Liraglutide – A Once-daily Human Glucagon-like Peptide-1 Analogue Treatment for Type 2 Diabetes

Chantal Mathieu

Professor of Medicine, Catholic University Leuven, and Head of Endocrinology, University Hospital Gasthuisberg

DOI:10.17925/EE.2009.05.00.38

Abstract

Type 2 diabetes is a progressive disease characterised by deteriorating β-cell function and glycaemic control. To counter this, affected individuals require regular intensification of their antidiabetes treatments to provide appropriate metabolic control. However, current treatment options – such as sulphonylureas, thiazolidinediones and insulins – induce weight gain, which can reduce patient acceptance and/or compliance with treatment and may have significant health implications. In addition, many of the antidiabetic therapies raise the risk of hypoglycaemic episodes. Therefore, patients, physicians and healthcare providers are looking for new therapeutic options to address this large and growing burden of diabetes. Incretin-based therapies – including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors – are becoming a popular treatment option for patients with type 2 diabetes because they offer many benefits compared with other antidiabetic therapies. First, incretin-based therapies are associated with significant reductions in glycated haemoglobin (HbA_{1c}) with a low inherent risk of hypoglycaemic events. In addition, GLP-1 receptor agonists are associated with reductions in bodyweight and systolic blood pressure. Incretin-based therapies such as liraglutide also offer the potential to improve β-cell function, an important underlying mechanism of type 2 diabetes.

Keywords

Dipeptidyl peptidase-4, exenatide, glucagon-like peptide, incretin, liraglutide, type 2 diabetes

Disclosure and Acknowledgements: Editorial assistance was provided by Dr Michael Lappin of Watermeadow Medical on behalf of Novo Nordisk.
Received: 26 May 2009 **Accepted:** 16 July 2009
Correspondence: Chantal Mathieu, LEGENDO, Katholieke Universitet, Leuven, UZ Gasthuisberg 0&N, Herestraat 49, B-3000 Leuven, Belgium.
E: chantal.mathieu@uz.kuleuven.ac.be

Incretin-based Therapies

The human incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide are released by the intestine following nutrient exposure. In normal individuals, incretin activity is estimated to be responsible for around 70% of post-prandial insulin secretion; however, the incretin effect is impaired in individuals with type 2 diabetes.[1] Human GLP-1 has many important actions that could directly benefit patients with type 2 diabetes, such as: stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner; promoting glucose uptake and glycogen synthesis by muscle, liver and adipose tissue; protecting β-cell function; and inducing feelings of satiety and reducing appetite.[2] Human GLP-1 has a short half-life of around two minutes in circulation,[3] as it is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), minimising its therapeutic potential.[4] Therefore, therapies are based on two main approaches. One approach has been the development of GLP-1 receptor agonists that are more resistant to DPP-4-mediated degradation than native GLP-1. This increases their circulating half-life *in vivo* and enables pharmacological levels of GLP-1 activity to be achieved. Another approach is taken by the group of DPP-4 inhibitors, which restore physiological GLP-1 activity by reducing the degradation of endogenous GLP-1.

There is currently one DPP-4 inhibitor available in both Europe and the US: sitagliptin (Velmetia®, Merck Sharp & Dohme Ltd, UK; Januvia™, Merck & Co., Inc, Whitehouse Station, NJ, US), while a second option, vildagliptin (Galvus®, Novartis Pharmaceuticals, East Hanover, NJ, US), is available only in Europe. At present, exenatide (Byetta®, Amylin/Lilly Pharmaceuticals Inc., San Diego, CA, US), a recombinant protein based on a salivary product of the 'gila monster' lizard (*Heloderma suspectum*), is the only available GLP-1 receptor agonist. Liraglutide (Novo Nordisk, Copenhagen, Denmark), a second GLP-1 receptor agonist, is awaiting formal EU approval after receiving a positive opinion from the Committee For Medicinal Products For Human Use, and is currently under regulatory review for marketing authorisation in the US. Exenatide shares 53% sequence homology with human GLP-1 and has a greater potency in terms of therapeutic action, largely due to its partial resistance to DPP-4.[5] The 2.4-hour half-life of exenatide requires twice-daily dosing. However, other formulations – such as liraglutide, a once-daily formulation, and exenatide long-acting release, a once-weekly formulation – are currently under regulatory review.[6]

Liraglutide

The aim of this article is to summarise clinical data for liraglutide and to highlight key considerations for physicians and patients.

Pharmacology, Pharmacokinetics and Pharmacodynamics

Liraglutide has 97% amino acid sequence identity to human GLP-1, resulting from a substitution of lysine at position 34 with arginine and the

addition of a fatty acid side chain linked via a glutamoyl spacer at position 26. From a therapeutic perspective, the modification of the amino acid sequence and the addition of a fatty acid side chain substantially improves the pharmacokinetics and pharmacodynamics of liraglutide compared with human GLP-1, increasing the *in vivo* half-life from approximately two minutes to 13 hours. This increase in the half-life of liraglutide is related to increased self-association (heptamer formation) and albumin binding and reduced susceptibility to DPP-4.[7] Therapeutic levels of liraglutide are sustained over 24 hours following a single dose, which means that liraglutide can be administered once daily. In addition, liraglutide has a glucose-dependent mechanism of action,[8] which means that it lowers blood glucose only when plasma glucose levels are high.

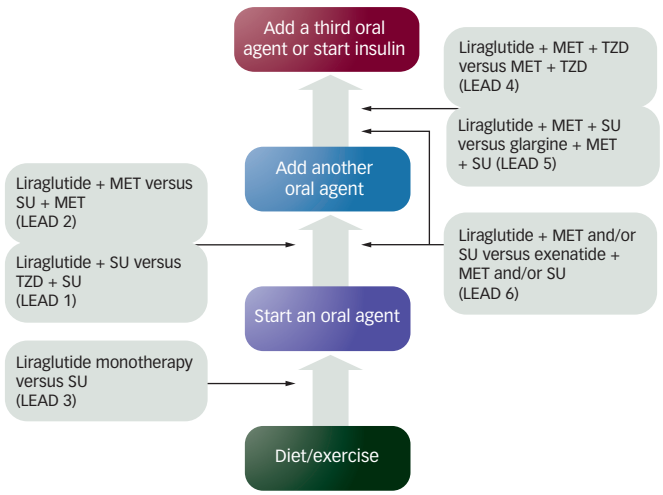
There is no evidence that liraglutide exhibits clinically relevant alteration in drug metabolism in individuals with renal and hepatic insufficiency, so these data suggest that liraglutide could be used without dose adjustment in these populations.[9,10] By contrast, exenatide is not recommended for patients with renal insufficiency.[11] Interestingly, sitagliptin is not recommended for patients with moderate or severe renal impairment in Europe, while in the US it is recommended that sitagliptin dosing be adjusted in individuals with renal insufficiency.[12,13] A study of atorvastatin, lisinopril, digoxin and griseofulvin, drugs with differing solubility and permeability properties, demonstrated that liraglutide does not induce clinically significant alterations in the pharmacokinetics of concomitantly administered oral drugs.[14] Other drug interaction studies have demonstrated that liraglutide has no clinically significant interactions with paracetamol or a low-dose oral contraceptive (ethinylestradiol/levonorgestrel).[15,16]

Clinical Data

In a 14-week phase II study of adult patients with type 2 diabetes, liraglutide demonstrated an average glycated haemoglobin (HbA_{1c}) reduction of 1.74% versus placebo from a baseline of 8.5%, and approximately 50% of patients met the American Diabetes Association (ADA) target of <10mmol/l for post-prandial hyperglycaemia (PPG) with 1.9 and 1.25mg/day liraglutide monotherapy.[17] In addition, liraglutide was associated with dose-dependent weight reduction (-2.99kg in the 1.9mg group; p=0.039 versus placebo), improvements in pancreatic β-cell function (p<0.0001 for all liraglutide doses versus placebo) and reductions in systolic blood pressure of 5.02–7.9mmHg versus placebo.[17] The 1.9mg dose was used in the phase II studies; however, in the phase III studies liraglutide was dosed at 1.2 or 1.8mg daily.

The six phase III Liraglutide Effect and Action in Diabetes (LEAD) trials examined the effect of liraglutide in patients with type 2 diabetes at various stages of the disease (see *Figure 1*). The LEAD studies demonstrated that liraglutide was effective as a monotherapy (LEAD 3)[18] in combination with one oral antidiabetic agent (OAD), such as metformin (LEAD 2),[19] or a sulphonylurea (SU) (LEAD 1[20] and LEAD 6[21]), or with two OADs such as metfomin and thiazolidinediones (TZD) in LEAD 4[22] or metformin and an SU in LEAD 5[23] and LEAD 6.[21] HbA_{1c} reductions of between 1 and 1.5% were observed across the trials with the 1.8mg once daily dose of liraglutide (see *Table 1*), and half of all LEAD patients who received this dose achieved HbA_{1c} levels of <7%. LEAD 3, which compared liraglutide and glimepiride monotherapy, demonstrated the maintenance of HbA_{1c} reductions (1.14% for the 1.8mg dose) over the 52-week study length,[18] while the other LEAD trials demonstrated sustained reductions over 26 weeks. Significant fasting plasma glucose (FPG) reductions of -1.4 to -2.4mmol/l and significant post-prandial glucose (PPG) reductions of -1.8 to -2.7mmol/l were observed with

Figure: 1 The Effect of Liraglutide Addition at Various Stages of Oral Antidiabetes Therapy Intensification



From the Liraglutide Effect and Action in Diabetes (LEAD) trials.
MET = metformin; SU = sulphonylurea; TZD = thiazolidinedione.

liraglutide 1.8mg compared with placebo, rosiglitazone and glimepiride.[18–22] Liraglutide was associated with significantly greater HbA_{1c} reductions (-1.12%) compared with exenatide (-0.79%) in the LEAD 6 study (p<0.0001).[21] The HbA_{1c} reduction observed with exenatide in LEAD 6 was similar to previously reported HbA_{1c} results (0.8–0.9%).[24–26] FPG concentrations were reduced by a maximum of 0.6mmol/l with exenatide compared with a gain of 0.8mmol/l in the placebo group (p<0.0001).[26] Sitagliptin monotherapy with 100 or 200mg once daily produced reductions in HbA_{1c} of -0.6 and -0.8%, respectively (p<0.001 versus placebo), and reductions in FPG of -0.7 and -0.9 mmol/l versus placebo, respectively.[27]

Low Risk of Hypoglycaemia

Liraglutide is associated with a low risk of hypoglycaemia. In total, only six patients in all of the LEAD trials treated with liraglutide reported major hypoglycaemic episodes.[18–20,22,23] Significantly lower rates of minor hypoglycaemia were reported with liraglutide versus glimepiride in the LEAD 2 and LEAD 3 trials (p<0.0001) and versus exenatide in the LEAD 6 trial (1.9 versus 2.6 events per patient-year; p=0.01). In LEAD 4, minor hypoglycaemia was low in all groups but was significantly higher in the liraglutide group than in the metformin + rosiglitazone group (0.64 versus 0.17 events per patient-year; p=0.004). Higher rates of hypoglycaemia were observed in trials where liraglutide or exenatide were combined with SUs, suggesting that SU dosing may need to be reduced when it is used in combination with GLP-1 receptor agonists. Low rates of hypoglycaemia were also observed in trials of exenatide and the DPP-4 inhibitor sitagliptin.[24–27]

Safety

Liraglutide is generally well tolerated: across the six LEAD trials approximately 22% of patients in the liraglutide 1.8mg/day dosage group experienced nausea.[18–23] The feelings of nausea may relate to the action of GLP-1 on delaying gastric emptying. Most cases of nausea were mild and transient in nature. Furthermore, studies with both liraglutide and exenatide have indicated that nausea can be largely avoided by gradually escalating the dose following initiation.[28,29] Lower rates of gastrointestinal (GI) adverse events were observed with the DPP-4 inhibitors such as sitagliptin compared with the GLP-1 receptor agonists, which may reflect the differing levels of GLP-1 receptor stimulation with

Table 1: Summary of Liraglutide Clinical Trials – Liraglutide Effect and Action in Diabetes (LEAD) Trials

Study/Publication	Description/Baseline Data	Comparators	Δ HbA_{1c} (%)	Δ SBP (mmHg)
LEAD 1[20]	26-week RCT, 1,018 patients on SU	Addition of:		
	HbA_{1c}: 8.4%	Liraglutide 1.2mg	-1.08	-2.6
	Bodyweight: 81.6kg	Liraglutide 1.8mg	-1.13	-2.8
		Placebo	+0.23	-2.3
		Rosiglitazone 4mg	-0.44	-0.9
LEAD 2[19]	26-week RCT, 1,091 patients on MET	Addition of:		
	HbA_{1c}: 8.4%	Liraglutide 1.2mg	-0.97	-2.8
	Bodyweight: 88.6kg	Liraglutide 1.8mg	-1.00	-2.3
		Placebo	+0.09	-1.8
		Glimepiride 4mg	-0.98	+0.4
LEAD 3[18]	52-week RCT, 746 patients, approximately one-third OAD-naïve and two-thirds with up to 50% maximum dose of OAD monotherapy	Monotherapy:		
		Liraglutide 1.2mg	-0.84	-2.1
		Liraglutide 1.8mg	-1.14	-3.6
	HbA_{1c}: 8.2%	Glimepiride 8mg	-0.51	-0.7
	Bodyweight: 92.6kg			
LEAD 4[22]	26-week RCT, 533 Patients on MET + TZD	Addition of:		
	HbA_{1c}: 8.5%	Liraglutide 1.2mg	-1.48	-6.7
	Bodyweight: 97.0kg	Liraglutide 1.8mg	-1.48	-5.6
		Placebo	-0.54	-1.1
LEAD 5[23]	26-week RCT, 581 patients on MET + SU	Addition of:		
	HbA_{1c}: 8.2%	Liraglutide 1.8mg	-1.33	-4.0
	Bodyweight: 85.4kg	Placebo	-0.24	-1.4
		Insulin glargine	-1.09	+0.5
LEAD 6[21]	26-week RCT, 464 patients on MET, SU or combination	Addition of:		
		Liraglutide 1.8mg	-1.12	-2.5
	HbA_{1c}: 8.2%	Exenatide 10µg BID	-0.79	-2.0
	Bodyweight: 93.5kg			

BID = twice daily; MET = metformin; OAD = oral antidiabetic agent; RCT = randomised controlled trial; SBP = systolic blood pressure; SU = sulphonylurea; TZD = thiazolidinedione.

the two treatment approaches.[27] However, there are some concerns that DPP-4 inhibitors may be immunomodulatory, and a meta-analysis of sitagliptin safety data suggested a 34% increased relative risk of developing infection versus controls (odds ratio [OR] 1.34, 95% confidence interval [CI] 1.10–1.64; p=0.004).[30]

Patients who receive repeated doses of recombinant protein therapeutics may develop neutralising antibodies, which in certain cases result in a reduction in product efficacy.[31] However, although a minority of patients (4–13%) in the LEAD studies developed liraglutide antibodies, there was no evidence that this affected the clinical efficacy of liraglutide. Higher levels of antibody induction were observed in three exenatide trials. Low-titre exenatide antibodies were observed in 38% of patients (366 of 963). An additional 6% of patients (58 of 963) had high-titre antibodies, which caused a loss of exenatide's glycaemic effect in 3% of patients.[11]

Weight

Obesity, together with dyslipidaemia, coagulation abnormalities and hypertension, forms the basis for the dramatic increase in cardiovascular (CV) risk in individuals with type 2 diabetes. For example, a five-unit increment in body mass index (BMI) can increase coronary heart disease (CHD) mortality by 30%.[32] In addition, an individual's concern about weight gain may be a barrier to intensifying diabetes treatment.[33,34] Human GLP-1 induces feelings of satiety and delays gastric emptying, which suggests benefits in terms of weight reduction (see *Table 2*). Liraglutide treatment was associated with weight loss of around 2–3kg, which was significantly better than the weight gains of 1–2kg observed with comparator treatments in LEAD 1–5 (see *Table 2*). In LEAD 6, an equivalent weight loss of 2–3kg was seen in patients on liraglutide and exenatide (see *Table 2*). In LEAD 3, the weight loss observed in the first 16 weeks was maintained over the 52-week study.[18] This maintenance of weight loss is confirmed by exenatide studies that demonstrated maintenance of weight loss over a two-year period.[35] However, patients in all BMI subgroups experienced weight loss with liraglutide, with the greatest decrease in bodyweight occurring in subjects with a high baseline BMI (≥35kg/m^2). By contrast, the DPP-4 inhibitors sitagliptin and vildagliptin are weight-neutral.[27,36,37]

Blood Pressure

Individuals with type 2 diabetes face an increased risk of hypertension compared with healthy individuals.[38] Hypertension raises the risk of CV disease, and treatments that can reduce hypertension can have a profound benefit. For example, a reduction of 5.6mmHg in systolic blood pressure (SBP) has been shown to reduce death from CV disease by 18% in patients with type 2 diabetes.[39] SBP reductions of this magnitude have been reported with liraglutide: across the LEAD trials, SBP was reduced by 2.3–5.6mmHg with the 1.8mg dose, suggesting that liraglutide could have a very positive impact on reducing CV risks in individuals with diabetes. Blood pressure reductions have been observed in trials of exenatide versus placebo;[35,40,41] in one trial, reductions in SBP of 3.7 and 0.3mmHg were observed with exenatide 10µg twice daily (BID) and placebo, respectively (p=0.010 for combined exenatide group versus placebo). By contrast, blood pressure reduction has not yet been widely studied with DPP-4 inhibitors.

Pancreatic Islet and β-cell Function

Type 2 diabetes is characterised by a progressive loss of pancreatic β-cell function, which leads to increasing impairment of insulin secretion.[41] Liraglutide has been shown to increase β-cell mass and decrease apoptosis in *in vitro* and *in vivo* rodent models.[42,43] In human studies, liraglutide treatment is also associated with improvements in

surrogate markers of β-cell function.[44,45] For example, in an *in vivo* study, first-phase insulin response was increased by 118% (10.6pmol/l x h) and 103% (9.09pmol/l x h) with liraglutide 1.25 or 1.9mg/day, respectively ($p<0.05$).[45] Homeostatic model assessment (HOMA) is a method for assessing β-cell function and insulin resistance from fasting glucose and insulin or C-peptide concentrations.[46] In the LEAD trials, liraglutide induced significant improvements in the HOMA index of β-cell function of between 28 and 34% compared with placebo ($p<0.03$) and reductions in the pro-insulin to insulin ratio of -0.09 to -0.12 versus placebo ($p<0.03$).[47] These data suggest that liraglutide may maintain, or potentially improve, β-cell function. Measures of β-cell function such as HOMA-B pro-insulin to insulin ratio also appear to be improved with exenatide and the DPP-4 inhibitors. Data confirming whether these beneficial effects on β-cell function that are associated with incretin-based therapies could translate into clinical improvements in disease progression in patients with type 2 diabetes are eagerly awaited.

Dosage and Administration

Liraglutide will be indicated for once-daily administration by subcutaneous injection. Patients will be able to take their liraglutide injection at any time of the day, irrespective of meals. However, patients should take liraglutide at the same time each day. In the case of a missed dose, the next dose should be taken as planned as it is not advisable to take two doses together. It will be recommended that patients are initiated on liraglutide at a dose of 0.6mg/day for one week to increase tolerability, following which the dose will be increased to 1.2mg/day. The dose can be increased to 1.8mg/day to achieve maximum efficacy if required. Liraglutide will be available in a pre-filled disposable pen that is compatible with fine-gauge needles (32G) to minimise injection pain. Liraglutide should be stored in a refrigerator (at 2–8°C). After first use of the liraglutide pen, the product can be stored for one month at room temperature (≤30°C) or in a refrigerator (2–8°C).

Summary

Incretin-based therapies, including GLP-1 receptor agonists and DPP-4 inhibitors, offer new treatment choices for patients with diabetes. Liraglutide is the first once-daily human GLP-1 analogue in a new class of GLP-1 agonists. Liraglutide's reduction of bodyweight, along with its ability to improve all aspects of glycaemic control and reduce systolic blood pressure, suggests that once-daily liraglutide can address the multiple co-morbidities commonly associated with type 2 diabetes. In addition, treatments that target the incretin system, such as liraglutide, offer the potential to preserve β-cell function, the deterioration of which is an important underlying pathogenic mechanism in type 2 diabetes. Liraglutide is generally well tolerated; the majority of adverse events were mild and transient GI events, which generally occurred early in the course of therapy. In addition, flexible once-daily administration of liraglutide means that patients can choose the most convenient time of day to administer their medication. By targeting the underlying disease pathology as well as the symptoms of diabetes, liraglutide and other incretin-based therapies offer great hope for diabetes treatment. ■

Table 2: Weight Loss Associated with Liraglutide – Liraglutide Effect and Action in Diabetes (LEAD) Trials

Study	Treatment	Δ Bodyweight (kg)
LEAD 1[20]	Liraglutide 1.2mg	+0.3*
	Liraglutide 1.8mg	-0.2*
	Rosiglitazone 4mg	+2.1
	Placebo	-0.1
LEAD 2[19]	Liraglutide 1.2mg	-2.6**
	Liraglutide 1.8mg	-2.8**
	Glimepiride 4mg	+1.0
	Placebo	-1.5
LEAD 3[18]	Liraglutide 1.2mg	-2.0†
	Liraglutide 1.8mg	-2.4†
	Glimepiride 4mg	+1.1
LEAD 4[22]	Liraglutide 1.2mg	-1.0††
	Liraglutide 1.8mg	-2.0††
	Placebo	+0.6
LEAD 5[23]	Liraglutide 1.8mg	-1.8‡
	Placebo	-0.4‡
	Insulin glargine	+1.6
LEAD 6[21]	Liraglutide 1.8mg	-3.2
	Exenatide 10µg BID	-2.9

**p<0.0001 versus rosiglitazone; **p<0.05 versus placebo and p<0.0001 versus glimepiride; †p<0.0001 versus glimepiride; ††p<0.0001 versus placebo; ‡p <0.0001 versus placebo or insulin glargine. BID = twice daily.*

Chantal Mathieu is Head of Endocrinology at University Hospital Gasthuisberg in Leuven, a Professor of Medicine at Catholic University Leuven and a clinical researcher for the Flemish Research Council. Her research activities include the pathogenesis of type 1 diabetes, as well as prevention of the disease and islet transplantation in animal models. Understanding the potential role of vitamin D in the process is a major interest.

1. Nauck M, et al., *Diabetologia*, 1986;29:46–52.
2. Drucker DJ, Nauck MA, *Lancet*, 2006;368:1696–1705.
3. Vilsbøll T, et al., *J Clin Endocrinol Metab*, 2003;88:220–24.
4. Mentlein R, et al., *Eur J Biochem*, 1993;214:829–35.
5. Gryskiewicz KA, Coleman CI, *Formulary*, 2005;40:86–90.
6. Drucker DJ, et al., *Lancet*, 2008. 372(9645):1240–50.
7. Agersø H, et al., *Diabetologia*, 2002;45:195–202.
8. Nauck MA, et al., *Diabetologia*, 1993;36:741–4.
9. Jacobsen LV, et al., *Diabetes Supplement*, 2007; abstract 0513P. Available at: professional.diabetes.org/Abstracts_Search.aspx (accessed 11 May 2009).
10. Flint A, et al., *Diabetes Supplement*, 2007; abstract 0545-P. Available at: professional.diabetes.org/Abstracts_Search.aspx (accessed 11 May 2009).
11. Byetta® (Exenatide), Summary of Product Characteristics, Eli Lilly Nederland BV, 2008.
12. Velmetia® (Sitagliptin), Summary of Product Characteristics, Merck Sharp & Dohme Ltd, 2007.
13. Januvia™ (Sitagliptin), Summary of Product Characteristics, Merck & Co., Inc., 2007.
14. Malm-Erjefält M, et al., American Diabetes Association, 68th Scientific Sessions (2008), San Francisco, California, US, 6–10 June 2008; 434-P.
15. Jacobsen LV, et al., American Diabetes Association, 68th Scientific Sessions (2008), San Francisco, California, US, 6–10 June 2008; 2047-PO.
16. Kapitza C, et al., American Diabetes Association, 68th Scientific Sessions (2008), San Francisco, California, US, 6–10 June 2008; 1245-PO.
17. Vilsbøll T, et al., *Diabetes Care*, 2007;30:1608–10.
18. Garber A, et al., *Lancet*, 2009;373(9662):473–81.
19. Nauck MA, et al., *Diabetes Care*, 2009;32;84–90.
20. Marre M, et al., *Diabet Med*, 2009;26;268–78.
21. Buse JB, et al., *Lancet*, 2009;374(9683):39–47.
22. Zinman B, et al., *Diabetes Care*, 2009;32:1224–30.
23. Russell-Jones D, et al., *Diabetologia*, 2009; DOI: 10.1007/s00125-009-1472-y.
24. DeFronzo RA, et al., *Diabetes Care*, 2005;28:1092–1100.
25. Buse JB, et al., *Diabetes Care*, 2004;27:2628–35.
26. Kendall DM, et al., *Diabetes Care*, 2005;28:1083–91.
27. Aschner P, et al., *Diabetes Care*, 2006;29:2632–7.
28. Fineman MS, et al., *Diabetes Metab Res Rev*, 2004;20:411–17.
29. Irie S, et al., *Int J Clin Pharmacol Ther*, 2008;46:273–9.
30. Richter B, et al., *Vasc Health Risk Manag*, 2008;4:753–68.
31. Schellekens H, *Nephrol Dial Transplant*, 2005;20(Suppl. 6): vi3–9.
32. Bogers RP, et al., *Arch Intern Med*, 2007;167:1720–28.
33. Davies M, *Int J Obes*, 2004;28(Suppl. 2):S14–S22.
34. Korytkowski M, et al., *Clin Ther*, 2003;25:2836–48.
35. Buse JB, et al., *Clin Ther*, 2007;29:139–53.
36. Hermansen K, et al., *Diabetes Obes Metab*, 2007;9:733–45.
37. Rosenstock J, et al., *Diabetes Care*, 2007;30:217–23.
38. Davis TME, et al., *Diabetes Care*, 2001;24:1167–74.
39. Patel A, et al., *Lancet*, 2007;370(9590):829–40.
40. Moretto TJ, et al., *Clin Ther*, 2008;30(8):1448–60.
41. Butler AE, et al., *Diabetes*, 2003;52:102–10.
42. Sturis J, et al., *Br J Pharmacol*, 2003:140(1):123–32.
43. Bregenholt S, et al., *Biochem Biophys Res Commun*, 2005;330:577–84.
44. Farilla L, et al., *Endocrinology*, 2003;144(12):5149–58. Comment in: *Endocrinology*, 2003;144(12):5145–58.
45. Vilsbøll T, et al., *Diabet Med*, 2008;25:152–6.
46. Matthews DR, et al., *Diabetologia*, 1985;28:412–19.
47. Matthews DR, et al., Presented at the 44th Annual Meeting of the European Association for the Study of Diabetes, Rome, Italy, 7–11 September 2008.