Diabetes is a progressive disease characterised by impaired beta-cell function, and reduced insulin sensitivity and secretion. Over time, glycaemic control deteriorates and exacerbates the risk of patients experiencing micro- and macrovascular complications (UKPDS, 1998).

Although there is an abundance of treatment options and guidelines available for the management of type 2 diabetes, they are unable to avert the natural progression of the disease and sustain glycaemic control in the long term. Furthermore, currently available treatment options (such as sulphonylureas, thiazolidinediones and most insulins) are often associated with hypoglycaemia and weight gain, (Kahn et al., 2006; UKPDS et al., 1998: Figure 1 and 2). Such adverse effects can have detrimental health implications for the patient. For example, hypoglycaemia can be an unpleasant side-effect of anti-diabetic therapy which can compromise patient adherence to treatment, and serious hypoglycaemic events, left untreated, can lead to a loss of consciousness, brain damage or even death. Moreover, obesity is a common co-morbidity in subjects with type 2 diabetes (60-90% of patients diagnosed). Additional weight gain as a consequence of treatment with SUs or insulin for example, can reduce patients' quality of life and hinder adherence to treatment. Obesity is also an independent risk factor for cardiovascular disease, further compromising patient outcomes (Hubert et al., 1983; Han et al., 1998; Odegard et al., 2007).

The greatest challenge in treating patients with type 2 diabetes is optimising therapy to address the current unmet needs:

- improve glycaemic control without compromising safety i.e. hypoglycaemia
- preserve beta-cell function
- provide clinically meaningful weight loss
- address CV risk factors accompanying diabetes
- offer a simple and flexible regimen

GLP1 receptor agonists may provide solutions to all of these challenges.
Background to the incretin effect

GLP-1 and GIP are gut-derived, receptor-specific hormones, known as ‘incretins’. The incretin hormones have multiple physiological actions; most importantly they play a crucial role in glucose homeostasis. The action of the incretin hormones accounts for 50–70% of insulin secretion after oral glucose intake. This “incretin effect” is characterised by the more pronounced plasma insulin secretion observed with oral vs. intravenous glucose administration despite matching glucose profiles (Figure 3).

The incretin effect is blunted in subjects with type 2 diabetes (Nauck et al., 1986; Figure 3c). In patients with type 2 diabetes, GLP-1 infusion (but not GIP) markedly improves both the early and late phases of insulin secretion in response to glucose (Vilsboll et al., 2002, Hojberg et al., 2008). As such, it is GLP-1 rather than GIP that has been the focus of research as a promising treatment for type 2 diabetes.

GLP-1 and Its Relevance to Treating the Unmet Needs in T2D

The action of GLP-1 on beta-cell receptors enhances insulin secretion in a glucose dependant manner (Nauck et al., 1993) which, in turn minimises the risk of hypoglycaemia. In addition, animal studies have indicated that GLP-1 has the ability to preserve beta-cell function by suppressing beta-cell apoptosis and stimulating neogenesis and proliferation (Bulotta et al., 2002, Farilla et al., 2003).

Other clinical advantages associated with GLP-1 may be explained by its hormonal influences on the gastrointestinal, CNS and CV systems (Figure 4). GLP-1 has demonstrated the ability to slow gastric emptying and suppress appetite, resulting in satiety and weight loss.

GLP-1 also appears to exert a protective effect on the myocardium, particularly in ischaemic conditions. For example, Bose and colleagues reported that an intravenous infusion of GLP-1 in rats, prior to induced ischaemia significantly reduced myocardial infarction compared with saline (Bose et al., 2005). Studies have also reported improved myocardial function in patients with type 2 diabetes and congestive heart failure (Thrainsdottir et al 2004), and infusion of recombinant GLP-1 has been shown to improve left ventricular function in patients with acute myocardial infarction after primary angioplasty (Nikolaidis Mankad et al 2004).

Improvement in endothelial function has also been reported with GLP-1; a significant increase in brachial artery diameter was observed in patients with type 2 diabetes (Nystrom et al 2004). Furthermore, GLP-1 has been found to reduce systolic blood pressure (SBP). This may be, in part, due to its ability to increase diuresis and natriuresis, thus reducing blood volume and central venous pressure. This is an important observation, since CV disease is a common co-morbidity of type 2 diabetes, and a mean reduction in systolic blood pressure (SBP) of 5.6 mmHg has been shown to reduce mortality from the disease by 18% (Patel et al., 2007).

Clinical Limitations of GLP-1 Due to the Presence of DPP-4

As active GLP-1 is secreted from L-cells in the distal small intestine, it is rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP-4). An i.v. bolus of GLP-1 has a half-life of 1.5-2.1 minutes.
Incretin-Based Therapy for Type 2 Diabetes: Overcoming Unmet Needs

meaning that a constant infusion of GLP-1 is required to provide any therapeutic value.

DEVELOPMENT OF LIRAGLUTIDE

In order to overcome the short half-life of native GLP-1, longer-acting GLP-1 agents such as liraglutide have been developed. Liraglutide is an analogue of native human GLP-1, in which Lys^{34} has been substituted with Arg^{34} at the N-terminal and a fatty acid chain added to Lys^{26}. These modifications mean that liraglutide shares 97% amino acid identity with native human GLP-1 compared with exenatide (a GLP-1 mimetic) which shares just 53% sequence identity.

Liraglutide’s fatty acid side chain allows it to self-associate and form heptamers. The size of the heptamer and the strong self-association allow liraglutide to be absorbed slowly via the subcutaneous route (Knudsen et al., 2000). Maximum plasma concentration levels are achieved between 9–12 h after dosing (Elbrom et al., 2002). The fatty acid moiety also allows liraglutide to bind to serum albumin in the bloodstream (Steensgaard 2008) and resist DPP-4 degradation, resulting in a half-life of approximately 13 hours (Agersø et al, 2002). These properties make liraglutide suitable for once-daily dosing (Agersø et al, 2002).

CLINICAL EFFECTS OF LIRAGLUTIDE

The phase 3a development programme for liraglutide, LEAD (Liraglutide Effect and Action in Diabetes), is the largest clinical development programme ever conducted by Novo Nordisk in diabetes. LEAD included 6 trials and was designed to investigate the efficacy and safety of liraglutide across the continuum of care of type 2 diabetes versus placebo. In the LEAD trials, liraglutide was also compared against some commonly used anti-diabetic therapies. An additional head-to-head trial against exenatide (LEAD-6) was also completed (Figure 7).

HbA₁c, FPG and PPG

The LEAD programme demonstrated that liraglutide, used as monotherapy or in combination with one or two OADs, provides substantial reductions in HbA₁c. Liraglutide reduced HbA₁c levels to a significantly greater extent than its active comparators, with LEAD-2 as the exception, in which HbA₁c reductions with
Liraglutide were comparable to glimepiride plus metformin (-1.0%). Reductions in HbA$_1c$ across the LEAD trials ranged from 0.84 to 1.6% with the highest doses of liraglutide (1.2 mg and 1.8 mg) relative to baseline (Marre et al., 2009; Nauck et al., 2009; Garber et al., 2009; Zinman et al., 2009; Russell-Jones et al., 2008; Buse et al., 2009). These reductions corresponded with a higher percentage of subjects in the liraglutide-treated groups reaching target HbA$_1c$ <7.0% in all LEAD studies compared with active comparators (Figure 8).

The greatest reduction in HbA$_1c$ (-1.60%) was experienced in the LEAD-3 trial (liraglutide monotherapy) by the subgroup of patients previously on diet and exercise: the true initial monotherapy population (Garber et al., 2009). In the head-to-head study of liraglutide 1.8 mg once daily vs. exenatide 10 μg twice daily (as add-on to metformin and/or SU therapy), mean HbA$_1c$ reduction was significantly greater with liraglutide treatment than with exenatide: −1.12% versus −0.79%, p<0.0001 (Buse et al., 2009).

A meta-analysis of LEAD trials 1-6 concluded that liraglutide provides the greatest reductions HbA$_1c$ in those patients with the highest HbA$_1c$ levels at baseline (Figure 9).

Liraglutide also provided substantial reductions in FPG across the continuum of care. FPG reductions of up to -2.4 mmol/L were reported with liraglutide across the LEAD 1-6 studies ((Marre et al., 2009; Nauck et al., 2009; Garber et al., 2009; Zinman et al., 2009; Russell-Jones et al., 2008; Buse et al., 2009). In the LEAD-6 study, there was a greater reduction in mean PPG after lunch with liraglutide compared with exenatide (2.74
versus 2.35; NS). However, exenatide is given twice daily, before morning and evening meals, thus PPG was reduced more with exenatide vs liraglutide during these peak times (Buse et al., 2009).

**Beta-cell function**

The LEAD trials have reported increases in beta-cell function (as measured by HOMA-B) of 28-34% from baseline after liraglutide treatment (Marre et al., 2009; Nauck et al., 2009; Garber et al., 2009; Zinman et al., 2009; Russell-Jones et al., 2008; Buse et al., 2009). As demonstrated by meta-analysis, the ability of liraglutide to lower HbA1c remains substantial regardless of baseline HOMA-B (Figure 11).

**Weight**

Treatment with liraglutide significantly reduced weight in the LEAD-1 trials (Nuack et al., 2009; 32:84-90 (LEAD-2)).

![Fig. 10: Change in FPG (mmol/L) in the LEAD 1-6 studies](image)

**Improving beta-cell function**

![Improving beta-cell function](image)

A quarter of patients lose an average of 7.7 kg with liraglutide
Lead 1–6 trials. Liraglutide has a more positive effect on weight than active comparators (Marre et al., 2009; Nauck et al., 2009; Garber et al., 2009; Zinman et al., 2009; Russell-Jones et al., 2008) and was similar to the weight reductions reported with exenatide (Buse et al., 2009).

Weight loss also appears to be sustained; a reduction of -2.45 kg was reported in patients treated with liraglutide 1.8 mg monotherapy (LEAD-3, Garber et al., 2009). The majority of this weight loss occurred primarily in the first 16 weeks and was maintained throughout the 52-week study period. In this trial, weight reduction was significantly greater with liraglutide vs. glimepiride (+1.12 kg, p<0.0001; Garber et al., 2009). Furthermore, weight loss has been demonstrated to increase with increasing baseline body mass index (BMI). This is of particular advantage in obese subjects and, at greater risk of developing CV disease, since they would appear to experience greater weight loss than leaner patients (Russell-Jones et al. 2008).

Of note, an analysis of body composition (measured by dual energy X-ray absorptiometry (DEXA)) in subjects from the LEAD 2 study suggested that the majority of weight loss observed with liraglutide was due to fat loss; 86% of weight loss reported was fat tissue and the majority of this was found to be visceral (Jendle et al. 2008).

LEAD 1–6 trials. Liraglutide provides clinically significant reductions in SBP and has been demonstrated across all LEAD trials (Marre et al., 2009; Nauck et al., 2009; Zinman et al., 2009; Russell-Jones et al., 2008, Buse et al., 2009; Figure 12).

SBP has also been shown to improve rapidly (as early as 2 weeks) following liraglutide initiation, and prior to significant treatment-induced weight loss.

As demonstrated in the meta-analysis, the effect on SBP with baseline SBP quartile was significant (p<0.0001), since the greatest reduction observed was in that with the highest SBP (Table 1).

**Fig. 12: Change in SBP across LEAD 1-6 trials**

**Table 1: Change in SBP by mean baseline quartile**

<table>
<thead>
<tr>
<th>Quartile, mmHg (Baseline)</th>
<th>Liraglutide 1.8 mg (n = 1363)</th>
<th>Liraglutide 1.2 mg (n = 896)</th>
<th>Placebo (n = 524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 80 to ≤ 120</td>
<td>+ 4.8 (1.0)</td>
<td>+5.4 (1.1)</td>
<td>+7.1 (1.3)</td>
</tr>
<tr>
<td>Q2 120 to ≤ 130</td>
<td>-0.4 (0.9)</td>
<td>+0.4 (1.1)</td>
<td>+0.9 (1.3)</td>
</tr>
<tr>
<td>Q3 130 to ≤ 140</td>
<td>-4.7 (1.0)</td>
<td>-6.2 (1.1)</td>
<td>-2.4 (1.3)</td>
</tr>
<tr>
<td>Q4 140 to ≤ 190</td>
<td>-11.4 (1.0)</td>
<td>-11.4 (1.2)</td>
<td>-7.7 (1.3)</td>
</tr>
</tbody>
</table>

* Effect on SBP with baseline SBP quartile was significant (p<0.0001)
* Greatest reduction observed in quartile with highest SBP

Fonseca et al. Diabetes 2009, 58 (Suppl 1): 545-P

**Fig. 13: Percentage of subjects reaching HbA₁c target of <7.0% with no hypoglycaemic events and no weight gain**

Liraglutide 1.8 mg is superior (**p<0.001; ***p<0.0001)
Liraglutide 1.2 mg is superior (††p<0.0001)
Percentages are from logistic regression model adjusted for trial, previous treatment and with baseline HbA₁c and weight as covariates

**Systolic blood pressure**

Liraglutide provides clinically significant reductions in SBP and has been demonstrated across all LEAD trials (Marre et al., 2009; Nauck et al., 2009; Zinman et al., 2009; Russell-Jones et al., 2008, Buse et al., 2009; Figure 12).

SBP has also been shown to improve rapidly (as early as 2 weeks) following liraglutide initiation, and prior to significant treatment-induced weight loss.

As demonstrated in the meta-analysis, the effect on SBP with baseline SBP quartile was significant (p<0.0001), since the greatest reduction observed was in that with the highest SBP (Table 1).
Safety and tolerability

Since liraglutide acts in a glucose-dependent manner (Nauck et al., 2003) the risk of hypoglycaemia is low. Throughout all the LEAD trials major hypoglycaemia was rare; of the 6 cases reported, one of these patients was undergoing treatment with liraglutide 1.8 mg plus glimepiride (Marre et al., 2009) and the other five were treated with liraglutide 1.8 mg in combination with glimepiride and metformin (Russell-Jones et al. 2008). Since hypoglycaemic risk is a recognised feature of SU treatment we can assume these reports are a consequence of combining liraglutide with SU. Indeed, when liraglutide was used in combination with OADs (other than SUs) and as monotherapy, no major hypoglycaemia was observed (Nauck et al. 2009, Garber et al., 2009; Zinman et al., 2009, Buse et al., 2009).

Minor hypoglycaemia is not uncommon with existing diabetes treatments, however, there was a lower number of minor hypoglycaemia events reported with liraglutide treatment compared to that encountered with conventional diabetes treatments. To exemplify this, reports of minor hypoglycaemia with liraglutide 1.2 mg and 1.8 mg was at placebo level and lower than glimepiride treatment in the LEAD 2 study: 0.03 and 0.09 events/patient/year (liraglutide 1.2 mg and 1.8 mg, respectively) vs. 0.13 (placebo) and 1.23 events/patient/year (glimepiride) (Nauck et al., 2009).

Overall, liraglutide is generally well tolerated with most adverse events across the LEAD studies reported as mild or moderate in severity and frequently gastrointestinal-related. Nausea was the most common adverse effect; it was reported by up to 40% of patients but tended to dissipate after a period of 4 weeks (Marre et al., 2009; Nauck et al. 2009, Garber et al., 2009; Zinman et al., 2009; Russell-Jones et al., 2008, Buse et al., 2009). This may be explained by liraglutide’s ability to delay gastric emptying. Of note, very few adverse effects were serious and withdrawals were rare; majority of these withdrawals were due to nausea (Marre et al., 2009; Nauck et al. 2009, Garber et al., 2009; Zinman et al., 2009; Russell-Jones et al., 2008, Buse et al., 2009).

CONCLUSION

The role of GLP-1 receptor agonists as a treatment option for type 2 diabetes is rapidly evolving. Liraglutide, the first human GLP-1 analogue, has the potential to overcome the shortcomings of conventional therapies and address the current unmet needs of patients with type 2 diabetes.

Liraglutide has with the once daily administration demonstrated superior clinical efficacy and a favourable safety profile in recent clinical trials versus standard therapies; glycaemic control improved substantially with liraglutide and hypoglycaemia was uncommon. Moreover, there is indication that liraglutide may have a positive effect not only on beta-cell function, but also on beta-cell mass that implies potential long-term benefits. Liraglutide has also been found to promote weight loss and reduce SBP, which in turn, may reduce the risk of cardiovascular disease.

For type 2 diabetes patients, liraglutide offers a new and flexible treatment alternative to standard therapies which may help to overcome the unmet needs of current therapies.

REFERENCES