Linagliptin (Tradjenta®)
National 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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

- Linagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretins glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production.

- Linagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. It has been studied as monotherapy and in combination with metformin, sulfonylureas (SU), and pioglitazone; combination studies with insulin are ongoing at this time.

- Linagliptin is administered 5mg orally once daily either as monotherapy or in combination with metformin, sulfonylureas, or TZDs. It may be taken with or without food. No dosage adjustment is needed for renal or hepatic insufficiency. When used with an insulin secretagogue such as SUs, the dose of the insulin secretagogue may need to be reduced in order to decrease the risk of hypoglycemia.

- Duration of the phase III trials ranged from 18-52 weeks. Monotherapy with linagliptin decreases mean hemoglobin A1c (A1C) by 0.4%. When used as add-on therapy to metformin or a sulfonylurea, the mean reduction in A1C ranged from 0.4-0.5%. When used as initial combination with pioglitazone, the mean decrease in A1C was 1.06%. When linagliptin was added to metformin + sulfonylurea, the average decrease was 0.7%. In head-to-head comparisons, the combination of linagliptin + metformin reduced mean A1C by 0.4-0.5% versus 0.6-0.7% with SU + metformin.

- Serious adverse events (3.1 vs. 3.8%) and adverse events leading to discontinuation (2.3 vs. 3.6%) occurred less frequently in the linagliptin than in the placebo or glimepiride groups.

- In the safety database which includes 12 trials, hypoglycemia was reported in 195/2566 (7.6%) patients receiving linagliptin and in 49/1183 (4.1%) of patients receiving placebo. In a head-to-head trial, hypoglycemia was reported more often in glimepiride + metformin group than the linagliptin + metformin group (30.5 vs. 5.3%). The rate of hypoglycemia was higher in studies that combined linagliptin with a SU.

- Linagliptin is considered to be weight neutral. However, when combined with pioglitazone, there was an increase in weight which was greater than pioglitazone alone (2.3 vs. 1.3kg respectively).

- Hypersensitivity reactions have been reported with the other DPP-4 inhibitors. In the pooled 12 trial safety data base, hypersensitivity reactions were reported in 0.7% and 0.5% of patients receiving linagliptin and comparators respectively. In the head-to-head trial, hypersensitivity reactions were reported more often in glimepiride + metformin group than the linagliptin + metformin group (1.8% vs. 1.3%).

- Long-term safety and efficacy outcomes data are not available at this time; however, the FDA-required major cardiovascular adverse events (MACE) meta-analysis does not appear to show a cardiovascular safety risk with linagliptin.

- Concerns have been raised that the DPP-4 inhibitors may be associated with an increased risk of infection. The rate of infection with linagliptin appears to be similar to that of the comparators.

- There have been post-marketing reports of acute pancreatitis, including hemorrhagic or necrotizing pancreatitis with incretin class (i.e., DPP-4 inhibitors and GLP-1 agonists). There were 11 cases of pancreatitis reported

with linagliptin. Eight cases occurred while on treatment and 3 were reported following the last administered dose. The event rate based on the 8 cases was 1per 538 pt-yrs (linagliptin) and 0 in 433 pt-yrs (comparator).

- Rifampin decreased linagliptin exposure. The efficacy of linagliptin may be reduced when co-administered with a strong P-glycoprotein (P-gp) or CYP3A4 inducer. Alternative treatment is recommended when linagliptin is to be administered with a P-gp or CYP3A4 inducer.

- The incidence of adverse events was greater in those with moderate to severe renal impairment receiving linagliptin compared to placebo. Some studies showed a slightly greater percentage of patients progressing to a higher stage of renal impairment in the linagliptin groups than with placebo.

- Based on current pricing, linagliptin has the highest acquisition cost among the DPP-4 inhibitors.

Introduction

Lingliptin was approved in May 2011 and is the third dipeptidyl peptidase-4 (DPP-4) inhibitor on the market to join sitagliptin and saxagliptin.

Pharmacology

Incretins such as glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) 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 whereas the insulinotropic effect of GIP is impaired. GLP-1 and GIP enhance glucose-dependent insulin secretion from the pancreas. Also, GLP-1 suppresses inappropriately elevated glucagon secretion from pancreatic α-cells ultimately leading to decreased hepatic glucose production. Incretins do not suppress normal counter-regulatory increase in glucagon secretion during hypoglycemia.

GLP-1 has a short plasma half-life; therefore, its utility as a pharmacologic agent is limited. Dipeptidyl peptidase-4 is the enzyme responsible for metabolizing GLP-1 and GIP. Inhibition of DPP-4 activity results in meal-based enhancement of GLP-1 and GIP. Linagliptin selectively inhibits the DPP-4 enzyme.

Pharmacokinetics[12]

Table 1: Pharmacokinetics of Linagliptin

Area under the curve (AUC)	139 nmol•h/L
Maximum plasma concentration (Cmax)	8.9 nmol/L
Time to maximum concentration (Tmax)	1.5h
Terminal half-life (t1/2)	12h
Protein binding	70-99% (concentration-dependent)
Metabolism	Undergoes minimal metabolism; 90% of drug recovered as unchanged parent compound. The remainder undergoes hydroxylation or oxidation as inactive metabolite
Elimination	Via enterohepatic system; 84.7% eliminated in the feces and 5% in urine

FDA approved indications[12]

Linagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Linagliptin has been studied as monotherapy and in combination with metformin, sulfonylureas, and pioglitazone; combination studies with insulin are ongoing at this time.

Current VA formulary alternatives

None in the DPP-4 inhibitor class; agents from other drug classes on the VANF include metformin, glipizide, glyburide, acarbose, and insulin (i.e., regular, NPH, aspart, glargine/detemir).

Dosing/Administration[12]

- 5 mg once daily taken with or without food
- When used in combination with an insulin secretagogue, a lower dose of the secretagogue may be required.
- No dosage adjustment is needed for patients with renal or hepatic impairment.

Dosage form/strengths

Available as a 5mg tablet

Efficacy

Linagliptin has been studied as monotherapy and in combination with metformin, pioglitazone, and sulfonylureas. Efficacy data are presented for 9 randomized Phase III clinical trials; 3 published, 6 unpublished. Among, the combination trials, 2 were initial combination trials and the others were add-on trials. One add-on trial was conducted in patients with severe renal impairment. Abstracts, FDA review data, and the manufacturer's dossier were used to provide information for the unpublished trials.

Patients underwent a 4-week washout period if they were receiving oral antidiabetic drugs (OAD) at baseline that were not being studied. For the combination studies with metformin and SUs, patients were required to have had inadequate glycemic control while taking those agents. For the combination with pioglitazone study, patients could have been treatment naïve or receiving any OAD. All studies allowed for rescue treatment with a diabetes agent from another class for patients who did not meet specific glycemic goals during the study period.

Hemoglobin A1C

Mean baseline A1C ranged from 7.7-8.6%. Linagliptin reduced A1C as shown in Table 2. There was no difference in response with regards to age, gender, or body mass index (BMI). Maximum glucose lowering effects were seen at 8-12 weeks.

Changes in A1C from baseline were greater in those who were drug treatment naïve than those who were on 1 oral antidiabetic drug (OAD) prior to study entry. Similarly, those who were on metformin alone at study entry had a greater response than those who were on metformin plus one other OAD.

As seen with other drugs used to treat diabetes, those with higher baseline A1C had a greater reduction than those with lower baseline values. For example, the mean change in A1C was <0.2% for those with baseline A1C < 7.5% compared to a change of >0.8% for those with baseline A1C ≥ 9.0%. (See appendices)

Fasting and post-prandial blood glucose

While fasting glucose improved more in the linagliptin group than placebo, the overall magnitude of change was relatively small. In the comparative study, decrease in fasting glucose was greater with SU + metformin than it was with linagliptin + metformin. Four studies evaluated post-prandial glucose. Linagliptin had a greater effect on improving post-prandial glucose (PPG) than placebo. The effect on PPG was similar with linagliptin + metformin and SU + metformin.

Table 2: Glycemic Efficacy of Linagliptin

Study	n	Duration	Treatment arms	Baseline A1C (%)	Change in A1C (%)	A1C < 7% (%)	Change in FPG (mg/dL)	Change 2h-PPG (mg/dL)‡
Del Prato[1] (Pivotal trial)	503	24-weeks	LIN 5mg	8.0	-0.44±0.05*	25.2*	-9.0±1.8*	-34.2±5.4*
			PBO	8.0	0.25±0.07	11.6	14.4±3.6	25.2±10.8
Taskinen[2] (Pivotal trial)	701	24-weeks	LIN 5mg + MET	8.1	-0.49±0.04*	26*	-10.8±1.8*	-48.6±7.2*
			PBO + MET	8.0	0.15±0.06	9	10.8±3.6	18±12.6
Gomis[3] (Pivotal trial)	389	24-weeks	LIN 5mg + PIO 30mg	8.6	-1.06±0.06*	42.9*	-32.4±1.8*	Not evaluated
			PBO + PIO 30mg	8.6	-0.56±0.09	30.5	-18.0±3.6	
Study 35[4, 5]	245	18-weeks	LIN 5mg+SU	8.6	-0.5±0.07*	15.2	-8.2±3.3	Not evaluated
			PBO+ SU	8.6	-0.1±0.1	3.7	-1.8±4.5	
Study 18[4, 6] (Pivotal trial)	1058	24-weeks	LIN 5mg+MET+SU	8.2	-0.7±0.86*	31.3*	-4.6±1.4*	Not evaluated
			PBO+MET+SU	8.1	-0.1±0.87	9.2	8.1±2.4	
Study 20[4, 9, 10]	1527	52-weeks†	LIN 5mg + MET	7.7	-0.4±0.03	29.6	-8.6±1.24	-32±5.2
			GLIM + MET	7.7	-0.6±0.03*	38.9	-16.2±1.25*	-29.9±5.2

Study 50[4, 8]	227	18-weeks	LIN 5mg PBO	8.1	-0.44±0.14* 0.14±0.16	23.5 11.8	-13.3±5.2* 7.2±6.0	Not evaluated
Study 43[7,10]	133	52-weeks	LIN 5mg + prior DM meds PBO + prior DM meds	8.2 8.2	-0.71±0.15* 0.01±0.16	18 9.8	NS between groups	Not evaluated
Study 46[10, 11]	143	24-weeks	LIN 2.5mg + MET 500mg BID	8.7	-1.22	30.1	-33.2	Treatment diff -50.8 * (LIN/MET500 vs. LIN)
	143		LIN 2.5mg + MET 1000mg BID	8.7	-1.59	53.6	-49.4	
	142		LIN 5mg	8.7	-0.45	10.4	-8.6	
	144		MET 500mg BID	8.7	-0.64	18.6	-15.8	-73.9 * (LIN/MET1000 vs. LIN)
	147		MET 1000mg BID	8.5	-1.07	30.7	-32.3	
	72		PBO	8.7	0.13	10.8	10.2	

FPG-fasting plasma glucose; GLIM=glimepiride; MET=metformin; PBO=placebo; PIO=pioglitazone; PPG=post-prandial glucose; SU=sulfonylurea
‡2-h PPG conducted in a subgroup of patients
†At 2 years, change in A1C was -0.16% (LIN) and -0.36% (GLIM) and % patients achieving A1C<7% was 21% (LIN) and 28.3% (GLIM)

Studies in Specific Populations

Study 43 was a 52-week study conducted in patients with severe renal impairment (GFR<30ml/min/1.73m2). Linagliptin or placebo was added to existing hypoglycemic agents including insulin. Glycemic improvement is shown in table 2 and appendix 3. [7, 10]

Extension Trials

There are ongoing open-label extension trials (78 weeks) for the 4 pivotal trials and for several of the supportive trials. Two year data for study 20 is available which shows noninferiority of linagliptin vs. glimepiride for change in A1C. Weight gain, hypoglycemia and CV events were reported more often in the glimepiride group.[9, 10]

Table 3: Extension Trials

Study	Comparison (parent studies)	Extensions	Results
Pivotal			
Gomis (Study 15) Del Prato (Study 16) Taskinen (Study 17) Study 18	LIN5mg +PIO vs. PBO+PIO LIN5mg vs. PBO LIN 5mg + MET vs. PBO + MET LIN5mg + MET+SU vs. PBO+MET+SU	Open-label extension to 78 weeks. Placebo patients switched to linagliptin	N/A
Study 20[9, 10]	LIN 5mg + MET vs. GLIM + MET	2 year trial	A1C (%): -0.4 (LIN); -0.5 (GLIM) Weight (kg): -1.4 (LIN); +1.3 (GLIM) Hypoglycemia (%): 7.5 (LIN); 36.1 (GLIM) CV events (%): 1.7 (LIN); 3.4 (GLIM)
Study 23‡	LIN vs. PBO vs. voglibose	Extension to 52-weeks	N/A
Study 50	LIN5mg vs. PBO	34-week extension period. Placebo patients switched to glimepiride	N/A

‡Study not discussed in review (Japanese trial with non-US approved comparator)

Lipids[4]

Pooled data from the 4 pivotal 24-week trials showed the following mean changes (±SD). Values are shown for linagliptin and placebo groups respectively.

Pooled Values from Pivotal 24-week Trials
Total cholesterol (mg/dL): 2±1; 4±16
LDL (mg/dL): 5±24; 7±24
HDL (mg/dL):1±11; 2±10
Triglycerides (mg/dL): -12±123; -5±189

Looking at individual trials, the product package insert shows that hyperlipidemia was reported in 2.7% vs. 0.8% patients receiving linagliptin + pioglitazone vs. placebo + pioglitazone. Hypertriglyceridemia was reported in 2.4% vs. 0 in patients receiving linagliptin + SU vs. placebo + SU.

Selected future studies of interest

- 52-week study linagliptin vs. placebo as add-on to basal insulin (anticipated completion 8/2011)
- Long-term study of linagliptin vs. glimepiride as add-on to usual care evaluating cardiovascular morbidity and mortality, relevant efficacy parameters, and safety (estimated primary completion date 9/2018)

Adverse Events

The clinical safety data base includes studies 15-18, 23, 35, 50, plus 3 phase II trials and 2 phase I trials. These studies have been pooled and will be referred to as SAF-2. Study 20 is discussed separately. Number of patients included in the safety database and patient-years of exposure are shown in table 4.[4]

Table 4: Number of Patients and Patient-Years of Exposure in Safety Evaluations[4]

	Study Duration	Linagliptin 5mg (n)	Comparator (n)	Linagliptin exposure (pt-yrs)	Comparator exposure (pt-yrs)
SAF-2	12 days-24 weeks	2566	1183	1041.4	433.8
Study 20	52 weeks	778	781	887.5	872

The frequency of patients with adverse events is shown in table 5. Adverse Events are listed as those occurring in >1% and >5% of patients in SAF-2 grouping and Study 20 respectively.[4] Although not evident when looking at the pooled data, events occurring in the individuals trials that occurred more often with linagliptin in the combination with SU trial were nasopharyngitis (4.3 vs. 1.2%) and hypertriglyceridemia (2.4 vs. 0%), and hypersensitivity (1.9 vs. 1.2%); in the combination with pioglitazone study, events occurring more often with linagliptin were hyperlipidemia (2.7 vs. 0.8%) and increased weight (2.3 vs. 0.8%).[12]

Table 5: Frequency of Adverse Events in Safety Evaluations[4]

	SAF-2 (AEs in > 1% of Patients)		Study 20 (AEs in > 5% of Patients)	
	Linagliptin 5mg [N (%)]	Comparator [N (%)]	Linagliptin 5mg [N (%)]	Glimepiride [N (%)]
Any AE	1412 (55)	636 (53.8)	611 (78.5)	662 (84.8)
GI disorders	127 (10.7)	269 (10.5)	168 (21.6)	177 (22.7)
Upper abdominal pain	15 (1.3)	18 (0.7)	-	-
Constipation	21 (1.8)	40 (1.6)	-	-
Diarrhea	27 (2.3)	53 (2.1)	36 (5.0)	52 (6.7)
Nausea	14 (1.2)	28 (1.1)	-	-
General Disorders	124 (4.8)	61 (5.2)	-	-
Asthenia	28 (1.1)	9 (0.8)	-	-
Fatigue	13 (0.5)	17 (1.4)	-	-
Infections	491 (19.1)	244 (20.6)	305 (39.2)	321 (41.1)
Nasopharyngitis	150 (5.8)	65 (5.5)	100 (12.9)	102 (13.1)
Bronchitis	-	-	35 (4.5)	40 (5.1)
URI	84 (3.3)	53 (4.5)	43 (5.5)	46 (5.9)
UTI	56 (2.2)	28 (2.4)	-	-
Metabolism and Nutrition	408 (15.9)	208 (17.6)	107 (13.8)	280 (35.9)
Dyslipidemia	31 (1.2)	13 (1.1)	-	-
Hyperglycemia	128 (5.0)	125 (10.6)	-	-
Hypoglycemia	195 (7.6)	49 (4.1)	41 (5.3)	237 (30.3)
Musculoskeletal/Connective Tissue Disorders	264 (10.3)	102 (8.6)	196 (25.2)	174 (22.3)
Arthralgia	47 (1.8)	21 (1.8)	44 (5.7)	27 (3.5)
Back pain	50 (1.9)	30 (2.5)	50 (6.4)	41 (5.2)
Pain in extremity	34 (1.3)	11 (0.9)	-	-
Nervous System Disorders	183 (7.1)	81 (6.8)	114 (14.7)	143 (18.3)
Dizziness	51 (2.0)	21 (1.8)	-	-
Headache	76 (3.0)	41 (3.5)	44 (5.7)	33 (4.2)
Respiratory Disorders	102 (4.0)	26 (2.2)	-	-
Cough	47 (1.8)	10 (0.8)	-	-
Vascular Disorders	92 (3.6)	28 (2.4)	71 (9.1)	82 (10.5)
Hypertension	58 (2.3)	22 (1.9)	34 (4.4)	41 (5.2)

Adapted from FDA

Serious adverse events (SAEs) and AEs leading to discontinuation occurred less frequently in the linagliptin than comparator groups. Overall rates and rates of events occurring more often in the linagliptin group are shown in table 6.4

Table 6: Serious Adverse Events and Adverse Events Leading to Discontinuation[4]

	SAF-2		Study 20	
	Linagliptin	**Comparator**	**Linagliptin**	**Glimepiride**
Serious AEs (SAEs) [N (%)]	**94 (3.1)**	**62 (3.8)**	**122 (15.7)**	**156 (20)**
SAEs occurring more often in the linagliptin vs. comparator group	Skin/subcutaneous tissue disorder (0.1 vs. 0%) Vascular disorders (0.4 vs. 0.1%)		Eye disorders (0.4 vs. 0.3%) Immune system disorders (0.4 vs. 0%) Injury/poisoning/procedure complication (1.7 vs. 1.3%) Increased AST (0.1 vs. 0%) Increased alkaline phosphatase (0.1 vs. 0%) Abnormal LFTs (0.1 vs. 0%) Neoplasms-benign, malignant, unspecified including cysts and polyps (2.2 vs. 1.9%) Respiratory disorders (1.0 vs. 0.5%) Surgical/medical procedures (0.3 vs. 0%)	
AEs Leading to Discontinuation [N (%)]	**58 (2.3)**	**43 (3.6)**	**45 (5.8)**	**77 (9.9)**
AEs Leading to Discontinuation and occurring more often in the linagliptin vs. comparator group	Cardiac disorders (0.2 vs. 0.1%) GI disorders (0.4 vs. 0.3%) Hepatobiliary disorders (0.1 vs. 0%) Infections (0.1 vs. 0%) Musculoskeletal/connective tissue disorders (0.2 vs. 0%) Respiratory disorders (0.1 vs. 0%) Skin/subcutaneous tissue disorders (0.2 vs. 0.1%) Vascular disorders (0.1 vs. 0%)		Cardiac disorders (0.6 vs. 0.5%) Increased alkaline phosphatase (0.1 vs. 0%) Injury/poisoning/procedure complication (0.4 vs. 0%) Abnormal LFTs (0.1 vs. 0%) Decreased weight (0.1 vs. 0%) Neoplasms-benign, malignant, unspecified including cysts and polyps (0.5 vs. 0.4%) Respiratory disorders (0.6 vs. 0%)	

Data obtained from FDA transcript

Hypoglycemia[4]

In SAF-2, hypoglycemia was reported in 195/2566 (7.6%) patients receiving linagliptin and in 49/1183 (4.1%) of patients receiving placebo. In study 20, hypoglycemia was more frequent in the glimepiride + metformin group than the linagliptin + metformin group (30.5 vs. 5.3%). The rate of hypoglycemia was higher in studies that combined linagliptin with a SU (see table 7).

Weight

Linagliptin is considered to be weight neutral. However, when combined with pioglitazone, there was an increase in weight which was greater than seen with pioglitazone alone.[3] See table 7 for average change in weight.

Table 7: Other Endpoints of Interest (Reported Hypoglycemia and Change in Weight)

Study	n	Duration	Treatment arms	Hypoglycemia (%)	Weight (kg)
Del Prato[1]	503	24-weeks	LIN 5mg PBO	0.3 0.6	- -
Taskinen[2]	701	24-weeks	LIN 5mg + MET PBO + MET	0.4 2.3	-0.4 -0.5
Gomis[3]	389	24-weeks	LIN 5mg + PIO 30mg PBO + PIO 30mg	1.2 0	2.3* 1.3
Study 35[4, 5]	245	18-weeks	LIN 5mg+SU PBO+ SU	5.6 4.8	-0.4 0
Study 18[4, 6]	1058	24-weeks	LIN 5mg+MET+SU PBO+MET+SU	22.7 14.8	No significant difference
Study 20[4, 9, 10]	1527	52-weeks 2-years	LIN 5mg + MET GLIM + MET	5.4 (52-wk)*; 7.1 (2-yr)* 31.8 (52-wk); 34.8 (2-yr)	-1.13 (52-wk)*; -1.4 (2-yr)* 1.36 (52-wk); 1.3 (2-yr)
Study 50[4, 8]	227	18-weeks	LIN 5mg PBO	1.3 0	-0.3 -1.4
Study 43[7,10]	133	52-weeks	LIN 5mg + prior DM meds PBO + prior DM meds	63.2* 49.2	-1.96 -0.04

Study 46[10, 11]	143	24-weeks	LIN 2.5mg + MET 500mg BID	3.5	Treatment difference 0.61 (LIN/MET500 vs. MET 500) -0.31 (LIN/MET500 vs. LIN) -0.23 (LIN/MET1000 vs. MET 1000) -0.96 (LIN/MET1000 vs. LIN)*
	143		LIN 2.5mg + MET 1000mg BID	0	
	142		LIN 5mg	0	
	144		MET 500mg BID	1.4	
	147		MET 1000mg BID	3.4	
	72		PBO	1.4	

*Significant vs. comparator
GLIM=glimepiride; LIN=linagliptin; MET=metformin; PBO=placebo; PIO=pioglitazone; SU=sulfonylurea

Infection[4]

Concerns have been raised that the DPP-4 inhibitors may be associated with an increased risk of infection. The rate of infection with linagliptin appears to be similar to that of the comparators.

Table 8: Infections Rates [4]

	SAF-2 (AEs in > 1% of Patients)		Study 20 (AEs in > 5% of Patients)	
	Linagliptin 5mg [N (%)]	Comparator [N (%)]	Linagliptin 5mg [N (%)]	Glimepiride [N (%)]
Infections	491 (19.1)	244 (20.6)	305 (39.2)	321 (41.1)
Nasopharyngitis	150 (5.8)	65 (5.5)	100 (12.9)	102 (13.1)
Bronchitis	-	-	35 (4.5)	40 (5.1)
URI	84 (3.3)	53 (4.5)	43 (5.5)	46 (5.9)
UTI	56 (2.2)	28 (2.4)	-	-

URI=upper respiratory tract infection; UTI=urinary tract infection

Hypersensitivity reactions[4]

Hypersensitivity reactions have been reported with the other DPP-4 inhibitors. Overall in SAF-2, hypersensitivity reactions were reported in 0.7% and 0.5% of patients receiving linagliptin and comparators respectively. Events occurring more often with linagliptin versus the comparator were circulatory collapse (0.1 vs. 0%), lip swelling (0.1 vs. 0%), and urticaria (0.2 vs. 0.1%). Events occurring with equal frequency to the comparator were face edema (0.1%).

In study 20, hypersensitivity reactions were reported in 1.3% of the linagliptin 5mg group and 1.8% in the glimepiride group. Events occurring more frequently in the linagliptin group were pharyngeal edema (0.1 vs. 0%) and urticaria (0.5% vs. 0.4%).

Cardiovascular Safety [4, 13]

Under FDA requirements, a meta- analysis of major adverse cardiovascular events (MACE) is to be conducted for new diabetes drugs submitted for approval. 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 and that the upper bound of the 95% CI is < 1.8. Endpoints for MACE included CV death, non-fatal stroke, non-fatal MI, and hospitalization for unstable angina. Eight trials were included in the analysis which included the 4 pivotal trials 15-18, studies 20, 35, 50 and 23.

Mean age was 58±10 years and 28% were > 65 years old. Approximately 60% of the population was white and 52.4% had diabetes for > 5 years. Nearly 83% had previously received ≥ 1 OAD.

The hazard ratio was 0.34 [95% CI 0.16, 0.70] indicating lower risk with linagliptin versus the comparators. Table 9 shows the events broken down by individual MACE events. Many of the AEs in the comparator/placebo group were driven by study 20 comparing linagliptin to glimepiride. (Johansen)

Table 9: Cardiovascular Events

	Linagliptin(n=3319) Rate/1000 pt-yr	Comparator/placebo (n=1920) Rate/1000 pt-yr
Composite endpoint	5.3	16.8
CV death	1.0	1.5
Non-fatal MI	2.9	5.1
Non-fatal stroke	1.0	8.0
Hosp. for unstable angina	0.5	2.2

Renal Safety
In the SAF-2 data base, 112 and 50 patients receiving linagliptin and placebo respectively had moderate renal impairment at baseline. In this group, the incidence of AEs was greater in the linagliptin group than placebo (65.2% vs. 50%). There was no difference in incidence of AEs between linagliptin and placebo in those who had normal renal function or mild renal impairment at baseline.[4]

In study 43 (Safety and Efficacy Trial with Severe Chronic Renal Impairment), there were more reports of AEs in the linagliptin group compared to placebo, which included hypoglycemia, renal impairment, GI (nausea, diarrhea, constipation), infection (pneumonia, bronchitis, influenza, sinusitis, nasopharyngitis), cardiovascular (angina, acute MI, atrial fibrillation, cardiac arrest). For adjudicated cardiovascular events, there was no difference between groups in the incidence of nonfatal stroke. The incidence of nonfatal MI was greater in the linagliptin group (5.9 vs. 3.1%) whereas the incidence of cardiovascular death was lower with linagliptin (2.9 vs. 4.6%).[10]

In study 43, the percentage of patients in the linagliptin group with stage 4 renal impairment decreased from 82.1% to 58.2%. This was due to 7.4% and 16.5% shifting to stages 3 and 5 renal impairment respectively. In comparison, the percentage of patients in the placebo group with stage 4 renal impairment increased slightly from 67.7% to 71%; 1.6% of these patients progressed to stage 5 renal impairment.[10]

Some Phase III clinical trials (studies 16, 35, 47, 50) showed decrease in the percentage of patients with normal renal function or mild renal impairment at end of study with linagliptin which was greater than that observed in the placebo groups.[10]

Pancreatitis[4, 12]
There have been post-marketing reports of acute pancreatitis, including hemorrhagic or necrotizing pancreatitis with incretin class (i.e., DPP-4 inhibitors and GLP-1 agonists).

There were 11 cases of pancreatitis reported with linagliptin. Eight cases occurred while on treatment and 3 were reported following the last administered dose. The event rate based on the 8 cases was 1per 538 pt-yrs (linagliptin) and 0 in 433 pt-yrs (comparator). Cases included both acute exacerbation of pancreatitis and diagnosis of chronic pancreatitis. In 3 cases, the duration of treatment was 1 month; in 1 case, duration of treatment was 4 months. In the remaining 4 cases treatment duration ranged from 11-14 months.

Musculoskeletal[4]
In SAF-2, the incidence of reported musculoskeletal conditions (e.g., arthralgia, asthenia, back pain etc.) was 0.5% and 0.3% for linagliptin and placebo respectively. In study 20, overall musculoskeletal and connective tissue disorders were reported in 25.2% and 22.3% of patients receiving linagliptin and glimepiride respectively. Arthralgia and back pain were the only 2 events occurring at an incidence of >5%. Specifically, arthralgia was reported in 5.7% (linagliptin) and 3.5% (glimepiride) and back pain in 6.4% (linagliptin) and 5.2% (glimepiride) of patients.

Contraindications[12]
Linagliptin is contraindicated in patients with a history of a hypersensitivity reaction to linagliptin (e.g., urticaria, angioedema, bronchial hyperreactivity)

Warnings and Precautions[12]
When used with an insulin secretagogue such as sulfonylureas, the dose of the insulin secretagogue may need to be reduced in order to decrease the risk of hypoglycemia.

Look-alike / Sound-alike (LA / SA) 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.

Table 10: Look-alike/Sound-alike Error Risk Potential

NME Drug Name	Lexi-Comp	First DataBank	USP	ISMP	Clinical Judgment
Linagliptin 5mg tab	None	None	None	None	Sitagliptin Liraglutide
Tradjenta®	None	None	None	None	Treanda Truvada

Drug Interactions[12]

Linagliptin did not affect the steady-state pharmacokinetics of digoxin, warfarin, glyburide, pioglitazone, simvastatin, metformin and ethinylestridiol and levonorgestrel.

Rifampin decreased linagliptin exposure. The efficacy of linagliptin may be reduced when co-administered with a strong P-glycoprotein (P-gp) or CYP3A4 inducer. Alternative treatment is recommended when linagliptin is to be administered with a P-gp or CYP3A4 inducer.

Comparative Cost

Based on current pricing, linagliptin has the highest acquisition cost among the DPP-4 inhibitors.

Table 11: VA Acquisition Cost

	Usual daily dose	Cost/day	Cost/month
Linagliptin	5mg	$4.82	$144.6
Saxagliptin	2.5mg	$3.94	$118.20
Saxagliptin	5mg	$3.85	$115.50
Sitagliptin	100mg	$3.95	$118.50
Pioglitazone	15mg	$3.00	$90.00
Pioglitazone	30mg	$4.60	$138.00
Pioglitazone	45mg	$4.98	$149.40
Exenatide	5mg	$4.53	$135.94
Exenatide	10mg	$5.19	$155.55
Liraglutide	1.2mg	$5.83	$175.03
Liraglutide	1.8mg	$8.81	$264.33

Prices current as of August 2011
When multiple pricing available (package size), the least expensive is shown

Conclusions

The DPP-4 inhibitors have a modest impact on A1C (average decrease tends to be < 1%). Adverse events that have been associated with this class include pancreatitis, hypersensitivity reactions, infections, renal changes, etc.

No dosage adjustment is necessary for linagliptin in patients with renal impairment; adjustment is necessary for sitagliptin and saxagliptin. Use of CYP3A4 or P-gp inducers with linagliptin is not recommended. A lower dose of saxagliptin is recommended if taken concurrently with a strong CYP3A4/5 inhibitor. There are no drug interactions requiring dosage adjustment of sitagliptin or other co-administered drugs.

It is unclear at this time if there is an efficacy or safety advantage of one DPP-4 inhibitor over another.

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Prepared by: Deb Khachikian, PharmD
Date: September 2011

Abbreviations used in appendices:

A1C=hemoglobin A1c; BMI=body mass index; CHF=congestive heart failure; CV=cardiovascular; DB= double-blind; DM=diabetes mellitus; FAS=full analysis set; FPG=fasting plasma glucose; GI=gastrointestinal; GLIM=glimepiride; LOCF=last observation carried forward; MET= metformin; PBO=placebo; PC=placebo-controlled; PIO=pioglitazone; PPG=post-prandial glucose; R=randomized; SB=single-blind; SU=sulfonylurea; Sx=symptoms; TZD=thiazolidinedione

Appendix 1: Monotherapy Trials

Study	Inclusion/Exclusion	Dosage	Demographics/Baseline values	Results
Del Prato 2011[1] Study 16 R, DB, PC 24-weeks N=503 Analysis: FAS with LOCF	**Inclusions:** Type 2 DM 18-80 years old Drug treatment naïve or received 1 OAD (excluding TZDs) A1C 7-10% (treatment naive); A1C 6.5-9.0% (1 OAD) BMI ≤ 40kg/m2 **Exclusions:** Treatment with a TZD, GLP-1 analog, insulin, or antiobesity drug within 3 months Change in dose of thyroid hormone tx within 6 weeks of screening Tx with systemic steroids at time of enrollment Impaired hepatic function at screening (ALT, AST, or ALP > 3 × ULN) MI, stroke, or TIA within 6 months of time of enrolment Alcohol or drug abuse Nursing or pregnant Women of child-bearing potential and not practicing an acceptable method of birth control	2-week placebo run-in (metformin only) 4-week washout and 2 week placebo run-in (metformin + 1 OAD) LIN 5mg once daily (n=336) PBO once daily (n=167) Rescue metformin may be initiated during randomized period if FPG was >240mg/dL with a minimum of 2 measurements made on different days with at least 1 measurement taken at the investigational site. If FPG remained > 240mg/dL despite rescue, the patient was discontinued from the study.	**Values for LIN and PBO respectively** **Age (years):** 56.4±10.1; 54.4±10.3 **Male (%):** 48.8; 47.3 **Weight (kg):** 78.5±16.7; 79.2±16.0 **BMI (kg/m2):** 29.0±4.8; 29.1±4.8 **A1C (%):** 8.0±0.05; 8.0±0.07 **FPG (mg/dL):** 163.8±1.8; 165.6±3.6 **Prior antidiabetes drugs (%)** **Treatment naive:** 56.2; 57.1 **1 OAD:** 43.8; 42.9 mean ±SD (age, weight, BMI) mean± SE (A1C, FPG)	<table><tr><th></th><th>Linagliptin</th><th>Placebo</th></tr><tr><td>d/c treatment n/N(%)</td><td>16/336 (4.8)</td><td>14/167 (8.4)</td></tr><tr><td>d/c due to AE n/N (%)</td><td>4/336 (1.2)</td><td>4/167 (2.4)</td></tr><tr><td>A1C (%)</td><td>-0.44±0.05*</td><td>0.25±0.07</td></tr><tr><td>FPG (mg/dL)</td><td>-9.0±1.8*</td><td>14.4±3.6</td></tr><tr><td>2-h PPG (mg/dL)†</td><td>-34.2±5.4*</td><td>25.2±10.8</td></tr><tr><td>Achieved A1C <7.0 (%)</td><td>25.2*</td><td>11.6</td></tr><tr><td>A1C reduction ≥ 0.5 (%)</td><td>47.1*</td><td>19</td></tr><tr><td>A1C stratified by baseline value‡</td><td></td><td></td></tr><tr><td>≥9.0%</td><td>-0.83*</td><td>0.15</td></tr><tr><td>8.0-<9.0</td><td>-0.55*</td><td>0.18</td></tr><tr><td>7.5-<8.0</td><td>-0.42*</td><td>0.14</td></tr><tr><td><7.</td><td>-0.19*</td><td>0.4</td></tr><tr><td>Need for rescue medication (%)</td><td>10.2*</td><td>20.9</td></tr><tr><td>Weight (kg)</td><td>0.0±2.1</td><td>-0.3±2.0</td></tr><tr><td>Hypoglycemia (%)</td><td>0.3</td><td>0.6</td></tr></table>Mean± SE (A1C, FPG, 2-h PPG) Mean± SD (weight) *Significant vs. placebo †2-h PPG evaluated in subgroup of patients (n=67 LIN; n=24 PBO) ‡ Values for A1C estimated from graph
Study 50[4, 8] R. DB, PC 18-weeks	**Inclusions:** Type 2 DM patients in whom metformin therapy is inappropriate	2-week placebo run-in (tx naive) 4-week washout and 2 week placebo run-in (on 1 OAD)	**Values for LIN and PBO respectively** **Age (years):** 56.4±10.6; 56.7±9.7 **Male (%):** 36.4; 43.4	<table><tr><th></th><th>Linagliptin</th><th>Placebo</th></tr><tr><td>d/c treatment n/N(%)</td><td>14/151 (9.3)</td><td>12/76 (15.8)</td></tr><tr><td>d/c due to AE n/N</td><td>1/151</td><td>0</td></tr></table>

N=227	18-80 years old Drug treatment naïve or received 1 OAD A1C 7-10% (treatment naive); A1C 6.5-9.0% (1 OAD) BMI: ≤ 40 kg/m2 **Exclusions:** Same as Study 16 plus the following: Severe renal impairment Hereditary galactose intolerance	LIN 5mg once daily (n=151) PBO once daily (n=76) Rescue therapy with pioglitazone or insulin may be initiated during the first 12 weeks of randomized treatment if the patient had a glucose level > 240 mg/dL after overnight fast. During the remaining weeks of treatment, rescue was initiated only if glucose level > 200 mg/dL.	**Weight (kg):** 77±18.8; 80.9±19.1 **BMI (kg/m2):** 29.1±5.6; 30.2±5.0 **A1C (%):**8.1±1.0; 8.1±0.9 **% pts. with A1C:** **< 7.0%:** 7.5; 6.8 **7.0 to <8.0% :** 40.8; 42.5 **8.0 to <9.0%:** 35.4; 35.6 **>9.0%:** 16.3; 15.1 **FPG (mg/dL):** 183.3±46.4; 180.5±44.7 **Prior antidiabetes drugs (%)** **Treatment naive:** 55.1; 52.1 **1 OAD:** 42.9; 46.6 **≥2 OADs:** 2.0; 1.4 Mean ± SD	A1C (%) -0.44±0.14* 0.14±0.16 A1C (%) Baseline < 8.5% -0.28±0.15 0.07±0.18 Baseline≥8.5% -0.79±0.18 0.22±0.23 FPG (mg/dL) -13.3±5.2* 7.2±6.0 Achieved A1C <7.0 (%) 23.5* 11.8 Need for rescue medication (%) 11.6 17.8 Weight (kg) -0.3±2.7 -1.4±4.5 Hypoglycemia (n) 2 0 Mean± SE (A1C, FPG) Mean± SD (weight) *Significant vs. placebo

Appendix 2: Add-On Combination Trials

Study	Inclusion/Exclusion	Dosage	Demographics/Baseline values	Results		
Taskinen 2011[2] Study 17 R, DB, PC	**Inclusions:** Type 2 DM 18-80 years old On metformin≥ 1500mg (or max tolerated dose) ± 1	2-week placebo run-in (metformin only) 4-week washout and 2 week placebo run-in (metformin + 1 OAD)	**Values for LIN and PBO respectively** **Age (years):** 56.5±10.1; 56.6±10.9 **Male (%):** 53;57 **Weight (kg):** 82.2±17.2; 83.3±16.6		**LIN + MET**	**PBO + MET**
				d/c treatment n/N(%)	39/523 (7.5)	14/177 (7.9)
				d/c due to AE n/N(%)	9/523 (1.7)	3/177 (1.7)

24-weeks N=701 Superiority trial Analysis: FAS with LOCF	additional antidiabetes med A1C 7-10% (metformin monotherapy) A1C 6.5-9.0% (2-drug tx) BMI ≤ 40kg/m2 **Exclusions:** Same as Study 16 plus the following: Renal failure or Scr >1.5mg/dL H/O acute or chronic metabolic acidosis Unstable or acute CHF Hereditary galactose intolerance, dehydration	3:1 randomization; stratified according to A1C <8.5% or ≥ 8.5% and according to use of monotherapy vs. combo therapy at enrolment LIN 5mg daily + MET (n=523) PBO + MET (n=177) Rescue with glimepiride may be initiated if during the first 12 weeks FPG >240mg/dL and if during the last 12 weeks FPG > 200mg/dL or random value > 400mg/dL	**BMI (kg/m2):** 29.9±4.8; 30.1±5.0 **A1C (%):** 8.09±0.86; 8.02±0.88 **FPG (mg/dL):** 169.2±43.2; 165.6±41.4 **Time since diagnosis (%)** **≤1 year:** 11; 13 **>1-5 years:** 34; 34 **> 5 years:** 56; 53 **Prior antidiabetes drugs (%)** **Metformin only:** 68; 69 **Metformin + 1 other:** 32; 31 Mean± SD	A1C (%): -0.49±0.04*; 0.15±0.06 FPG (mg/dL): -10.8±1.8*; 10.8±3.6 2-h PPG (mg/dL): -48.6±7.2*; 18±12.6 Achieved A1C <7.0 (%): 26*; 9 A1C reduction ≥ 0.5 (%): 50; 22 A1C stratified by baseline value† ≥9.0%: -0.95*; -0.23 8.0-<9.0: -0.6*; 0.15 7.5-<8.0: -0.35*; 0.25 <7.5: -0.2*; 0.4 Need for rescue medication (%): 8*; 19 Weight (kg): -0.4±.3; -0.5±3.3 Hypoglycemia (%)‡: 0.6*; 2.8 Mean ± SE (A1C, FPG, 2-h PPG) Mean ±SD (weight) *Significant vs. PBO + MET †Values for stratified A1C estimated from graph ‡Hypoglycemia defined as blood glucose < 70mg/dL

Appendix 2-cont.

Study 35[4, 5] R, DB,PC 18-weeks N=245	**Inclusions** Type 2 DM 18-80 years old On an SU ± 1 additional anti-diabetes med A1C 7.5-10% (SU monotherapy) A1C 7.0-9.0% (2-drug tx) BMI ≤ 40kg/m2	2-week placebo run-in 4-week washout for those on OAD other than SU LIN 5mg+SU (n=161) PBO+ SU (n=84) SU dose remained unchanged during study	**Values shown for combined study population** **Age (years):** 57.2±9.8; 56.2±10.2 **≥65y (%):** 25.5; 16.7 **Male (%):** 47.8; 61.9 **Weight (kg):** 74.5±17; 76.1±17 **BMI (kg/m2):** 28.4±5.0; 28.2±5.1 **A1C (%):** 8.6±0.85; 8.6±0.72	**LIN + SU** / **PBO + SU** d/c treatment n/N(%): 10/161 (6.2); 7/84 (8.3) d/c due to AE n/N(%): 5/161 (3.1); 3/84 (3.6) A1C (%): -0.54±0.07*; -0.07±0.1 FPG (mg/dL): -8.2±3.3; -1.8±4.5 Achieved A1C <7.0 (%): 15.2*; 3.7 Need for rescue medication (%): 7.6*; 15.9

	Exclusions Same as Study 16 plus the following: Severe renal impairment Hereditary galactose intolerance	Randomization was stratified by HbA1c (<8.5% versus ≥8.5%) Pioglitazone was used as rescue therapy. During the first 12 weeks, rescue medication was initiated if glucose level > 240 mg/dL after an overnight fast. During the last 6 weeks of treatment, rescue was to be initiated only for glucose level of > 200 mg/dL after an overnight fast.	**% pts. with A1C:** **< 7.0%:** 1.3; 0 **7.0 to <8.0% :** 19; 22 **8.0 to <9.0%:** 44.3; 42.7 **>9.0%:** 35.4; 35.4 **FPG (mg/dL):** 182±52; 175±49 **Prior antidiabetic meds (%):** **One:** 64.6; 67.1 **Two:** 35.4; 32.9 Mean ± SD	Weight (kg) 0.4±2 0.0±1.8 Hypoglycemia (%) 5.6 4.8 Mean± SE (A1C, FPG) Mean±SD (weight) *Significant vs. PBO + SU
Study 18[4, 6] R, DB, PC N=1058 24-weeks	**Inclusions** Type 2 DM 18-80 years old Insufficient control on metformin + SU A1C 7-10% BMI ≤ 40kg/m2 **Exclusions** Same as study 16 plus the following: Serum creatinine ≥1.5 mg/dl Unstable or acute congestive heart failure Acute or chronic metabolic acidosis Dehydration	2-week placebo run-in LIN 5mg daily + MET + SU (n=792) PBO + MET + SU (n=263) Pioglitazone rescue	**Values for LIN and PBO respectively** **Age (years):** 58.3±9.9; 57.6±9.7 **Male (%):** 46.8; 48.5 **Weight (kg):** **BMI (kg/m2):** 28.4±4.8; 28.2±4.5 **DM duration > 5 years (%):** 73.1; 73.7 **A1C (%):** 8.1±0.8; 8.0±0.8 **FPG (mg/dL):** 159.3±36.5; 162.6±37.1 Mean ± SD	**LIN + MET + SU** / **PBO + MET + SU** d/c treatment (%) 7.3 8.0 d/c due to AE (%) 2.9 1.9 A1C (%) -0.7±0.86* -0.1±0.87 FPG (mg/dL) -4.6±1.4* 8.1±2.4 Achieved A1C <7.0 (%) 29.2* 8.1 Need for rescue medication (%) 5.4* 13 Weight (kg) No significant difference between groups Hypoglycemia (%) 23.7 16 *Significant vs. PBO + MET + SU Mean± SD

Appendix 2-cont.

Study 20[4, 9, 10] R, DB, active control N=1527 52weeks; 104-weeks Non-inferiority trial Analysis: ITT with LOCF	**Inclusions** Type 2 DM Age 18-80 years On metformin≥ 1500mg (or max tolerated dose) ± 1 additional antidiabetes med A1C 6.5-10% (metformin monotherapy) A1C 6.0-9.0% (2-drug tx) BMI ≤ 40kg/m2 **Exclusions** Same as study 16 plus the	2-week placebo run-in 4-week washout for those on an additional med to metformin LIN 5mg daily + MET (n=776) GLIM + MET (n=775) MET dose ≥1500mg/day Initial GLIM dose 1mg/day then titrated to a max of 4mg day over 12 weeks (**mean 3mg/day**). Thereafter dose kept constant, but may be decreased to avoid	**Values shown for LIN+MET and GLIM+MET respectively** **Age (years):** 59.7±9.4; 59.7±9.4 **≥65y (%):** 32.3; 32.7 **Male (%):** 59.4; 61.1 **Weight (kg):** 86.1±17.4; 86.3±16.7 **BMI (kg/m2):** 30.2±4.7; 30.3 ±4.6 **A1C (%):** 7.7±0.88; 7.7±0.87 **% pts. with A1C:** **< 7.0%:** 22.7; 21.3 **7.0 to <8.0% :** 41.6; 45.7 **8.0 to <9.0%:** 26.5; 23.1	**52-week data** **LIN + MET** / **GLIM + MET** d/c treatment n/N(%) 140/779 (18) 145/781 (18.6) d/c due to AE n/N(%) 45/779 (5.8) 77/781 (9.9) A1C (%) -0.4±0.03 -0.6±0.03* FPG (mg/dL) -8.6±1.24 -16.2±1.25* A1C stratified by baseline value (%) ≥9.0% -0.95±0.1 -1.4±0.09 8.0-<9.0 -0.58±0.06 -0.86±0.06 7.5-<8.0 -0.28±0.07 -0.54±0.06 <7.5 -0.[illegible]±0.04 -0.33±0.05

	following: Serum creatinine ≥ 1.5mg/dL Hereditary galactose intolerance	hypoglycemia Randomization was stratified by HbA1c (<8.5% versus ≥8.5%) Pioglitazone was allowed as rescue medication during the treatment phase of the trial only if the glucose level was > 240 mg/dL after an overnight fast or A1C >8.5% during the treatment phase from week 28 to week 104.	**>9.0%:** 9.1; 9.9 **FPG (mg/dL):** 164.3±43; 166.7±42.5 **Prior antidiabetic meds in addition to metformin (%):** **None:** 70; 71 **One:** 29.9; 28.9 **Two:** 0.1; 0.1 **Daily dose of metformin at randomization (% pts.)** <1500mg: 7.6; 5.9 ≥1500mg: 92.4; 94.1 Mean ± SD	2-h PPG (mg/dL) -32±5.2 -30±5.2 Achieved A1C<7.0 (%) 29.6 38.9* Need for rescue medication (%) 16.3 12.1* Weight (kg) -1.13±0.14† 1.36±0.14 Hypoglycemia (%) 5.4* 31.8 **104-week data** **LIN + MET** **GLIM + MET** d/c treatment (%) 24.4 22.1 d/c due to AE (%) 7.9 11.6 A1C (%) -0.16±0.03 -0.36±0.03* FPG (mg/dL) Treatment difference was 6.38 mg/dL ± 1.97 [95% CI, 2.51 to 10.25]* 2-h PPG (mg/dL) Treatment difference was –9.74 mg/dL ± 5.77 [95% CI, -21.07 to 1.59] Achieved A1C<7.0 (%) 21 28.3* Need for rescue medication (%) 24.7 21.5 Weight (kg) -1.4±0.16† 1.3±0.16 Hypoglycemia (%) 7.1* 34.8 Mean ± SE (A1C, FPG, 2-h PPG) Mean ± SD (weight) *Significant vs. LIN+MET †Significant vs. GLIM+MET

Appendix 3: Initial Combination Studies

Study	Inclusion/Exclusion	Dosage	Demographics/Baseline values	Results
Gomis 2011[3] Study 15 R, DB,PC 24-weeks N=389 Analysis: FAS with LOCF	**Inclusions** Type 2 DM 18-80 years old Drug naïve or previously treated with any OAD A1C 7.5-11% BMI ≤ 40kg/m2 **Exclusions** Same as Study 16 plus the following: Hemodialysis patients FBG >240mg/dL NYHA class III or IV heart	2-week placebo run-in (OAD naïve) 4-week washout and 2 week placebo run-in (prior OAD) LIN 5mg daily + PIO 30mg daily (n=259) PBO + PIO 30mg daily (n=130) Metformin was allowed as rescue therapy	**Values for LIN and PBO respectively** **Age (years):** 57.7±9.6; 57.1±10.1 **≥65y (%):** 24.7; 26.9 **Male (%):** 58.7; 65.4 **Weight (kg):** 78.3±15.6; 82.7±15.8 **BMI (kg/m2):** 28.7±4.8; 29.7±4.8 **A1C (%):** 8.6±0.79; 8.58±0.87 **% pts. with A1C:** **< 7.0%:** 0; 0 **7.0 to <8.0% :** 23.4; 27.3 **8.0 to <9.0%:** 45.6; 40.6 **>9.0%:** 31; 32 **FPG (mg/dL):** 189±43.2; 190.8±2.4	**LIN + PIO** **PBO + PIO** d/c treatment n/N(%) 15/259 (5.8) 19/130 (14.6) d/c due to AE n/N(%) 4/259 (1.5) 6/130 (4.6) A1C (%) -1.06±0.06* -0.56±0.09 FPG (mg/dL) -32.4±1.8* 18±3.6 Achieved A1C <7.0 (%) 42.9* 30.5 A1C reduction ≥ 0.5 (%) 75* 50.8 A1C stratified by baseline value† ≥9.0% -0.65 [-1.02, -0.28]* 8.0-<9.0 -0.49 [-0.82, -0.16]* 7.5-<8.0 -0.48 [-0.95, -0.01]*

	failure or h/o heart failure prior to study DKA in past 6 months		**Prior antidiabetic meds (%):** **None:** 49.2; 50.8 **1:** 32.1; 31.3 **≥2:** 18.7; 18 Mean ± SD	<7.5 — No difference between groups Need for rescue medication (%) — 7.9* — 14.1 Weight (kg) — 2.3* — 1.2 Hypoglycem□a (%) — 1.2 — 0 Mean± SE †Values shown are placebo-adjusted [95% CI] *Significant vs. PIO + placebo
Study 46[10, 11] R, DB, PC 24-weeks N=857	**Inclusions** Type 2 DM 18-80 years old Drug naïve or previously treated with 1 OAD A1C at screening: A1C 7.0% -10.5% (prior OAD) A1C≥ 7.5% -11.0% (no prior OAD) Patients with A1C ≥ 11% will be eligible to participate in an additional open-label study BMI ≤ 40kg/m2 **Exclusions** Same as Study 16 plus the following: Renal impairment Gastric bypass Dehydration Unstable or acute congestive heart failure History of acute or chronic metabolic acidosis Hereditary galactose intolerance	2-week placebo run-in (OAD naïve) 4-week washout and 2 week placebo run-in (prior OAD) LIN 2.5mg + MET 500mg BID (n=143) LIN 2.5mg + MET 1000mg BID (n=143) LIN 5mg once daily (n=142) MET 500mg BID (n=144) MET 1000mg BID (n=147) Placebo (N=72)	**Values for LIN2.5/MET500; LIN2.5/MET1000; LIN5; MET500; MET1000; PBO** **Age (years):** 55.6±11.2; 56.4±10.7; 56.2±10.8; 52.9±10.4; 55.2±10.6; 55.7±11 **Male (%):** 51; 53.8; 56.3; 56.9; 53.1; 50 **Weight (kg):** 80.8±19; 76.7±16; 79.1±17.3; 79.9±18.4; 80±18.5; 76.8±17.5 **BMI (kg/m2):** 29.7±5.3; 28.6±4.8; 29±4.7; 28.9±4.8; 29.5±5.3; 28.6±5.2 **A1C (%):** 8.71±0.95; 8.68±1.0; 8.7±0.97; 8.66±0.9; 8.52±87; 8.67±0.95 **FPG (mg/dL):** 198.6±60; 196.9±51; 195.3±50; 191.2±47; 192.3±53; 203.7±51 **Treatment naïve (%):** 47.7; 46.4; 45.2; 48.9; 48.6; 49.2 Mean ± SD	

	LIN2.5 MET 500bid	LIN2.5 MET 1000bid	LIN 5	MET 500bid	MET 1000bid	PBO
d/c tx (%)	11.2	7.7	14.8	4.8	14.3	25
d/c due to AE (%)	3.5	1.4	4.2	2.8	4.1	4.2
A1C (%)	-1.22	-1.59	-0.45	-0.64	-1.07	0.13
FPG (mg/dL)	-33.2	-49.4	-8.6	-15.8	-32.2	10.2
Achieved A1C <7.0 (%)	30.1	53.6	10.4	18.6	30.7	10.8
Need for rescue tx (%)	7.3	4.3	11.1	13.5	8.0	29.2
Hypoglyc (%)	3.5	0	0	1.4	3.4	1.4

Appendix 4: Trials in Special Populations

Study	Inclusion/Exclusion	Dosage	Demographics/Baseline values	Results
Study 43[7,10] R, DB, PC 52-weeks	Type 2 DM 1-80 years old Treated with insulin or any combination of insulin, sulfonylurea or glinides as	2-week placebo run-in LIN 5mg daily + background meds (n=68)	**Values for LIN and PBO respectively** **Age (years):** 64±10.9; 64.9±9.6 **Male (%):** 66.2; 53.8	

	LIN + background meds	PBO + background meds
d/c treatment (%)	27.9	26.2

	monotherapy and pioglitazone or any other antidiabetics excluding DPP-4 inhibitors other than linagliptin(stable for at least 8 weeks) A1C 7-10% **Severe chronic renal insufficiency (GFR < 30 mL/min)** BMI ≤ 45 kg/m2 **<u>Exclusions</u>** Same as Study 16 plus the following: Renal impairment requiring chronic dialysis or requiring acute dialysis in the 3 months prior to informed consent Treatment with any other DPP-4 inhibitor within 3 months prior to informed consent Renal transplant recipient Unstable or acute congestive heart failure	PBO + background meds (n=65) Dose of background meds remained unchanged during first 12 weeks; dose reduction was allowed in cases of hypoglycemia. Dose of background meds may be adjusted after 12 weeks during remainder of trial.	**Weight (kg):** 9.9±19; 85.7±17.6 **BMI (kg/m2):** 32.3±5.9; 31.7 ±5.9 **A1C (%):** 8.2±1.1; 8.2±0.9 **FPG (mg/dL):** 149.5±79.5; 160.1±65.4 **Receiving ≥2 background meds (%):** 30.3; 17.7 **GFR for entire study group (ml/min/1.73m2):** 23.5±6.7 Data on breakdown of background meds used was not provided Mean±SD	d/c due to AE (%) 11.8 16.9 <u>A1C (%)</u> Week 12 -0.76±0.14* -0.18±0.15 Week 52 -0.71±0.15* 0.01±0.16 FPG (mg/dL) No significant difference vs. placebo Treatment diff 1.34mg/dL±8.17 Achieved A1C <7.0 (%) 18 9.8 Need for rescue medication (%) 24.2* 48.4 Weight (kg) -1.96±0.9 -0.04±0.52 Hypoglycemia (%) 63.2‡ 49.2 Severe hypoglycemia (%) 7.0 9.4 CV deaths (n) 1 3 Mean±SE (A1C, FPG) Mean±SD (weight) *Significant vs. PBO ‡In the LIN group, 43 patients reported hypoglycemia; 23 were receiving insulin, 6 were receiving insulin + another antidiabetic agent, and 6 were receiving SU