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SHORT COMMUNICATION

Pharmacokinetic Properties of Liraglutide as Adjunct to Insulin in Subjects with Type 1 Diabetes Mellitus

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Abstract

Background The pharmacokinetic properties of liraglutide, a glucagon-like peptide-1 receptor agonist approved for the treatment of type 2 diabetes mellitus (T2D), have been established in healthy individuals and subjects with T2D. Liraglutide has been under investigation as adjunct treatment to insulin in type 1 diabetes mellitus (T1D). This single-center, double-blind, placebo-controlled, crossover, clinical pharmacology trial is the first to analyze the pharmacokinetic properties of liraglutide as add-on to insulin in T1D.

Methods Subjects (18–64 years; body mass index 20.0–28.0 kg/m^2; glycated hemoglobin ≤9.5 %) were randomized 1:1:1 to 0.6, 1.2, or 1.8 mg liraglutide/placebo. Each group underwent two 4-week treatment periods (liraglutide then placebo or placebo then liraglutide) separated by a 2- to 3-week washout. Both trial drugs were administered subcutaneously, once daily, as adjunct to insulin. A stepwise hypoglycemic clamp was performed at the end of each treatment period (data reported previously). Pharmacokinetic endpoints were derived from liraglutide concentration–time curves after the final dose and exposure was compared with data from previous trials in healthy volunteers and subjects with T2D.

Results The pharmacokinetic properties of liraglutide in T1D were comparable with those observed in healthy volunteers and subjects with T2D. Area under the steady-state concentration–time curve (AUC) and maximum plasma concentration data were consistent with dose proportionality of liraglutide. Comparison of dose-normalized liraglutide AUC suggested that exposure in T1D, when administered with insulin, is comparable with that observed in T2D.

Conclusions Liraglutide, administered as adjunct to insulin in subjects with T1D, shows comparable pharmacokinetics to those in subjects with T2D.

ClinicalTrials.gov Identifier: NCT01536665.

Key Points

This is the first trial to describe the pharmacokinetic properties of liraglutide as adjunct treatment to insulin in type 1 diabetes mellitus (T1D).

Based on data obtained at steady-state, pharmacokinetic properties were comparable with those previously observed in healthy volunteers and subjects with type 2 diabetes mellitus. Pharmacokinetic endpoints derived from liraglutide concentration–time curves after the last dose were consistent with dose proportionality.

These results add to the clinical profile of liraglutide in T1D. The efficacy and safety of liraglutide as adjunct therapy to insulin in this population have also been evaluated in three phase III trials (http://www.clinicaltrials.gov; NCT02098395, NCT01836523, NCT02092896) and one phase IV trial (NCT01612468).

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1 Introduction

The glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) have multiple physiologic effects, including glucose-dependent stimulation of insulin secretion from the pancreas and reduction of glucagon secretion [1]. They are also associated with weight loss and reductions in systolic blood pressure [1], in conjunction with a minor increase in heart rate of 1–2 beats/min [2]. Positive results in phase III clinical trials have made them a well-established therapeutic class in type 2 diabetes mellitus (T2D).

GLP-1 RAs have shown potential in the treatment of type 1 diabetes mellitus (T1D) in preclinical and clinical studies [3–7], and their glucose-dependent mode of action [8] leads to low risk of hypoglycemia and may reduce excessive postprandial glucagon secretion (allowing subjects to reduce their total daily insulin dose). Among these GLP-1 RAs is liraglutide, a once-daily human GLP-1 RA that has 97 % homology to native GLP-1 and is already widely used for the treatment of T2D [9, 10].

Liraglutide, in combination with insulin, has demonstrated potential benefits to glycemic control in several small studies in subjects with T1D [4, 5, 11, 12], including reduced frequency and amplitude of fasting and postprandial hyperglycemic excursions (believed to be due to inhibition of postprandial hyperglucagonemia), decreased incidence of hypoglycemia, decreased insulin requirement, reductions in systolic blood pressure, and weight loss.

The pharmacokinetics of liraglutide have been established in several populations, including healthy volunteers of different ethnicities [13–17], non-diabetic individuals with varying degrees of hepatic [18] or renal [19] impairment, and adults [10, 20, 21] and children [22] with T2D. Understanding the pharmacokinetic properties of liraglutide in subjects with T1D is important in establishing its clinical profile in this population.

In a recent, randomized, controlled clinical pharmacology trial, liraglutide preserved the counter-regulatory response to hypoglycemia, decreased subjects' insulin requirements, and was associated with reduced body weight relative to placebo in subjects with T1D [7]. Liraglutide was well tolerated and safety observations were in line with those observed previously in subjects with T2D. The present article, based on analysis of subjects enrolled in this clinical pharmacology trial, is the first to describe the pharmacokinetic properties of liraglutide as adjunct therapy to insulin in T1D.

2 Materials and Methods

2.1 Participants

The trial included male and female subjects aged 18–64 years (inclusive) with a clinical diagnosis of T1D for ≥12 months. All participants had been treated with multiple daily insulin injections or continuous subcutaneous insulin infusion for ≥12 months. Subjects also had a body mass index of 20.0–28.0 kg/m^2 (inclusive), body weight ≥52 kg, and glycated hemoglobin (HbA_{1c}) ≤9.5 %.

Key exclusion criteria included the use of liraglutide or exenatide within 3 months before randomization, recurrent severe hypoglycemia (more than one episode within the past 12 months), hypoglycemia unawareness, or severe autonomic neuropathy.

2.2 Trial Design

The design of the main trial, including confirmation of the ethical conduct and approval of the trial, has been previously reported in full [7]. Briefly, it was a randomized, single-center, double-blind, placebo-controlled, crossover trial in three parallel groups of subjects with T1D. Subjects were randomized 1:1:1 to one of three liraglutide dose groups (0.6, 1.2, or 1.8 mg), and placebo in equivalent volume, administered once daily in the evening by subcutaneous injection, as adjunct to insulin.

Each group underwent two 4-week treatment periods (half liraglutide then placebo and half placebo then liraglutide) separated by a 2- to 3-week washout period before crossover. Liraglutide was initiated at 0.6 mg/day, irrespective of the dose group to which the subject had been randomized, followed by weekly dose escalations of 0.6 mg until the target dose of 0.6, 1.2, or 1.8 mg was reached.

At the end of each treatment period, a stepwise hypoglycemic clamp was performed. The design and results of the clamp were reported by Pieber et al. [7]. The final dose of trial product was given in the evening, at 22:00 h on the day before the clamp, and serial sampling for plasma concentration of liraglutide was initiated at that timepoint and continued for 60 h post-dose. In this publication, only the pharmacokinetic data for the liraglutide dosing period are reported.

2.3 Pharmacokinetic Assessments and Statistical Analysis

The current article summarizes pharmacokinetic endpoints derived from the steady-state concentration–time curves for liraglutide 0.6, 1.2, and 1.8 mg, including area under the curve (AUC), maximum serum concentration (C_{max}), time to C_{max} (t_{max}), terminal half-life ($t_{½}$), clearance (CL/F), volume of distribution (V_z/F), and the minimum liraglutide concentration in a dosing interval (C_{trough}; measured just before the final dose). Blood samples for assessment of these pharmacokinetic endpoints were drawn at steady-state immediately prior to, and nominally at 2, 5,

8, 10, 12, 14, 16, 20, 24, 36, 48, and 60 h after, administration of the final dose.

Liraglutide was analyzed in plasma using a specific enzyme-linked immunosorbent assay (ELISA) that employed two monoclonal antibodies directed against different liraglutide epitopes [13]. The two antibodies used for this sandwich assay were directed against the N- and C-terminal region of the liraglutide molecule. The calibration range of the assay was 20–2000 pmol/L, with a lower limit of quantification (LLOQ) of 30 pmol/L and an upper limit of quantification (ULOQ) of 2000 pmol/L. An additional calibration anchor point at 20 pmol/L was included to assist the curve-fitting process and was not subjected to any acceptance criteria.

Dose-normalized liraglutide AUCs from this trial were compared against those from three trials of liraglutide in subjects with T2D [20, 23, 24]. Two of these were clinical pharmacology studies [20, 23], selected because they included steady-state liraglutide pharmacokinetic profiles. The third trial was a phase III trial [25] of liraglutide monotherapy, including pharmacokinetic data used for population pharmacokinetic analysis [24].

Pharmacokinetic endpoints were determined using non-compartmental methods. Actual time since the start of final dose administration was used for all endpoints.

AUC was approximated using the trapezoidal rule on the observed concentrations. C_{max} for each liraglutide dose was derived as the maximum of all valid concentrations, and t_{max} was then determined as the corresponding time point to C_{max}. The terminal elimination rate constant (λ_z) was estimated by log-linear regression on the terminal part of the concentration–time curve, and $t_{½}$ was then calculated as $t_{½} = \ln 2/\lambda_z$. CL/F was calculated as CL/F = dose/$AUC_{0–24\ h}$. V_z/F was estimated as $V_z/F = (CL/F)/\lambda_z$.

All pharmacokinetic endpoints were summarized by treatment using descriptive statistics. Post hoc statistical analysis of dose proportionality of selected endpoints was conducted using a linear model of log ($AUC_{0–24\ h}$) and log (C_{max}) with logarithmic-transformed dose as the covariate. According to the model, doubling the dose resulted in an increase in the endpoint with a factor of 2^{β}, where β is the slope of the linear regression, i.e. $\beta = 1$ corresponds to perfect dose proportionality

3 Results

3.1 Demographics

Pharmacokinetic profiles were available for 40/45 subjects enrolled in the trial (liraglutide 0.6 mg, $n = 14$; 1.2 mg, $n = 13$; 1.8 mg, $n = 13$) [7].

Demographics and baseline characteristics were similar across the three dose groups analyzed (Table 1). All subjects were White, and the majority (65 %) were male. Across the three dose groups, mean age ranged from 32.4 to 38.1 years, mean body weight from 72.3 to 75.2 kg, and mean duration of diabetes from 15.4 to 18.6 years. Serum creatinine was <126 μmol/L (male) or <111 μmol/L (female) in all groups. Mean fasting C-peptide levels were very low, as expected in an exclusively T1D population; a total of eight subjects (three in each of the 0.6 and 1.2 mg dose groups; two in the 1.8 mg dose group) were C-peptide-positive (≥0.06 nmol/L).

3.2 Pharmacokinetics

Pharmacokinetic profiles for all three liraglutide doses are presented in Fig. 1. Median t_{max} and geometric mean $t_{½}$ were comparable between the three dose groups (Table 2). Median t_{max} values ranged from 8 to 10 h (10 h for the entire trial population), while geometric mean $t_{½}$ values ranged from 15.3 to 18.8 h (16.7 h for the entire population). CL/F and V_z/F were also comparable between dose groups, with geometric mean values of 0.85 L/h and 27.4 L, respectively, across the trial population (Table 2).

Plots of steady-state AUC and C_{max} versus dose (post hoc analysis) were consistent with dose proportionality

Table 1 Participant demographics and baseline characteristics

	Liraglutide 0.6 mg [$n = 14$]	Liraglutide 1.2 mg [$n = 13$]	Liraglutide 1.8 mg [$n = 13$]	Liraglutide All doses [$n = 40$]
Males/females [n (%)]	8 (57)/6 (43)	10 (77)/3(23)	8 (62)/5 (38)	26 (65)/14 (35)
Age, years [range]	38.1 (11.2) [20.0–55.0]	34.3 (12.9) [20.0–55.0]	32.4 (8.8) [18.0–45.0]	35.0 (11.1) [18.0–55.0]
Body weight, kg [range]	75.2 (14.4) [55.7–91.4]	72.3 (9.6) [57.5–86.1]	74.6 (10.4) [60.0–89.8]	74.1 (11.5) [55.7–91.4]
BMI, kg/m^2 [range]	24.0 (2.7) [20.2–28.2]	23.1 (2.1) [20.2–26.2]	24.5 (2.4) [20.5–28.0]	23.9 (2.4) [20.2–28.2]
Duration of diabetes, years [range]	18.5 (8.9) [6.4–33.9]	18.6 (10.7) [6.7–43.8]	15.4 (9.1) [1.9–33.7]	17.5 (9.5) [1.9–43.8]
Serum creatinine, μmol/L [range]	74.8 (14.2) [52.0–97.0]	85.2 (20.0) [54.0–117.0]	74.5 (8.7) [58.0–92.0]	78.1 (15.5) [52.0–117.0]

Data are mean (SD) unless otherwise stated

BMI body mass index, *SD* standard deviation, *SD* standard deviation

(Fig. 2): estimated 2^{β} for $AUC_{0–24\ h}$ and C_{max} (95 % CI) were 2.06 (1.83–2.33) and 2.10 (1.86–2.37), respectively. The finding of dose proportionality was supported by the liraglutide C_{trough} for the three dose groups (concentration value at time zero on the concentration–time profile) (Fig. 1).

Visual comparison of dose-normalized liraglutide AUC for subjects with T1D in this trial, alongside results from two clinical pharmacology studies in subjects with T2D ($n = 12$, Hermansen et al. [20]; and $n = 32$, Morrow et al. [23]), and one population pharmacokinetic analysis in T2D (458 subjects who received liraglutide 1.2 or 1.8 mg, Ingwersen et al. [24]), suggested that liraglutide exposure largely overlaps in subjects with T1D and T2D (Fig. 3). However, differences in the aforementioned studies in demographic characteristics such as body weight (mean, kg: 98.2 [23], 88.2 [20], 93.1 [24], and 74.1 in the current study) and sex distribution (male:female ratio: 2.3 [23], 1.2 [20], 0.9 [24], and 1.9 in the current study) should be taken into account when interpreting these findings.

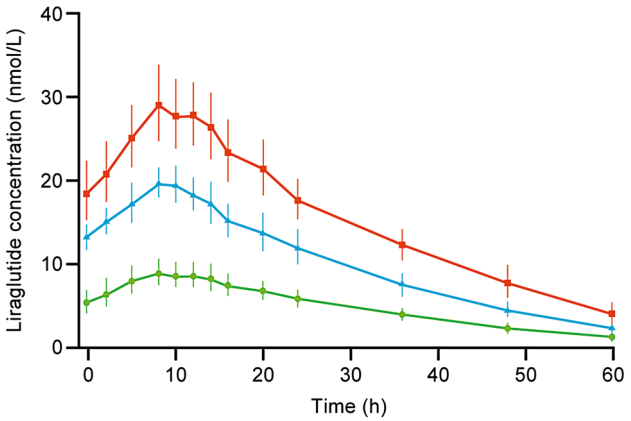

Fig. 1 Liraglutide concentration profiles in patients with type 1 diabetes. *Green curve* represents liraglutide 0.6 mg; *blue curve* represents liraglutide 1.2 mg; *orange curve* represents liraglutide 1.8 mg. Data are geometric mean with 95 % confidence intervals

4 Discussion

This analysis of steady-state pharmacokinetic data in subjects with T1D receiving liraglutide 0.6, 1.2, or 1.8 mg as adjunct to insulin indicates similar pharmacokinetic properties in individuals with T1D and T2D. The minor differences identified between these populations were slightly higher V_z/F (27.4 vs.11–17 L) and longer plasma half-life (16.7 vs. 13 h) in individuals with T1D than previously reported in healthy volunteers and individuals with T2D [26, 27]; methodological differences between studies (e.g. differences in trial eligibility criteria, background medications, blood sampling times) may also have contributed to these differences. The analysis also demonstrates that liraglutide is consistent with dose-proportional pharmacokinetics in T1D, which aligns with results from studies in healthy volunteers and in adults and adolescents with T2D, including both White and Asian populations [13, 14, 16, 17, 21, 22]. Based on dose-normalized AUC values, exposure appeared to largely overlap between liraglutide-treated subjects with T1D in the current trial and subjects with T2D receiving liraglutide 1.8 mg in two clinical pharmacology studies and one population pharmacokinetic study [20, 23, 24], although baseline demographic and clinical characteristics were different across the studies compared in this analysis and will have had an impact on the pharmacokinetic data obtained (e.g. there was a larger proportion of heavier male subjects in the study by Morrow et al. than the study by Hermansen et al., leading to reduced exposure in the former). Covariate

Table 2 Pharmacokinetic parameters from a non-compartmental analysis

	Liraglutide 0.6 mg [$n = 14$]	Liraglutide 1.2 mg [$n = 13$]	Liraglutide 1.8 mg [$n = 13$]	Liraglutide All doses [$n = 40$]
$AUC_{0–24\ h}$, pmol h/L	181,464 (33)	384,151 (20)	569,771 (26)	–
C_{max}, pmol/L	9257 (33)	20,067 (18)	29,751 (28)	–
C_{trough}, pmol/L	5209 (43)	13,051 (20)	18,287 (32)	–
t_{max}, h	9	8	10	10
$t_{½}$, h	15.3 (15.6)	16.4 (135.2)	18.8 (144.1)	16.7 (128.8)
CL/*F*, L/h	0.88 (28.4)	0.83 (18.2)	0.84 (23.4)	0.85 (23.6)
V_z/F, L	27.0 (36.2)	26.0 (88.1)	29.3 (120.2)	27.4 (95.4)

Data are geometric mean (CV, %), with the exception of t_{max}, which is median. Overall liraglutide data (all doses) are included for dose-independent parameters

$AUC_{0–24\ h}$ area under the curve from time zero to 24 h, *C_{max}* maximum concentration, *CL/F* clearance, *C_{trough}* trough concentration, *CV* coefficient of variation, *$t_{½}$* terminal half-life, *t_{max}* time to C_{max}, *V_z/F* volume of distribution

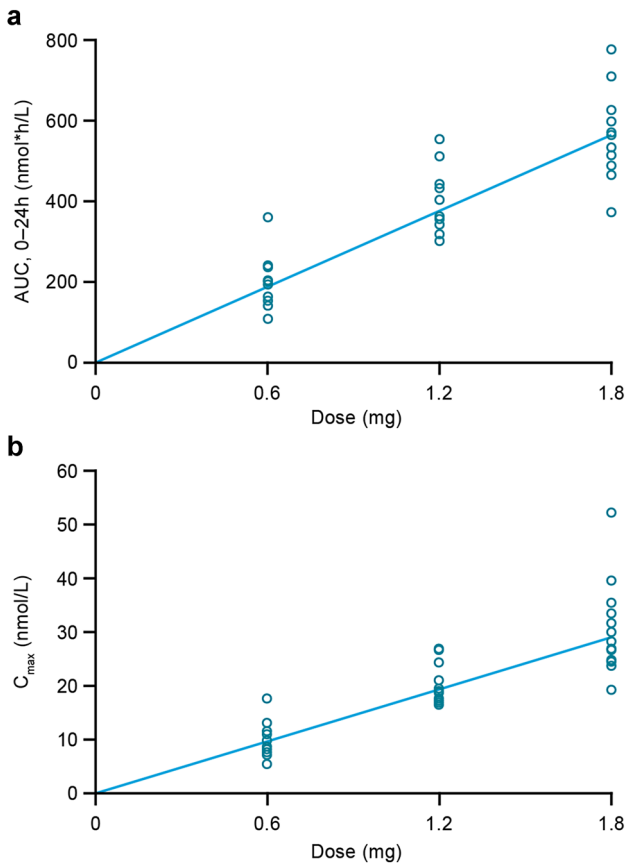

Fig. 2 Liraglutide **a** AUC and **b** C_{max} according to dose in patients with type 1 diabetes. *Solid lines* represent the estimated curves based on a linear model with logarithmic transformed dose as covariate fitted to the logarithmic transformed endpoint under the assumption of dose proportionality (i.e. an exponent of 1 in the regression model). *Symbols* represent observed values. *AUC* area under the curve, C_{max} maximum concentration

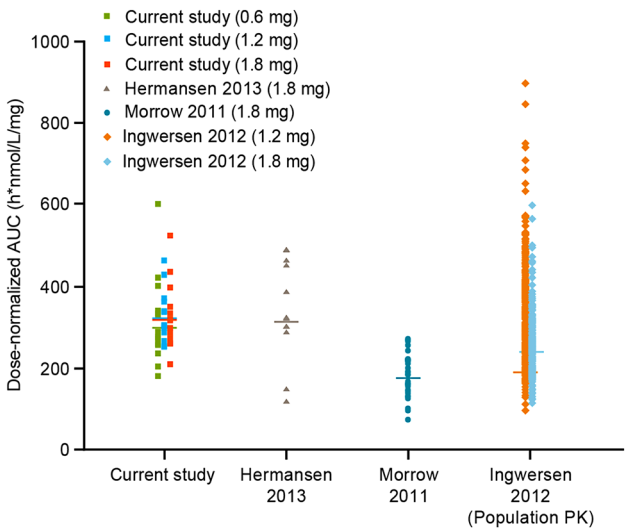

Fig. 3 Scatter plot of dose-normalized liraglutide AUC for patients with type 1 diabetes taking insulin compared with patients with type 2 diabetes. *Horizontal lines* represent the geometric mean of the group. Data from the three trials in type 2 diabetes are also dose-normalized. Differences in baselines demographics, particularly sex and body weight, as described in the text, may have influenced outcomes. *AUC* steady-state area under the curve, *PK* pharmacokinetics

analysis was not carried out in the current study due to small sample size.

Overall, pharmacokinetic parameters in subjects with T1D in the current trial were comparable with those in healthy volunteers and subjects with T2D in previous studies [13, 14, 16–20, 26]. In particular, median t_{max} (10 h) was within the range of 8–12 h observed in studies with healthy volunteers and subjects with T2D, as was geometric mean CL/*F* (0.85 L/h in the current trial; 1.2 L/h in studies with healthy volunteers and subjects with T2D) [26]. Geometric mean $t_{½}$ was 16.7 h, which is above the approximately 13 h observed in previous studies [26], while geometric mean V_z/F in the current analysis (27.4 L) was also slightly higher than values in previous studies in healthy volunteers and subjects with T2D (11–17 L) [26]. These differences may possibly reflect different half-lives in types 1 and 2 diabetes, driven by differences in V_z/F. Despite these minor differences, and notwithstanding possible differences in baseline demographics, liraglutide exposure (in terms of AUC) largely overlapped, and therefore appeared comparable, in T1D and T2D. This finding is in accordance with the similar clearance values in these populations. Establishing that the pharmacokinetic profile of liraglutide in T1D is consistent with that observed in healthy subjects and in T2D was also an important step in clinical development. Five recently completed studies, two conducted by Novo Nordisk (NCT02098395, NCT01836523) and three investigator-initiated trials [28–30] examined the efficacy and safety of liraglutide as adjunct therapy to insulin in the treatment of T1D to further clarify the clinical picture.

This trial is the first to present information on the pharmacokinetic properties of liraglutide as adjunct therapy to insulin in subjects with T1D, including across three different liraglutide doses; however, there are some limitations to the current work. First, all subjects were Caucasian and further work will be required to assess the pharmacokinetic properties of liraglutide in non-White populations with T1D and how these compare with T2D. Second, although allocation to active or placebo treatment was blinded, the dose level was not; however, this is unlikely to have affected the pharmacokinetic outcomes given that participants would not have been able to influence these outcomes based on knowledge of the randomization group. Third, although the results are consistent with dose proportionality of liraglutide in T1D, this trial was not specifically designed to address this, and the analysis was performed post hoc. Finally, the trial was

performed in subjects with T1D only, meaning that the comparison to pharmacokinetics in subjects with T2D was made using historical data.

5 Conclusions

On the basis of results from this trial, we conclude that when liraglutide is administered as adjunct therapy to insulin in subjects with T1D, liraglutide exposure is dose-proportional and overlaps with that in subjects with T2D, and its pharmacokinetic properties are comparable with those in healthy volunteers and subjects with T2D.

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Compliance with Ethical Standards

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Conflict of interest Julia Mader has received speaker honoraria from Novo Nordisk, Roche Diabetes Care, Nintamed, and Takeda, and has served on the advisory boards of Sanofi, Boehringer–Ingelheim and Eli Lilly. Erik Christiansen, Lene Jensen, and Steen Ingerwersen are employees and shareholders of Novo Nordisk A/S. Simon Heller has served as a consultant to Novo Nordisk, Eli Lilly, Sanofi, Boehringer–Ingelheim and Takeda, served on the speaker panel of Novo Nordisk, Eli Lilly, Sanofi, MSD, and Takeda, and received research support from Medtronic. Thomas Pieber has received research support from Novo Nordisk and has served on the advisory board or speakers' bureau of Novo Nordisk, AstraZeneca, and Eli Lilly.

References

1. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. Diabetes Care. 2011;34(Suppl. 2):S279–84.
2. Katout M, Zhu H, Rutsky J, Shah P, Brook RD, Zhong J, et al. Effect of GLP-1 mimetics on blood pressure and relationship to weight loss and glycemia lowering: results of a systematic meta-analysis and meta-regression. Am J Hypertens. 2014;27:130–9.
3. Varanasi A, Bellini N, Rawal D, Vora M, Makdissi A, Dhindsa S, et al. Liraglutide as additional treatment for type 1 diabetes. Eur J Endocrinol. 2011;165:77–84.
4. Kielgast U, Krarup T, Holst JJ, Madsbad S. Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in type 1 diabetic patients with and without residual beta-cell function. Diabetes Care. 2011;34:1463–8.
5. Pettus J, Hirsch I, Edelman S. GLP-1 agonists in type 1 diabetes. Clin Immunol. 2013;149:317–23.
6. Unger J. Rational use of GLP-1 receptor agonists in patients with type 1 diabetes. Curr Diab Rep. 2013;13:663–8.
7. Pieber TR, Deller S, Korsatko S, Jensen L, Christiansen E, Madsen J, et al. Counterregulatory hormone responses to hypoglycaemia in subjects with type 1 diabetes following 4 weeks of treatment with liraglutide adjunct to insulin: a randomized, placebo-controlled, double-blind, crossover trial. Diabetes Obes Metab. 2015;17:742–50.
8. Neumiller JJ, Sonnett TE, Wood LD, Setter SM, Campbell RK. Pharmacology, efficacy and safety of liraglutide in the management of type 2 diabetes. Diabetes Metab Syndr Obes. 2010;3:215–26.
9. Knudsen LB, Nielsen PF, Huusfeldt PO, Johansen NL, Madsen K, Pedersen FZ, et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. J Med Chem. 2000;43:1664–9.
10. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, et al. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. Diabetes. 2004;53:1187–94.
11. Harrison LB, Mora PF, Clark GO, Lingvay I. Type 1 diabetes treatment beyond insulin: role of GLP-1 analogs. J Investig Med. 2013;61:40–4.
12. Kuhadiya ND, Malik R, Bellini NJ, Patterson JL, Traina A, Makdissi A, et al. Liraglutide as additional treatment to insulin in obese patients with type 1 diabetes mellitus. Endocr Pract. 2013;19:963–7.
13. Agersø H, Jensen LB, Elbrønd B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. Diabetologia. 2002;45:195–202.
14. Elbrønd B, Jakobsen G, Larsen S, Agersø H, Jensen LB, Rolan P, et al. Pharmacokinetics, pharmacodynamics, safety, and tolerability of a single-dose of NN2211, a long-acting glucagon-like peptide 1 derivative, in healthy male subjects. Diabetes Care. 2002;25:1398–404.
15. Damholt B, Golor G, Wierich W, Pedersen P, Ekblom M, Zdravkovic M. An open-label, parallel group study investigating the effects of age and gender on the pharmacokinetics of the once-daily glucagon-like peptide-1 analogue liraglutide. J Clin Pharmacol. 2006;46:635–41.
16. Irie S, Matsumura Y, Zdravkovic M, Jacobsen LV, Kageyama S. Tolerability, pharmacokinetics and pharmacodynamics of the once-daily human GLP-1 analog liraglutide in Japanese healthy subjects: a randomized, double-blind, placebo-controlled dose-escalation study. Int J Clin Pharmacol Ther. 2008;46:273–9.
17. Jiang J, Zhang J, Jacobsen LV, Hu P. The pharmacokinetics, pharmacodynamics, and tolerability of liraglutide, a once-daily human GLP-1 analogue, after multiple subcutaneous administration in healthy Chinese male subjects. J Clin Pharmacol. 2011;51:1620–7.
18. Flint A, Nazzal K, Jagielski P, Hindsberger C, Zdravkovic M. Influence of hepatic impairment on pharmacokinetics of the human GLP-1 analogue, liraglutide. Br J Clin Pharmacol. 2010;70:807–14.
19. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. Br J Clin Pharmacol. 2009;68:898–905.

20. Hermansen K, Bækdal TA, Düring M, Pietraszek A, Mortensen LS, Jørgensen H, et al. Liraglutide suppresses postprandial triglyceride and apolipoprotein B48 elevations after a fat-rich meal in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, cross-over trial. Diabetes Obes Metab. 2013;15:1040–8.
21. Ingwersen SH, Petri K, Tandon N, Yoon KH, Chen L, Vora J, et al. Liraglutide pharmacokinetics and dose-exposure response in Asian subjects with type 2 diabetes from China, India and South Korea. Diabetes Res Clin Pract. 2015;108:113–9.
22. Klein DJ, Battelino T, Chatterjee DJ, Jacobsen LV, Hale PM, Arslanian S, et al. Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Diabetes Technol Ther. 2014;16:679–87.
23. Morrow L, Hompesch M, Guthrie H, Chang D, Chatterjee DJ. Co-administration of liraglutide with insulin detemir demonstrates additive pharmacodynamic effects with no pharmacokinetic interaction. Diabetes Obes Metab. 2011;13:75–80.
24. Ingwersen SH, Khurana M, Madabushi R, Watson E, Jonker DM, Le Thi TD, et al. Dosing rationale for liraglutide in type 2 diabetes mellitus: a pharmacometric assessment. J Clin Pharmacol. 2012;52:1815–23.
25. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373:473–81.
26. Novo Nordisk. Victoza®, summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf. Accessed 19 May 2015.
27. Jacobsen LV, Flint A, Olsen AK, Ingwersen SH. Liraglutide in type 2 diabetes mellitus: clinical pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. doi:10.1007/s40262-015-0343-6. Epub 23 Nov 2015.
28. Frandsen CS, Dejgaard TF, Holst JJ, Andersen HU, Thorsteinsson B, Madsbad S. Twelve-week treatment with liraglutide as add-on to insulin in normal-weight patients with poorly controlled type 1 diabetes: a randomized, placebo-controlled, double-blind parallel study. Diabetes Care. 2015;38:2250–7.
29. Dejgaard TF, Frandsen CS, Hansen TS, Almdal T, Urhammer S, Pedersen-Bjergaard U, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2015;4:221–32.
30. Kuhadiya ND, Dhindsa S, Ghanim H, Mehta A, Makdissi A, Batra M, et al. Addition of liraglutide to insulin in patients with type 1 diabetes: a randomized placebo-controlled clinical trial of 12 weeks. Diabetes Care. doi:10.2337/dc15-1136. Epub 5 Apr 2016.