Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus

Kira B. Harris and Delilah J. McCarty

Ther Adv Endocrinol Metab

2015, Vol. 6(1) 3–18

DOI: 10.1177/
2042018814558242

© The Author(s), 2014.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Glucagon-like peptide-1 (GLP-1) has been evaluated for use in the treatment of type 2 diabetes mellitus (T2DM) due to its role in glucose regulation. Four GLP-1 receptor agonists (RAs) are currently indicated for T2DM in the USA. Exenatide and liraglutide are short-acting and require twice-daily and daily dosing, respectively. Two longer acting agents, exenatide long-acting release (LAR) and albiglutide, were formulated to allow for once-weekly dosing. All four GLP-1 RAs have demonstrated reductions in hemoglobin A1c, fasting blood glucose, and body weight both as monotherapy and in combination with first- and second-line diabetes agents including metformin, sulfonylureas, thiazolidinediones, and insulin. Greater glycemic control was seen with liraglutide compared with the other GLP-1 treatment options; however, the two long-acting agents were superior to exenatide twice daily. All agents were well tolerated with most adverse events being mild or moderate in nature. The most common adverse event was transient nausea which typically resolved 4–8 weeks after treatment initiation. Long-acting agents had lower rates of nausea but an increased incidence of injection site reactions. Trials have suggested GLP-1 RAs may improve cardiovascular risk factors including blood pressure, lipid parameters and inflammatory markers. Future trials are needed to confirm the clinical outcomes of these agents. Overall, GLP-1 RAs will provide benefit for patients with T2DM intolerant to or not reaching glycemic goals with first-line agents, especially in patients in need of weight loss.

Keywords: albiglutide, exenatide, exenatide long-acting release, GLP-1 RAs, liraglutide, type 2 diabetes mellitus

Introduction

Glucagon-like peptide 1 (GLP-1) is an endogenous hormone produced and released by intestinal epithelial endocrine L cells in response to food intake [Holst, 2007; Frias and Edelman, 2007; Nauck *et al.* 2004]. While the effects of GLP-1, including increased insulin secretion, decreased glucagon secretion, slowed gastric emptying, and maintenance of blood glucose (BG) levels, are maintained, GLP-1 secretion is often reduced in patients with type 2 diabetes mellitus (T2DM) [Holst, 2007; Frias and Edelman, 2007; Nauck *et al.* 2004; Kreymann *et al.* 1987; Nauck *et al.* 1986]. When exogenous GLP-1 is administered to patients with T2DM, fasting BG (FBG) is decreased while c-peptide and insulin secretion are increased until BG returns to normal [Nauck *et al.* 1993; Toft-Nielsen

et al. 1999]. This glucose-dependent effect reduces the risk of hypoglycemia.

The use of GLP-1 therapy was limited by its rapid breakdown by dipeptidyl peptidase IV (DPP-IV) [Holst, 2006, 2007]. However, several GLP-1 receptor agonists have been discovered that are DPP-IV resistant, making them valuable in diabetes treatment. Exenatide and liraglutide were US Food and Drug Administration (FDA) approved in 2005 and 2010 and are administered subcutaneously twice daily and daily, respectively [Amylin Pharmaceuticals, Inc., 2011; Novo Nordisk A/S, 2013]. In 2012 and 2014, exenatide long-acting release (LAR) and albiglutide were approved. These agents were modified to increase the half life, allowing for once weekly subcutaneous

Correspondence to:
Kira B. Harris, PharmD, BCPS, CDE
Assistant Professor,
Wingate University School
of Pharmacy, 515 North
Main Street, Wingate,
NC 28174, USA
k.brice@wingate.edu
Delilah J. McCarty,
PharmD, CPP, BCACP,
CDE
Wingate University School
of Pharmacy, Wingate,
NC, USA

administration [Amylin Pharmaceuticals, Inc., 2012; GlaxoSmithKline LLC, 2014].

The consensus treatment algorithm from the American Diabetes Association and the European Association for the Study of Diabetes recommends metformin first line for patients diagnosed with T2DM. If metformin does not reach glycemic goals, add-on therapy with either pioglitazone, a sulfonylurea (SU), a DPP-IV inhibitor, a GLP-1 RA, or insulin is recommended. Medication choices should be based on patient-specific conditions considering the effect on glycemic control and body weight, the risk of hypoglycemia and other potential advantages or disadvantages [Inzucchi *et al.* 2012]. The following sections discuss the efficacy and safety of exenatide, liraglutide, exenatide LAR, and albiglutide and characteristics that may influence their use.

Short-acting GLP-1 RAs

Efficacy

Exenatide 5 and 10 µg twice daily as well as liraglutide 0.6 mg, 1.2 mg, and 1.8 mg daily have been studied as monotherapy and in combination with metformin, SUs, thiazolidinediones (TZDs), and insulin. Liraglutide 0.6 mg showed minimal reduction in glycemic parameters and therefore results from the higher doses are reported here. Results from selected trials are summarized in Table 1.

Exenatide monotherapy lowered hemoglobin A1c (HbA1c) by 0.7–0.9%, FBG by 17.5–18.7 mg/dl (0.97–1.03 mmol/liter) postprandial BG (PBG) excursions by 21.3–24.7 mg/dl (1.18–1.37 mmol/liter). In addition, exenatide monotherapy resulted in body weight reductions of 2.8–3.1 kg [Moretto *et al.* 2008]. In a small study of 58 patients with obesity and newly diagnosed T2DM, exenatide monotherapy compared with metformin monotherapy showed similar reductions in FBG [–32.4 mg/dl (–1.8 mmol/liter) *versus* –28.8 mg/dl (–1.6 mmol/liter)] as well as significantly greater reductions in HbA1c (–2.1% *versus* –1.66%), 2 h oral glucose tolerance test [–91.9 mg/dl (–5.1 mmol/liter) *versus* –50.4 mg/dl (–2.8 mmol/liter)] and body weight (–5.8 kg *versus* –3.42 kg) [Yuan *et al.* 2012]. In 746 patients with T2DM, monotherapy with liraglutide 1.2 and 1.8 mg daily compared with glimepiride 8 mg daily significantly decreased

HbA1c (–0.84% and –1.14% *versus* –0.51%) and FBG [–15.1 and –25.6 mg/dl (–0.84 and –1.42 mmol/liter) *versus* –5.2 mg/dl (–0.28 mmol/liter)]. Liraglutide also significantly reduced body weight while glimepiride resulted in weight gain [Garber *et al.* 2009]. An extension trial demonstrated continued reductions in HbA1c, FBG, and body weight for 2 years of liraglutide therapy [Garber *et al.* 2011]. Based on these results, exenatide and liraglutide are good first-line options for patients unable to take metformin.

Three 30-week trials evaluated exenatide added to metformin, a SU, and both. Exenatide 5–10 µg twice daily reduced HbA1c, FBG, and body weight by 0.4–0.86%, 5.4–10.8 mg/dl (0.3–0.6 mmol/liter), and 0.9–2.8 kg, respectively [Buse *et al.* 2004; Kendall *et al.* 2005; DeFronzo *et al.* 2005]. Extension trials demonstrated the durability of exenatide added to metformin or SU therapy with sustained reductions in HbA1c and FBG as well as progressive body weight reductions extending for up to 3 years of therapy [Ratner *et al.* 2006; Buse *et al.* 2007; Riddle *et al.* 2006; Blonde *et al.* 2006; Klonoff *et al.* 2008]. When stratified by baseline HbA1c, larger reductions in HbA1c were seen in patients with baseline HbA1c greater than 9% [Buse *et al.* 2004; Kendall *et al.* 2005; Riddle *et al.* 2006; Blonde *et al.* 2006]. When directly compared, 26 weeks of liraglutide significantly lowered HbA1c (–1.12% *versus* –0.79%) and FBG [–28.9 mg/dl (–1.6 mmol/liter) *versus* –10.8 mg/dl (–0.6 mmol/liter)] compared with exenatide in 464 patients with uncontrolled T2DM while taking metformin, a SU, or both. Exenatide significantly lowered PBG after breakfast and dinner. Reductions in body weight between groups were similar [Buse *et al.* 2009]. In combination with a TZD with or without metformin, exenatide significantly lowered HbA1c by 0.8–0.9% and FBG by 14.4–28.6 mg/dl (0.8–1.59 mmol/liter) compared with placebo [Liutkus *et al.* 2010; Zinman *et al.* 2007]. However, body weight reductions (–1.4 to –1.7 kg) were only significant in one of two trials [Liutkus *et al.* 2010; Zinman *et al.* 2007]. Liraglutide added to a TZD and metformin also significantly reduced HbA1c (–1.5% *versus* –0.5%), FBG [–40 to –44 mg/dl (–2.22 to –2.44 mmol/liter) *versus* –8 mg/dl (–0.44 mmol/liter)], body weight (–1 to –2 kg *versus* +0.6 kg) and 90 min PBG [–47 to –49 mg/dl (–2.61 to –2.72 mmol/liter) *versus* –14 mg/dl (0.77 mmol/liter)] compared with placebo [Zinman *et al.*

Table 1. Summary of clinical trials evaluating exenatide and liraglutide.

Study	No. of patients	Study duration	Baseline therapy	Treatment groups	Change in HbA1c (%)	Change in FBG (mg/dl) [mmol/liter]	Change in body weight (kg)
Moretto <i>et al.</i> [2008]	233	24 weeks	Drug naïve	Exenatide 5 µg twice daily	-0.7	-17.5 [-0.97]	-2.8
				Exenatide 10 µg twice daily	-0.9	-18.7 [-1.04]	-3.1
				Placebo	-0.2	-5.2 [-0.28]	-1.4
Yuan <i>et al.</i> [2012]	58	26 weeks	Drug naïve	Exenatide 10 µg twice daily	-2.1	-32.4 [-1.8]	-5.8
				Metformin 500–1000 mg twice daily	-1.6	-28.8 [-1.6]	-3.4
Garber <i>et al.</i> [2009]	746	52 weeks	Diet and exercise	Liraglutide 1.2 mg daily	-0.84	-15.1 [-0.84]	NR
				Liraglutide 1.8 mg daily	-1.14	-25.6 [-1.42]	
				Glimepiride 8 mg daily	-0.51	-5.2 [-0.28]	
Garber <i>et al.</i> [2011]	440	104 weeks	Diet and exercise	Liraglutide 1.2 mg daily	-0.9	-34.2 [-1.9]	-2.1
				Liraglutide 1.8 mg daily	-1.1	-46.8 [-2.6]	-2.7
				Glimepiride 8 mg daily	-0.6	-34.4 [-1.91]	+1.1
Buse <i>et al.</i> [2004]	377	30 weeks	SU	Exenatide 5 µg twice daily	-0.46	-5.4 [-0.3]	-0.9
				Exenatide 10 µg twice daily	-0.86	-10.8 [-0.6]	-1.6
				Placebo	0.12	+7.2 [+0.4]	-0.6
Kendall <i>et al.</i> [2005]	733	30 weeks	Metformin + SU	Exenatide 5 µg twice daily	-0.55	-9.0 [-0.5]	-1.6
				Exenatide 10 µg twice daily	-0.77	-10.8 [-0.6]	-1.6
				Placebo	0.23	+14.4 [+0.8]	-0.9
DeFronzo <i>et al.</i> [2005]	272	30 weeks	Metformin	Exenatide 5 µg twice daily	-0.4	-7.2 [-0.4]	-1.6
				Exenatide 10 µg twice daily	-0.8	-10.8 [-0.6]	-2.8
				Placebo	0.1	+14.4 [+0.8]	-0.3
Buse <i>et al.</i> [2007]	283	104 weeks	Metformin, SU or both	Exenatide 10 µg twice daily	-0.8	-16 [-0.89]	-3.6
Klonoff <i>et al.</i> [2008]	217	3 years	Metformin, SU or both	Exenatide 10 µg twice daily	-1.0	-23.5 [-1.3]	-5.3
Buse <i>et al.</i> [2009]	464	26 weeks	Metformin, SU or both	Exenatide 10 µg twice daily	-0.79	-10.8 [-0.6]	-2.87
				Liraglutide 1.8 mg daily	-1.12	-28.9 [-1.6]	-3.24
Liutkus <i>et al.</i> [2010]	165	26 weeks	TZD ± metformin	Exenatide 10 µg twice daily	-0.84	-14.4 [-0.8]	-1.4
				Placebo	-0.1	-7.2 [-0.4]	-0.8
Zinman <i>et al.</i> [2009]	533	26 weeks	Metformin and rosiglitazone	Liraglutide 1.2 mg daily	-1.5	-40.0 [-2.22]	-1.0
				Liraglutide 1.8 mg daily	-1.5	-44.0 [-2.44]	-2.0
				Placebo	-0.5	-8.0 [-0.44]	+0.6
Buse <i>et al.</i> [2011]	261	30 weeks	Insulin glargine ± metformin or pioglitazone	Exenatide 10 µg twice daily	-1.74	-28.8 [-1.6]	-1.78
				Placebo	-1.04	-27.0 [-1.5]	+0.96
Apovian <i>et al.</i> [2010]	194	24 weeks	Metformin, SU or both	Exenatide 10 µg twice daily + TLC	-1.2	-36.2 [-2.01]	-6.2
				TLC	-0.7	-16.9 [-0.94]	-4.0
Derosa <i>et al.</i> [2011]	111	12 months	Metformin	Exenatide 10 µg twice daily	-1.2	-27.0 [-1.5]	-4.9
				Glimepiride 2 mg three times daily	-1.4	-28.0 [-1.55]	-0.9
Derosa <i>et al.</i> [2010]	128	12 months	Metformin	Exenatide 10 µg twice daily	-1.5	-27 [-1.5]	-8.0
				Glyburide 5 mg three times daily	-1.8	-32 [-1.77]	+4.3

(Continued)

Table 1. (Continued)

Study	No. of patients	Study duration	Baseline therapy	Treatment groups	Change in HbA1c (%)	Change in FBG (mg/dl) [mmol/liter]	Change in body weight (kg)
Nauck <i>et al.</i> [2009]	1091	26 weeks	Metformin	Liraglutide 0.6 mg daily	-0.7	-19.8 [-1.1]	-1.8
				Liraglutide 1.2 mg daily	-1.0	-28.8 [-1.6]	-2.6
				Liraglutide 1.8 mg daily	-1.0	-30.6 [-1.7]	-2.8
				Glimepiride 4 mg daily	-1.0	-23.4 [-1.3]	+1.0
				Placebo	+0.1	+7.2 [+0.4]	-1.5
Marre <i>et al.</i> [2009]	1041	26 weeks	Glimepiride	Liraglutide 0.6 mg daily	-0.6	-12.6 [-0.7]	+0.7
				Liraglutide 1.2 mg daily	-1.1	-28.8 [-1.6]	+0.3
				Liraglutide 1.8 mg daily	-1.1	-28.8 [-1.6]	-0.2
				Rosiglitazone 4 mg daily	-0.4	-16.2 [-0.9]	+2.1
				Placebo	+0.2	+18.0 [+1]	-0.1
Pratley <i>et al.</i> [2010]	665	26 weeks	Metformin	Liraglutide 1.2 mg daily	-1.24	-33.7 [-1.87]	-2.86
				Liraglutide 1.8 mg daily	-1.50	-38.5 [-2.14]	-3.38
Pratley <i>et al.</i> [2011]	497	52 weeks	Metformin	Sitagliptin 100 mg daily	-0.90	-14.9 [-0.83]	-0.96
				Liraglutide 1.2 mg daily	-1.29	-30.8 [-1.71]	-2.78
				Liraglutide 1.8 mg daily	-1.51	-36.7 [-2.04]	-3.68
Heine <i>et al.</i> [2005]	551	26 weeks	Metformin and SU	Sitagliptin 100 mg daily	-0.88	-10.6 [-0.59]	-1.16
				Exenatide 10 µg twice daily	-1.11	-25.7 [-1.43]	-2.3
Davies <i>et al.</i> [2009]	235	26 weeks	2-3 oral diabetes therapies	Insulin glargine (titrated to FBG < 100 mg/dl)	-1.11	-51.5 [-2.86]	+1.4
				Exenatide 10 µg twice daily	-1.25	-38.16 [-2.12]	-2.73
Gallwitz <i>et al.</i> [2011]	363	26 weeks	Metformin	Insulin glargine (titrated to FBG < 100 mg/dl)	-1.26	-64.98 [-3.61]	+2.98
				Exenatide 10 µg twice daily	-1.0	NR	-4.1
Nauck <i>et al.</i> [2007]	501	52 weeks	Metformin and SU	PIA 70/30	-1.14	NR	+1.0
				Exenatide 10 µg twice daily	-1.04	-32.4 [-1.4]	-2.5
Bergenstal <i>et al.</i> [2009]	372	24 weeks	Metformin and SU	PIA 70/30	-0.89	-30.6 [-1.7]	+2.9
				Exenatide 10 µg twice daily	-1.75	-21.4 [-1.19]	-1.9
				PIA 70/30 twice daily	-2.76	-62.7 [-3.48]	+4.1
Russell-Jones <i>et al.</i> [2009]	581	26 weeks	Metformin and glimepiride	PIA 70/30 daily	-2.34	-52.4 [-2.91]	+2.8
				Liraglutide 1.8 mg daily	-1.33	-27.9 [-1.55]	-1.8
				Insulin glargine daily	-1.09	-32.2 [-1.79]	+1.6
				Placebo	-0.24	+9.5 [+0.53]	-0.42

FBG, fasting blood glucose; HbA1c, hemoglobin A1c; NR, not reported; PIA, premixed insulin aspart; SU, sulfonylurea; TZD, thiazolidinedione.

2009]. Earlier studies included primarily patients of European and American descent, however several studies demonstrated similar results in glycemic control and body weight reductions in patients of Asian descent [Lu *et al.* 2013; Gao *et al.* 2009; Kadowaki *et al.* 2009; Yang *et al.* 2011], indicating exenatide and liraglutide provide improvement in glycemic control and body weight in most patients when used in combination with other oral antidiabetic medications (OAMs).

Exenatide and liraglutide have recently been approved for use in combination with long-acting insulin. Two retrospective trials showed a significant decrease in both HbA1c (-0.5% to -0.7%) and body weight (-2.5 to -5.8 kg) when exenatide was added to insulin therapy. Changes in diabetes treatments varied, with one study showing significant decreases in insulin doses (-0.3 U/kg) as well as the proportion of patients taking metformin and SUs while the other showed increases in insulin doses (0.1 U/kg) and no change in oral

diabetic therapies [Thong *et al.* 2011; Levin *et al.* 2012]. In a randomized, controlled trial including 261 patients, exenatide significantly reduced HbA1c (-1.74 versus -1.04%) and body weight (-1.78 versus $+0.96$ kg) compared with placebo when added to insulin glargine. FBG reductions were similar between groups [-28.8 versus -27.0 mg/dl (-1.6 versus -1.5 mmol/liter)]; however, PBG excursions were significantly lower after morning and evening meals with exenatide. Insulin doses increased in both groups but increased more in the placebo group (20 versus 13 U/day) [Buse *et al.* 2011]. The addition of insulin detemir to metformin and liraglutide was studied in 988 patients with T2DM. Subjects receiving insulin detemir experienced a decrease in HbA1c of 0.51% compared with an increase of 0.02% with placebo. Although significantly greater with placebo, both groups continued to experience weight loss (-0.16 kg with insulin versus -0.95 kg with placebo) [DeVries *et al.* 2012]. An extension study found reductions in HbA1c were maintained in each group for 52 weeks [Rosenstock *et al.* 2013b]. Both therapies showed benefit in combination with insulin and may provide additional PBG reductions.

When compared with oral, add-on therapies, exenatide and liraglutide continued to demonstrate benefit on glycemic control. In combination with metformin, a SU or both, exenatide plus intensive lifestyle modifications compared with lifestyle modifications alone significantly reduced HbA1c (-1.2 versus -0.7%), FBG [-36.2 versus -16.9 mg/dl (-2.01 versus -0.94 mmol/liter)] and body weight (-6.2 versus -4.0 kg) [Apovian *et al.* 2010]. Two studies comparing exenatide with a SU in combination with metformin found similar decreases in HbA1c (-1.2% to -1.5% versus -1.4% to -1.8%) and FBG [-27 and -28 to -32 mg/dl (-1.5 and -1.55 to -1.77 mmol/liter)]. However, exenatide resulted in significant weight reduction while SUs were weight neutral or resulted in weight gain [Derosa *et al.* 2010, 2011]. Exenatide also demonstrated greater durability than glimepiride with fewer treatment failures (41% versus 54%) and longer duration before treatment failure (180 weeks versus 142 weeks) when added to metformin [Gallwitz *et al.* 2012]. Liraglutide 1.2 and 1.8 mg daily and glimepiride 4 mg daily in combination with metformin resulted in similar reductions in HbA1c (-1.0% for all groups), FBG [-28.8 mg/dl (-1.6 mmol/liter), -30.6 mg/dl (-1.7 mmol/liter) versus -23.4 mg/dl (-1.3 mmol/liter)] and PBG [-41.4 mg/dl

(-2.3 mmol/liter), -46.8 mg/dl (-2.6 mmol/liter) versus -45 mg/dl (-2.5 mmol/liter)]. Liraglutide significantly decreased body weight (-1.8 to -2.8 kg) compared with increased body weight with glimepiride ($+1.0$ kg) [Nauck *et al.* 2009]. These studies suggest exenatide and liraglutide may be a better option than a SU as an add on to metformin therapy, especially in patients who are overweight or obese. In 1041 patients receiving concurrent therapy with glimepiride, liraglutide 1.2 and 1.8 mg daily were found to be superior to rosiglitazone 4 mg daily with regard to reductions in HbA1c (-1.1% versus -0.4%), FBG [-28.8 mg/dl (-1.6 mmol/liter) versus -16.2 mg/dl (-0.9 mmol/liter)], and PBG [-45.0 and -48.6 mg/dl (-2.5 and -2.7 mmol/liter) versus -32.4 mg/dl (-1.8 mmol/liter)]. While liraglutide did not result in significant decreases in body weight, rosiglitazone resulted in significant weight gain, so between group differences were significant [Marre *et al.* 2009]. Compared with sitagliptin, 26 weeks of liraglutide 1.2 and 1.8 mg in combination with metformin significantly decreased HbA1c (-0.9% versus -1.24% and -1.5%), FBG [-14.9 mg/dl (-0.83 mmol/liter) versus -33.7 mg/dl (-1.87 mmol/liter) and -38.5 mg/dl (-2.14 mmol/liter)], and body weight (-0.96 kg versus -2.86 kg and -3.38 kg) [Pratley *et al.* 2010]. In a 1-year extension of this trial, liraglutide maintained significant reductions in HbA1c, FBG, and body weight over sitagliptin [Pratley *et al.* 2011]. Following the extension, patients receiving sitagliptin were switched to liraglutide 1.2 or 1.8 mg daily for an additional 26 weeks and experienced additional decreases in HbA1c (-0.2 to -0.5%), FBG [-14.4 to -25.2 mg/dl (-0.8 to -1.4 mmol/liter)], and body weight (-1.6 to -2.5 kg) [Pratley *et al.* 2012]. Another study randomized 653 patients on metformin to an oral treatment strategy receiving sitagliptin 100 mg daily and an injectable treatment strategy using liraglutide 1.2 mg daily for 12 weeks. If HbA1c less than 7% was not achieved, glimepiride was added to the oral treatment strategy (47.2% patients) and liraglutide was increased to 1.8 mg in the injectable treatment strategy (25% patients) for an additional 14 weeks. At the end of the total 26-week trial, HbA1c and FBG were reduced similarly [-1.3% and -34.3 mg/dl (-1.83 mmol/liter) in the oral strategy group versus -1.4% and -39.6 mg/dl (-2.2 mmol/liter) in the injectable strategy group]. Body weight was significantly reduced by the injectable strategy (-2.8 kg) compared with the oral strategy (-0.4 kg) [Charbonnel *et al.* 2013]. Based on the result of these studies, liraglutide may provide better

glycemic control and body weight reduction when added to baseline therapy compared with sitagliptin. For patients resistant to injectable therapy, oral therapy may achieve similar HbA1c reductions but may require additional medications and may not result in weight loss.

Both exenatide and liraglutide have been compared with basal insulin as an add on to oral therapy. When added to metformin and a SU in 551 patients, exenatide and insulin glargine reduced HbA1c comparably (−1.11% in both groups) over 1 year. Insulin glargine significantly lowered FBG [−51.5 *versus* −25.7 mg/dl (−2.86 *versus* −1.43 mmol/liter)]; however PBG excursions were significantly lower with exenatide. Body weight was significantly reduced with exenatide therapy (−2.3 kg) compared with insulin glargine (+1.4 kg) [Heine *et al.* 2005]. A 16-week crossover study of 138 patients taking metformin or a SU showed similar reductions in HbA1c (−1.36%), smaller reductions in FBG [−52.2 mg/dl (−2.9 mmol/liter) *versus* −73.8 mg/dl (−4.1 mmol/liter)], larger reductions in body weight (−2.2 kg *versus* +2.3 kg), and larger reductions in PBG excursions with exenatide 10 µg twice daily compared with insulin glargine [Barnett *et al.* 2007]. In 235 patients with uncontrolled type 2 diabetes and taking two to three OAMs, exenatide 10 µg twice daily resulted in significantly more patients reaching the composite endpoint of an HbA1c less than 7.4% and weight gain up to 1 kg compared with insulin glargine (53.4% *versus* 19.8%) [Davies *et al.* 2009]. FBG reductions with insulin glargine may have been greater due to the titration to FBG targets; however, this titration is common in clinical practice and may better predict practical application. When added to metformin and glimepiride, liraglutide 1.8 mg daily showed significant reductions in HbA1c (−1.33% *versus* −1.09%) and body weight (−1.8 kg *versus* +1.6 kg) compared with insulin glargine. Reductions in FBG and PBG were similar between treatment groups [Russell-Jones *et al.* 2009]. Both exenatide and liraglutide show benefit in weight loss compared with insulin glargine, but liraglutide may provide more benefit on HbA1c reductions. Exenatide has also been compared with premixed insulin aspart 70/30 (PIA) in three trials showing mixed results. Two studies found exenatide 10 µg twice daily to be noninferior to PIA with regard to reductions in HbA1c, FBG, and PBG excursions [Gallwitz *et al.* 2011; Nauck *et al.* 2007]. However, the third study resulted in significantly reduced HbA1c (−2.34%

to −2.76% *versus* −1.75%) and FBG [−52.4 to −62.7 mg/dl *versus* −21.4 mg/dl (−2.91 to −3.48 *versus* −1.18 mmol/liter)] with PIA [Bergenstal *et al.* 2009]. Exenatide resulted in significant body weight reductions in all three trials compared with PIA [Gallwitz *et al.* 2011; Nauck *et al.* 2007; Bergenstal *et al.* 2009]. Based on these results, exenatide may be an appropriate option but patients requiring a larger HbA1c reduction (>2%) may require premixed insulin.

Safety

Overall, side effects were minor and rarely required discontinuation of therapy. The primary side effect of both exenatide and liraglutide was nausea, which occurred in 8–51% and 10.5–45% of patients in trials, respectively [Moretto *et al.* 2008; Yuan *et al.* 2012; Buse *et al.* 2004, 2007; Kendall *et al.* 2005; DeFronzo *et al.* 2005; Ratner *et al.* 2006; Riddle *et al.* 2006; Liutkus *et al.* 2010; Zinman *et al.* 2007, 2009; Garber *et al.* 2009]. Nausea tended to be transient following treatment initiation and dose escalation, resolving over the first 8 weeks for exenatide and 4 weeks for liraglutide [Yuan *et al.* 2012; Buse *et al.* 2004, 2007; Kendall *et al.* 2005; DeFronzo *et al.* 2005; Ratner *et al.* 2006; Riddle *et al.* 2006; Zinman *et al.* 2007, 2009; Garber *et al.* 2009; Marre *et al.* 2009]. Nausea was less persistent in patients receiving liraglutide compared with exenatide [Buse *et al.* 2009].

Rates of hypoglycemia were relatively low, occurring in 4–12% of patients receiving exenatide and 3–12% of patients receiving liraglutide without concurrent SU [Moretto *et al.* 2008; Yuan *et al.* 2012; DeFronzo *et al.* 2005; Ratner *et al.* 2006; Buse *et al.* 2007; Liutkus *et al.* 2010; Zinman *et al.* 2007; Garber *et al.* 2009; Nauck *et al.* 2009]. Incidence of hypoglycemia with both therapies was higher in patients receiving concurrent SU therapy [Buse *et al.* 2004, 2009; Kendall *et al.* 2005; Apovian *et al.* 2010]. Compared with insulin, exenatide and liraglutide had lower or similar rates of overall hypoglycemia and reduced nocturnal hypoglycemia [Heine *et al.* 2005; Barnett *et al.* 2007; Davies *et al.* 2009; Gallwitz *et al.* 2011; Bergenstal *et al.* 2009; Russell-Jones *et al.* 2009].

Postmarketing reports of pancreatitis resulted in a black box warning (BBW) for both exenatide and liraglutide [Amylin Pharmaceuticals, Inc., 2011; Novo Nordisk A/S, 2013]. Four patients have

reported pancreatitis with liraglutide in clinical trials; however, all recovered and two continued in the study [Garber *et al.* 2009; Nauck *et al.* 2009; Marre *et al.* 2009]. One patient receiving liraglutide was diagnosed with pancreatic carcinoma on day 11 of therapy; however, this was considered to be unrelated to liraglutide [Pratley *et al.* 2010]. Liraglutide also carries a black box warning for thyroid C-cell tumors due to occurrence in rat and mice studies. Carcinoma has not been seen in clinical trials but caution should be used in patients with a personal or family history of medullary thyroid carcinoma [Novo Nordisk A/S, 2013].

Development of antibodies occurs with both exenatide (27–49%) and liraglutide therapy (4.1–13%); however, the presence of antibodies has not affected clinical results [Moretto *et al.* 2008; Buse *et al.* 2004; Kendall *et al.* 2005; DeFronzo *et al.* 2005; Zinman *et al.* 2007, 2009; Marre *et al.* 2009; Russell-Jones *et al.* 2009]. The safety and tolerability of exenatide has been consistent across all nationalities [Lu *et al.* 2013; Gao *et al.* 2009; Kadowaki *et al.* 2009; Heine *et al.* 2005; Yang *et al.* 2011].

Long-acting GLP-1 RAs

Efficacy

Exenatide LAR 2 mg and albiglutide 30 and 50 mg are both dosed once weekly and have been studied as monotherapy, in combination with OAMs, and have been compared with various conventional diabetes treatment options [Amylin Pharmaceuticals, Inc., 2012; GlaxoSmithKline LLC, 2014].

Exenatide LAR monotherapy was compared with metformin, pioglitazone, and sitagliptin monotherapy in a 26-week study. HbA1c was reduced by –1.53% with exenatide LAR, –1.48% with metformin, –1.63% with pioglitazone, and –1.15% with sitagliptin from an average baseline HbA1c of 8.4–8.6%. Exenatide LAR was noninferior to metformin and superior to sitagliptin ($p = 0.620$ and $p < 0.001$, respectively), but did not reach noninferiority compared with pioglitazone ($p = 0.328$). Weight reductions were significantly greater with exenatide LAR compared with pioglitazone and sitagliptin but similar between exenatide once weekly and metformin [Russell-Jones *et al.* 2012].

Add-on therapy with exenatide LAR once weekly was evaluated against sitagliptin or pioglitazone in patients nonresponsive to metformin monotherapy in a 26-week randomized, double-blind trial. The baseline average HbA1c of 8.5% was reduced to 7.2% in the exenatide LAR treatment arm, 7.7% in the sitagliptin treatment arm, and 7.4% in the pioglitazone treatment arm. Reductions in HbA1c were significantly greater with exenatide LAR than sitagliptin and pioglitazone ($p < 0.0001$ and $p = 0.0165$, respectively). FBG was reduced by all treatments. Exenatide LAR had a greater reduction in FBG than sitagliptin but not pioglitazone ($p = 0.0038$ and $p = 0.3729$, respectively). Exenatide LAR also provided significant weight loss of –2.3 kg compared with –0.8 kg weight loss with sitagliptin ($p = 0.0002$) and the 2.8 kg weight gain with pioglitazone ($p < 0.0001$) [Bergenstal *et al.* 2010]. An extension study, in which patients were continued on exenatide LAR or switched from sitagliptin and pioglitazone to exenatide once weekly, showed sustained HbA1c, FBG, and weight reduction in the patients that continued on exenatide LAR and improved results in these parameters for patients that switched from sitagliptin and pioglitazone to exenatide LAR for up to 1 year. The most significant changes were seen in glycemic control improvement in the sitagliptin to exenatide LAR group (additional –0.3% HbA1c reduction; $p = 0.0010$) and in weight reduction in the pioglitazone to exenatide LAR group (–3.0 kg weight loss; $p < 0.0001$) [Wysham *et al.* 2011].

In a 104-week randomized, placebo and active controlled trial, albiglutide was compared with placebo, sitagliptin, and glimepiride in patients inadequately controlled on metformin. Average baseline HbA1c was 8.1%. Albiglutide provided a significantly greater reduction in HbA1c (–0.63%) than all of the other treatment arms (–0.27% with placebo, –0.28% with sitagliptin, and –0.36% with glimepiride; $p < 0.001$, $p = 0.001$, and $p = 0.0033$, respectively). Patients in the albiglutide group lost more weight on average but the secondary outcome of weight change from baseline to week 104 was only significantly greater in the albiglutide group compared with glimepiride [Ahren *et al.* 2014].

Exenatide LAR was compared with insulin glargine in patients with an insufficient response to metformin with or without a SU. After 26 weeks, HbA1c was significantly reduced with exenatide LAR compared with insulin glargine (–1.5 *versus* –1.3 respectively; $p = 0.017$) [Diamant *et al.*

2010]. Initial results were maintained through an 84-week extension study [Diamant *et al.* 2012]. A second study of exenatide LAR *versus* insulin detemir studied patients with an inadequate response to metformin with or without SUs. Patients were randomized to exenatide LAR 2 mg once weekly or insulin detemir once or twice daily. After 30 weeks, more participants met the primary outcome ($\text{HbA1c} \leq 7\%$ with weight loss ≥ 1.0 kg, in the exenatide LAR group compared with the insulin detemir group (44.1% in the exenatide group *versus* 11.4% in the insulin detemir group, $p < 0.0001$) [Davies *et al.* 2013]. Additionally, there was a statistically significant change in HbA1c from baseline to week 26 among exenatide LAR users compared with insulin detemir users (-1.30 *versus* -0.88 , respectively; $p < 0.0001$) [Davies *et al.* 2013].

Safety

Over the 3-year follow up of the DURATION-1 study comparing exenatide LAR once weekly with exenatide twice daily, most adverse events with exenatide LAR were mild to moderate and included nausea, vomiting, diarrhea, upper respiratory tract infection, nasopharyngitis, and sinusitis [MacConell *et al.* 2013]. The incidences of nausea, vomiting, and diarrhea were highest during the first 12 weeks of exenatide LAR use and decreased to 1% during the last 12 weeks [MacConell *et al.* 2013]. Hypoglycemia was minor and occurred more often in patients on concomitant SU therapy than patients not treated with SUs (19.3% *versus* 1%, respectively). Hypoglycemia was similar with exenatide LAR compared with insulin detemir and did not lead to study drug discontinuation in any trials comparing exenatide LAR with insulin [Diamant *et al.* 2010; Davies *et al.* 2013].

There were no reported episodes of pancreatitis, pancreatic cancer, or thyroid cancer during the 3-year DURATION-1 study [MacConell *et al.* 2013]. Asymptomatic increases in pancreatic enzymes were observed in five subjects in the exenatide LAR group compared with none in the insulin glargine group at the conclusion of the DURATION-3 trial [Diamant *et al.* 2010].

Safety of exenatide LAR was studied as a primary outcome in a 26-week extension trial conducted by Onishi and colleagues [Onishi *et al.* 2013]. Patients from Japan originally enrolled in a 26-week study comparing the safety and

efficacy of twice-daily exenatide with once-weekly exenatide LAR in an Asian population were enrolled. Patients receiving twice-daily exenatide were switched to once-weekly exenatide LAR and patients receiving exenatide LAR continued once-weekly dosing [Onishi *et al.* 2013]. Researchers noted that of the patients initially on twice-daily exenatide, the majority of adverse events that led to study discontinuation occurred during the first 26 weeks before the patients were switched to once-weekly exenatide LAR. Typically, adverse events such as nausea, vomiting, diarrhea, and minor hypoglycemia decreased when patients were switched from twice-daily exenatide to once-weekly exenatide LAR. Conversely, the frequency of injection-site reactions increased in patients switching from twice-daily dosing to once-weekly dosing. Adverse event rates remained consistent in patients continuing on once-weekly exenatide LAR dosing. These findings are consistent with differences noted between the safety profiles of twice-daily exenatide *versus* once-weekly exenatide LAR in other clinical trials [Onishi *et al.* 2013].

Similar rates of adverse events have been reported in trials comparing albiglutide with conventional therapy. Nausea, diarrhea, and injection site reactions continue to be the most reported adverse events in the albiglutide treatment groups, with no increased occurrence of serious adverse events when matched to comparator treatment arms [Ahren *et al.* 2014; Pratley *et al.* 2014].

Comparison of short- and long-acting agents

Exenatide LAR and liraglutide were compared head to head in a 26-week study. Both agents provided clinically significant lowering in HbA1c; however, liraglutide had a statistically greater reduction in HbA1c than exenatide LAR (-1.48% *versus* -1.28% , respectively; $p = 0.02$). Additionally, the treatment difference of 0.21% [95% confidence interval (CI) 0.08–0.33] did not meet predetermined noninferiority criteria for exenatide LAR (upper limit of CI < 0.25) [Buse *et al.* 2013]. Liraglutide also decreased FBG and weight significantly more than exenatide LAR ($p = 0.02$). Both agents had comparable improvements in cardiovascular measures such as blood pressure (BP), C-reactive protein (CRP), and lipids. Exenatide LAR had a favorable side effect profile compared with liraglutide with fewer incidences

of nausea, diarrhea, and vomiting [Buse *et al.* 2013].

Albiglutide was also compared with liraglutide in patients with T2DM inadequately controlled on metformin, TZD, SU, or a combination of the three in a 32-week noninferiority trial. Albiglutide lowered HbA1c but did not meet noninferiority criteria compared with liraglutide ($p = 0.0846$). Change in weight was also significantly greater with liraglutide (-0.62 kg with albiglutide *versus* -2.21 kg with liraglutide). Gastrointestinal adverse events were reported more in the liraglutide group, whereas injection site reactions were more commonly reported among the albiglutide group [Pratley *et al.* 2014].

DURATION-1, a 30-week randomized, noninferiority study, compared exenatide LAR 2 mg once weekly with exenatide 10 μ g twice daily in treatment-naïve patients and patients on one or more OAMs. Although both treatment groups had significant reductions in HbA1c, greater reductions were observed in the exenatide LAR group (-1.9 *versus* -1.5 , $p = 0.0023$). Both groups had similar reductions in body weight (-3.6 kg with once weekly treatment *versus* -3.7 kg with twice daily treatment, $p = 0.89$) [Drucker *et al.* 2008]. Extensions of DURATION-1 evaluated glycemic control and cardiometabolic effects at 52 weeks, 2 years, and 3 years from baseline. Patients were either continued on exenatide LAR once weekly or changed from exenatide twice daily to exenatide LAR once weekly for the duration of the extension studies. Exenatide LAR maintained initial improvements in HbA1c over the full 3 years of follow up with a change from baseline of -2.1% at 30 weeks, -2.0% at 52 weeks, -1.71% at 2 years, and -1.6% at 3 years [Buse *et al.* 2010; Taylor *et al.* 2011; MacConell *et al.* 2013]. Patients who were switched to once-weekly exenatide LAR had further reductions in HbA1c after the switch [Buse *et al.* 2010]. Body weight continued to decrease in a similar fashion between the two groups [Buse *et al.* 2010; Taylor *et al.* 2011; MacConell *et al.* 2013]. Patients switching from twice-daily exenatide to once-weekly exenatide LAR experienced a temporary increase in FBG for 2 weeks followed by a sharp decline in FBG levels that ultimately returned to levels similar to those prior to the switch [Buse *et al.* 2010].

Once-weekly exenatide LAR was shown to be superior to twice-daily exenatide in a 24-week open-label study in patients who were either drug

naïve or previously treated with one or more OAMs and had an average HbA1c of 8.5%. The average change in HbA1c was -1.6 in the once-weekly exenatide LAR arm and -0.9 in the twice-daily exenatide arm ($p < 0.0001$) [Belvins *et al.* 2011]. A significantly greater number of patients in the once-weekly exenatide LAR group also achieved HbA1c targets of less than 7% and less than 6.5% compared with the twice-daily exenatide group ($p < 0.0001$ for both outcomes). Significant decreases in FBG were observed in the once-weekly treatment group compared with the twice-daily treatment group [-35 mg/dl (-1.94 mmol/liter) *versus* -12 mg/dl (-0.66 mmol/liter), $p = 0.0008$]. Reductions in body weight were significantly greater in the patients on once-weekly treatment compared with those on twice-daily treatment (-2.3 kg *versus* -1.4 kg, respectively; $p < 0.05$) [Belvins *et al.* 2011].

Ji and colleagues conducted a similar study in an Asian population. Patients were randomized to exenatide 10 μ g twice daily or exenatide LAR 2 mg weekly. Again, exenatide LAR significantly lowered HbA1c compared with exenatide twice daily (-1.43 *versus* -1.12 , $p < 0.001$). Exenatide LAR once weekly also significantly reduced FBG compared with twice-daily dosing [-40.57 mg/dl (-2.25 mmol/liter) *versus* -23.90 mg/dl (-1.33 mmol/liter), $p < 0.001$]. However, significant reductions in morning and evening PBG were greater in the twice-daily dosing arm compared with the once-weekly dosing arm [-87 mg/dl (-4.83 mmol/liter) *versus* -63 mg/dl (-3.5 mmol/liter), $p < 0.001$]. Contrary to previously published trials, a significantly greater weight loss was observed in the exenatide twice-daily dosing group compared with the exenatide LAR once-weekly dosing group (-2.45 kg and -1.63 kg, respectively; $p < 0.001$) [Ji *et al.* 2013].

Additional benefits of GLP-1 therapy

Although results were mixed, the secondary outcomes of initial trials with exenatide and liraglutide suggested a potential benefit for cardiovascular risk factors. Exenatide 5–10 μ g twice daily decreased systolic BP (SBP) by 3.5–9.4 mmHg and diastolic BP (DBP) by 0.8–4.1 mmHg [Moretto *et al.* 2008; Ratner *et al.* 2006; Buse *et al.* 2007; Liutkus *et al.* 2010; Apovian *et al.* 2010; Klonoff *et al.* 2008]. A placebo-controlled trial randomized 54 patients controlled on metformin, a TZD, or both to receive exenatide 10 μ g twice daily to specifically evaluate its effects

on heart rate (HR) and BP. Exenatide showed no significant effect on HR or BP, although SBP was lowered by 5.6 mmHg compared with placebo [Gill *et al.* 2010]. Liraglutide 1.2–1.8 mg daily decreased SBP by 2.0–5.6 mmHg but tended to have no significant effect on DBP [Garber *et al.* 2009; Zinman *et al.* 2009; Marre *et al.* 2009; Russell-Jones *et al.* 2009]. Liraglutide 1.8 mg daily significantly reduced SBP compared with glimepiride [Garber *et al.* 2009; Nauck *et al.* 2009]. Exenatide LAR has also shown significant reductions in SBP and DBP [MacConell *et al.* 2013; Davies *et al.* 2013]. Some studies have seen significant improvement in low-density lipoprotein (LDL) [Buse *et al.* 2004; Klonoff *et al.* 2008; Zinman *et al.* 2009], triglycerides (TGs) [Ratner *et al.* 2006; Klonoff *et al.* 2008; Zinman *et al.* 2009], high-density lipoprotein (HDL) [Ratner *et al.* 2006; Klonoff *et al.* 2008], and apolipoprotein B (ApoB) [Buse *et al.* 2004; Ratner *et al.* 2006] with exenatide and liraglutide but others found no significant effects on lipids [Moretto *et al.* 2008; DeFronzo *et al.* 2005; Liutkus *et al.* 2010]. *Post hoc* analysis of the DURATION-1 study revealed improvements in ApoB, ApoB/ApoA1, TGs, LDL4-C, and HDL2-C with exenatide LAR ($p < 0.05$) compared with significant changes in TGs and very-low-density lipoprotein with twice-daily exenatide ($p < 0.05$) [Chiquette *et al.* 2012]. Over the 3-year follow up of the DURATION-1 study population, significant reductions in DBP, total cholesterol, LDL, and TGs were maintained throughout the 3-year follow up [MacConell *et al.* 2013]. The first long-term phase IV trial evaluating cardiovascular outcomes in patients on exenatide LAR compared with usual care without exenatide is underway to evaluate a composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke over a 7.5-year follow up [ClinicalTrials.gov identifier: NCT01144338].

Initial studies of both exenatide and liraglutide found improvements in β -cell function and insulin sensitivity based on Homeostasis Model Assessment HOMA-B [Moretto *et al.* 2008; Buse *et al.* 2007; Liutkus *et al.* 2010; Zinman *et al.* 2007; Klonoff *et al.* 2008; Derosa *et al.* 2012; Zinman *et al.* 2009; Nauck *et al.* 2009; Marre *et al.* 2009; Pratley *et al.* 2010] and HOMA-S values [Buse *et al.* 2007] as monotherapy and in combination with metformin, SUs, or TZDs. Compared with exenatide, liraglutide had significantly greater improvements in β -cell function [Buse *et al.* 2009]. Compared with SUs, exenatide and liraglutide

demonstrated significant improvements in insulin resistance (based on HOMA-IR) [Derosa *et al.* 2011; Garber *et al.* 2009, 2011] and β -cell function (based on HOMA-B) [Derosa *et al.* 2010] whereas therapy with SUs did not [Derosa *et al.* 2010, 2011; Garber *et al.* 2009]. In a 3-year study, exenatide significantly improved β -cell function based on disposition index. When exenatide was discontinued for 4 weeks after 1 year, β -cell function returned to baseline; however, after 3 years of therapy β -cell function remained elevated after exenatide discontinuation, suggesting long-term treatment may result in longstanding effects on β -cell function [Bunck *et al.* 2011].

Early studies of exenatide found evidence to suggest exenatide may decrease liver enzymes, aspartate aminotransferase and alanine aminotransferase (ALT), especially in patients with elevated baseline levels [Buse *et al.* 2007; Klonoff *et al.* 2008], which may suggest benefits for patients with liver impairment. In a study of 24 patients with T2DM on diet or metformin therapy, hepatic fat content was significantly reduced in patients randomized to receive a combination of pioglitazone and exenatide compared with pioglitazone alone (-4.5% versus 7.4% ; $p < 0.001$). ALT was also significantly reduced with combination therapy [Sathyanarayana *et al.* 2011]. These results suggest a potential benefit in patients with liver impairment or high liver fat content.

Secondary endpoints of early trials suggested significant improvement in inflammatory markers, including tumor necrosis factor α and CRP with exenatide twice daily and once-weekly therapy [Derosa *et al.* 2010, 2011; Chiquette *et al.* 2012; Davies *et al.* 2013]. A 16-week study also found a decrease in CRP with exenatide compared with placebo (-0.2 mg/liter versus $+0.8$ mg/liter) [Wu *et al.* 2011]. In a placebo-controlled trial, 174 patients with T2DM uncontrolled on metformin were randomized to exenatide 10 μ g twice daily or placebo. After 1 year of therapy, exenatide plus metformin significantly reduced resistin levels but not vaspin or chemerin compared with placebo [Derosa *et al.* 2013]. The clinical implications of these changes are not known.

GLP-1 RAs in development

Four additional GLP-1 RAs, taspoglutide, lixisenatide, dulaglutide, and semaglutide are currently in development. Add-on therapy with

taspoglutide 10 mg and 20 mg once weekly was compared with TZDs and basal insulin in patients whose condition was uncontrolled on metformin with or without a SU [Nauck *et al.* 2013; Pratley *et al.* 2013]. Taspoglutide 20 mg weekly was found to be noninferior to pioglitazone and insulin glargine, with average reduction in HbA1c of -1.36 and -0.98 , respectively [Nauck *et al.* 2013; Pratley *et al.* 2013]. Compared with exenatide twice daily and sitagliptin in patients whose condition is inadequately controlled on metformin with or without a TZD, taspoglutide 20 mg weekly reduced HbA1c and FBG to a significantly greater extent ($p < 0.0001$) [Bergental *et al.* 2012; Rosenstock *et al.* 2013a]. However, gastrointestinal disorders and injection-site reactions have been observed more frequently in the taspoglutide treatment arm of several phase III clinical trials, leading to a higher withdrawal rate among participants [Nauck *et al.* 2013; Pratley *et al.* 2013; Bergental *et al.* 2012; Rosenstock *et al.* 2013a]. The negative side-effect profile seen in clinical trials led to the discontinuation of phase III trials of taspoglutide. The product is now under investigation for reformulation by the company Ipsen, Basking Ridge, NJ [Rosenstock *et al.* 2013a].

Lixisenatide is available in Europe, Mexico, Australia, and Japan as the brand name Lyxumia; however, the US FDA new drug application was recently withdrawn by the manufacturer [Sanofi, 2013, Bridgewater, NJ]. Lixisenatide had positive results in HbA1c, FBG, and weight reductions compared with placebo in patients whose condition was uncontrolled on metformin with or without a SU [Bolli *et al.* 2014; Rosenstock *et al.* 2014]. The manufacturer, Sanofi, plans to resubmit the application to the US FDA after the current cardiovascular outcomes trial, ELIXA, has concluded [Sanofi, 2013].

Dulaglutide has been studied against placebo and conventional therapy options in several clinical trials. Dulaglutide 1.5 mg and 0.75 mg weekly provided significant reductions in HbA1c over 26 weeks compared with placebo. Dulaglutide monotherapy was also compared with metformin monotherapy and was found to be noninferior to metformin for HbA1c lowering, with no differences in side-effect profile and weight reduction. Dulaglutide was also shown to be noninferior to sitagliptin in HbA1c reduction from baseline to 52 weeks [Lilly, 2013]. Several trials are still underway comparing dulaglutide with insulin glargine and evaluating cardiovascular outcomes with dulaglutide use.

Semaglutide is an investigational once-weekly GLP-1 RA. In a dose-finding, phase II trial, semaglutide 0.8 mg and 1.6 mg once weekly produced greater reductions in HbA1c at 12 weeks than liraglutide 1.2 mg and 1.8 mg daily and greater weight reductions compared with placebo. Participant withdrawals were related to gastrointestinal adverse events [Nauck *et al.* 2012]. A phase II pharmacokinetic study in subjects with or without renal impairment suggested dose adjustment may not be needed for patients with renal insufficiency, although more studies are needed [Marbury *et al.* 2014]. Semaglutide is currently undergoing phase III trials.

Place in therapy

All four FDA-approved GLP-1 RAs, exenatide, liraglutide, exenatide LAR, and albiglutide, have demonstrated efficacy in regard to glycemic control with significant reductions in HbA1c, FBG, and PBG both as monotherapy and in combination with common first- and second-line agents. HbA1c reductions ranged from 0.5% to 1.8%, indicating GLP-1 RAs are most appropriate in patients with an HbA1c less than 9% in order to reach HbA1c targets. Long-acting GLP-1 RAs seem to be superior in glycemic control compared with exenatide but not compared with liraglutide. Only exenatide and liraglutide are currently approved and have been shown to provide additional lowering of PBG for use in combination with long-acting insulin. Long-acting GLP-1 RAs still require additional studies to determine if benefit is seen. Body weight reductions were also significant with all GLP-1 RAs, which may make them a superior option for patients who are overweight or obese compared with treatments which may increase weight, including SUs, TZDs, and insulin. In general, GLP-1 RAs were well tolerated with most adverse effects being mild and gastrointestinal in nature. Nausea was the most common adverse effect and tended to resolve after the first weeks of treatment. Incidence of nausea was lower and less persistent in longer-acting agents. All agents carry a warning for the potential to cause pancreatitis. In patients with a history of pancreatitis, other options may be more prudent. Liraglutide, exenatide LAR, and albiglutide all carry a BBW for C-cell thyroid tumors. These agents should not be used in patients with a personal or family history of medullary thyroid carcinoma. Given the increased risk of cardiovascular disease with diabetes, the effects of medications on CV risk factors should be considered.

While studies have suggested potential benefits on BP, lipids, and inflammatory markers with GLP-1 RAs, larger trials are needed to determine the clinical relevance of these effects.

Conclusion

GLP-1 RAs provide improved glycemic control and weight reduction along with a good safety profile. The addition of GLP-1 RAs may be considered in patients not tolerating first-line medications, patients receiving metformin, a SU, a TZD, or insulin therapy and not meeting glycemic goals, or patients in need of weight loss.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

- Ahren, B., Johnson, S., Stewart, M., Cirkel, D., Yang, F., Perry, C. *et al.* (2014) HARMONY 3: 104-week randomized, double-blind, placebo- and active- controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care* 37: 2141–2148.
- Amylin Pharmaceuticals, Inc. (2011) Byetta (exenatide) package insert. Available at: http://documents.byetta.com/Byetta_PI.pdf (accessed 12 July 2014).
- Amylin Pharmaceuticals, Inc. (2012) Bydureon (exenatide extended release) package insert. Available at: http://documents.bydureon.com/Bydureon_PI.pdf (accessed 12 July 2014).
- Apovian, C., Bergenstal R., Cuddigy R., Qu Y., Lenox, S., Lewis, M. *et al.* (2010) Effects of exenatide combined with lifestyle modifications in patients with type 2 diabetes. *Am J Med* 123: e9–17.
- Barnett, A., Burger, J., Johns, D., Brodows, R., Kendall, D., Roberts, A. *et al.* (2007) Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. *Clin Ther* 29: 2333–2348.
- Belvins, T., Pullman, J., Malloy, J., Yan, P., Taylor, K. and Schulteis, C. (2011) DURATION:5 Exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab* 96: 1301–1310.
- Bergenstal, R., Forti, A., Chiasson, J., Wolochak, M., Boldrin, M. and Balena, R. (2012) Efficacy and safety of tasoglutide versus sitagliptin for type 2 diabetes mellitus (T-Emerge 4 trial). *Diabetes Ther* 3: 13.
- Bergenstal, R., Lewin, A., Bailey, T., Chang, D., and Roberts, V. (2009) Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. *Curr Med Res Opin* 25:65–75.
- Bergenstal, R., Wysham, C., MacConell, L., Malloy, J., Walsh, B., Yan, P. *et al.* (2010) Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomized trial. *Lancet* 376: 431–439.
- Blonde, L., Klein, E., Han, J., Zhang, B., Mac, S., Poon, T. *et al.* (2006) Interim analysis of the effects of exenatide treatment on A1c, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab* 8: 436–447.
- Bolli, G., Munteanu, M., Dotsenko, S., Neimoeller, E., Boka, G., Wu, Y. *et al.* (2014) Efficacy and safety of lixisenatide once daily *vs.* placebo in people with type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). *Diabetes Med* 31: 176–184.
- Bunck, M., Cornner, A., Eliasson, B., Heine, R., Shaginian, R., Taskinen, M. *et al.* (2011) Effects of exenatide on measure of β -cell function after 3 years in metformin-treated patients with type 2 diabetes. *Diabetes Care* 34: 2041–2047.
- Buse, J., Drucker, D., Taylor, K., Kim, T., Walsh, B., Hu, H. *et al.* (2010) DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care* 33: 1255–1261.
- Buse, J., Bergenstal, R., Glass, L., Heilmann, C., Lewis, M., Kwan, A. *et al.* (2011) Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 154: 103–112.
- Buse, J., Henry, R., Han, J., Kim, D., Fineman, M. and Baron, A. (2004) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 27: 2628–2635.
- Buse, J., Klonoff, D., Nielsen, L., Guan, X., Bowlus, C., Holcombe, J. *et al.* (2007) Metabolic effects of two

- years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. *Clin Ther* 29: 139–153.
- Buse, J., Rosenstock, J., Sesti, G., Schmidt, W., Montanya, E., Brett, J. *et al.* (2009) Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 374: 39–47.
- Buse, J., Nauck, M., Forst, T., Sheu, W., Shenouda, S., Heilmann, C. *et al.* (2013) Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomized, open-label study. *Lancet* 381: 117–124.
- Charbonnel, B., Steinberg, H., Eymard, E., Xu, L., Thakkar, P., Prabhu, V. *et al.* (2013) Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: a randomised clinical trial. *Diabetologia* 56: 1503–1511.
- Chiquette, E., Toth, P., Ramirez, G., Cobble, M. and Chilton, R. (2012) Treatment with exenatide once weekly or twice daily for 30 weeks is associated with changes in several cardiovascular risk markers. *Vasc Health Risk Manag* 8: 621–629.
- Davies, M., Donnelly, R., Barnett, A., Jones, S., Nicolay, C. and Kilcoyne, A. (2009) Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the helping evaluate exenatide in patients with diabetes compared with long-acting insulin (HEELA) study. *Diabetes Obes Metab* 11: 1153–1162.
- Davies, M., Heller, S., Sreenan, S., Sapin, H., Adetunji, O., Tahbaz, A. *et al.* (2013) Once-weekly exenatide versus once- or twice- daily insulin detemir. *Diabetes Care* 36: 1368–1376.
- DeFronzo, R., Ratner, R., Han, J., Kim, D., Fineman, M. and Baron, A. (2005) Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28: 1092–1100.
- Derosa, G., Franzetti, I., Querci, F., Carbone, A., Ciccarelli, L., Piccinni, M. *et al.* (2012) Exenatide plus metformin compared with metformin alone on β -cell function in patients with type 2 diabetes. *Diabet Med* 29: 1515–1523.
- Derosa, G., Franzetti, I., Querci, F., Carbone, A., Ciccarelli, L., Piccinni, M. *et al.* (2013) Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial. *Pharmacotherapy* 33: 817–826.
- Derosa, G., Maffioli, P., Salvadeo, S., Ferrari, I., Ragonesi, P., Querci, F. *et al.* (2010) Exenatide versus glibenclamide in patients with diabetes. *Diabetes Technol Ther* 12: 233–240.
- Derosa, G., Putignano, P., Bossi, A., Bonaventura, A., Querci, F., Franzetti, I. *et al.* (2011) Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients. *Eur J Pharmacol* 666: 251–256.
- DeVries, J., Bain, S., Rodbard, H., Seufert, J., D'Alessio, D., Thomsen, A. *et al.* (2012) Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1c targets. *Diabetes Care* 35: 1446–1454.
- Diamant, M., Gaal, L., Stranks, S., Guerci, B., MacConell, L., Haber, H. *et al.* (2012) Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. *Diabetes Care* 35: 683–689.
- Diamant, M., Gaal, L., Stranks, S., Northrup, J., Cao, D., Taylor, K. *et al.* (2010) Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (Duration-3): an open-label randomized trial. *Lancet* 375: 2234–2243.
- Drucker, D., Buse, J., Taylor, K., Kendall, D., Trautmann, M., Zhuang, D. *et al.* (2008) Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. *Lancet* 372: 1240–1250.
- Frias, J. and Edelman, S. (2007) Incretins and their role in the management of diabetes. *Curr Opin Endocrinol Diabetes Obes* 14: 269–276.
- Gallwitz, B., Bohmer, M., Segiet T., Molle, A., Milek, K., Becker, B. *et al.* (2011) Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia. *Diabetes Care* 34:604–606.
- Gallwitz, B., Guzman, F., Dotta, F., Guerci, B., Simo, R., Basson, B. *et al.* (2012) Exenatide twice daily versus glimepiride for prevent of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomized controlled trials. *Lancet* 379: 2270–2278.
- Gao, Y., Yoon, K., Chuan, L., Mohan, V., Ning, G., Shah, S. *et al.* (2009) Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea. *Diabetes Res Clin Pract* 83: 69–76.

- Garber, A., Henry, R., Ratner, R., Garcia-Hernandez, P., Rodriguez-Pattzi, H., Olvera-Alvarez, I. *et al.* (2009) Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52 week, phase III, double-blind, parallel-treatment trial. *Lancet* 373: 473–481.
- Garber, A., Henry, R., Ratner, R., Hale, P., Chang, C., Bode, B. *et al.* (2011) Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provide sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab* 13: 348–356.
- Gill, A., Hoogwerf, B., Burger, J., Bruce, S., MacConell, L., Yan, P. *et al.* (2010) Effect of exenatide on heart rate and blood pressure in subjects with type 2 diabetes mellitus: a double-blind, placebo-controlled, randomized pilot study. *Cardiovasc Diabetol* 9: 1–7.
- GlaxoSmithKline, LLC (2014) Tanzeum (albiglutide) package insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125431s000lbl.pdf (accessed 12 July 2014).
- Heine, R., Van Gaal, L., Johns, D., Mihm, M., Widel, M. and Brodows, R. (2005) Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes; a randomized trial. *Ann Intern Med* 143: 559–569.
- Holst, J. (2006) Glucagon-like peptide-1: from extract to agent. The Claude Bernard Lecture, 2005. *Diabetologia* 49: 253–260.
- Holst, J. (2007) The physiology of glucagon-like peptide 1. *Physiol Rev* 87: 1409–1439.
- Inzucchi, S., Bergenstal, R., Buse, J., Diamant, M., Ferrannini, E., Nauck, M. *et al.* (2012) Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 35: 1364–1379.
- Ji, L., Onishi, Y., Ahn, C., Agarwal, P., Chou, C., Haber, H. *et al.* (2013) Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus. *J Diabetes Invest* 4: 53–61.
- Kadowaki, T., Namba, M., Yamamura, A., Sowa, H., Wolka, A. and Brodows, R. (2009) Exenatide exhibits dose-dependent effects on glycemic control over 12 weeks in Japanese patients with suboptimally controlled type 2 diabetes. *Endocrine* 56: 415–424.
- Kendall, D., Riddle, M., Rosenstock, J., Zhuang, D., Kim, D., Fineman, M. *et al.* (2005) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 28: 1083–1091.
- Klonoff, D., Buse, J., Nielsen, L., Guan, X., Bowlus, C., Holcombe, J. *et al.* (2008) Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type diabetes treated for at least 3 years. *Curr Med Res Opin* 24: 275–286.
- Kreymann, B., Ghatti, M., Williams, G. and Bloom, S. (1987) Glucagon-like peptide-1 7–36: a physiological incretin in man. *Lancet* 2: 1300–1304.
- Levin, P., Mersey, J., Zhou, S. and Bromberger, L. (2012) Clinical outcomes using long-term combination therapy with insulin glargine and exenatide in patients with type 2 diabetes mellitus. *Endocr Pract* 18: 17–25.
- Lilly (2013) Lilly’s investigational GLP-1 receptor agonist, dulaglutide, showed superior glycemic control versus comparators in patients with type 2 diabetes: safety and efficacy results from three phase III registration clinical trials presented at the 73rd American diabetes association scientific sessions. Available at: <http://lilly.mediaroom.com/index.php?s=9042&item=137218%20> (accessed 15 July 2014).
- Liutkus, J., Rosas Guzman, J., Norwood, P., Pop, L., Northrup, J., Cao, D. *et al.* (2010) A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin. *Diabetes Obes Metab* 12: 1058–1065.
- Lu, C., Wu, T., Shih, K., Ni, E., Reed, V., Yu, M. *et al.* (2013) Safety and efficacy of twice-daily exenatide in Taiwanese patients with inadequately controlled type 2 diabetes mellitus. *J Formos Med Assoc* 112: 144–150.
- MacConell, L., Pencek, R., Li, Y., Maggs, D. and Porter, L. (2013) Exenatide once weekly: sustained improvement in glycemic control and cardiometabolic measures through 3 years. *Diabetes Metab Syndr Obes* 6: 31–41.
- Marbury, T., Flint, A., Segel, S., Lindegaard, M. and Lasseter, K. (2014) *Poster 1010 presented at: 74th American Diabetes Association Scientific Sessions; 13–17 June 2014; San Francisco, CA.*
- Marre, M., Shaw, J., Brandle, M., Bebakar, W., Kamaruddin, N., Strand, J. *et al.* (2009) Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabet Med* 26: 268–278.
- Moretto, T., Milton, D., Ridge, T., MacConell, L., Okerson, T., Wolka, A. *et al.* (2008) Efficacy

- and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 230: 1448–1460.
- Nauck, M., Baller, B. and Meier, J. (2004) Gastric inhibitory polypeptide and glucagon-like peptide-1 in the pathogenesis of type 2 diabetes. *Diabetes* 53: S190–S196.
- Nauck, M., Duran, S., Kim, D., Johns, D., Northup, J., Festa, A. *et al.* (2007) A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 50: 259–267.
- Nauck, M., Frid, A., Hermansen, K., Shah, N., Tankova, T., Mitha, I. *et al.* (2009) Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. *Diabetes Care* 32: 84–90.
- Nauck, M., Horton, E., Andjelkovic, M., Ampudia-Blasco, F., Parusel, C., Boldrin, M. *et al.* (2013) Taspoglutide, a once-weekly glucagon-like peptide 1 analogue, *vs.* insulin glargine titrated to target in patients with type 2 diabetes: an open-label randomized trial. *Diabet Med* 30: 109–113.
- Nauck, M., Kleine, N., Orskov, C., Holst, J., Willms, B. and Creutzfeldt, W. (1993) Normalization of fasting hyperglycemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36: 741–744.
- Nauck, M., Petrie, J., Sesti, G., Mannucci, E., Courreges, J., Atkin, S. *et al.* (2012) The once-weekly human GLP-1 analogue semaglutide provides significant reductions in HbA1c and body weight in patients with type 2 diabetes. *Diabetologia* 55(Suppl. 1): abstract 2-OR.
- Nauck, M., Stockmann, F., Ebert, R. and Creutzfeldt, W. (1986) Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 29: 46–52.
- Novo Nordisk A/S (2013) Victoza (liraglutide) package insert. Available at: <http://www.novo-pi.com/victoza.pdf> (accessed 12 July 2014).
- Onishi, Y., Koshiyama, H., Imaoka, T., Haber, H., Scism-Bacon, J. and Boardman, M. (2013) Safety of exenatide once weekly for 52 weeks in Japanese patients with type 2 diabetes mellitus. *J Diabetes Invest* 4: 182–189.
- Pratley, R., Nauck, M., Bailey, T., Montanya, E., Cuddihy, R., Filetti, S. *et al.* (2010) Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomized, parallel-group, open-label trial. *Lancet* 375: 1447–1456.
- Pratley, R., Nauck, M., Bailey, T., Montanya, E., Cuddihy, R., Filetti, S. *et al.* (2011) One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. *Int J Clin Pract* 65: 397–407.
- Pratley, R., Nauck, M., Bailey, T., Montanya, E., Filetti, S., Garber, A. *et al.* (2012) Efficacy and safety of switching from the DPP-4 inhibitor sitagliptin to the human GLP-1 analog liraglutide after 52 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 35: 1986–1993.
- Pratley, R., Nauck, M., Barnett, A., Feinglos, M., Ovalle, F., Harman-Boehm, I. *et al.* (2014) Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomized, open-label, multicenter, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol* 2: 289–297.
- Pratley, R., Urošević, D., Boldrin, M. and Balena, R. (2013) Efficacy and tolerability of taspoglutide versus pioglitazone in subjects with type 2 diabetes uncontrolled with sulphonylurea or sulphonylurea-metformin therapy: a randomized, double-blind study (T-emerge 6). *Diabetes Obesity Metabolism* 15: 234–240.
- Ratner, R., Maggs, D., Nielsen, L., Stonehouse, H., Poon, T., Zhang, B. *et al.* (2006) Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 8: 419–428.
- Riddle, M., Henry, R., Poon, T., Zhang, B., Mac, S., Holcombe, J. *et al.* (2006) Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes Metab Res Rev* 22: 483–491.
- Rosenstock, J., Balas, B., Charbonnel, B., Bolli, G., Boldrin, M., Ratner, R. *et al.* (2013a) The fate of taspoglutide, a weekly GLP-1 receptor agonist, versus twice-daily exenatide for type 2 diabetes. *Diabetes Care* 36: 498–504.
- Rosenstock, J., Hanefeld, M., Shamanna, P., Min, K., Boka, G., Miossec, P. *et al.* (2014) Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulphonylurea with or without metformin (GetGoal-S). *J Diabetes Complications* 28: 386–392.
- Rosenstock, J., Rodbard, H., Bain, S., D'Alessio, D., Seufert, J., Thomsen, A. *et al.* (2013b) One-year sustained glycemic control and weight reduction

- in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA1c target. *J Diabetes Complications* 27: 492–500.
- Russell-Jones, D., Cuddihy, R., Hanefeld, M., Kumar, A., Gonzalez, J., Chan, M. *et al.* (2012) Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4). *Diabetes Care* 35: 252–258.
- Russell-Jones, D., Vaag, A., Schmitz, O., Sethi, B., Lalic, N., Antic, S. *et al.* (2009) Liraglutide *vs* insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 52: 2046–2055.
- Sanofi (2013) Sanofi provides update on lixisenatide new drug application in U.S. Available at: http://m-en.sanofi.com/Images/33756_20130912_lixisenatide_en.pdf (accessed 8 July 2014).
- Sathyanarayana, P., Jogi, M., Muthupillai, R., Krishnamurthy, R., Samson, S. and Bajaj, M. (2011) Effects of combined exenatide and pioglitazone therapy on hepatic fat content in type 2 diabetes. *Obesity* 19: 2310–2315.
- Taylor, K., Gurney, K., Han, J., Pencek, R., Walsh, B. and Trautmann, M. (2011) Exenatide once weekly treatment maintained improvements in glycemic control and weight loss over 2 years. *BMC Endocrine Disord* 11: 1–9.
- Thong, K., Jose, B., Sukumar, N., Cull, M., Mills, A., Sathyapalan, T. *et al.* (2011) Safety, efficacy and tolerability of exenatide in combination with insulin in the association of British clinical diabetologists nationwide exenatide audit. *Diabetes Obes Metab* 13: 703–710.
- Toft-Nielsen, M., Madsbad, S. and Holst, J. (1999) Continuous subcutaneous infusion of glucagon-like peptide 1 lowers plasma glucose and reduces appetite in type 2 diabetic patients. *Diabetes Care* 22: 1137–1143.
- Wu, J., Xu, X., Zhu, J., Ding, B., Du, T., Gao, G. *et al.* (2011) Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus. *Diabetes Technol Ther* 13: 143–148.
- Wysham, C., Bergenstal, R., Malloy, J., Yan, P., Walsh, B., Malone, J. *et al.* (2011) DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. *Diabet Med* 28: 705–714.
- Yang, W., Chen, L., Ji, Q., Liu, X., Ma, J., Tandon, N. *et al.* (2011) Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea, and India: a 16-week, randomized, double-blind, active control trial. *Diabetes Obes Metab* 13: 81–88.
- Yuan, G., Song, W., Huang, Y., Guo, X. and Gao, Y. (2012) Efficacy and tolerability of exenatide monotherapy in obese patients with newly diagnosed type 2 diabetes: a randomized, 26 weeks metformin-controlled, parallel-group study. *Chin Med J* 125: 2677–2681.
- Zinman, B., Hoogwerf, B., Garcia, S., Milton, D., Gioconia, J., Kim, D. *et al.* (2007) The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes. *Ann Intern Med* 146: 477–485.
- Zinman, B., Gerich, J., Buse, J., Lewin, A., Schwartz, S., Raskin, P. *et al.* (2009) Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 32:1224–1230.