

# Lixisenatide reduces postprandial hyperglycaemia via gastrostatic and insulinotropic effects

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## Abstract

**Background** Lixisenatide is a once-daily, prandial, short-acting glucagon-like peptide-1 receptor agonist. Its main antidiabetic effect is to delay gastric emptying to control postprandial plasma glucose excursions. The dose–response relationship of the integrated insulinotropic and gastrostatic response to lixisenatide in healthy volunteers after a standardized liquid meal was investigated.

**Methods** Twenty healthy subjects received acetaminophen 1000 mg with a standardized liquid meal 60 min after a single subcutaneous injection of placebo or lixisenatide 2.5, 5, 10 or 20 µg in randomized order separated by a 2- to 7-day washout. Acetaminophen pharmacokinetics served as a surrogate to assess rate of gastric emptying. Postprandial plasma glucose, insulin, C-peptide and glucagon were assessed for 5 h after the meal test, and lixisenatide pharmacokinetics were determined for 6 h.

**Results** After lixisenatide administration and prior to the standardized meal, insulin and C-peptide transiently increased, while fasting plasma glucose decreased in a dose-dependent manner. After the meal, postprandial plasma glucose, insulin and C-peptide were dose proportionally reduced with lixisenatide *versus* placebo for up to 6 h. Compared with placebo, glucagon levels were transiently lower after any lixisenatide dose, with more sustained reductions after the meal and no apparent dose-related trends. Acetaminophen absorption was significantly reduced and delayed compared with placebo for lixisenatide doses  $\geq 5$  µg and demonstrated dose-dependent slowing of gastric emptying. Lixisenatide displayed near dose-proportional exposure, with gastrointestinal events increasing with dose.

**Conclusions** Lixisenatide reduced fasting plasma glucose via stimulation of glucose-dependent insulin release and controlled postprandial plasma glucose by delaying gastric emptying, demonstrating it to be a valuable option for overall glycaemic control. Copyright © 2015 John Wiley & Sons, Ltd.

**Keywords** healthy subjects; lixisenatide; gastric emptying; glycaemic control; pharmacokinetics; type 2 diabetes mellitus

## Introduction

Both postprandial and fasting plasma glucose (PPG and FPG respectively) contribute to overall glycated haemoglobin (HbA<sub>1c</sub>) levels, with the relative importance of PPG and FPG depending on several factors, including current treatment regimens and actual HbA<sub>1c</sub> level [1–3]. In patients with type 2 diabetes mellitus (T2DM) receiving basal insulin, with resulting well-controlled

FPG, the contribution of PPG to overall HbA<sub>1c</sub> levels seems to be especially prominent [3]. A major determinant of PPG control is the rate of gastric emptying, accounting for up to 35% of the variance in response to a meal or glucose challenge [4]. Gastric emptying is accelerated in hypoglycaemia and slowed in hyperglycaemia, in both healthy subjects and those with T2DM [5–8]. Furthermore, patients with diabetes with gastroparesis have blunted PPG excursions and reduced insulin use [6,9], and pharmacologically induced delay of gastric emptying is being pursued as a method of improving glycaemic control.

Glucagon-like peptide-1 (GLP-1) is a naturally occurring, gut-derived incretin hormone [10,11]. It is released postprandially and involved in the stimulation of insulin secretion and the suppression of glucagon release in the pancreas, and delay of gastric emptying in the stomach. GLP-1 receptor agonists (GLP-1 RAs) mimic the activity of GLP-1 while also having a prolonged half-life and more long-lasting activity compared with endogenous GLP-1 [12]. Delay of gastric emptying, over and above stimulation of glucose-dependent insulin release, is thought to be the predominant determinant of PPG control with the once-daily, short-acting prandial GLP-1 RA lixisenatide (Lyxumia<sup>®</sup>, Sanofi, Paris, France) [13] and has been shown to be an important mechanism for control of PPG with the prandial GLP-1 RA exenatide twice-daily (BID) [14].

A recent study aiming to elucidate the insulinotropic effect of lixisenatide assessed glucose disposal after an intravenous glucose challenge and revealed that lixisenatide can resensitize glucose-dependent insulin release in patients with T2DM, particularly in individuals with early-stage disease and modestly elevated HbA<sub>1c</sub> levels. In the presence of lixisenatide, glucose disposal was returned to almost normal intensities, without impairing counter-regulation to low glucose by glucagon [15].

The primary objective of this study was to investigate the integrated insulinotropic and gastrostatic response of lixisenatide on PPG, and corresponding insulin and glucagon release in healthy volunteers after an oral glucose challenge (standardized meal). A further aim was to establish the pharmacokinetic and pharmacodynamic dose–response relationship between lixisenatide and gastric emptying.

## Materials and methods

### Study design

This was a Phase I, single-centre, randomized, open-label, placebo-controlled, crossover (5-sequence, 5-period, 5-treatment) study conducted at PAREXEL International GmbH, Berlin, Germany, from January to March 2013. The study protocol was submitted to an Independent

Ethics Committee for review and written approval, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent prior to any procedure that was related to the study.

### Study participants

Subjects were volunteers aged 18–45 years with a body mass index of 18–28 kg m<sup>-2</sup>, inclusive. All subjects were certified healthy by a comprehensive clinical assessment.

### Treatment

Each of the five treatment periods lasted 1 day, followed by a 2- to 7-day washout period before the next treatment period. An end-of-study visit occurred 2–7 days after the last treatment period. The overall duration of observation was approximately 6 weeks for each subject. At 3–6 months after the last treatment period, subjects had the option of attending a post-study visit if they had converted to being anti-lixisenatide antibody-positive at the end-of-study visit.

After an overnight fast of at least 10 h, single doses of lixisenatide 2.5, 5, 10 or 20 µg or matched placebo were administered to each subject into the abdominal subcutis during one of the five distinct treatment periods. At 60-min post-lixisenatide or post-placebo administration, a standardized liquid meal (400 mL of Ensure Plus Next Generation Vanilla [600 kcal]) was administered and followed within 10–15 min by oral acetaminophen 1000 mg. A 1000-mg dose of acetaminophen is a commonly administered therapeutic dose in adults and was expected to produce adequate concentrations for pharmacodynamic analysis. Acetaminophen absorption has been shown to be reliably dependent on the rate of gastric emptying [16] and, hence, is commonly used as a surrogate for gastric emptying.

Blood specimens for determination of lixisenatide, acetaminophen and glucose, insulin, C-peptide and glucagon were taken at predefined times from 90 min before to 300 min after meal intake.

### Assessments

The primary endpoint was the area under the PPG curve from 0 to 1 h after the meal challenge (PPG–AUC<sub>0–1 h</sub>). Secondary pharmacodynamic endpoints included area under the serum insulin concentration curve from 0 to 1 h after meal intake (INS–AUC<sub>0–1 h</sub>), maximum plasma glucose and maximum serum insulin concentrations (PPG–C<sub>max</sub> and INS–C<sub>max</sub> respectively) and time of PPG–C<sub>max</sub> and INS–C<sub>max</sub> (PPG–t<sub>max</sub> and INS–t<sub>max</sub> respectively). Mean serum glucagon and plasma C-peptide

concentrations were also measured. Pharmacokinetic parameters included the area under the lixisenatide plasma concentration time curve to the last observed time (LIXI-AUC<sub>last</sub>) and extrapolated to infinity (LIXI-AUC), fractional areas under the plasma acetaminophen curve from 0 to 5 h after meal challenge (ACT-AUC<sub>0-xh</sub>; where x is 1, 2, 3, 4 or 5 h), as well as maximum plasma lixisenatide and acetaminophen concentrations (LIXI-C<sub>max</sub> and ACT-C<sub>max</sub>), and time of LIXI-C<sub>max</sub> and ACT-C<sub>max</sub> (LIXI-t<sub>max</sub> and ACT-t<sub>max</sub>). Safety endpoints included adverse events (AEs) and serious AEs reported by subject/observed by investigator and bedside blood glucose tests.

## Statistical analysis

### Pharmacodynamics

PPG-AUC<sub>0-1h</sub>, PPG-C<sub>max</sub>, INS-AUC<sub>0-1h</sub> and INS-C<sub>max</sub> were analysed using an analysis of covariance model with treatment, sequence and period as fixed effects, subjects within sequence as a random effect and the corresponding baseline (T<sub>-0.5h</sub>) levels as a covariate. The least squares mean differences between treatment groups and 90% confidence intervals (CIs) were calculated within the model framework. For PPG-t<sub>max</sub> and INS-t<sub>max</sub>, descriptive statistics were provided.

### Pharmacokinetics

Pharmacokinetic parameters of acetaminophen and lixisenatide were summarized by treatment using descriptive statistics. Log-transformed acetaminophen and lixisenatide pharmacokinetic parameters were compared among the five acetaminophen (i.e. four lixisenatide arms and one placebo arm) or four lixisenatide treatments using a linear mixed effects model, with fixed terms of treatment, sequence and period, with an unstructured 5 × 5 (4 × 4 for lixisenatide) matrix for treatment-specific variances and covariances for subject within sequence. For all parameters, estimates and 90% CIs for the ratio of treatment means were computed for the differences between treatment means within the linear mixed effects model framework, and then converted to ratios by the antilog transformation.

## Results

### Population characteristics

Twenty healthy volunteers were randomized and commenced treatment. A summary of demographics and subject characteristics is shown in Table 1. A total of 19 subjects

completed all five treatment periods. One subject withdrew consent because of personal reasons after completion of treatment period 3. At the time of leaving the study, the subject had failed to complete the placebo and lixisenatide 20-μg treatment periods.

### Pharmacodynamics

#### *Prior to the standardized meal*

Before the standardized meal, FPG generally decreased in a dose-dependent manner after the lixisenatide injection compared with placebo (Figure 1a). Corresponding with the reduction in FPG, small and transient increases in insulin (Figure 1b) and C-peptide (Figure 1c) concentration were observed. Additionally, there appeared to be a slight decrease in glucagon concentrations from 1 h before the meal (Figure 1d).

#### *After the standardized meal*

For the primary endpoint (PPG-AUC<sub>0-1h</sub>) and secondary endpoints (INS-AUC<sub>0-1h</sub>, PPG-C<sub>max</sub> and INS-C<sub>max</sub>), a general dose-dependent treatment effect was demonstrated for lixisenatide 2.5 to 20 μg (Table 2 [PPG] and Table 3 [INS]), with no substantial difference between lixisenatide 10 and 20 μg. Compared with placebo, a dose-dependent reduction in PPG was demonstrated with lixisenatide 2.5 to 20 μg (Figure 1a), again without a substantial difference between lixisenatide 10 and 20 μg. Corresponding to the reduction in PPG, insulin (Figure 1b) and also C-peptide concentration (Figure 1c) were reduced compared with placebo in a dose-dependent manner up to 300 min after the meal. Lixisenatide 20 μg produced a more sustained delay in insulin secretion than

**Table 1. Demographics and subject characteristics at baseline, safety population**

	All subjects (N = 20)
Age (years)	
Mean (SD)	31.0 (7.3)
Min:Max	18:44
Sex [n (%)]	
Male	10 (50.0)
Female	10 (50.0)
Race [n (%)]	
Caucasian/White	19 (95.0)
Asian/Oriental	1 (5.0)
Height (cm)	
Mean (SD)	174.2 (11.5)
Min:Max	155:192
Weight (kg)	
Mean (SD)	69.7 (14.6)
Min:Max	51.7:99.9
BMI (kg m <sup>-2</sup> )	
Mean (SD)	22.8 (2.7)
Min:Max	18.3:27.1

BMI, body mass index; SD, standard deviation.

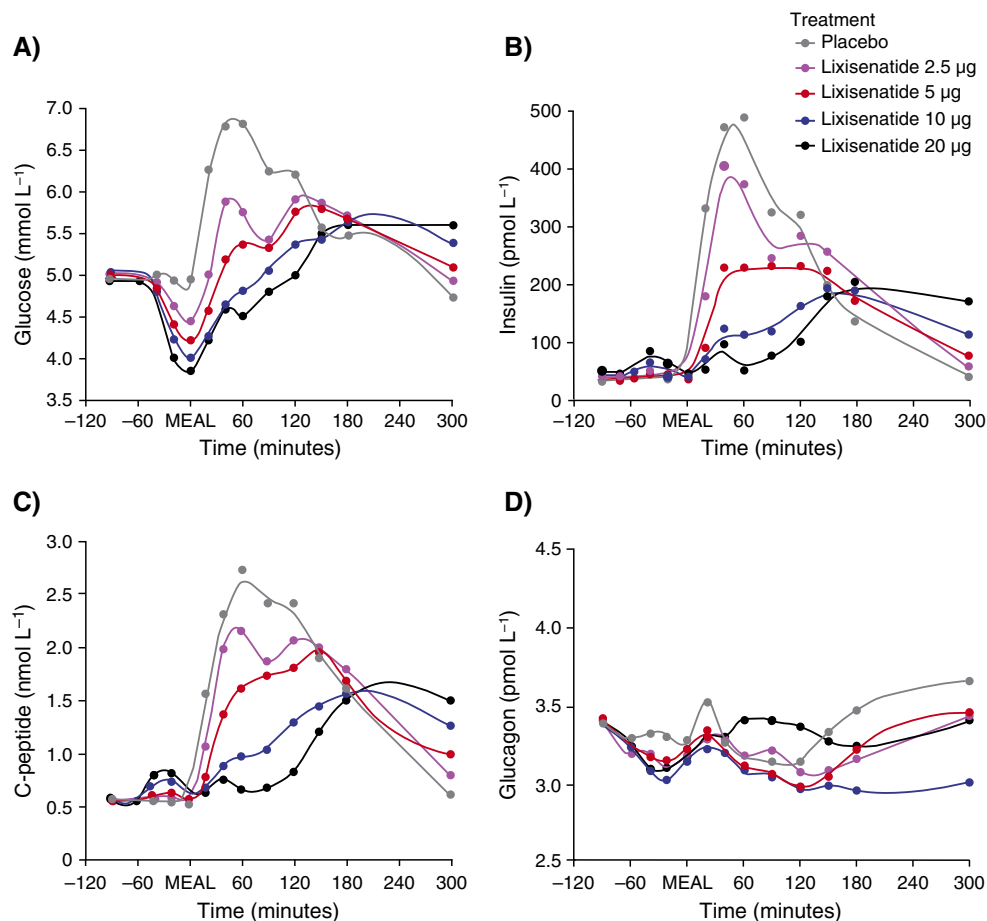


Figure 1. Mean (A) plasma glucose (mmol L<sup>-1</sup>), (B) insulin (pmol L<sup>-1</sup>), (C) C-peptide (nmol L<sup>-1</sup>) and (D) glucagon (pmol L<sup>-1</sup>) over time from -120 to 300 min. 'MEAL' marks the meal challenge time point (60 min after lixisenatide administration)

lixisenatide 10 µg. While glucagon levels were transiently lower after any lixisenatide dose with more sustained reductions after the meal, in contrast with insulin, there were no apparent dose-related trends in plasma glucagon concentrations compared with placebo (Figure 1d).

## Pharmacokinetics

### Lixisenatide

Lixisenatide exposure increased in a slightly less than dose-proportional manner (Figure 2a). LIXI-AUC and LIXI-C<sub>max</sub> increased 0.85-fold (90% CI 0.78, 0.91) and 0.77-fold (90% CI 0.72, 0.82) respectively (data not shown). For lixisenatide 2.5 to 10 µg, LIXI-t<sub>max</sub> was reached at a median of 1.5 h after meal administration *versus* a median of 2.0 h with lixisenatide 20 µg (data not shown).

### Acetaminophen

Fractional ACT-AUC<sub>0-1 h</sub>, ACT-AUC<sub>last</sub> and ACT-C<sub>max</sub> decreased with lixisenatide dose, while ACT-t<sub>max</sub> increased from 3 to 5 h after the meal (Table 4); for AUC<sub>0-1 h</sub> and C<sub>max</sub>,

these differences were significant ( $p < 0.05$ ) compared with placebo for lixisenatide doses of 5 µg or more. Both Figure 2b, which shows the mean plasma acetaminophen concentrations *versus* the different doses of lixisenatide over time, and Figure 3a, which displays the ratios of cumulative hourly acetaminophen exposure to placebo, demonstrate the delaying effect of lixisenatide on gastric emptying. Figure 3a shows that lixisenatide doses >2.5 µg given 1 h prior to the standardized liquid meal significantly blunted gastric emptying by, on average, more than 50% up to a maximum of >80%. For lixisenatide 5 and 10 µg, the rate of gastric emptying began to gradually recover 2 h after the meal, while with lixisenatide 20 µg, the initial inhibition of gastric emptying was prolonged for an additional hour. Although acetaminophen concentrations were comparable at 3-h post-meal among the lower doses of lixisenatide, cumulative exposure of acetaminophen and, hence, glucose absorption continued to be incomplete compared with placebo beyond the 6-h observation period with all doses, with the overall recovery possibly taking more than 12 h (data not shown). Figure 3b displays the inverse relationship between lixisenatide exposure and acetaminophen absorption. The lixisenatide

Table 2. Pharmacodynamic outcomes for primary endpoint PPG-AUC<sub>0-1 h</sub> and secondary endpoint PPG-C<sub>max</sub>

Parameter	Lixisenatide treatment group	Effect estimate vs placebo	90% confidence intervals	p-value
PPG-AUC <sub>0-1 h</sub> (mmol min L <sup>-1</sup> )	2.5 µg	-61.2	-75.2, -47.3	<0.001
	5 µg	-92.3	-106.2, -78.4	<0.001
	10 µg	-118.4	-132.4, -104.4	<0.001
	20 µg	-121.1	-135.2, -107.1	<0.001
PPG-C <sub>max</sub> (mmol L <sup>-1</sup> )	2.5 µg	-0.8	-1.1, -0.5	<0.001
	5 µg	-1.0	-1.3, -0.7	<0.001
	10 µg	-1.5	-1.8, -1.2	<0.001
	20 µg	-1.2	-1.6, -0.9	<0.001
Parameter	Lixisenatide treatment group	Effect estimate between doses	90% confidence intervals	p-value
PPG-AUC <sub>0-1 h</sub> (mmol min L <sup>-1</sup> )	5 µg vs 2.5 µg	-31.1	-44.7, -17.4	<0.001
	10 µg vs 2.5 µg	-57.2	-70.9, -43.4	<0.001
	20 µg vs 2.5 µg	-59.9	-73.8, -46.0	<0.001
	10 µg vs 5 µg	-26.1	-39.8, -12.4	0.002
	20 µg vs 5 µg	-28.9	-42.8, -14.9	<0.001
	20 µg vs 10 µg	-2.8	-16.7, 11.2	NS
PPG-C <sub>max</sub> (mmol L <sup>-1</sup> )	5 µg vs 2.5 µg	-0.3	-0.6, 0.1	NS
	10 µg vs 2.5 µg	-0.7	-1.0, -0.4	<0.001
	20 µg vs 2.5 µg	-0.5	-0.8, -0.2	0.015
	10 µg vs 5 µg	-0.5	-0.8, -0.2	0.015
	20 µg vs 5 µg	-0.2	-0.6, 0.1	NS
	20 µg vs 10 µg	0.2	-0.1, 0.6	NS

AUC, area under the curve; C<sub>max</sub>, maximum concentration; NS, non-significant p-value; PPG, postprandial plasma glucose. Data are point estimates of treatment group differences with 90% confidence intervals for lixisenatide treatment groups (2.5, 5, 10 and 20 µg) versus placebo or between lixisenatide doses.

Table 3. Pharmacodynamic outcomes for secondary endpoint INS-AUC<sub>0-1 h</sub> and INS-C<sub>max</sub>

Parameter	Lixisenatide treatment group	Effect estimate vs placebo	90% confidence intervals	p-value
INS-AUC <sub>0-1 h</sub> (pmol min L <sup>-1</sup> )	2.5 µg	-8648	-12,713, -4584	<0.001
	5 µg	-16,762	-20,848, -12,676	<0.001
	10 µg	-21,896	-25,936, -17,856	<0.001
	20 µg	-24,848	-29,078, -20,618	<0.001
INS-C <sub>max</sub> (pmol L <sup>-1</sup> )	2.5 µg	-101	-216, 15	NS
	5 µg	-277	-391, -164	<0.001
	10 µg	-428	-543, -314	<0.001
	20 µg	-388	-509, -268	<0.001
Parameter	Lixisenatide treatment group	Effect estimate between doses	90% confidence intervals	p-value
INS-AUC <sub>0-1 h</sub> (pmol min L <sup>-1</sup> )	5 µg vs 2.5 µg	-8114	-12,173, -4055	0.001
	10 µg vs 2.5 µg	-13,248	-17,214, -9281	<0.001
	20 µg vs 2.5 µg	-16,200	-20,262, -12,137	<0.001
	10 µg vs 5 µg	-5134	-9170, -1098	0.038
	20 µg vs 5 µg	-8086	-12,322, -3850	0.002
	20 µg vs 10 µg	-2952	-7049, 1145	NS
INS-C <sub>max</sub> (pmol L <sup>-1</sup> )	5 µg vs 2.5 µg	-177	-289, -64	0.011
	10 µg vs 2.5 µg	-328	-440, -216	<0.001
	20 µg vs 2.5 µg	-288	-403, -173	<0.001
	10 µg vs 5 µg	-151	-263, -40	0.027
	20 µg vs 5 µg	-111	-229, 6	NS
	20 µg vs 10 µg	40	-76, 156	NS

AUC, area under the curve; C<sub>max</sub>, maximum concentration; INS, insulin; NS, non-significant p-value. Data are point estimates of treatment group differences with 90% confidence intervals for lixisenatide treatment groups (2.5, 5, 10 and 20 µg) versus placebo or between lixisenatide doses.

exposure required to achieve a reduction of more than 50% in acetaminophen absorption 2 h after the liquid meal was estimated to be on average 244 (interquartile range of 151–357) ng h mL<sup>-1</sup>. This was achieved in all subjects treated with lixisenatide dose ≥10 µg.

### Safety endpoints (data not shown)

No serious AEs were reported, and no subjects discontinued the study because of treatment-emergent AEs. The most frequent treatment-emergent AEs were nausea

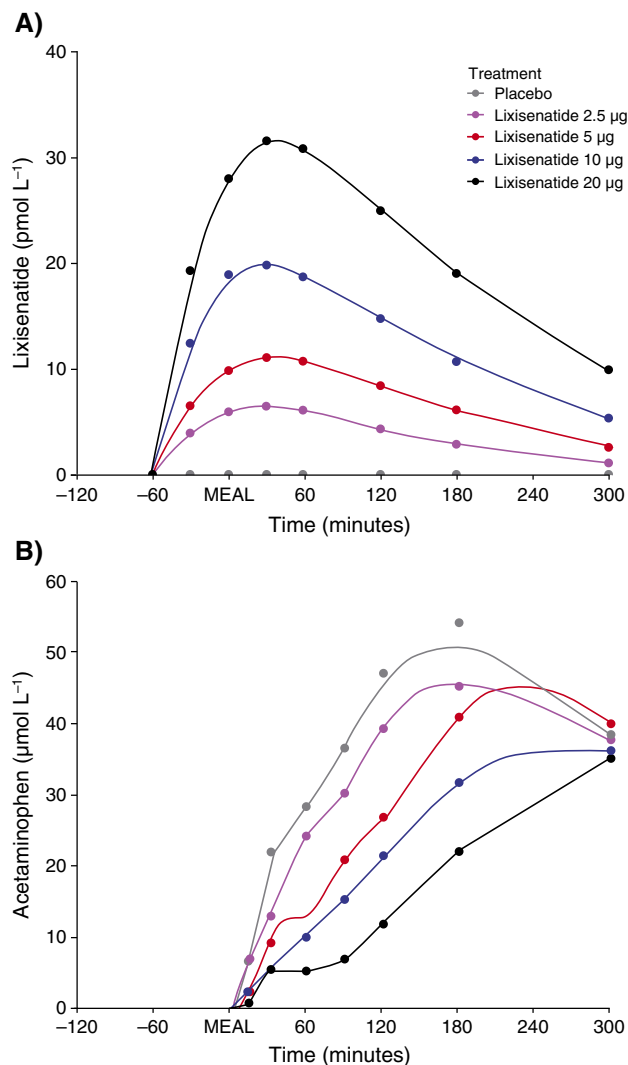


Figure 2. Mean (A) lixisenatide plasma time profiles from 0 to 360 min and (B) acetaminophen plasma time profiles (as a surrogate measure for gastric emptying) for different doses of lixisenatide over time from -120 to 300 min. 'MEAL' marks the meal challenge time point (60 min after lixisenatide administration)

and vomiting, which increased in a dose-dependent manner. Blood glucose levels below the lower limit of normal ( $3.5 \text{ mmol L}^{-1}$ ) were detected in 3/20, 5/20 and 10/19 subjects administered lixisenatide 5, 10 and  $20 \mu\text{g}$  respectively. One subject had mild hypoglycaemic symptoms

beginning approximately 50 min after the administration of lixisenatide  $20 \mu\text{g}$ , with blood glucose levels decreasing from 4.8 (predose) to  $3.0 \text{ mmol L}^{-1}$  at 60 min post-dose. Within 30 min of the standardized meal (given at the normal time of 1 h post-lixisenatide injection), the subject's blood glucose had increased to  $4.1 \text{ mmol L}^{-1}$ , and to  $4.3 \text{ mmol L}^{-1}$  after an additional 30 min, when all hypoglycaemic symptoms had resolved.

## Discussion

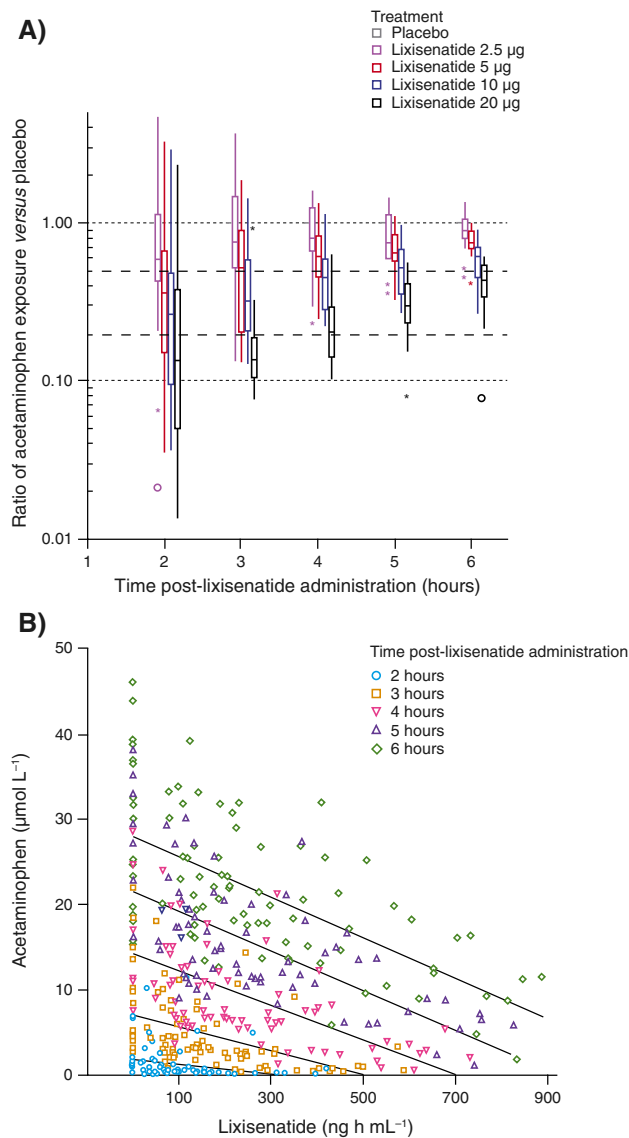
In this study of healthy volunteers, lixisenatide dose-dependently decreased FPG, transiently elevated fasting insulin concentrations and effectively reduced PPG excursions after a standardized meal challenge compared with placebo. Reductions in PPG excursions were associated with slowed gastric emptying (indicated by reduced acetaminophen exposure) and reduced postprandial insulin secretion compared with placebo. This suggests that delayed gastric emptying, rather than insulinotropic effects, is the main driver of PPG reduction with lixisenatide.

The exposure–effect relationships (pharmacokinetics/pharmacodynamics) for the different parameters in this study showed that lixisenatide at a dose as low as  $2.5 \mu\text{g}$  had minor effects on PPG with little impact on gastric emptying, while lixisenatide  $5 \mu\text{g}$  demonstrated a significant reduction in PPG and delay of gastric emptying. The maximum effect on PPG was reached with lixisenatide  $10 \mu\text{g}$ , while lixisenatide  $20 \mu\text{g}$  demonstrated the greatest delays in gastric emptying. The absorption of acetaminophen, and hence the recovery of gastric emptying, was incomplete at the end of the 3-h observation period following administration of all doses of lixisenatide. In contrast to insulin, glucagon was transiently lower after any lixisenatide dose; this reduction was more sustained after the meal. Although no difference was observed between the different lixisenatide doses in terms of changes in glucagon levels, this effect is in line with the suppression of glucagon release through elevation of insulin secretion with lixisenatide, a mechanism visible in the fasting state, and with enhanced glucose-dependent stimulation of insulin release in the fed state.

Table 4. Pharmacokinetic data for acetaminophen by lixisenatide dose administered

	Placebo	Lixisenatide $2.5 \mu\text{g}$	Lixisenatide $5 \mu\text{g}$	Lixisenatide $10 \mu\text{g}$	Lixisenatide $20 \mu\text{g}$
N	19	20	20	18	16
ACT- $C_{\text{max}}$ ( $\mu\text{g mL}^{-1}$ )	9.9 (5.2)	8.7 (2.5)	7.4 (2.3)	5.9 (2.0)	5.9 (2.4)
ACT- $t_{\text{max}}$ (h), median (min–max)	3.0 (0.5–5.1)	3.0 (0.3–5.0)	3.0 (0.5–5.1)	5.0 (0.5–5.2)	5.0 (0.5–5.1)
ACT- $\text{AUC}_{0-1 \text{ h}}$ ( $\mu\text{g h mL}^{-1}$ )	2.6 (3.2)	1.9 (2.2)	1.1 (1.8)	0.8 (1.2)	0.5 (1.2)
ACT- $\text{AUC}_{\text{last}}$ ( $\mu\text{g h mL}^{-1}$ )	29.9 (9.0)	25.6 (6.6)	21.6 (6.2)	17.4 (5.1)	12.9 (6.0)

ACT, acetaminophen; AUC, area under the curve;  $C_{\text{max}}$ , maximum concentration;  $t_{\text{max}}$ , time to maximum concentration. Data are mean (standard deviation) unless stated otherwise, summarizing the dose-dependent behaviour of lixisenatide in plasma.



**Figure 3.** (A) Ratios of cumulative hourly acetaminophen exposure\* and (B) the inverse relationship between lixisenatide exposure and acetaminophen absorption, for different doses of lixisenatide over time \*Placebo at each time point can be seen at a ratio of 1.0. Values that fall within 1.5–3 times the interquartile range are plotted with asterisks. Far-outside values that are >3.0 times the interquartile range are plotted with open circles

The validity of using acetaminophen absorption to measure the rate of gastric emptying compared with scintigraphy, considered to be the gold standard for assessing gastric emptying, has been evaluated in a systematic literature review [17]. Eight of 13 identified studies showed a good correlation between gastric emptying assessed by acetaminophen absorption and scintigraphy, and the general conclusion of the review was that the acetaminophen absorption technique is a valuable tool for clinical use and research purposes. Acetaminophen absorption has been used as a proxy for gastric emptying in a number of earlier

studies of GLP-1 RAs that clearly differentiated the effects of long-acting and prandial, short-acting agents. In these studies, exenatide BID substantially slowed gastric emptying in healthy volunteers and patients with T2DM, while liraglutide and placebo demonstrated equivalent effects on acetaminophen exposure [18–20]. Moreover, these significant reductions in gastric emptying with exenatide BID have been confirmed using scintigraphy [14]. Sustained plasma concentrations of long-acting GLP-1 RAs, such as liraglutide, result in pronounced reductions in FPG but also lead to tachyphylaxis of the delay in gastric emptying, limiting their effect on PPG [21–25]. Indeed, in a head-to-head study, lixisenatide has demonstrated significant delays in gastric emptying *versus* liraglutide [26] and these changes in gastric emptying correlated with significant reductions in PPG with lixisenatide [13]. Of interest, a randomized, crossover study comparing exenatide BID with the dipeptidyl peptidase-4 inhibitor sitagliptin [27] reported that the short-acting GLP-1 RA resulted in significantly greater reductions in 2-h PPG and significantly greater delays in gastric emptying compared with sitagliptin. These findings differentiate prandial, short-acting GLP-1 RAs from this alternative incretin-based approach in terms of achieving optimal postprandial glycaemic control.

While this Phase I study was conducted in healthy volunteers, the Phase III GetGoal trial programme has demonstrated that lixisenatide treatment can bring about a placebo-subtracted change from baseline in 2-h PPG of between  $-3.2$  and  $-7.8$  mmol L<sup>-1</sup> and in HbA<sub>1c</sub> of between  $-0.32$  and  $-0.88\%$ , with an accompanying beneficial effect on body weight [28–36]. Importantly, elevated PPG excursions (more than FPG) are a strong predictor of cardiovascular disease and all-cause mortality [37]. Whether better control of PPG with short-acting GLP-1 RAs results in improved cardiovascular outcomes is, as yet, unknown; however, the ongoing Evaluation of Lixisenatide in Acute coronary syndrome study should be informative in this matter. Evaluation of Lixisenatide in Acute coronary syndrome is an event-driven cardiovascular outcome study in 6000 patients with high cardiovascular risk (defined as patients who recently experienced an acute coronary event). Complete results are scheduled to be available in 2015.

In summary, lixisenatide treatment resulted in dose-dependent reduction of FPG by stimulation of glucose-sensitive insulin release and effective reduction of PPG after a meal by delaying gastric emptying, demonstrating it to be a valuable option for overall glycaemic control.

## Acknowledgements

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Reinhard Becker initiated the investigation, reviewed and interpreted the data, wrote, reviewed and edited the manuscript and approved the final manuscript for submission. Reinhard Becker is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Jens Stechl jointly supervised the investigation, reviewed and edited the manuscript and approved the final manuscript for submission. Axel Steintraesser and Franck Pellissier reviewed and interpreted the data, provided input into the development of the manuscript and approved the final manuscript for submission. Georg Golor

conducted the study and reviewed, edited and approved the final manuscript for submission.

## Conflicts of interest

Reinhard Becker, Jens Stechl and Franck Pellissier are employees of Sanofi. Axel Steintraesser is a consultant and shareholder at Sanofi. Georg Golor is an employee of PAREXEL International GmbH.

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