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Efficacy of lixisenatide in patients with type 2 diabetes: A post hoc analysis of patients with diverse β-cell function in the GetGoal-M and GetGoal-S trials

Daisuke Yabe [a,b,c,*], Anu Ambos [d], Bertrand Cariou [e], Lea Duvnjak [f], Marc Evans [g], Guillermo González-Gálvez [h], Jay Lin [i], Elena V. Nikonova [j], Pedro de Pablos-Velasco [k], Jean-François Yale [l], Bo Ahrén [m]

[a] Kansai Electric Power Hospital, 2-1-7 Fukushima, Fukushima-ku, Osaka 553-0003, Japan
[b] Kansai Electric Power Medical Research Institute, 1-5-6 Minatojimaminamimachi, Chuo-ku, Kobe 650-0047, Japan
[c] Kobe University Graduate School of Medicine, 1-5-6 Minatojimaminamimachi, Chuo-ku, Kobe 650-0047, Japan
[d] North Estonia Medical Center, 19 Sütiste Street, 13419 Tallinn, Estonia
[e] The Thorax Institute, CHU Nantes, Boulevard Jacques Monod, F-44093 Nantes, France
[f] Vuk Vrhovac Clinic–Merkur University Hospital, University of Zagreb, Dugi dol 4a, 10000 Zagreb, Croatia
[g] University Hospital Llandough, Penlan Road Llandough, CF64 2XX, UK
[h] Jalisco Institute of Diabetes and Obesity Research SC, Morelos 1952, Guadalajara, CP 44600, Mexico
[i] Novosys Health, 7 Crestmont Court, Flemington, NJ 08822, USA
[j] Artech Information Systems, LLC, 360 Mt. Kemble Ave. #2000, Morristown, NJ 07960, USA
[k] Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria, Barranco de la Ballena sn, 35010 Las Palmas de Gran Canaria, Spain
[l] McGill University, 687 Pine Avenue West, Montréal, QC H3A 1A1, Canada
[m] Lund University, Sölvegatan 19, SE-22184 Lund, Sweden

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ABSTRACT

Aims: To evaluate the impact of β-cell function on the efficacy of lixisenatide, a once-daily prandial glucagon-like peptide-1 receptor agonist, in patients with type 2 diabetes (T2D).
Materials and methods: In this post hoc analysis, patients from the Phase 3 GetGoal-M and GetGoal-S clinical trials randomized to lixisenatide 20 μg once daily were stratified into quartiles by baseline β-cell function, as measured by the secretory units of islet in transplantation (SUIT) index.
Results: Patients ($N = 437$) were distributed evenly among SUIT index quartiles 1 to 4 (lowest to highest β-cell function). Clinical outcomes improved from baseline across all SUIT quartiles; mean changes at week 24 were: glycated hemoglobin (HbA1c; % [mmol/mol]), −0.99 (−10.8), −0.87 (−9.5), −0.86 (−9.4), −0.83 (−9.1); and postprandial plasma glucose (PPG; mmol/L), −7.9, −5.6, −5.5, −4.3 (overall effect $P < 0.0001$). Furthermore, postprandial glucagon was reduced in all SUIT quartiles, while insulinogenic index improved only in patients with higher baseline SUIT (overall effect $P = 0.0286$). No severe symptomatic hypoglycemic events were reported.
Conclusions: Lixisenatide treatment resulted in reductions in HbA1c and PPG levels across all SUIT quartiles. This suggests that non-insulin-related actions of lixisenatide contribute to improved glycemic control in T2D.

Conflicts of interest: D.Y. has received funding from Novartis, Novo Nordisk and Sanofi, and has participated in speakers bureaus for Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Takeda Pharmaceuticals. A.A. has nothing to disclose. B.C. has served as a consultant and/or on advisory panels for Amgen, AstraZeneca, Debiopharm, Janssen, Eli Lilly, Genfit, Novo Nordisk, Regeneron Pharmaceuticals Inc. and Takeda, and has received research funding from Sanofi. L.D. has served on advisory panels for AstraZeneca, has served as a board member for Eli Lilly and Novo Nordisk, and has acted as a consultant for Merck Sharp & Dohme and Novartis. M.E. has served as a consultant for Janssen Pharmaceuticals, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi. G.G-G. has served on advisory panels for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen Pharmaceuticals, Merck, Novo Nordisk and Sanofi. J.L. is an employee of Novosys Health, which received funding for the study from Sanofi. E.V.N. is an employee of Artech Information Systems, LLC, under contract with Sanofi as a Clinical Data Associate. P.dP-V. has served on advisory panels for AstraZeneca, Boehringer Ingelheim and Sanofi, and has served on speakers' bureaus for Bristol-Myers Squibb, Eli Lilly, Novartis and Sanofi. J-F.Y. has served on advisory panels for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Pharmaceuticals, Merck, Novo Nordisk and Sanofi, has received research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Pharmaceuticals, Medtronic, Merck and Novo Nordisk, and has participated in speakers' bureaus for Abbott Diabetes Care, AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen Pharmaceuticals, Merck, Novo Nordisk and Sanofi. B.A. has received honoraria for lecturing and/or consultancy from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novartis, Novo Nordisk, Sanofi and Takeda.

Clinical trial registry: GetGoal-M (NCT00712673) and GetGoal-S (NCT00713830).

* Corresponding author at: Center for Diabetes, Endocrinology and Metabolism, Kansai Electric Power Hospital, 2-1-7 Fukushima-ku, Osaka, 553-0003, Japan. Tel.: +81 6 6458 5821; fax: +81 6 6458 6994.
E-mail addresses: ydaisuke-kyoto@umin.ac.jp (D. Yabe), Anu.Ambos@regionaalhaigla.ee (A. Ambos), Bertrand.Cariou@univ-nantes.fr (B. Cariou), lduvnjak@idb.hr (L. Duvnjak), marcevans4@sky.com (M. Evans), doctorggg@gmail.com (G. González-Gálvez), jay.lin@novosyshealth.com (J. Lin), Elena.Nikonova@sanofi.com (E.V. Nikonova), pablos.velasco@ulpgc.es (P. de Pablos-Velasco), jean-francois.yale@mcgill.ca (J-F. Yale), bo.ahren@med.lu.se (B. Ahrén).

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1. Introduction

As β-cell function declines and type 2 diabetes (T2D) progresses, oral antihyperglycemic drugs (OADs) become insufficient and the addition of other antihyperglycemic agents is required to maintain glycemic control (Garber et al., 2013; Rydén et al., 2007). Studies have indicated that adjunctive incretin-based agents, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), can help patients successfully achieve glycemic targets while potentially providing β-cell function benefits (Charbonnel & Cariou, 2011; Garber, 2010; Shomali, 2011). GLP-1 is a naturally occurring peptide that is released within minutes of eating a meal, and is known to suppress glucagon secretion from pancreatic α-cells and stimulate insulin secretion by pancreatic β-cells in a glucose-dependent manner (Drucker, 2013; Holst, 2007; Nauck, Vardarli, Deacon, Holst, & Meier, 2011; Seino, Fukushima, & Yabe, 2010). GLP-1 RA therapies potentiate activity at GLP-1 receptors and therefore mimic the effects of endogenous GLP-1, thereby stimulating glucose-dependent insulin release and suppressing glucagon secretion, in addition to promoting the delay of gastric emptying (Meier, 2012). Due to the varying mechanisms of action associated with some GLP-1 RAs, such as non-insulinotropic gastric emptying in the case of short-acting GLP-1 RAs, it has been postulated that such therapies could be efficacious regardless of β-cell function (Meier, 2012; Yabe & Seino, 2014); however, this is yet to be established in a clinical setting.

Lixisenatide is a once-daily prandial GLP-1 RA for the treatment of patients with T2D. Lixisenatide exerts insulinotropic effects and is associated with a significant delay in gastric emptying (Ahrén, Leguizamo, Miossec, Saubadu, & Aronson, 2013; Fonseca et al., 2012; Petersen, Knop, & Christensen, 2013; Riddle, Aronson, et al., 2013; Riddle, Forst, et al., 2013; Seino, Min, Niemoeller, & Takami, 2012). In preclinical studies, lixisenatide reduced the proportion of β-cells undergoing apoptosis and prevented insulin depletion following lipotoxic stress (Tews, Werner, & Eckel, 2008; Werner et al., 2008), although the β-cell protective effects of lixisenatide are yet to be demonstrated in clinical studies. Treatment of T2D with lixisenatide significantly improves levels of glycated hemoglobin (HbA1c), and is associated with pronounced reductions in postprandial plasma glucose (PPG) (Ahrén et al., 2013). The significantly improved control of PPG excursions seen with lixisenatide is likely a result of prolonged glucose absorption caused by delayed gastric emptying (Lorenz et al., 2013). However, the relative contributions of β-cell-dependent and -independent mechanisms towards the improved glycemic control demonstrated by lixisenatide have yet to be established.

The Phase 3 GetGoal clinical trial program evaluated the use of lixisenatide in combination with OADs and/or basal insulin in adult patients with T2D. It was reported that lixisenatide improves glycemic control and has a favorable tolerability profile and acceptable adverse event frequency, supporting lixisenatide use for the treatment of T2D (Ahrén et al., 2013; Fonseca et al., 2012; Pinget et al., 2013; Riddle, Aronson, et al., 2013; Riddle, Forst, et al., 2013; Rosenstock et al., 2013; Seino et al., 2012).

As β-cell function varied in the GetGoal clinical trial program due to the different patient populations evaluated, it allowed us to evaluate the efficacy and safety of lixisenatide treatment plus OADs (metformin and/or a sulfonylurea [SU]) in patients with T2D and varying levels of β-cell function. In this study, we measured β-cell function using the secretory units of islet in transplantation (SUIT) index (Yamada et al., 2006), and used these analyses to investigate the effect of lixisenatide in patients with varying β-cell function.

2. Materials and methods

This was a post hoc pooled analysis of data from the previously reported 24-week main treatment periods of the randomized, double-blind, placebo-controlled, parallel-group, multicentre, Phase 3 GetGoal-M (NCT00712673) and GetGoal-S (NCT00713830) trials. The methodology and primary results of these studies have been reported previously (Ahrén et al., 2013; Rosenstock et al., 2014). Briefly, patients included in the GetGoal-M and GetGoal-S trials had been diagnosed with T2D at least 1 year before screening, and had HbA1c ≥7% (53 mmol/mol) and ≤10% (86 mmol/mol) at screening. Patients in the GetGoal-M trials had been treated with metformin at a stable dose of at least 1.5 g/day for at least 3 months before the screening visit, whereas patients included in the GetGoal-S trial had been treated with an SU with or without metformin at a stable dose of at least 1.5 g/day (except at least 0.75 g/day in Japan and 1.0 g/day in South Korea) for at least 3 months before the screening visit. In both GetGoal-M and GetGoal-S, patients were enrolled and randomized to receive lixisenatide (Lyxumia®, Sanofi, Paris, France) 20 μg once daily or placebo, both plus background OADs. In both studies, the 600 kcal standardized liquid meal (400 mL Ensure Plus; Abbott Nutrition, Columbus, OH, USA; comprising 53.8% carbohydrate, 16.7% protein and 29.5% fat) was given 30 min after drug administration at baseline and at the end of the main 24-week treatment period (hereafter referred to as 'end of study').

Lixisenatide was administered subcutaneously using the Opticlik® (Sanofi, Paris, France) self-injector device. Lixisenatide 10 μg once daily was administered for 1 week, then 15 μg once daily for 1 week, followed by the maintenance dose of 20 μg once daily until the end of the study.

This study complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocols also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted. Informed consent was obtained prior to the conduct of any study-related procedures.

2.1. Design of the post hoc analysis

The post hoc analyses presented here were based on the modified intent-to-treat (mITT) population ($N = 437$), which comprised all patients from the GetGoal-M ($n = 195$) and GetGoal-S ($n = 242$) trials who were randomized to receive lixisenatide, in addition to previous OAD therapy, and had an HbA1c measurement at baseline and end of study. SUIT index estimates β-cell function based on a single fasting blood sample and, as such, is a useful tool in the clinical management of diabetes. SUIT index (nmol/mmol) was calculated for each patient in the mITT population based on their baseline characteristics, using the formula: 250 × fasting C-peptide nmol/L/fasting plasma glucose mmol/L − 3.43, where a greater SUIT index score indicates better β-cell function (Yamada et al., 2006). Patients were classified into quartiles according to median SUIT values, where patients in quartile 1 had the lowest baseline SUIT value (lowest β-cell function) and those in quartile 4 had the highest baseline SUIT value (highest β-cell function). The threshold values for SUIT quartiles 1–4 were <24.5, ≥24.5–<34.7, ≥34.7–<49.6, and ≥49.6 nmol/mmol, respectively.

Clinical outcomes at baseline and end of study were analyzed for each quartile and included: change in HbA1c and the proportion of patients achieving <7% (53 mmol/mol) target; change in fasting plasma glucose (FPG) and the proportion of patients achieving <6.1 mmol/L target; change in 2-h PPG post-standardized meal test and the proportion of patients achieving <10.0 mmol/L target; absolute changes in body weight and body mass index (BMI); change in insulinogenic index (defined as [insulin at 2-h postprandial − insulin at post-lixisenatide injection, preprandial]/[glucose at 2-h postprandial −glucose at post-lixisenatide injection, preprandial]); and change in postprandial glucagon.

Symptomatic hypoglycemia and severe symptomatic hypoglycemia were monitored throughout the trials. Symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to be a result of a hypoglycemic episode with plasma glucose <3.3 mmol/L, or was associated with prompt recovery after

Table 1
Lixisenatide patient baseline demographics and clinical characteristics (mITT population).

Characteristic	SUIT quartile 1 (<24.5 nmol/mmol) ($n = 110$)	SUIT quartile 2 (≥24.5–<34.7 nmol/mmol) ($n = 109$)	SUIT quartile 3 (≥34.7–<49.6 nmol/mmol) ($n = 109$)	SUIT quartile 4 (≥49.6 nmol/mmol) ($n = 109$)	*P*-value*
Age, years	55.7 (10.1)	55.9 (9.4)	55.5 (9.6)	55.9 (9.6)	0.9875
Female, *n* (%)	48 (43.6)	68 (62.4)	62 (56.9)	64 (58.7)	**0.0307**
Body weight, kg	75.5 (16.5)	85.7 (22.8)	89.8 (25.2)	95.7 (23.4)	<**0.0001**
BMI, kg/m^2	27.7 (4.9)	31.6 (7.3)	32.8 (7.2)	35.0 (7.6)	<**0.0001**
Ethnicity, n (%)					<**0.0001**
Asian	59 (53.6)	33 (30.3)	27 (24.8)	19 (17.4)	
Black/African American	4 (3.6)	3 (2.8)	9 (8.3)	3 (2.8)	
White	46 (41.8)	73 (67.0)	72 (66.1)	86 (78.9)	
Other	1 (0.9)	0 (−)	1 (0.9)	1 (0.9)	
T2D duration, years	9.9 (6.1)	8.0 (5.6)	7.5 (6.1)	7.0 (5.9)	**0.0019**
OAD use, *n* (%)					
Metformin	96 (87.3)	97 (89.0)	95 (87.2)	98 (89.9)	0.9022
SU	79 (71.8)	61 (56.0)	55 (50.5)	47 (43.1)	**0.0002**
OAD history, years	5.8 (4.3)[§]	5.1 (4.1)	4.9 (5.0)[‡]	4.5 (4.6)	0.2320
HbA1c, %	8.55 (0.86)	8.30 (0.77)	8.09 (0.84)	7.72 (0.83)	<**0.0001**
mmol/mol	70 (9.4)	67 (8.4)	65 (9.2)	61 (9.1)	
FPG, mmol/L	10.1 (2.0)	9.6 (2.1)	9.3 (1.8)	8.6 (1.8)	<**0.0001**
PPG post-meal test, mmol/L	19.2 (4.2)[†]	16.4 (3.2)[‡]	15.6 (3.4)[§]	13.5 (3.4)	<**0.0001**
SUIT index, nmol/mmol	18.2 (4.8)	29.9 (2.9)	40.9 (3.9)	90.2 (201.9)	<**0.0001**

Data are mean (SD), unless otherwise stated.
ANOVA, analysis of variance; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; mITT, modified intent-to-treat; OAD, oral antidiabetic drug; PPG, postprandial plasma glucose; SD, standard deviation; SU, sulfonylurea; SUIT, secretory units of islet in transplantation.
* ANOVA test for continuous variables and chi-square test for categorical variables, with the *P*-value denoting the difference in effect of baseline SUIT index across SUIT quartiles.
† $n = 109$.
‡ $n = 108$.
§ $n = 107$.

oral carbohydrate if no plasma glucose measurement was available. Severe symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to be a result of a hypoglycemic episode and required the assistance of another person, with plasma glucose <2.0 mmol/L, if available.

2.2. Statistical methods

The mITT population was used to conduct post hoc analyses. Descriptive statistics for the SUIT quartiles were used to describe patient baseline characteristics and safety outcome measurements. Count and mean (standard deviation [SD]) values were reported for continuous variables (age, weight, HbA1c, FPG and PPG). Patient baseline characteristics, glycemic outcomes and safety outcome measurements for the SUIT quartiles were compared using an analysis of variance test for continuous variables and a chi-square test for categorical variables with the *P*-value denoting the difference in overall effect across SUIT quartiles (*P*-values < 0.05 indicated statistical significance). Receiver operator curve (ROC) analyses were carried out to assess the sensitivity and specificity of using baseline SUIT index score to predict the likelihood of achieving glycemic targets at week 24, including FPG <7.2 mmol/L, PPG <10.0 mmol/L and HbA1c <7% (53 mmol/mol).

3. Results

Patient demographics and baseline characteristics of the safety populations from the GetGoal-M and GetGoal-S trials have been reported previously (Ahrén et al., 2013; Rosenstock et al., 2014). The mITT population for this analysis was distributed among SUIT quartiles (SUIT quartile 1 [<24.5 nmol/mmol], $n = 110$; quartile 2 [≥24.5–<34.7 nmol/mmol], $n = 109$; quartile 3 [≥34.7–<49.6 nmol/mmol], $n = 109$; quartile 4 [≥49.6 nmol/mmol], $n = 109$). Baseline demographics and clinical characteristics according to SUIT index quartile are shown (Table 1). Sex was significantly different among quartiles ($P = 0.0307$ for overall effect), with a greater proportion of women versus men in quartiles 2, 3 and 4. Body weight and BMI were both greater for patients with higher β-cell function ($P < 0.0001$ for overall effect of both). Patient ethnicity was significantly different among quartiles ($P < 0.0001$ for overall effect), with higher proportions of white versus Asian patients in quartiles 2, 3 and 4 compared with similar proportions of white and Asian patients in quartile 1. As expected, disease duration was longer for patients with reduced baseline β-cell function ($P = 0.0019$ for overall effect), and glycemic parameters were lower for patients with higher β-cell function ($P < 0.0001$ for overall effect for HbA1c, FPG and PPG).

3.1. SUIT index scores at baseline and end of study

Baseline mean (SD) SUIT index scores were 18.2 (4.8) nmol/mmol for quartile 1, 29.9 (2.9) nmol/mmol for quartile 2, 40.9 (3.9) nmol/mmol for quartile 3 and 90.2 (201.9) nmol/mmol for quartile 4 ($P < 0$ .0001 for overall effect; Table 1). At week 24, absolute mean (SD) SUIT scores remained greater in patients with higher β-cell function at baseline ($P < 0.0001$ for overall effect; quartile 1 34.0 [17.7], quartile 2 54.7 [54.3], quartile 3 61.8 [25.4] and quartile 4 89.0 [58.3] nmol/mmol), and the mean (SD) changes in SUIT index score from baseline to end of study were 15.8 (16.8), 24.8 (53.8), 20.9 (25.4) and −1.2 (215.3) nmol/mmol for SUIT quartiles 1, 2, 3 and 4, respectively. The overall effect of baseline SUIT index on the mean changes from baseline of the SUIT index scores was not significant ($P = 0.3299$). However, the individual improvements in SUIT index for quartiles 1 to 3 were significant ($P < 0.0001$) for each quartile change from baseline.

3.2. Clinical outcomes according to SUIT index

Patients with lower β-cell function at baseline had higher baseline levels of HbA1c ($P < 0.0001$ for overall effect; Table 1), with fewer patients achieving HbA1c <7% (53 mmol/mol) ($P = 0.0021$ for overall effect; Fig. 1A). Improvements in the mean levels of HbA1c from baseline to end of study were seen in each SUIT quartile, and the overall effect of baseline SUIT index on mean changes from baseline was not significant between quartiles ($P = 0.5756$; Fig. 1B). However, as would be expected based on the differences in baseline mean SUIT

scores, higher proportions of patients in quartile 3 and 4 achieved HbA1c <7% (53 mmol/mol) by week 24 ($P < 0.0001$ for overall effect; Fig. 1A).

Patients with lower β-cell function at baseline had higher baseline FPG ($P < 0.0001$ for overall effect between SUIT quartiles; Table 1), although there was no significant overall effect for SUIT quartile on the proportions of patients achieving FPG <6.1 mmol/L at baseline ($P = 0.0945$; Fig. 1C). Reductions in FPG from baseline to end of study were observed in each SUIT quartile; there was no significant overall effect for SUIT quartiles ($P = 0.9488$, Fig. 1D). There was also no

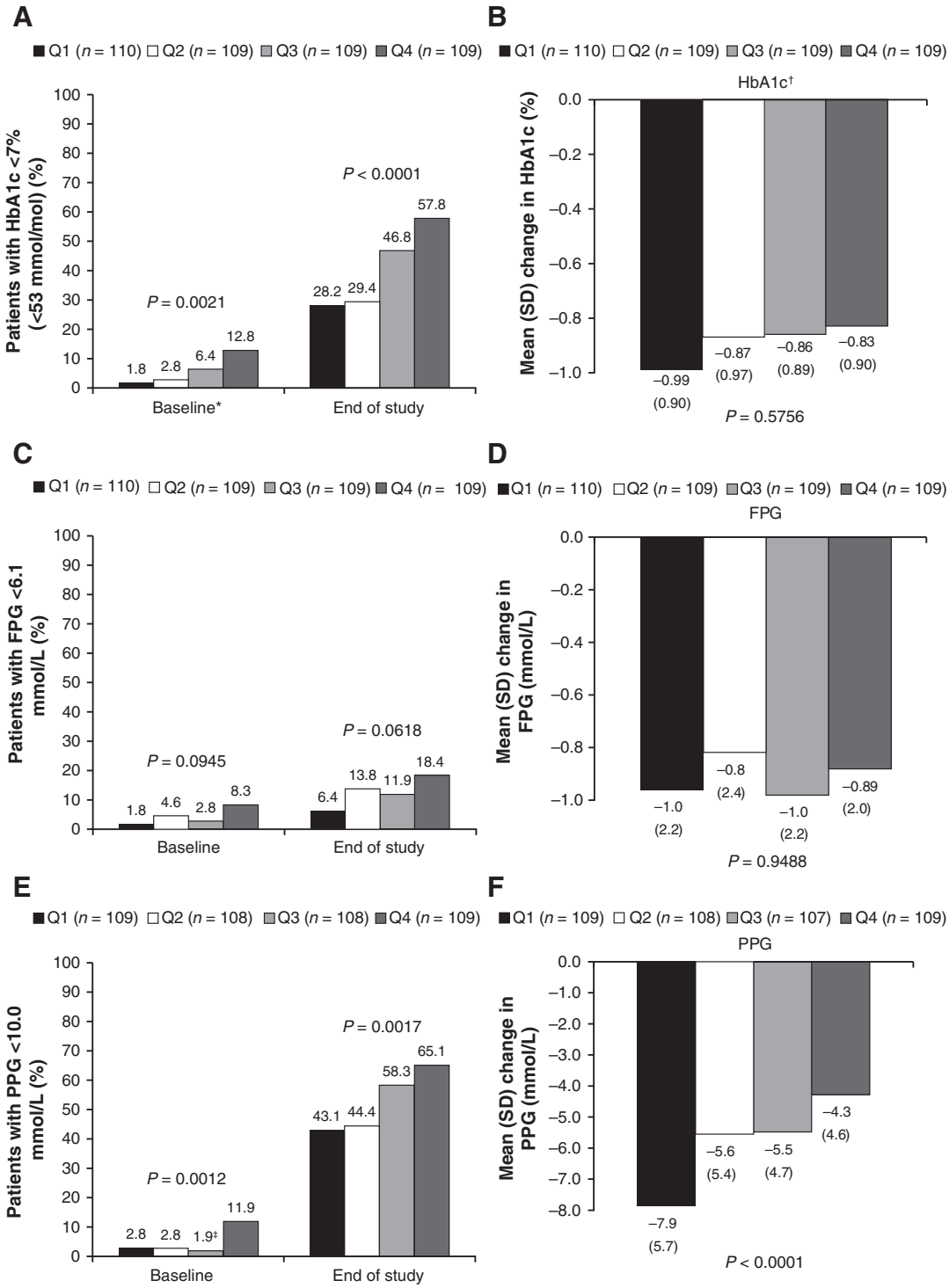

Fig. 1. Improvements in glycemic outcomes according to SUIT index. The proportion of patients achieving (A) HbA1c <7%, (C) FPG <6.1 mmol/L and (E) PPG <10.0 mmol/L at baseline and end of study; and the improvements from baseline in (B) HbA1c, (D) FPG and (F) PPG. Threshold values for SUIT quartiles 1–4 were: <24.5, ≥24.5–<34.7, ≥34.7–<49.6 and ≥49.6 nmol/mmol, respectively. *P*-values denoting the difference in effect of baseline SUIT index across SUIT quartiles are shown. *Despite inclusion criteria of HbA1c 7–10% (53–86 mmol/mol), the mITT population included a small proportion of patients with HbA1c <7% (53 mmol/mol) at baseline. †Equivalent mmol/mol mean (SD) changes in HbA1c for SUIT quartiles 1–4 were: −10.8 (9.8), −9.5 (10.6), −9.4 (9.7) and −9.1 (9.8) mmol/mol, respectively. ‡$n = 107$. FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; mITT, modified intent to treat; PPG, postprandial plasma glucose; SUIT, secretory units of islet in transplantation.

significant overall effect for baseline SUIT quartile on the proportions of patients achieving target FPG <6.1 mmol/L at week 24 ($P = 0.0618$, Fig. 1C).

Patients with lower β-cell function at baseline had higher baseline levels of PPG post-meal test ($P < 0.0001$ for overall effect; Table 1), with fewer patients achieving PPG <10.0 mmol/L ($P = 0.0012$ for overall effect; Fig. 1E). Improvements in PPG from baseline to end of study were seen in all SUIT quartiles (Fig. 1F). The greatest improvements in PPG were seen in patients in the lower SUIT quartiles ($P < 0.0001$ for overall effect, Fig. 1F), which were expected given that these patients had the highest PPG levels at baseline. However, greater proportions of patients in the higher SUIT quartiles achieved PPG <10.0 mmol/L by week 24 ($P = 0.0017$ for overall effect; Fig. 1E).

Baseline SUIT index had a significant positive overall effect on the changes in insulinogenic index post-meal test ($P = 0.0286$; Fig. 2A), but not on the improvements in levels of plasma glucagon post-meal test ($P = 0.3618$; Fig. 2B).

Reductions in body weight and BMI were seen across all four quartiles ($P = 0.7087$ and $P = 0.7238$ for overall effect, respectively). Improvements in body weight were −1.6, −1.6, −1.9 and −2.0 kg for SUIT quartiles 1, 2, 3 and 4, respectively. Improvements in BMI were −0.62, −0.60, −0.71 and −0.74 kg/m^2 for SUIT quartiles 1, 2, 3 and 4, respectively.

3.3. Hypoglycemic events according to SUIT index

Symptomatic hypoglycemic events (plasma glucose <3.3 mmol/L) were reported in 12 (10.9%) patients in quartile 1, 13 (11.9%) in quartile 2, 13 (11.9%) in quartile 3 and 5 (4.6%) in quartile 4. Baseline SUIT index did not have a significant overall effect on the number of patients who reported symptomatic hypoglycemic events ($P = 0.2034$). No severe symptomatic hypoglycemic events (requiring the assistance of another person) occurred in any SUIT quartile.

3.4. Baseline SUIT index as a predictor of glycemic outcomes

A SUIT index cut-off value of >36 nmol/mmol was indicated by ROC analysis of the sensitivity and selectivity trade-off as predicting FPG <7.2 mmol/L at end of study (Supplemental Fig. 1A). A SUIT index cut-off value of >35 nmol/mmol was indicated by ROC analysis as predicting PPG <10.0 mmol/L (Supplemental Fig. 1B) and HbA1c <7% (53 mmol/mol) (Supplemental Fig. 1C) at end of study.

4. Discussion

Here we evaluated the efficacy and safety of lixisenatide in patients with T2D and varying levels of baseline β-cell function, with uncontrolled glycemia despite treatment with OADs, including metformin alone, or an SU with or without metformin. The main finding of the study was that lixisenatide improved glycemic control irrespective of β-cell function, as assessed by SUIT index. Differences in baseline β-cell function were associated with differences in disease characteristics and baseline glycemic parameters and, as expected, patients with worse baseline β-cell function had longer disease duration and higher levels of hyperglycemia. β-cell function improved over 24 weeks in this analysis, irrespective of baseline β-cell function, and as measured by change from baseline in SUIT index score. However, it should be noted that this analysis is based on 24-week data, which represent a relatively short time-frame in which to evaluate changes in β-cell function.

Glycemic outcomes, including HbA1c, FPG and PPG post-meal test, improved from baseline to week 24 across all baseline SUIT quartiles. This is consistent with findings from the original GetGoal-M and GetGoal-S trials, in which lixisenatide was associated with significant improvements in overall HbA1c, FPG and PPG versus placebo (Ahrén et al., 2013; Rosenstock et al., 2014). As expected, and consistent with the original studies, overall improvements in FPG seen in this analysis were relatively small (between −0.8 and −1.0 mmol/L across quartiles), whereas the improvements in PPG (between −4.3 and −7.9 mmol/L across quartiles) were more substantial. The overall effect of baseline SUIT index on reductions in HbA1c and FPG was not significant, suggesting that lixisenatide exerts a similar effect on glycemic outcomes regardless of baseline SUIT score, although the greatest improvement in HbA1c was still seen in patients with the highest baseline levels of HbA1c. For PPG, the improvement from baseline was particularly pronounced for patients with lower SUIT index at baseline, likely because these patients had the highest baseline PPG levels.

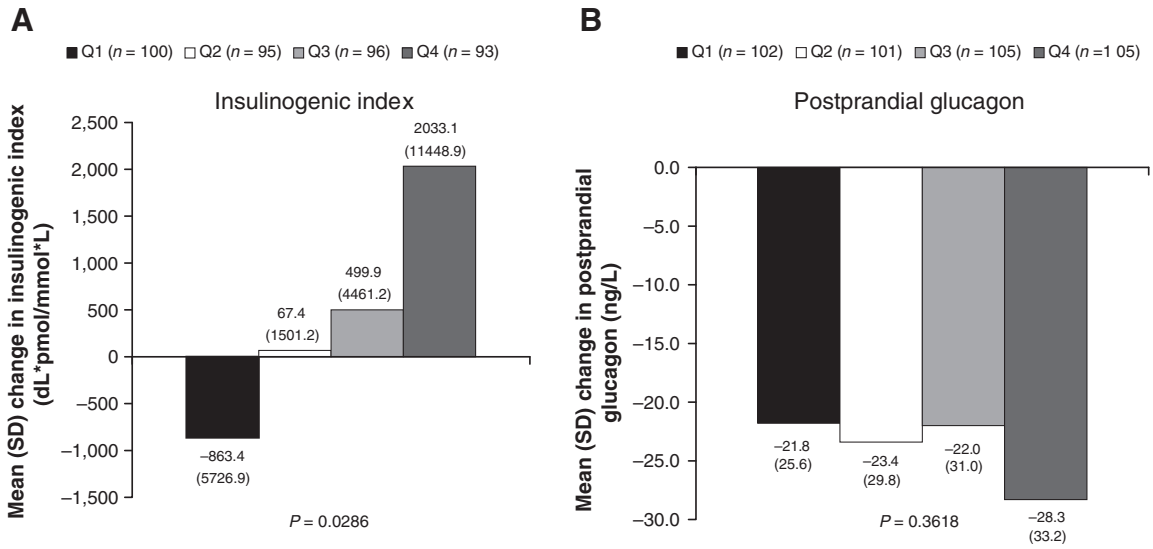

Fig. 2. Improvements in (A) insulinogenic index* and (B) plasma glucagon levels post-meal test according to SUIT index. Threshold values for SUIT quartiles 1–4 were: <24.5, ≥24.5–<34.7, ≥34.7–<49.6 and ≥49.6 nmol/mmol, respectively. *P*-values denoting the difference in effect of baseline SUIT index across SUIT quartiles are shown. *Insulinogenic index is defined as (insulin at 2 hours postprandial – insulin at post-lixisenatide injection, preprandial)/(glucose at 2 hours postprandial – glucose at post-lixisenatide injection, preprandial), with a unit of 10*pmol/mmol, or dL*pmol/mmol*L.

Further to the mean improvements seen in glycemic outcomes across all SUIT index quartiles, we evaluated whether baseline β-cell function could predict likelihood of achieving glycemic targets. Despite seeing comparable mean improvements in glycemic outcomes across SUIT quartiles, we found that baseline β-cell function did have an overall effect on the proportions of patients reaching glycemic targets at week 24 of lixisenatide as add-on to OAD therapy, with greater proportions of patients in the higher versus lower baseline SUIT quartiles reaching glycemic targets. Indeed, baseline glycemic values were lower for patients in the higher SUIT index quartiles, making it easier for them to achieve these low glycemic targets at endpoint. Further examination of these data using a ROC analysis confirmed this by demonstrating that baseline SUIT index values of >36, >35 and >35 nmol/mmol were able to predict patients reaching target FPG, PPG and HbA1c levels, respectively, with an accuracy of approximately 60% following treatment with lixisenatide as add-on to OAD therapy. A previous study reported average SUIT index values among patients with T2D who achieved FPG <7.2 mmol/L with and without insulin to be 31.1% and 47.2%, respectively, where SUIT index was defined as: 1500 × fasting C-peptide immunoreactivity (ng/mL)/(FPG [mg/dL] − 61.7) (Funakoshi et al., 2011). Treatment with lixisenatide has been shown previously to be clinically efficacious and tolerable in patients when administered as add-on to basal insulin therapy due to the complementary effects of basal insulin on FPG plus lixisenatide on PPG (Charbonnel, Bertolini, Tinahones, Domingo, & Davies, 2014; Riddle, Aronson, et al., 2013; Seino et al., 2012). Taken together, these data suggest that baseline SUIT scores could be used to identify patients with T2D who may respond well to potential basal insulin/lixisenatide combination therapy, as has been used previously to identify patients requiring multiple daily insulin injections (Fujiwara et al., 2013). Further investigation to validate the association between SUIT index and response to lixisenatide/OADs or basal insulin/lixisenatide combination therapy is warranted.

The overall improvements in glycemic parameters seen in patients with low β-cell function, in particular the improvements in PPG in these patients, support evidence that lixisenatide can mediate glycemic control via β-cell-independent mechanisms such as gastric emptying and glucagon release. Indeed, significant reductions in PPG with lixisenatide have been shown previously to be associated with significant slowing of gastric emptying and suppression of postprandial glucagon in patients with T2D (Becker, Stechl, Msihid, & Kapitza, 2014; Kapitza et al., 2013). This is consistent with reports on the mechanism of action of lixisenatide and other short-acting GLP-1 RAs (Meier, 2012; Yabe & Seino, 2014), as well as pilot studies conducted in patients with type 1 diabetes (Ghazi, Rink, Sherr, & Herold, 2014). Hence, as lixisenatide can mediate its effects via β-cell-dependent and -independent mechanisms, this should enable lixisenatide to be an effective and durable treatment regardless of β-cell loss resulting from disease progression. Long-acting GLP-1 RAs, on the other hand, exert their clinical effects primarily by promoting the direct secretion of insulin and the indirect suppression of glucagon release (Kapitza et al., 2013; Meier, 2012; Yabe & Seino, 2014), yet also show efficacy in patients with type 1 diabetes (Kielgast, Krarup, Holst, & Madsbad, 2011).

Baseline SUIT index had no significant overall effect on the occurrence of symptomatic hypoglycemia, and no severe symptomatic hypoglycemic events were reported following lixisenatide treatment in the GetGoal-M or GetGoal-S trials. Reports from the lixisenatide clinical trial program suggest that lixisenatide is associated with a generally low risk of hypoglycemia (Ahrén et al., 2013; Rosenstock et al., 2013), probably because the effects of lixisenatide on insulin secretion are glucose-dependent.

SUIT index is a useful tool to assess β-cell function in patients with T2D, since it has been shown to significantly correlate with stimulated C-peptide levels ($r^2 = 0.34$, $P < 0.001$) (Kubota, Matsuba, Saito, Nabe, & Seino, 2011; Yamada et al., 2006). SUIT index is similar to a fasting C-peptide/glucose ratio reported previously, which has been shown to significantly correlate with β-cell mass (Meier et al., 2009). An additional benefit of using the SUIT index is that calculations are independent of the amount of exogenous insulin administered by the patient (Yamada et al., 2006). This is in contrast to the homeostasis model assessment estimated β-cell function (HOMA-b) method, for example, where calculations are based on insulin levels (Wallace, Levy, & Matthews, 2004). Furthermore, data published previously have questioned the use of HOMA-b as a surrogate marker of insulin secretion as it does not correlate with other measures of insulin secretion (Ahrén & Larsson, 2002).

This is the first time that SUIT index has been evaluated in patients with T2D outside of Japan, although the current study suggests that SUIT index can contribute to global clinical management decisions in patients with T2D. Patient ethnicity was significantly different among SUIT quartiles. A greater proportion of Asian patients displayed lower versus higher β-cell function at baseline; a greater proportion of white patients demonstrated higher versus lower β-cell function at baseline. However, this result may have been influenced by the characteristics of the two trial populations: GetGoal-S recruited a higher proportion of Asian patients than GetGoal-M (approximately 45% vs 8%, respectively). As the entry requirements for GetGoal-S specified that patients be inadequately controlled on an SU with or without metformin, this may have been a population selected for lower β-cell function than that in patients entered into GetGoal-M, which specified only inadequate control with metformin. Therefore, the apparently lower β-cell function in Asian patients should be regarded with caution. There are also differences in the pathophysiology of diabetes between Asian and white patients that may account for some of this variation. Asian patients tend to have a pathophysiology of insulin deficiency rather than insulin resistance, and there is some evidence of underlying GLP-1 insufficiency in these patients (Seino et al., 2010; Yabe et al., 2010; Yabe et al., 2012). Indeed, it has been reported that Japanese people may be particularly susceptible to developing T2D owing to particularly fragile β-cell function (Fukushima, Suzuki, & Seino, 2004), and a decrease in β-cell function has been proposed as a primary etiological factor in the development of T2D in Asian Indians (Staimez et al., 2013).

Additionally, patients with higher β-cell function had increased body weight and BMI versus patients with lower β-cell function. These differences may also be associated with the characteristics of the two trial populations, as the patient population of the GetGoal-M trial was mostly white and had higher baseline mean body weight and BMI (Ahrén et al., 2013) compared with the patient population of the GetGoal-S trial, which comprised a higher proportion of Asian patients (Rosenstock et al., 2014). The increased use of SUs in patients with lower β-cell function may also in part be due to the longer disease duration in these patients versus patients with higher β-cell function.

Limitations of this study include the use of pooled data; patients in the GetGoal-M trials had been treated with metformin, whereas patients in the GetGoal-S trial had been treated with an SU with or without metformin. Although murine and *in vitro* studies have suggested that SUs may have an effect on incretin secretion (Nielsen et al., 2007; Reimann et al., 2008), SUs have been shown to have little effect on incretin secretion in Japanese patients with T2D (Yabe et al., 2012). Furthermore, the increased use of OAD therapy in patients with lower versus higher β-cell function may be indicative of further disease progression compared with patients who have only previously received metformin. Data from the original studies highlight the treatment effect of lixisenatide versus placebo; as such, SUIT analysis of the placebo treatment arm to further confirm the effect of lixisenatide is warranted. Additionally, as baseline HbA1c is often the most effective predictor of response for antidiabetic drugs, it would have been interesting to correct the improvements seen in HbA1c for the baseline levels of HbA1c. However, as SUIT index is highly correlated with baseline HbA1c, correcting for HbA1c was not

possible as the patients would have been artificially forced (in a mathematical sense) to have the same SUIT index level also, and this would have resulted in very small patient numbers.

These data demonstrate that lixisenatide confers overall glycemic control and pronounced reductions in PPG, and that lixisenatide is well tolerated, across all levels of β-cell function, highlighting the importance of the non-insulin-related actions of lixisenatide. Thus, lixisenatide represents a useful treatment option in patients with T2D who are inadequately controlled using OADs, regardless of β-cell function.

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