DOI: 10.1111/j.1464-5491.2010.03074.x

# Short Report: Treatment

# Liraglutide improves treatment satisfaction in people with Type 2 diabetes compared with sitagliptin, each as an add on to metformin

M. Davies, R. Pratley*, M. Hammer†, A. B. Thomsen† and R. Cuddihy‡

University of Leicester, Leicester, UK, *University of Vermont, Burlington, VT, USA, †Novo Nordisk A/S, Bagsvaerd, Denmark and ‡International Diabetes Center, Minneapolis, MN, USA

*Accepted 23 June 2010*

## Abstract

**Aims** Patient-reported outcomes from clinical trials offer insight into the impact of disease on health-related quality of life, including treatment satisfaction. This patient-reported outcomes evaluation was a substudy of a 26-week randomized, open-label trial comparing the once-daily injectable human GLP-1 analogue liraglutide with once-daily oral sitagliptin, both added to metformin. The patient reported outcomes substudy aimed to evaluate treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at baseline and 26 weeks.

**Methods** In the main 26-week randomized, open-label study (n = 658), liraglutide, 1.2 or 1.8 mg, injected with a pen, led to greater HbA1c reduction than oral sitagliptin, 100 mg once daily, both added to metformin = 1500 mg daily: mean HbA1c reduction was 1.5, 1.2 and 0.9% (7, 10 and 14 mmol/mol) for liraglutide 1.8 mg, 1.2 mg and sitagliptin, respectively ($P < 0.0001$ for both liraglutide doses vs. sitagliptin) and liraglutide patients lost more weight (3 vs.1 kg; $P < 0.0001$). In this patient-reported outcomes substudy (liraglutide 1.8 mg, n = 171; 1.2 mg, n = 164; sitagliptin, n = 170) DTSQ scores were analyzed by ANCOVA with treatment and country as fixed effects and baseline value as covariate.

**Results** Overall treatment satisfaction, calculated by adding satisfaction scores for 'current treatment', 'convenience', 'flexibility', 'understanding', 'recommend', and 'continue', improved in all groups at 26 weeks; greater improvement with liraglutide (4.35 and 3.51 vs. 2.96; $P = 0.03$ for liraglutide 1.8 mg vs. sitagliptin) may reflect greater HbA1c reduction and weight loss. Patients perceived themselves to be hyperglycaemic significantly less frequently with liraglutide 1.8 mg (difference = −0.88; $P < 0.0001$) and 1.2 mg (difference = −0.49; $P = 0.01$). Perceived frequency of hypoglycaemia was similar across all groups.

**Conclusions** Injectable liraglutide may lead to greater treatment satisfaction than oral sitagliptin, potentially by facilitating greater improvement in glycaemic control, weight loss and/ or perception of greater treatment efficacy.

Diabet. Med. 28, 333–337 (2011)

**Keywords** Diabetes Treatment Satisfaction Questionnaire, liraglutide, sitagliptin, treatment satisfaction, Type 2 diabetes

**Abbreviations** DPP-4, dipeptidyl peptidase 4; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GLP-1, glucagon-like peptide-1; HRQoL, health-related quality of life

## Introduction

In addition to the multiple physical sequelae of diabetes mellitus and its treatment, psychosocial factors significantly affect the disease course [1,2] as well as influencing patients' health-related quality of life (HRQoL), including treatment satisfaction [3,4].

Patient-reported outcomes from clinical trials provide information on the impact of a disease on HRQoL and may identify the extent to which treatment meets patients' needs and expectations. Patient-reported outcomes data typically reflect perceptions of the efficacy and tolerability of treatment, as well as treatment preferences and, as such, complement physician

*Correspondence to*: Melanie Davies, Professor of Diabetes Medicine, University Hospitals of Leicester, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, UK. E-mail: melanie.davies@uhl-tr.nhs.uk

appraisals of the clinical value of specific therapies. As greater treatment satisfaction may be associated with improved adherence to treatment and self-management behaviour [5], patient-reported measures of treatment satisfaction offer a clinically valuable indication of the likelihood that patients will choose, and adhere to, a given treatment. In the case of incretin-based therapies, a relatively new class of anti-diabetic agents, healthcare practitioners require quantitative and qualitative patient feedback to guide prescribing decisions. This is particularly important given the advantages some of these agents appear to offer over traditional oral anti-diabetic drugs and insulin, namely significantly lower risks of hypoglycaemia and weight gain [6,7], both of which may affect treatment satisfaction [8,9]. The present patient-reported outcomes evaluation was conducted in a predefined subpopulation of a randomized controlled trial that compared the efficacy and safety of approved doses of two incretin-based therapies, liraglutide, an injectable once-daily human glucagon-like peptide-1 (GLP-1) analogue and the orally administered dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin, each added on to metformin in patients with Type 2 diabetes poorly controlled on metformin alone [10].

In patients with Type 2 diabetes, adding liraglutide to failing metformin monotherapy improves glycaemic control and lowers weight with low hypoglycaemic risk, while reducing systolic blood pressure [11]. Synergism between sitagliptin and metformin also seems logical, as metformin stimulates GLP-1 secretion [6], while sitagliptin increases the half-life of endogenous GLP-1. In clinical trials, adding sitagliptin to metformin therapy decreased key glycaemic control parameters with minimal hypoglycaemia [12–14]. However, the magnitude of $HbA_{1c}$ reduction appears significantly lower with DPP-4 inhibitors than with GLP-1 receptor agonists [10,15]. Other key differentiators between these two therapy classes are their effects on weight and mode of administration: GLP-1 receptor agonists facilitate weight loss whereas DPP-4 inhibitor monotherapy is usually weight neutral [6] and, while GLP-1 receptor agonists are injected, DPP-4 inhibitors are taken orally. Although it is often stated that patients resist injectable therapies, published data suggest this is not by any means a universal finding [4,5,16] and it is possible that this stance may at times be overvalued, representing a form of physician-driven clinical inertia rather than an evidence-based concern [17].

## Materials and methods

Liraglutide, 1.2 or 1.8 mg, injected once daily using a pen device, was compared with oral sitagliptin, 100 mg once daily, both added to a stable dose of metformin (≥ 1500 mg daily), in a 26-week randomized, open-label study carried out in 13 countries. Study design, methods, efficacy and safety results are reported elsewhere [10]. The primary efficacy endpoint was change in $HbA_{1c}$ from baseline to week 26, with secondary endpoints including proportion of subjects reaching $HbA_{1c}$ < 7% (53 mmol/mol) and ≤ 6.5% (48 mmol/mol), fasting plasma glucose, indices of B-cell function, body weight, fasting lipids and treatment satisfaction. Safety assessments included adverse events and self-reported hypoglycaemia.

Treatment satisfaction was assessed at baseline and 26 weeks, or on withdrawal if this occurred prior to study completion, using the status version of the validated Diabetes Treatment Satisfaction Questionnaire (DTSQs) in a subgroup that included all exposed subjects from the 10 countries where patient-reported outcomes data were gathered ($n$ = 505/658; 77% of exposed subjects). The remaining three countries were excluded from the patient-reported outcomes substudy because of lack of local, linguistically validated patient-reported outcomes measures. As the DTSQ was completed either at 26 weeks or on withdrawal, no subjects were excluded from the patient-reported outcomes analysis. DTSQs consisted of eight items, each analysed individually, while overall treatment satisfaction was calculated by summing individual scores from six items: satisfaction with 'current treatment', 'convenience', 'flexibility', 'understanding', 'recommend' and 'continue', where 'recommend' and 'continue' indicate the likelihood that a patient would recommend or continue treatment after study completion. Each item was scored on a scale from 0 ('very dissatisfied/inconvenient') to 6 ('very satisfied/convenient'); a higher score indicates greater treatment satisfaction. Perceived frequency of hyperglycaemia and hypoglycaemia was measured separately using one item each, also scored on a scale from 0 ('none of the time') to 6 ('most of the time'), where lower scores indicate lower frequency of perceived hypo- or hyperglycaemia and therefore better perceived glycaemic control. Subjects did not receive guidance on how to determine whether their blood glucose level was high or low; they simply answered the questions 'How often have you felt that your blood sugars have been unacceptably high/low recently?' Patients were not specifically asked about their appetite or about symptoms of nausea. Treatment satisfaction scores were analysed using an ANCOVA model, with treatment and country as fixed effects and baseline value as covariate, with no imputation for missing values.

## Results

Baseline characteristics of the full analysis set for the main study population and patient-reported outcomes subpopulation were comparable and treatment group demographics well balanced. Baseline mean $HbA_{1c}$ values were 8.4% (68 mmol/mol) in both liraglutide groups and 8.5% (69 mmol/mol) in the sitagliptin group and baseline weights were 93.7, 94.6 and 93.1 kg in the 1.2 mg, 1.8 mg and sitagliptin groups, respectively. Corresponding body mass indices were 32.6, 33.1 and 32.6 kg/m$^2$. The main study randomized 665 individuals, of which 658 were exposed to at least one dose of trial product, and 554 (83%) completed the trial. A total of 505 subjects (liraglutide 1.2 mg $n$ = 164; liraglutide 1.8 mg $n$ = 171; sitagliptin $n$ = 170) were included in the current patient-reported outcomes analysis.

In this trial, liraglutide led to significantly greater reduction in $HbA_{1c}$ than sitagliptin (mean $HbA_{1c}$ reduction: 1.50, 1.24 and 0.90% (7, 10 and 14 mmol/mol) for liraglutide 1.8 mg, 1.2 mg and sitagliptin, respectively; $P < 0.0001$ for both liraglutide doses vs. sitagliptin). The proportion of patients reaching $HbA_{1c} < 7\%$ (53 mmol/mol) was 54.6, 43.4 and 22.4%, respectively, and liraglutide-treated subjects lost significantly more weight (~3 vs. ~1 kg). Treatment-emergent adverse events occurred in 66.1% (1.2 mg) and 72.9% (1.8 mg) of liraglutide-treated subjects vs. 58.0% of sitagliptin-treated patients. For liraglutide, the majority of excess adverse events were early gastrointestinal side effects, typically nausea that was mostly mild and transient [10]; although nausea occurred more frequently during the first few weeks with liraglutide (21–27%) than with sitagliptin (5%), symptoms had decreased to levels observed with sitagliptin (< 3%) by the end of the trial. The most common adverse events in sitagliptin-treated patients were nasopharyngitis and headache, reported in 11.9 and 10.0% of patients, respectively. The proportion of subjects experiencing hypoglycaemia (mostly minor) was low and comparable in all groups [10].

Table 1 presents the patient-reported outcomes results. Overall, treatment satisfaction was comparable between groups at baseline and improved in all groups after 26 weeks. However, improvement in overall treatment satisfaction was significantly greater with liraglutide 1.8 mg (4.35) than sitagliptin (2.96) [between-group difference = 1.39 (95% CI 0.13; 2.64); $P = 0.03$]; differences in overall treatment satisfaction between liraglutide 1.2 mg and sitagliptin, and between the two liraglutide doses, were not significant. Patients reported significantly greater improvement in treatment satisfaction with liraglutide 1.8 mg than sitagliptin on three items: 'current treatment' (difference = 0.35; $P = 0.01$), 'recommend' (difference = 0.41; $P = 0.003$) and 'continue' (difference = 0.44; $P = 0.01$). Patients perceived themselves to be hyperglycaemic significantly less frequently with liraglutide 1.8 mg than sitagliptin (difference = −0.88; $P < 0.0001$) and the same was found when comparing the 1.2-mg dose of liraglutide with sitagliptin (difference = −0.49; $P = 0.01$). The perceived frequency of hypoglycaemia was similar across all three groups.

## Discussion

While all groups reported an increase in treatment satisfaction, subjects receiving liraglutide 1.8 mg reported significantly greater improvement in overall treatment satisfaction than those taking sitagliptin, despite the fact that liraglutide was injected while sitagliptin was oral, and that treatment-emergent adverse events occurred in more liraglutide patients. This could reflect patients' recognition that the GLP-1 analogue offered better control of hyperglycaemia and the potential for weight loss, although further data are needed to confirm this. Our data also highlight the positive impact of improved glycaemic control on treatment satisfaction. Of interest, there was no difference between liraglutide and sitagliptin on DTSQ items relating to treatment convenience and flexibility, indicating that patients were no less satisfied with the injectable than the oral agent. These findings concur with much of the published literature in suggesting that patients may prefer an injected to an oral therapy if it leads to greater improvement in glycaemic control, perception of greater treatment efficacy and/or facilitates weight loss [4,5,16]. As obese subjects with Type 2 diabetes report poorer health status and greater symptom impact than non-obese patients [18,19], the improvement in HRQoL afforded by weight-lowering therapies may be particularly welcome. Our finding of reduced perceived frequency of hyperglycaemia with liraglutide is also in accordance with data showing that the association between $HbA_{1c}$ and HRQoL may be mediated by the perceived frequency of hyper- and hypoglycaemic episodes [4,20].

**Table 1** Patient-reported outcomes summary

| | Liraglutide 1.2 mg + metformin | Liraglutide 1.8 mg + metformin | Sitagliptin + metformin | Difference between liraglutide 1.2 mg and sitagliptin* | Difference between liraglutide 1.8 mg and sitagliptin* |
|---|---|---|---|---|---|
| Overall treatment satisfaction | 3.51 | 4.35 | 2.96 | 0.55 (−0.72; 1.81) $P = 0.40$ | 1.39 (0.13; 2.64) $P = 0.03$† |
| Current treatment | 0.62 | 0.84 | 0.50 | 0.12 (−0.15; 0.39) $P = 0.38$ | 0.35 (0.08; 0.62) $P = 0.01$† |
| Convenience | 0.39 | 0.54 | 0.51 | −0.12 (−0.38; 0.14) $P = 0.36$ | 0.03 (−0.23; 0.28) $P = 0.83$ |
| Flexibility | 0.57 | 0.66 | 0.40 | 0.17 (−0.13; 0.46) $P = 0.27$ | 0.26 (−0.03; 0.55) $P = 0.08$ |
| Understanding | 0.66 | 0.63 | 0.50 | 0.16 (−0.06; 0.37) $P = 0.16$ | 0.13 (−0.08; 0.34) $P = 0.23$ |
| Recommend | 0.54 | 0.78 | 0.37 | 0.17 (−0.09; 0.44) $P = 0.21$ | 0.41 (0.14; 0.67) $P = 0.003$† |
| Continue | 0.64 | 0.87 | 0.43 | 0.21 (−0.11; 0.52) $P = 0.19$ | 0.44 (0.13; 0.75) $P = 0.01$† |
| Perceived frequency of hyperglycaemia | −1.82 | −2.21 | −1.33 | −0.49 (−0.86; −0.12) $P = 0.01$† | −0.88 (−1.25; −0.51) $P < 0.0001$† |
| Perceived frequency of hypoglycaemia | 0.08 | −0.12 | −0.03 | 0.11 (−0.18; 0.41) $P = 0.46$ | −0.08 (−0.38; 0.21) $P = 0.58$ |

Data are differences in Diabetes Treatment Satisfaction Questionnaire score least square means between weeks 0 and 26.
*Columns on the right show estimated treatment difference with 95% confidence intervals.
†*P*-values indicate statistical significance at the 5% level.

Despite the potential for greater glucose-lowering efficacy and weight loss with GLP-1 receptor agonists compared with DPP-4 inhibitors, and the reported effects on patient satisfaction and adherence, some clinicians remain hesitant to use GLP-1 receptor agonists, perhaps perceiving injectable therapies to be more complex and less desirable than a once-daily oral medication. However, this reluctance to prescribe GLP-1 receptor agonists fails to take into account the fact that many commonly used anti-diabetic therapies are associated with weight gain and hypoglycaemia, both of which negatively affect patient quality of life, and that weight gain itself may exacerbate other components of the metabolic syndrome.

Patient-reported outcomes and treatment satisfaction are important factors to consider when choosing a glucose-lowering therapy for patients with Type 2 diabetes. This study provides evidence of greater improvement in treatment satisfaction with an injectable GLP-1 agent, liraglutide 1.8 mg, than an oral DPP-4 inhibitor, sitagliptin, potentially by facilitating greater improvement in glycaemic control and weight loss. These results challenge the perception that patients 'prefer' oral to injected glucose-lowering therapies.

## Competing interests

MD has acted as consultant, advisory board member and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Roche, BMS and speaker for Servier. She has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp & Dohme, GlaxoSmithKline and Servier. RP has received research grants, funds for speaking, honoraria and consulting fees from Novartis and has ownership interests in Novartis; research grants, speakers fees, honoraria and consulting fees from Takeda; research grants speakers fees, honoraria and consulting fees from Novartis fees from Merck; research grants, honoraria and consulting fees from Roche; research grants, honoraria and consulting fees from GlaxoSmithKline; research grants from Eli Lilly; research grants, speakers fees, honoraria and consulting fees from Novo Nordisk; research grants from Mannkind, Sanofi-Aventis and Pfizer, and honoraria and consulting fees from Eisai, Glenmark and AstraZeneca/BMS. MH is an employee and stakeholder of Novo Nordisk A/S. ABT is an employee of Novo Nordisk and has shares in the company. RC serves as PI or co-investigator for sponsored clinical trials research for Amylin, Abbott, Bayer, Daiichi-Sankyo, Dexcom, Edwards Lifesciences, Eli Lilly, Intarcia, Johnson and Johnson/Lifescan, Mannkind, Medtronic, Novo Nordisk, Quotient Diagnostics, ResMed, Roche, Sanofi-Aventis and Takeda; is an advisory board member for Abbott, Bayer, CeQur, Eli Lilly, Novo Nordisk and Roche; receives support for educational activities from Lifescan, Eli Lilly, Merck, Novartis and Sanofi-Aventis.

### Acknowledgements

The authors accept direct responsibility for this paper and are grateful for the contribution made by Watermeadow Medical (supported by Novo Nordisk A/S, Bagsvaerd, Denmark) in developing the draft manuscript from an agreed outline and for editorial assistance.

## References

1 Davis WK, Hess GE, Hiss RG. Psychosocial correlates of survival in diabetes. *Diabetes Care* 1988; **11**: 538–545.
2 Lustman PJ, Anderson RJ, Freedland KE, De Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000; **23**: 934–942.
3 Bradley C, Speight J. Patient perceptions of diabetes and diabetes therapy: assessing quality of life. *Diabetes Metab Res Rev* 2002; **18**: S64–69.
4 Nicolucci A, Cucinotta D, Squatrito S, Lapolla A, Musacchio N, Leotta S *et al.*; QuoLITy Study Group. Clinical and socio-economic correlates of quality of life and treatment satisfaction in patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis* 2009; **19**: 45–53.
5 Peyrot M, Rubin RR. How does treatment satisfaction work?: modeling determinants of treatment satisfaction and preference. *Diabetes Care* 2009; **32**: 1411–1417.
6 Ahren B. Emerging dipeptidyl peptidase-4 inhibitors for the treatment of diabetes. *Expert Opin Emerg Drugs* 2008; **13**: 593–607.
7 Lovshin J, Drucker D. Incretin-based therapies for type 2 diabetes mellitus. *J Nat Rev Endocrinol* 2009; **5**: 262–269.
8 Marrett E, Stargardt T, Mavros P, Alexander C. Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: associations with hypoglycaemia and weight gain. *Diabetes Obes Metab* 2009; **11**: 1138–1144.
9 Pollack MF, Purayidathil FW, Bolge SC, Williams SA. Patient-reported tolerability issues with oral antidiabetic agents: associations with adherence; treatment satisfaction and health-related quality of life. *Diabetes Res Clin Pract* 2010; **87**: 204–210.
10 Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy E, Filetti S *et al.*, for the 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010; **375**: 1447–1456.
11 Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH *et al.*; LEAD-2 Study Group Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009; **32**: 84–90.
12 Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006; **29**: 2638–2643.
13 Raz I, Chen Y, Wu M, Hussain S, Kaufman KD, Amatruda JM *et al.* Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. *Curr Med Res Opin* 2008; **24**: 537–550.
14 Scott R, Loeys T, Davies MJ, Engel SS. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2008; **10**: 959–969.

15 Gilbert MP, Pratley RE. Efficacy and safety of incretin-based therapies in patients with type 2 diabetes mellitus. *Eur J Intern Med* 2009; **20**: S309–318.
16 Houlden R, Ross S, Harris S, Yale JF, Sauriol L, Gerstein HC. Treatment satisfaction and quality of life using an early insulinization strategy with insulin glargine compared to an adjusted oral therapy in the management of Type 2 diabetes: The Canadian INSIGHT Study. *Diabetes Res Clin Pract* 2007; **78**: 254–258.
17 Kruger D, Spollett G. Addressing barriers to timely intensification of diabetes care: the relationship between clinical inertia and patient behavior. *Consultant* 2009; **49**: S20–25.
18 Matza L, Yurgin N, Boye KS, Malley K, Shorr JM. Obese versus non-obese patients with type 2 diabetes: patient-reported outcomes and utility of weight change. *Curr Med Res Opin* 2007; **23**: 2051–2062.
19 Sundaram M, Kavookjian J, Patrick J, Miller LA, Madhavan SS, Scott VG. Quality of life, health status and clinical outcomes in type 2 diabetes patients. *Qual Life Res* 2007; **16**: 165–167.
20 Kleefstra N, Ubink-Veltmaat L, Houweling S, Groenier KH, Meyboom-de Jong B, Bilo HJ. Cross-sectional relationship between glycaemic control, hyperglycaemic symptoms and quality of life in type 2 diabetes (ZODIAC-2). *Neth J Med* 2005; **63**: 215–221.