

Efficacy of once-daily glucagon-like peptide-1 receptor agonist lixisenatide as an add-on treatment to basal insulin in Asian and white adults with type 2 diabetes mellitus: An individual-level pooled analysis of phase III studies

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Keywords

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ABSTRACT

Aims/Introduction: The prevalence and pathophysiological background of type 2 diabetes mellitus vary across ethnicities, and can affect treatment responses. Adding lixisenatide to basal insulin (BI) in type 2 diabetes mellitus patients has shown improvements in glycated hemoglobin (HbA1c) and postprandial glycaemic (PPG) excursions, without increasing hypoglycaemic events. We aim to compare the efficacy of lixisenatide in Asian and white patients inadequately controlled with basal insulin.

Materials and Methods: An individual-level pooled analysis of two multi-national phase III studies, GetGoal-L and GetGoal-L-C, was carried out to assess the efficacy of lixisenatide versus placebo as an add-on treatment to BI ± metformin in Asian and white patients with type 2 diabetes mellitus. Change in HbA1c, 2-h PPG and PPG excursion were analyzed, along with possible predictors of glycaemic control.

Results: Pooled data showed that baseline characteristics were similar between Asian and white patients with the exception of bodyweight, body mass index and BI dose being higher in white patients. After 24 weeks, lixisenatide reduced HbA1c in both ethnic groups, with no statistically significant difference between the two groups (Asian patients least squares mean difference -0.49 , 95% confidence interval -0.68 to -0.30 and white patients least squares mean difference -0.45 , 95% confidence interval -0.63 to -0.26 ; $P = 0.6287$). Similarly, no significant difference was found in 2-h PPG reduction between both groups (least squares mean difference for Asian vs white patients: -3.37 vs -3.93 ; $P = 0.3203$). Treatment with lixisenatide contributed to HbA1c reduction of -0.56% after adjustment of baseline HbA1c level in Asian patients, and -0.41% in white patients.

Conclusions: Adding lixisenatide to BI significantly reduced HbA1c and 2-h PPG levels in both Asian and white participants with type 2 diabetes mellitus. No differences in treatment effect were observed between the two populations.

INTRODUCTION

According to a 2019 report by the International Diabetes Federation, currently 463 million adults aged 20–79 years are living with diabetes, and this will increase to 700 million by the year

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2045¹. The number of people living with diabetes is increasing, especially in the Asiatic and European region, with approximately 58 million and 82 million people reported to be living with diabetes in Europe and South-East Asia, respectively¹.

Owing to pathophysiological differences across various ethnic populations, the risk factors for onset of type 2 diabetes mellitus might differ among ethnic groups. Asians are more susceptible to type 2 diabetes mellitus than Western and white counterparts, despite lower body mass index (BMI)². Also, it has been observed that the development of type 2 diabetes mellitus in Asian people is associated with impaired early phase insulin secretion³. A comparative study of postprandial glucose (PPG) levels between Asian and white people reported higher glycemic index among Asian people; however, this increase suggests that glycemic index is independent of the glucose tolerance of the consumer⁴. Due to the pathophysiological differences in type 2 diabetes mellitus, the therapeutic response to different pharmacological intervention is also assumed to show variations among different ethnicities.

Despite the availability of multiple pharmacological interventions for maintaining glycemic control in type 2 diabetes mellitus, it is difficult to maintain the glycemic target level of <6.5% or <7%, in the long-term^{5–7}. Glucagon-like peptide-1 receptor agonist (GLP-1 RA) is a newly established therapy option for the treatment of type 2 diabetes mellitus, and has shown positive effects owing to its ability to potentiate endogenous insulin responses to hyperglycemia and inhibit glucagon secretion⁸. Lixisenatide, a once daily^{7,9} short-acting GLP-1RA, improves glycemic control by increasing postprandial insulin secretion, delaying gastric emptying and reducing postprandial glucagon¹⁰. Various studies have reported that adding lixisenatide to basal insulin (BI) with or without other oral antidiabetic drugs led to significant reduction in glycated hemoglobin (HbA1c) levels in type 2 diabetes mellitus patients^{9,11–14}. The results from these studies also showed that adding lixisenatide to BI led to weight reduction, as opposed to the usual weight gain, with lower risk of hypoglycemia and lower total insulin dose.

The previously published GetGoal-L-C¹⁵ and GetGoal-L¹³ clinical trials evaluated the efficacy and safety of lixisenatide as add-on therapy in participants with type 2 diabetes mellitus inadequately controlled with BI therapy with or without metformin^{13,15}. However, there is limited information on whether treatment response of lixisenatide as add-on treatment to BI could differ between ethnic groups. A comprehensive evaluation of the efficacy of this therapy in different ethnic populations will help make better informed decisions in disease management. Hence, the present pooled analysis was carried out to analyze the efficacy of lixisenatide as add-on therapy to BI, along with determining possible predictors for glycemic control between the Asian and white participants with type 2 diabetes mellitus.

METHODS

Study design and treatment plan

The present study included the pooled data from two individual studies, which were randomized, placebo-controlled, two-arm,

parallel group, double-blind, multicenter, phase III studies with 24-week treatment periods ([GetGoal-L EFC6016] and [GetGoal-L-C EFC12382]). Adults with type 2 diabetes mellitus diagnosed for ≥ 1 year and receiving treatment with BI regimen for ≥ 3 months with a stable dose for ≥ 2 months, with HbA1c level of 7–10.5% and a stable metformin dose of ≥ 1.0 g/day for ≥ 3 months before the screening visit, if treated with metformin were included. The included individuals were then randomized to either lixisenatide 20 μ g or the placebo group as an add-on therapy to BI \pm metformin in the two randomized controlled studies. An individual-level meta-analysis of the efficacy of lixisenatide as an add-on therapy to BI \pm metformin was carried out in Asian and white individuals with type 2 diabetes mellitus.

Ethical considerations

This article is based on the analysis of data from previously carried out studies. All the procedures in the original studies involved human participants. The studies were approved by the institutional review boards or ethics committees of the participating centers, and were in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants gave prior written informed consent. An independent Data Monitoring Committee provided an ongoing review of unmasked efficacy and safety data, and an Allergic Reaction Assessment Committee and a Cardiovascular Event Adjudication Committee reviewed masked events.

End-points assessments

The primary end-point of the present study was to analyze the change in HbA1c levels from randomization to the end of treatment period (week 24) in Asian and white participants. Other assessments included change in 2-h PPG (2h-PPG), 2h-PPG excursions, fasting plasma glucose (FPG) levels and body-weight. Possible baseline predictors of glycemic control were also analyzed. Data from the respective individual studies reported that samples for FPG and HbA1c measurements were analyzed by high-performance liquid chromatography at a central laboratory (Covance, Princeton, NJ, USA). Participants underwent a standardized meal challenge test (Ensure Plus[®] or Nutrison[®]), which was consumed between 15 and 30 min after study drug administration to assess the 2h-PPG and plasma glucose excursions once during the run-in phase and at week 24.

Statistical analysis

The end-points of glycemic control were analyzed using analysis of covariance (ANCOVA) with treatment groups (lixisenatide or placebo), randomization strata of HbA1c (<8.0, ≥ 8.0 %), randomization strata of metformin use (yes, no), study, sex and country as fixed effects, and baseline HbA1c, baseline 2h-PPG, baseline FPG, baseline insulin dose, baseline BMI, duration of diabetes and age as a covariate. Least squares mean differences (LSMD) were calculated for describing the treatment effect of lixisenatide versus placebo. The multiplicative interaction term

of treatment \times race was used to explore consistency of treatment effect between Asian and white participants, and the interaction *P*-value was presented. A two-sided level of significance of 0.05 was applied. All analyses were carried out using SAS Enterprise Guide 7.13 HF8 (SAS Institute, Cary, NY, USA).

RESULTS

Baseline characteristics

Out of the total 944 participant data from two individual studies, 916 individuals were included in this analysis. Out of 916 individuals, 468 (placebo $n = 220$; lixisenatide $n = 248$) individuals were of Asian ethnicity, and 448 (placebo $n = 164$; lixisenatide $n = 284$) individuals were of white ethnicity. The remaining 28 individuals were excluded from the analysis, as they belonged to ethnicities other than Asian and white.

The baseline characteristics were found to be comparable between the treatment groups in both the populations. The mean duration of diabetes was 10.49 years for lixisenatide and 10.63 years for the placebo group in Asian participants, and was 12.50 and 11.94 years in white participants. The mean dose of BI use was 39.03 IU/day for lixisenatide and 38.18 IU/day for the placebo group in Asian participants, and 54.42 and 56.01 IU/day for lixisenatide and placebo groups in white participants, respectively. The mean HbA1c at baseline was similar in the treatment and placebo groups for both Asian and white participants. The descriptive analysis of baseline characteristics showed that bodyweight, BMI and BI daily dose were higher in the white population compared with Asian participants for both the lixisenatide and placebo treatment groups (Table 1). The geographical regions from where Asian and white participants were recruited for the present study are shown in Table S1 and Figure S1.

Response to lixisenatide + BI therapy

The efficacy end-points of change in HbA1c, 2h-PPG, FPG values, and bodyweight were measured at week 24 after completion of the treatment period. Overall, 911 individuals were included in the analysis with 467 Asian participants (placebo $n = 220$; lixisenatide $n = 247$) and 444 white participants (placebo $n = 162$; lixisenatide $n = 282$).

A statistically significant greater reduction in the mean change in HbA1c was observed from baseline to week 24 in the lixisenatide group than the placebo group in both Asian and white participants ($P < 0.0001$ for both Asian and white participants). There was no significant difference in the effect of lixisenatide among the two ethnic groups (LSMD -0.49% , 95% confidence interval [CI] -0.68 to -0.30 vs LSMD -0.45% , 95% CI -0.63 to -0.26 ; $P = 0.6287$; Table 2). As lixisenatide was added on to a completely titrated BI before randomization, mean FPG levels were not significantly reduced from baseline to week 24 in both Asian and white participants.

There was a significant reduction in the 2h-PPG in the lixisenatide group compared with placebo in both the

populations ($P < 0.001$) for both Asian and white participants. No significant difference in the treatment effect of 2h-PPG was observed between Asian and white participants (LSMD -3.37 mmol/L, 95% CI -4.19 to -2.54 vs LSMD -3.93 mmol/L, 95% CI -4.80 to -3.05 ; $P = 0.3203$; Table 3). The mean change in 2h-PPG excursions was significant between the placebo groups and lixisenatide treatment groups for both Asian and white participants ($P < 0.0001$). Similar to the treatment effect of 2h-PPG, no significant difference in the treatment effect of 2h-PPG excursions was found between the two ethnic groups (LSMD -3.00 mmol/L, 95% CI -3.74 to -2.26 vs LSMD -3.76 mmol/L, 95% CI -4.54 to -2.98 ; $P = 0.1290$; Table 4).

The addition of lixisenatide to BI led to a statistically significant reduction in bodyweight among both Asian and white participants at week 24 compared with the baseline ($P < 0.0001$). However, no significant difference in treatment effect of bodyweight was observed between the two ethnic groups (LSMD -0.98 kg, 95% CI -1.39 to -0.57 vs LSMD -1.55 kg, 95% CI -2.14 to -0.97 ; $P = 0.1694$; Table 5).

Baseline factors predicting response to treatment in Asian and white participants

The present analysis showed that the treatment groups (lixisenatide or placebo) and baseline HbA1c levels predicted treatment response. Thus, treatment with lixisenatide compared with placebo contributed to an HbA1c reduction of -0.56% (95% CI -0.75 to -0.37% ; $P < 0.001$) after adjustment of baseline HbA1c level in Asian participants, and -0.41% (95% CI -0.61 to -0.21% ; $P < 0.001$) in white participants. For every 1.0% higher baseline HbA1c, the change in HbA1c was more pronounced with -0.27% (95% CI -0.39 to -0.15%) in Asian participants and -0.41% (95% CI -0.53 to -0.29%) in white participants from baseline to week 24, respectively.

Similarly, treatment with lixisenatide contributed to a significant change in 2h-PPG values in Asian participants (LSMD -3.69 mmol/L, 95% CI -4.59 to -2.78 ; $P < 0.0001$) and in white participants (LSMD -3.67 mmol/L, 95% CI -4.51 to -2.82 ; $P < 0.001$) from baseline to week 24. Treatment with lixisenatide significantly contributed to a reduction in 2h-PPG excursions (Asians participants LSMD -3.29 mmol/L, 95% CI -4.08 to -2.51) and white participants LSMD -3.76 mmol/L, 95% CI -4.52 to -3.00 ; both $P < 0.0001$ (Table 6).

DISCUSSION

The current analysis of pooled data from previously published GetGoal studies was carried out to evaluate the differential efficacy of lixisenatide as add-on therapy to BI with or without metformin in Asian and white populations. As reported previously, type 2 diabetes mellitus in East Asian individuals is characterized primarily by β -cell dysfunction rather than insulin resistance, as observed in the white population^{16–19}. Also, the risk of diabetes is significantly higher in the Asian population than the white population due to a higher amount of visceral fat^{20–22}.

Table 1 | Pooled demographic data and baseline clinical characteristics

	Asian		White	
	Placebo (n = 220)	Lixisenatide (n = 248)	Placebo (n = 164)	Lixisenatide (n = 284)
Age (years)				
Mean (SD)	55.2 (9.3)	53.3 (9.9)	58.3 (8.9)	58.2 (9.1)
Sex, n (%)				
Male	107 (48.6%)	123 (49.6%)	67 (40.9%)	122 (43.0%)
Baseline BMI (kg/m ²)				
Mean (SD)	27.01 (3.70)	26.75 (3.74)	33.62 (5.85)	32.91 (5.99)
Baseline HbA1c (%)				
Mean (SD)	8.00 (0.76)	8.05 (0.80)	8.28 (0.80)	8.34 (0.85)
Duration of diabetes (years)				
Mean (SD)	10.63 (6.19)	10.49 (6.30)	11.94 (6.44)	12.50 (7.05)
Duration of basal insulin treatment (years)				
Mean (SD)	2.29 (2.45)	2.27 (2.65)	2.83 (3.61)	2.95 (3.16)
Baseline FPG (mmol/L)				
Mean (SD)	6.95 (1.86)	7.15 (2.20)	8.04 (2.59)	8.24 (2.75)
Baseline 2-h postprandial glucose (mmol/L)				
Mean (SD)	14.39 (3.70)	14.13 (4.54)	15.64 (3.96)	16.29 (4.08)
Baseline basal insulin daily dose (IU/day)				
Mean (SD)	38.18 (19.63)	39.03 (17.99)	56.01 (32.56)	54.42 (34.87)
Baseline bodyweight (kg)				
Mean (SD)	72.21 (12.63)	71.57 (12.92)	91.48 (18.28)	90.27 (19.38)

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SD, standard deviation

Table 2 | Change of glycated hemoglobin from baseline to week 24

HbA1c (%)	Asian		White	
	Placebo (n = 220)	Lixisenatide (n = 247)	Placebo (n = 162)	Lixisenatide (n = 282)
Baseline				
n	219	246	160	277
Mean (SD)	7.99 (0.76)	8.04 (0.80)	8.29 (0.80)	8.34 (0.86)
Week 24				
n	196	226	136	231
Mean (SD)	7.99 (1.14)	7.49 (1.15)	7.97 (1.02)	7.57 (1.04)
Change from baseline to week 24 LOCF				
n	219	240	151	257
Mean (SD)	0.01 (0.98)	-0.49 (1.10)	-0.26 (0.93)	-0.69 (0.96)
LS mean (SE)	-0.46 (0.23)	-0.95 (0.22)	-0.56 (0.14)	-1.01 (0.13)
LS mean difference (SE)	-0.49 (0.10)		-0.45 (0.09)	
95% CI	(-0.68 to -0.30)		(-0.63 to -0.26)	
P-value	<0.0001		<0.0001	
Interaction P-value for race and treatment			0.6287	

Data are mean (standard deviation [SD]) unless stated otherwise. The ANCOVA model has terms: treatment groups (lixisenatide or placebo), randomization strata of glycated hemoglobin (HbA1c; <8.0, ≥8.0%), randomization strata of metformin use (yes, no), study, sex and country as fixed effects, and baseline HbA1c, baseline 2-h postprandial glycemia, baseline fasting plasma glucose, baseline insulin dose, baseline body mass index, duration of diabetes and age as a covariate. Races with less than five patients in either of the treatment groups were combined into 'Other' race category. CI, confidence interval; LOCF, last observation carried forward; LS, least squares; SE, standard error.

The therapeutic efficacy of different pharmacological interventions in various ethnicities might be influenced by different dietary food habits, younger age²³, and the amplitude and pattern of

GLP-1 secretion after a meal²⁴. Thus, the heterogeneity of different ethnic groups might impact the individual's response to various diabetes therapies, and this is of interest to physicians in Asia.

Table 3 | Change of 2-h postprandial glycemia from baseline to week 24

2h-PPG (mmol/L)	Asian		White	
	Placebo (<i>n</i> = 220)	Lixisenatide (<i>n</i> = 247)	Placebo (<i>n</i> = 162)	Lixisenatide (<i>n</i> = 282)
Baseline				
<i>n</i>	191	209	141	235
Mean (SD)	14.40 (3.70)	14.02 (4.59)	15.38 (3.77)	16.27 (4.02)
Week 24				
<i>n</i>	179	197	132	219
Mean (SD)	14.30 (4.18)	10.66 (5.00)	14.47 (3.56)	10.98 (4.19)
Change from baseline to week 24 LOCF				
<i>n</i>	184	199	128	209
Mean (SD)	0.04 (3.98)	-3.41 (6.11)	-0.68 (4.06)	-5.19 (5.24)
LS mean difference (SE)	-3.37 (0.42)		-3.93 (0.44)	
95% CI	(-4.19 to -2.54)		(-4.80 to -3.05)	
<i>P</i> -value	<0.0001		<0.0001	
Interaction <i>P</i> -value for race and treatment			0.3203	

Data are mean (standard deviation [SD]) unless stated otherwise. The ANCOVA model has terms: treatment groups (lixisenatide or placebo), randomization strata of glycated hemoglobin (HbA1c; <8.0, ≥8.0%), randomization strata of metformin use (yes, no), study, sex and country as fixed effects, and baseline HbA1c, baseline 2-h postprandial glycemia (2h-PPG), baseline fasting plasma glucose, baseline insulin dose, baseline body mass index, duration of diabetes and age as a covariate. Races with less than figure patients in either of the treatment group were combined into 'Other' race category. CI, confidence interval; LOCF, last observation carried forward; LS, least squares; SE, standard error.

Table 4 | Change of 2-h postprandial glycemia excursion from baseline to week 24

2h-PPG excursion (mmol/L)	Asian		White	
	Placebo (<i>n</i> = 220)	Lixisenatide (<i>n</i> = 247)	Placebo (<i>n</i> = 162)	Lixisenatide (<i>n</i> = 282)
Baseline				
<i>n</i>	191	207	138	234
Mean (SD)	7.28 (3.11)	6.69 (3.57)	6.65 (3.48)	7.47 (3.42)
Week 24				
<i>n</i>	179	196	131	218
Mean (SD)	6.91 (3.58)	3.47 (4.38)	6.75 (3.58)	3.28 (3.84)
Change from baseline to week 24 LOCF				
<i>n</i>	184	198	126	209
Mean (SD)	-0.33 (3.37)	-3.28 (5.07)	0.15 (3.71)	-4.15 (4.18)
LS mean difference (SE)	-3.00 (0.38)		-3.76 (0.40)	
95% CI	(-3.74 to -2.26)		(-4.54 to -2.98)	
<i>P</i> -value	<0.0001		<0.0001	
Interaction <i>P</i> -value for race and treatment			0.1290	

Data are mean (standard deviation[SD]) unless stated otherwise. The ANCOVA model has terms: treatment groups (lixisenatide or placebo), randomization strata of glycated hemoglobin (HbA1c; <8.0, ≥8.0%), randomization strata of metformin use (yes, no), Study, Gender and country as fixed effects and baseline HbA1c, baseline 2-h postprandial glycemia (2h-PPG), baseline fasting plasma glucose, baseline insulin dose, baseline body mass index, duration of diabetes and age as a covariate. Races with less than five patients in either of the treatment groups were combined into 'Other' race category. CI, confidence interval; LOCF, last observation carried forward; LS, least squares; SE, standard error.

Previous studies have explored the efficacy of incretin-based therapies in different ethnic groups. A meta-analysis of 15 trials carried out to explore the HbA1c-lowering efficacy of GLP-1RAs reported a greater reduction of HbA1c among Asian-dominated studies than in non-Asian-dominated studies²⁵. However, whether the differential glycaemic effect of GLP-1RA was due to BMI or due to potential ethnic differences was

unclear²⁵. An individual-level pooled analysis with exenatide b.i.d., another short-acting GLP-1RA, showed that Asian patients exhibited significantly greater reductions in HbA1c and PPG than white patients²⁶. Nevertheless, that study reported many confounding factors that might have contributed to the differences between the exenatide therapies. For example, outcomes between Asian and white patients were not directly

Table 5 | Change of bodyweight from baseline to week 24

Bodyweight (kg)	Asian		Caucasian	
	Placebo (n = 220)	Lixisenatide (n = 247)	Placebo (n = 162)	Lixisenatide (n = 282)
Baseline				
n	220	247	162	282
Mean (SD)	72.21 (12.63)	71.54 (12.94)	91.46 (18.34)	90.34 (19.38)
Week 24				
n	199	225	131	223
Mean (SD)	71.97 (12.68)	70.99 (13.00)	91.27 (18.82)	88.68 (18.45)
Change from baseline to week 24 LOCF				
n	218	241	156	270
Mean (SD)	0.08 (2.09)	-0.95 (2.21)	-0.14 (2.89)	-1.54 (3.03)
Median	0.00	-0.80	0.00	-1.10
Min: max	-10.5: 6.0	-8.0: 4.4	-15.0: 9.5	-11.5: 6.7
LS mean (SE)	-0.76 (0.49)	-1.74 (0.47)	-0.87 (0.44)	-2.42 (0.42)
LS mean difference (SE)	-0.98 (0.21)		-1.55 (0.30)	
95% CI	(-1.39 to -0.57)		(-2.14 to -0.97)	
P-value	<0.0001		<0.0001	
Interaction P-value for race and treatment				0.1694

Data are mean (standard deviation [SD]) unless stated otherwise. The ANCOVA model has terms: treatment groups (lixisenatide or placebo), randomization strata of glycated hemoglobin (HbA1c; <8.0, ≥8.0%), randomization strata of metformin use (yes, no), study, sex and country as fixed effects, and baseline HbA1c, baseline 2-h postprandial glycemia, baseline fasting plasma glucose, baseline insulin dose, duration of diabetes and age as a covariate. CI, confidence interval; LOCF, last observation carried forward; LS, least squares; SE, standard error.

compared within the same study. Furthermore, although change in HbA1c was significantly reduced to a greater extent in Asian patients compared with white patients in the exenatide b.i.d. group, the magnitude of HbA1c reductions with exenatide q.w. was greater than exenatide b.i.d. regardless of race. Also, in terms of PPG, Asian patients who received exenatide b.i.d. showed a significantly greater reduction in PPG and post-meal PPG excursions than white patients.

In contrast, Asian patients receiving exenatide q.w. showed numerically similar decreases from baseline in PPG to white patients, and significantly greater reductions than white patients in post-breakfast and post-lunch glucose excursions. Thus, the differing patterns of PPG response between these exenatide therapies need to be further discussed. Finally, PPG might be a predominant factor for influencing HbA1c and resulted in greater responses in Asian patients. However, higher baseline HbA1c and lower baseline BMI in the Asian population, which are predictors for greater HbA1c reductions, might have affected their analysis and cannot be ruled out²⁶.

Interestingly, a nationwide audit from the UK showed lower efficacy of liraglutide and exenatide in South Asian patients compared with white patients with respect to HbA1c reduction and weight reduction²⁷. These controversial results from previous studies suggest that the differential effect in different populations cannot be generalized to all the drugs belonging to GLP-1RA and requires further investigation.

In the present analysis, adding lixisenatide in participants receiving BI therapy with or without metformin significantly

reduced HbA1c levels in both the Asian and white population to a similar extent, and no interaction was found between treatment and ethnicity. The HbA1c reduction of LSMD - 0.49% in Asian participants and -0.45% in white participants was consistent with their individual studies (-0.4%¹³ and -0.51%¹⁵, respectively). However, this HbA1c reduction was not associated with the BMI and bodyweight difference between Asian and white participants at baseline, suggesting that adding lixisenatide would be a beneficial option for participants inadequately controlled with BI irrespective of bodyweight or BMI.

The main antidiabetic effect of lixisenatide is to delay gastric emptying, which in turn controls PPG excursions²⁸. PPG excursions are reported to be more pronounced in Asian individuals than in white individuals with type 2 diabetes mellitus, and might be associated with dietary factors, and with faster β -cell degeneration in Asian individuals^{17,18}.

Several studies have reported significantly more pronounced PPG reduction in Asian individuals than white individuals after insulin or oral antidiabetic therapy²⁹⁻³¹. In the present analysis, no difference of PPG level was observed at baseline in Asian and white participants, possibly because the individual clinical studies were randomized control trials in which the assessment of 2h-PPG was taken after a standardized meal. We also found that lixisenatide as an add-on therapy to BI led to a significant reduction in 2h-PPG levels in both white and Asian participants, with no difference of treatment effect on PPG reduction between the two ethnicities. ANCOVA model analysis found that

Table 6 | Baseline predictors affecting the response to treatment at week 24 evaluated by ANCOVA model

Baseline predictors	Asian		White	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Change in HbA1c as an outcome (%)				
Lixisenatide vs placebo	-0.56 (-0.75 to -0.37)	<0.0001	-0.41 (-0.61 to -0.21)	<0.0001
Baseline HbA1c (per 1.0%)	-0.27 (-0.39 to -0.15)	<0.0001	-0.41 (-0.53 to -0.29)	<0.0001
Age (per year)	-0.01 (-0.02 to 0.01)	0.3948	-0.00 (-0.01 to 0.01)	0.9159
Diabetes duration	-0.01 (-0.02 to 0.01)	0.4755	-0.00 (-0.02 to 0.01)	0.6236
Female vs male	0.05 (-0.15 to 0.24)	0.6368	0.01 (-0.18 to 0.21)	0.9059
Baseline BMI (kg/m ²)	-0.01 (-0.04 to 0.02)	0.4680	0.01 (-0.01 to 0.03)	0.1987
Basal insulin dose (IU)	0.00 (-0.00 to 0.01)	0.2758	-0.00 (-0.00 to 0.00)	0.7912
Change in 2h-PPG as an outcome (mmol/L)				
Lixisenatide vs placebo	-3.69 (-4.59 to -2.78)	<0.0001	-3.67 (-4.51 to -2.82)	<0.0001
Baseline HbA1c (per 1.0%)	0.55 (-0.12 to 1.22)	0.1084	0.49 (-0.06 to 1.04)	0.0783
Age (per year)	-0.04 (-0.09 to 0.02)	0.1808	0.02 (-0.02 to 0.07)	0.3240
Diabetes duration	-0.05 (-0.13 to 0.04)	0.2911	-0.02 (-0.09 to 0.05)	0.5330
Female vs male	-0.09 (-0.99 to 0.81)	0.8388	0.36 (-0.48 to 1.20)	0.3993
Baseline 2h-PPG (mmol/L)	-0.70 (-0.82 to -0.58)	<0.0001	-0.78 (-0.89 to -0.66)	<0.0001
Baseline BMI (kg/m ²)	-0.07 (-0.21 to 0.06)	0.2874	0.01 (-0.06 to 0.09)	0.7143
Basal insulin dose (IU)	-0.00 (-0.03 to 0.02)	0.8683	-0.00 (-0.01 to 0.01)	0.7991
Change in 2h-PPG excursion as an outcome (mmol/L)				
Lixisenatide vs placebo	-3.29 (-4.08 to -2.51)	<0.0001	-3.76 (-4.52 to -3.00)	<0.0001
Baseline HbA1c (per 1.0%)	0.42 (-0.14 to 0.98)	0.1408	0.21 (-0.26 to 0.67)	0.3873
Age (per year)	-0.01 (-0.06 to 0.03)	0.5886	0.00 (-0.04 to 0.05)	0.9023
Diabetes duration	-0.03 (-0.10 to 0.05)	0.5073	0.01 (-0.05 to 0.07)	0.8261
Female vs male	0.38 (-0.40 to 1.16)	0.3402	0.22 (-0.54 to 0.97)	0.5749
Baseline 2h-PPG excursion (mmol/L)	-0.66 (-0.79 to -0.54)	<0.0001	-0.60 (-0.72 to -0.49)	<0.0001
Baseline BMI (kg/m ²)	-0.09 (-0.21 to 0.03)	0.1418	-0.03 (-0.10 to 0.03)	0.3305
Basal insulin dose (IU)	-0.01 (-0.03 to 0.01)	0.4193	0.00 (-0.01 to 0.02)	0.4417

Data are mean (standard deviation [SD]) unless stated otherwise. The ANCOVA model has terms: treatment groups (lixisenatide or placebo), randomization strata of glycated hemoglobin (HbA1c; <8.0, ≥8.0%), randomization strata of metformin use (yes, no), study, sex and country as fixed effects, and baseline HbA1c, baseline 2-h postprandial glycemia (2h-PPG), baseline fasting plasma glucose, baseline insulin dose, baseline body mass index, duration of diabetes and age as a covariate. Races with less than five patients in either of the treatment groups were combined into 'Other' race category. CI, confidence interval; LOCF, last observation carried forward; LS, least squares; SE, standard error.

individuals with higher baseline PPG levels are more likely to show better PPG reduction.

Similar to the present results, in another study carried out among Asian individuals to assess lixisenatide efficacy as add-on therapy to BI ± sulfonylurea, baseline 2h-PPG was 17.81 and 17.75 mmol/L for the treatment and placebo group, which was relatively higher than that for Asian individuals reported in the present study. PPG reduction was also more pronounced in this study (-7.83 mmol/L)⁹. Thus, baseline PPG might be an important contributor to determining the efficacy of lixisenatide rather than ethnicity. Lixisenatide therapy as add-on treatment to BI could be more beneficial to individuals with higher baseline 2h-PPG.

In the present analysis, no significant improvement in FPG level was observed between the treatment groups and between the populations. This could be due to the fact that BI was completely titrated before randomization, and kept stable after

randomization for evaluation of lixisenatide²³. Thus, there was no further decrease in FPG. In addition, the ANCOVA analysis showed that treatment with lixisenatide contributed to an HbA1c and 2h-PPG reduction after adjustment of baseline HbA1c and 2h-PPG levels in Asian and white participants, signifying that lixisenatide treatment, baseline HbA1c and 2h-PPG were significant contributors for predicting change in HbA1c levels and PPG levels in participants with type 2 diabetes mellitus.

When selecting treatments for glycemic control, the impact of type 2 diabetes mellitus treatment regimens on bodyweight is an important factor, because patients are often reluctant to start, comply with or intensify treatments that result in weight gain, in particular insulin³². In the present study, the addition of lixisenatide significantly reduced bodyweight in both ethnic groups, showing that patients with type 2 diabetes mellitus uncontrolled with BI might benefit from lixisenatide addition.

HbA1c, FPG and PPG are all important targets of diabetes treatment and glycemic control. PPG was found to be a main reason for not reaching the HbA1c target in BI-treated participants. Analysis of databases from randomized controlled studies, registries and electronic health records showed 24–54% of individuals with type 2 diabetes mellitus treated with BI globally had residual hyperglycemia with HbA1c not at target, despite achieving FPG control. PPG excursions are reported to be more pronounced in Asian individuals than in white individuals with type 2 diabetes mellitus in real-world settings, indicating a significant unmet need^{17,18}.

The results from the present analysis provided evidence that lixisenatide has clinical benefit in Asian and white inadequately controlled individuals with type 2 diabetes mellitus. Adding lixisenatide to BI was found to be beneficial in both ethnicities, irrespective of bodyweight or BMI. Also, PPG reductions might be more effective in individuals with higher PPG excursion or residual hyperglycemic defects. However, the study was limited by the retrospective design, which was carried out in two datasets of randomized trials. Therefore, further prospective, randomized trials based on ethnicity need to be carried out to compare the efficacy of lixisenatide as add-on therapy to BI in various races. This would help to comprehensively evaluate the efficacy of lixisenatide on glycemic control in individuals of different ethnicities.

In conclusion, adding lixisenatide to BI with or without metformin showed a significant reduction in HbA1c and 2h-PPG levels in both Asian and white populations, and no differences of treatment effect was observed between the two populations. Lixisenatide might help improve glycemic control in these clinically challenging populations.

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DISCLOSURE

MZ Liu is an employee of BDM Consulting Inc. contracted full-time to Sanofi. GY Wu, ML Zhang, X Zhang, N Cui and HQ Yin are employees of Sanofi. FQ Liu and L Chen declare no conflict of interest.

REFERENCES

- International Diabetes Federation – Facts & figures [Internet]. Available from: <https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html>. Accessed November 15, 2019.
- Chan JCN, Malik V, Jia W, *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
- Matsumoto K, Miyake S, Yano M, *et al.* Glucose tolerance, insulin secretion, and insulin sensitivity in nonobese and obese Japanese subjects. *Diabetes Care* 1997; 20: 1562–1568.
- Venn BJ, Williams SM, Mann JI. Comparison of postprandial glycaemia in Asians and Caucasians: glycaemia in Asians and Caucasians. *Diabet Med* 2010; 27: 1205–1208.
- Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach | diabetes care [Internet]. Available from: <https://care.diabetesjournals.org/content/35/6/1364>. Accessed November 15, 2019.
- Bolli GB, Owens DR. Lixisenatide, a novel GLP-1 receptor agonist: efficacy, safety and clinical implications for type 2 diabetes mellitus. *Diabetes Obes Metab* 2014; 16: 588–601.
- Ratner RE, Rosenstock J, Boka G, *et al.* Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial. *Diabet Med* 2010; 27: 1024–1032.
- Campbell RK. Clarifying the role of incretin-based therapies in the treatment of type 2 diabetes mellitus. *Clin Ther* 2011; 33: 511–527.
- Seino Y, Min KW, Niemoeller E, *et al.* Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). *Diabetes Obes Metab* 2012; 14: 910–917.
- Fonseca VA, Alvarado-Ruiz R, Raccach 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: 1225–1231.
- Seino Y, Takami A, Boka G, *et al.* Pharmacodynamics of the glucagon-like peptide-1 receptor agonist lixisenatide in Japanese and Caucasian patients with type 2 diabetes mellitus poorly controlled on sulphonylureas with/without metformin. *Diabetes Obes Metab* 2014; 16: 739–747.
- Božek T, Bilić-Ćurčić I, Berković MC, *et al.* The effectiveness of lixisenatide as an add on therapy to basal insulin in diabetic type 2 patients previously treated with different insulin regimens: a multi-center observational study. *Diabetol Metab Syndr* 2018; 10: 16.
- Riddle MC, Aronson R, Home P, *et al.* Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care* 2013; 36: 2489–2496.
- Rosenstock J, Guerci B, Hanefeld M, *et al.* Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 trial. *Diabetes Care* 2016; 39: 1318–1328.
- Yang W, Min K, Zhou Z, *et al.* Efficacy and safety of lixisenatide in a predominantly Asian population with type 2 diabetes insufficiently controlled with basal insulin: the

- GetGoal-L-C randomized trial. *Diabetes Obes Metab* 2018; 20: 335–343.
16. Wang T, Lu J, Shi L, *et al.* Association of insulin resistance and β -cell dysfunction with incident diabetes among adults in China: a nationwide, population-based, prospective cohort study. *Lancet Diabetes Endocrinol* 2020; 8: 115–124.
 17. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci* 2013; 1281: 64.
 18. Yabe D, Seino Y, Fukushima M, *et al.* β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. *Curr Diab Rep* 2015; 15: 602.
 19. Incretin-based drugs for type 2 diabetes: focus on East Asian perspectives [Internet]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4854513/>. Accessed November 15, 2019
 20. Ntuk UE, Gill JMR, Mackay DF, *et al.* Ethnic-specific obesity cutoffs for diabetes risk: cross-sectional study of 490,288 UK biobank participants. *Diabetes Care* 2014; 37: 2500–2507.
 21. Tanaka S, Horimai C, Katsukawa F. Ethnic differences in abdominal visceral fat accumulation between Japanese, African-Americans, and Caucasians: a meta-analysis. *Acta Diabetol* 2003; 40(Suppl 1): S302–S304.
 22. Kadowaki T, Sekikawa A, Murata K, *et al.* Japanese men have larger areas of visceral adipose tissue than Caucasian men in the same levels of waist circumference in a population-based study. *Int J Obes (Lond)* 2006; 30: 1163–1165.
 23. Hu Y, Block G, Sternfeld B, *et al.* Dietary glycemic load, glycemic index, and associated factors in a multiethnic cohort of midlife women. *J Am Coll Nutr* 2009; 28: 636–647.
 24. Singh AK. Incretin response in Asian type 2 diabetes: are Indians different? *Indian J Endocrinol Metab* 2015; 19: 30–38.
 25. Kim YG, Hahn S, Oh TJ, *et al.* Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. *Diabetes Obes Metab* 2014; 16: 900–909.
 26. Sheu WH-H, Brunell SC, Blase E. Efficacy and tolerability of exenatide twice daily and exenatide once weekly in Asian versus White patients with type 2 diabetes mellitus: a pooled analysis. *Diabetes Res Clin Pract* 2016; 114: 160–172.
 27. Melbourne: International Diabetes Federation, 2013. The efficacy of exenatide and liraglutide among South Asians in the Association of British Clinical Diabetologists nationwide audits; p. 1349 – Google Search [Internet]. Available from: https://www.google.com/search?q=Melbourne%3A+International+Diabetes+Federation%3B+2013.+The+efficacy+of+exenatide+and+liraglutide+among+South+Asians+in+the+Association+of+British+Clinical+Diabetologists+nationwide+audits%3B+p.+1349&rlz=1C1GCEU_enIN872IN872&oq=Melbourne%3A+International+Diabetes+Federation%3B+2013.+The+efficacy+of+exenatide+and+liraglutide+among+South+Asians+in+the+Association+of+British+Clinical+Diabetologists+nationwide+audits%3B+p.+1349&aqs=chrome..69i57j69i58&sourceid=chrome&ie=UTF-8. Accessed March 16, 2020.
 28. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs Context*. 2015; 4: 212283.
 29. Herman WH, Dungan KM, Wolffenbuttel BHR, *et al.* Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. *J Clin Endocrinol Metab* 2009; 94: 1689–1694.
 30. Cai X-L, Ji L-N. Treatment response between Asian and non-Asian patients with type 2 diabetes: is there any similarity or difference? *Chin Med J (Engl)* 2019; 132: 1–3.
 31. Su Q, Liu J, Li P, *et al.* Relative contribution of fasting and postprandial blood glucose in overall glycemic control: post hoc analysis of a phase IV randomized trial. *Diabetes Ther* 2018; 9: 987–999.
 32. Shu H, Gu L, Men L, *et al.* Lixisenatide improves glycemic control in Asian type 2 diabetic patients inadequately controlled with oral antidiabetic drugs: an individual patient data meta-analysis. *Diabetes Ther* 2016; 7: 777–792.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Randomized population of Asian people based on geographical regions.

Figure S1 | Randomized population of Asian and white people in individual studies (GetGoal-L and GetGoal-L-C).