Efficacy and safety of lixisenatide in elderly (≥65 years old) and very elderly (≥75 years old) patients with type 2 diabetes: an analysis from the GetGoal phase III programme†

Denis Raccah1*
Patrick Miossec2
Virginie Esposito2
Elisabeth Niemoeller3
Meehyung Cho4
John Gerich5

1Department of Diabetology, University Hospital Sainte Marguerite, Marseille, France
2Sanofi R&D, Paris, France
3Sanofi R&D, Frankfurt am Main, Germany
4Sanofi R&D, Bridgewater, NJ, USA
5Department of Medicine, University of Rochester School of Medicine, Rochester, NY, USA

*Correspondence to: Denis Raccah, Service de Nutrition Endocrinologie, Maladies Metaboliques, Hôpital Sainte Marguerite, 270 Boulevard de Sainte Marguerite, 13009 Marseille, France. E-mail: denis.raccah@ap-hm.fr

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Abstract

Background The objective of this article is to evaluate the pharmacokinetics, efficacy and safety of lixisenatide (subcutaneous injection) in elderly (≥65 years old) and very elderly (≥75 years old) patients with type 2 diabetes mellitus.

Methods We conducted a phase I, single-centre, open-label study to evaluate the safety and pharmacokinetics of a single lixisenatide 20 μg dose and a pooled analysis of six randomized, placebo-controlled, phase III studies (12-month or 24-month duration) that evaluated glycaemic parameters and safety in patients receiving lixisenatide 20 μg once daily or placebo.

Results The pharmacokinetics study included 36 healthy subjects, including 18 elderly healthy subjects (≥65 years old) and 18 matched young healthy subjects (18–45 years old). The pooled analysis included 3188 patients, including 2565 patients <65 years old and 623 patients ≥65 years old (including 79 patients ≥75 years old). Mean exposure with lixisenatide 20 μg was ~30% higher in elderly than in young subjects, and the terminal half-life was prolonged by ~1.6 times. Maximum concentration (Cmax) and time to Cmax (tmax) were comparable in both groups. Equal numbers of elderly and young subjects reported treatment-emergent adverse events, the majority of which were gastrointestinal disorders. In the pooled analysis, lixisenatide 20 μg once daily provided significant reductions in HbA1c versus placebo for all age groups. There was a similar incidence of treatment-emergent adverse events across all age groups (range: 69–73%). The incidence of symptomatic hypoglycaemia was generally comparable between lixisenatide-treated and placebo-treated patients.

Conclusion These data suggest that lixisenatide is effective and well tolerated in elderly and very elderly patients with type 2 diabetes mellitus. © 2014 The Authors. Diabetes/Metabolism Research and Reviews published by John Wiley & Sons, Ltd.

Keywords elderly; efficacy; lixisenatide; pharmacokinetics; type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is a significant health issue in the ageing population. At least 20% of patients over 65 years of age now have T2DM, and this proportion is expected to rise rapidly over the coming decades [1]; there is also likely to be a large number of older people with undiagnosed diabetes [2–4]. Diabetes is a major cause of morbidity and mortality in the elderly; poor glycaemic control, as evidenced by high glycated haemoglobin (HbA1c), is a predictor of cardiovascular mortality and stroke in elderly people [1,4,5]. Furthermore, high HbA1c level is a significant risk factor for diabetic retinopathy and its progression [6,7], possibly associated with poor vision increasing the risk of falls. Acute diabetic complications, such as ketoacidosis or hyperosmolar coma, also increase with age [8,9]. In addition, studies have demonstrated that cognitive function is impaired in elderly patients with diabetes compared with age-matched nondiabetic patients and that T2DM is associated with an increased risk of Alzheimer’s disease and dementia [10,11]. Hypoglycaemia is a particular concern in elderly patients. Older people have diminished counterregulatory responses to hypoglycaemia and the risk of severe or fatal hypoglycaemia associated with oral anti-diabetic drugs (OADs), such as chlorpropamide and glyburide, and insulin increases with age [12,13]. The elderly are also more likely to be compromised by hypoglycaemic events, which can lead to dysrhythmias, dizziness, falls and confusion [14].

The management of elderly patients with T2DM is complex because of the clinical and functional heterogeneity of this population [1]. Older patients often have comorbidities requiring polypharmacy and may have a range of physical and/or cognitive impairments, all of which pose particular challenges [1,14]. Although the principles of managing elderly patients with T2DM are similar to those in younger patients, clinicians should pay special attention to possible side effects and drug interactions [14]. Notably, elderly patients with diabetes are at an increased risk of gastrointestinal (GI) side effects, including anorexia, nausea and abdominal discomfort [14]. As important pharmacokinetic and pharmacodynamic changes occur with advancing age [15], changes in drug absorption, distribution, metabolism and clearance must be carefully considered when prescribing anti-diabetic treatments or other medications in the elderly patient.

Guidelines published over the past decade generally distinguish the patient in good overall health, with a single disorder, and the frail or dependent patient, with multiple pathologies. Crucially, current guidelines allow for both clinical judgement and patient wishes, with the patient being acknowledged as an integral member of the team and empowered to take an active role in their treatment. Glycaemic targets need to be individualized in older patients, and this has been reflected in a number of different treatment guidelines that have been developed for managing diabetes in older adults [1,14,16–19]. A position statement of the American Diabetes Association and the European Association for the Study of Diabetes recommends a patient-centred approach, with a target HbA1c of <6.5% to 7.0% to prevent vascular complications over time, but less stringent HbA1c goals (7.5% to 8.0%) for patients with reduced life expectancy, higher cardiovascular disease burden and who are at risk for adverse events (AEs) from polypharmacy [14]. The European Diabetes Working Party for Older People recommend that, for frail patients (dependent; multisystem disease; care home residency, including those with dementia), the target HbA1c range is 7.6–8.5%, and for nonfrail patients, free of other major comorbidities, the target HbA1c range should be 7.0–7.5% [15]. With the exception of contraindications for renal and cardiac disorders with metformin and thiazolidinedione, pharmacological options for elderly patients are essentially the same as for younger patients [1]. Sulfonylureas, except chlorpropamide and glyburide [20], and insulin are widely prescribed to elderly patients as they are generally considered an effective and relatively safe option in this population. However, the risk for hypoglycaemia is clearly recognized, and this can make optimizing glycemic control a challenge, especially in the frail or very elderly [1,21].

Glucagon-like peptide-1 (GLP-1) receptor agonists are a relatively recent addition to the treatment options for T2DM and are recommended by the American Diabetes Association and the European Association for the Study of Diabetes as second-line (in combination with metformin) or third-line (in combination with OADs and/or basal insulin) treatment for T2DM [1,14]. The GLP-1 receptor agonists can further be characterized into short-acting and long-acting formulations, which have differential effects on their mechanism of action, ultimately resulting in differential effects on gastric emptying and fasting and postprandial glycaemia [22]. Overall, GLP-1 receptor agonists are associated with significant improvements in HbA1c, with a particularly profound effect on postprandial plasma glucose (PPG) having been observed with short-acting GLP-1 receptor agonists [22]. Importantly, GLP-1 receptor agonists have a glucose-dependent mechanism of action, meaning that there is minimal risk of hypoglycaemia [22], and beneficial effects on body weight [23], which may be advantageous in some older people with T2DM.

Lixisenatide is a once-daily prandial GLP-1 receptor agonist for the treatment of T2DM, administered via subcutaneous injection. In an extensive series of phase III trials known as the GetGoal clinical trial programme, lixisenatide 20 μg once daily, as monotherapy [24], in combination with OADs [25–29], or as add-on to basal

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insulin [30–32], produced significant reductions in HbA1c with limited risk of hypoglycaemia and a beneficial effect on body weight. To evaluate the safety and efficacy of lixisenatide in elderly patients, we conducted a phase I study of lixisenatide pharmacokinetics in elderly patients and performed an analysis of data from elderly patients with T2DM treated with lixisenatide in the phase III clinical trial programme. Here, we present the results from these analyses.

Materials and methods

Two separate analyses designed to evaluate the pharmacokinetics, efficacy and safety of lixisenatide in elderly (≥65 years of age) and very elderly (≥75 years of age) patients are reported. The phase I pharmacokinetic study and the individual studies included in this meta-analysis were approved by the local institutional review boards or ethics committees and were conducted in agreement with the Declaration of Helsinki and Good Clinical Practice guidelines.

Pharmacokinetic analysis

Study design

This was a phase I, single-centre, open-label study designed to evaluate the pharmacokinetics and tolerability of lixisenatide as a single 20 μg dose in elderly healthy subjects (≥65 years with at least 30% of subjects ≥75 years old) and matched young healthy subjects (age range 18–45 years old). Pharmacokinetic endpoints were lixisenatide maximum concentration (Cmax), time to Cmax (tmax), area under the time–concentration curve (AUClast and AUC), terminal half-life (t1/2), and safety (clinical, laboratory and electrocardiogram parameters, vital signs and AEs). Blood samples were collected predose and at: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h postdose after injection of study medication.

Statistical analysis

Lixisenatide pharmacokinetic parameters were summarized using descriptive statistics for each age group. For log-transformed Cmax, AUClast, AUC and t1/2, the age effect on a single dose of lixisenatide between elderly and young healthy groups was analysed using a linear fixed-effects model with fixed terms for age group and gender and with weight as covariates. Estimates and 95% confidence intervals (CIs) for the geometric means ratio (point estimate) of the elderly group versus the young group were provided for Cmax, AUClast, AUC and t1/2. The safety analysis was conducted on all subjects who received the study drug. The on-treatment phase was defined as the time from the single investigational product administration of lixisenatide 20 μg up to the end of day 2 (included) for each age group.

Phase III pooled analysis

Design

An analysis of pooled data from the main treatment period (24 weeks) of six placebo-controlled phase III trials from the lixisenatide GetGoal programme [24,25,28–30,32] (Table 1) conducted to evaluate the efficacy and safety of lixisenatide in elderly patients with T2DM is presented. Patients were categorized as elderly (≥65 years of age) and very elderly (≥75 years of age). Efficacy was assessed using on-treatment measurements for the modified intent-to-treat population, defined as all randomized patients exposed to double-blind treatment and who had both a baseline assessment and a postbaseline assessment of efficacy variables. Safety was assessed for the safety population (all randomized patients exposed to double-blind treatment) by treatment-emergent AEs (TEAEs) for the main treatment period, categorized by system organ class and preferred terms by age group categories (<65, ≥65 years and <75, ≥75 years old). Symptomatic hypoglycaemia was evaluated according to background treatment regimen and was defined as an event with clinical symptoms associated with plasma glucose <3.3 mmol/L (60 mg/dL) or with prompt recovery after oral carbohydrate, intravenous

Table 1. GetGoal studies used for the phase III pooled analysis

| Study number | Study name | Description |
|--------------|------------|-------------|
| NCT00688701  | GetGoal-Mono [24] | Lixisenatide monotherapy versus placebo in patients not treated with anti-diabetic agents. 12-week randomized controlled trial |
| NCT00712673  | GetGoal-M [25] | Lixisenatide versus placebo added to existing MET. 24-week randomized controlled trial |
| NCT00763451  | GetGoal-F1 [29] | Lixisenatide versus placebo added to existing MET. 24-week randomized, controlled trial |
| NCT00713830  | GetGoal-S [28] | Lixisenatide versus placebo added to existing SU ± MET. 24-week randomized, controlled trial |
| NCT00763451  | GetGoal-L [32] | Lixisenatide versus placebo added to existing basal insulin ± MET. 24-week randomized, controlled trial |
| NCT00866658  | GetGoal-L-Asia [30] | Lixisenatide versus placebo added to existing basal insulin ± SU. 24-week randomized, controlled trial |

The main treatment period was 24 weeks in all studies except GetGoal-Mono, which had a main treatment period of 12 weeks. MET, metformin; SU, sulphonylurea.

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glucose or glucagon administration if no plasma glucose measurement was available. Severe symptomatic hypoglycaemia was defined as symptomatic hypoglycaemia that required the assistance of another person and that was associated either with a plasma glucose level <2.0 mmol/L (36 mg/dL) or, if no plasma glucose measurement was obtainable, with prompt recovery with carbohydrate, intravenous glucose or glucagon injection.

**Statistical analysis**

Efficacy was assessed by least squares (LS) mean difference (lixisenatide versus placebo) in HbA1c change from baseline to the end of the main treatment period in the subgroup analysis by age group categories via a meta-analysis using the inverse of variance as weights across the six included studies. LS mean difference between treatment groups within each age group category for a study was obtained from an analysis of covariance with treatment group, randomization strata, country, age group categories and treatment by age group interaction as fixed effects and baseline HbA1c as covariates.

**Results**

**Pharmacokinetics study**

A total of 36 subjects (elderly, \( n = 18 \); young, \( n = 18 \)) were enrolled and all subjects received the study drug.

**Pharmacokinetics results**

The mean exposure in elderly subjects was higher than in young subjects [point estimates for AUC_{last} and AUC were 1.26 (90% CI: 1.03–1.55) and 1.29 (90% CI: 1.06–1.57), respectively]. The \( t_{1/2} \) was prolonged by approximately 1.6 times in elderly subjects compared with young subjects [point estimate for \( t_{1/2} \) was 1.57 (90% CI: 1.41–1.75)]. \( C_{\text{max}} \) and \( t_{\text{max}} \) were comparable in both groups (Table 2).

**Safety results**

There were no serious AEs or severe TEAEs and no discontinuation because of TEAEs during this study. Of the 36 subjects enrolled, the same number of elderly (15 of 18) and young subjects (16 of 18) reported TEAEs. The majority of TEAEs reported were GI disorders, including nausea (22 of 36 subjects; 8 elderly subjects and 14 young subjects) and vomiting (13 of 36 subjects; 9 elderly subjects and 4 young subjects). The other more frequently reported TEAEs were headache (9 of 36 subjects; 8 elderly subjects and 1 young subject) and decrease in appetite (6 of 36 subjects; 1 elderly subject and 5 young subjects). All TEAEs reported were short-lasting (rarely up to 24 h) and of mild or moderate intensity, with no corrective treatment given. There were no clinically relevant abnormalities in the clinical laboratory evaluations. No significant findings were reported in vital signs and electrocardiogram parameters, with no subjects presenting with prolonged QTc (>450 ms for men and >470 ms for women) or an increase in QTc from baseline of more than 60 ms.

**Phase III pooled analysis**

A total of 3188 patients were randomized and exposed (safety population) in six placebo-controlled phase III trials (lixisenatide \( n = 2127 \), placebo \( n = 1061 \)). This included 2565 patients <65 years of age and 623 patients \( \geq 65 \) years of age. A total of 79 patients were \( \geq 75 \) years of age.

**Analysis of efficacy**

Meta-analysis of the pooled data for change in HbA1c to the end of main treatment period demonstrated greater reductions from baseline with lixisenatide compared with placebo for all age groups assessed (Figure 1A). LS mean treatment difference (±standard error) in HbA1c was \(-0.56\% \pm 0.039\%\), \(-0.66\% \pm 0.076\%\), \(-0.58\% \pm 0.035\%\) and \(-0.50\% \pm 0.241\%\) for patients aged <65, \( \geq 65, <75 \) and \( \geq 75 \) years, respectively (Figure 1B). In each of the individual studies, lixisenatide also showed consistent improvements in HbA1c over placebo for all age groups, irrespective of background treatment (data not shown).

**Analysis of safety and tolerability**

There was a similar incidence of TEAEs for lixisenatide across all age groups (range: 69–73%) for the main treatment

| Table 2. Lixisenatide pharmacokinetics parameters |
|-----------------------------------------------|
| **Elderly subjects (\( n = 18 \))** | **Young subjects (\( n = 18 \))** | **Point estimate (95% CI)** |
| \( C_{\text{max}} \) (pg/mL), mean ± SD | 173 ± 46.1 | 179 ± 50.0 | 0.94 (0.81, 1.09) |
| \( t_{\text{max}} \) (h), median* | 1.75 (1.00–3.02) | 1.51 (0.5–3.0) | NE |
| \( t_{\text{1/2}} \) (h), mean ± SD | 2.83 ± 0.61 | 1.77 ± 0.38 | 1.57 (1.41, 1.75) |
| AUC_{last} (pg.h/mL), mean ± SD | 970 ± 394 | 733 ± 291 | 1.26 (1.03, 1.55) |
| AUC (pg.hr/mL), mean ± SD | 1060 ± 440 | 776 ± 297 | 1.29 (1.06, 1.57) |

CI, confidence interval; \( C_{\text{max}} \), maximum concentration; SD, standard deviation; \( t_{\text{max}} \), time to \( C_{\text{max}} \); \( t_{\text{1/2}} \), terminal half-life; AUC, area under the curve; NE, not evaluated.

*Median (minimum–maximum).
period. The most common TEAEs were GI disorders. The overall incidence of GI disorders was also similar for lixisenatide across all age groups (range: 41–46%). Nausea was the most common GI TEAE with lixisenatide across all age groups (range: 26–33%) (Table 3).

The highest incidences of symptomatic hypoglycaemia were seen in patients treated with insulin with or without OADs as background therapy. Within each background treatment regimen for the main treatment period, the incidence of symptomatic hypoglycaemia was generally comparable between age groups for lixisenatide-treated patients; only in patients treated with a combination of basal insulin and sulphonylurea was the incidence higher in patients receiving lixisenatide versus placebo (Table 4).

A total of five patients treated with lixisenatide reported severe symptomatic hypoglycaemia during the main treatment period. None of the patients was elderly.

Discussion

With the ageing population and the increasing incidence of diabetes, evaluation of the efficacy and safety of new anti-diabetic drugs in elderly patients is essential. Management of older patients with diabetes can be particularly challenging, especially in the presence of comorbidities and polypharmacy [14]. Despite this clear and growing need, a limited number of guidelines are specifically targeted towards the needs of older patients.

In our pooled analysis of the phase III trials, lixisenatide produced significant reductions in HbA1c versus placebo in all age groups studied. Placebo-adjusted reductions in HbA1c in elderly (≥65 years old) and very elderly (≥75 years old) patients were comparable with those observed in the younger age groups (<65 and <75 years old), demonstrating that the efficacy of lixisenatide is maintained in patients that may have more severe β-cell dysfunction. The clinical course of T2DM is characterized by a progressive decline in β-cell mass and function [33]. Studies also suggest that ageing itself is associated with a progressive decline in β-cell function, with a corresponding reduction in insulin release [34–36]. Older patients with a longer duration of diabetes are therefore likely to have a more severe β-cell dysfunction.

Table 3. Treatment-emergent adverse events (safety population)

| Age          | <65 years | ≥65 years | <75 years | ≥75 years |
|--------------|-----------|-----------|-----------|-----------|
|              | PBO       | Lixisenatide | PBO       | Lixisenatide | PBO       | Lixisenatide | PBO       | Lixisenatide |
|              | (n = 817) | (n = 1748) | (n = 244) | (n = 379) | (n = 1030) | (n = 2079) | (n = 31)  | (n = 48)    |
| Any TEAE, n (%) | 516 (63.2) | 1203 (68.8) | 144 (59.0) | 272 (71.8) | 645 (62.6) | 1440 (69.3) | 15 (48.4) | 35 (72.9)   |
| GI disorders, n (%) | 170 (20.8) | 715 (40.9) | 40 (16.4) | 164 (43.3) | 205 (19.9) | 857 (41.2) | 5 (16.1) | 22 (45.8)   |
| Nausea, n (%) | 47 (5.8)  | 446 (25.5) | 19 (7.8)  | 110 (29.0) | 64 (6.2)  | 540 (26.0) | 2 (6.5)  | 16 (33.3)   |
| Vomiting, n (%) | 13 (1.6)  | 170 (9.7)  | 6 (2.5)   | 54 (14.2)  | 19 (1.8)  | 218 (10.5) | 0       | 6 (12.5)    |
| Diarrhoea, n (%) | 53 (6.5)  | 141 (8.1)  | 11 (4.5)  | 35 (9.2)   | 64 (6.2)  | 173 (8.3)  | 0       | 3 (6.3)     |
| GI/abdominal pain, n (%) | 28 (3.4)  | 71 (4.1)   | 4 (1.6)   | 18 (4.7)   | 32 (3.1)  | 88 (4.2)   | 0       | 1 (2.1)     |
| Dyspepsia, n (%) | 3 (0.4)   | 62 (3.5)   | 0         | 24 (6.3)   | 3 (0.3)   | 84 (4.0)   | 0       | 2 (4.2)     |

PBO, placebo; TEAE, treatment-emergent adverse event; GI, gastrointestinal.

Data from the main treatment period of the included studies [GetGoal-Mono (12 weeks) and GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-L and GetGoal-L-Asia (all 24 weeks)] – safety population.
and higher PPG levels compared with their younger counterparts. Interestingly, unlike long-acting GLP-1 receptor agonists, which lower fasting plasma glucose primarily via stimulation of insulin secretion from β-cells, short-acting agents function primarily to lower PPG levels via a delay in gastric emptying [37]. It follows, therefore, that short-acting prandial agents, such as lixisenatide, will demonstrate efficacy even in patients with a comparatively low rate of β-cell function, such as older patients and those with a longer duration of diabetes.

Regarding the pharmacokinetic parameters, the mean exposure with lixisenatide was ~30% higher and the $t_{1/2}$ was prolonged by ~1.6 times in elderly subjects compared with young subjects. However, $C_{\text{max}}$ and $t_{\text{max}}$ were comparable in both groups, and this finding did not increase the risk of AEs. Indeed, the incidence of TEAEs was similar across the different age groups in both the pharmacokinetics and the pooled phase III analysis, highlighting that the tolerability profile of lixisenatide does not worsen with age. AEs are of particular relevance in elderly patients as they may be more frequent and/or more severe in this population. In our analyses, despite the higher lixisenatide exposure observed in elderly versus younger patients, this did not translate into an increased incidence of TEAEs, and the overall incidence of TEAEs for lixisenatide was similar across the different age groups. The most frequent TEAEs in both younger and elderly patients were GI disorders (mainly nausea and vomiting), which is consistent with the known tolerability profile of lixisenatide and other GLP-1 receptor agonists [24–32,38,39]. Crucially, the incidence of TEAEs was not significantly increased in older patients, which is an important drug safety issue in this population with this type of drug. Avoidance of hypoglycaemia is a particularly important issue in the elderly as these patients are more susceptible to its consequences than younger patients [13]. The incidence of symptomatic hypoglycaemia with lixisenatide as monotherapy was generally comparable across the different age groups, with no differences versus placebo. In combination with metformin, the incidence was low and generally similar across age groups. As would be expected, the incidence of symptomatic hypoglycaemia in all age groups was increased in patients receiving background basal insulin therapy. This was due to the background basal insulin, as evidenced by the similar incidences in the placebo and lixisenatide groups in both younger and elderly patients. A higher incidence of hypoglycaemia versus placebo was observed in combination with basal insulin + sulphonylureas in all age groups and with sulphonylureas alone in most age groups; these findings are not unexpected given the propensity of both insulin and sulphonylureas for hypoglycaemia [1], and, importantly, the incidence of hypoglycaemia was not increased in older patients. The effect of ageing may also contribute to severe hypoglycaemia, and both insulin and sulphonylureas (alone or in combination) should, therefore, be used with caution in the elderly [1,14]. Importantly, in general, the incidence of severe hypoglycaemia was low. Only 5/2127 lixisenatide patients reported severe hypoglycaemia, and none of these was elderly. A number of factors predispose elderly patients with T2DM to hypoglycaemia, and these should be considered when evaluating hypoglycaemic risk. These include poor or erratic nutritional intake, changes in mental status that impair perception or response to hypoglycaemia, increased polypharmacy and noncompliance to medication and impaired renal or hepatic metabolism [40]. Dependence or isolation that limits receipt of early treatment for hypoglycaemia and the presence of comorbid conditions that can mask or lead to misdiagnosis of hypoglycaemic symptoms are also important considerations when treating patients with T2DM.

Table 4. Incidence of symptomatic hypoglycaemia by background treatment (safety population)

| Age | Treatment background | <65 years | ≥65 years | <75 years | ≥75 years |
|-----|----------------------|-----------|-----------|-----------|-----------|
|     | PBO                  | Lixisenatide | PBO      | Lixisenatide | PBO     | Lixisenatide | PBO | Lixisenatide |
|     | n/N (%)              | n/N (%)    | n/N (%)  | n/N (%)    | n/N (%) | n/N (%)     | n/N (%) | n/N (%)     |
| Overall | Monotherapy<sup>a</sup> | 1/104 (1.0) | 4/211 (1.9) | 1/18 (5.6) | 0/28 (0) | 1/117 (0.9) | 4/233 (1.7) | 1/5 (20.0) | 0/6 (0) |
|       | MET<sup>b</sup>      | 2/258 (0.8) | 21/726 (2.9) | 0/72 (0)   | 5/106 (4.7) | 2/321 (0.6) | 25/822 (3.0) | 0/9 (0) | 1/10 (10.0) |
|       | SU alone<sup>c</sup> | 0/33 (0)   | 10/61 (16.4) | 4/13 (30.8) | 6/27 (22.2) | 4/44 (9.1)   | 15/85 (17.6) | 0/2 (0) | 1/3 (33.3) |
|       | SU + MET<sup>d</sup> | 24/178 (13.5) | 52/382 (13.6) | 7/61 (11.5) | 20/104 (19.2) | 30/232 (12.9) | 72/474 (15.2) | 1/7 (14.3) | 0/12 (0) |
|       | Basal insulin<sup>e</sup> | 9/30 (30.0) | 10/34 (29.4) | 4/16 (25.0) | 5/12 (41.7) | 13/44 (29.5) | 15/44 (34.1) | 0/2 (0) | 0/2 (0) |
|       | Basal insulin + SU<sup>f</sup> | 29/131 (22.1) | 72/258 (27.9) | 7/36 (19.4) | 19/70 (27.1) | 34/163 (20.9) | 89/319 (27.9) | 2/4 (50.0) | 2/9 (22.2) |
|       | Basal insulin + SU<sup<g</sup> | 15/83 (18.1) | 34/76 (44.7) | 9/28 (32.1) | 17/32 (53.1) | 24/109 (22.0) | 49/102 (48.0) | 0/2 (0) | 2/6 (33.3) |

PBO, placebo; MET, metformin; SU, sulphonylurea.

Data from the main treatment period of included studies:
<sup>a</sup>GetGoal-Mono (12 weeks) and
<sup>b</sup>GetGoal-M and -F1,
<sup>c</sup>GetGoal-S,
<sup>d</sup>GetGoal-L-Asia and
<sup>e</sup>GetGoal-L (all 24 weeks) – safety population.

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the elderly patient with diabetes. One of the main challenges in treating the elderly diabetic patient is that hypoglycaemia occurs more frequently as glycaemic targets are lowered, and this is especially applicable to the use of nonglucose-dependent glucose-lowering drugs such as sulphonylureas and insulin [14]. The use of glucose-dependent anti-hyperglycaemic agents, such as lixisenatide, circumvents this issue, as shown in this analysis by the minimal hypoglycaemic risk across all age groups when lixisenatide is given as monotherapy or in combination with metformin.

There are some limitations to this analysis that should be considered. These analyses in elderly patients were performed in a post-hoc manner, and the pooled safety analysis included patients from different studies with similar treatment duration. This included two studies with different treatment allocations in order to allow a broad patient population for evaluation. The assessment for the difference between treatment groups from the pooled safety summaries should, therefore, be made cautiously. The different studies also included patients treated with a range of different background therapies, and although an analysis of hypoglycaemia for these different background therapies was reported, this was not conducted for HbA1c, and results for improvement in glycaemic control are therefore not applicable to individual treatment regimens. Patient numbers in the ≥75 years age group were also low, particularly in the analysis of hypoglycaemia by treatment background, and these results may not be applicable to the general very elderly population, particularly frail patients. Furthermore, it must be recognized that elderly patients recruited to clinical trials may be healthier than the general population, because of exclusion criteria applied in clinical studies, so trial results should be interpreted with caution.

Despite these limitations, our results provide important insights into the effects of lixisenatide across different age groups and support its safety and efficacy in both elderly and very elderly patients. With the availability of this once-daily GLP-1 receptor agonist, it will be possible to obtain additional control of hyperglycaemia in elderly patients with minimal risk of hypoglycaemia in combination with metformin and with minimal increased risk of hypoglycaemia as add-on to insulin ± OADs and sulphonylureas ± OADs.

Conclusion

The number of elderly people with T2DM is increasing; therefore, the evaluation of the efficacy and safety of anti-diabetic drugs for vulnerable patients is essential. In this analysis, lixisenatide provided significant improvements in glycaemic control versus placebo in elderly (≥65 years old) and very elderly (≥75 years old) patients with T2DM, comparable with that observed in younger patients. Overall, the safety profile of lixisenatide was comparable across age groups, with similar incidences of TEAEs and GI events. The incidence of symptomatic hypoglycaemia was generally comparable between lixisenatide-treated and placebo-treated patients, except in patients receiving insulin or sulphonylureas as background treatment who experienced a higher incidence of symptomatic hypoglycaemia with lixisenatide compared with placebo, with no relevant differences being observed between different age groups. These data suggest that the once-daily prandial GLP-1 receptor agonist lixisenatide is an effective and well-tolerated treatment option for elderly and very elderly patients with T2DM.

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Author contributions

Denis Raccah: Analysis and interpretation of data and preparation of manuscript
Patrick Miossec: Study concept and design, analysis and interpretation of data and preparation of manuscript
Virginie Esposito: Study concept and design, analysis and interpretation of data and preparation of manuscript
Elisabeth Niemoeller: Study concept and design, analysis and interpretation of data and preparation of manuscript
Meehyung Cho: Study design, statistical analysis and interpretation of results for phase III data and preparation of manuscript
John Gerich: Study design, data analysis and manuscript preparation

Conflicts of interest

Denis Raccah: Speaker for symposia and consultant for Novo Nordisk, Lilly, Sanofi, Merck Serono, MSD, BMS and Medtronic
Patrick Miossec: Sanofi employee
Virginie Esposito: Sanofi employee
Elisabeth Niemoeller: Sanofi employee
Meehyung Cho: Sanofi employee
John Gerich: Advisory Boards and Speakers Bureau for Eli Lilly, Merck, Sanofi, Boehringer Ingelheim, Janssen, BMS and AstraZeneca

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References

1. American Diabetes Association. Standards of medical care in diabetes – 2012. Diabetes Care 2012; 35(Suppl 1): S1–S63.
2. Men lensky GS, Tessier D. Diabetes in elderly adults. J Gerontol A Biol Sci Med Sci 2001; 56(1): M5–M13.
3. Chau D, Edelman SV. Clinical management of diabetes in the elderly. Clin Diabetes 2001; 19: 172–175.
4. Selvin E. The burden and treatment of diabetes in elderly individuals in the US. Diabetes Care 2006; 29: 2415–2419.
5. Bethel MA, Sloan FA, Belsky D, et al. Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. Arch Intern Med 2007; 167(9): 921–927.
6. Li X, Wang Z. Prevalence and incidence of retinopathy in elderly diabetic patients receiving early diagnosis and treatment. Exp Ther Med 2013; 5(5): 1393–1396.
7. Kato S, Takemori M, Kitano S, et al. Retinopathy in older patients with diabetes mellitus. Intrarenal Res Clin Pract 2002; 58(3): 187–192.
8. Westerberg DP. Diabetic ketoacidosis: evaluation and treatment. Am Fam Physician 2012; 87(5): 337–346.
9. American Diabetes Association. Hyperglycemic crisis in diabetes. Diabetes Care 2004; 27(Suppl 1): S94–S102.
10. Strachan MW, Reynolds RM, Marioni RE, et al. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol 2011; 7(2): 108–114.
11. Biessels GJ, Kappelle LJ. Increased risk of Alzheimer’s disease in type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? Biochem Soc Trans 2005; 33(Pt 5): 1041–1044.
12. Meineilly GS, Cheung E, Tuokko H. Counterregulatory hormone responses to hyperglycemia in the elderly patient with diabetes. Diabetes 1994; 43(3): 403–410.
13. Zammit NF, Frierson BM. Hypoglycemia in type 2 diabetes. Diabetes Care 2005; 28(12): 2948–2961.
14. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35(6): 1364–1379.
15. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 2004; 57(1): 6–14.
16. Sinclair AJ, Paolillo G, Castro M, et al. European Diabetes Working Party for Older People 2011. clinical guidelines for type 2 diabetes mellitus. Diabetes Metab 2011; 37(Suppl 3): S27–S38.
17. Brown AF, Mangione CM, Saliba D, et al. Guidelines for improving care of the older person with diabetes mellitus. J Am Geriatr Soc 2003; 51(5 Suppl Guidelines): S265–S280.
18. Koch L. Diabetes: individualized HbA1c targets in elderly patients with T2DM. Nat Rev Endocrinol 2013; 9(8): 440.
19. American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes Mellitus, Moreno G, Mangione CM, Kimbro L, Vaisberg E. Guidelines abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 update. J Am Geriatr Soc 2013; 61(11): 2020–2026.
20. The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012; 60(4): 616–631.
21. Ober SK, Watts S, Lawrence RH. Insulin use in elderly diabetic patients. Clin Interv Aging 2006; 1(2): 107–113.
22. Fineman MS, Cirincione BB, Maggs D, DiMatteo MR. The relative differential effects on fasting and postprandial glucose. Diabetes Obes Metab 2012; 14(8): 675–688.
23. Garber AJ. Novel GLP-1 receptor agonists for diabetes. Expert Opin Investig Drugs 2012; 21(1): 45–57.
24. Fonseca VA, Alvarado-Ruiz R, Raccah D, et al. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). Diabetes Care 2012; 35(6): 1225–1231.
25. Ahrén B, Dimas A, Miossec P, Saubadu S, Aronson R. Efficacy and safety of lixisenatide once daily morning or evening injections in type 2 diabetes inadequately controlled on basal insulin: a 24-week, randomized, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). Diabetes Care 2013; 36(9): 2497–2503.
26. Butler AE, Janson J, Bonner-Weiser S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003; 52(1): 102–110.
27. Iozzo P, Beck-Nielson H, Laakso M, Smith U, Yki-Järvinen H, Ferrannini E. Independent influence of age on basal insulin secretion in nondiabetic humans. European Group for the Study of Insulin Resistance. J Clin Endocrinol Metab 1999; 84(3): 863–868.
28. Chiu KC, Lee NP, Cohan P, Chuang LM. Beta cell function declines with age in glucose tolerant Caucasians. Clin Endocrinol (Oxf) 2006; 55(3): 311–315.
29. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003; 46(1): 3–19.
30. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012; 8(12): 728–742.
31. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liarglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label, active-controlled study (GetGoal-X). Diabetes Care 2013; 36(10): 2945–2951.
32. Ratner R, Hanyefield M, Shamanna P, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care 2013; 36(10): 2945–2951.
33. Butler AE, Janson J, Bonner-Weiser S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003; 52(1): 102–110.
34. Iozzo P, Beck-Nielson H, Laakso M, Smith U, Yki-Järvinen H, Ferrannini E. Independent influence of age on basal insulin secretion in nondiabetic humans. European Group for the Study of Insulin Resistance. J Clin Endocrinol Metab 1999; 84(3): 863–868.
35. Chiu KC, Lee NP, Cohan P, Chuang LM. Beta cell function declines with age in glucose tolerant Caucasians. Clin Endocrinol (Oxf) 2006; 55(3): 311–315.
36. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003; 46(1): 3–19.
37. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012; 8(12): 728–742.
38. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liarglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013; 381(9861): 117–124.
39. Favel BA, McDaniel DL, Ross RM, Moores KG, Starry MJ. Specific considerations for treatment of type 2 diabetes mellitus in the elderly. Am J Health Syst Pharm 2011; 68(6): 500–509.