td>
<table>
<tr><th></th><th>LIR 0.6 + GLIM</th><th>LIR 1.2 + GLIM</th><th>LIR 1.8 + GLIM</th><th>PBO + GLIM</th><th>GLIM + RSG</th></tr>
<tr><td>Completers (%)</td><td>89</td><td>86</td><td>91</td><td>73</td><td>84</td></tr>
<tr><td>A1C (%)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>All patients</td><td>-0.60*</td><td>-1.08*^</td><td>-1.13*^</td><td>+0.23</td><td>-0.44</td></tr>
<tr><td>Prior monotx</td><td>-0.8*</td><td>-1.4*^</td><td>-1.5*^</td><td>-0.4</td><td>-0.8</td></tr>
<tr><td>Prior combotx</td><td>-0.4*</td><td>-0.7*^</td><td>-0.8*^</td><td>+0.7</td><td>-0.01</td></tr>
<tr><td>A1c <7% (%)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>All patients</td><td>24*</td><td>35*^</td><td>42*^¶</td><td>8</td><td>22*</td></tr>
<tr><td>Prior monotx</td><td>31</td><td>55</td><td>52</td><td>11</td><td>36</td></tr>
<tr><td>Prior combotx</td><td>20</td><td>24</td><td>36</td><td>5</td><td>15</td></tr>
<tr><td>FPG (mg/dL)</td><td>-13*</td><td>-28.3*^</td><td>28.6*^</td><td>+18.2</td><td>-15.8*</td></tr>
<tr><td>PPG (mg/dl) ‡</td><td>-32.4*</td><td>-45*^</td><td>-48.6*^</td><td>-7.2</td><td>-32.4*</td></tr>
<tr><td>Weight (kg)</td><td>+0.7*^</td><td>+0.3^</td><td>-0.2^</td><td>-0.1</td><td>+2.1</td></tr>
<tr><td>SBP (mmHg)§</td><td>-0.9</td><td>-2.6</td><td>-2.8</td><td>-0.9</td><td>-2.3</td></tr>
<tr><td>Liraglutide antibodies (%)</td><td>Not shown</td><td>12.7</td><td>9.3</td><td>NA</td><td>NA</td></tr>
<tr><td>Calcitonin (ng/L)</td><td>Not shown</td><td>1.04</td><td>1.01</td><td>0.93</td><td>0.97</td></tr>
</table>
*Significant vs. GLIM + PBO
^Significant vs. GLIM + RSG
¶Significant vs. LIR 1.2 + GLIM
‡Average of values obtained 90 minutes after breakfast, lunch and dinner
§Reduction in DBP occurred in all groups (0.7-1.4mmHg) with no significant difference between groups
</td>
</tr>
<tr>
<td>Nauck 2009
LEAD-2
R, DB, DD, PC
26-week
N=1087

ITT (at least 1 dose of drug and 1 post-baseline measurement of parameter)</td>
<td><u>Inclusions:</u>
Type 2 DM
18-80 years old
HbA1c 7-11% on OHA monotherapy ≥ 3 months
HbA1c 7-10% on OHA combination therapy ≥ 3 months
BMI ≤ 40kg/m2

<u>Exclusions:</u>
Used insulin during previous 3 months</td>
<td>2:2:2:2:1 randomization
• Stratified according to OHA mono or combination therapy
• Prior to randomization: 3-week forced titration of metformin to 2000mg/d then 3-week metformin maintenance period (if on prior metformin, may advance to maintenance period)
• After randomization, 2-3 week titration period for LIRA or glimepiride

LIR 0.6mg +metformin
LIR 1.2mg + metformin</td>
<td><u>Values for LIR 0.6; LIR 1.2; LIR 1.8; GLIM; PBO respectively</u>

Age (years): 56±11; 57±9; 57±9; 57± 9; 56± 9
Male (%): 62; 54; 59; 57; 60
BMI (kg/m2): 30.5±4.8; 31.1±4.8; 30.9±4.6; 31.2±4.6; 31.6± 4.4
DM duration (years): 7 ±5; 7 ±5; 8 ± 5; 8 ± 5; 8 ± 6
HbA1c (%): 8.4±0.9; 8.3±1.0; 8.4±1.0; 8.4±1.0; 8.4±1.1
FPG (mg/dL): 183.6 ±43.2; 178.2± 41.4; 181.8 ±41.4; 180 ±46.8; 180 ± 41.4</td>
<td>
<table>
<tr><th></th><th>LIR 0.6 + MET</th><th>LIR 1.2 + MET</th><th>LIR 1.8 + MET</th><th>GLIM + MET</th><th>PBO + MET</th></tr>
<tr><td>Completers (%)</td><td>86</td><td>82</td><td>79</td><td>86</td><td>61</td></tr>
<tr><td>A1C (%)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>All patients</td><td>-0.69± 0.1*</td><td>-0.97± 0.1*</td><td>-1.0± 0.1*</td><td>-0.98± 0.1</td><td>+0.09± 0.1</td></tr>
<tr><td>Prior monotx</td><td>-0.86</td><td>-1.25</td><td>-1.30</td><td>-1.15</td><td>-0.38</td></tr>
<tr><td>Prior combotx</td><td>-0.51</td><td>-0.68</td><td>-0.71</td><td>-0.78</td><td>+0.47</td></tr>
<tr><td>A1c <7% (%)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>All patients</td><td>28*</td><td>35.3*</td><td>42.4*</td><td>36.3</td><td>10.8</td></tr>
<tr><td>Prior monotx</td><td>43.2</td><td>52.8</td><td>66.3</td><td>56</td><td>22.5</td></tr>
<tr><td>Prior combotx</td><td>20.3</td><td>24.5</td><td>30.1</td><td>25.3</td><td>5</td></tr>
<tr><td>FPG (mg/dL)</td><td>-19.8*</td><td>-28.8*</td><td>-30.6*</td><td>-23.4</td><td>+7.2</td></tr>
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<tr>
<td></td>
<td></td>
<td>LIR 2.8mg + metformin
Glimepiride 4mg + metformin
Placebo + metformin</td>
<td>Monotherapy (%): 34; 38; 34; 37; 34
Pre-study metformin (%): 86; 86; 87; 92; 93
Pre-study SU (%): 11; 13; 13; 8; 7
HOMA-B (%): 40; 47; 43; 43; 45

Mean ±SD unless otherwise noted</td>
<td>
<table>
<tr><td>PPG (mg/dl) ‡</td><td>-30.8*</td><td>-41.4*</td><td>-46.8*</td><td>-45</td><td>-10.8</td></tr>
<tr><td>Weight (kg)</td><td>-1.8± 0.2^</td><td>-2.6± 0.2^</td><td>-2.8± 0.2^</td><td>+1.0±0.2</td><td>-1.5± 0.3</td></tr>
<tr><td>SBP (mmHg)§</td><td>-0.6</td><td>- 2-3^</td><td>- 2-3^</td><td>- 0.4</td><td>-1.8</td></tr>
<tr><td>Calcitonin (ng/L)</td><td>Not reported</td><td>0.96</td><td>0.94</td><td>0.87</td><td>0.86</td></tr>
</table>
*Significant vs. PBO + MET
^Significant vs. GLIM + MET
Significance not determined for GLIM + MET vs. PBO + MET
‡ mean post-prandial glucose from self-monitored 7-point measurements at end of study
§no change in diastolic BP
</td>
</tr>
<tr>
<td>Garber 2008
LEAD-3
R, DB, DD, AC, PR

Conducted in USA (126 sites) and Mexico(12 sites)

N=745

52-weeks

ITT (LOCF)</td>
<td><u>Inclusions:</u>
Type 2 DM
18-80 years old
Diet/exercise treated or up to half maximum dose of OHA as monotherapy for ≥ 2 months
HbA1c 7-11% (diet/ exercise treated)
HbA1c 7-10% (OHA treated)
BMI ≤ 45kg/m^2

<u>Exclusions:</u>
Treatment with insulin during previous 3 months (unless short-term for intercurrent illness)
Treatment with systemic steroids
Hypoglycemia unawareness or recurrent severe hypoglycemia
AST or ALT ≥ 2.5x ULN</td>
<td>Groups stratified by prior treatment (diet/exercise vs. OHA)
1:1:1 randomization
Prior OHAs were discontinued

Liraglutide 1.2mg once daily (n=251)
Liraglutide 1.8mg once daily (n=246)
Glimepiride 8mg once daily (n=248)

Forced-titration to above doses</td>
<td><u>Values for LIR 1.2; LIR 1.8, GLIM 8 respectively</u>

Age (years): 53.7±11; 52±10.8; 53.4±10.9
Male (%): 47; 49; 54
Weight (kg): 92.5±19.2; 92.8±20.7; 93.4±19.2
BMI (kg/m2): 33.2±5.6; 32.8±6.3; 33.2±5.6
DM duration (years): 5.2±5.5; 5.3±5.1; 5.6±5.1
HbA1c (%): 8.3±1.0; 8.3±1.1; 8.4±1.2
FPG (mg/dL): 167.4±46.8; 171±46.8; 171±46.8
PPG (mg/dL): 203.4±43.2; 205.2±45; 205.2±48.6
% prestudy tx (diet/exercise): 36; 35; 38

Mean ±SD unless otherwise noted</td>
<td>
<table>
<tr><th></th><th>LIR 1.2mg</th><th>LIR 1.8mg</th><th>GLIM 8mg</th></tr>
<tr><td>Completers (%)</td><td>64.5</td><td>70</td><td>61.3</td></tr>
<tr><td>A1C(%)</td><td></td><td></td><td></td></tr>
<tr><td>All patients</td><td>-0.84±1.23*</td><td>-1.14±1.24*^</td><td>-0.51±1.2</td></tr>
<tr><td>Prior diet/exercise</td><td>-1.19±0.15*</td><td>-1.6±0.15*</td><td>-0.88±0.13</td></tr>
<tr><td>Prior OHA</td><td>-0.47 ±0.1*</td><td>-0.71±0.09*</td><td>-0.17±0.08</td></tr>
<tr><td>A1C <7% (%)</td><td></td><td></td><td></td></tr>
<tr><td>All patients</td><td>42.8</td><td>50.9</td><td>27.8</td></tr>
<tr><td>Prior diet/exercise</td><td>58.3*</td><td>62*^</td><td>30.8</td></tr>
<tr><td>Prior OHA</td><td></td><td></td><td></td></tr>
<tr><td>FPG (mg/dL)</td><td>-15.1*</td><td>-25.6*^</td><td>-5.2</td></tr>
<tr><td>PPG (mg/dL)¶</td><td>-30.8</td><td>-37.4*</td><td>-2.5</td></tr>
<tr><td>Weight (kg)</td><td></td><td></td><td></td></tr>
<tr><td>Had no or < 7d nausea</td><td>-1.85*</td><td>-2.26*</td><td>+1.22</td></tr>
<tr><td>Had ≥ 7d nausea‡</td><td>-3.24</td><td>-3.39</td><td>-1.43</td></tr>
<tr><td>SBP (mmHg)</td><td>-2.12</td><td>-3.64</td><td>+0.69</td></tr>
<tr><td>Calcitonin (ng/L)</td><td>0.93</td><td>0.94</td><td>0.83</td></tr>
</table>
*Significant vs. GLIM
^Significant vs. LIR 1.2
¶Determined from self-monitored 8-point glucose profiles
‡Number of patients were 29, 38 and 9 for LIR 1.2, LIR 1.8 and GLIM respectively
</td>
</tr>
<tr>
<td>Zinman 2009
LEAD-4
USA and Canada
R, DB, PC
26-week
N=533

ITT analysis</td>
<td><u>Inclusions:</u>
Type 2 DM
Age 18-80 years
HbA1c 7-11% on OHA monotherapy ≥ 3 months
HbA1c 7-10% on OHA combination therapy ≥ 3 months
BMI ≤ 45kg/m2
Had FPG 135-230mg/dL</td>
<td>1:1:1 randomization
Before randomization, 6-9 week metformin and RSG run-in

LIR 1.2mg + MET 1g BID + RSG 4mg BID

LIR 1.8mg + MET 1g BID + RSG 4mg BID</td>
<td><u>Values for LIR 1.2; LIR 1.8; PBO respectively</u>

Age (years): 55±10; 55±11; 55±10
Male (%): 57; 51; 62
BMI (kg/m2): 33.2±5.4; 33.5±5.1; 33.9±5.2
DM duration (years): 9 ±6; 9 ±6; 9 ± 6
HbA1c (%): 8.5±1.2; 8.6±1.2;</td>
<td>
<table>
<tr><th></th><th>LIR 1.2 + MET + RSG</th><th>LIR 1.8 + MET + RSG</th><th>MET + RSG + PBO</th></tr>
<tr><td>Completers (%)</td><td>86</td><td>75</td><td>68</td></tr>
<tr><td>A1C (%)</td><td>−1.5±0.1*</td><td>−1.5±0.1*</td><td>−0.5±0.1</td></tr>
<tr><td>A1C<7% (%)</td><td>57.5*</td><td>53.7*</td><td>28.1</td></tr>
<tr><td>FPG (mg/dL)</td><td>-40*</td><td>-44*</td><td>-8</td></tr>
<tr><td>PPG (mg/dL)</td><td>-47*</td><td>-49*</td><td>-14</td></tr>
<tr><td>Weight (kg)</td><td>-1.0±0.3*</td><td>-2.0±0.3*</td><td>+0.6±0.3kg</td></tr>
<tr><td>SBP (mmHg)</td><td>-6.7± 1.1*</td><td>-5.6± 1.1*</td><td>-1.1± 1.2</td></tr>
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</table>

	after run-in period on RSG 8mg daily and metformin 2gm daily **Exclusions:** Previous insulin treatment	MET 1g BID + RSG 4mg BID + PBO Other pre-study DM drugs were discontinued	8.4±1.2 **FPG (mg/dL):** 182 ±43; 185± 43; 180 ±47 **Monotherapy (%):** 16; 16; 18 Mean ±SD unless otherwise noted	Liraglutide antibodies (%) 4.1 6.7 NA Calcitonin (ng/L) 0.89 0.83 0.75 Peripheral edema (%) 5.1 1.7 8.0 Values ± SE *Significant vs. MET + RSG +PBO Mean 90-min PPG (man of 3 meals) from self-monitored 7-oint glucose measurements at end of study
Russell-Jones 2009 LEAD-5 R, DB (glargine open-label), PC 26-weeks ITT and per-protocol analysis N=581 (ITT n=576) Non-inferiority against glargine Superiority against placebo	**Inclusions:** Type 2 DM 18-80 years old HbA1c 7.5-10% (on monotx) HbA1c 7-10% (on combotx) BMI ≤ 45kg/m2 Treated with OHA for at least 3 months before screening FPG 135-230mg/dl agter 6-week run-in **Exclusions:** Insulin treatment within 3 months prior to trial Impaired renal or liver function Clinically significant CV disease Proliferative retinopathy/ maculopathy BP ≥ 180/100mmHg Cancer Pregnant Recurrent hypoglycemia or hypoglycemia unawareness Hepatitis B antigen + Hepatitis C antibody + Use of other drugs that can affect glucose levels	6-week run-in period with titration of metformin to 2g/day and glimepiride to 4mg/day 2:1:2 randomization (stratified according to prestudy monotx or combo OHA use) LIR 1.8mg + MET + GLIM Placebo + MET + GLIM Glargine + MET + GLIM Insulin glargine once daily with dosage titration using the AT-LANTUS protocol. **Did not use treat-to-target approach.** Average dose at end-of-trial visit: Glargine 24 U/day Glimepiride 3.4mg, 3.9mg, 3.6mg in lira, placebo, and glargine groups respectively	**Values for liraglutide; placebo; glargine respectively** **Age (years):** 57.6±9.5; 57±9; 57.5±9.6 **Male (%):** 57; 49; 60 **BMI (kg/m2):** 30.4±5.3; 31.3±5.0; 30.3±5.3 **DM duration (years):** 9.2 ±5.8; 9.4 ±6.2; 9.7 ± 6.4 **HbA1c (%):** 8.3±0.9; 8.3±0.9; 8.2±0.9 **FPG (mg/dL):** 163.8 ±37.8; 169.2± 36; 163.8 ±36 **Weight (kg):** 85.5 ±19.4; 85.7± 16.7; 85 ±17.9 **Systolic BP (mmHg):** 135± 15; 133± 14; 133±14.7 **Diastolic BP (mmHg):** 80.8± 9.1; 80.4 ± 9.1; 80.5±8.0 **Previous monotx (%):** 5 Mean ±SD unless otherwise noted	**LIR + MET +GLIM** / **PBO + MET +GLIM** / **Glargine+ MET +GLIM** Completers (%) 89 83 94 A1C (%) -1.33 ± 0.09*^ -0.24 ± 0.11 -1.09 ± 0.09* Final A1C (%) 7.0 8.1 7.2 A1C <7% (%) FPG (mg/dL) -27.9* +9.54 -32.2* PPG (mg/dL) -32.4* +0.54 -29* Weight (kg) -1.8 ± 0.33*^ -0.42 ± 0.39 +1.6 ± 0.33 Waist circumference (cm) -1.5^ -0.62 +0.89 SBP (mmHg)§ -4.0 ^ -1.4 +0.54 Liraglutide antibodies (%) 9.8 NA NA Calcitonin (ng/L) 1.27 1.24 1.04 *Significant vs. placebo ^Significant vs. glargine Mean ± SEM §No significant reduction in DBP relative to either placebo or glargine

Buse 2009 R, OL 26-weeks	**Inclusions:** Type 2 DM 18-80 years old	1:1 randomization Stratified by prior OHA treatment 2-week dose escalation period (LIR)	**Values for liraglutide and exenatide respectively**	**Liraglutide** / **Exenatide** Completers (%) 86 81

<table>
<tr>
<td>LEAD-6

ITT and per-protocol analysis

N=464</td>
<td>HbA1c 7-11%
BMI ≤ 45kg/m2
On maximally tolerable doses of metformin, SU or both

<u>Exclusions:</u>
Previous insulin treatment
Previous exposure to exenatide or liraglutide
Impaired renal or liver function
Clinically significant CV disease
Retinopathy/maculopathy requiring acute treatment
BP ≥ 180/100
Cancer</td>
<td>4-week dose escalation period (EXN)

Liraglutide 1.8mg once daily
Exenatide 10mcg BID

No reduction of dose allowed once final maintenance dose was reached

Background OHA maintained. If hypoglycemia occurred, SU dose could be reduced by up to 50%</td>
<td>Age (years): 56.3± 9.8; 57.1± 10.8
Male (%): 49; 55
BMI (kg/m2): 32.9± 5.5; 32.9± 5.7
Weight (kg): 93.1± 20.1; 93 ± 19.5
DM duration (years): 8.5± 6.2; 7.9 ± 5.9
HbA1c (%): 8.2± 1.0; 8.1± 1.0
FPG (mg/dL): 176.4 ± 45; 171 ± 43.2
<u>Pre-study medications:</u>
• Metformin alone (%): 27; 27
• SU alone (%):10; 9
• Combination metformin+SU: 62; 64
Systolic BP (mmHg): 132± 16.2; 134± 17
Diastolic BP (mmHg): 79.6± 8.4; 78.9± 8.9
Fasting C-peptide (nmol/L): 1.25± 0.56; 1.26 ± 0.58

Mean ±SD unless otherwise noted</td>
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<table>
<tr><td>A1C (%)</td><td>-1.12 ± 0.08*</td><td>-0.79 ± 0.08</td></tr>
<tr><td>A1C (%) in those with baseline ≥ 10%</td><td>-2.4 ± 0.21*</td><td>-1.2± 0.37</td></tr>
<tr><td>A1C <7% (%)</td><td>54*</td><td>43</td></tr>
<tr><td>FPG (mg/dL)</td><td>-29 ± 3.6*</td><td>-10.8 ± 3.6</td></tr>
<tr><td>PPG (mg/dL)
estimated tx difference</td><td colspan="2">23.94 (breakfast)§
18.18 (dinner)§</td></tr>
<tr><td>Weight (kg)</td><td>-3.24 ± 0.33</td><td>-2.87 ± 0.33</td></tr>
<tr><td>Pts. who lost weight (%)</td><td>78</td><td>76</td></tr>
<tr><td>SBP (mmHg)</td><td>-2.51 ± 1.15</td><td>-2.0 ± 1.18</td></tr>
<tr><td>DBP (mmHg)</td><td>-1.05 ± 0.71</td><td>-1.98 ± 0.71</td></tr>
<tr><td>Calcitonin (ng/L)</td><td>0.38</td><td>0.36</td></tr>
</table>
Mean ± SE
*Significant vs. exenatide
§Significant vs. liraglutide
</td>
</tr>
<tr>
<td>Nauck (dossier)
Open-label extension of LEAD-2

1.5 year extension (total 2 years)</td>
<td>See Nauck 2009</td>
<td>LIR 0.6mg +metformin
LIR 1.2mg + metformin
LIR 2.8mg + metformin
Glimepiride 4mg + metformin
Placebo + metformin

780 entered extension; 529 completed 2 years</td>
<td></td>
<td>
<table>
<tr><th></th><th>LIR 0.6 + MET</th><th>LIR 1.2 + MET</th><th>LIR 1.8 + MET</th><th>GLIM + MET</th><th>PBO + MET</th></tr>
<tr><td>Completers</td><td colspan="5">529/780 (68%)</td></tr>
<tr><td>A1C (%) at endpoint</td><td>7.74</td><td>7.44</td><td>7.38</td><td>7.49</td><td>8.12</td></tr>
<tr><td>A1C < 7% (%)</td><td>1.7</td><td>29.9</td><td>31.1*</td><td>23.5</td><td>10.8</td></tr>
<tr><td>Weight (kg)</td><td>-2.1</td><td>-3.0</td><td>-2.9</td><td>+0.68</td><td>Not reported</td></tr>
<tr><td>Waist circum (cm)</td><td colspan="3">-1.8 to -2.8</td><td>+0.2</td><td>Not reported</td></tr>
<tr><td>Minor hypo (events/pt-yr)</td><td>0.15</td><td>0.15</td><td>0.15</td><td>1.60^</td><td>0.16</td></tr>
<tr><td>Liraglutide antibodies (%)</td><td>Not shown</td><td>4.3</td><td>4.6</td><td></td><td></td></tr>
</table>
*Significant vs. glimepiride + metformin
^Significant vs. all liraglutide doses
</td>
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</table>

<table>
<tr>
<td>Garber (abstract, poster, dossier)
Open-label extension of LEAD-3</td>
<td>See Garber 2008</td>
<td>Liraglutide 1.2mg once daily (n=110)
Liraglutide 1.8mg once daily (n=114)
Glimepiride 8mg once daily (n=97)</td>
<td>Male (%): 51
Age (years): 53±10
BMI (kg/m2): 33±6
DM duration (years): 5±5</td>
<td>
<table>
<tr><th></th><th>LIR 1.2mg</th><th>LIR 1.8mg</th><th>GLIM 8mg</th></tr>
<tr><td>Completers</td><td colspan="3">321/440 (73%)</td></tr>
<tr><td>A1C (%)</td><td></td><td></td><td></td></tr>
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<table>
<tr>
<td>1-year extension
(total 2 years)</td>
<td></td>
<td>440 pts entered open-label study and 321 completed 2-years</td>
<td>HbA1c (%): 8.1±1.0
FPG(mg/dL): 163.8±41.4
Prior diet/exercise only (%): 36
Prior OAD monotherapy (%): 64</td>
<td>
<table>
<tr><td>All patients</td><td>-0.9*</td><td>-1.1*</td><td>-0.6</td></tr>
<tr><td>Prior diet/exercise</td><td>-1.4</td><td>-1.4</td><td>-1.0</td></tr>
<tr><td>DM duration < 3yrs</td><td>-1.1</td><td>-1.4*</td><td>-0.7</td></tr>
<tr><td>DM duration ≥ 3yrs</td><td>-0.8</td><td>-1.0*</td><td>-0.4</td></tr>
<tr><td>A1C < 7% (%)</td><td>53.3*</td><td>58*</td><td>37</td></tr>
<tr><td>FPG (mg/dL)</td><td>-23.6*</td><td>-27.1*</td><td>-6.2</td></tr>
<tr><td>PPG (mg/dl)</td><td>-34</td><td>-46.6</td><td>-32.8</td></tr>
<tr><td>Weight (kg)</td><td>-2.3*</td><td>-2.8*</td><td>+1.0</td></tr>
<tr><td>Waist circum (cm)</td><td>-4.0</td><td>-4.86</td><td>-0.96</td></tr>
<tr><td>Minor hypo (events/pt-yr)</td><td>0.21*</td><td>0.22*</td><td>1.75</td></tr>
<tr><td>SBP (mmHg)</td><td>-0.01</td><td>0.15</td><td>0.21</td></tr>
</table>
*Significant vs. glimepiride
Efficacy data shown for 2-year completers
</td>
</tr>
<tr>
<td>Buse 2010 and poster
Open-label extension of LEAD-6

14-week extension
(total 40 weeks)

N=389</td>
<td>See Buse 2009</td>
<td>Those on liraglutide 1.8mg continued dose

Those on exenatide were switched to liraglutide 0.6mg x 1 week, then 1.2mg x 1 week, then 1.8mg for remainder

Background oral agents remained stable</td>
<td>Values for Exenatide→liraglutide and liraglutide→liraglutide respectively

Male (%): 59.7; 51.5
Age (years): 57.2±10; 56.2±9.4
BMI (kg/m2): 32.8±5.3; 33.1±5.5
DM duration (years): 7.7±5.6; 8.3±5.9
A1C (%): 8.0±0.9; 8.2±1.0
A1C at week 26 (%): 7.2; 7.0
FPG(mg/dL): 169.2±41.4; 176.4±45
Previous treatment (%)
Metformin: 27.4; 28
SU:10.2; 10.5
Metformin + SU: 62.4; 61.5</td>
<td>
<table>
<tr><th></th><th>Liraglutide→ liraglutide</th><th>Exenatide→ liraglutide</th></tr>
<tr><td>Completers (%)</td><td>98.5</td><td>94.7</td></tr>
<tr><td>A1C (%)</td><td>-0.1±0.04</td><td>-0.3±0.04</td></tr>
<tr><td>A1C < 7% (%)</td><td>54 to 61</td><td>43 to 57</td></tr>
<tr><td>FPG (mg/dL)</td><td>-3.6±1.9</td><td>-16.2±2.9</td></tr>
<tr><td>Weight (kg)</td><td>-0.4±0.2</td><td>-0.9±0.2</td></tr>
<tr><td>SBP (mmHg)</td><td>-2.2±0.9</td><td>-3.8±0.8</td></tr>
<tr><td>Minor hypoglycemia (events/pt-yr)</td><td>0.74</td><td>1.3†</td></tr>
</table>
Mean ± SE
Changes from week 26 to 40 in each treatment group. No between treatment comparisons were conducted
†Rate of minor hypoglycemia was 2.6 episodes/patient-year at week 26 with exenatide
</td>
</tr>
</table>

<table>
<tr>
<td>Pratley 2010
R, OL
26 weeks
N=665</td>
<td><u>Inclusions:</u>
Type 2 DM
18-80 years old
HbA1c 7.5-10%
BMI ≤ 45kg/m2</td>
<td>1:1:1 stratification
Liraglutide 1.2mg once daily (n=221)
Liraglutide 1.8mg once daily (n=218)
Sitagliptin 100mg once daily (n=219)</td>
<td>Values for LIR1.2, LIR1.8, and sitagliptin respectively

Male (%): 52; 52; 55
Age (years): 55.9± 9.6; 55± 9.1; 55±</td>
<td>
<table>
<tr><th></th><th>LIR1.2 +MET</th><th>LIR1.8+ MET</th><th>SIT+MET</th></tr>
<tr><td>Completers (%)</td><td>76.5</td><td>87.6</td><td>88.6</td></tr>
<tr><td>A1C (%)</td><td>-1.24*
[-1.37, -1.11]</td><td>-1.5*
[-1.63. -1.37]</td><td>-0.9
[-1.03, -0.77]</td></tr>
</table>
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<table>
<tr>
<td>Assessment non-inferiority then by superiority</td>
<td>Treated with metformin ≥ 1500mg/day for ≥ 3 months

<u>Exclusions:</u>
Prior treatment with any hypoglycemic agent other than metformin within 3 months of trial
Recurrent major hypoglycemia or hypoglycemia unawareness
Other drugs that could affect glucose
CI to trial drugs
Impaired renal or hepatic function
Clinically significant CV disease
Cancer</td>
<td>Added to background metformin</td>
<td>9.0
Weight (kg): 93.7±18.4; 94.6±18.1; 93.1±18.9
BMI (kg/m2): 32.6±5.2; 33.1±5.1; 32.6±5.4
DM duration (years): 6.0±4.5; 6.4±5.4; 6.3±5.4
A1C (%): 8.4±0.8; 8.4 ±0.7; 8.5± 0.7
FPG(mg/dL): 181.8±43.2; 178.2 ±43.2; 180±36</td>
<td>
<table>
<tr><td>A1C <7% (%) OR vs. SIT</td><td>2.75</td><td>4.50</td><td></td></tr>
<tr><td>FPG (mg/dL)</td><td>-33.7*
[-38.9, -28.3]</td><td>38.5*
[-43.7, -33.1]</td><td>-14.9
[-20.3, -9.72]</td></tr>
<tr><td>Weight (kg)</td><td>-2.86*
[-3.39, -2.32]</td><td>-3.38*
[-3.91, -2.84]</td><td>-0.96
[-1.5, -0.42]</td></tr>
<tr><td>Waist circumference (cm)‡</td><td>-2.69*
[-3.38, -1.99]</td><td>-2.63*
[-3.33, -1.92]</td><td>-1.12
[-1.82, -0.42]</td></tr>
<tr><td>SBP (mmHg)</td><td>-0.55</td><td>-0.72</td><td>-0.94</td></tr>
<tr><td>DBP (mmHg)</td><td>-0.71</td><td>0.07</td><td>-1.78§</td></tr>
<tr><td>Calcitonin (ng/L)</td><td colspan="3">Change from baseline similar among across groups</td></tr>
</table>
*Significant vs. sitagliptin
‡There was no significant difference in waist to hip ratio
§Significant vs. LIR 1.8mg
</td>
</tr>
</table>